INTRALIMB COORDINATION AND INTERMUSCULAR COHERENCE IN WALKING AFTER STROKE

by

Peter Y. Jo

A Dissertation
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of
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of
Doctor of Philosophy
Rehabilitation Science

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Fairfax, VA

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DEDICATION

This is dedicated to my beautiful wife, Michelle, and my amazing children, Cosette, Cami and Eli. Thank you for loving me, cheering for me and encouraging me through this crazy roller coaster ride. I love you D-S, H-S, W-U, forever, I promise, no matter what.

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I would like to thank my parents, Sung Soo and Miriam, for continuing to shape my life. Every year, I see more of your steadfast love, dedication and vision for our family. You are more remarkable than I ever knew. To my brother and sister in law, Mark and Betty- what would life be without you and the boys? Thank you for always reminding me of what is most important. I'm so lucky to have you.

Thank you to the RHBS team, past and present, for your guidance and support. Thank you, Dr. Clint Wutzke, for your constant encouragement, especially when things looked bleak. Thank you, Dr. Andrew Guccione, for helping me keep the main thing the main thing. Thank you, Dr. Sangwook Lee, for bringing fancy calculations to life, revealing patterns within human performance. Thank you to Drs. Kevin Terry and Michelle Harris-Love for investing so much time and effort in my journey into science. Finally, I would like to thank my classmates who assisted with various aspects of data collection. But more importantly, you were always quick with a smile, word of encouragement, hug or high five. You brought meaning to the phrase, "it takes a village…"

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ABSTRACT

INTRALIMB COORDINATION AND INTERMUSCULAR COHERENCE IN WALKING AFTER STROKE

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George Mason University, 2019

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Purpose: Following stroke, reduced motor control may lead to walking impairment with subsequent limitations in community participation and quality of life. Kinematic variability may reveal changes to motor control of the paretic limb compared to the non-paretic limb and may relate to walking performance. Frequency domain characteristics of the EMG reflects the activity of motor neuronal pools and the degree of synchronization, estimated as intermuscular coherence, between motor units of separate muscles. Together, kinematic measures of coordination may be a function of common neural drive to motor neuronal pools. Interlimb symmetry of stance time and average knee-ankle angle over stride may also reflect motor control. The purpose of this work is to characterize motor control in walking performance post-stroke. **Methods:** Twenty chronic stroke participants with mild to moderate walking impairment were recruited and completed a treadmill walking trial at preferred walking speed for up to 5 minutes. Kinematic data were acquired over the pelvic and lower extremity and EMG data was captured over the vastus lateralis and tibialis anterior bilaterally. The primary clinical measure was 10 meter walk time. Additional measures were Timed up and Go test, and the Stroke Impact Scale 3.0. Variability of sagittal plane

knee-ankle angle was calculated over an average of 76 strides. **Results:** Knee-ankle angle-angle variability was greater on the paretic limb than the non-paretic limb (p=0.002) with greater variability in swing phase than in stance phase (p=0.001). Paretic swing variability relates to 10MW time (p=0.035) and lower self-reported motor function (p= 0.015) (SIS). Stance time was greater on the non-paretic limb than the paretic limb (p=0.019) and stance asymmetry related to all clinical measures. The difference between mean cyclograms of paretic and non-paretic limbs did not relate to any clinical measure. Asymmetry ratio and paretic swing variability were the greatest predictors of 10MW time. Median frequency of the tibialis anterior was lower on the paretic limb compared to the non-paretic limb (p=0.009). Within the group data, there were no differences in intermuscular coherence between the paretic and non-paretic limb and no relationship between intermuscular coherence and clinical measures. However, 13 of 17 participants showed differences in intermuscular coherence between limbs with 6 participants showing greater coherence on the paretic limb, 6 with greater coherence on the non-paretic limb and 1 with mixed results between stance and swing phase. Within the pooled data, intermuscular coherence was greater in the non-paretic limb than the paretic limb (p=0.023). **Conclusion:** Interlimb symmetry and knee-ankle variability relate to walking performance. However, interlimb angle-angle asymmetry does not relate to walking performance. Frequency domain characteristics between the non-paretic and paretic limb are unclear as differences are not present in the group data but are present in pooled data. The relationship between intermuscular coherence and walking performance may require more detailed characterization of bilateral stance-swing dynamics in order to meaningful relate to 10MW time.

PROJECT INTRODUCTION

Stroke is diagnosed in nearly 800,000 Americans each year [1] often leading to significant motor impairment. Although early perspectives on post-stroke rehabilitation primarily focused on remediating impairment, the relationships between motor impairment, function and disability were often unclear [2] and led to undue heterogeneity in clinical and research frameworks. The International Classification of Function (ICF) was established to offer a consistent and more holistic framework for clinicians and researchers to contextualize patient function and has been utilized following stroke.[3] When viewed through the lens of the ICF, it is apparent that the initial stroke and ensuing motor impairment have far-reaching consequences to include significant restrictions to activities and participation, both of which have been described as central components in rehabilitation science. Recovery within those domains is regarded as the primary goal of the discipline. [4, 5]

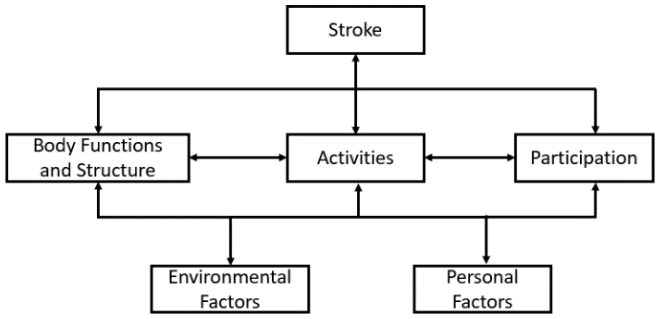


Figure 1. International Classification of Function Framework

Walking falls under the "activities" component of the ICF framework. Following inpatient rehabilitation, 75% of patients have deficits in walking velocity and ability to navigate varied terrain such as inclines and uneven surfaces. These abilities are considered essential for community based walking [6] and are an important requirement for meaningful participation. Unfortunately, participation restrictions persist many years after the initial stroke. For example, when 349 patients

were followed for six years after stroke, only 35% were able to engage in the same level of participation (e.g. chores, leisure, work, outdoor activities) compared to prior to stroke while 65% had reduced levels of participation. A primary predictor of participation was walking ability, categorized as an activity within the ICF framework, with greater walking ability associated with greater participation.[7] In addition to reduced participation, there are physiological sequelae to mobility restriction. Step counts of less than 5000 are considered "sedentary" behavior.[8] In 79 chronic stroke patients who were categorized as community ambulators, participants averaged 1389 steps and demonstrated decreased aerobic fitness, [9] potentially increasing the risk of recurrent stroke. With the risk of stroke recurrence at 26.4% and 39.2% at 5 and 10 years [10], respectively, reduction of risk factors is of reasonable clinical concern. This is an example of an adverse cycle where stroke-induced body function/structure deficits lead to activity limitation. Activity limitation then perpetuates a decline in body function/structure components such as reduced aerobic capacity. Moreover, limited walking activity has deleterious effects beyond aerobic capacity and is reported to contribute to diminished quality of life.

One determinant of quality of life is the ability to live independently. Independent living requires mobility and is usually reflected in stable community ambulation. In patients with chronic stroke, walking ability positively correlated with independence.[11] Walking is also related to greater ability for self-care, participation in activities, fewer symptoms of anxiety and depression [12] and improved health-related quality of life.[13, 14]

Given the benefits to activity, participation and quality of life, walking recovery is a primary goal among patients and clinicians.[15,16] Various body function/structure elements such as impaired muscle strength, balance, diminished proprioception and coordination contribute to reduced

walking. Alterations to motor control, whether due to the initial injury or post-injury adaptations, [17] commonly lead to limitations in mobility. This again highlights the interplay between the ICF components of body function/structure and activities.

This project consists of two sections that attempt to elucidate the relationship between the body functions/structure and activities components of the ICF framework. It is clear that walking activity serves as a central nexus within the framework leading to both participation restrictions and additional decline in body function/structure post-stroke. This positions walking recovery as a critical aim of rehabilitation. Given the interaction of the ICF components, it is prudent to identify those influences that might be potent in diminishing walking activity. Within the ICF core sets for stroke, established by consensus in 2004, [18] there are several categories within the body function component that are of interest in this project. In particular, the categories are "control of voluntary movement" (ICF code b760) and "gait pattern" (ICF code b770). The category of interest within the body structures component is "structure of brain" (ICF code s110) though not explicitly investigated in the current study.

Herein, we aim to identify patterns of changes to the aforementioned body functions categories and explore their contributions to limitations in the walking category (ICF code d450) of the "activities" component. These two 'body functions' categories will be addressed through the lens of coordination, expressed as interlimb temporal symmetry and intralimb coordination, and neural synchronization, expressed as coherence in muscle electrical

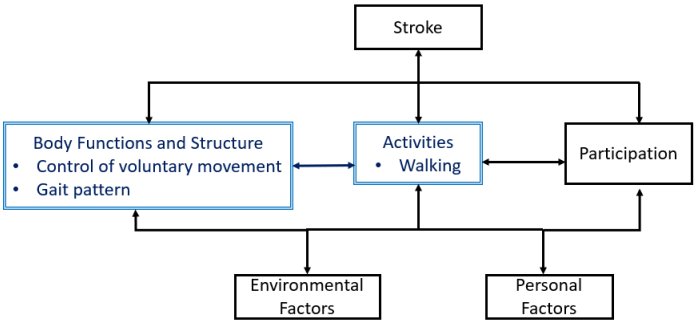


Figure 2. ICF Framework for Stroke with areas of research interest highlighted.

activity. These two categories were selected with the assumption that neural synchronization leads to limb coordination.

Coordination, captured through kinematic evaluation, was addressed in part 1 of this project. Neural synchronization, inferred from frequency-domain EMG analysis, was addressed in part 2. Both parts examined the relationship between their respective body functions and the activity of interest, walking. The focus on neural and joint *coordination* rather than force generation is intentional as it is our view that walking activity, though predicated on many categories within the body functions/structure component, is compromised in stroke primarily due to loss of motor control rather than diminished peripheral (e.g. muscle strength) capacity. This is congruent with Lodha et al. (2019) who found that in chronic stroke, measures of motor control such as lower extremity movement accuracy predicted walking speed while muscle strength did not.[19]

We view motor control through a dynamical systems model where emergence of movement solutions depends on the constraints within the individual, nature of the task and the environment in which the task in executed.[20] We contend that post-stroke, individual constraints exist in multiple categories of the body functions/structure component and self-organization of the system occurs to discover optimal solutions after unconscious negotiation of various "costs" associated with movement. These costs might include bioenergetics, fatigue, need for accuracy, jerkiness etc. [21,22] Many rehabilitative strategies in the post-acute stage depend on motor learning principles, conceptually intertwined with neuroplasticity, [23,24] that allow for exploration of movement strategies to permit optimization of costs, often accounting for considerable variability. However, once movement repertoires have been established, variability is diminished as motor priorities shift from exploration of solutions to exploitation of discovered solutions.[25]

The discovery of novel solutions invariably involves neuroplasticity, a phenomenon that has been described as the basis for motor learning, [26] recovery,[27] and maladaptation after injury.[28] Though the resulting neurological and motoric phenotypes are poorly described, [29] walking patterns are a solution that emerge through interaction of the newly imposed individual constraints with the environment. One form of neuroplastic change may be in patterns of synchronization of motoneuronal pools.

Nowak et al. (2017) argue that complexity of human behavior requires coordination across and within various domains; neurological, psychological, social for example. This includes even the most unremarkable tasks (e.g. driving a car, preparing a meal) that are routinely conducted in our multi-faceted social environment.[30] Synchronization of functional units within domains and concurrent synchronization across domains are regarded as a necessity for meaningful behavior. If we restrict this to motor behavior such as gait, we see that we are not far removed from dynamical systems where interactions among self, task and environment allow movement to emerge. Similarly, synchronization of motor neurons across different levels of the neuraxis may then allow coordination between or within limbs.

With these embedded views, we recruited mild-moderately impaired community ambulators with the assumption that motor learning strategies had been previously exercised. In the study, participants walked at preferred speed with no intrinsic or extrinsic perturbations that might precipitate a search for novel solutions. Our observations and measurements, therefore, reflected system solutions that were exploited during the trial.

Insight into neural synchronization can be garnered from muscle EMG [31] and quantified by measures of coherence. Intralimb coordination can be quantified by measures of knee-ankle angle variability. We explored both concepts as well as their relationship to walking. The aim of the work was to characterize motor control in walking performance post-stroke. The hope was that improved characterization would be a harbinger of novel rehabilitative strategies to promote walking recovery.

PART 1: INTRODUCTION

Although walking performance, commonly operationalized as gait velocity,[32,33,34] is regarded as an important measure of function,[35] there is consensus that velocity reflects a component of an individual's capacity for meaningful community-based walking. In a survey of 115 people post-stroke, gait velocity was able to discriminate between different levels of community ambulation.[36] To complement gait velocity as an indicator of walking performance, interlimb gait symmetry may represent an additional critical component of motor recovery.[37]

Commonly, indicators of interlimb symmetry include stance, swing or total stride times of each limb and calculated as a ratio. For example, a study by Patterson et al. (2008) showed that temporal asymmetry related to both gait velocity and functional mobility. In 54 people post-stroke, gait asymmetry was negatively correlated with gait velocity whereas temporal asymmetry was positively to related to clinical motor scores on the Chedoke-McMaster Stroke Assessment. This relationship was particularly pronounced among those individuals with greater asymmetry. [38] A larger study including 171 people post-stroke found that symmetry measures worsened over time while gait velocity did not change over time. Patterson et al. (2010) suggest that interlimb symmetry and velocity capture different characteristics of gait and both provide meaningful clinical information.[39] These findings suggest that measures of symmetry offer a different window into clinical gait function than velocity measures alone.

While velocity and interlimb symmetry are both useful components of a quantitative portfolio to capture walking function, *intralimb* coordination may also be a functionally distinct category. Intralimb coordination (ILC) is defined as the functional synchronization between segments within an extremity. It has been suggested that inter- and intra- limb coordination are developmentally

discrete processes that mature together but may be differentially moderated.[40] Therefore, despite correlations that might exist, interlimb and intralimb coordination provide qualitatively independent kinematic information.

Gait adaptations may show tendencies (interlimb vs. intralimb) depending on disease [41] and task constraints.[42] For example, when unimpaired individuals were given a gait perturbation by adding a peripheral load on the leg, changes in interlimb coordination were more pronounced than changes in intralimb coordination.[43] Intralimb coordination is thought to reflect the neural control of movement and is of interest not only in its effect on walking, but as a window into the neural control of movement.[44] Intralimb coordination is commonly affected after stroke and is observed through changes in hip, knee and ankle angles.[45] Though we made observations on interlimb symmetry, intralimb coordination was the primary focus in this study due to our interest in the relationship between the typically focal structural lesions in stroke and subsequent lateralization of dysfunction.

Differences in joint angles between paretic and non-paretic limbs during gait are expected and the existing literature has previously described these differences with the paretic limb angles showing greater deviations from that of healthy controls.[46] Although differences between limbs has been reported, it remains unclear if an individual post-stroke should strive to restore paretic joint angles to those of the non-paretic limb. There is general consensus that there is no optimal phenotype of intralimb coordination despite the common practice of measuring joint angles. Given the range of lower extremity joint angles in unimpaired individuals and influence of velocity, sex and age [47, 48], inter-individual heterogeneity of lower extremity joint angles should be anticipated rather than dismissed as error or a deviation from an optimal value.

Additionally, much of the literature focuses on a single plane of analysis though compensation after stroke may involve multi-joint coupling in multiple planes. For example, in a study involving 18 people post-stroke, hip and knee motion was aberrantly coupled in the coronal and sagittal planes, respectively, compared to unimpaired controls.[49] Understanding that multi-planar compensations may occur after injury, assumptions of uniformity based on measurements in a single plane may errantly conceal variability present within the other 2 spatial dimensions.[50] (limitations ?)

Stride to stride variability of coordination patterns, even with angle differences between limbs, may be an important component of gait function and can be captured through kinematic evaluation and visually expressed through a cyclogram. This method has been employed to quantify gait quality and has been beneficial in identifying gait patterns in pathological populations as well as describing differences between unimpaired and pathological populations. Intralimb coordination was evaluated in 14 patients with chronic spinal cord injury and 12 weeks of locomotor training resulted in a reduction hip-knee variability. The reduction in variability was accompanied by faster walking velocity in both overground and treadmill conditions.[51] Based on this finding, there is evidence to suggest that people post-stroke may exhibit increased variability in lower extremity joint angles.

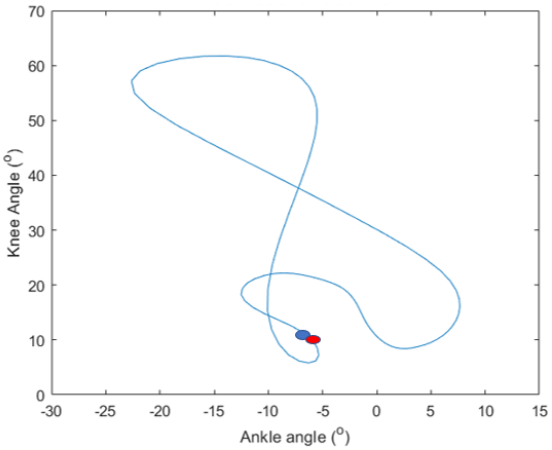


Figure 3. Representative cyclogram with knee-ankle angles during a single stride.

To visually represent the angle of one joint with the concurrent angle of another joint, a cyclogram is often employed. The time domain is removed from this visualization of the gait cycle thereby allowing angle-angle relationships to be evaluated. A representative cyclogram (figure 3) with the

blue circle indicating the point of initial contact and the red circle indicating final contact with the surface. The trace, therefore, represents one gait cycle.

There has been increased interest in quantification of variability of motor performance, specifically gait, commonly categorized as either coordinative variability or end point variability. Coordinative variability is suggestive of exploration and optimal ranges are thought to depend on the stage of learning.[52] End point variability, on the other hand, may indicate poor performance. For example, there may be multiple hip-knee-ankle strategies to place the foot in a position to allow both stability and continued forward progression. However, to maintain a constant velocity, there is far less freedom in the location of foot placement.

For the purposes of this project, a focus on coordinative variability and adoption of the assumption of optimal ranges of variability has been employed. [53] Deviations from optimal ranges have been observed in several clinical population including increased stride length and temporal variability among individuals with neurodegenerative disease.[54] Similar changes have been observed in spinal cord injury where joint-joint angle variability among patients was greater than among unimpaired individuals.[45] It is worth noting that changes to variability alone are unremarkable unless there is clinical impact. Such changes have been shown to relate to decrements in performance and poorer clinical outcomes. Parkinson's patients have less variability of spatiotemporal gait parameters when they are "on" levodopa compared to "off" periods. Moreover, "on" periods are associated with demonstrable improvements in gait stability that coincide with reduced variability.[55]

In 32 individuals with chronic stroke, intralimb coordination of the hip and knee was shown to relate to walking performance in both gait speed and 6-minute walk outcomes. Those with increased variability of joint angles over 30 strides had poorer walking performance outcomes such

as gait speed and 6 minute walk time. Kinematic variability proved to be malleable and amenable to training. Twelve weeks of gait training led to reduced variability of joint angles and correlated with improvements in gait speed and 6 minute walk time over that period.[56]

It is evident that excessive variability may be associated with disease. Within the model of optimal variability, diminished variability is similarly unwelcome and may also be accompanied by clinically meaningful changes. For example, fall risk has been shown to increase when gait variability is excessively low. [57,58] The reasons are unclear, but it has been proposed that low variability reflects excessive system rigidity that is unable to adapt to task demands.

It is assumed that for a cyclical task such as walking with consistent conditions at preferred walking speeds (PWS) [59] such as on a treadmill, a reduction in stride to stride variability is optimal.[60] Under dynamical systems, we can infer that when the task (treadmill walking) and environment (no environmental perturbations) remain consistent, an individual is likely to remain in a discovered attractor state resulting in little change in movement characteristics.[61] In other words, with the relative consistency in 2 of the 3 sets of constraints (task and environment), it can be assumed that the range of probabilistic output of the 3rd set of constraints (the individual) is similarly limited.

Evaluation of intralimb kinematics and variability require instrumented measures of gait but must be part of a broader measurement portfolio if there are to be clinically meaningful interpretations. Commonly used clinical measures include 10 meter walk time, preferred walking speed, Timed Up and Go Test and the Stroke Impact Scale.

Ten-meter walk (10MW) speed is a reliable[62] and standardized measure of gait performance in stroke.[63] Interestingly, gait coordination, influenced by synchronization, changes along with 10m speed after intervention [64] suggesting that the two might be related. Causal directionality of the relationship is plausible both ways with improved gait coordination conceivably permitting higher velocity or higher velocity constraining coordination.

Preferred walking speed (PWS) captures additional characteristics of an individual's functional status as it does not reflect capacity; only his or her preference. It is possible that an individual's preferred speed is lower than his/her capacity if a fear of falling or lack of confidence exists. Because of its relationship to participation in community based activities and overall health status [65, 66] PWS is a useful clinical measure offering a complementary description of gait quality.

Another valid and reliable[67] clinical instrument commonly used to capture functional movement in neurologically compromised populations is the Timed Up and Go Test (TUG).[68, 69] Finally, the Stroke Impact Scale 3.0 (SIS) is a valid and reliable self-report of an individual's status in 8 domains.[70, 71, 72]

For the purposes of this project, 10MW speed was the primary clinical measure of interest. Secondary clinical measures included PWS, TUG, SIS and the SIS mobility domain (SIS-m).

Specific Aims

Specific aim 1: **To characterize differences between the paretic and non-paretic limb including temporal asymmetry, shape of the mean knee-ankle cyclogram and variability of joint angles across all strides.**

We hypothesized:

H1. Paretic limb would have lower stance time than the non-paretic limb.

H2. Paretic knee-ankle joint angles would demonstrate greater variability than the non-paretic limb during a gait cycle.

Specific aim 2: **To relate stance asymmetry, angle-angle symmetry, and limb variability to the primary clinical measure, 10MW and secondary clinical measures; PWS, TUG and SIS scores.**

We hypothesized:

H1. Stance asymmetry would negatively relate to performance on clinical measures.

H2. Difference in angle-angle relationship between limbs would negatively relate to performance on clinical measures.

H3. Paretic limb variability would negatively correlate with performance on clinical measures.

PART 1: METHODS

This study was approved by the Institutional Review Board of George Mason University. All participants read, comprehended and signed an approved consent form prior to participation.

Procedural Methods

Design: A cross- sectional study with data collected in a single session.

Participants: Twenty participants with chronic stroke (>6 months, 8 female, age 62.1 +/- 10.3) were recruited from regional outpatient rehabilitation facilities and support groups. Inclusion criteria included mild to moderate walking impairment, ability to walk without assistive devices for more than 5 minutes and ability to voluntarily dorsiflex the ankle and extend the knee. Individuals with a history of any condition that affected walking, other than stroke, were excluded. This included neurological disease other than stroke, musculoskeletal injury or chronic pain that affects walking, inability to walk without assistive device for more than 5 minutes, inability to voluntarily dorsiflex the ankle or extend the knee, severe active medical conditions to include arthritides and joint deformities.

Instrumented data: Preferred treadmill walking speed was evaluated on the treadmill prior to data collection. Participants were given the instruction to find a "comfortable walking speed" that more closely mirrored "a leisurely walk in the park" rather than "exercise" speed. Treadmill settings (Woodway USA,) were increased by 0.1 mph in approximately 10 second increments up to the

preferred speed. After an acclimation to the treadmill at self-selected speed for a minimum of 30 seconds, adjustments to walking velocity were made as necessary. Participants were encouraged to maintain unimpaired arm swing but were permitted to hold handrails on the treadmill if necessary. Additionally, a safety harness with no body weight support was available upon request.

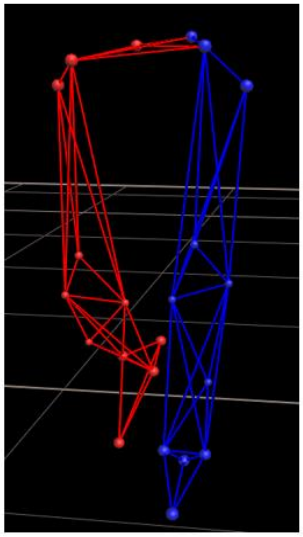


Figure 4. Spatial model of lower extremity markers.

After acclimation to the treadmill and determination of PWS, participants sat in a chair for a rest period of approximately 10-15 minutes while instrumented with EMG and reflective markers. Skin over the muscles of interest was cleaned and shaved as necessary. Wireless EMG sensors with a 16 channel desktop receiver unit was used (Noraxon USA, Desktop DTS, 1500 Hz). Self-adhesive Ag/AgCl solid gel dual electrodes were placed on the muscle bellies of tibialis anterior and vastus lateralis bilaterally. The placement on the tibialis anterior was approximately 15% of the distance from the tibial tuberosity to the intermalleoli line beginning at the tibial tuberosity. The placement on the vastus lateralis was approximately 9cm superior to the lateral border of the patella on a line between the lateral patella and the anterior superior iliac spine.[73] Signals were pre-amplified and low pass filtered at 500Hz.

Passive reflective markers were placed on the following locations, bilaterally, for kinematic data acquisition with a motion capture system (Vicon Nexus 2.6.1, 100 Hz): posterior superior iliac spine, anterior superior iliac spine, greater trochanter, anterior thigh, medial & lateral knee, anterior shank, medial & lateral malleoli, heel and first toe. Participants were permitted to re-acclimate to treadmill walking at their selected speed for approximately 30 seconds prior to data acquisition.

Clinical measures:

Preferred walking speed was determined prior to the treadmill walking trial and was reported as a secondary clinical measure. The 10MW was regarded as our primary clinical measure and was assessed following the treadmill walking trial along with the Timed Up and Go test (TUG). Both 10MW and TUG were performed up to 3 times and values were averaged over all trials. The Stroke Impact Scale (SIS) 3.0 scores were added with higher values indicating higher function. Section 6 of the SIS, the mobility domain, was reported as SIS mobility. This section of the instrument consists of six questions asking about the participant's ability to sit, stand and walk without losing balance, move from a bed to a chair, walk one block, walk fast, climb one flight of stairs, climb several flights of stairs and get in and out of a car. The SIS has a maximum score of 295 and the SIS mobility has a maximum score of 45.

Data Analysis

Lower extremity kinematics derived from reflective markers placed on the pelvis and lower extremity were labeled and gap-filled using Vicon Nexus 2.6.1 software. Kinematic data were exported to Visual 3D (C-Motion Inc., Germantown, MD, USA) and a custom model was employed to determine sagittal plane joint angles for the knee and ankle. Joint angle and EMG analysis was conducted with a custom Matlab script (MATLAB and Statistics Toolbox Release 2018b, The Mathworks, Inc., Natick, Massachusetts, USA). Statistical analysis was conducted with SPSS 25 (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Initial and final contacts were identified using the z-coordinate of the heel and toe marker respectively and visually confirmed with the video file. The whole trial data was arranged into individual strides with an average of 76 strides analyzed for each limb. Other studies had reported on an average stride number of eight,[51] twenty, [45] and 30-75.[97]

Temporal interlimb asymmetry was quantified by the Asymmetry ratio (AR), calculated as:

$$AR = |1 - \frac{non - paretic\ stance\ time}{paretic\ stance\ time}|$$

Angle data over all strides was averaged to form an average cyclogram for both the paretic and non-paretic limbs. Centroids were shifted to the origin and the difference in shape between the paretic and non-paretic cyclogram was quantified as the sum of squared distances (SSD) between the paretic limb and the non-paretic limb (Awai and Curt, 2014).

$$SSD_{j,k} = \sqrt{\sum_{i} (\alpha_{j,i} - \alpha_{k,i})^2 + (\beta_{j,i} - \beta_{k,i})^2}$$

j and k represent 2 cyclograms for knee and ankle. α and β are the knee and ankle angles respectively, at point *i*. A value of zero would indicate identical shapes of the two cyclograms and higher values indicate greater difference. Knee and ankle angles were time-normalized to 1 gait cycle using linear interpolation. Angle-angle cyclograms were generated for each stride with knee angle on the y-axis and ankle angle on the x-axis.

Using a vector coding technique to determine angular component of coefficient of correspondence (ACC), we quantified overall variability of all cycles with a value of 1 signifying absolute consistency.[74]

$$l_{1,2} = \sqrt{(k_{1,2})^2 + (f_{1,2})^2}$$

$k_{1,2} = k_2 - k_1$ = *knee angle change from frame 1 to frame 2*

$f_{1,2} = f_2 - f_1$ = *ankle angle change from frame 1 to frame 2*

$l_{1,2}$ = *angular direction of line segment from frame 1 to frame 2*

$\left(\frac{\bar{f}_{1,2}}{\bar{l}_{1,2}}\right)^2$ average "proportion" of angular distance from ankle angle change from frame 1 to 2.

$\left(\frac{\bar{k}_{1,2}}{\bar{l}_{1,2}}\right)^2$ average "proportion" of angular distance from knee angle change from frame 1 to 2

$$a_{1,2} = \sqrt{\left(\frac{\bar{k}_{1,2}}{\bar{l}_{1,2}}\right)^2 + \left(\frac{\bar{f}_{1,2}}{\bar{l}_{1,2}}\right)^2}$$

$a_{1,2}$ = *mean vector length for that frame to frame interval over all steps*

** larger value of a indicates less variability*

$$\bar{a} = \frac{a_{1,2} + a_{2,3} + a_{3,4} \ldots a_{n-1,n}}{n}$$

n= number of frames per cycle
$\bar{a}$ = angular component of the coefficient of correspondence (ACC)

The ACC is a measure of variability and was calculated for both paretic and non-paretic limbs. Each cycle was also divided into stance and swing phase so that ACC values could be reported for each phase.

Statistical analyses:

Wilcoxon signed rank test was used to determine difference in stance time between non-paretic and paretic limbs. Asymmetry ratios were evaluated against clinical measures using Spearman correlation. The difference in cyclogram shape was similarly also correlated with clinical measures.

Differences in non-paretic vs. paretic variability was determined with Wilcoxon signed rank test. These differences were also evaluated for both stance and swing phases between limbs. Additionally, differences in variability between stance and swing phase within a limb were determined with Wilcoxon signed rank test. Hierarchical multiple regression was used to find the best fit model in predicting 10MW. The threshold for significance was set at $p < 0.05$.

PART 1: RESULTS

Data from 17 of 20 participants were analyzed. Three participants were omitted from analysis due to data corruption. Additional participant data is provided in Table 1 including number of years post injury, preferred walking speed, 10MW time, TUG time and SIS scores.

Table 1.Demographics, injury, SIS details, 10MW, TUG

Code/sex	Age	Yrs. post injury	PWS (m/s)	10MW (s)	TUG (s)	SIS total (max 295)	SIS mobility (max 45)
1M	74	5.5	1.03	7.8	9.1	247	42
2M	64	2.5	0.45	16.2	21.6	190	29
3F	75	5.8	1.03	7.6	8.8	236	39
4M	69	4.8	0.18	27.3	41.7	215	34
8M	63	1.4	0.31	5.6	6.6	220	31
9F	57	5.2	0.58	6.7	6.9	219	43
10M	56	14	0.89	7.7	9.3	275	45
11M	66	16.5	0.45	5.0	7.3	226	41
12F	68	6.1	0.09	9.2	8.3	239	36
13F	52	14.4	0.36	8.4	8.4	224	42
14F	46	2.4	0.80	7.9	8.6	254	40
15M	73	2.8	0.22	19.5	19.9	249	36
16M	77	4.8	0.22	6.8	8.7	243	37
17F	42	4.2	0.27	11.8	11.8	259	39
18M	49	4.5	0.36	10.4	12.5	267	45
19M	62	1.9	0.09	64.0	68.0	197	30
20F	74	0.8	0.13	17.3	22.5	227	41
Mean	**62.8**	**5.7**	**0.44**	**14.1**	**16.5**	**234.5**	**38.2**

Asymmetry ratios

Stance time and asymmetry ratios are presented in Table 2. A value of zero would indicate identical stance times on the non-paretic and paretic limbs. Greater values indicate greater difference in stance times. The mean stance time for the non-paretic and paretic limbs were 1.24 +/- 0.58 and 1.16 +/- 0.48 seconds, respectively. Wilcoxon signed rank test detected a significantly greater non-paretic stance time ($p= 0.019$).

Table 2. Stance times for non-paretic (NP) and paretic (P) limbs, asymmetry ratios.

Participant #	NP stance time	P stance time	Asymmetry ratio
1	0.89	0.92	0.038
2	1.15	0.96	0.161
3	0.79	0.80	0.010
4	0.73	0.66	0.096
8	1.18	1.16	0.010
9	0.89	0.88	0.008
10	0.87	0.86	0.006
11	0.80	0.77	0.044
12	1.41	1.51	0.068
13	0.99	0.92	0.064
14	0.83	0.78	0.062
15	1.73	1.62	0.074
16	0.80	0.86	0.072
17	2.19	2.03	0.074
18	1.57	1.44	0.083
19	2.87	2.36	0.175
20	1.33	1.18	0.111
Mean	**123.6**	**116.0**	**0.068**

Asymmetry ratio represents the degree of temporal asymmetry during stance phase. As temporal asymmetry is hypothesized to relate to clinical measures, these are plotted in figure 5 with Spearman correlation coefficients and p-values presented in Table 3. Greater temporal asymmetry was related to longer 10MW time, slower PWS, longer TUG time and lower SIS scores.

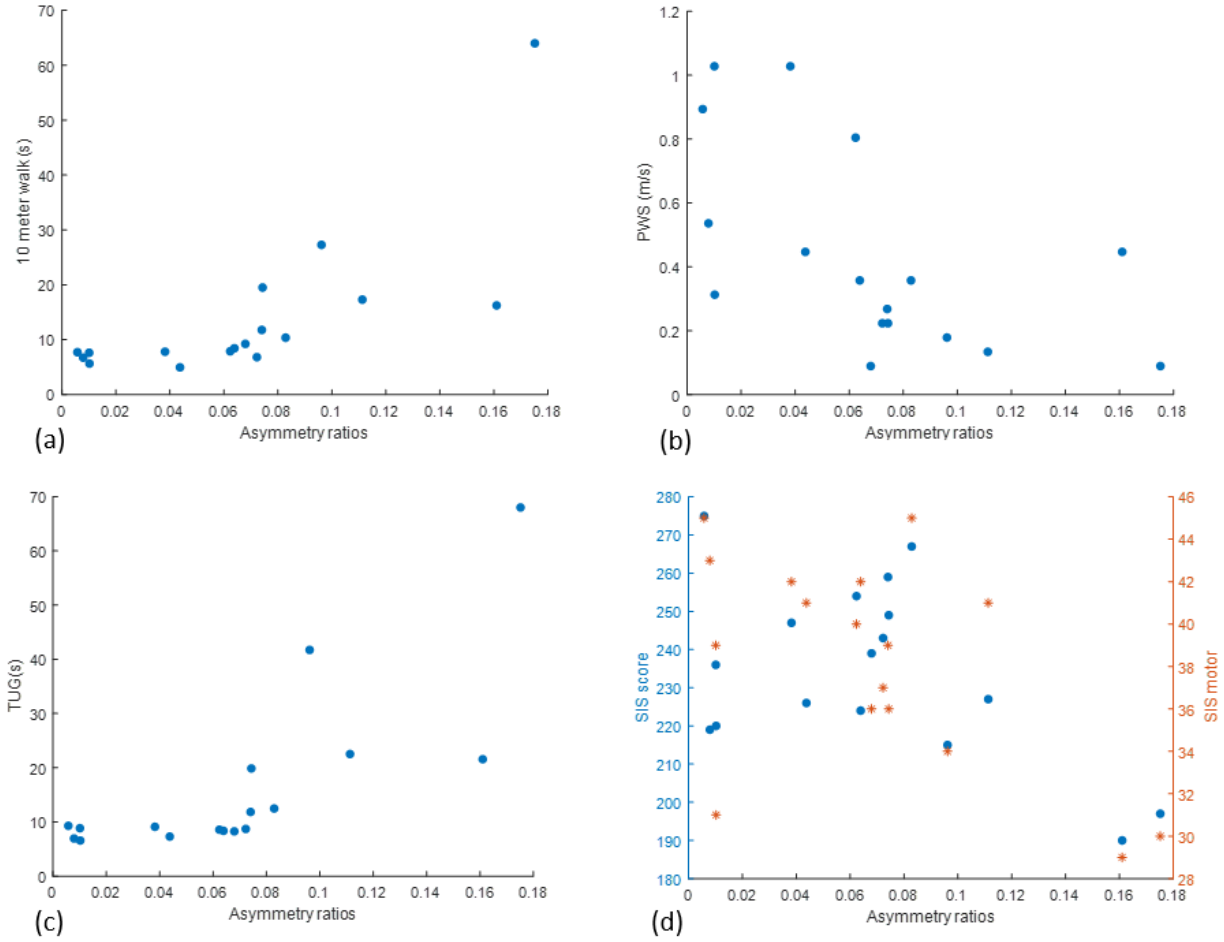


Figure 5a-d. Asymmetry ratio and clinical measures.
A. 10-meter walk time and asymmetry ratio. B. preferred walking speed and asymmetry ratio. C. Timed Up and Go and asymmetry ratio. D. SIS mobility score and asymmetry ratio.

Table 3. Spearman correlation of clinical variables with temporal asymmetry ratios.

Variable	Spearman coefficient	P value
10MW	0.842	< 0.0001 *
PWS	- 0.686	0.002 *
TUG	0.769	<0.0005 *
SIS	- 0.277	0.281
SIS mobility	-0.498	0.042 *

Non-paretic vs. paretic cyclogram difference

The difference in shape between non-paretic vs paretic angle-angle cyclograms was quantified as the sum of squared differences between cyclograms (SSD) and are reported in Table 4. Two representative plots are shown in Figure 6. The cyclograms were generated using averaged values over all strides. SSD scores did not correlate with any clinical measures. Spearman correlation coefficients and p-values are presented in Table 5. Participant in 2a (47.0) shows greater similarity in the angle-angle plot for this participant than the participant in 2b (99.5). Angles are shown in arbitrary units (a.u.).

Table 4. SSD values for all participants

Participant #	***SSD***
1	81.49
2	122.39
3	84.98
4	38.06
8	46.00
9	44.17
10	41.05
11	48.02
12	46.00
13	132.03
14	84.55
15	99.52
16	47.03
17	147.20
18	141.87
19	122.51
20	136.77
Mean	**85.92**

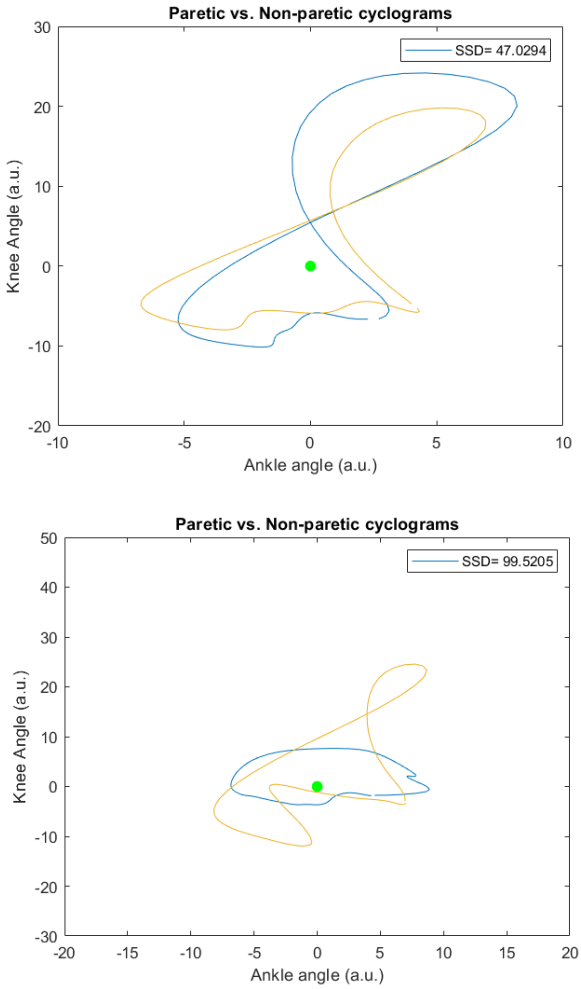


Figure 6. SSD for 2 participants. Non-paretic limb in yellow. Paretic limb in blue.

Figure 7 shows no correlation between cyclogram difference and all clinical measures. P values of the Spearman correlations are shown in Table 5.

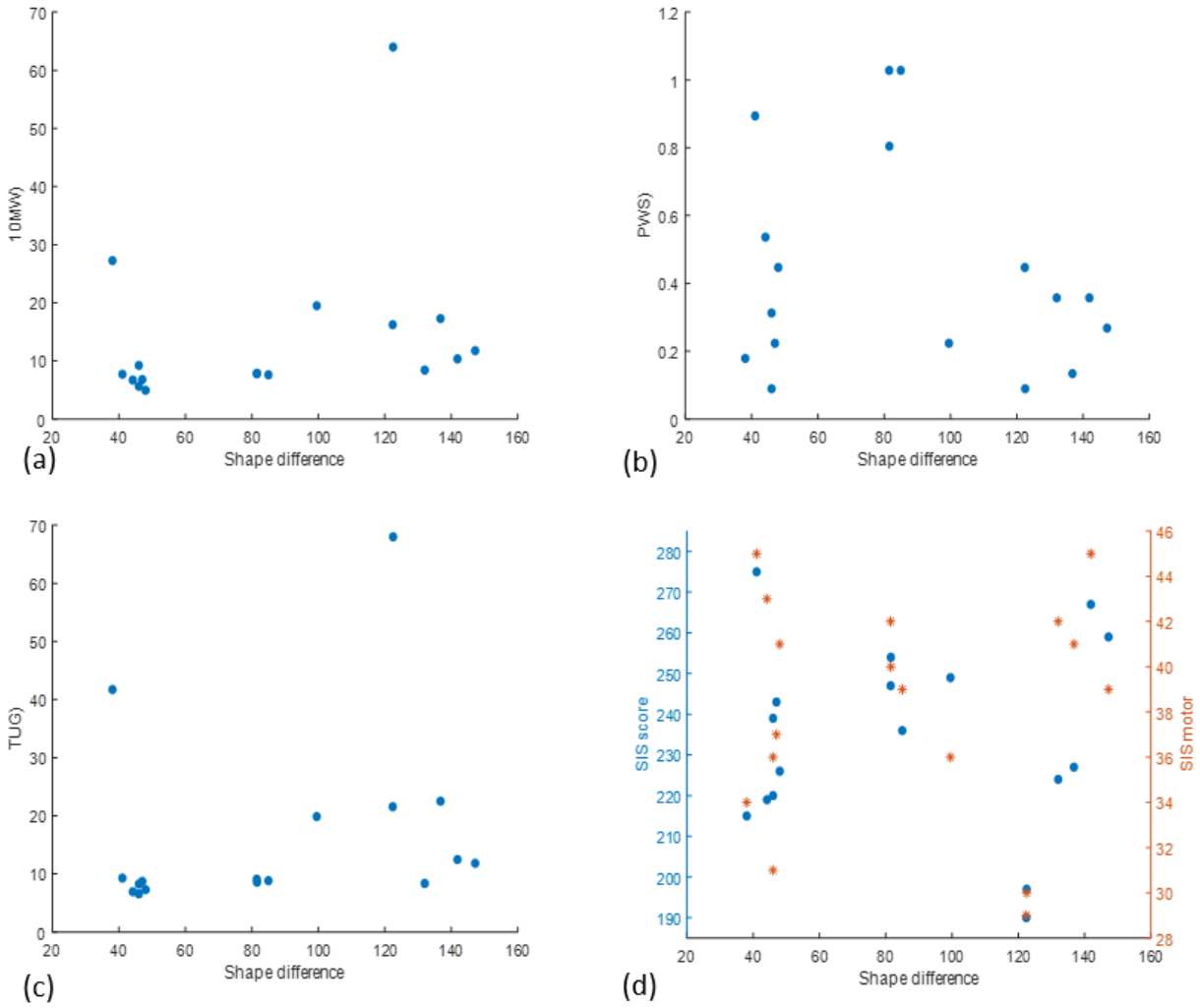


Figure 7a-d. SSD and clinical measures.
A. 10 meter walk. B. Preferred walking speed. C. Timed Up and Go. D. SIS score, SIS mobility score and SSD.

Table 5. Spearman correlation of clinical variables with SSD.

Variable	Spearman coefficient	P value
10MW	0.444	0.074
PWS	-0.142	0.587
TUG	0.399	0.113
SIS	0.153	0.557
SIS mobility	0.042	0.872

Variability

Knee-ankle angle-angle variability over the entire stride is reported in Table 6a. Additionally, swing and stance phases for each stride were delineated and variability was calculated for each phase. A value of 1 indicates absolute consistency in joint angles from one stride to the next with lower values indicating greater variability. The results of the Wilcoxon signed rank test comparing variability between non-paretic and paretic limbs is reported in Table 6b.

The paretic limb showed greater variability than the non-paretic limb over the entire cycle ($p= 0.002$) and swing phase ($p= 0.001$). There was no difference in stance phase variability. For the non-paretic limb, there was significantly greater variability in stance compared to swing phase ($p=0.005$). In the paretic limb, however, there was no difference in variability between stance and swing phase. Overall, variability appears to be primarily determined by significant limb differences during swing phase. Representative cyclogram variability plots are shown in figure 8.

Table 6. Variability of knee-ankle angles in non-paretic (NP) and paretic (P) limbs over the entire cycle, swing phase only and stance phase only.

Participant #	NP variability	NP stance	NP swing	P variability	P stance	P swing
1	0.941	0.931	0.960	0.811	0.832	0.764
2	0.927	0.922	0.944	0.791	0.801	0.774
3	0.965	0.979	0.939	0.869	0.874	0.857
4	0.833	0.808	0.886	0.755	0.735	0.787
8	0.771	0.740	0.833	0.715	0.727	0.693
9	0.892	0.884	0.906	0.881	0.879	0.885
10	0.895	0.863	0.948	0.947	0.932	0.971
11	0.877	0.832	0.957	0.844	0.772	0.961
12	0.603	0.524	0.727	0.526	0.452	0.639
13	0.749	0.721	0.833	0.734	0.738	0.725
14	0.883	0.873	0.906	0.839	0.825	0.865
15	0.867	0.879	0.828	0.750	0.778	0.673
16	0.880	0.846	0.947	0.891	0.872	0.937
17	0.932	0.931	0.939	0.920	0.955	0.825
18	0.946	0.941	0.961	0.926	0.960	0.846
19	0.734	0.710	0.951	0.696	0.771	0.484
20	0.859	0.877	0.915	0.883	0.890	0.868
Mean	**0.858**	**0.834**	**0.905**	**0.810**	**0.811**	**0.797**

Table 7. Wilcoxon signed rank test results of non-paretic vs. paretic limb variability and stance vs. swing phases.

	Comparison of NP vs P limb			Comparison of Stance vs. Swing phases	
Phase	**Entire**	**Stance**	**Swing**	**Non-paretic**	**Paretic**
P value	0.002 *	0.142	0.001 *	0.005 *	0.619

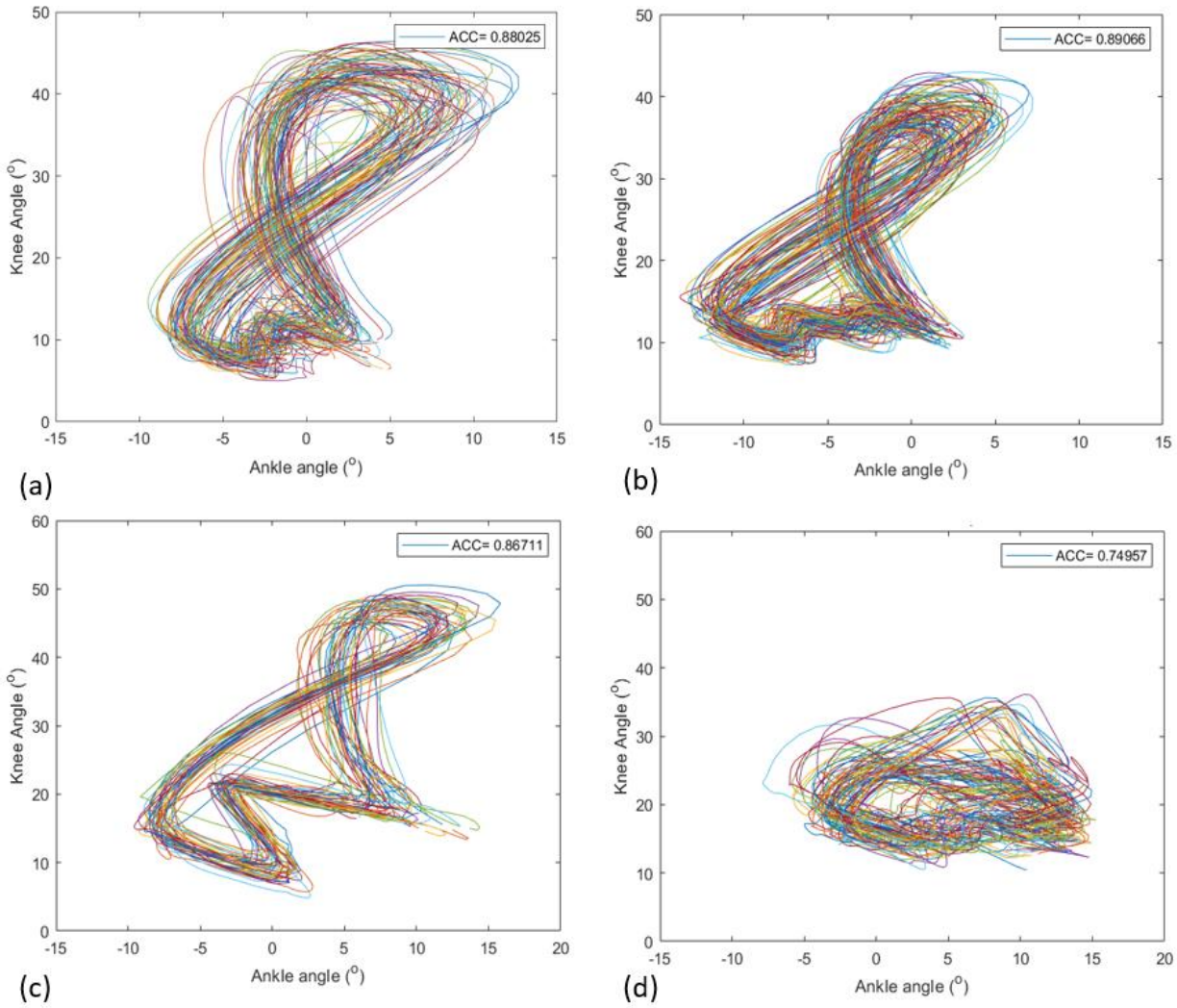


Figure 8a-d. Non-paretic and paretic knee-ankle cyclograms for 2 participants.
A. Non-paretic knee-ankle for participant in figure 6 top. B. Paretic knee ankle for participant in figure 6 top. C. Non-paretic knee-ankle for participant in figure 6 bottom. D. Paretic knee-ankle for participant in figure 6 bottom.

For the participant in figure 8a-b, ACC scores are very similar indicating the same level of variability in knee-ankle between non-paretic and paretic limbs. For the participant in figure 8c-d, variability scores are different with greater variability in the paretic knee-ankle. Higher ACC scores indicate less variability.

Figures 9a-d show clinical measures plotted against total paretic limb variability. Only the SIS scores correlated with overall paretic limb variability. Greater SIS scores, indicating higher function, was associated with lower variability. As most of the difference between non-paretic and paretic limb variability appears to occur in the swing phase, figure 10a-d show clinical measures plotted against *swing phase* paretic limb variability. Swing phase variability correlated with 10MW and SIS mobility scores. Greater variability related to slower times on the 10MW walk and less mobility. Spearman coefficients and p-values for total variability, swing variability and clinical measures are reported in Table 7.

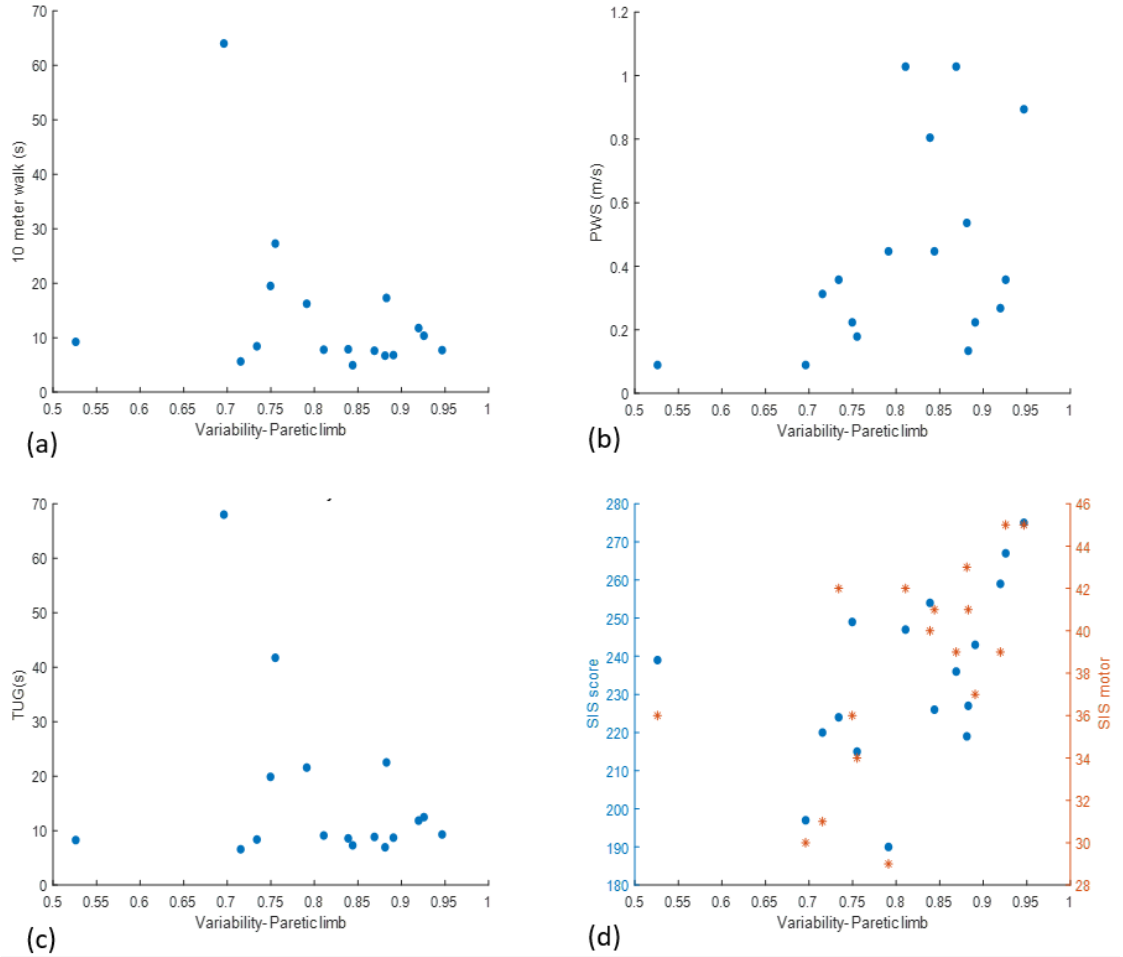


Figure 9a-d. Paretic total variability and clinical scores.
A. 10 meter walk time. B. Preferred walking speed. C. Timed Up and Go. D. SIS scores.

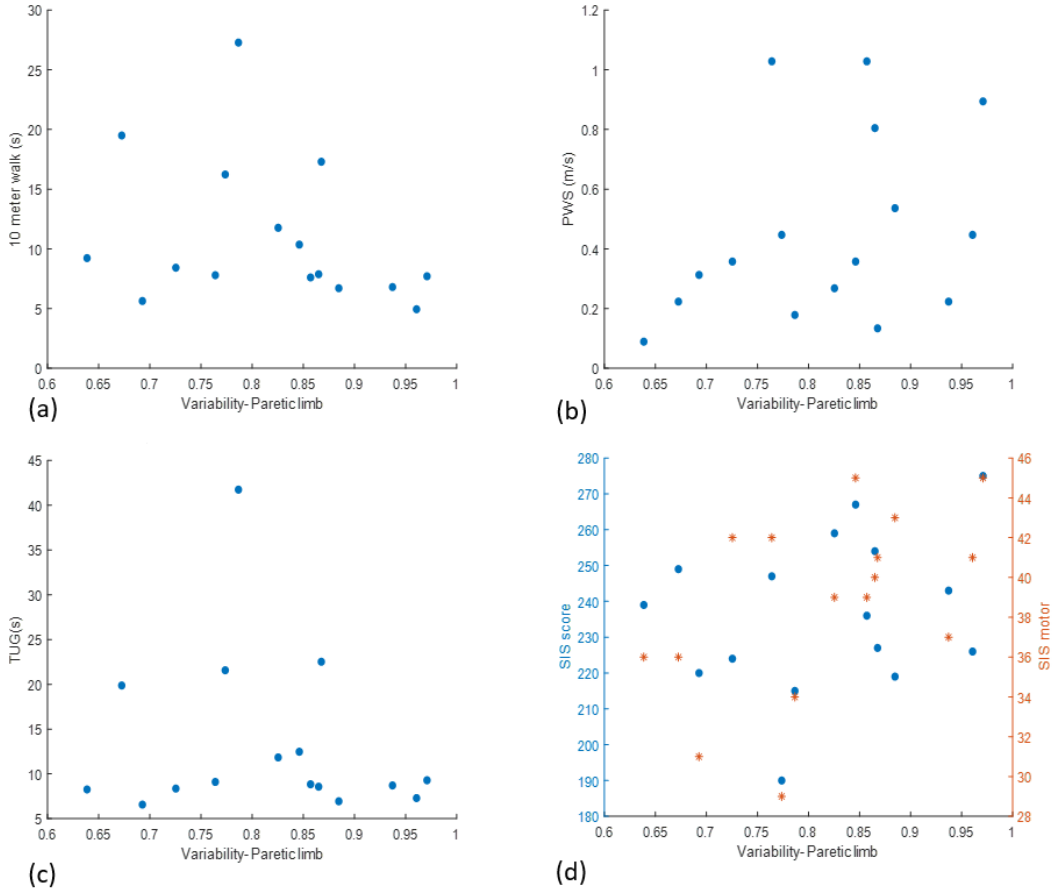


Figure 10a-d. Paretic swing phase variability and clinical scores.
A. 10 meter walk time. B. Preferred walking speed. C. Timed Up and Go. D. SIS scores.

Table 8. Spearman correlation coefficients and p values for clinical measures vs. paretic limb total variability.

Paretic	Total cycle variability		Swing phase variability	
Variable	**Spearman coefficient**	**P value**	**Spearman coefficient**	**P value**
10MW	- 0.255	0.323	- 0.515	0.035 *
PWS	0.393	0.118	0.455	0.067
TUG	0.076	0.772	- 0.194	0.456
SIS	0.571	0.017 *	0.306	0.232
SIS mobility	0.639	0.006 *	0.580	0.015 *

It was observed that variability throughout the entire gait cycle was consistent in the paretic limb but significantly diminished, as indicated by the greater ACC scores, in the non-paretic limb from

stance to swing (Table 6b). These data coupled with significant correlations between paretic swing and 10MW motivated a *post-hoc* inquiry into the relationship between stance temporal asymmetry and paretic swing variability. Analysis revealed no relationship between asymmetry and paretic swing variability with a Spearman's correlation coefficient of – 0.387 (*p= 0.125)*.

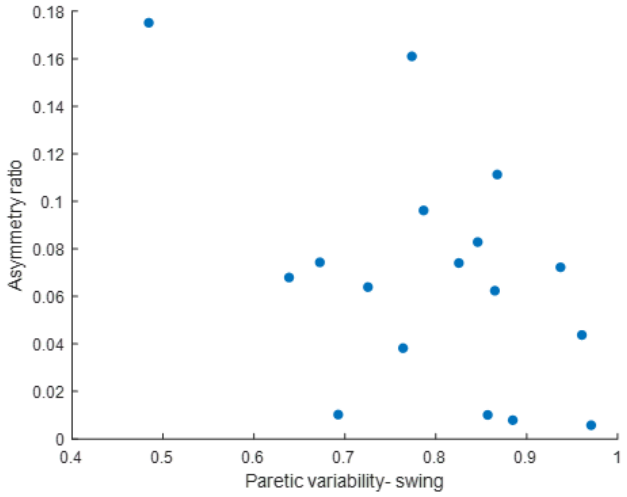


Figure 11. Asymmetry ratio vs paretic swing variability.

As asymmetry ratio and paretic swing phase variability both relate to 10MW but were uncorrelated to one another, these were used to build a statistical model to determine their relative contribution in predicting variance in the 10MW. The SSD did not have any meaningful relationship to clinical measures so was excluded from the model.

The independent variable in the first model was asymmetry ratio. In the second model, paretic swing phase variability was included. Asymmetry ratio was included as the first independent

variable because of the greater magnitude of its Spearman coefficient (0.842 vs. - 0.515) when correlated with 10MW.

Table 9. Hierarchical multiple regression predicting 10MW from asymmetry ratio and paretic swing phase variability.

Model Summary

Change statistics

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	R Square Change	F Change	df1	df2	Sig. F Change
1	0.731[a]	0.535	0.504	9.9731	0.535	17.253	1	5	0.001
2	0.816[b]	0.665	0.617	8.7574	0.130	5.454	1	14	0.035

a. Predictors: (Constant), Asymmetry ratio
b. Predictors: (Constant), Asymmetry ratio, Paretic variability- swing phase

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig
1	Regression	1716.036	1	1716.036	17.253	0.001[b]
	Residual	1491.940	15	99.463		
	Total	3207.975	16			
2	Regression	2134.290	2	1067.145	13.915	< 0.005[c]
	Residual	1073.686	14	76.692		
	Total	3207.975	16			

a. Dependent variable: 10 meter walk
b. Predictors: (Constant), Asymmetry ratio
c. Predictors: (Constant), Asymmetry ratio, Paretic variability- swing phase

Coefficients

	Model 1		Model 2	
Variable	**B**	**β**	**B**	**β**
Constant	- 0.240		40.569	
Asymmetry ratio	210.456	0.731	152.326	0.529
Paretic swing variability			- 46.227	- 0.414
R^2	0.535		0.665	
F	17.253 **		13.915 **	
Δ R^2	0.535		0.130	
Δ F	17.256 **		5.454 *	

B= unstandardized coefficient ** $p < 0.01$
β= standardized coefficient * $p < 0.05$

The addition of paretic swing phase variability (Model 2) significantly increased R^2 by 0.130, F (1,14) = 5.4 54, p=0.035. The full model of asymmetry ratio and paretic swing phase variability (Model 2) was statistically significant, R^2 = 0.665 F (2,14) = 13.915, p =0.0005, adjusted R^2 = 0.617. The final regression equation takes the form:

10 MW time = 40.569 + 152.33(asymmetry ratio) - 46.23(paretic swing variability)

PART 1: DISCUSSION

We aimed to characterize differences between non-paretic and paretic limbs with respect to stance time and variability. Our hypotheses that the paretic limb would have lower stance time and increased variability than the non-paretic limb was supported.

Our second aim was to relate gait asymmetry and limb variability to clinical measures. It was assumed that a portfolio of clinical gait assessments provided a better indicator of a participant's functional status by capturing preferences (PWS), capacity (10MW), related mobility components (TUG) and impact on daily living (SIS).[75] It has been suggested that walking velocities of 0.4-0.8 m/s predict functional community ambulation but lose their discriminative properties outside of this range.[76] Our participant group had a mean velocity of 0.44 m/s, consistent with previously reported community ambulators.

Our hypothesis that stance asymmetry would negatively relate to performance on clinical measures was supported. Our hypothesis that the difference in angle-angle relationship would negatively relate to performance on clinical measures was not supported. Our hypothesis that paretic limb variability would negative correlate with performance on clinical measures was partly supported.

Is symmetry important?

The hypothesis that the paretic limb will have lower stance time than the non-paretic limb was supported and is consistent with earlier work examining temporal asymmetry.[77] Stance time depends, in part, on sufficient strength of the lower extremity to bear weight and weakness is a well-known feature of chronic stroke. Several mechanisms may cause muscle weakness after stroke and this impairment is known to lead to gait limitations.[78] Adaptations during standing

balance control have also been observed where the paretic limb tends to bear less weight. This leads to a diminished contribution to balance control during perturbation.[79] Barela et al. (2000) reported found significantly longer stance time on the non-paretic limb of individuals with chronic stroke with a strong trend toward a reduction in paretic limb single-limb support. Periods of double-limb support were comparable between both paretic and non-paretic limbs. They suggest that training single-limb support of the paretic limb should be a critical part of rehabilitation.[80]
Hsu et al. (2003) examined muscle spasticity and found that paretic plantarflexors were the primary contributors to spatiotemporal asymmetry.[81] They found that asymmetry was negatively related to overground walking velocity and suggest that an impairment based approach to reduce spasticity may be a critical factor in regaining single-limb support to subsequently reduce temporal asymmetry and increase velocity. We did not perform a sensorimotor exam so cannot support this supposition, but the directionality between impairment and functional limitation are plausible and warrant future investigation.

In additional to impaired muscles of the paretic limb, the contributions of the non-paretic limb must be considered. The non-paretic limb compensates for the paretic limb with increased plantarflexion to increase propulsion[82], a common deficit post-stroke[83, 99], and may explain the diminished paretic stance time.

The hypothesis that stance asymmetry will negatively relate to clinical measures was supported. Temporal stance gait asymmetry correlates with 10MW, PWS, TUG test and SIS mobility scores. As with any measure of correlation, it is unclear whether asymmetry is a mediator, moderator or co-occurring phenomenon to clinical measures. Nonetheless gait asymmetry tends to increase as time from the injury increases [39] and given the correlation with clinical findings, this is of concern.

Spatiotemporal asymmetry at 1 month post-stroke negatively correlated with walking speed and was associated with greater fall risk up to 6 months after injury.[84] The negative effects persist in chronic stroke where greater spatiotemporal asymmetry is associated with reduced standing balance[85] and dynamic balance during gait.[86] Interestingly, asymmetry in chronic stroke may not be perceived [87] though whether this is a loss of perceptual abilities or appropriate adaptation toward more meaningful parameters is unknown. However, it has been suggested that individuals post-stroke have the neuromotor capacity to regain symmetry in stance times with appropriate rehabilitation.[88]

Measurements of gait asymmetry are sensitive to the constraints in which they are performed. For example, interlimb asymmetry is known to vary within an individual depending on gait speed.[89] Furthermore, kinematic asymmetries are reduced on a treadmill compared to overground conditions.[90] This suggests a potential limitation of this study in that participants' asymmetries are underestimated in our study. A study of 10 healthy individuals found that walking asymmetry was associated with increased metabolic costs.[91] However, the asymmetry was induced through manipulation of a split-belt treadmill rather than an intuitive arrival at a movement solution. When asymmetry is observed due to injury and not imposed, Brouwer et al. (2009) found that stance time asymmetries in people post-stroke were more pronounced in overground vs treadmill conditions. Intriguingly, the overground condition was associated with a lower metabolic cost.

This supports the framework that while temporal asymmetry is related to clinical measures as we detected, there may be other physiological costs associated with targeting symmetry in rehabilitation.[92] It is possible that non-paretic compensation for the impaired limb, despite perpetuation of asymmetry, is a movement solution for the organism when additional variables

such as metabolic cost are holistically considered. Asymmetry is known to be present in the gait of healthy humans [93] suggesting that there might, as with variability, exist an optimal region of asymmetry.

Another indicator of interlimb symmetry in our study was knee-ankle angles between non-paretic and paretic limbs. Knee-ankle angles were plotted as a cyclogram and the difference between non-paretic and paretic cyclograms was quantified by the SSD value. A higher SSD indicates a greater difference in shape between the non-paretic and paretic limb cyclogram. Our hypothesis that greater differences in cyclogram shape would relate to poorer performance on clinical measures was not supported.

A change in joint angles is not unexpected after injury. However, angle differences between limbs in our participants did not explain clinical outcomes. Interestingly, temporal asymmetry did predict clinical scores while joint angle asymmetry did not. Just as variability can be categorized as either coordinative or endpoint, one might consider angle-angle asymmetry as being permissible provided it constrains endpoint symmetry. We cannot justify this perspective through our data as endpoint foot placement was not measured. However, one might imagine a condition where the end goal of foot placement to support the center of mass is relatively invariant, whereas the proximal joint angles to achieve this goal have more degrees of freedom.

A practical implication is that rehabilitation targeted toward "normalizing" joint ranges of motion or efforts to promote angle symmetry between limbs is not recommended. The nature of the injury may preclude an individual from ever regaining kinematic behaviors that mirror the pre-injury state. Whether this limitation also precludes functional recovery is questionable.

Arguments against a focus on locomotor symmetry have been present for some time. Griffin et al. (1995) argued that emphasizing symmetry may lead to reductions in contributions of the unaffected limb. In other words, symmetry may come at a cost of reducing function of the unaffected limb rather than increasing function of the affected limb. The unintended constraints would then reduce walking velocity.[94] Hof et al. (2007) have suggested that when foot placement is unilaterally compromised, the contralateral side must adapt, intentionally promoting asymmetry, in order to maintain direction of movement. In these cases, they argue against the goal of symmetry through rehabilitation.[95]

Gait symmetry has been evaluated through many different variables so a blanket conclusion to support or discredit the merits of symmetry is unwise. In our data, it would seem that temporal asymmetry, whatever the origins, is clinically meaningful. Kinematic interlimb symmetry, however, is not. This is consistent with previous reports that in chronic stroke, lower extremity joint angles remain unchanged after 12 sessions of locomotor training even with an increase in preferred walking speed. Interestingly, cyclogram variability did change after 12 sessions of training and may have played a role in improving walking speed.[96]

Angle-angle variability

As hypothesized, variability was greater in the paretic limb compared to the non-paretic limb as evidenced by the lower ACC score on the paretic limb. As limb control may operate differently during open kinetic chain movements such as swing phase compared to closed chain movements such as stance, it was reasoned that there may be a difference between stance and swing phase variability so that characterization during each phase was warranted. Much of the difference in variability between limbs appears to come from the differences in stance phase as non-paretic swing variability diminishes while paretic swing variability remains unchanged from stance.

Walking speed depends heavily on propulsive force generated by the lower extremity during stance phase. The non-paretic limb is known to compensate for the paretic limb and increase propulsive forces during stance.[82] This may explain the reduction in non-paretic variability that accounts for the difference in non-paretic and paretic swing phase. The demand for additional propulsive force on the non-paretic limb, coupled with the reduced stance time on the paretic limb, creates additional constraints on non-paretic swing that may have diminished its variability. We interpret the decrease in non-paretic swing variability (ACC=0.905) as appropriately adaptive as it more closely mirrors previous reports of knee-ankle ACC values of uninjured adults (ACC=0.95+/- 0.02).[97]

Differences in intralimb coordination have been shown to manifest in distinct segments of the gait cycle depending on disease severity.[98] Additionally, swing phase differences in the paretic limb were previously reported to include reduced knee flexion and increased mechanical energetic cost.[99] Increases in swing time variability in the paretic compared to the non-paretic limb were reported in individuals with chronic stroke.[100] Similarly, Barela et al. (2000) reported that decomposition of intralimb coordination of the paretic limb was primarily observed in the last 1/3 of the gait cycle where there was clear change in behavior of the paretic limb during swing phase.

Conversely, we report that paretic variability did not differ between stance and swing phases. Notably, Barela et al. (2000) examined ILC between the hip and knee whereas we studied distal behavior of the knee and ankle. Sohn et al. (2018) found that in chronic SCI, distal variability (knee-ankle) was more impacted than proximal variability (hip-knee) suggesting different control mechanisms are involved in proximal vs. distal joints coordination.

Angle-angle variability of the paretic lower extremity can improve (diminish) with locomotor training and is associated with faster preferred walking speed. High variability, however, is not always detrimental. With respect to motor learning, it has been proposed that initial variability of movement may predict motor learning ability [101] as an individual searches for effective methods of task completion. Those with low variability are thought to be unwilling to "explore" and are likely to have a more difficult time finding a solution.

With respect to motor control, movement variability may be indicative of a robust motor repertoire and suggest high level of expertise.[102] On the other hand, low variability has also been interpreted as a consequence of an effective and easily reproducible system solution to task demands; likewise suggesting expertise.[103]

We interpreted the nature of the task as an exercise in motor control rather than motor learning given that the participants were community ambulators in a chronic stage. As such, we viewed greater variability as adverse and assumed that they had discovered the most effective solution, provided their physiological constraints, at the time of data collection.

Assistive devices that facilitate normal gait patterns have also been shown to reduce spatiotemporal variability.[104, 105] Although no assistive devices were used on the treadmill, participants were permitted to use the handrails for support as needed. This may have served to artificially diminish intralimb variability.

Clinical scores

We hypothesized that paretic variability would negatively correlate with clinical measures. This was partly supported. With respect to entire-stride variability of the paretic limb, only the SIS scores had any statistically significant relationship. SIS scores were negatively correlated such that

higher variability was related to lower self-reported functional status. There was no relationship, however, between overall paretic variability and our primary clinical measure, 10MW. Previous reports found that knee-ankle ACC in chronic SCI significantly related to overground walking speed with an adjusted R^2 of 0.59.[97] While this was not observed in entire-stride variability, a relationship between swing phase variability and 10MW time was detected.

Swing phase variability of the paretic limb was negatively correlated with 10MW times and SIS mobility scores such that higher variability was related to slower walk times and lower mobility scores. Preferred walking speed approached significance ($p=0.067$) with higher variability correlating with slower preferred walking speed.

These measures suggest that paretic limb variability, specifically within swing phase may be an indicator of clinical dysfunction.

PART 1: LIMITATIONS

As in any trial, our primary concern was for safety of the participants. Although they were discouraged from using the handrails or to apply minimal pressure, nearly all participants used the treadmill handrails for part or all of the walking trial. This likely influenced movement patterns to some extent as a reduction in arm swing has been shown to have effects on walking movement patterns.

All joint findings herein relate to sagittal plane function though all joints operate in 3 spatial dimensions. Variability may be present in the joint even if it is not identifiable in the sagittal plane. The small sample size may have resulted in an underpowered study. Additionally, all participants were recruited from stroke support meetings which may overrepresent patients with certain characteristics.

The familywise error rate across statistical tests was not controlled in this study.

PART 1: CONCLUSION

Interlimb and intralimb coordination were both evaluated to characterize gait in people with mild to moderate walking impairment post-stroke. We found significant differences in both interlimb and intralimb coordination between paretic and non-paretic limbs among people with chronic stroke and significant correlation to clinical measures. Coordination measures may serve as clinical targets to monitor progress or design rehabilitation programs.

The two categories of coordination, thought to have separate centers of control, may be sensitive to area of the lesion. In evaluating 13 patients with ataxia and 27 with parkinsonism, Matsuo et al. (2005) hypothesized that intralimb coordination is mediated by the cerebellum and interlimb coordination is mediated by the basal nuclei. This supports the idea that in evaluating the merits of interlimb and intralimb coordination, one cannot conclude that one is more discriminating or sensitive than the other. Rather, each type of coordination reflects a separate element of motor control.

Using functional MRI, Lo et al. (2017) studied older, injured individuals to assess functional brain connectivity in two circuits; frontoparietal and dorsal attentional networks. They found that gait speed was associated with the frontoparietal network while stride time variability was associated with the dorsal attentional network.[106] Although this early stage pilot work should be interpreted with caution, it is supportive of the notion that velocity and variability are somewhat independent elements of gait with different components of higher order control.

Given the complexity of motor behavior, it may be an oversimplification to attribute specific gait characteristics to local neural regions. In fact, doing so runs counter to dynamical models that

adopt a probabilistic view of behavioral emergence through interaction of similarly complex agents. Nonetheless, attempts at ascribing function to specific brain regions as in the aforementioned studies do point to a broader model of differentially moderated control of movement components and offer insight into one aspect of a complex system such as the nervous system.

Coordination patterns are a clear expression of motor control. If we simplify the system into input and output components, we can imagine the output to be the temporally synchronized motor units across muscles to generate torque around related joints thus enabling intralimb coordination. The input into those effectors, serving as 1 degree of higher order control, are of interest to assist in the justification of kinematic observations. Such input allows coordination between 2 joints or among multiple related joints involved in a task.

Coordination is achieved through various muscle synergies; patterns of muscle activation that achieve an action and are regarded as a type of building block upon which complex movements emerge.[107] Involved in both interlimb and intralimb coordination, they provide insight the nervous system and are profoundly disrupted in stroke.[108] When fewer muscle synergies are appropriately activated, there is a decrease in walking speed as well as an increased likelihood of spatiotemporal asymmetries. [109] Muscle synergies are thought to reflect neural strategies and capturing elements of these kinematic patterns may yield insight into neural organization in both unimpaired individuals [110] and people post-stroke.[111] These findings offer a clinically rich model when kinematic observations are coupled with an understanding of the neural substrates on which they are, in part, predicated.[112]

PART 2: INTRODUCTION

Electromyogram (EMG) captures information about electrical activity of muscles and has traditionally been used to make inferences regarding force production [113] and motor neuron activity.[114] The signal from the surface EMG reflects a large number of motor units within the muscle thereby representing activity of the motor neuronal pool. As such, it is widely believed that analysis of these signals permits the retrieval of an "embedded neural code" [115] thus providing insight into the control of muscles. Therefore, detailed analysis of the EMG signal provides a glimpse into motor control [116] and is valuable when coupled with kinematic data.

Although EMG signals have traditionally been quantified in terms of amplitude or area under the curve, neural inferences benefit from a complementary method of analysis within the frequency domain. Using Fourier based transformation techniques, time series data such as the EMG signal collected over a trial, may be deconstructed so that its frequency content and relative power are identified.[117, 118] Information on the frequency content of EMG signals can be used to infer changes to the skeletal muscle or the neural discharge to the muscle. For example, changes in muscle fiber composition may reduce conduction velocity along its membrane leading to a shift toward low frequency signals. Alternately, low frequency shifts may occur due to changes in firing of motor units.[119, 120]

Changes within the frequency domain have been observed in various pathologies such as Parkinson and stroke [121, 122] with a commonly used metric, the median frequency. Children with cerebral palsy show a decline in median frequency as they fatigue during overground walking.[123] Go et al. have found that the median power frequency may similarly shift to lower values in dystonic muscles

of the lower extremity compared to non-dystonic muscles.[124] They also report that median frequency was used with 73% sensitivity and 67% specificity in detecting dystonia. A spectral shift to lower frequencies has also been observed in muscles of the upper extremity in people post-stroke compared to healthy [125] and non-paretic limbs. [126] Together, these data raise the interesting possibility of using spectral analysis as a simple method to aid both diagnosis and monitoring of neurological conditions.

Aside from shifts in the median frequency, another commonly used approach is the assessment of synchronization within specific frequency bands through the evaluation of coherence. Coherence indicates the correlation of phase and amplitude between two signals in the frequency domain.[127] If signals are identical, coherence, a unitless measure, is valued at 1. The lower bound of the measurement is zero in absence of any correlation. Inferences drawn from coherence depend on the frequency band in which the correlation exists. Though there is lack of consensus on cutoff frequencies and the source of each band is incompletely understood, the ranges and suggested source of these coherent signals are estimated as:

a. Alpha, 8-12 Hz: spinal mechanisms [128, 129]
b. Beta, 15-30 Hz: corticospinal, upper motor neuron integrity [130,131, 132, 133]
c. Gamma, 35-60 Hz: subcortical [134], corticospinal [135]

Coherence estimates can be used to make inferences to changes in neural circuitry[136] and may reveal meaningful change following stroke. Given the supraspinal lesions in stroke, our interest lies in the beta band as it may have greater specificity to cortical lesions[137] compared to the gamma band and allow for muscular coordination. For example, Reyes et al. (2017) reported that hand muscles

showed less beta band coherence during tasks when finger individuation was required compared to tasks that demanded coordination.[138] Additionally, corticomuscular coherence in the beta band is significantly lower in people post-stroke compared to healthy individuals [139] and changes in the beta band have been shown in the subacute phase post-stroke with increases in coherence associated with motor recovery.[140]

Coherence between paired EMG signals is believed to result from common neural drive (CND) to those motor units. It is important to note that the sources of input into the motor neuron pool are diverse and include both bulbospinal and corticospinal projections as well as afferent input from the periphery.[141, 142] Although disparate motor neuronal pools have discrete inputs, some portion of their respective inputs may arise from a common source. The degree of common input leading to synchronization is termed, “motor unit short-term synchronization". To an extent, motor unit synchronization is a normal physiological event. Synchronization within motor neuron pools of synergistic muscles increases with healthy neurodevelopment [143, 144] as it allows muscles to adequately generate force around a joint.[31]

The selection of muscles in that pair is critical and can be summarized as a comparison of coherence between motor unit pools *within* a single muscle or *between* two different muscles; intramuscular vs. intermuscular. Synchronization during gait both within and between muscles has been described by several groups who have characterized their findings in healthy individuals. In one study by Halliday et al. (2003), 10 participants (21-41 yrs.) walked on a treadmill for a minimum of 5 minutes at a speed of 4 km/hr. (~2.5 mph). Intramuscular coherence in the tibialis anterior (TA) was dependent on the specific segment of swing phase; described as early, middle and late

(ended at 100ms after initial contact). Coherence value were greatest at early and late swing with smaller coherence during mid-swing with peaks between 8-15 Hz and 15-20 Hz.

Between muscles, Halliday et al. found weak coherence among the triceps surae (MG:Sol, LG:Sol, MG:LG), hamstrings (BF:ST)and quadriceps (VL:VM).[1] No clear relationship was detected among muscle pairs that involved two joints (Sol:VL, MG:VL, LG:VL, TA:VL, TA:BF) or proximal antagonists (BF-VL).[145]

Hansen et al. (2001) measured EMG activity from TA, triceps surae and knee extensors in 25 healthy (21-66 yrs.) individuals and found strong intramuscular synchronization within the TA during treadmill walking. Additionally, synchronization was not apparent between muscles from different regions of the lower extremity (shank vs. thigh). In interpreting their findings on intramuscular and intermuscular coherence, Hansen et al. suggest coherence is stronger between muscles that are synergistic in their actions around a single joint.[146]

These findings indicate that common neural drive (CND) is likely a normative phenomenon within a single muscle but weaker when two joints are involved. That is to say that in unimpaired individuals, intramuscular coherence may be evident but there is little intermuscular coherence. This is conceptually congruent with Farina and Negro's review which posits that CND to a single muscle is necessary to control torque around a joint.[147] Though these findings may apply to healthy individuals, it is unclear if neurological injury influences coherence. Adaptations of the remaining structural reserve may be beneficial or maladaptive, supporting the notion that neural organization

* TA= tibialis anterior, MG= medial gastrocnemius, LG= lateral gastrocnemius, Sol= soleus, BF= biceps femoris, ST= semitendinosus, VL= vastus lateralis, VM= vastus medialis

following injury is unlikely to reliably mirror the pattern of organization before injury.[148] In the event of neurological injury, coherence may increase beyond what is found in the unimpaired population in order to recover function.

In patients with chronic incomplete SCI, Norton and Gorassini (2006) reported that intermuscular coherence correlated with functional walking scores and increased as walking performance increased. They also found that baseline coherence at 24-40Hz, only present in those with moderate volitional motor strength, could be used to predict responders vs. non-responders to therapy.[149] Moreover, when coherence values were assessed in the unimpaired control group, the results were consistent with Halliday in that there was little to no coherence between muscles. Neural reorganization among SCI "responders" was functionally useful but did not mirror the pattern in uninjured individuals. This supports the argument against rehabilitating individuals toward patterns observed in healthy people.

In a study conducted with individuals with incomplete spinal cord injury (iSCI), intramuscular coherence of the TA was examined in 14 patients during isometric and isokinetic contractions.[150] Coherence in the 15-30 Hz positively correlated with muscle strength; unsurprising given the consensus that motor unit synchronization relates to force. However, coherence was also positively correlated with clinical measures of gait function and negatively correlated with spasticity. It should be noted that when compared to a healthy population, coherence among people with SCI in the 10-16Hz and 15-30 Hz bands was different only during fast isokinetic movements with no difference during isometric or slow isokinetic movements. Additional differences between healthy and iSCI participants were detected at high frequencies with higher functioning participants demonstrating greater coherence at 40-60Hz bands. Although speculative, Bravo-Esteban et al.

(2014) propose coherence at higher frequencies may indicate extrapyramidal contributions to re-establish motor control.

Although intramuscular coherence is evident in isometric and isokinetic contractions, these properties are also preserved in gait. Coherence was reported when 20 individuals with chronic iSCI walked on a treadmill at preferred speed. Measures of TA intramuscular coherence in the 10-20Hz band were diminished in injured participants compared to healthy individuals though there was no relationship to maximal walking speed, a commonly used measure of walking performance. [151] As TA is not responsible for generating propulsive force, its function may be more related to gait quality rather than velocity dependent performance measures.

Barthelemy et al. (2010) re-examined intramuscular coherence of the TA and its relationship to gait speed as well as more relevant functional outcomes; toe elevation and ankle movement during swing. Synchronization findings were confirmed to be decreased in the 10-20 Hz band in 24 iSCI participants during treadmill walking. The authors found that coherence positively related to gait speed, toe elevation and ankle movement during swing. As Bravo-Estaban et al. (2010) had shown, both impaired and unimpaired groups showed coherence in some frequency bands (10-20Hz). But only the unimpaired group demonstrated coherence at higher frequencies (20-50Hz).[152] This suggests a loss of coherence in the 20-50Hz band in a neurologically compromised population.

Similar results were reported in a study of 16 children with cerebral palsy. [153] Intramuscular coherence of the TA increased after 30 days of inclined treadmill training and positively related to maximal voluntary dorsiflexion, toe elevation and ankle range of motion during swing. Baseline coherence predicted kinematic changes with the greatest influence in the 35-65 Hz band. A second

post-test was conducted one month post training. Gains in both functional and coherence measures persisted, suggesting motor learning had occurred and coherence may have played a role.

Changes to coherence have also been detected in people post-stroke. Several studies have shown increased synchronization with training as well as functional improvement after stroke,[154] possibly by influencing intersegmental coordination within a limb. Therefore, measures that point to patterns of neural synchrony may serve as prognostic indicators or as potential markers of rehabilitative efficacy during performance plateaus.

When the lateralization of the lesion is better defined such as occurring following stroke, deficits in intramuscular coherence of the TA are primarily present on the more affected side.[155] Although this may be due to loss of supraspinal input, changes to spinal organization may also contribute to changes in coherence. For example, Achache et al. (2010) found afferent input from the tibialis anterior (experimentally induced through stimulation of the common peroneal nerve) enhanced excitability of spinal neurons to the VL on the paretic limb of stroke participants. Enhanced excitability was not observed in the non-paretic limb or in healthy individuals.[156] Changes in hip-knee coordination have been noted to impact gait after stroke[157] and may be due in part to alterations in heteronymous reflex patterns between proximal and distal joints.[158] This may be due to changes in afferentation [159] or from changes in descending command to interneuronal networks within the cord.[160]

In non-human primate models, propriospinal neurons contribute to functional recovery after corticospinal lesion.[161] Though propriospinal mechanisms of recovery in humans are unclear, there is mounting interest in these circuits as possible sites of meaningful adaptation.[162] Common neural

drive may then be an aggregate of both descending, local spinal and afferent input. This is a non-trivial point when interpreting coherence values. Though there is agreement that beta band coherence reflects corticospinal integrity, there is also widespread concession that current estimations are incomplete and identifying the cause of coherence remains an area of considerable ambiguity.[163]

These studies support the hypothesis that following injury, impairment may be associated with diminished CND. The study of intermuscular coherence may guide our understanding of motor control beyond force generation. Synchronization of force across two joints during a task requires a higher order of control than force generation in a single muscle. The strength of intermuscular coherence in a compromised system, such as in people with mild to moderate impairment post stroke, is not well understood. Although intermuscular coherence is limited in healthy individuals, the physiological constraints following neurological injury may result in an altered attractor state to adequately perform a task such as walking.

The body of work in neuromotor coherence points to several observations. First, coherence is diminished after injury and is likely to relate to some movement impairment. Second, neural reorganization with or without rehabilitation may affect the degree of coherence and the various degrees of recovery among chronic patients. Third, heterogeneity is present in coherence measures as well as movement outcomes and the two may be related. Therefore, there is a need to characterize CND in an injured population and to relate it to measures of motor control.

Figure 12 (left) represents healthy individuals, where control of the tibialis anterior (yellow) and vastus lateralis (blue) are relatively independent. There is little intermuscular coherence even

during temporally synchronous firing. However, there is high intramuscular coherence in both muscles as it is needed to generate adequate force. After stroke (figure 12, right), the relative independence of muscles is lost and the remaining structural reserve reorganizes to maintain control of the limb. In doing so, increases in intermuscular coherences are observed while intramuscular coherence of both muscles is relatively preserved.

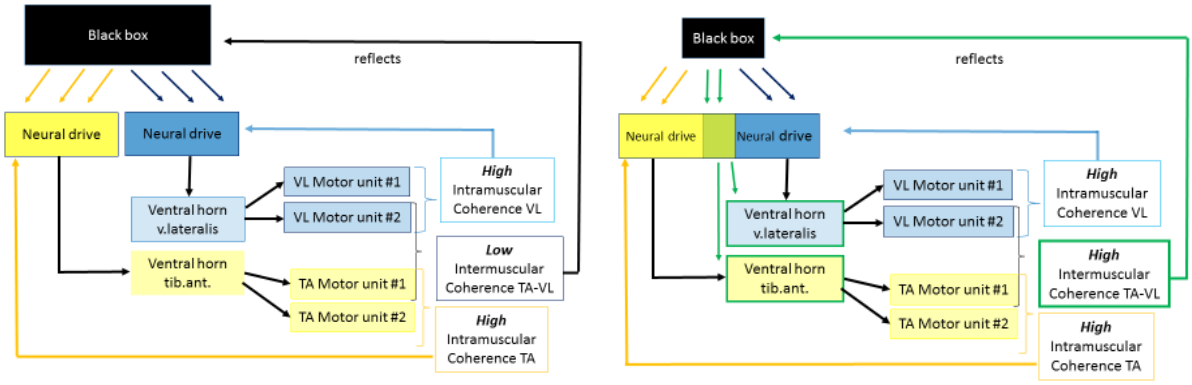


Figure 12. Conceptual framework for intermuscular coherence in healthy and post-stroke.

The purpose of these lines of inquiry is that intermuscular coherence may hold prognostic value for patients if it reflects the current level of motor control or the capacity to improve motor control. Furthermore, if coherence is shown to be a moderator of motor learning, it may be viewed as an intermediate target of rehabilitation and conceptually guide the development of treatment strategies that optimize synchronization.

PART 2: METHODS

Procedural methods including design, participant and instrumented data have been previously described. EMG data from vastus lateralis and tibialis anterior bilaterally, over an average of 78 strides on each limb were analyzed. Previous studies evaluated coherence on 70-72 steps.[149] A 4th order Butterworth filter was applied with high pass cutoff at 5Hz and low pass cutoff at 450 Hz. Analysis was performed on the unrectified signal as there is disagreement regarding the benefits of rectification [135, 164] due to the possibility of masking desired signal components.[165, 166]

Frequency domain analysis was performed over the entire trial and the median frequency of each muscle was identified as the frequency at 50% of the cumulative power. Power spectra were also generated for each stride and these data were used to determine whether there were differences in the median frequency between the non-paretic and the paretic limb in each individual. Additionally, an averaged power spectrum was generated for each limb in each participant to contribute to group data.

Wavelet transform was conducted for each VL-TA pair, for each stride, using the Matlab function (**wcoherence).** Wavelet transforms are used to evaluate signals in the frequency domain over time and are suitable for signals where an assumption of stationarity is violated as is the case for muscle activity during a gait cycle. Coherence at each frequency over the beta band (15-30 Hz) was calculated at each sampled time point for each stride. In doing so, coherence values were generated for each stride of the trial. Average IMC over the entire trial, within stance and swing phase are reported for each participant. Participant means were evaluated and were reported as "*group*" values (N=17). All coherence estimates over the entire trial for each participant were evaluated and reported as "*pooled*" values (N=1338).

Paired t-tests were conducted to determine differences in IMC between limbs for each participant. Wilcoxon signed rank tests were used to compare group means and Spearman correlation was conducted to assess relationship between paretic coherence and clinical measures.

PART 2: RESULTS

Median frequency

Among individual participants, 15 of 17 participants had significantly different median frequencies between the non-paretic and paretic VL muscles with 11 of those 15 showing a decrease. Nine of 17 participants had significantly different median frequencies in the TA muscles with 7 of those 9 showing a decrease.

Median frequency is reported in Table 8. Participants with significant differences in median frequency between non-paretic and paretic limbs over all strides in the trial are marked in the NP columns.

As a group, the median frequency of the VL was shifted lower in the paretic limb compared to the non-paretic limb although it failed to reach significance ($p=0.068$). A significant downward frequency shift was identified in the paretic TA compared to the non-paretic TA ($p=0.009$).

When correlated with clinical measures, the median frequency of the paretic VL was negatively correlated with PWS and SIS score. The median frequency of the TA did not correlate with any clinical measures.

Table 10. Median frequency of each muscle group during entire stride.
Non-paretic vastus lateralis (NP VL-50), paretic vastus lateralis (P VL-50), non-paretic tibialis anterior (NP TA-50), paretic tibialis anterior (P TA-50)

Participant #	NP VL-50	P VL-50	NP TA-50	P TA-50
1	9.55 *	7.45	85.74 *	77.27
2	68.91*	89.01	80.38 *	85.37
3	12.89 *	8.62	55.57	57.49
4	68.99	67.03	95.12 *	65.52
8	40.71 *	59.73	81.86 *	78.00
9	54.11 *	37.85	61.34	59.75
10	50.10 *	8.65	86.63 *	77.36
11	47.06 *	51.94	89.16 *	91.78
12	38.41	37.71	75.43	73.41
13	9.21 *	11.44	76.86	73.31
14	32.56 *	15.21	93.33	92.35
15	64.69 *	48.22	93.82 *	69.88
16	51.63 *	46.95	81.23	79.96
17	51.21 *	29.56	110.07 *	78.05
18	75.75 *	54.01	90.39 *	69.86
19	66.79 *	55.04	66.10	61.57
20	54.31 *	46.68	105.13	102.46
Mean	**46.88**	**39.71**	**84.01**	**76.08**

Table 11. Results of Wilcoxon signed rank test comparing median frequencies for each muscle.

	Comparison of NP vs P limb	
Muscle	**VL**	**TA**
P value	0.068	0.009 *

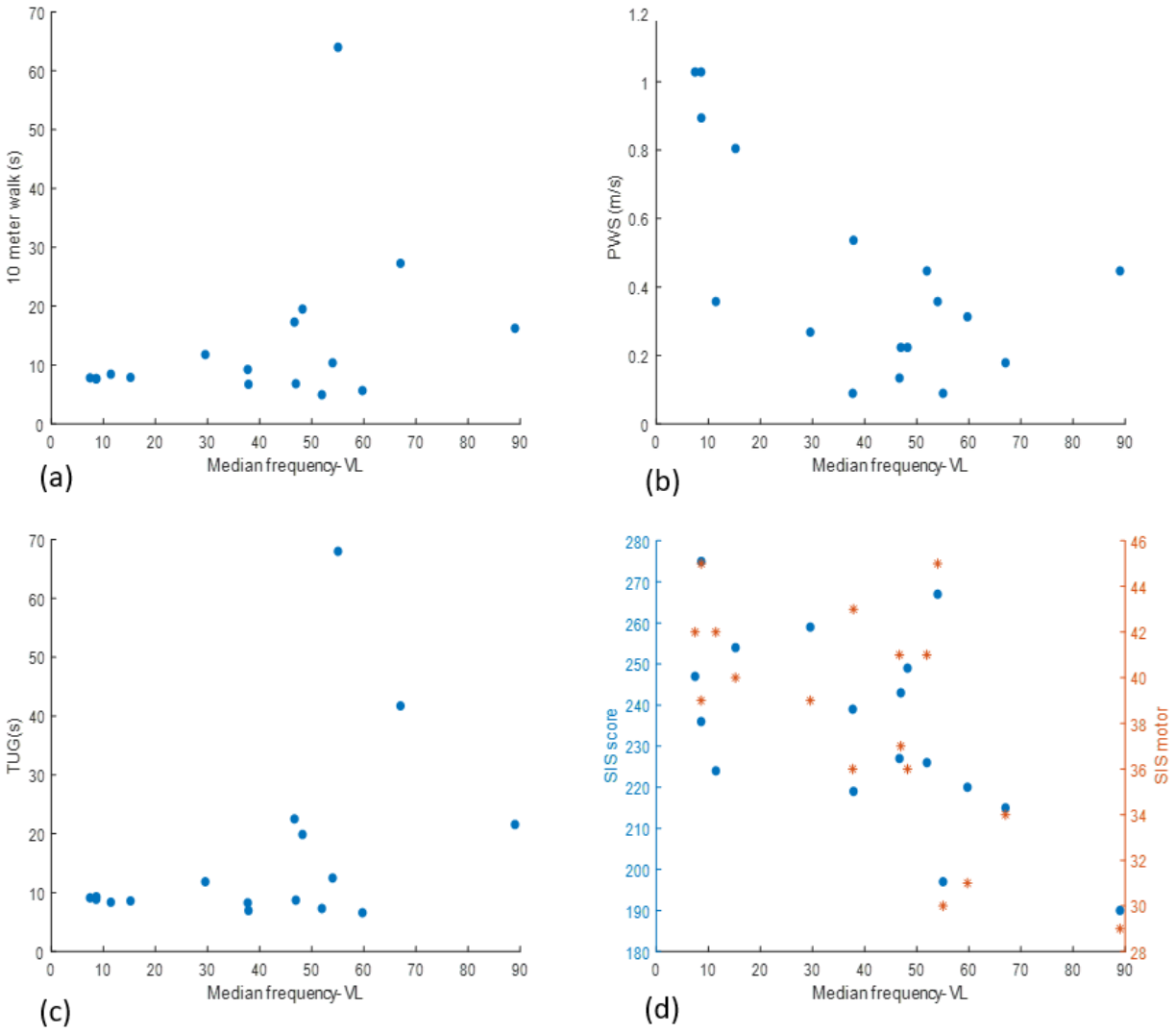


Figure 13a-d. Paretic median frequency-VL and clinical measures.
A. 10MW. B. Preferred walking speed. C. Timed Up and Go. D. SIS scores.

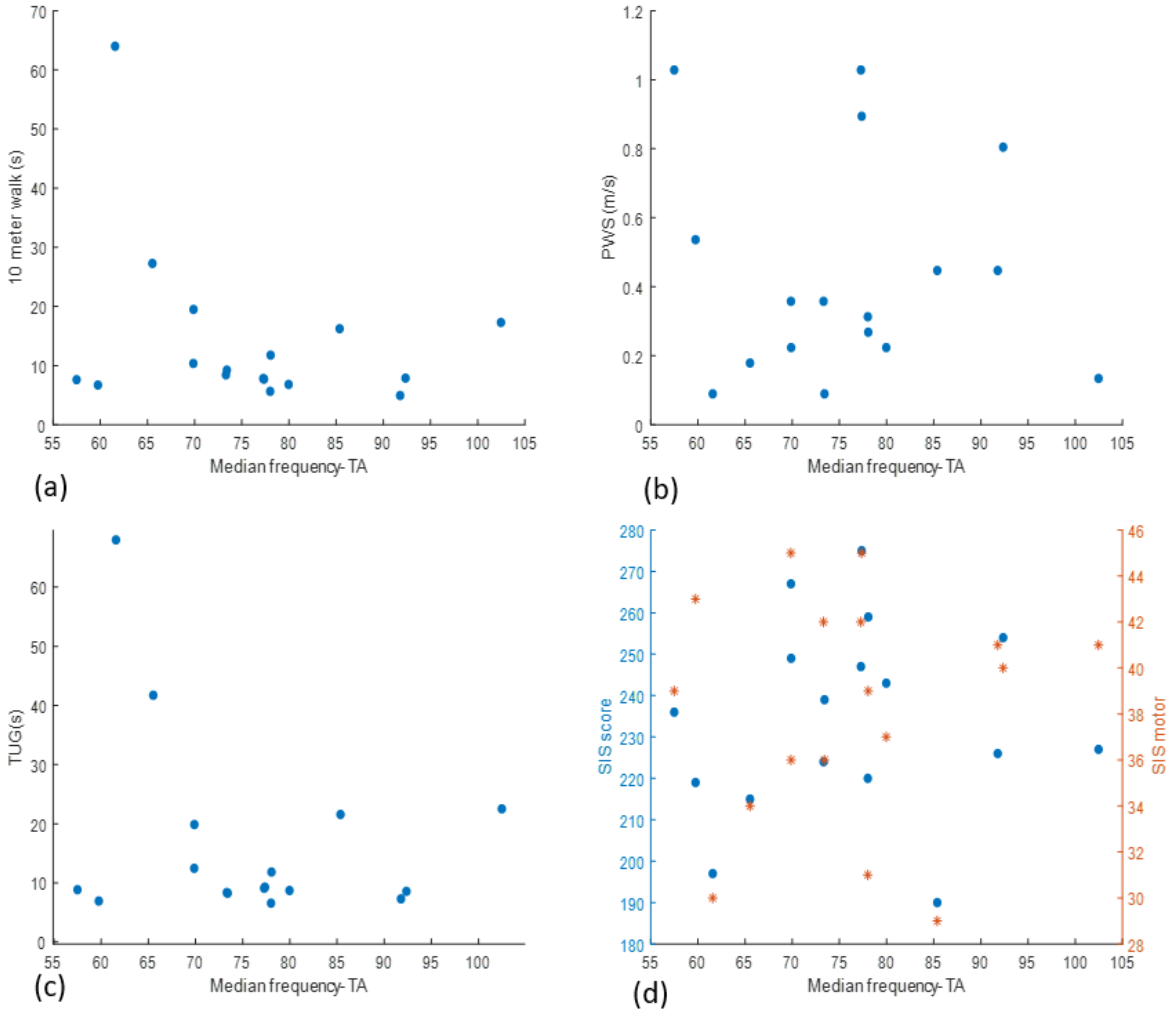


Figure 14a-d. Paretic median frequency-TA and clinical measures.
A. 10 MW. B. Preferred walking speed. C. Timed Up and Go. D. SIS scores.

Table 12. Correlation of median frequencies of VL and TA with clinical measures.

Paretic	Vastus lateralis		Tibialis anterior	
Variable	Spearman coefficient	P value	Spearman coefficient	P value
10MW	0.321	0.209	- 0.145	0.580
PWS	- 0.525	0.032	- 0.011	0.966
TUG	0.306	0.232	- 0.093	0.722
SIS	- 0.551	0.022	0.179	0.492
SIS mobility	- 0.597	0.11	- 0.020	0.940

Intermuscular coherence

Representative wavelet plots are shown below with remaining plots in Appendix A. The figure represents the averaged spectra over all strides. The non-paretic limb is above (NP) and the paretic limb shown below (P). Time is represented on the x-axis and varies among participants depending on their stride time. Initial contact is at time 0 and final contact is indicated by the vertical white line. Frequency is on the left y-axis and ranges from 5-60 Hz though the region of interest in our study is the beta band (15-30Hz). The scale for intermuscular coherence is presented on the right y-axis.

In the representative plot below, there is a region of greater coherence at 5-10 Hz at approximately 0.4 seconds and at 5-15 Hz at approximately 1.2 seconds in the non-paretic limb as distinguished by the difference in color compared to the remainder of the stride. In the paretic limb, a region of greater coherence appears between 0.2-0.4 seconds and moderate coherence at approximately 1.2 seconds. In order to draw relationships with kinematic variability, coherence was reported over the entire stride, stance phase and swing phase.

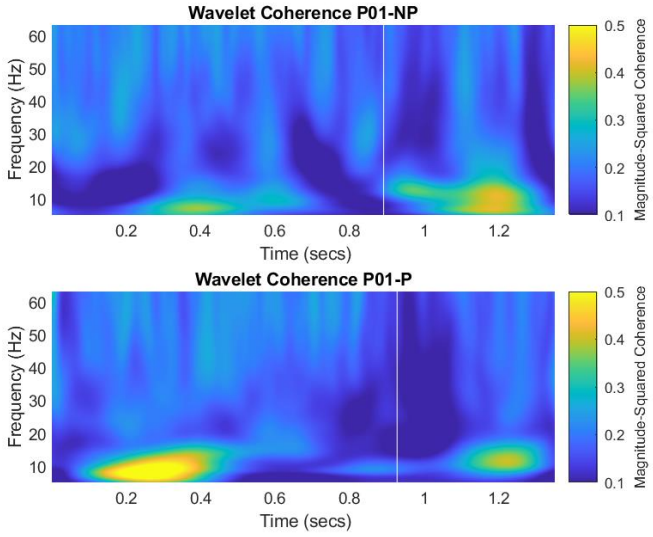


Figure 15. Representative wavelet for single participant.

Coherence values are indicated on the color bar on figure 15 while frequency ranges are indicated on the left y-axis. Initial contact occurs at time 0. Final contact is indicated by the vertical white line.

Mean vastus lateralis-tibialis anterior IMC values in the 15-30Hz band for each limb are reported in Table 10. In the group data, there was no significant difference between IMC over the entire stride, stance phase or swing phase. There was no significant difference between stance and swing phases for either limb. Paretic coherence did not relate to any clinical measure. Given the interest in swing phase for reasons described in part 1 of this project, additional investigation of paretic swing phase coherence was conducted and no significant relationship with clinical measures was identified. The relationship between paretic limb coherence and paretic limb variability was explored. The results of this analysis are located in Appendix B.

Table 13. Mean coherence in the beta frequency band (15-30Hz).

	Non-paretic IMC			Paretic IMC			p values		
	All	Stance	Swing	All	Stance	Swing	All	Stance	Swing
P01	0.161	0.151	0.178	0.159	0.169	0.138	0.77	< 0.01	< 0.01
P02	0.219	0.204	0.271	0.215	0.197	0.249	0.52	0.32	0.11
P03	0.237	0.250	0.210	0.196	0.198	0.191	< 0.01	< 0.01	0.08
P04	0.219	0.232	0.192	0.224	0.221	0.229	0.44	0.19	< 0.01
P08	0.218	0.228	0.198	0.236	0.242	0.225	< 0.01	0.03	< 0.01
P09	0.250	0.243	0.265	0.230	0.235	0.221	< 0.01	0.33	< 0.01
P10	0.224	0.199	0.267	0.169	0.178	0.156	< 0.01	0.01	< 0.01
P11	0.232	0.227	0.239	0.235	0.232	0.239	0.67	0.61	0.99
P12	0.227	0.230	0.221	0.248	0.270	0.210	< 0.01	< 0.01	0.17
P13	0.187	0.191	0.174	0.203	0.219	0.165	0.01	< 0.01	0.44
P14	0.225	0.225	0.224	0.224	0.222	0.227	1.00	0.84	0.70
P15	0.236	0.225	0.269	0.223	0.212	0.253	0.02	0.04	0.11
P16	0.174	0.204	0.116	0.208	0.232	0.150	< 0.01	< 0.01	< 0.01
P17	0.226	0.228	0.219	0.228	0.230	0.223	0.70	0.71	0.67
P18	0.239	0.234	0.251	0.225	0.207	0.266	0.02	< 0.01	0.15
P19	0.230	0.238	0.157	0.233	0.242	0.209	0.45	0.38	< 0.01
P20	0.226	0.240	0.185	0.203	0.206	0.198	< 0.01	< 0.01	0.14
Mean	**0.219**	**0.221**	**0.214**	**0.215**	**0.218**	**0.209**	0.451	0.712	0.586

Table 14. Wilcoxon signed rank tests for group coherence.

Coh	**Comparison of NP vs P limb**			**Comparison of Stance vs. Swing phases**	
Phase	**Entire**	**Stance**	**Swing**	**Non-paretic**	**Paretic**
P value	0.670	0.758	0.756	0.602	0.201

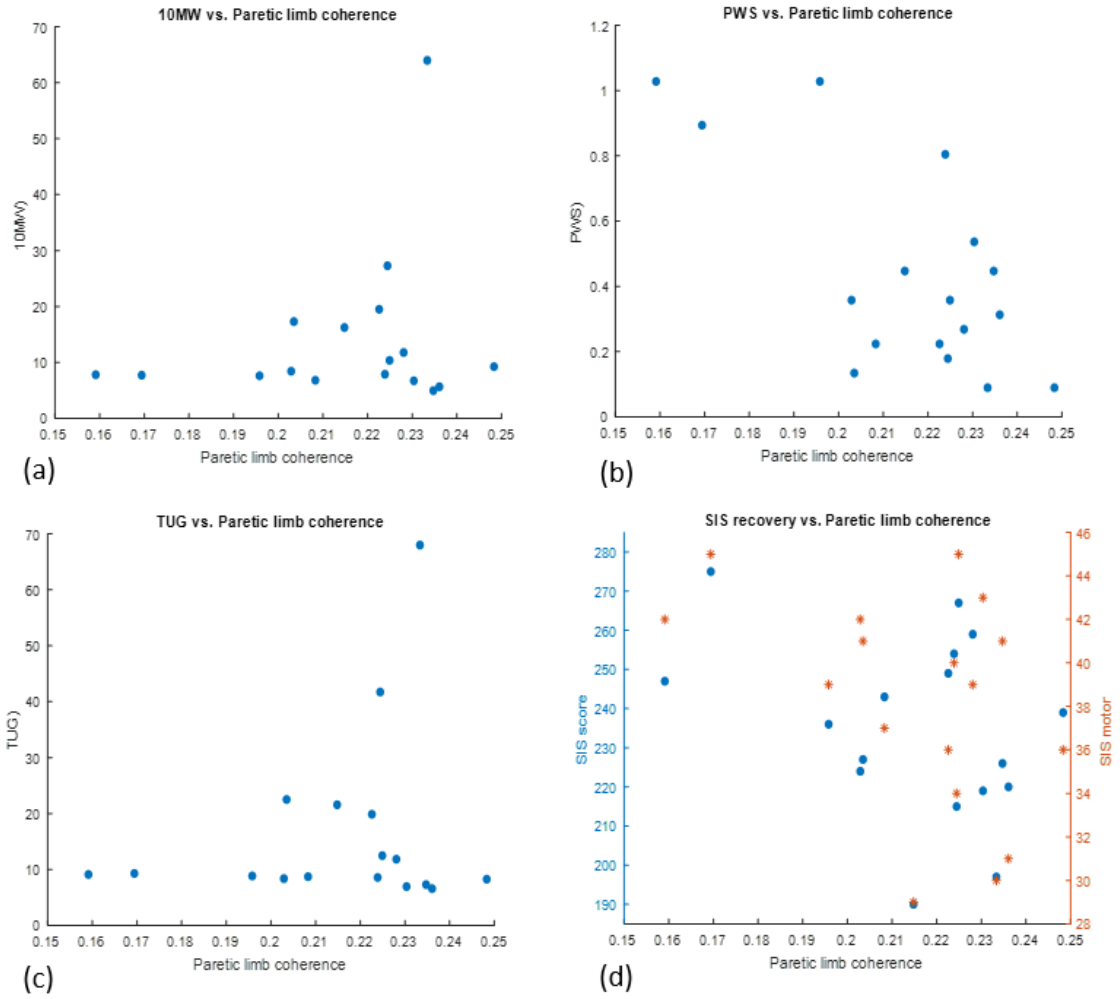


Figure 16. Paretic limb coherence and clinical measures.
A. 10 MW. B. Preferred walking speed. C. Timed Up and Go. D. SIS scores.

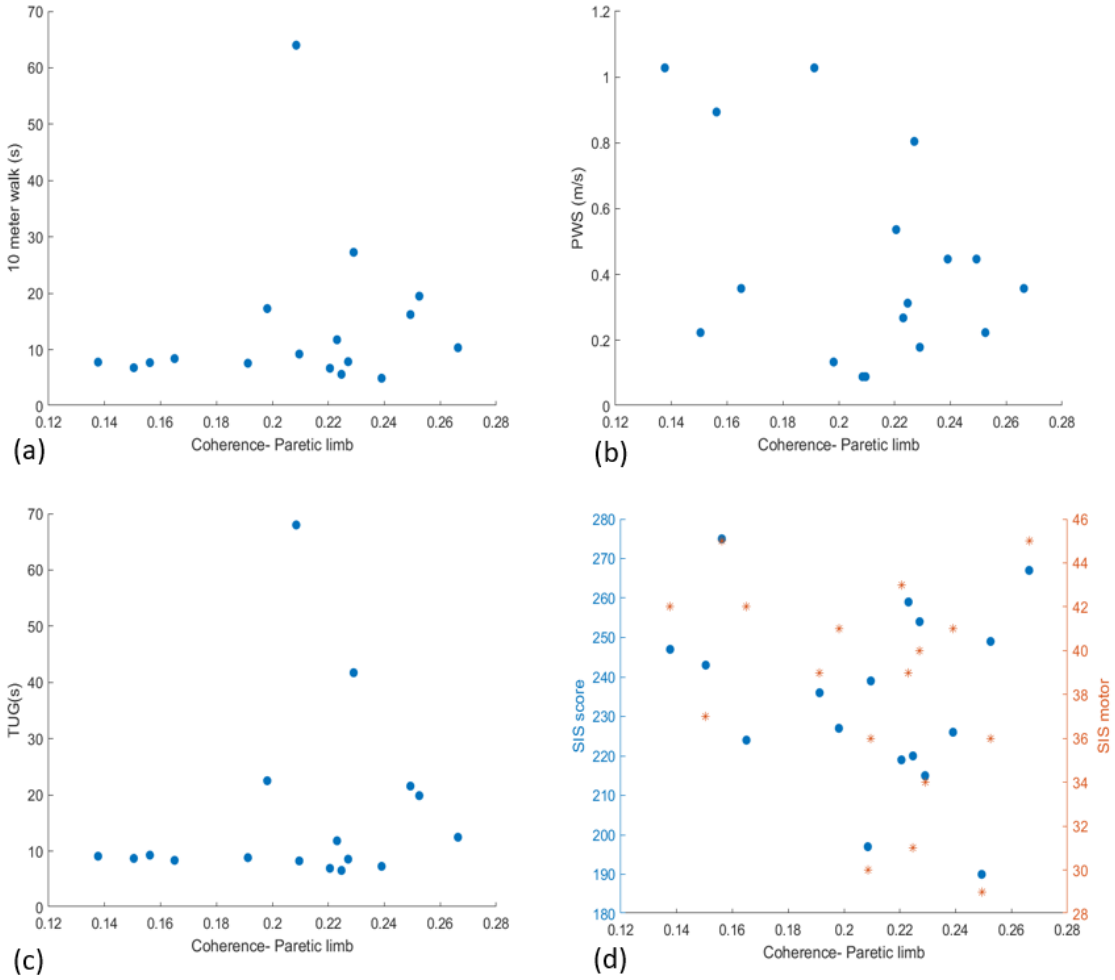


Figure 17. Paretic swing phase coherence and clinical measures.
A. 10 MW. B. Preferred walking speed. C. Timed Up and Go. D. SIS scores.

Table 15. Spearman coefficient for coherence and clinical measures.

Paretic	Total cycle coherence		Swing phase coherence	
Variable	Spearman coefficient	P value	Spearman coefficient	P value
10MW	- 0.430	0.870	0.2672	0.2988
PWS	- 0.472	0.056	- 0.1610	0.5369
TUG	- 0.304	0.235	0.1471	0.5723
SIS	- 0.274	0.288	- 0.0980	0.7084
SIS mobility	- 0.359	0.157	- 0.2631	0.3077

Thirteen of 17 participants demonstrated differences in IMC between the non-paretic and paretic limbs at a minimum of one aspect of the gait cycle; stance or swing. Ten of 17 participants had significantly different IMC between the non-paretic and paretic limbs throughout the entire cycle. Ten of 17 participants had significantly different IMC between limbs in stance phase. Seven of 17 participants had significantly different IMC between limbs in swing phase.

Of the 10 of 17 participants that had significantly different coherence between limbs through the entire cycle, 4 showed greater coherence in the paretic limb and 6 showed greater coherence in the non-paretic limb. These individuals were grouped together in a post-hoc analysis so that group characteristics could be described. Those results are presented in Appendix C.

In the pooled data, there was a significant difference in beta coherence between the non-paretic and paretic limb (p=0.023).

Table 16. Paired t tests for pooled coherence.

Coh	**Comparison of NP vs P limb**			**Comparison of Stance vs. Swing phases**	
Phase	**Entire**	**Stance**	**Swing**	**Non-paretic**	**Paretic**
P value	0.023	0.287	0.110	0.002	< 0.0001

PART 2: DISCUSSION

Median Frequency

We hypothesized that the median frequency would be lower in the paretic than the non-paretic limb. The data partly supported this hypothesis. As a group, the median frequency was lower in the paretic limb only in the tibialis anterior while the lower median frequency of the paretic vastus lateralis compared to the non-paretic vastus lateralis trended toward significance (p= 0.069). Median frequency of the tibialis anterior was greater than the vastus lateralis in both non-paretic and paretic limbs in nearly all participants; 16 of 17 participants in the non-paretic limb and 15 of 17 participants in the paretic limb. This is consistent with previous reports where the median frequency of 12 uninjured individuals was greater in the tibialis anterior (115 Hz) than the vastus lateralis (97 Hz) during treadmill walking.[167]

Go et al. reported similar findings in both dystonic and non-dystonic limbs where the median frequency of the TA was greater than the VL.[124] The difference in non-paretic vs. paretic TA median frequency is anticipated as the tibialis anterior is often impaired post-stroke, possibly due to changes in corticomotor excitability secondary to the injury.[168, 169] Tibialis anterior is known to be more difficult to recruit than other lower extremity muscles following injury [170, 171] and is a consistent target of rehabilitative efforts.[172] The TA is of particular importance in control of the ankle and injury to the cortex may lead devastating loss to distal limb function during gait.[173] Regardless of the mechanism of dysfunction, impairment of the tibialis anterior is known to relate to walking velocity impairment so is regarded with particular interest in stroke.[174]

While the differences in paretic and non-paretic TA are notable, we must also attend to the findings within the VL. Although group means did not differ in the VL (p=0.069), changes were evident

within participants. Across all strides for individuals, there was a pattern of downward frequency shift in the vastus lateralis (11 of 17 patients). It appears that the downward shift may be characteristic of the injured limb in both proximal and distal muscles. We report a 15.3% lower median frequency on the paretic VL and a 9.4% lower median frequency on the paretic TA. A similar downward shift was detected in the upper extremity of 14 stroke patients during isometric tasks. The mean frequency of the paretic limb was approximately 9.3% lower on the paretic than the non-paretic limb.[175]

The cause of the downward shift of median frequency may be due to either central or peripheral causes. Muscle fatigue and fatigability results in a decrease in median frequency. [176, 177] In our study, EMG recording began after approximately 30 seconds of walking at PWS in order to avoid fatigue-related signal changes. Participants were asked to inform the research team if they felt pain, discomfort or fatigue or any other sensation that noticeable impacted their gait. All trials were discontinued after 5 minutes of walking or earlier if a sufficient number of steps had been taken (>80 steps). No participant asked to discontinue earlier than the scheduled termination. Therefore, fatigue is an unlikely cause for differences in median frequency.

Muscle fiber types are also known have different spectral properties due to differences in conduction velocity. Fast glycolytic and fast oxidative glycolytic fibers have higher median frequencies than slow oxidative fibers.[178] However, it has been shown that skeletal muscles tend to shift toward fast fiber phenotypes following stroke [179] therefore our observed frequency shifts are unlikely to result from muscle fiber change.

Another possible cause of a shift to lower frequencies is a decrease in motor unit firing in the paretic muscles.[180] Muscles affected by stroke are known to have increased motor unit firing rates at rest [181] but decreased firing rates during contraction.[182] Murphy et al. (2018) reported that alterations to sensory pathways post-stroke may lead to greater inhibition of motor neurons in the lower extremity.[183] With decreased firing rate of motor units, a decrease in median frequency may result.

The median frequency of the paretic TA had no significant relationship with any clinical measure. This is consistent with Ma et al. (2017) who found reduced mean frequency of several lower extremity muscles, including tibialis anterior, in the paretic limb post-stroke but no relationship between mean frequencies and clinical measures such as the Fugl-Meyer Assessment and the Berg Balance Scale.[184] On the other hand, the median frequency of the paretic VL showed a significant negative correlation with PWS, and SIS scores in our participants. The relationship between median frequency and PWS is easily reconciled as frequency profiles closer to "normal" may lead to walking improvement. However, the negative correlation between median frequency and SIS scores was unanticipated.

While the changes in median frequency alone might lead one to claim that there is a shift in frequency profile of the paretic limb, coupling these data with coherence may yield a more robust interpretation.

Intermuscular Coherence

The hypothesis that intermuscular coherence would be greater in the paretic limb than the non-paretic limb was not supported. Within the group data, there was no difference in coherence through the entire cycle, stance phase or swing phase. The hypothesis that paretic leg IMC would relate to 10 m walk time was also unsupported. Paretic limb coherence was not significantly related

to any clinical measure. Given the interest in swing phase as described in the section 1, we also related swing phase coherence to clinical measure and detected no significant relationships.

The finding that 10 of 17 participants had differences between limbs when evaluating all strides within their individual trials is notable. Moreover, 13 of 17 (76% of participants) had differences in at least one point in the cycle. Previous studies that examined coherence customarily isolated a small portion of each gait cycle during co-contraction of the muscles of interest. This was due in large part to avoid violating the assumption of stationarity necessary for analysis. For example, Norton and Gorassini (2006) isolated a 225 millisecond (+/- 15) window during the cycle claiming the signal to be "quasi-stationary." Halliday et al. (2003) examined 200 ms windows to demarcate early, middle and late swing as they examined intramuscular coherence within the tibialis anterior.

Rather than isolating small sections of the trial, we utilized wavelet coherence to retain time domain characteristics. This allowed us to average coherence through larger segments of the cycle permitting reporting on the entire cycle, swing phase and stance phase possible.

As we explored the 10 participants who had differences in coherence over the entire stride, there was an apparent stratification. Our initial hypothesis was that intermuscular coherence would be greater on the paretic limb. Within this subset of 10, 4 had greater coherence in the paretic limb and 6 had greater coherence in the non-paretic limb. When we expand the assessment to include the 3 additional participants who had significant differences between limbs in one or more phases but no difference in the overall cycle, we see that 2 of those had IMC values in the paretic limb greater than the non-paretic in swing phase. The 3rd participant had significantly lower IMC in the non-paretic limb during stance, but significantly greater IMC in the non-paretic limb during stance and was not placed in one of the strata.

With this method of grouping, we identified 6 participants who had greater coherence in the non-paretic limb (NP>P) and 6 who had greater coherence in the paretic limb (P>NP). When Mann Whitney U test was performed, the two groups differed in both non-paretic (p=0.004) and paretic variability (p=0.041). Greater variability in *both* limbs was detected in the group with greater paretic coherence. The NP>P group had significantly greater NP coherence. There was no difference in paretic coherence between groups. The table with results can be found in Appendix B. These results suggest that greater coherence in the non-paretic limb is associated with reduced variability in both non-paretic and paretic limbs.

Our focus was on paretic limb changes and their impact on gait performance and clinical measures. The non-paretic limb was used as a comparison to quantify the changes to the paretic limb. However, adaptive changes aimed at both recovery and compensation require neural reorganization that is likely to be bilateral.[185] The non-paretic limb is certain to interact with the paretic limb but was not factored into our conceptual or statistical models in this study. The subgroup data (NP>P vs P>NP) suggests the need to include non-paretic variables and develop models that allow interlimb-intralimb interactions. Those models should also adopt a more nuanced view of coherence as a more complex reflection of motor control than originally imagined.

Several studies point to the dynamics of coherence as dependent on the task and conditions surrounding the performance of the task. Kilner et al. (1999) reported that values are task dependent and suggested that 20 Hz signals may indicate an "idling frequency" of baseline oscillatory activity. Other frequencies within the beta band activity were involved with the "hold" phase of a grip task that diminished as participants increased force.[186] Additionally, coherence has been shown to

decrease with increased feedback through repetition and adaptation.[187] Interestingly, motor memory may also influence coherence. When participants completed a task that varied in force and the predictability of those fluctuations immediately before the observed task, coherence varied depending on the pre-performance state. [188] Together, these studies suggest that coherence should be viewed in light of a dynamical systems model with its emergence predicated on other variables. There is immediate impact to inferences drawn as alterations to coherence during swing phase may actually result from stance phase events rather than an inherent characteristic of swing phase. While there remains lack of clarity in interpretation of intermuscular coherence, it is evident that coherence should not be regarded as a "state" of the individual but as an additional complex variable of a complex system.

PART 2: LIMITATIONS

The most notable limitation is in the method utilized to quantify coherence through the entire cycle as well as stance and swing phases. As described, coherence was averaged within the beta frequency band through the entire cycle. However, coherence between muscles of two joints is known to be intermittent even during stationary tasks like standing balance.[189] The use of the wavelet transformations allowed visualization of coherence changes throughout the gait cycle and visual inspection, as in figure 15, showed clearly discernible periods of coherence. Visual inspection of the remaining wavelets in Appendix A indicate regions of coherence and are highly suggestive of significant differences at various points throughout the cycle. However, the method of averaging coherence through large sections is likely to have diluted significant differences.

It is possible that if we further divided each phase, there would be significant findings in some segments. This would allow characterization of coherence during specific segments of gait such as "early stance, mid stance etc." Studies on gait biomechanics have traditionally fractionated the gait cycle into these segments so parallel estimations of coherence during those segments may be conceptually warranted.

There was also concern that inferences from the group data, especially with a relatively small sample (N=17), may mask relationships that exist. Evidence that pointed toward this is the pooled data where coherence of all paretic stride across all participants (1337 strides) was compared to all non-paretic strides across all participants. The paretic limb showed significantly *lower* coherence than the non-paretic limb ($p=0.023$). While contrary to the original hypothesis, it nevertheless reveals a difference between limbs that should be considered.

Finally, we may have failed to capture some effect by our choice of beta frequency bounds, 15-30 Hz. Some authors use lower floors of the beta frequency range such as 12-30 Hz. [190, 191, 192] Seeing much of the VL-TA coherence at lower frequency ranges in the wavelets, a lower defined floor may have captured additional differences in coherence.

PART 2: CONCLUSION

EMG spectral analysis was conducted with specific interest in median frequency and intermuscular coherence as well as their relationships to clinical measures. Decreases in the median frequency of the paretic limb in the tibialis anterior were detected as well as trends toward lower median frequency in the vastus lateralis. Median frequency may be an indicator of motor unit dysfunction suggesting a potential role as a marker of clinical utility. Median frequency of EMG signals is reliable [193] and may help assess effectiveness of rehabilitation in recovery of motor unit activity post-stroke. [194] However, median frequency is not an independent predictor of clinical scores so contextualization within a broader functional framework such as the ICF is necessary.

In the evaluation of intermuscular coherence within the group data, there were no differences between paretic and non-paretic limbs. Paretic coherence did not relate to 10 meter walk time or other clinical measures. However, given the findings in individual participants as well as the pooled coherence, it would be premature to dismiss intermuscular coherence as a meaningful indicator of motor control.

PROJECT CONCLUSION

This project consisted of two parts. Part 1 focused on kinematic changes post-stroke and part 2 made attempts to explain these through estimations of intermuscular coherence and the inferences allowed.

Within the ICF framework, we characterized gait patterns through stance time asymmetry, interlimb angle-angle symmetry and variability of intralimb coordination. Control of voluntary movements, the other category within the body functions/structure component was inferred through spectral analysis of EMG and coupled with observations of gait patterns. The relationship of stance asymmetry and knee-ankle angle variability to walking performance was confirmed though findings from spectral analysis were less conclusive. The Stroke Impact Scale 3.0 evaluates several additional categories in the activity and participation components of the ICF framework, however, a detailed description was beyond the scope of this project.

That kinematic changes occur post-stroke was well-established prior to this project. We assessed paretic limb variability of those kinematic changes and related them to clinical measures. Recognizing that changes in IMC may result from cortical changes that synchronize corticospinal input [195] and the possible consequences to variability, we investigated the relationship between IMC and variability.

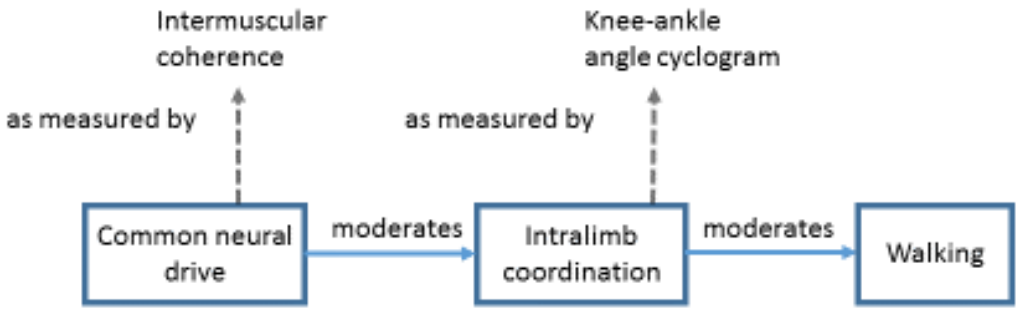


Figure 18. Conceptual framework linking common neural drive, kinematics and walking.

Figure 18 depicts a framework where common neural drive is a significant moderator of intralimb coordination (ILC). It is not likely to mediate ILC because each segment maintains some degree of independent input from supraspinal and afferent connection. ILC is a significant moderator of walking performance.

Our conceptual framework assumed that the participants were exercising their previously realized optimal motor solution to the task. All participants identified as mild-moderately impaired walkers and were in a chronic stage post-stroke. Nevertheless, it is arguable that they are still in the midst of a learning process of discovering solutions given new physiological constraints. This is buttressed by the fact that some participants had spent very little time on a treadmill prior to the data collection. This view, while possible, would alter the interpretation of observed variability. A temporal course to motor learning exists with the activation of various neural substrates during different stages[196] and if a model of learning continuity is preferred, higher variability might be desirable. As in any scientific inquiry, inferences from the data largely depend on the conceptual framework through with which one frames the question. We have attempted to make our view clear.

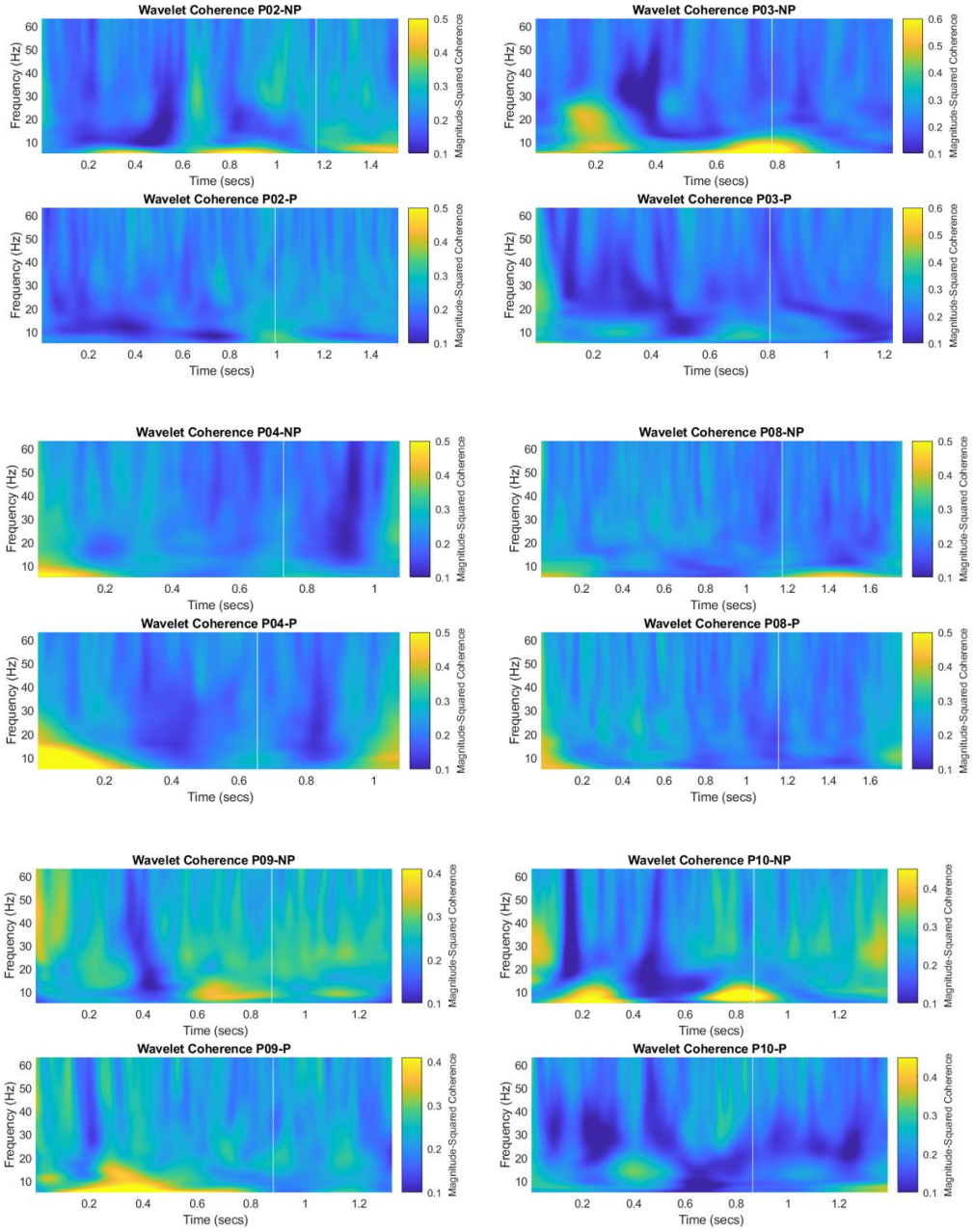
Inferences from the frequency domain data are bound by the same framework. A higher coherence on the paretic limb was hypothesized under the assumption that neuroplastic changes post-injury permitted walking recovery and might be observed through motor unit synchronization, albeit with variable kinematic results. While this hypothesis was unsubstantiated, the identification of coherence strata and their association to variability clearly demand a more elegant model than what was proposed in figure 18 and similarly refined hypotheses for future studies.

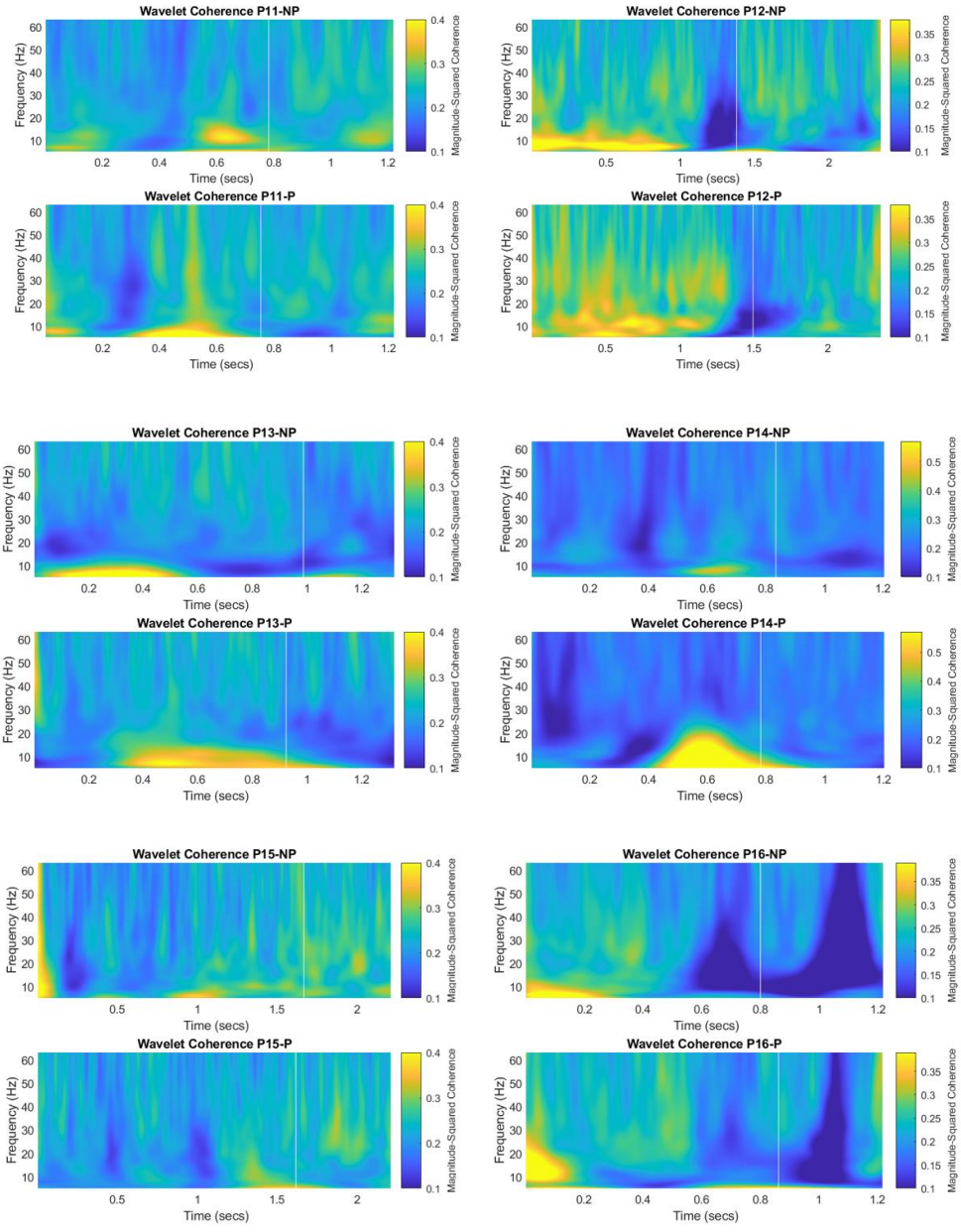
If neuroplastic changes have consequences to kinematic behavior, then changes to patterns of synchronization of neuronal firing may prove significant [197] and merit further investigation. A better understanding of the heterogeneous neuroplastic changes post-stroke will open opportunities for individualized clinical applications.[198] There have been multiple training strategies to improve walking in post-stroke rehabilitation. Various training approaches adhere to conceptual models that emphasize, for example, neural facilitation, strength or task-specificity. Invariably, there exists overlap of techniques and consensus that concepts such as intensity and repetition deserve higher-order theoretical primacy in the design stage of exercise programs.[199] But a better understanding of meaningful neural categories of patients, while adding complexity to diagnosis and treatment, may be useful in promoting coordination, [200] a core component of optimal motor execution.

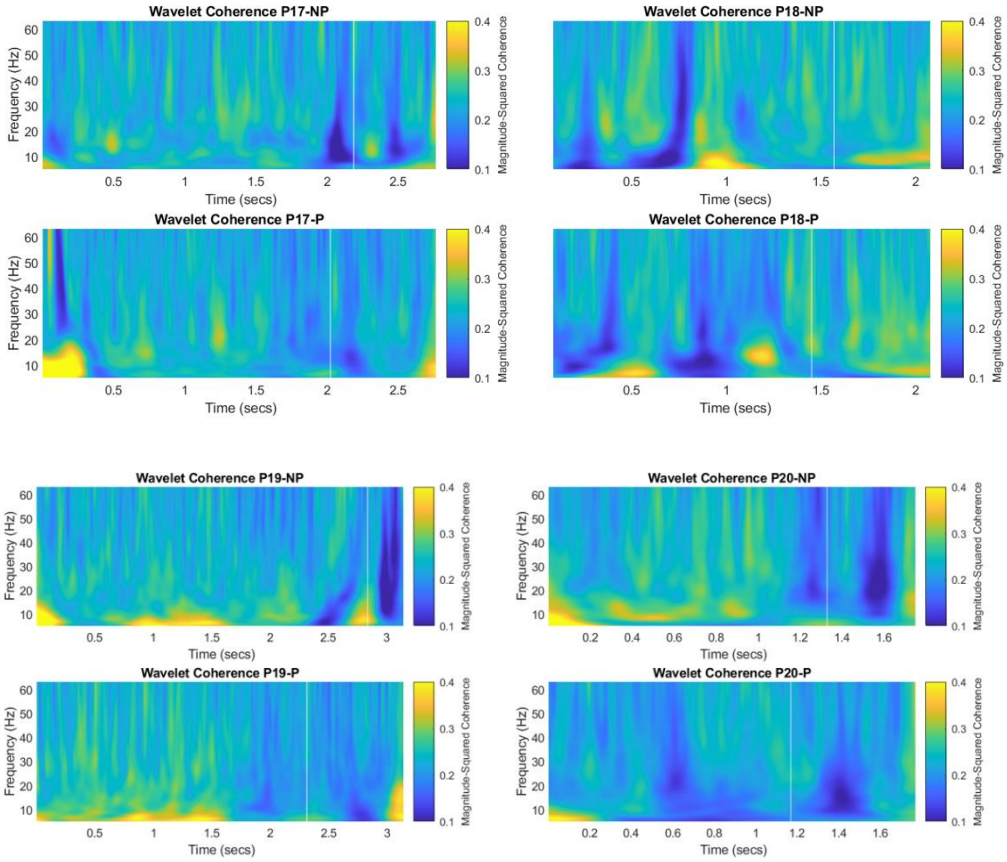
As growing evidence suggests a link between cognitive and motor function, improved walking, though of incontestable merit, is likely to lead to benefits beyond solely motor activity.[201] For rehabilitation scientists, this intuition, categorically outlined in the ICF core sets for stroke, is a fertile region for translational research to improve movement and function for life for individuals post-stroke.

APPENDIX A

Wavelets for all participants




Wavelet Coherence P11-NP
Wavelet Coherence P12-NP
Wavelet Coherence P11-P
Wavelet Coherence P12-P
Wavelet Coherence P13-NP
Wavelet Coherence P14-NP
Wavelet Coherence P13-P
Wavelet Coherence P14-P
Wavelet Coherence P15-NP
Wavelet Coherence P16-NP
Wavelet Coherence P15-P
Wavelet Coherence P16-P
Frequency (Hz)
Time (secs)
Magnitude-Squared Coherence


Wavelet Coherence P17-NP
Wavelet Coherence P18-NP
Wavelet Coherence P17-P
Wavelet Coherence P18-P
Wavelet Coherence P19-NP
Wavelet Coherence P20-NP
Wavelet Coherence P19-P
Wavelet Coherence P20-P
Frequency (Hz)
Time (secs)
Magnitude-Squared Coherence

APPENDIX B

Mean values for 12 participants with significant difference in coherence between limbs and results of Mann Whitney U test comparing means.

	NP coh > P coh	**P coh > NP coh**	**p value**
# of participants	6	6	
10MW	11.531	20.217	1.000
PWS	0.529	0.209	0.093
TUG	13.323	23.617	0.699
SIS	245	223.0	0.132
SIS- mobility	41.5	35	0.026 *
Asym ratio	0.049	0.808	0.485
NP variability	0.909	0.762	0.004 *
P variability	0.876	0.720	0.041 *
NP coh	0.235	0.209	0.026 *
P coh	0.208	0.225	0.132

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