Quantifying gait stability based on body segment coordination relationships measured with wireless sensors

By

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Abstract

SUMMARY: The purpose of this study was to investigate how the relationships between upper body (trunk) and lower body (feet) motion are affected by multiple sclerosis (MS), and how these relationships can be used to characterize gait stability in persons with MS (PwMS). In Aim 1, we determined how segment relationships are affected by changing walking speed and sensory input in PwMS compared to healthy controls. PwMS and healthy age-matched controls walked on a treadmill at a range of speeds while wireless inertial sensors measured foot and trunk acceleration. The ratio of acceleration variability between upper and lower body segments, referred to as the gait stability index (GSI), was used to represent the segment coordination relationship during gait and was compared across all walking trials and groups. In Aim 2, we determined how the GSI was related to pathophysiology, clinical disability, and mobility scales in PwMS. Physiological deficits in PwMS were measured through postural response latencies and somatosensation thresholds. Clinical disability and mobility were measured by self-report fall history and clinical questionnaires. In Aim 3, GSI cutoff values and amount of overground walking needed to separate MS fallers from MS non-fallers were determined using data collected continuous 4-minutes of walking over a 10-meter walkway in the laboratory.

RELEVANCE: Falls are a leading cause of non-fatal injury and a significant health problem for persons with multiple sclerosis. The current study utilizes a novel technique to examine how critical relationships between motion of upper and lower body segments respond under normal and challenging conditions, and how the maintenance of these relationships is tied to instability and fall risk. Investigation of these segmental relationships during walking is significant to developing gait assessment methods for any population to monitor stability in daily life, identify risk of future falls, and longitudinally track disease progression or treatment efficacy.

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1 Specific Aims

Persons with multiple sclerosis (PwMS) have high incidence of falls with 60% of individuals reporting at least one fall within a 6-month period [1]. Falls can lead to injury [2] and reduced participation in daily life activities [3] but to develop methods to monitor gait stability and fall risk in PwMS, we must first identify relevant characteristics of gait that can be measured in real world environments where falls are most likely to take place [4, 5]. *The purpose of this dissertation was to investigate how the relationships between upper body (trunk) and lower body (feet) segment motion during walking are affected by MS and how these relationships can be used to characterize gait stability in PwMS.* During locomotion, stability is characterized as the ability to attenuate disturbances and maintain functional gait [6]. Interaction between an individual's center of mass (CoM) and base of support (BoS) allows for stability to be maintained [7]. When this interaction is not sufficiently controlled, an individual's gait will become unstable and may lead to increased fall risk [8]. The central hypothesis for this line of research is that a necessary, healthy relationship between the CoM and BoS is maintained by continuous sensorimotor feedback and any changes to the healthy, optimal state of this relationship would indicate instability during walking. Our preliminary findings show that there is a significant relationship between acceleration variability at the trunk (CoM) and at the foot (BoS) in healthy young adults [9] and that this relationship is altered in PwMS [10]. It is unknown how this relationship is maintained by healthy subjects and PwMS across challenging walking conditions, or how such relationships can assess fall risk outside of a laboratory. To quantify this relationship, the ratio of acceleration variability between upper and lower body segments is calculated as the gait stability index (Eq. 1) and will be calculated for several variability outcomes.

Gait stability index = Trunk Acceleration Variability / Foot Acceleration Variability **Eq. (1)**

Aim 1: *Determine how the gait stability index is affected by changing walking speed and sensory input in persons with MS compared to healthy controls.*

The gait stability index was calculated during treadmill walking at preferred, fast, and slow speeds and under altered somatosensory and visual input conditions.

Hypothesis 1a: The gait stability indices will change with changing gait speed during walking in healthy subjects but will not change in subjects with multiple sclerosis.

Hypothesis 1b: The gait stability indices will change under altered sensory conditions in healthy subjects but will not change in subjects with multiple sclerosis.

Aim 2: *Determine how the gait stability index is related to physiological impairments in persons with MS and if it is a clinically valid measure of fall risk in persons with MS.*

Physiological impairments of multiple sclerosis was measured via EMG sensorimotor delays to postural perturbation, vibrotactile sensation, and clinical disability status. Sensitivity of the gait stability index to separate MS fallers from MS non-fallers was compared to sensitivity of standard clinical and self-report measures.

Hypothesis 2a: The gait stability indices will show moderate to strong correlations with measures of pathophysiology in people with multiple sclerosis.

Hypothesis 2b: The gait stability indices will more sensitively differentiate fallers from non-fallers compared to standard clinical and self-report measures.

Aim 3: *Identify minimum number of walking bouts and cutoff values of the gait stability index needed to differentiate MS fallers from MS non-fallers using over ground walking data.*

In a laboratory, number of short over-ground gait bouts and cutoff values needed to separate groups was identified during four minutes of continuous walking over a 10-meter walkway.

Hypothesis 3a: At least one gait stability index will be reliably estimated with 10 or fewer short over-ground walking bouts.

Hypothesis 3b: At least one gait stability index will differentiate MS fallers from MS non-fallers, from which cutoff values will be found to separate MS fallers from MS non-fallers.

Potential Impact: A quantitative assessment of gait stability will allow for identifying risk of an impending fall and monitoring of an individual's functional status over time, assisting in clinical decision-making by indicating progression of disability or efficacy of prescribed interventions.

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2 Background and Preliminary Studies

2.1 Statement of problem and purpose

In persons with multiple sclerosis (PwMS), the best predictor of a future fall is a history of previous falls [1], but little is known about why falls occur or how to identify individuals at risk of suffering an initial fall. Preventing intial falls is of particular importance in PwMS in order to avoid a cycle of falls, reduced activity, and deconditioning. *The long-term goal of this line of research is to develop a quantitative method of measuring gait stability and acute fall risk in PwMS during walking that can be implemented in a real-world environment.* Currently, simple functional tests are often used to screen persons for fall risk [2], but these tests performed in clinical environments (Timed-Up and Go Test, Berg Balance Scale, Dynamic Gait Index, Dizziness Handicap Inventory, Activities-Specific Balance Confidence scale) are inadequate in predicting fall risk [3, 4]. To identify persons at risk of future falls, sensitive measures of fall risk must be developed.

2.2 Existing knowledge

2.2.1 Interaction between base of support and center of mass.

During gait, the feet act as the point of contact between the body and the ground and provide a dynamic base of support (BoS). Maintaining stability during gait requires controlling the interaction between the BoS and the body's center of mass (CoM) located within the trunk segment [5]. Both trunk motion and foot placement affect stability during walking [6-8] while acceleration variability of these segments during walking can provide information about how motion of these segments is controlled [9, 10]. When healthy subjects walk at non-preferred gait speed, their foot and trunk motion variability is altered compared to walking at their preferred

speed [11, 12]. Previous studies have examined foot or trunk motion independently, but control of these segments is likely highly interdependent for maintaining stability during walking [13-15]. Margin of stability has been used during gait to quantify dynamic stability based on motion of the BoS and CoM [16] and margin of stability is significantly altered in PwMS [17], persons with history of stroke [18], and elderly populations [19]. However, it is not possible to measure margin of stability without using a full motion capture system, which is not practical in clinical or real-world environments. Small, wireless inertial sensors are a feasible alternative tool to assess movement of the BoS and CoM during walking and can be used in any environment [20]. This technology is ideal for monitoring gait in and around the home where many falls occur [21].

2.2.2 Impairments in PwMS

The feedback control between the BoS and CoM is of particular interest in PwMS, as slowed spinal somatosensory conduction may cause dysfunction of underlying control systems governing this relationship [22]. *It is not clear how the relationship between trunk and foot movement changes in response to changing walking conditions in PwMS (Aim 1).* Since the relationship between the BoS and CoM is fundamental to maintaining gait stability, this relationship should be able to appropriately adapt to any walking condition. It's possible that the inability to adapt to walking conditions may be an underlying cause of falls in PwMS. It has been speculated, based on variability analysis of center of pressure sway patterns, that PwMS are less adaptable in their postural control movement patterns [23, 24]. Center of pressure sway is significantly influenced by sensorimotor delays [25] and these sensorimotor delays may provoke an altered relationship between the BoS and CoM [26]. Thus, the lack of adaptability in postural control is likely to also be reflected in the relationship between the BoS and CoM during gait. *It is not known whether the relationship between BoS and CoM during gait is reflective of specific*

pathophysiological deficits in PwMS (Aim 2). There are many kinetic and kinematic differences in the gait of PwMS compared to healthy control subjects including reduced walking speed and stride length [27], decreased ankle and knee angular excursions [28], altered trunk sway variability [29], and altered step length and step width variability [30]. These altered gait parameters in PwMS are influenced by decreased somatosensation [31], altered sensorimotor responses [22], muscle asymmetry [32], and spasticity [33] and these parameters lead to altered gait stability and increased fall risk [22, 34-36]. In the current study, the gait stability index is being introduced as a novel quantitative measure of dynamic balance during gait, therefore it is also necessary to evaluate how this measure is related to disease specific physiological changes in PwMS.

2.2.3 Clinical fall risk assessment in PwMS.

Current clinical assessments, such as the Activities Balance Confidence questionnaire, don't directly assess gait stability and poor outcomes on these measures, such as worse questionnaire scores and slower walking speed, are indicative of a fear of falling but are not directly associated with risk of future falls [37]. Using a measure of fall risk based on segmental control relationships may provide clinicians with a more sensitive and objective measure than what current clinical assessments offer, as the relationship between the CoM and BoS is directly tied to stability [5]. *It is currently not known how the ability to maintain segmental relationships relates to clinical or self-report measures of fall risk in persons with multiple sclerosis (Aim 2).* Prevention and rehabilitation care in aging and neuropathological populations would benefit from access to an objective measure of gait stability to track how a person's functional capabilities change over time. The ability to sensitively track these changes would allow for clinicians and researchers to monitor progression of disease, changes to an individual's

functional status, or monitor the efficacy of prescribed interventions.

2.2.4 Fall risk in daily life

Measures of gait stability in laboratory or clinical settings are only able to provide information about a person's gait at the specific time of day and environment in which the testing occurs. Since many falls occur in and around the home [21], it is of interest to measure gait stability in these complex real-world environments under normal daily-life conditions. Previous studies using wireless sensors to monitor gait of aging adults in at-home settings have shown that at-home monitoring is able to better differentiate fallers from non-fallers [38] and more accurately predict prospective falls [39] compared to standard clinical assessments. The long-term goal of this line of research is to measure gait stability during walking outside of a laboratory in real world environments. *It is currently not clear if a wireless sensor-based method of measuring segmental relationships will be sensitive and robust enough to measure fall risk during short bouts of overground walking (Aim 3).* Therefore, the current project includes an intermediate step of testing the gait stability index during short bouts of overground walking in the laboratory setting. However, measuring gait and balance outside of a laboratory setting is inherently challenging, as data is collected under less controlled conditions, and walking bouts are variable in length with many direction changes and complexities in the environment. Therefore, it is necessary to examine the gait stability index over an increasing number of short bouts of walking to determine how much walking data is appropriate for accurate differentiation of fallers from non-fallers.

2.3 Summary

- The relationship between the CoM and BoS is important for maintaining stability during walking.

- Altered sensorimotor communication in PwMS may impact this relationship and change dynamic balance.
- Measuring this relationship via the gait stability index may provide a useful measure of fall risk and stability that is related to disease specific physiology in PwMS.
- Testing the gait stability index during short bouts of overground walking will determine feasibility for monitoring gait in at-home environments.

2.4 Innovation

The current project proposes that relationships between variability at the trunk and at the feet are representative of stability and fall risk during walking. This innovative approach combines two established concepts of gait stability from previous literature: 1) Movement variability is reflective of the level of control and adaptability of the sensorimotor system [40, 41] and 2) Coordination between the base of support and the center of mass is fundamental for stability during walking [16, 42]. The current study combines these concepts to examine variability of foot movement (base of support) and trunk movement (center of mass) and quantify the relationship between them by calculating the gait stability index. To our knowledge, this is the first analysis technique which considers the variability of upper and lower body motion simultaneously during walking to produce a single outcome measure.

A healthy sensorimotor system is able to achieve a gait pattern that optimizes the interaction between the BoS and CoM through control mechanisms constantly providing feedback from step to step [15]. In PwMS, the relationship between the trunk and foot segments is altered [43] due to problems with sensorimotor conduction [34] which decreases adaptability during challenged walking and likely leads to greater instability and increased fall risk. Our novel approach seeks to identify how relationships between movement variability at the trunk

and feet are maintained during normal and challenged walking, which is of particular interest in PwMS since we know their sensorimotor feedback is altered. By examining the gait stability index in a healthy population and in MS fallers and MS non-fallers, we will identify how segment relationships are maintained during walking and how these relationships relate to fall risk.

2.5 Preliminary Data

Segmental relationship in PwMS: The gait stability index was calculated for 40 MS subjects and 40 healthy control subjects during treadmill walking at preferred pace. Between group differences were found for 5 of the 6 gait stability indices in the frontal plane (Figure 2.1). The results demonstrate that the gait stability indices can identify altered relationships between trunk and foot motion, particularly in the frontal plane, for persons with MS compared to healthy controls. *However, we do not know how these relationships change in persons with MS when walking at different speeds or under different sensory input conditions.*

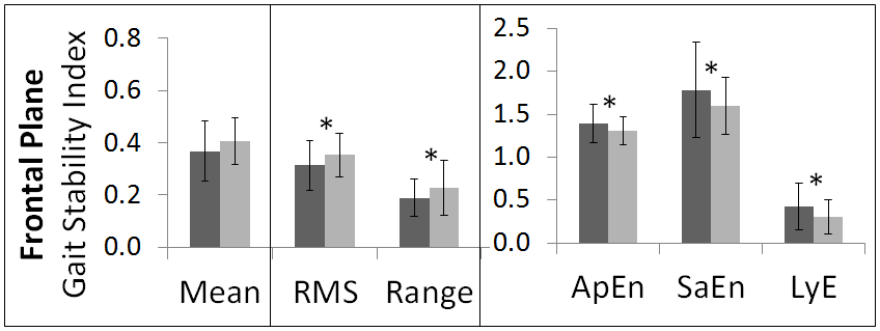

Figure 2.1. Gait Stability Index for healthy controls (gray) and MS (black). *Sig diff, $p<0.05$. RMS-root mean square, ApEn-approximate entropy, SaEn-sample entropy, LyE-Lyapunov exponent.

Gait stability indices in healthy young and healthy elderly walking at different speeds: The gait stability indices were calculated for 20 healthy young and 20 healthy elderly adults during treadmill walking at 80-120 percent of their preferred walking speed. The gait stability indices for frontal plane acceleration were calculated using root mean square (RMS) and sample entropy (SaEn). Results (Figure 2.2) show that healthy young adults increase their gait stability index for RMS and decrease their gait stability index for SaEn in response to increasing walking speeds, while healthy elderly adults' gait stability indices do not adapt to changing walking speeds. These findings demonstrate that *different subject groups adapt to walking speed differently which may be related to group-specific physiological characteristics.*

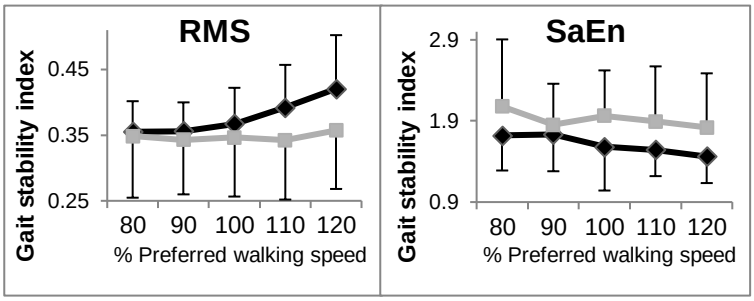

Figure 2.2. Frontal plane gait stability index across walking speeds in healthy young (Black line) and healthy elderly (gray line).

MS fallers and MS non-fallers have different physiological impairment: Physiological impairment based on sensorimotor delays and plantar vibration threshold was assessed in 27 MS fallers and 28 MS non-fallers [44]. Compared to non-fallers, fallers had higher vibration threshold (p=0.003) and longer sensorimotor delays (p=0.002) (Figure 2.3). These results show that *there are differences in physiological impairments between MS fallers and MS non-fallers.*

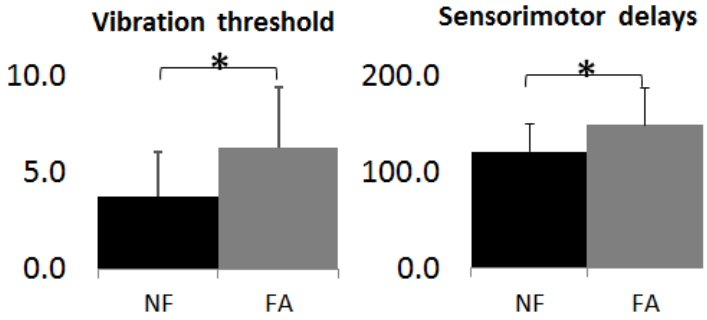

Figure 2.3. Vibration threshold and sensorimotor delays in MS non-fallers (NF, black) and fallers (FA, grey).

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3 Walking speed changes influence trunk and foot acceleration variability in persons with multiple sclerosis and in healthy controls

3.1 Abstract

Falling is a major problem for persons with multiple sclerosis (PwMS) but identifying individuals at risk of falling is difficult as the important characteristics of unstable gait in PwMS are not clear. The purpose of the current study was to determine how relationships between upper and lower segments movement variability are maintained across altered walking speeds and to determine if MS fallers and non-fallers adapt to speed changes differently. 25 MS non-fallers, 15 MS fallers, and 25 age-matched healthy controls participated in the current study. Subjects walked on a motorized treadmill at 80, 90, 100, 110, and 120% of their preferred walking speed for 90 seconds at each speed. Two wireless inertial measurement units recorded accelerations at their lumbar back and at the right foot during each walking trial. Variability of accelerations was quantified using root mean square (RMS), range, sample entropy (SaEn), and Lyapunov exponents (LyE). These variability measures were then used to calculate the gait stability index (GSI) which was taken as the ratio of lumbar acceleration variability divided by foot acceleration variability. MS fallers, MS non-fallers, and healthy controls increased their sagittal and frontal GSI_{RMS} ($p<0.01$) and frontal GSI_{Range} ($p<0.01$) with increasing walking speed, but MS fallers consistently maintained a lower ($p=0.014$) sagittal GSI_{RMS} across all walking speeds compared to healthy controls. Healthy controls also adapted their GSI_{SaEn} ($p<0.017$) in the frontal plane in response to walking speed, while none of the MS subjects demonstrated this adaptation. The current results demonstrate PwMS adapt their trunk and foot movement patterns differently to walking speed compared to healthy controls.

3.2 Introduction

Multiple sclerosis (MS) is an inflammatory demyelination disorder which affects over 400,000 persons in North America [1] and can cause a wide range of disabilities such as weakness, fatigue, altered cognition, visual impairment, and physical function deficits [2-5]. Approximately 80% of persons with MS (PwMS) report problems with walking and balance [6] with at least 50% of PwMS reporting at least 1 fall within a 6-month period [7]. PwMS who demonstrate worse disability as measured by clinical scales tend to also walk slower than both healthy control subjects and PwMS who do not report walking and balance problems [8]. Slower walking speed in PwMS may be a response to an increased fear of falling [9] with individuals who are afraid of falling adopting slower and more conservative gait strategies characterized by wider and shorter steps.

Walking speed can provide a simple measure of ambulatory function which is useful in functional screening across a range of populations [10-12]. However, previous studies have identified that other quantitative outcomes may provide more information about the mechanisms behind increased risk of falling during walking. Maki et al. previously showed that walking variability was more strongly related to an increased fall risk than was walking speed in older adults [9]. While a conservative gait strategy was adopted by fallers, stride to stride variability was shown to be an independent predictor of falls [9]. Previous studies have shown that compared to healthy controls, PwMS demonstrate larger amounts of variability in their step width [13], and smaller amounts of variability in their trunk sway [14] during walking. PwMS also demonstrate more predictable step length and step width [15], and less predictable trunk accelerations [14] compared to healthy controls. Examining variability of movement rather than only walking speed during walking may provide more specific information about an individual's

stability during walking, which could be useful for monitoring progression of disease or assessing fall risk.

Stability during walking can be defined as the ability to attenuate disturbances during walking and maintain upright functional gait [16]. In order to maintain stability, the body must control movement of the center of mass (CoM) and base of support (BoS) from step to step [17]. While previous work has shown that movement variability of the trunk or feet can be related to instability, the relationship between acceleration variability at these segments may be more powerful indicator of how total body stability is maintained during walking [18-20]. For example, one individual may demonstrate a larger amount of acceleration variability at the trunk compared to normal, but it's possible that this is coordinated with a compensatory amount of acceleration variability at the feet, and the result is an overall stable gait pattern. Previous work has shown that PwMS may have an altered relationship between CoM and BoS movement compared to healthy controls [19, 21], and that this altered relationship may be different between MS fallers and MS non-fallers [18, 21]. However, it is not clear how this relationship is maintained when gait is challenged under non-preferred walking speeds. Individuals are most stable when they are walking at their preferred walking speed and walking at speeds faster or slower than preferred speed can be challenging and inherently destabilizing [22, 23]. Healthy individuals demonstrate optimal stability at preferred walking speeds, while walking slower or faster than preferred speed resulted in less adaptability [22]. Similarly, slower walking speeds result in decreased instability compared to normal walking speed but also resulted in increased amounts of variability [23]. Since the relationship between acceleration variability at the trunk and at the feet may be a stronger indicator of whole body stability compared to examining only a single segment [19, 24], it is of interest to understand how this relationship is maintained under

challenging walking speeds. It is also of interest to evaluate whether PwMS adapt to speeds similarly compared to healthy controls which could illuminate mechanisms of increased falls in PwMS.

The purpose of the current study was to determine how relationships between upper and lower segment movement variability are maintained across altered walking speeds and to determine if MS fallers and non-fallers adapt to speed differently compared to healthy controls. Healthy controls demonstrate optimal control over their movements, and therefore their adaptations to walking speed will be considered optimal as well. However, it is possible that PwMS may not be capable of adapting to non-preferred walking speed in the same way as healthy controls. If this is the case, it is possible that the inability to appropriately maintain the relationship between upper and lower body movement during walking could be an underlying mechanism responsible for increased risk of falls in PwMS and that the inability to adapt to speeds would result in significant fall risk during daily life walking where speed changes are common. Therefore, we hypothesized that 1) the trunk and foot acceleration variability relationships will be different between healthy controls, MS fallers, and MS non-fallers, and 2) that PwMS will not adapt their relationships in response to speed in the same way that healthy controls do.

3.3 Methods

Forty persons with multiple sclerosis (15 fallers, 25 non-fallers) and 25 healthy age-matched adult controls (HC) participated in the current study. Subject demographic information is summarized in Table 3.1. The MS subjects were split up into MS non-fallers (MSN) who did not report any falls in the previous 12 months and MS fallers (MSF) self-reported 2 or more falls

in the previous 12 months [20, 25]. The University of Kansas Medical Center Human Research Committee approved this study and all participants gave informed written consent prior to testing. Exclusion criteria for PwMS and healthy controls included any additional neurological or orthopedic co-morbidities possessing the potential to alter balance or gait mechanics, female subjects who were currently or recently pregnant, history of vestibular disfunction, diabetes, or a pre-existing condition which could make exercising difficult (i.e. myocardial infarction, chest pain, unusual shortness of breath, congestive heart failure, etc.). PwMS were required to be able to walk a distance of 100 meters without the assistance of a mobility aid and could not be currently prescribed symptom specific medication therapies (i.e. Fampridine) which can directly affect gait. Additionally, PwMS were excluded if they had a Kurtzke Expanded Disability Status Scale (EDSS) [26] score greater than 5.5.

Subjects were fitted with two wireless inertial measurement unit sensors (Opal, APDM, Portland, OR, USA; 128 Hz) secured by elastic strap to the right ankle, lumbar spine. The right ankle inertial measurement unit was placed over the lateral surface of the lower shank, on the distal most point of the shank, superior to the ankle joint such that footwear would not cause any disturbance to the position of the sensor. The lumbar inertial measurement unit was placed on the posterior surface of the lumbar spine at the L4-L5 level. Subjects' preferred walking speed (PWS) was calculated from the average of three timed 10-meter walks overground at their normal comfortable pace. Subjects then completed five, 90-second walking trials on a treadmill (Woodway Bari-Mill, Eugene, OR, USA) at 80, 90, 100, 110, and 120% of their PWS while the accelerometers collected data for the duration of each trial. Speeds were presented in a randomized order, and all PwMS were required to take a 3-minute rest between each walking trial.

The acceleration time series from each sensor was translated from local Cartesian coordinates to resultant frontal and sagittal plane time series local to each sensor. This translation was carried out via a resultant vector calculation such that a resultant of two acceleration axes were taken as the respective sagittal or frontal plane local to each individual sensor. The frontal and sagittal planes were analyzed individually since control of movement in the frontal plane may use more active control mechanisms compared to passive control in the sagittal plane [27]. To account for differences in number of strides across different walking speeds, the middle 60 strides of each trial were selected for analysis [28, 29]. A custom Matlab program was used to calculate all variability measures. All subsequent analyses were performed on the resultant sagittal and frontal plane time series. Data was left unfiltered for appropriate analysis of time series characteristics [30].

Linear measures root mean square (RMS) and range were calculated from both the frontal and sagittal plane acceleration time series [19]. Root mean square was calculated as the square root of the mean of squares of the numbers in the time series and was used to quantify the dispersion of the acceleration traces. Range was calculated as the difference between the maximum and minimum acceleration values within the time series.

Nonlinear variability measures were used to quantify the temporal structure of variability within the time series, which provides information about how movement of the foot and trunk segments is controlled [31]. Sample entropy (SaEn) and Lyapunov exponents (LyE) were calculated from the foot and lumbar time series in the frontal and sagittal planes. A thorough explanation of sample entropy can be found in previous literature [31-34]. Methods for all variability calculations have been outlined in detail previously [19]. Time series specific time delay and embedding dimension were calculated using the Average Mutual Information

algorithm [31, 35, 36] and False Nearest Neighbors algorithm [31] respectively. Time delays ranged from 8 to 27. The median embedding dimension of 8 was used for LyE analysis.

The gait stability index (GSI) metrics were calculated as the ratio of lumbar acceleration (ACC) variability divided by foot acceleration (ACC) variability, for each of the 4 variability metrics (RMS, range, SaEn, LyE) in the frontal and sagittal planes [37].

$$Gait\ Stability\ Index = \frac{Lumbar\ ACC\ Variability_{Frontal\ or\ Sagittal}}{Foot\ ACC\ Variability_{Frontal\ or\ Sagittal}} \qquad \textbf{Eq. (1)}$$

Four GSI metrics were calculated in the frontal and sagittal planes: GSI_{RMS}, GSI_{Range}, GSI_{SaEn}, GSI_{LyE}, resulting in 8 GSI metrics total used in the statistical analysis. The GSI metrics are unitless measures to examine lumbar acceleration variability relative to foot acceleration variability within an individual subject. A GSI equal to 1 indicates that acceleration variability at the two segments is exactly equal, a GSI greater than one indicates more lumbar acceleration variability relative to foot acceleration variability, and a GSI of less than one indicates less lumbar acceleration variability relative to foot acceleration variability [37]. The accelerations were not normalized to subjects' walking speed since the GSI calculation uses a ratio of lumbar to foot acceleration variability and normalization of the accelerations would cancel out in the GSI calculation. Therefore, the calculation of the GSI metrics are not directly dependent on walking speed.

The Shapiro-Wilks normality test demonstrated that all data sets were normally distributed. To assess the effect of walking speed on the GSI metrics across groups, a 5 Speed (80, 90, 100, 110, 120% PWS) x 3 Group (HC, MSN, MSF) ANOVA was performed on each GSI metric. Post-hoc t-tests were used to explore significant main effects and interactions. Statistical significance was set at the $p<0.05$ level for all analyses.

3.4 Results

Speed Effects

The GSI_{RMS} showed a main effect of Speed in the sagittal ($F=22.443$, $p<0.01$) and frontal ($F=29.520$, $p<0.01$) planes (Figure 3.1). In the sagittal plane, GSI_{RMS} was significantly lower at the two slowest speeds than the three faster speeds; 80% vs. 100% ($p=0.014$), 90% vs 100% ($p<0.01$), 80% and 90% vs. 110% and 120% ($p<0.01$ for all comparisons). In the frontal plane, GSI_{RMS} was significantly lower at the two slowest speeds than the three faster speeds; 80% and 90% vs 100%, 110%, and 120% ($p<0.01$ for all comparisons). The GSI_{Range} showed a main effect of Speed in the sagittal ($F=5.738$, $p<0.01$) plane (Figure 3.1) but not the frontal plane ($F=4.026$, $p=0.051$), where the sagittal plane GSI_{Range} was higher for the two fastest speeds compared to the three slower speeds; 80% vs 110% ($p=0.029$) and 120% ($p<0.01$), 90% vs 110% and 120% ($p<0.01$), 100% vs 110% and 120% ($p<0.01$), 110% vs 120% ($p=0.025$). The GSI_{SaEn} showed a main effect of Speed in the sagittal ($F=3.181$, $p=0.015$) and frontal ($F=3.107$, $p=0.017$) planes (Figure 3.1) and a significant Group and Speed interaction in the frontal plane ($F=2.441$, $p=0.016$). Frontal plane GSI_{SaEn} was higher for the two slowest speeds compared to the three faster speeds in the HC group only; 80% vs 100% ($p=0.032$), 80% vs 110% ($p=0.030$), 80% vs 120% ($p<0.01$), 90% vs 120% ($p=0.012$). LyE demonstrated no main effect of Speed in the sagittal ($F=0.021$, $p=0.886$) or frontal ($F=1.689$, $p=0.200$) planes.

Group Effects

The GSI_{RMS} in the sagittal plane was the only GSI metric to show a main effect of Group ($F=4.686$, $p=0.014$), where the GSI_{RMS} was larger for HC compared to MSF for the 80% PWS ($p=0.023$) and 110% PWS ($p=0.026$) trials (Figure 3.1). No Group effects were found for frontal plane GSI_{RMS} ($F=0.400$, $p=0.673$), sagittal plane GSI_{Range} ($F=2.091$, $p=0.135$), frontal plane

GSI_{Range} (F=0.628, p=0.538), sagittal plane GSI_{SaEn} (F=0.521, p=0.598), frontal plane GSI_{SaEn} (F=0.958, p=0.392), sagittal plane GSI_{LyE} (F=0.016, p=0.984), frontal plane GSI_{LyE} (F=0.193, p=0.825).

3.5 Discussion

The purpose of the current study was to determine how relationships between upper and lower segment movement variability are maintained across altered walking speeds and to determine if MS fallers and non-fallers adapt to speed differently compared to healthy controls. Our first hypothesis regarding differences between groups was partially supported, as we found that the GSI_{RMS} and the GSI_{Range} was significantly larger for HC compared to MSF at two of the walking speeds. Our second hypothesis regarding the effect of Speed was also partially supported as the GSI_{SaEn} results demonstrated that the MS subjects did not adapt their segment relationships to speed, while the HC group did show an adaptation speed. However, all subjects adapted their GSI_{RMS} and GSI_{Range} similarly to speed, indicating that the amount of acceleration variability at the trunk and feet adapted to speed similarly across the three groups.

The GSI_{RMS} and GSI_{Range} increased in response to faster walking speeds similarly in all three groups. This indicates that while magnitudes of acceleration at the trunk and at the feet are likely increasing with faster walking speeds, the acceleration variability at the trunk is increasing at a faster rate relative to the accelerations at the feet. Previous studies have shown than trunk accelerations increase as walking speed increases [38]. The results of the current study show in HC and PwMS that trunk acceleration variability increases more than foot acceleration variability as walking speed increases. There was also an effect of group in GSI_{RMS} in the sagittal plane, with MSF having a lower GSI_{RMS} compared to HC. This finding indicates that MSF may

constrain their trunk motion more compared to HC during walking which follows the findings that fall-prone subjects adopt a conservative gait strategy [39]. By reducing motion of the trunk within the base of support, individuals who are unstable or have a fear of falling can spend more time with their CoM within their BoS in an effort to increase stability [13, 39]. In contrast to the MSF group, HC subjects appear to allow for larger amounts of trunk accelerations relative to foot accelerations during walking. It is possible that healthy controls can leverage the momentum of their upper body segment and safely use it for added efficiency towards movement in the sagittal plane. Ceccato et al. previously showed that the trunk segment's erector spinae musculature activates in anticipation of the propulsive stepping events during walking, further suggesting that gait involves whole body control across upper and lower body segments [40]. Future studies should further investigate the role of upper body movement in forward propulsion during walking in healthy controls and individuals with movement disorders.

While the GSI_{RMS} and GSI_{Range} results showed that all groups adapted to speed similarly, the GSI_{SaEn} results demonstrated that MSN and MSF groups adapted to speed differently compared to the HC group. Specifically, MSN and MSF subjects showed no effect of speed, while HC demonstrated a decrease in their frontal plane GSI_{SaEn} at faster walking speeds. A decrease in GSI_{SaEn} indicates that the SaEn values at the trunk are decreasing relative to the SaEn values at the feet, signifying more regular motion at the trunk relative to more irregular motion of the feet in the frontal plane. A recent study has shown that healthy controls demonstrate increased SaEn of foot accelerations with increased walking speed [41]. The speed-dependent behavior in the frontal plane aligns with the understanding that there is a greater demand on the neuromuscular control systems to maintain stable walking at faster speeds [41]. The demand on neuromuscular control would be considerably important in the frontal plane, as movement in this

plane is considered to be controlled by more active feedback mechanisms [27, 42]. The results of the current study seem to indicate that PwMS are not able to make a similarly appropriate adaptation to their walking at different speeds since we know healthy controls demonstrate optimal variability [43]. PwMS have altered feedback control between upper and lower segments [19, 21, 44, 45] so this lack of feedback control and decreased adaptability may be a fundamental underlying characteristic of walking in MS which negatively impacts their ability to maintain stability during normal walking and when faced with any type of perturbation or challenging walking condition.

One limitation is that the walking tests were performed on a motorized treadmill. Treadmill walking may reduce variations in speed since the walking speed is controlled and maintained over each individual trial. However, it was necessary to control specific speeds in order to accurately test the effect of speed on the GSI metrics. While the GSI metrics may demonstrate different results during overground walking, it is likely that the trends observed in the current study from treadmill walking would remain similar during overground walking. A second limitation is that the current study only examined walking at 80% - 120% of preferred walking speed, and more extreme speeds such as 70% or 130% may have revealed more significant differences in the GSI metrics between groups. However, the range of speeds selected in the current study were used to ensure that all subjects could safely complete testing, as using more extreme walking speeds may be too challenging for some individuals. It should also be noted that the MS subjects enrolled were fully ambulatory and caution should be taken in translating the current results to a wider population of MS subjects with worse balance or gait disability or different types of functional deficits.

Controlling the relationship between trunk and the foot motion during walking is an important role of the neuromuscular control system for maintaining stability. The results of the current study demonstrate that as walking is challenged by faster speeds, PwMS maintain lower acceleration variability magnitudes at the trunk relative to the feet, and accelerations at their feet become more regular relative to their trunk, compared to adaptations shown in healthy controls. While both healthy controls and PwMS adapted their trunk and foot acceleration variability magnitudes with increasing walking speed, MSF subjects consistently maintained a lower amount of acceleration variability at their trunk relative to their feet across all walking speeds, demonstrating a conservative gait compared to the healthy controls. Additionally, PwMS did not demonstrate any adaptation in the irregularity of their trunk and foot accelerations with increasing walking speeds. The GSI metrics used in the current study were able to characterize differences in segmental relationships and walking speed adaptations in healthy controls and PwMS with and without falls. Future studies will determine which of these GSI metrics are appropriate for use in fall risk screening in clinical or daily-life settings.

3.6 Tables and Figures

Table 3.1. Summary of subject demographics.

	Healthy Controls N = 25	MS Non-fallers N = 25	MS Fallers N = 15
Age	41 (8.5) yrs	44 (9.9) yrs	48 (9.6) yrs
M / F	7 / 18	5 / 20	7 / 8
BMI	44.3 (7.7)	47.5 (11.4)	47.5 (10.3)
EDSS	N/A	3.3 (1.9)	4.4 (1.1)
Preferred Walking Speed	1.33 (0.14)	1.24 (0.20)	1.00 (0.33)
Falls in previous 12 months	0	0	3.75 (1.7)

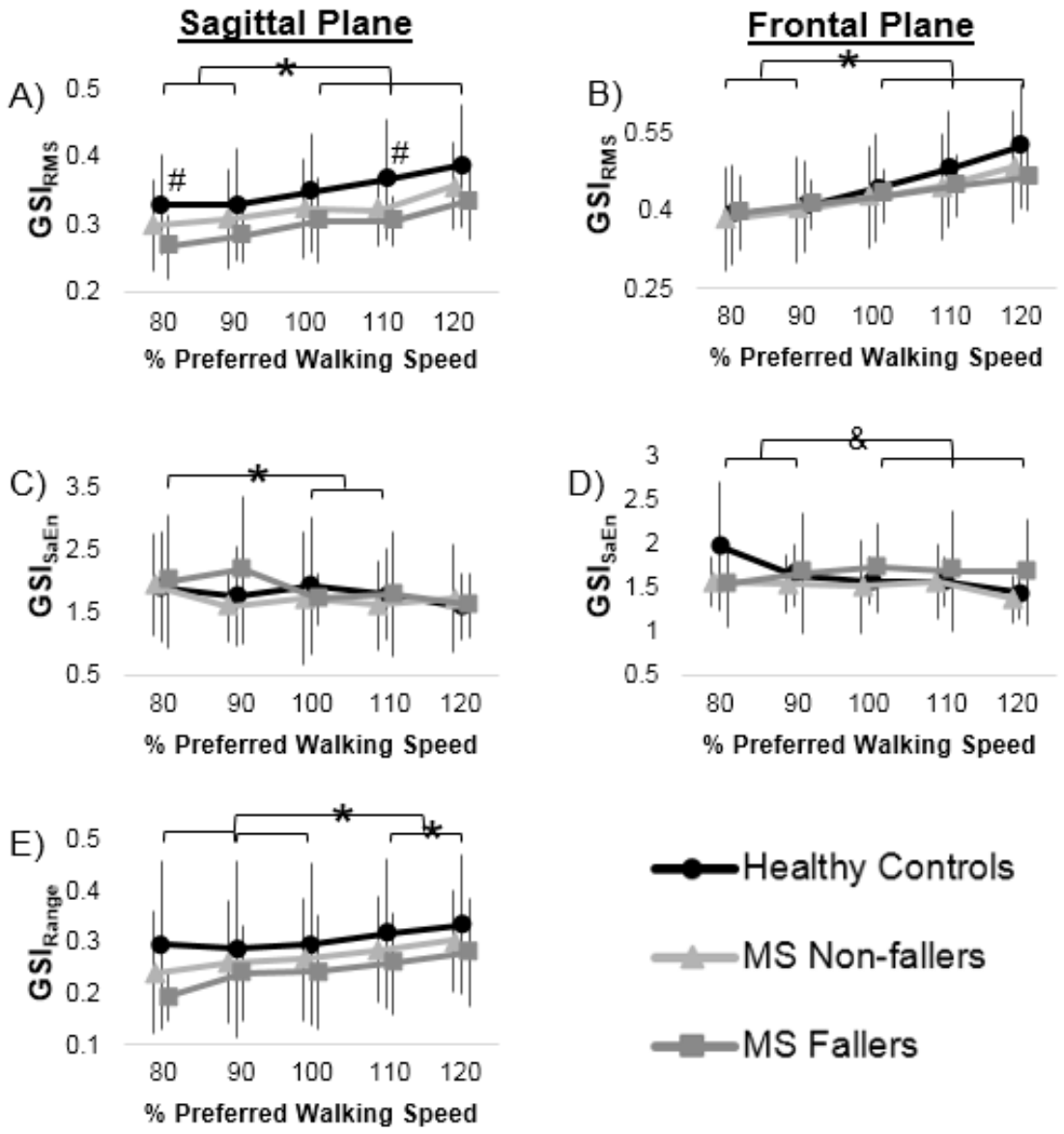

Figure 3.1. Means and standard deviations for GSI metrics. A) Sagittal plane GSI_{RMS}, B) Frontal plane GSI_{RMS}, C) Sagittal plane GSI_{SaEn}, D) Frontal plane GSI_{SaEn}, E) Sagittal plane GSI_{Range}. Main effect of Speed *; Interaction - effect of Speed in HC only &; Main effect of Group #.

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4 Altered visual and somatosensory feedback affects gait stability in persons with multiple sclerosis

4.1 Abstract

Persons with multiple sclerosis (PwMS) often report problems due to sensory loss and have an inability to appropriately reweight sensory information. Both of these issues can affect individual's ability to maintain stability when walking under challenging conditions. The purpose of the current study was to determine how gait stability is adapted when walking under challenging sensory conditions where vision and somatosensation at the feet is manipulated**.** 25 healthy adults and 40 PwMS (15 fallers, 25 non-fallers) walked on a treadmill at their preferred normal walking speed under 3 conditions: normal walking, altered vision using goggles that shifted visual field laterally, and altered somatosensation using shoes with compliant foam soles. Inertial measurement united recorded acceleration at the lumbar and right ankle, and acceleration variability measures were calculated including root mean square (RMS), range, sample entropy (SaEn), and Lyapunov exponents (LyE). A gait stability index (GSI) was calculated using each of the four variability measures as the ratio of lumbar acceleration variability divided by foot acceleration variability in the frontal and sagittal planes. The sagittal and frontal GSI_{RMS} were larger in the somatosensory condition compared to the normal and visual conditions ($p<0.001$). The frontal GSI_{SaEn} was greater in the visual condition compared to the somatosensory condition ($p=0.021$). The frontal and sagittal GSI_{LyE} was greater in the somatosensory condition compared to the normal and visual conditions ($p<0.002$). The current study showed that HC, MSN and MSF subjects largely adapted to altered sensory feedback during walking in a similar manner. However, MSF subjects may be more reliant on visual feedback compared to MSN and HC subjects.

4.2 Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system, which can result in a wide range of disability and disrupt signaling throughout the brain and spinal cord [1]. Persons with MS (PwMS) often report functional deficits and disabilities related to any combination of cognition, somatosensation, vision, and gait and balance function [2, 3]. Gait and visual function have been identified as the two most valuable areas of physical function by MS patients [4]. Approximately 80% of PwMS report problems with walking and balance [5], and 50% of PwMS experience at least 1 fall per year [6]. During walking, stability is maintained through constant interaction between the base of support (BoS) and center of mass [7], driven by sensory feedback and motor output controlled by the sensorimotor system [8, 9]. Vision, proprioception, and information from the vestibular system can be tuned and reweighted as necessary due to changes in environment in order to maintain balance [9, 10]. For example, when standing or walking altered visual input, feedback from proprioception and the vestibular system becomes more relied upon [11-13]. While sensory reweighting has been studied in PwMS during quiet standing [14, 15], it is not clear how PwMS adapt their walking under challenging sensory conditions.

Visual disturbances occur in up to 85 percent of PwMS, often due to inflammation or demyelination of the optic nerve [16]. These disturbances in the optic nerve can cause symptoms such as dimmed or altered visual fields, loss of vision, abnormal eye movements, and double vision [16]. Previous studies have shown that impaired vision negatively influences balance in PwMS and is a risk factor for increased risk of falls [17]. The Romberg ratio, a measure relating to reliance on visual feedback during standing sway, has been shown to be related to disability level and fall risk in PwMS [18]. Persons with moderate to severe MS demonstrate a greater

reliance on visual feedback during standing compared to those with mild disability [18]. When visual information is removed or altered, the sensorimotor system must compensate using proprioceptive feedback and information from the vestibular system to maintain balance. This sensory reweighting is an important aspect of stability control, and PwMS may have a decreased ability to appropriately reweight sensory information between the visual, somatosensory, and vestibular systems compared to healthy adults [14, 15].

Altered or loss of sensory feedback from the lower extremity is common in PwMS and results in symptoms such as tingling or numbness [19, 20]. Subjects who report such symptoms often present with altered walking mechanics in order to compensate for the altered sensation, which is typically characterized as a conservative gait strategy presenting with shorter and wider steps and resulting in an overall slower walking speed [21]. Previous studies have tested the effects of altering lower extremity somatosensation during quiet standing by having subjects stand on a foam pad [22, 23] which reduces the pressure and proprioceptive feedback from the lower extremity, and altering this somatosensory information results in a larger sway area in PwMS [24]. While standing on a foam pad provides information about sensory reweighting during standing [9, 22, 23], it is not clear how PwMS adapt to altered sensory information during walking. However, since the majority of falls occur during walking [25, 26], and altered or diminished sensorimotor feedback can lead to increased fall risk, it is important to understand how PwMS adapt to walking under challenged sensory conditions.

Maintaining stability during walking involves a controlled relationship between the BoS and CoM. Acceleration variability from the trunk and foot segments can provide information about how movement is being controlled at these individual segments [27-29]. Therefore, the purpose of the current study was to determine how the relationships between trunk and foot

acceleration variability are adapted when walking under challenging sensory conditions. The current study uses an analysis of the relationship between trunk and foot acceleration variability called the gait stability index [30]. Since healthy adults demonstrate optimal variability [29] and will optimally adapt their walking under challenging conditions, we hypothesized that healthy adults will adapt their GSI metrics under the challenging visual and somatosensory conditions, but PwMS with and without falls will not demonstrate similar adaptations.

4.3 Methods

Forty PwMS (15 fallers, 25 non-fallers), and 25 age matched healthy controls participated in the current study. MS fallers were selected as PwMS who self-reported 2 or more falls in the previous 12 months [31, 32]. All participants gave informed written consent prior to testing, and all study protocols were approved by the University of Kansas Medical Center Human Research Committee. Subjects were excluded if they had any orthopedic or neuromuscular co-morbidities that could affect their walking or balance, history of vestibular disfunction, diabetes, women who were currently or recently pregnant, or any pre-existing conditions that could make exercise dangerous such as myocardial infarction, chest pain, unusual shortness of breath, etc. MS subjects were excluded if they were currently prescribed symptom specific medication (i.e. Fampridine) which can affect gait, or if they were unable to walk at least 100 meters without rest or use of a mobility aide. Any PwMS with a Kurtzke Expanded Disability Status Scale (EDSS) greater that 5.5 [19] were also excluded from the study.

Wireless inertial measurement units (Opal, APDM, Portland, OR, USA) were placed on the subjects' right ankle and lumbar spine. The right ankle inertial measurement unit was placed over the lateral surface of the distal shank, just superior to the ankle joint. The lumbar inertial

measurement unit was placed over the posterior surface of the lumbar spine at the L4-L5 level [33]. To determine subjects' preferred walking speed, subjects were timed while walking over a 10-meter walkway at their normal comfortable speed, and an average of three trials was used to calculate their preferred walking speed [34]. Subjects were then asked to walk on a treadmill at this preferred walking speed for three individual trials of 90 seconds each, with the wireless inertial measurement units recording at 128 Hz for the duration of each trial. The first trial was the normal walking condition where subjects walked on the treadmill with not sensory input manipulation. The second trial was the altered vision condition where subjects walked at their preferred speed while wearing glasses with a prism film (Press-On Prism, 30 degrees, 3M Health Care, St. Paul, MN, USA) that shifts gaze by approximately 30 degrees which has been shown to significantly alter spatial and temporal walking parameters during gait [35]. The prism glasses were large enough to fit comfortably over any subjects' personal prescription glasses. The third and final walking trial was the altered somatosensory condition where subjects walked at the preferred speed while wearing shoes with 2" of dense foam [22] (2.8 lbs/ft^3, Foam Factory Inc, Milford, MI, USA) affixed to their soles which deforms and does not greatly change subject height. Standing on dense foam has been shown to significantly alter somatosensory input and alter postural sway parameters [22, 23].

The acceleration time series from each sensor was translated from local Cartesian coordinates to resultant frontal and sagittal plane time series local to each sensor. The frontal and sagittal planes were analyzed individually since movement in each of these planes during walking may use different control strategies, with frontal plane using more active control and sagittal plane using more passive mechanisms [36]. To account for differences in number of strides across different walking speeds, the middle 60 strides of each trial were selected for

analysis [37, 38]. A custom Matlab program (Matlab version R2013b, The MathWorks Inc., Natick, MA, USA) was used to calculate all variability measures. All subsequent analyses were performed on the resultant sagittal and frontal plane time series, and data was left unfiltered for appropriate analysis of time series characteristics [39].

Root mean square was calculated as the square root of the mean of squares over all data points in the time series and was used to quantify the average dispersion of the acceleration traces [33]. Range was calculated as the difference between the maximum and minimum acceleration values within the time series and was used to quantify the absolute spread of acceleration data across the entire time series [33]. These linear variability measures overall quantified the magnitude or amount of acceleration variability present in the respective time series.

Nonlinear variability measures Sample entropy (SaEn) and Lyapunov exponents (LyE) were used to quantify the temporal structure of variability within the time series, providing information about how movement of the foot and trunk segments is controlled [40]. A thorough explanation of SaEn and LyE and their calculation can be found in previous literature [33, 40-43]. Time series specific time delay and embedding dimension were calculated using the Average Mutual Information algorithm [40, 44, 45] and False Nearest Neighbors algorithm [40] respectively. Time delays ranged from 8 to 27. The median embedding dimension of 8 was used for the LyE analysis.

The gait stability index (GSI) metrics were calculated as the ratio of lumbar acceleration (ACC) variability divided by foot acceleration (ACC) variability, for each of the 4 variability metrics (RMS, range, SaEn, LyE) in the frontal and sagittal planes [46].

$$Gait\ Stability\ Index = \frac{Lumbar\ ACC\ Variability_{Frontal\ or\ Sagittal}}{Foot\ ACC\ Variability_{Frontal\ or\ Sagittal}} \qquad \textbf{Eq. (1)}$$

Four GSI metrics were calculated in each plane using each of the four variability measures: GSI_{RMS}, GSI_{Range}, GSI_{SaEn}, GSI_{LyE}, resulting in 8 GSI metrics total used in the statistical analysis. The GSI metrics are unitless and used to examine lumbar acceleration variability relative to foot acceleration variability within an individual subject. A GSI equal to 1 indicates that acceleration variability at the trunk and foot segments are exactly equal, a GSI greater than one indicates more lumbar acceleration variability relative to foot acceleration variability, and a GSI of less than one indicates less lumbar acceleration variability relative to foot acceleration variability [46].

To assess the effect of altered sensory conditions on the GSI metrics across groups, a 3 Condition x 3 Group ANOVA was performed on each GSI metric. Post-hoc t-tests were used to explore significant main effects and interactions. Statistical significance was set at the $p<0.05$ level for all analyses, and all analyses were completed in SPSS 2013 (version 22, IBM Corp., Armonk, NY).

4.4 Results

GSI_{RMS} showed a main effect of Condition in the frontal ($F=17.982$, $p<0.001$) and sagittal ($F=26.635$, $p<0.001$) planes, where the GSI_{RMS} in the somatosensory condition was greater than in the normal ($p<0.001$) and visual ($p<0.001$) conditions (Figure 4.1 A and B). GSI_{SaEn} showed a main effect of Condition in the frontal plane ($F=4.344$, $p=0.016$), where the GSI_{SaEn} in the visual condition was greater than in the somatosensory condition ($p=0.021$) (Figure 4.1 C). GSI_{LyE} showed a main effect of Condition in the frontal ($F=11.770$, $p<0.001$) and sagittal ($F=17.462$) planes, where the GSI_{LyE} was greater in the somatosensory condition than in the normal condition ($p<0.002$) and visual condition ($p<0.001$) (Figure 4.1 B and C). GSI_{LyE} also showed a

significant interaction between Group and Condition in the sagittal plane ($F=3.188$, $p=0.016$), where HC and MSF showed larger GSI_{LyE} in the somatosensory condition compared to the normal ($p<0.008$) and visual ($p<0.018$) conditions, and only MSF showed a larger sagittal plane GSI_{LyE} in the visual condition compared to the normal condition ($p=0.001$) (Figure 4.1 D). There were no significant main effects of Group found for any GSI metrics.

4.5 Discussion

The purpose of the current study was to determine how the relationships between trunk and foot acceleration variability are adapted when walking under challenging sensory conditions. Our results show that there was an effect of Condition indicating that HC, MSN, and MSF all adapted to the challenging sensory conditions. There was one GSI metric which revealed an adaptation during the visual condition which was made only by MSF group in the sagittal plane. There were no main effects of Group found for any of the GSI metrics during any of the conditions which indicates that all three groups adapted relatively similarly to the changing sensory conditions.

The GSI_{RMS} results in the frontal and sagittal planes showed that accelerations were larger at the trunk relative to the feet during the altered somatosensation condition compared to the visual and normal conditions across the three groups. Previous studies have shown that individuals with loss of sensation in their lower extremity adapt their walking to maintain a more conservative gait strategy characterized by shorter and wider steps [21, 47]. The goal of a conservative gait strategy is to contain the CoM more within the BoS in order to have a larger safety margin in case of a perturbation such as a trip of a slip, therefore it may be expected that the GSI_{RMS} would decrease with the adoption of a conservative gait. However, the results of the current study show that the trunk accelerations relative to the foot accelerations are larger in the

somatosensory condition compared to the normal condition across all groups. A post-hoc analysis of the individual trunk and foot segment accelerations showed that the trunk and foot accelerations both showed an increased RMS in the somatosensory condition (Figure 4.2). Together, these results demonstrate that while whole body accelerations increased during the somatosensory condition, the trunk accelerations relative to the foot accelerations are still larger in the somatosensory condition compared to the normal walking condition. Altered somatosensory feedback likely results in an altered sense of the body CoM position relative to the ground and surrounding environment, which has been previously shown to be related to worse dynamic stability and falls in PwMS [21, 48]. Healthy adults have been shown to walk with increased hip, knee, and trunk range of motion when walking on a compliant surface, increasing foot clearance during walking [49]. While the need to raise the foot higher may partly be due to the physical demands of walking on a compliant surface, previous studies have shown similar adaptations made by individuals who have worse somatosensation [50, 51], and individuals who have plantar sensation experimentally altered [52]. It is also possible that these adaptations in the gait pattern serve to increase amplitudes of proprioceptive feedback in other areas such as the knees and hips to compensate for the altered plantar pressure and ankle proprioception feedback [53].

The GSI_{SaEn} results showed that in the frontal plane, trunk accelerations were more irregular relative to foot accelerations in the visual condition compared to the somatosensory condition. However, the GSI_{LyE} in the frontal and sagittal planes showed the trunk accelerations were more predictable compared to the foot accelerations in the visual condition compared to the somatosensory condition. Together these results indicate that when visual information is not reliable during walking, trunk accelerations may be actively constrained so that small

perturbations can be quickly attenuated in order to minimize movement and provide a stable base for the neck and head. This attenuation could result in increased irregularity in trunk movement over repeating cycles as demonstrated by the altered GSI_{LyE}. Previous studies have similarly shown that altering visual information can lead to constrained trunk movement in order to minimize motion of the trunk segment and to maintain a cautious gait [35, 54]. Additionally, the results for the MSF group showed that across the three conditions, the sagittal GSI_{LyE} was smallest in the normal walking condition and significantly increased in both the visual condition and somatosensory condition. The MSF group was the only group that demonstrated a larger sagittal GSI_{LyE} in the visual condition compared to the normal condition. This may highlight that the MSF group is more reliant on their visual feedback to maintain stability and therefore is more affected by altered visual feedback than MSN and HC. This finding is in parallel to previous studies which have shown that fall-prone PwMS who have somatosensory loss become heavily reliant on their visual information during quiet stance, become more unstable when vision is altered [15]. The current results seem to indicate a similar reliance on visual information during walking in the MSF group.

Since PwMS have been shown to have altered ability to reweight sensory information during quiet stance [14, 15], it was expected that the MS subjects would show different adaptations to challenging sensory conditions during walking compared to healthy adults. However, the GSI metrics in the current study largely showed no main effects of Group. One possible explanation is that the GSI metrics are designed to study whole body stability during walking and all subjects were fully ambulatory and able to maintain stable gait since there were no subjects who fell during testing. Therefore, since subjects remained stable in all three conditions, it can be expected that the GSI metrics would reflect similar adaptations across all

groups. It is also possible that there may be differences between how these groups adapt to the challenging sensory conditions that were not able to be observed using the GSI metrics. For example, Killeen et al. showed that altered visual feedback resulted in changes to minimal toe clearance in older adult subjects but not in healthy young subjects, where older adults increased their minimum toe clearance during the challenging condition [55]. Similar toe-clearance adaptations, for example, may occur in PwMS and future studies should examine other outcome measures to further determine if PwMS adapt to walking in challenging sensory conditions similar to healthy adults.

There are some limitations in the current study that should be noted. First, a treadmill was used in order to record sufficiently long time series for analysis, and while many previous studies have used treadmill gait for similar variability analyses [33, 56-58], there have been few studies which introduced challenging sensory conditions on a treadmill. It is possible that the lack of visual flow, constrained walking speed, and constrained walking path on the treadmill masked some variability that may be observed in overground walking. However, it is expected that trends similar to those observed in the current study would be observed during overground as well. A second limitation is that while walking on compliant foam does alter sensory feedback, it may also alter some physical mechanics of walking which are not solely due to altered sensory information such as the need to raise the foot higher. However, it is likely that these physical changes are minimal relative to the altered sensations of the foam shoes inducing altered gait characteristics. Finally, it is important to consider that all MS subjects in the current study were ambulatory without the need for an assistive device. Since MS can present in a wide range of symptoms which may or may not result in walking and balance deficits, it may be of interest in

future studies to identify specific functional deficits in a larger cohort of MS subjects that may be linked with an inability to appropriately adapt in challenging conditions.

During walking, visual, vestibular, and somatosensory feedback is integrated and used to help monitor where the body is relative to the surrounding environment in order to maintain upright balance during standing and walking. When one of the three sensory modes is altered, more weight can be placed on the others to compensate and maintain reliable sensory feedback though the system may still demonstrate instability or changes in the walking pattern due to the altered sensory feedback. The current study showed that HC, MSN and MSF subjects largely adapted to altered sensory feedback during walking in a similar manner. However, MSF subjects may be more reliant on visual feedback compared to MSN and HC subjects. Future studies should determine if specific symptomology or functional deficits in PwMS make adaptations more difficult when walking under altered sensory conditions and should further explore gait adaptations to challenging sensory conditions using other types of outcome measures.

4.6 Tables and Figures

Table 4.1. Summary of subject demographics.

	Healthy Controls N = 25	MS Non-fallers N = 25	MS Fallers N = 15
Age	41 (8.5) yrs	44 (9.9) yrs	48 (9.6) yrs
M / F	7 / 18	5 / 20	7 / 8
BMI	43.7 (8.3)	46.9 (8.7)	53.4 (6.5)
EDSS	N/A	3.3 (1.9)	4.4 (1.1)
Falls in previous 12 months	0	0	3.75 (1.7)

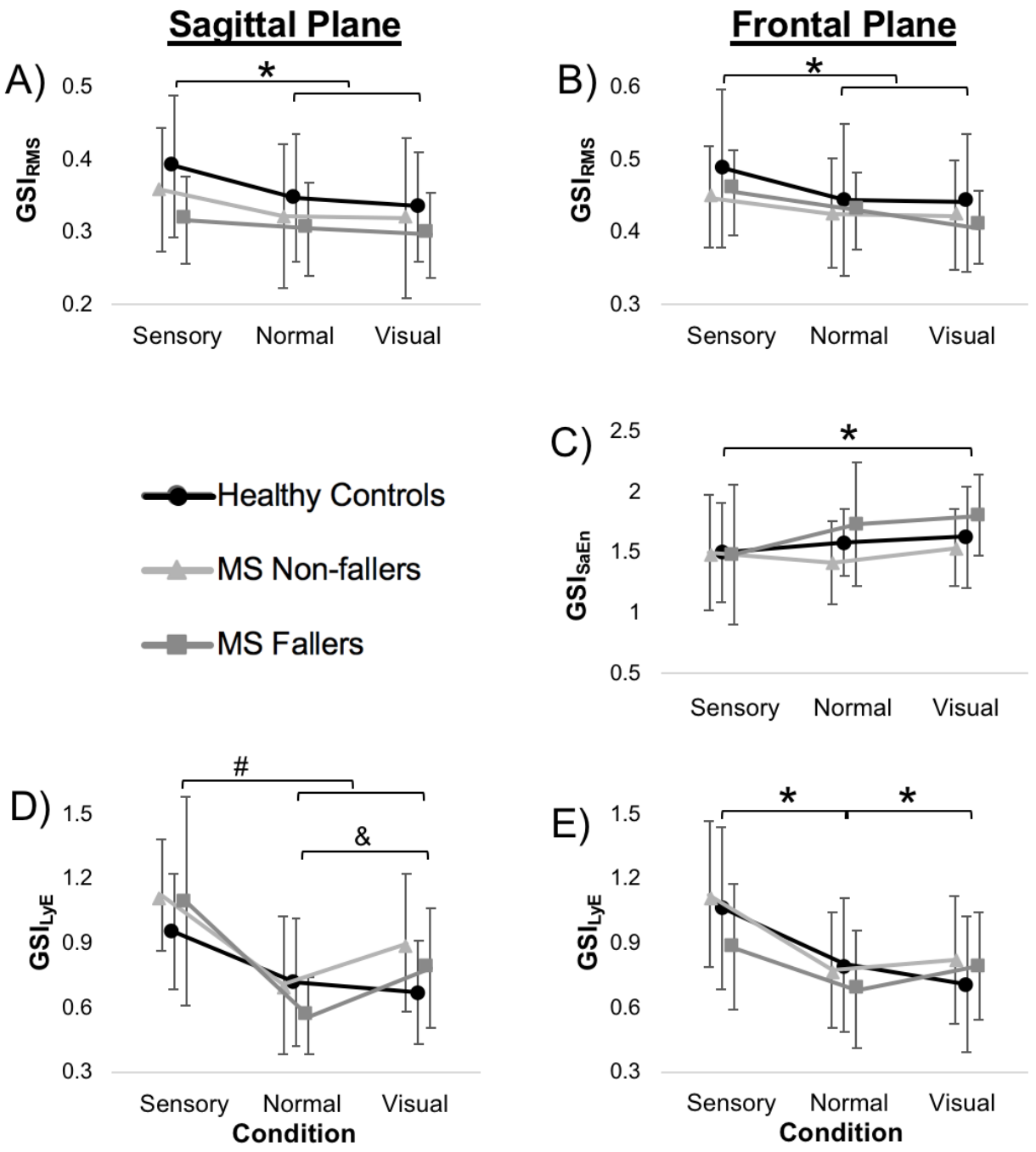

Figure 4.1. Means and standard deviations for GSI metrics. A – Sagittal plane GSI_{RMS}, B – Frontal plane GSI_{RMS}, C – Frontal plane GSI_{SaEn}, D – Sagittal plane GSI_{LyE}, E – Frontal plane GSI_{LyE}. Effect of condition for: all groups *; healthy controls and MS Fallers #; MS Fallers only &.

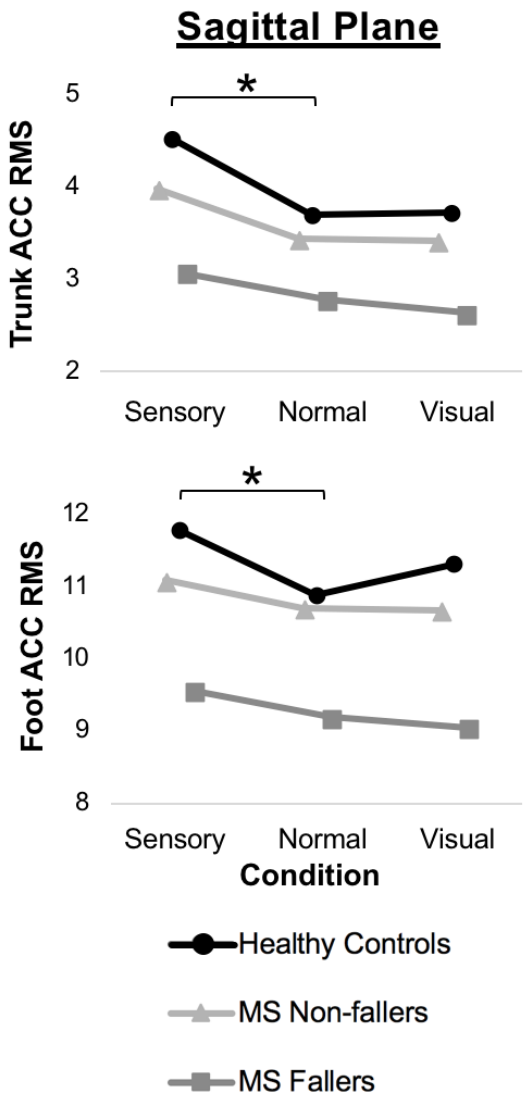

Figure 4.2. Root mean square of individual trunk and foot accelerations during the three walking conditions. Effect of condition all groups *, $p<0.01$.

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5 The gait stability index is related to fall history and clinical disability in persons with multiple sclerosis

5.1 Abstract

Persons with multiple sclerosis (PwMS) are often at higher risk for falling, but clinical disability scales and fall risk questionnaires are subjective and don't provide specific feedback about why an individual is unstable. Relationships between trunk and foot acceleration variability, as represented by gait stability index (GSI) metrics, may provide sensitive and objective fall risk assessments which highlight how an individual's movement pattern is contributing to their instability. The purpose of this study was to determine if gait stability index metrics are related to physiological impairments, clinical disability scales, and mobility questionnaires in PwMS. 40 PwMS (including 15 PwMS with history of falls) walked on a treadmill at normal walking speed while trunk and foot accelerations were recorded with wireless accelerometers and variability measures were extracted and used to calculate the GSI metrics as a ratio of trunk acceleration variability divided foot acceleration variability. Subjects' sensorimotor delays and lower extremity vibration sensitivity were tested. Subjects also completed clinical disability scales (Guy's Neurological Disability Scale and Patient Reported Expanded Disability Status Scale) and mobility questionnaires (Falls Efficacy Scale, Activities Balance Confidence Scale, 12 Item MS Walk Scale). Multiple GSI metrics were significantly correlated with clinical measures of disability and mobility in MS (r=0.354-0.528), but no correlations were found for sensorimotor delays or lower extremity sensation. Multiple GSI metrics performed at least as well as clinical questionnaires for separating MS fallers from MS non-fallers. The results of the current study indicate that stability during gait, as measured by the GSI metrics, is related to disability and mobility outcomes in PwMS.

5.2 Introduction

Multiple sclerosis (MS) is an inflammatory demyelination disorder which disrupts neural signaling in the central nervous system resulting in a wide range of disabilities [1]. Approximately 80% of persons with MS (PwMS) report difficulty with walking and balance [2], and half of PwMS experience at least one fall per year [3]. Falling is a significant problem for PwMS as falls can lead to injury [4] and decreased activity which subsequently leads to deconditioning and worse quality of life [5]. Previous studies have shown that MS symptomology includes physiological deficits that can have an effect on the gait and balance function in PwMS [6-9]. PwMS have been shown to have delayed sensorimotor responses to standing surface translations compared to healthy controls [6, 8], with longer sensorimotor delays being shown to be related to larger standing sway area and larger sagittal plane trunk range of motion during walking [8]. PwMS also commonly experience altered or lost sensation in the extremities [10], with worse vibration sensation at the feet being shown to be related to worse dynamic stability during walking [9]. Because stability during walking involves a combination of physiological mechanisms, it is important to understand how these altered physiological mechanisms in PwMS are related to gait stability.

Current clinical outcomes for monitoring walking and balance deficits in PwMS include tests of walking speed such as the timed 25-foot walk and self-report questionnaires related to self-perceived functional status such as the Activities Balance Confidence scale [11]. Unfortunately, these assessments are often subjective and lack sensitivity, which limits their ability to accurately detect changes in function over time or predict risk of future falls [12, 13]. In addition, these questionnaires don’t specifically measure the source of an individual’s instability. Therefore, there is a need for objective assessments that can be used in the clinic or in

real-world environments to supplement patient outcomes and quantify risk of falls in PwMS. Such an objective assessment could be useful for monitoring progression of disease, efficacy of treatment, and tracking changes in walking function over time. Wireless inertial sensors have been growing in popularity as a feasible alternative for collecting data during walking in clinical and real-world settings [14, 15]. Previous studies using accelerometers have found that variability of accelerations can be a sensitive indicator of fall risk [16-19]. Van Schooten et al found that acceleration range and Lyapunov exponents significantly contributed to a model that predicted future falls with good accuracy [19]. These previous studies examined movement of individual segments during walking, however it is likely that whole body stability requires a controlled interaction between upper and lower body segments [15, 20]. Instead of evaluating only one body segment at a time to quantify stability, the gait stability index which examines acceleration variability at the trunk and at the foot segment simultaneously during walking to quantify whole body stability [20, 21].

The purpose of this study was to determine how the gait stability index metrics are related to physiological impairments, clinical disability scales, and mobility questionnaires in PwMS. Additionally, the current study determined if the gait stability index metrics are capable of separating MS fallers from MS non-fallers. Coordination of upper and lower body movement during walking may be controlled by underlying sensorimotor feedback within the central nervous system which has been shown to be altered in PwMS [6, 8, 22]. We hypothesize that 1) the GSI metrics will show moderate to strong correlations with measures of pathophysiology and self-report disability scales in PwMS, and 2) the GSI will more sensitively differentiate fallers from non-fallers compared to self-report mobility questionnaires.

5.3 Methods

5.3.1 Participants

The current study enrolled 25 PwMS with no fall history, and 15 PwMS with a history of 2 or more falls in the previous 12 months [23]. PwMS were excluded if they were currently prescribed symptom targeting medication (i.e. Fampridine) due to its proposed effect on gait, if they had experienced an MS symptom exacerbation in the previous 60 days that required treatment, or if they were unable to walk 100 meters without assistance or use of a walking aid corresponding to a Kurtzke Expanded Disability Status Scale (EDSS) score $\leq$ 5.5 [24]. Participants were excluded if they were not between 20 – 60 years of age, had vestibular impairments, diabetes, pre-existing conditions that could make exercise dangerous (i.e. myocardial infarction, chest pain, etc.). Female participants were excluded if they were pregnant, or within 3 months post-partum. Subjects were free of any additional diagnosed neurological or musculoskeletal impairment that could affect their balance or gait. All subjects gave informed written consent, and all study protocols were reviewed by the University of Kansas Medical Center Institutional Review Board. Demographic information for all subjects is listed in Table 5.1.

5.3.2 Treadmill Walking

Subjects wore two wireless inertial sensors (Opal sensors, APDM, Portland, OR, USA) secured by elastic straps during the entirety of testing. The lumbar sensor was mounted over the posterior surface of the lumbar spine at the L5 level, and the foot sensor was mounted on the lateral surface of the distal shank just superior to the ankle joint [25]. Subjects' comfortable walking speed was measured three times over a 10-meter walkway, and this preferred walking

speed was used as subjects' preferred walking speed on the treadmill (Woodway Bari-Mill, Eugene, OR, USA) [26]. Subjects completed one walking trial at this preferred speed on the treadmill while the wireless inertial sensors recorded at 128 Hz for 90-seconds.

The acceleration time series from each sensor was translated from local Cartesian coordinates to resultant frontal and sagittal plane time series local to each sensor. To account for differences in number of strides across subjects' walking speeds, the middle 60 strides of each trial were selected for analysis [27, 28]. Acceleration data was left unfiltered for accurate analysis of variability within the time series [29]. Linear and nonlinear variability metrics were calculated using custom Matlab programs (MATLAB version R2013b, MathWorks, Natick, Massachusetts, USA) to quantify the amount and the temporal structure of variability respectively [30-32]. Linear metrics included range and root mean square (RMS), nonlinear metrics included sample entropy (SaEn) and the maximum Lyapunov exponent (LyE). RMS was calculated as the square root of the mean of squares over the entire time series and was used to quantify the average dispersion of the acceleration traces. Range was calculated as the difference between the maximum and minimum acceleration values with the time series. LyE and SaEn are nonlinear variability measures which quantify the predictability and regularity of the cyclical gait pattern. Delay-embedded state spaces were reconstructed for each anatomical plane. Embedding dimensions were found using the global false nearest neighbor algorithm and the median of 8 was used for the LyE analysis [33]. Time delays for each individual subject were found using the average mutual information algorithm and ranged from 8 to 27. LyE was calculated using Wolf's algorithm which identifies the maximum LyE [33, 34]. SaEn was calculated using a vector length $m = 3$, and tolerance $r = 0.2$ (20% of the time series standard deviation) as these parameters were shown to have good relative consistency [25, 35].

The gait stability index (GSI) metrics were calculated as the ratio of lumbar acceleration (ACC) variability divided foot acceleration variability for each of the 4 variability measures (RMS, range, SaEn, LyE) in the frontal and sagittal planes [20]. Therefore, four GSI metrics were calculated in each plane using each of the four variability measures: GSI_{RMS}, GSI_{Range}, GSI_{SaEn}, GSI_{LyE}, resulting in 8 GSI metrics total used in the statistical analysis.

$$Gait\ Stability\ Index = \frac{Lumbar\ ACC\ Variability_{Frontal\ or\ Sagittal}}{Foot\ ACC\ Variability_{Frontal\ or\ Sagittal}} \qquad \textbf{Eq. (1)}$$

5.3.3 Sensorimotor Delays

Subjects stood on a servo-controlled motorized treadmill which was translated forward to cause a backward body sway [8]. The treadmill translated 4cm forward at a rate of approximately 15cm/s which elicited a step response from participants in order to regain balance. Surface electromyography (EMG) electrodes (Trigno Lab, Delsys Inc., Boston, MA) were placed bilaterally over the tibialis anterior. EMG signals were sampled at 1800Hz, amplified, band-pass filtered at 70-2000Hz. The participant's sensorimotor delay was measured as the time between the beginning of treadmill surface translation and the onset of muscle activity. Muscle activity onset was defined as EMG activity greater than 2 standard deviations above the resting average sustained for at least 50ms [6, 8]. The average sensorimotor delay was found from three trials including both legs for each MS subject [8].

5.3.4 Lower Extremity Sensation

Lower extremity vibrotactile sensation was measured using a Vibratron II (Physitemp Instruments, Clifton, NJ). Subjects were seated and asked to touch their big toe to two pedestal pedestals and say which one was vibrating. The vibration amplitude of the pedestals was

decreased until the subject could no longer feel the vibration which defined the vibration sensation threshold [36].

Lower extremity cutaneous sensation was measured using a monofilament test. Subjects were seated with eyes closed and a monofilament was pressed against the anterior surface of the foot, just proximal to the first metotarsophalangeal joint. Subjects were asked to raise their hand when they felt the touch on their foot. Testing began with the highest stiffness monofilament and proceed through 5 total filaments of decreasing stiffness until the subject could no longer feel the touch of the filament which defined a cutaneous sensation threshold of that monofilament's weight [37].

5.3.5 Clinical Disability Scales and Questionnaires

All MS subjects self-reported number of falls from previous 12 months, with 2 or more falls categorizing them as faller [23]. Disability status was assessed using the patient reported EDSS [38], and the Guy's Neurological Disability Scale [39]. Subjects also completed the Falls Efficacy Scale-International (FES-I), Activities-specific Balance Confidence scale (ABC), and the 12-Item Multiple Sclerosis Walking scale (MSW12) which have all been validated in MS [40-42].

5.3.6 Statistical Analysis

Pearson's correlations were used to determine how the gait stability index metrics were related to fall history, sensorimotor delays, lower extremity sensation thresholds, and disability status in PwMS. All data was found to be normally distributed by Shapiro-Wilks tests. A receiver operating characteristic (ROC) curve was constructed for each gait stability index and

clinical questionnaire (FES-I, ABC, MSW12), and the area under the curve (AUC) was calculated and compared to random chance (AUC=0.5) to determine each measure's strength of separation between MS fallers and MS non-fallers. Target significance was set as $p<0.05$, and the Holm-Bonferroni correction was applied to test for significance within the multiple correlations [43].

5.4 Results

Fall history was significantly correlated with GSI_{SaEn} ($r=0.528$, $p=0.002$) and GSI_{LyE} ($r=-0.354$, $p=0.047$) in the frontal plane (Figure 5.1 A and B). The Guy's Neurological Disability Scale was significantly correlated with GSI_{SaEn} in the frontal ($r=0.435$, $p=0.016$) and sagittal ($r=0.428$, $p=0.021$) planes (Figure 5.1 C and D). Patient reported EDSS was significantly correlated with GSI_{LyE} ($r=-0.484$, $p=0.005$) in the sagittal plane (Figure 5.1 E). There were no correlations between any GSI metrics and sensorimotor delays or lower extremity sensation thresholds. All correlations are reported in Table 5.2.

For the GSI metrics, the strongest separator of MS fallers from MS non-fallers was the GSI_{SaEn} in the frontal plane, with an AUC = 0.920 ($p=0.001$). In the frontal plane, the AUC for GSI_{RMS} was 0.630 ($p=0.326$), GSI_{Range} was 0.660 ($p=0.226$), and GSI_{LyE} was 0.640 ($p=0.290$). In the sagittal plane, the AUC for GSI_{RMS} was 0.800 ($p=0.023$), GSI_{Range} was 0.730 ($p=0.082$), GSI_{SaEn} was 0.760 ($p=0.049$), and GSI_{LyE} was 0.690 ($p=0.151$). For the clinical questionnaires, the strongest separator of MS fallers from MS non-fallers was MSWS12 with an AUC of 0.900 ($p=0.002$). The AUC for the ABC scale was 0.760 ($p=0.049$), and for FES-I was 0.770 ($p=0.041$). ROC curves for separating MS fallers from non-fallers are shown for the best

performing GSI metric frontal plane GSI_{SaEn} and best performing clinical questionnaire MSWS12 in Figure 5.2.

5.5 Discussion

The goal of the current study was to determine how the gait stability index metrics are related to physiological impairments, clinical disability scales, and mobility questionnaires in PwMS. Additionally, the current study determined if the gait stability index metrics are capable of separating MS fallers from MS non-fallers. Acceleration data was collected from wireless sensors and the GSI metrics were calculated to examine how trunk movement was controlled relative to foot movement. We hypothesized that 1) the GSI metrics would show moderate to strong correlations with measures of pathophysiology and disability in PwMS, and 2) the GSI would more sensitively differentiate fallers from non-fallers compared to standard clinical questionnaires. Our results partially supported our first hypothesis, as GSI metrics did show relationships to disability level in MS, but there were no significant correlations found between GSI metrics and sensorimotor delays or lower extremity sensation thresholds. Our results did support our second hypothesis, as multiple GSI metrics separated MS fallers from MS non-fallers as well or better than the clinical mobility questionnaires.

Our results show that fall history was significantly correlated with the GSI_{SaEn} and GSI_{LyE} in the frontal plane. During walking, movement in the frontal plane is considered to be governed by active control systems which use closed-loop feedback to make minor adjustments and maintain stability from step to step [44, 45]. This active control uses sensory feedback to drive motor output in both upper [46, 47] and lower [8, 48] body musculature in order to maintain stability throughout the gait cycle. The current results demonstrate that the frontal plane GSI

metrics which use nonlinear variability were related to fall history. Specifically, individuals who had more falls demonstrated more irregular and less divergent frontal plane trunk accelerations relative foot accelerations during walking. These results may indicate that persons who have a greater history of falls have altered frontal plane control over their trunk segment during walking, which may be an underlying characteristic driving their increased number of falls. An inability to maintain appropriate trunk motion during walking likely affects an individual's ability to respond to and attenuate any perturbation during walking [49, 50], making individuals more at risk of falls.

The frontal and sagittal GSI_{SaEn} and the sagittal GSI_{LyE} were significantly related to self-report disability level in PwMS. Our results showed that individuals with worse disability as measured by the Guy's Neurological Disability Scale tended to have more irregular accelerations at the trunk relative to the feet, and individuals with worse disability as rated by the patient reported EDSS tended to have less divergence in sagittal trunk accelerations relative to the feet. The self-report disability scales used in the current study include a wide range of symptom types including sensory and motor symptoms, cognition, fatigue, bowel and bladder, vision, and speech. Many of these symptoms are not directly involved in walking and balance maintenance, which may be why more relationships with the GSI metrics were not found. Altered and inappropriate control of trunk and foot movement during walking in individuals with more falls follows the loss of complexity hypothesis which indicates a decreased amount of adaptability in the sensorimotor control system, which could ultimately give rise to increased fall risk [51]. This loss of complexity in sensorimotor control may be related to other, more widespread functional deficits measured by other physiological categories assessed in the self-report disability scales.

These results demonstrate that the GSI metrics may provide different information that can supplement clinical assessments of disability in PwMS.

Surprisingly the results of the current study did not show any correlations between any GSI metrics and sensorimotor delays or sensation thresholds. Previous studies have shown that PwMS demonstrate delayed sensorimotor responses to postural perturbations compared to healthy adults [6, 8]. These delayed sensorimotor responses have also been showed to be related to measures of dynamic stability during walking [9]. We expected to find that individuals with worse sensation and longer sensorimotor delays would also demonstrate more altered relationships between their trunk and foot acceleration variability during walking, but this was not the case even though the GSI metrics were related to fall history (Table 5.2) and were able to separate fallers from non-fallers (Figure 5.2). One potential reason for this finding is that the important gait adjustments that are critical to maintaining stability may happen over a longer time scale than what is examined in the sensorimotor delay testing and may not be solely driven by the same pathways which are examined in sensorimotor delay testing. Sensorimotor delays range from 100-200 ms in PwMS [8, 9], while a single stride occurs over approximately one second [52]. Therefore, while sensorimotor delays may be one factor related to maintaining stability during gait, there may be other mechanisms on longer time-scales that are driving the results of the GSI metrics. For example, PwMS experience strength asymmetries [53], overall muscle weakness [54], and altered timing of trunk muscle activation [47]. This altered control of muscle activation could result in an inability of the trunk to appropriately respond to and attenuate perturbations over one or more steps during walking. Future studies could examine how the GSI metrics relate to altered strength or control of muscle activation during gait.

Our second hypothesis that GSI metrics would separate fallers from non-fallers at least as

well as clinical mobility questionnaires was partially supported, as multiple GSI metrics were as good or better at separating MS fallers from non-fallers compared to the clinical disability and mobility questionnaires. The frontal plane GSI_{SaEn} was stronger than all clinical questionnaires, while sagittal plane GSI_{RMS}, GSI_{Range}, and GSI_{SaEn} also demonstrated strong separation between MS fallers and non-fallers. These results provide support for the ability to use the GSI metrics as a mobility assessment. Current clinical questionnaires don't directly assess gait stability, and worse outcomes on these questionnaire scores are indicative of a fear of falling but are not directly associated with risk of future falls [55]. Using a measure of fall risk based on segmental control relationships can provide clinicians with an objective measure of stability, as the relationship between the center of mass and base of support is directly tied to stability [56]. Prevention and rehabilitation care in aging and neuropathological populations would benefit from access to an objective measure of gait stability to track how a person's mobility may change over time. Future studies will determine whether or not it is feasible to measure the GSI metrics in clinical and real-world settings, and which GSI metrics should be used for such fall risk assessments.

Because of the wide range of disability subcategories examined in the various clinical questionnaires and disability scales, examining relationships between the GSI metrics and disability subscales may be warranted in a larger cohort of MS subjects with a larger range of mobility disability. One should also keep in mind that the GSI metrics in the current study were calculated during treadmill walking, while practical application of these measures for clinical or real-world fall risk assessment will likely use overground walking. While it is possible that there may be differences between treadmill and overground walking, it is likely that the GSI metrics during overground walking would demonstrate similar trends to those seen from treadmill

walking in the current study. However, future work will need to investigate the GSI metrics during overground walking to validate their use for separating MS fallers from MS non-fallers.

Symptoms of MS can widely vary, but walking disability is reported to be one of the most detrimental symptoms by persons with MS. It is important to identify objective measures that are clinically valid and sensitive to different mobility levels in PwMS. The current study demonstrates that the GSI metrics may be valid for use as a clinical assessment, and that they relate to standard clinical questionnaires and disability scales. However, the GSI metrics were not related to lower extremity sensation thresholds or postural response latencies indicating that coordination of the trunk and feet during walking may be driven by other factors that were not assessed in the current study. Additionally, the GSI metrics showed strong separation of MS fallers from MS non-fallers. Future studies will need to determine how the GSI metrics perform during overground walking as will be necessary for application in clinical and real-world environments.

5.6 Tables and Figures

Table 5.1. Summary of subject demographics.

	MS Non-fallers N = 25	MS Fallers N = 15
Age	44 (9.9) yrs	48 (9.6) yrs
M / F	5 / 20	7 / 8
BMI	46.9 (8.7)	53.4 (6.5)
EDSS	3.3 (1.9)	4.4 (1.1)
Falls in previous 12 months	0	3.75 (1.7)

Table 5.2. Pearson's correlation coefficients (and p-value) between clinical outcomes and GSI metrics. Significant correlations in bold following Holm-Bonferroni correction.

		Fall History	*Vibration Threshold*	*Monofilament Test*	*Guy's Scale*	*Patient EDSS*	*Sensorimotor Delay*
Frontal Plane	GSI_{RMS}	-0.033 (0.860)	0.068 (0.715)	-0.045 (0.819)	-0.278 (0.145)	-0.061 (0.742)	0.169 (0.380)
	GSI_{Range}	-0.210 (0.241)	0.008 (0.964)	0.181 (0.339)	-0.014 (0.942)	-0.131 (0.466)	-0.102 (0.586)
	GSI_{SaEn}	**0.528** **(0.002)**	-0.062 (0.735)	-0.156 (0.420)	**0.435** **(0.016)**	0.203 (0.266)	0.142 (0.456)
	GSI_{LyE}	**-0.354** **(0.047)**	0.058 (0.753)	0.247 (0.196)	-0.220 (0.242)	-0.090 (0.623)	-0.277 (0.139)
Sagittal Plane	GSI_{RMS}	-0.318 (0.106)	-0.200 (0.317)	-0.039 (0.854)	-0.349 (0.081)	-0.041 (0.839)	-0.168 (0.422)
	GSI_{Range}	-0.114 (0.549)	0.076 (0.691)	-0.026 (0.898)	0.057 (0.772)	0.037 (0.845)	-0.057 (0.773)
	GSI_{SaEn}	0.354 (0.055)	0.179 (0.343)	-0.031 (0.879)	**0.428** **(0.021)**	0.240 (0.202)	0.057 (0.771)
	GSI_{LyE}	-0.151 (0.410)	-0.093 (0.612)	-0.117 (0.544)	-0.221 (0.241)	**-0.484** **(0.005)**	-0.222 (0.230)

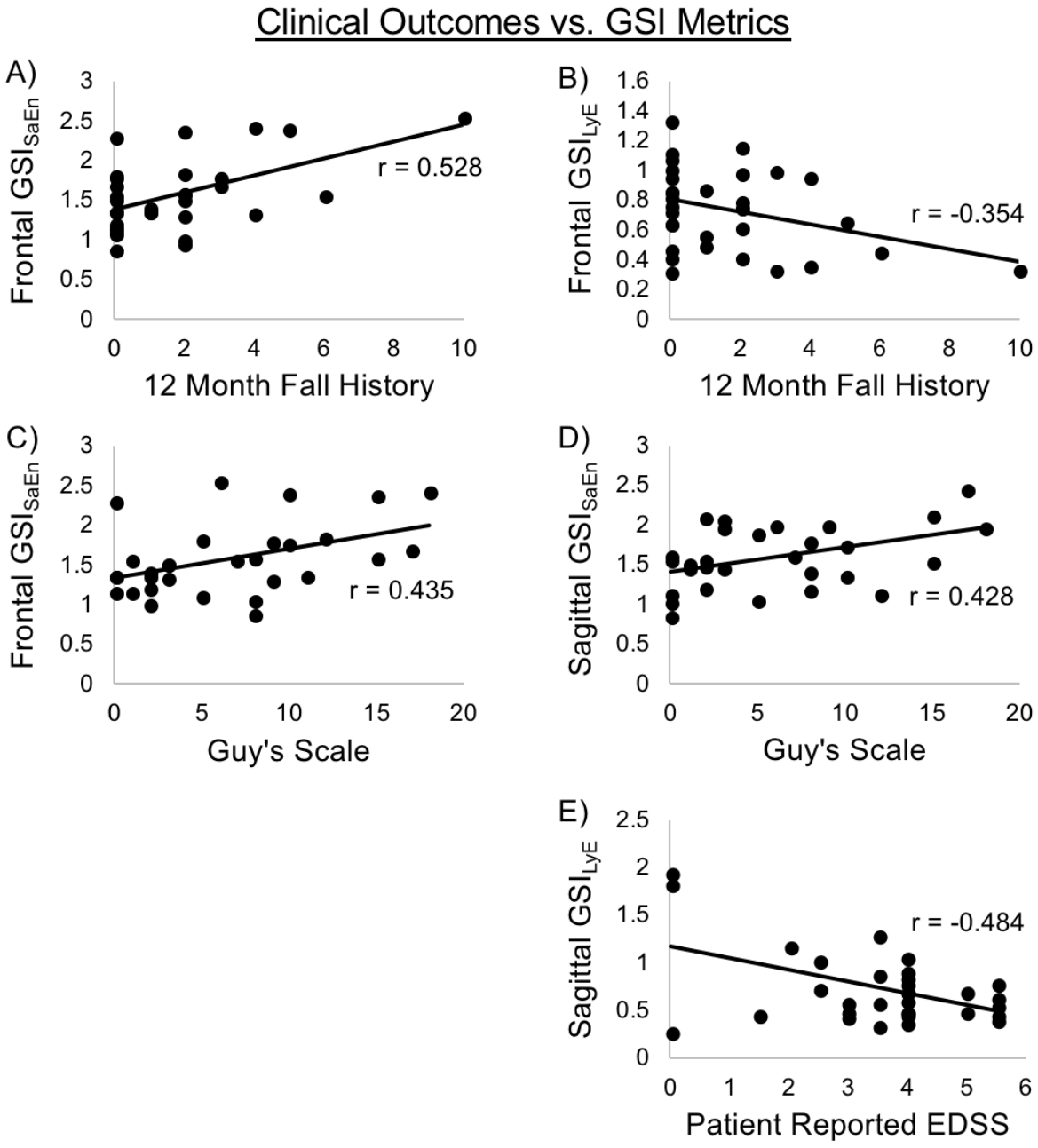

Figure 5.1. Scatter plots of significant correlations between clinical outcomes and GSI metrics. A) Fall history vs. frontal GSI_{SaEn}; B) Fall history vs. frontal GSI_{LyE}; C) Guy's scale vs. frontal GSI_{SaEn}; D) Guy's Scale vs. sagittal GSI_{SaEn}; E) Patient reported EDSS vs. Sagittal GSI_{LyE}. All correlations significant.

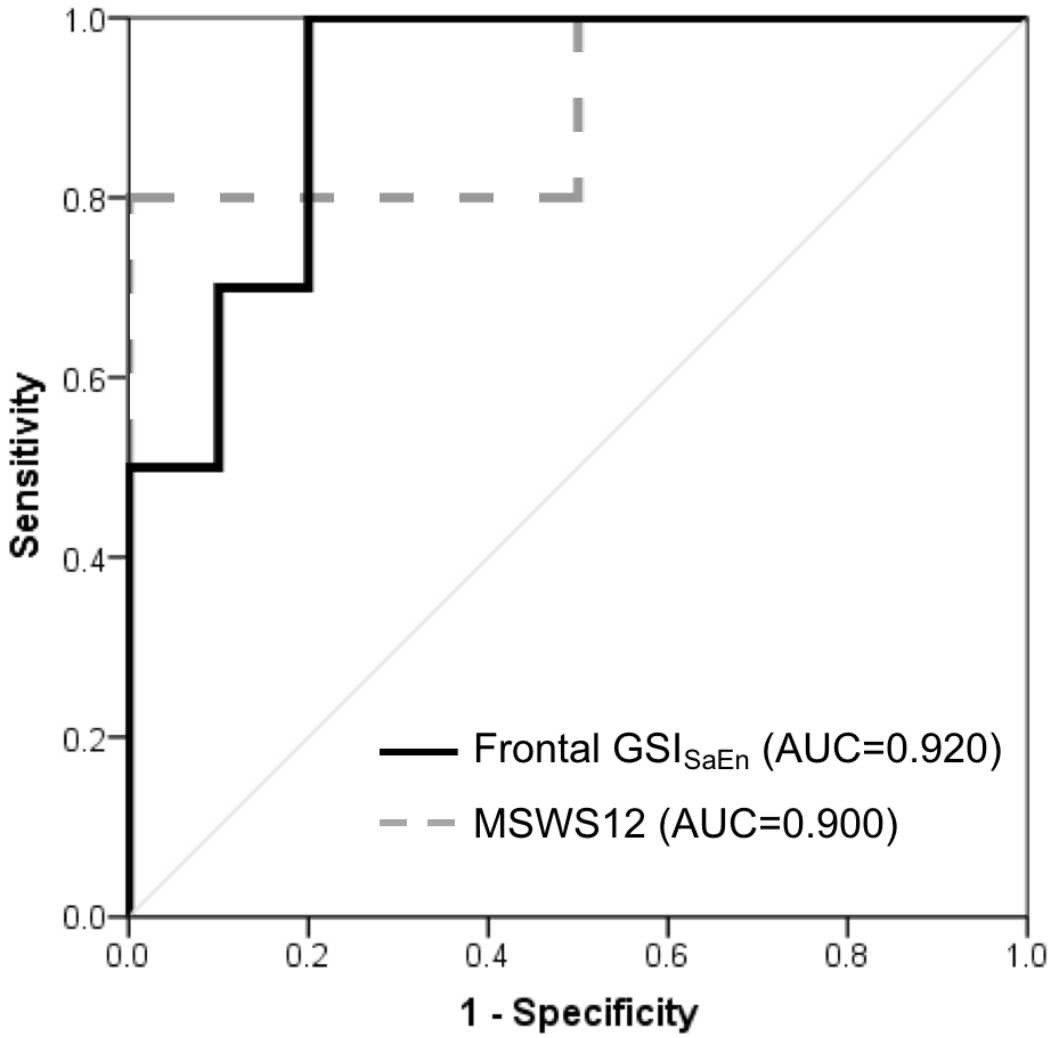

Figure 5.2. Receiver operating characteristic curves for the best performing GSI metric and clinical questionnaire for separating MS fallers from MS non-fallers. Frontal plane GSISaEn – Black; MSWS12 – Dotted Gray.

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6 The gait stability index separates fallers from non-fallers in persons with multiple sclerosis using short bouts of overground walking

6.1 Abstract

The gait stability index (GSI) quantifies the relationship between upper and lower body acceleration variability during walking and the GSI has previously demonstrated the ability to identify walking characteristics related to fall risk from long recordings of treadmill walking. However, long uninterrupted recordings of walking are not a feasible expectation for practical application of the GSI in clinical or daily life settings. The purpose of the current study was to identify the minimum number of short overground walking bouts needed to estimate the GSI metrics and, using those short walking bouts, to identify cutoff values for the GSI to separate persons with multiple sclerosis (MS) with and without a history of falls. 40 persons with multiple sclerosis (15 fallers, 25 non-fallers) walked back and forth over a 10-meter walkway at their normal walking speed while wearing wireless accelerometers on their right ankle and over their lumbar spine. Root mean square, range, sample entropy, and Lyapunov exponents were calculated from the foot and lumbar acceleration time series, and the respective GSI was calculated with each variability measure in the sagittal and frontal planes. Minimum number of walking bouts required and cutoff values were identified for GSI metrics to separate MS fallers from MS non-fallers. The minimum required number of bouts for estimation ranged from 4 to 18 walking bouts. The GSI for sagittal plane root mean square, sagittal plane range, and frontal plane Lyapunov exponents demonstrated significant separation between groups (area under receiver operating curve > 0.70). The results of the current study indicate that the GSI is feasible for classifying individuals with a falls history using relatively few short walking bouts which could likely be obtained in clinical and daily life applications.

6.2 Introduction

Falls are a major concern for persons with multiple sclerosis (PwMS), with over 50% of PwMS experiencing at least one fall within a 6-month period [1]. In order for targeted therapies [2] and fall prevention strategies [3, 4] to be implemented effectively, PwMS who are at risk of falling need to be accurately identified and monitored for changes in function. Current fall risk assessments largely rely on patient reported fall history, fear of falling questionnaires, or walking and balance observations made by a clinician. However, these measures only provide fair to moderate fall prediction ability in PwMS [5, 6]. Additionally, as has been observed in older adults, current assessments may be more indicative of a fear of falling rather than providing feedback regarding the walking or balance characteristics responsible for a patient's increased risk of falling [7]. With the majority of falls occurring in or around the home [8], it is important to be able to measure fall risk in daily life settings where falls actually occur. An objective assessment of fall risk that can be implemented in both clinical daily life settings would be of significant value for fall risk screening and monitoring changes in functional status over time.

Previous laboratory-based studies have identified many quantitative measures of walking which are related to fall risk in PwMS [9-13]. However, it is not feasible for clinicians to rely on laboratory-based outcomes, and therefore need a way to gather objective assessments outside of the laboratory setting. Wireless accelerometers are portable, low cost, and feasible to use in virtually any environment. Such sensors have gained popularity in recent years for use in instrumented gait and balance assessments for clinical use due to their objective nature and ability to identify sub-clinical functional changes [14-19]. Variability of accelerations at the trunk and at the feet during walking have been shown to relate to fall history and physiological impairments in PwMS [12, 13]. While this previous work studied acceleration variability of

individual segments, whole-body stability during walking is maintained through a controlled interaction between the dynamically changing base of support (feet) and movement of the center of mass (trunk) [20, 21]. Previous work has investigated how the relationship between acceleration variability at the trunk and the feet is related to fall risk in PwMS [22-24]. A recently introduced metric, the gait stability index (GSI), quantifies how variability is weighted between the trunk and the feet during walking [25, 26] and GSI metrics previously identified differences in MS fallers compared to MS non-fallers during walking [23]. However, this previous study calculated the GSI in PwMS during treadmill walking in a laboratory setting which allowed for long recordings of constant walking speed as is generally needed for appropriate variability analysis [27-29]. Since clinical assessments need to be performed as quickly as possible, and in a constrained space such as a hallway, it is not feasible to collect a long sample of uninterrupted walking. Additionally, walking in daily life consists of variable lengths of walking bouts with lots of turns rather than long uninterrupted bouts of straight walking. Therefore, in order for the GSI metrics to be used for walking assessment outside of a laboratory setting, it is important to identify the minimum number of short bouts of walking necessary for appropriate estimation of these outcomes.

Because an objective walking assessment that requires few short walking bouts will be feasible for clinical or real-world adaptation, the purpose of the current study was to identify the minimum number of walking bouts needed for appropriate estimation of the GSI metrics and to identify appropriate cutoff values of the GSI metrics in order to differentiate MS fallers from MS non-fallers using short bouts of over ground walking. We expect at least one GSI metric to be able to be reliably calculated with 10 or fewer short over ground walking bouts. We also expect at least one GSI metric will be capable of differentiating MS fallers from MS non-fallers using

these short overground walking bouts, from which a cutoff value for that GSI metric will be found which separates MS fallers from MS non-fallers.

6.3 Methods

Forty PwMS between the ages of 20 and 60 were recruited for this study and divided into 15 fallers and 25 non-fallers based on self-report fall history. Fallers experienced 2 or more falls in the past year [30]. Exclusion criteria included any additional neurological or orthopedic disabilities which could potentially alter balance or gait mechanics, female subjects who were pregnant or within 3 months post-partum at the time of collection, persons with vestibular disorders, diabetes, or a pre-existing condition which could make exercise dangerous such as heart disease or shortness of breath. Subjects could not be currently prescribed symptom specific medication therapies (Fampridine) which can affect gait [2]. Subjects also were required to be able to walk 300 meters without assistance or mobility aid, corresponding to a Kurtzke Expanded Disability Status Scale (EDSS) score of $\leq$ 4.5. A summary of subject demographics can be found in Table 6.1.

Subjects wore two wireless inertial sensors (Opal, APDM, Portland, OR, USA), one over the posterior surface of their lumbar spine at the L5 level, and one on the lateral surface of their right distal shank just superior to the ankle joint [26]. Accelerations were recorded at 128Hz while subjects walked along a 10m walkway marked by two cones for a total of 4 minutes. Subjects were asked to walk at their comfortable walking speed, turning around the outside of the cones, back and forth over the 10m walkway for the entire 4-minute duration.

A previously validated Matlab script [31] was used to identify turns during the walking test, and the periods of steady state walking between these turns were segmented out from the

full 4-minute time series for analysis. The raw acceleration time series from these straight walking bouts were exported to Matlab (MATLAB version R2013b, The MathWorks, Inc., Natick, Massachusetts, USA) and axes were combined to form resultant frontal and sagittal plane time series local to each individual sensor. All outcome measures were calculated from these frontal and sagittal acceleration time series. For appropriate analysis of the acceleration time series variability, data was left unfiltered [32].

Linear variability measures root mean square (RMS) and range were calculated from the frontal and sagittal plane acceleration time series. RMS was calculated as the square root of the mean of squares over all data points in the time series and was used to measure the absolute dispersion of the acceleration traces [24]. Range was calculated as the difference between maximum and minimum acceleration values over the entire time series to quantify the absolute spread of accelerations in the time series [24].

Nonlinear variability measures sample entropy (SaEn) and maximum Lyapunov exponent (LyE) were also calculated from the frontal and sagittal plane acceleration time series. The time lag and embedding dimension were found using an average mutual information algorithm [28, 33, 34] and global false nearest neighbors analysis [28], respectively. A time lag was found for each subjects' time series, and the median embedding dimension was used for analysis. Time lags ranged from 3 to 16 samples, and the median embedding dimension was found to be 6. A thorough explanation of SaEn and LyE can be found in previous literature [29, 35-37]. SaEn was calculated using custom Matlab software based on methodology from Pincus and Richman [36], using vector length m=3 and tolerance r=0.2*(time series standard deviation). These parameters were chosen after testing for relative consistency with neighboring parameter values. SaEn calculates the amount of regularity or complexity in the time series, with larger values of SaEn

being indicative of a more irregular or random time series. LyE was calculated using custom Matlab software based on Wolf's algorithm [37] which calculates the largest LyE. Larger values of LyE indicate more divergence or less predictability of a system [28].

Each of the variability metrics were used to calculate the respective gait stability index (GSI). The GSI metrics were calculated as the ratio of the lumbar acceleration variability metric divided by the same foot acceleration variability metric (Eq. 1) [25, 26]. This measure provides a clear understanding of the degree of acceleration variability at the trunk relative to the foot, with GSI > 1 indicating a larger number for the lumbar variability metric compared to the foot variability metric. This analysis resulted in a total of 8 GSI metrics, with 4 GSI metrics for each of the two anatomical planes, GSI_{RMS}, GSI_{Range}, GSI_{SaEn}, and GSI_{LyE}.

$$Gait\ Stability\ Index = \frac{Lumbar\ ACC\ Variability_{Frontal\ or\ Sagittal}}{Foot\ ACC\ Variability_{Frontal\ or\ Sagittal}} \qquad \textbf{Eq. (1)}$$

Statistical Analysis

The number of short bouts required for accurate estimation of the GSI metrics was found by taking the mean GSI value over an increasing number of bouts and comparing this estimate to the mean value over all 20 bouts from each subject [38]. This process was done for MS fallers and MS non-fallers separately. For each subject, the short walking bouts were randomly selected from their set of 20 bouts without replacement and the mean of their GSI metrics over these bouts was calculated. The estimate was found for 1 to 20 bouts. For each number of included bouts, the estimated GSI was correlated to the values found from the subjects' total bouts (actual GSI), and the explained variance (r^2) was calculated for each of the 20 estimates (1 bout included – 20 bouts included). The minimum bouts for estimation of each GSI metric was selected as the number of bouts for which adding additional bouts did not improve the r^2 value by more than 1%

[38].

The area under the receiver operating characteristic curve (AUC) was calculated to determine which GSI metrics were strongest for separating MS fallers from MS non-fallers, with an AUC>0.70 indicating strong separation between groups [39]. To identify appropriate cutoff values to separate fallers from non-fallers, Youden's index was calculated which finds the cutoff value maximizes both sensitivity and specificity with equal weights. Cutoff values were determined for each GSI metric in frontal and sagittal planes.

6.4 Results

Summary statistics of the GSI metrics can be found in Table 6.2. The frontal GSI_{RMS} was estimated for MS non-fallers with 4 walking bouts (r^2 = 97.1%), and for MS fallers with 6 walking bouts (r^2 = 95.7%). The frontal GSI_{Range} was estimated for MS non-fallers with 5 walking bouts (r^2 = 96.5%), and for MS fallers with 7 walking bouts (r^2 = 94.5%). The frontal GSI_{SaEn} was estimated for MS non-fallers with 11 walking bouts (r^2 = 94.3%), and for MS fallers with 14 walking bouts (r^2 = 95.0%). The frontal GSI_{LyE} was estimated for MS non-fallers with 13 walking bouts (r^2 = 94.3%), and for MS fallers with 18 walking bouts (r^2 = 96.1%) (Figure 6.1 A).

The sagittal GSI_{RMS} was estimated for MS non-fallers with 5 walking bouts (r^2 = 95.2%), and for MS fallers with 6 walking bouts (r^2 = 96.4%) (Figure 6.1 B). The sagittal GSI_{Range} was estimated for MS non-fallers with 8 walking bouts (r^2 = 94.7%), and for MS fallers with 6 walking bouts (r^2 = 96.1%) (Figure 6.1 C). The sagittal GSI_{SaEn} was estimated for MS non-fallers with 14 walking bouts (r^2 = 94.9%), and for MS fallers with 18 walking bouts (r^2 = 96.5%). The sagittal GSI_{LyE} was estimated for MS non-fallers with 14 walking bouts (r^2 = 92.9%), and for MS

fallers with 17 walking bouts (r^2 = 95.6%).

In the frontal plane, the GSI_{LyE} was the strongest separator of MS fallers from MS non-fallers with an AUC = 0.736 (p=0.022). The cutoff value for the frontal GSI_{LyE} is 1.030 (sensitivity = 66.7%, specificity = 90.0%), with higher values indicating fall risk. The AUC for frontal GSI_{RMS} is 0.578, for GSI_{Range} is 0.633, and for GSI_{SaEn} is 0.600. In the sagittal plane, the GSI_{RMS} was the strongest separator of MS fallers from MS non-fallers with an AUC = 0.845 (p=0.009) and was the strongest separator of all GSI metrics. The cutoff value for GSI_{RMS} is 0.225 (sensitivity = 100%, specificity = 60.0%), with higher values indicating fall risk. GSI_{Range} also showed strong separation with an AUC = 0.827 (p=0.010). The cutoff value for GSI_{Range} was 0.263 (sensitivity = 93.3%, specificity = 57.1%), with lower values indicating fall risk. The AUC for sagittal GSI_{SaEn} is 0.578 and for GSI_{LyE} is 0.661. The receiver operating characteristic curves for the three significant separators of MS fallers from MS non-fallers are shown in Figure 6.2.

6.5 Discussion

Measuring the relationship between trunk acceleration variability and foot acceleration variability has shown potential for identifying altered walking characteristics in PwMS [25] and in elderly adults [26]. While larger samples of walking are typically used for analysis of an individual's gait pattern, such long walking bouts are often not practical for clinical or daily life assessments, and therefore methods must be developed that can use a small number of short walking bouts for analysis. The current study examined GSI metrics calculated from a number of short bouts to determine how many short bouts were needed for accurate calculation and determined which gait stability index metrics were strongest for separating MS fallers from MS non-fallers using these short walking bouts.

The current study found that the minimum number of walking bouts needed to estimate GSI metrics in the frontal plane ranged from 4 bouts (MS non-faller GSI_{RMS}) to 18 bouts (MS faller GSI_{LyE}). The sagittal GSI metrics demonstrated a similar minimum number of bouts for estimation, with a range of 5 bouts (MS non-faller GSI_{RMS}) to 18 bouts (MS faller GSI_{SaEn}). These results indicate that estimation of the GSI metrics using linear variability measures (RMS, Range) can be estimated from a very small number of short walking bouts, while the GSI metrics using nonlinear variability measures (SaEn, LyE) require a somewhat larger number of walking bouts for accurate estimation. This result was expected since nonlinear variability measures inherently require a large sample of walking data to appropriately characterize the temporal structure of variability in a subject's gait pattern [28, 29]. Similar to the results of the current study, a previous study determined that local dynamic stability, a nonlinear variability measure, calculated from trunk accelerations during short bouts of walking could be estimated using 15 short bouts of walking [38] which is close to our GSI_{LyE} minimum bout numbers ranging from 13 – 18 short bouts. Previous studies have recommended that a sample of at least 50 strides of uninterrupted steady state walking is used for calculation of nonlinear variability outcomes [40]. While 50 strides of uninterrupted walking can be recorded in a laboratory setting with a treadmill, it is not feasible for such a long walking bout to be collected in clinical settings. Short walking bouts make up the majority of walking in daily life for PwMS, with 58% of walking bouts being less than 50 steps [41]. A previous study has shown that older adults had an average of over 1000 10-second bouts of walking in a week-long period [42]. Based on the results of the current study, all of the GSI metrics could be estimated using short walking bout data recorded during daily life, with none requiring more than 18 short walking bouts for accurate estimation. However, since clinical walking assessments must be quick to perform, the GSI_{RMS} and GSI_{Range}

metrics would be best suited for clinical use because of their low number of required bouts.

The minimum number of walking bouts was almost always found to be higher for MS fallers than for MS non-fallers. Two possible explanations for this are that the MS faller group had either more intersubject or intrasubject variability compared to the MS non-faller group. A higher amount of intersubject variability would indicate that the individual MS fallers may adopt their own gait strategies which are optimized according to their own functional deficits. For example, some subjects may widen their stance due to sensory loss, while other subjects may lift their feet higher due to foot drop. This could result in the GSI metrics requiring different amounts of data for accurate calculation from different MS faller subjects, whereas the MS non-fallers may not have as many variations in their gait patterns across subjects. It is also possible that the MS fallers have a higher amount of intrasubject variability, indicating that they are less consistent compared to MS non-fallers across each walking bout. The r^2 results in the current study seem to support this latter option, as the explained variance improved more quickly with added bouts in MS non-fallers for almost all GSI metrics. This would be an important note for future analyses, as care should be taken to collect enough bouts to estimate the GSI metrics in both MS non-fallers and MS fallers.

Out of all GSI metrics in the current study, the sagittal plane GSI_{RMS}, sagittal plane GSI_{Range}, and frontal plane GSI_{LyE} were the strongest separators of MS fallers from MS non-fallers. MS fallers tended to have sagittal plane GSI_{RMS} values above 0.225. A larger GSI_{RMS} indicates larger magnitudes of trunk accelerations relative to foot accelerations, which may demonstrate a lack of ability for MS fallers properly attenuate accelerations from lower body to upper body segments during walking. Previous studies have demonstrated that appropriate attenuation of accelerations from lower body to upper body segments is important for

maintaining stability during walking [43]. It is possible that this attenuation is altered in MS fallers, which may be an underlying mechanism relating to their increased risk of falling. While a larger GSI_{RMS} was indicative of fall risk, MS fallers also tended to have smaller values of GSI_{Range} indicating that MS fallers have a smaller range of trunk accelerations relative to the range of their foot accelerations. These results indicate that PwMS have trouble controlling their trunk accelerations appropriately, with MS fallers demonstrating larger and less predictable trunk accelerations relative to foot accelerations during walking. While this has been shown in previous studies using movement variability [12, 13, 24, 44] and the GSI metrics [23, 25], this is the first study to demonstrate this characteristic in MS fallers using an analysis applied to short overground walking bouts.

The current study provides support for the GSI metrics to be used in clinical and daily life settings, but there are some limitations that should be noted. The overground walking bouts recorded in the current study were all of equal length over a flat tile floor in a straight line with no obstacles or distractions. While this experimental setup could be used in a clinical setting, it is likely that walking in daily life settings would include obstacles and changes in walking surfaces and angles. Future work should determine if the number of bouts and the cutoff values determined in the current study will be valid for use in daily life. The current study also only tested PwMS who were able to ambulate freely. While previous studies have shown the GSI metrics to identify altered walking characteristics in other patient populations [26], the current study is the first to use the GSI metrics to analyze short overground walking bouts. Future studies will need to validate or determine the minimum number of short overground bouts and appropriate cutoff values for GSI metrics in patient populations other than MS.

The results of the current study demonstrate that an accurate estimation of each GSI

metric is possible using short overground walking bouts. Sagittal plane GSI_{RMS}, sagittal plane GSI_{Range}, and frontal plane GSI_{LyE} estimated from the short overground walking bouts were all able to separate MS fallers from MS non-fallers using 18 or fewer bouts. While this demonstrates that each of these GSI metrics could feasibly be calculated from daily life recordings, the sagittal plane GSI_{RMS} exhibited the most potential to be employed for clinical walking assessments as it combines the fewest number of short bouts required for estimation with the strongest separation between MS fallers and MS non-fallers. Future studies should improve on the current findings for use in data collected from daily life, and in data collected from other patient populations with increased risk of falls.

6.6 Tables and Figures

Table 6.1. Summary of subject demographics.

	MS Non-fallers N = 25	MS Fallers N = 15
Age	44 (9.9) yrs	48 (9.6) yrs
M / F	5 / 20	7 / 8
BMI	46.9 (8.7)	53.4 (6.5)
EDSS	3.3 (1.9)	4.4 (1.1)
Falls in previous 12 months	0	3.75 (1.7)

Table 6.2. Means and standard deviations for all GSI metrics.

	GSI Metric	**MS Non-fallers**	**MS Fallers**	**Minimum Bouts**
Frontal	GSI_{RMS}	0.401 (0.092)	0.429 (0.033)	4
	GSI_{Range}	0.376 (0.142)	0.442 (0.114)	5
	GSI_{SaEn}	2.37 (0.627)	2.51 (0.398)	11
	GSI_{LyE}	0.797 (0.231)	1.12 (0.257)	13
Sagittal	GSI_{RMS}	0.223 (0.062)	0.310 (0.049)	5
	GSI_{Range}	0.316 (0.052)	0.218 (0.066)	6
	GSI_{SaEn}	2.49 (0.479)	2.39 (0.343)	14
	GSI_{LyE}	0.863 (0.264)	1.05 (0.295)	14

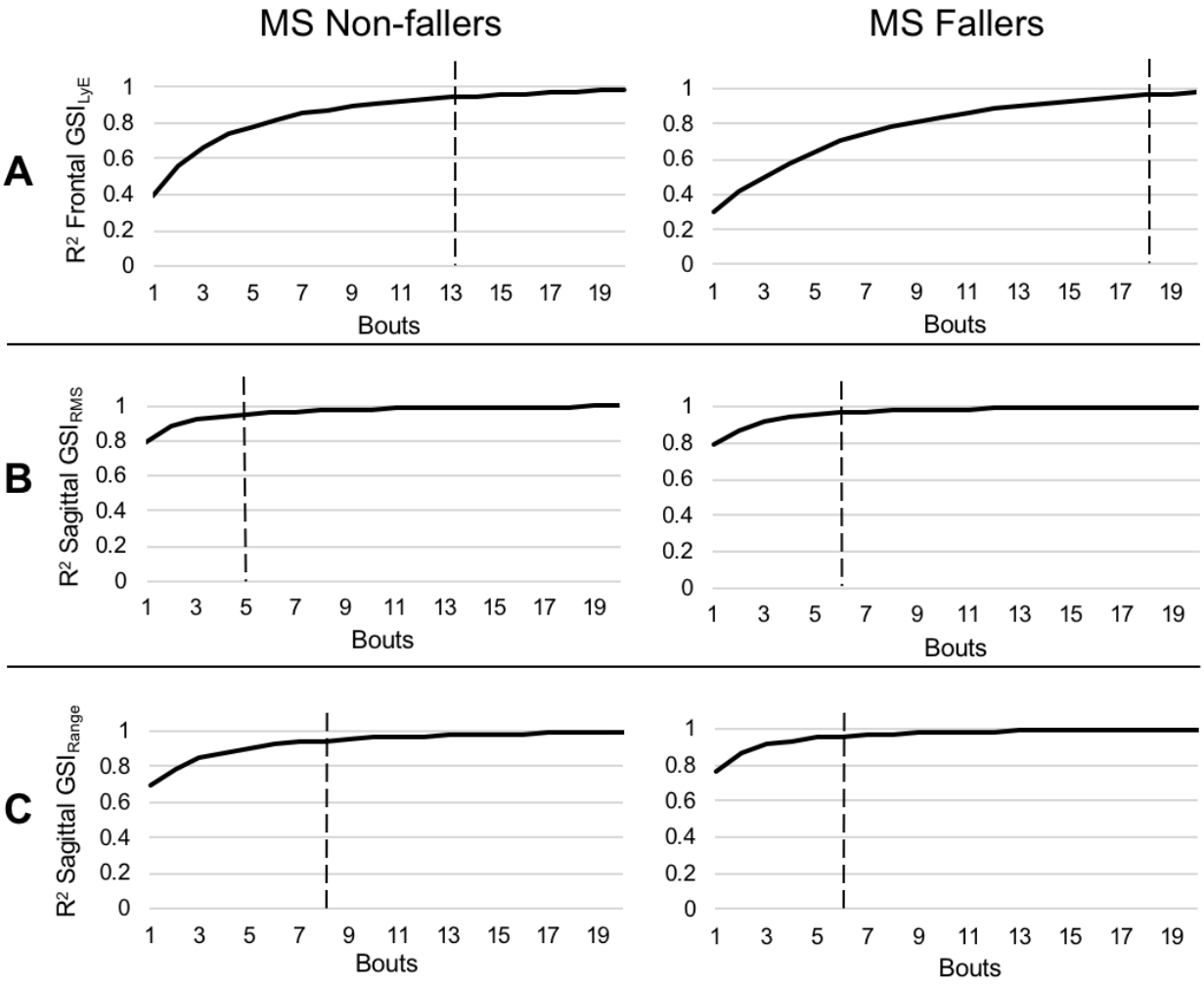

Figure 6.1. Estimation of the GSI metrics which demonstrated significant separation between MS fallers from MS non-fallers using an increasing number of bouts – A) Frontal GSI_{LyE}, B) Sagittal GSI_{RMS}, C) Sagittal GSI_{Range}. Amount of variance (R^2) explained in the estimate is plotted against the number of bouts used for the estimation for MS non-fallers (left) and MS fallers (right). Dotted vertical line indicates the point at which adding additional bouts improves the estimate by less than 1%.

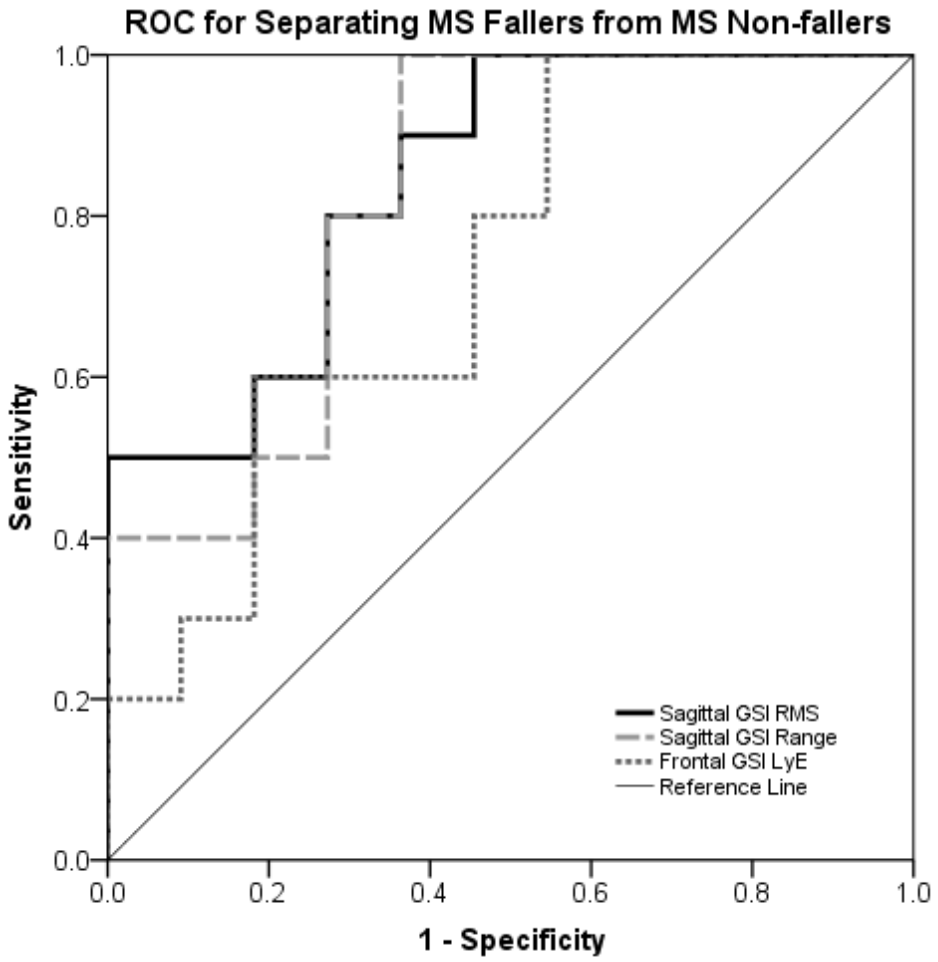

Figure 6.2. Receiver operating curves (ROC) for the three GSI metrics that demonstrated strong separation between MS fallers and MS non-fallers. Area under the curve (AUC) for Sagittal GSI_{RMS} = 0.845, Sagittal GSI_{Range} = 0.827, Frontal GSI_{LyE} = 0.736; significance $p<0.05$.

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7 Conclusions

The primary purpose of this dissertation research was to investigate how the relationships between upper body (trunk) and lower body (feet) segment motion during walking are affected by MS and how these relationships can be used to characterize gait stability in PwMS. PwMS with a history of falls (MS fallers), PwMS without a history falls (MS non-fallers), and age-matched healthy adults were studied during treadmill and overground walking trials in addition to a battery of clinical and physiological assessments. The primary outcomes studied in this dissertation are referred to as gait stability indices (GSI), which quantify acceleration variability at the trunk relative to the feet during walking as a means to examine whole-body stability. First, the GSI metrics were examined under normal and challenged treadmill walking to determine how healthy adults and PwMS maintain relationships between trunk and foot movement across different walking conditions (Aim 1, Chapters 3 and 4). Second, the GSI metrics were examined in relation to standard clinical and physiological outcomes in PwMS (Aim 2, Chapter 5). And lastly, the GSI metrics were assessed using short overground walking bouts in order to determine if these metrics could be feasibly calculated and used for walking assessments in clinical or real-world settings (Aim 3, Chapter 6).

Chapter 3 determined that relationships between accelerations at the CoM and BoS were adapted similarly across walking speeds for healthy controls, MS fallers, and MS non-fallers. Results showed that MS fallers, MS non-fallers, and healthy controls increased their sagittal and frontal GSI_{RMS} and frontal GSI_{Range} with increasing walking speed, but MS fallers consistently maintained a lower sagittal GSI_{RMS} across all walking speeds compared to healthy controls. Healthy controls also adapted their GSI_{SaEn} in the frontal plane in response to walking speed, while none of the MS subjects demonstrated this adaptation. In contrast to the MS faller group,

the healthy control group seemed to allow for larger amounts of trunk accelerations relative to the foot accelerations during walking. It is possible that healthy controls can leverage the momentum of the upper body segment for safe and efficient use in sagittal plane movement. Future studies should investigate the role of upper body movements in forward propulsion during walking in healthy controls and individuals with movement disorders.

Chapter 4 determined that relationships between accelerations at the CoM and BoS were adapted similarly across altered sensory conditions for healthy controls, MS fallers, and MS non-fallers. Results showed that the sagittal and frontal GSI_{RMS} were larger in the altered somatosensory condition compared to the normal and altered visual conditions. The frontal GSI_{SaEn} was greater in the visual condition compared to the somatosensory condition. The frontal and sagittal GSI_{LyE} was greater in the somatosensory condition compared to the normal and visual conditions. The current study showed that while healthy controls, MS non-fallers, and MS fallers adapted to altered sensory feedback during walking in a similar manner. However, MS fallers may be more reliant on visual feedback compared to MS non-fallers and healthy control subjects, as MS Fallers were the only group that demonstrated a larger sagittal GSI_{LyE} in the visual condition compared to the normal condition. Since not all MS symptoms directly cause walking and balance deficits, it may be of interest in future studies to identify specific functional mobility deficits in a larger cohort of MS subjects that may be linked with a difficulty to appropriately adapt in challenging walking conditions.

Chapter 5 examined how the gait stability indices were related to physiological impairments and how the gait stability indices performed for separating MS fallers from MS non-fallers compared to standard clinical mobility questionnaires. Multiple gait stability indices were significantly correlated with measures of disability in MS, but no correlations were found

between the gait stability indices and sensorimotor delays or lower extremity sensation. Multiple GSI metrics performed at least as well as clinical mobility questionnaires for separating MS fallers from MS non-fallers, with GSI_{SaEn} showing strongest separation with an area under the receiver operating curve of 0.920. The GSI metrics demonstrated validity in assessing MS disability and mobility in MS but were not related to lower extremity sensation thresholds or postural response latencies. This finding indicates that coordination of trunk and feet acceleration during walking may be driven by other factors that were not assessed in the current study. Future studies should examine how the GSI metrics relate to altered strength or control of muscle activation during gait.

Chapter 6 determined which GSI metrics were appropriate for use in separating MS fallers from MS non-fallers during short bouts of overground walking. Chapter 6 also identified how much walking was necessary for accurate calculation of the GSI metrics. The minimum required number of overground walking bouts for estimation ranged from 4 to 18 walking bouts. The sagittal GSI_{RMS}, sagittal GSI_{Range}, and frontal GSI_{LyE} demonstrated significant separation between MS fallers from MS non-fallers. These results indicate that GSI metrics are feasible for classifying individuals with a falls history using relatively few short walking bouts which could likely be obtained in clinical and daily life applications. While each of these GSI metrics could feasibly be calculated from daily life recordings, the sagittal plane GSI_{RMS} exhibited the most potential to be employed for clinical walking assessments as it combines the fewest number of short bouts required for estimation with the strongest separation between MS fallers and MS non-fallers. Future studies should improve upon the current findings by calculating the GSI metrics using data collected from daily life and in data collected from other patient populations with increased risk of falls.

Having an assessment of stability during walking that can be performed using portable wireless sensors without the need for more expensive or sophisticated motion capture systems could provide clinicians an objective measure of fall risk that can supplement standard clinical outcomes to monitor progression of functional decline over time and identify efficacy of treatment interventions. Additionally, it is possible to employ the GSI metrics to examine walking during normal daily life since this analysis has been shown to be able to be calculated appropriately using small amounts of walking. Daily life walking assessments would offer the ability to monitor effects of fatigue throughout the day and to potentially monitor real-time changes in walking patterns to alert individuals of acute fall risk. Future work will be necessary for integrating the GSI metrics with existing wireless sensor systems and to demonstrate the use of this assessment technique in clinical settings. Identifying individuals at risk of falling can allow for appropriate interventions to decrease the number of falls which will provide a tangible benefit to the care of patients with MS and potentially other movement disorders.

8 Appendix A: Cited abstracts

TRUNK AND FOOT ACCELERATION VARIABILITY DURING TREADMILL AND OVERGROUND WALKING

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INTRODUCTION

There is a need to monitor people for fall risk while they are functioning in the real world rather than solely assessing fall risk within laboratory settings. The purpose of this line of research is to develop a quantitative method of measuring individuals' stability related to fall risk during walking in a clinical or real world environment. Such a method must measure stability without the use of a motion capture system, which would not be feasible for every day, real world assessment. Wireless inertial sensors are a feasible alternative tool to assess movement, and can measure accelerations of individual body segments in any environment [1].

Previous work has shown that variability measures can provide information about how human movement is controlled [1, 2]. Linear measures such as root mean square (RMS) and range quantify amount of variability, while nonlinear measures such as sample entropy (SaEn) and Lyapunov exponent (LyE) quantify structure of variability. Unfortunately, nonlinear measures generally require relatively long time series for accurate analysis [3, 4], which may be difficult to achieve in clinical or real-world settings where uninterrupted bouts of gait are likely over a short distance.

The aim of this study was to examine how results from linear and nonlinear variability measures would differ between segment acceleration data from short bouts of overground walking compared to long periods of treadmill gait. We hypothesized that linear measures would show no significant difference but nonlinear measures would show significant differences between conditions. These findings are relevant to applying variability metrics to acceleration data collected over shorter bouts of walking in a real world setting.

METHODS

Twenty healthy adult subjects participated in this study (mean 43.5 years, range 27-58 years). Participants were instructed to walk at their self-selected comfortable pace over a 25 foot walk way (overground condition). Participants also walked on a treadmill at a self-selected normal pace for 3 minutes (treadmill condition). During both walking trials, participants wore tri-axial accelerometers (Opal, APDM, Portland, OR) on their right ankle and sternum that recorded accelerations at 128 Hz for the duration of each trial. Linear (RMS, range) and nonlinear (SaEn, LyE) measures of variability were calculated for the trunk and foot acceleration time series in the frontal and sagittal planes separately which resulted in four values for each variability measure – trunk sagittal, trunk frontal, foot sagittal, and foot frontal. All metrics were calculated in MATLAB. Time series length was 530 data points for overground trials and 23100 data points for treadmill trials. A vector length of m=3 was used to calculate SaEn. For SaEn and LyE, time delay (τ) was calculated for each data set via the average mutual information algorithm, the embedding dimension was calculated via the false nearest neighbors algorithm. Two-way ANOVA assessed main effect of sensor location (foot, trunk) and walking condition (treadmill, overground) for frontal and sagittal planes separately.

RESULTS

Frontal plane: RMS was significantly higher at the foot compared to the trunk ($F=225.973$, $p<0.01$) and higher during overground compared to treadmill ($F=67.696$, $p<0.01$). Range was significantly higher at the foot compared to the trunk ($F=113.759$, $p<0.01$) but not different between treadmill and overground. SaEn was significantly lower at the foot compared to the trunk ($F=131.008$, $p<0.01$) and significantly lower during overground compared to treadmill walking ($F=159.742$, $p<0.01$). LyE was significantly higher at the foot compared to the

trunk (F=44.629, p<0.01), with no main effect of condition but there was a difference at the trunk between conditions (p<0.01) (Fig 1).

Sagittal plane: RMS was significantly higher at the foot compared to the trunk (F=1074.397, p<0.01), and higher during overground compared to treadmill walking (F=63.486, p<0.01). Range was significantly higher at the foot compared to the trunk (F=120.739, p<0.01) but not different between treadmill and overground. SaEn was significantly lower at the foot compared to the trunk (F=255.987, p<0.01) and significantly lower during overground compared to treadmill (F=52.260, p<0.01). LyE was significantly higher at the foot compared to the trunk (F=41.450, p<0.01), with no main effect of condition but there was a difference at the trunk between conditions (p<0.01) (Fig 1).

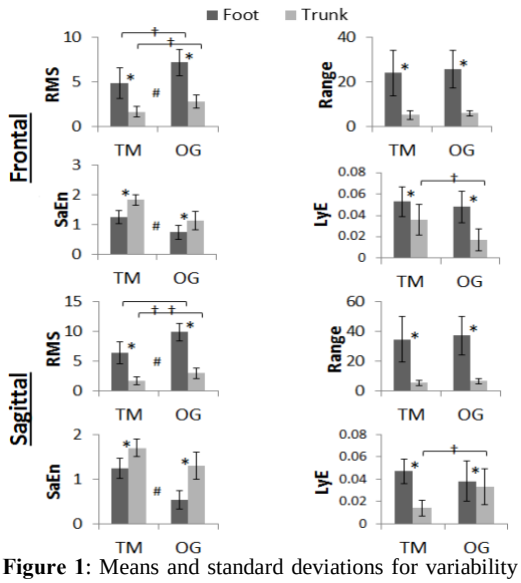

Figure 1: Means and standard deviations for variability measures during treadmill (TM) and overground (OG) walking in the frontal (top) and sagittal (bottom) plane. * main effect of location; # main effect of condition; † significant interaction.

DISCUSSION

These results show that RMS and SaEn showed a main effect of condition, LyE at the trunk showed differences between conditions but not at the foot, and range was not effected by condition. The overground walking trials represent short bouts of gait that are more likely in the real world, but short data length impacts nonlinear measure calculations (SaEn, LyE). However, we also see that RMS was significantly different between the treadmill and overground trials. RMS is a linear variability measure and its calculation should not be impacted by data length. Previous work has shown that gait kinematics do not differ between treadmill and overground walking, but muscle activation, joint moments and joint powers do show differences between the two conditions [5]. It is possible that these differences are reflected in the acceleration time series examined in the current study. Range demonstrated the most consistent results between conditions, indicating its potential for use real world analysis. LyE was also similar between conditions for foot accelerations, possible due to the greater magnitude of foot acceleration relative to trunk acceleration. While RMS and SaEn showed effects of walking condition, the differences between segments for all metrics are relatively consistent regardless of walking condition. Further study should be done to examine relationships between segments under different conditions.

CONCLUSIONS

The results of this study illustrate difficulties in analyzing variability from short bouts of gait in the real world. Further work is needed to develop techniques that are robust to short data lengths that will be encountered in real world time series analyses. Trends between upper and lower body segments appear to be relatively consistent between conditions, and may be of interest in future studies.

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Segment Relationships Adapt to Walking Speed Differently in Healthy Young and Elderly Adults

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INTRODUCTION

Walking at non-preferred gait speed alters variability of foot and trunk motion in healthy young and elderly subjects[1]. While it is known that movement variability of individual segments changes relative to gait speed, it is not clear how relationships between segments are maintained when changing walking speeds, and what role these relationships play in maintaining stability. For example, altered trunk movement could stabilize center of mass motion in order to compensate for altered foot movement, thus maintaining whole body stability even though motion of an individual segment is abnormal. Elderly individuals often have weakness or decreased range of motion, which could alter these segmental relationships and ultimately lead to a higher rate of falls[2]. Therefore, it is important to examine how relationships between trunk and foot movement adapt to challenging gait requirements (i.e. speed) in healthy elderly adults compared to the optimal gait characteristics of healthy young adults.

The aim of the current study was to determine the effects of walking at non-preferred speeds on the relationship between foot and trunk acceleration variability in healthy young and healthy elderly adults in the frontal plane. The frontal plane was examined since gait is laterally unstable, and control of movement in this plane requires active control compared to passive control in the sagittal plane[3]. Since lower body segment motion is mechanically tied to upper body segment motion[4], we hypothesized that the relationship between trunk and foot acceleration variability will not change significantly with varying gait speed in healthy young or healthy elderly adults.

METHODS

Twenty healthy young adults (mean 23, range 20-30 yrs.) and twenty healthy elderly adults (mean 73, range 67-85 yrs.) with no history of falls participated in this study. All subjects were free from orthopedic or neurological deficits which may affect their walking or balance. Participants walked on a treadmill at 80%, 90%, 100%, 110%, and 120% of their self-selected preferred walking speed for 3 minutes at each speed. During all walking trials, participants wore tri-axial accelerometers (Opal, APDM, Portland, OR) on their right ankle and sternum that recorded accelerations at 128 Hz for the duration of each trial. Root mean square (RMS) and sample entropy (SaEn) were calculated for the trunk and foot acceleration time series in the frontal plane using a custom MATLAB script. The segment variability ratio was calculated as the ratio of trunk variability divided by foot variability. A 2 (group) x 5 (speed) ANOVA was performed to examine main effect of group (healthy young, healthy elderly) and walking speed (80%-120%) on the segment variability ratio for RMS and SaEn.

RESULTS

Preferred walking speed was significantly faster in HY (1.25$\pm$0.13 m/s) compared to HE (1.10$\pm$0.27) (p=0.02). The segment variability ratio using RMS did not exhibit a main effect of group, but there was a main effect of speed (F=9.19, p<0.001) where the ratio increased as speed increased (Figure 1). There was a significant speed x group interaction (F=5.37, p<0.001). One-way ANOVA and post-hoc Tukey's test subsequently determined HE demonstrated no main effect of speed, while HY demonstrated a significant main effect of speed (F=5.018, p<0.001), where the ratio at 120% preferred walking speed was significantly greater than 80% (p=0.002), 90% (p=0.005) and 100% (p=0.022) of preferred walking speed. The segment variability using SaEn showed a main effect of group (F=5.83, p=0.02) where the ratio was higher for healthy elderly compared to healthy young adults, and also a main effect of speed (F=2.77, p=0.029) where the ratio decreased as speed increased.

DISCUSSION

We hypothesized that a constant relationship between acceleration variability at the trunk and foot segment would be maintained in healthy young and healthy elderly individuals regardless of walking speed. Contrary to our hypothesis, our

results show that healthy young adults adapt to non-preferred walking speeds differently compared to healthy elderly adults, as evidenced by how the segmental ratio changes with respect to walking speed. Specifically, the results showed that healthy young adults adapt their RMS segment variability ratio relative to speed, while healthy elderly adults do not adapt. This may in part be due to the attenuation of accelerations from inferior to superior segments being altered in elderly adults compared to healthy young adults[5]. Previous work has shown that healthy elderly adults prioritize head stability at the cost of adopting an altered trunk coordination strategy compared to healthy younger adults[5]. The altered accelerations at the trunk segment in healthy elderly may lead to a change in the relationship between acceleration variability at the trunk and at the feet which is not adaptable to different gait speeds. The SaEn segment variability ratio results show that there is a main effect of speed across both groups, where the ratio decreases as speed increases. However, the main effect of group for the SaEn segment variability ratio shows that the variability structure at the trunk relative to the feet is different between the two groups. Older adults have shown similar approximate entropy values for trunk accelerations compared to young adults[5], indicating that our observed differences in segment variability ratio using SaEn may stem from altered acceleration variability at the feet during walking.

RMS segmental ratio is <1 in both groups, indicating that the magnitude of acceleration variability is larger at the foot compared to the trunk for all speeds. The SaEn segmental ratio is >1 in both groups, indicating that accelerations at the trunk are less predictable compared to accelerations at the feet for all speeds. These results indicate that both groups exhibit less overall motion at the trunk relative to the feet, but more irregular patterns of motion at the trunk relative to the feet across walking speeds. None of the healthy elderly adults in the current study had a history of falls, but it is possible that fall-prone elderly adults exhibit further differences in segment variability ratios compared to healthy young adults, which could be a walking characteristic tied to their instability and fall risk.

CONCLUSIONS

The relationship between trunk and foot motion likely plays a role in maintaining stability during gait. From our current results, it appears healthy elderly adults with no fall history do not adapt their segmental relationships to task requirements in a way similar to healthy young adults. Future studies should examine the segmental variability ratio in elderly subjects with a history of falls to determine how this measure is related to fall risk.

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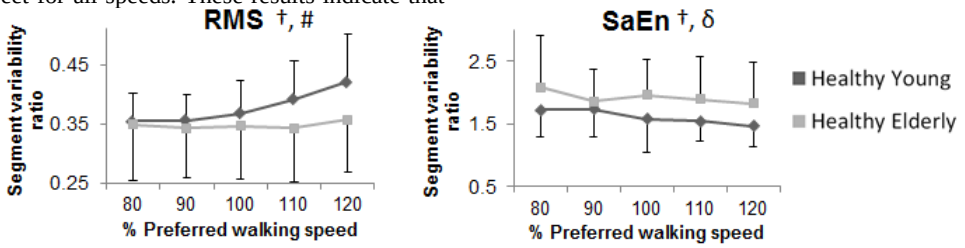

Figure 1: Means and standard deviations for segment variability ratio for root mean square (RMS) and sample entropy (SaEn), at 80%-120% preferred walking speed, in healthy young (dark grey) and healthy elderly (light grey) adults. Main effect of speed †; main effect of group δ, significant interaction #.

Movement variability of the trunk and feet during walking is altered in persons with multiple sclerosis compared to healthy controls

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Background and Purpose: Maintaining stability requires controlled interactions between the center of mass (trunk) and base of support (feet). The interaction between segments may be altered in persons with multiple sclerosis (PwMS) due to neural degradation disrupting sensorimotor feedback between upper and lower body segments. The purpose of this study was to determine if relationships between acceleration variability at the trunk and at the foot are altered in PwMS compared to healthy control subjects (HC) during walking.

Methods: Forty PwMS (age 21-57) and forty age-matched HC walked on a treadmill at self-selected pace for 3 minutes while wearing inertial sensors on their sternum and right ankle. Root mean square (RMS), range, sample entropy (SaEn), and Lyapunov exponents (LyE) were calculated from the acceleration time series in the frontal and sagittal planes. To examine relationships between the trunk and feet, the ratio of trunk acceleration variability to foot acceleration variability was calculated for each plane. Independent samples t-tests examined differences between groups for each ratio measure.

Results: In the frontal plane, the ratio was significantly lower in PwMS compared to HC for RMS (p=0.004) and range (p=0.024), but significantly higher in PwMS compared to HC for SaEn (p=0.044) and LyE (p=0.041). In the sagittal plane, the ratio was significantly lower in PwMS compared to HC for RMS (p=0.041) and significantly higher in PwMS compared to HC for LyE (p<0.001).

Discussion: The present study demonstrates that PwMS have an altered relationship between trunk and foot motion during walking compared to HC particularly in the frontal plane. Examining the ratio between acceleration variability at the trunk and at the feet may provide a description of whole body control during gait. Real time assessment of whole body control during gait could be of interest for portable fall risk assessment in clinical and real-world settings.

The relationship between trunk and foot movement variability during walking is altered in persons with multiple sclerosis with history of falls

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Background and Purpose: Persons with multiple sclerosis (PwMS) demonstrate altered relationships between trunk and foot movement during walking compared to healthy controls. However, it is not clear if these altered relationships are linked to disability status or fall history in PwMS. The purpose of this study was to determine if relationships between acceleration variability at the trunk and at the foot are related to disability status, and if they are different between PwMS with and without history of falls.

Methods: Twenty-Six PwMS (age 22-60) with no fall history and twenty-six age-matched PwMS with history of 2 or more falls in the previous 6-months walked on a treadmill at self-selected pace for 3-minutes while wearing inertial sensors on their sternum and right ankle. Root mean square (RMS) and sample entropy (SaEn) were calculated from the acceleration time series in the frontal and sagittal planes. To examine relationships between the trunk and feet, a ratio of trunk acceleration variability to foot acceleration variability was calculated. Spearman's correlations examined the relationship between EDSS and each ratio measure. Independent samples t-tests examined differences between groups for each ratio measure.

Results: The ratio for SaEn in the sagittal plane was significantly correlated with EDSS ($r=0.411$, $p=0.003$), no other correlations reached significance. The ratio was significantly higher in fallers compared to non-fallers for RMS ($p=0.036$) and SaEn ($p=0.004$) in the sagittal plane.

Discussion: The present study demonstrates that relationships between trunk and foot movement regularity in the sagittal plane have a significant but weak relationship to disability status. Additionally, segment relationships in the sagittal plane are different between MS fallers and non-fallers. Examining relationships between upper and lower segments may allow for a better understanding of whole-body stability, which is of interest for portable fall risk assessment in clinical and real-world settings.

The relationship between trunk and foot movement variability during walking is sensitive to separate fallers from non-fallers

Craig, J., Bruetsch, A., Lynch, S., Huisinga, J.

Background and Purpose: During walking, stability is maintained by controlling the interaction between the base of support (feet) and center of mass (trunk). Controlling this interaction requires appropriate sensorimotor feedback such that each step correctly guides the movement of the trunk. When sensorimotor feedback is altered or delayed stability is decreased and individuals have a higher risk for falling. While previous studies have shown that altered trunk movement variability may be an indicator of fall risk, measuring the relationship between upper and lower body motion may provide a stronger indicator of fall risk compared to trunk measures alone. Persons with multiple sclerosis (MS) have high risk of falls and display delayed sensorimotor feedback so the present study determined if relationships between acceleration variability at the trunk and at the foot more sensitively separate MS fallers from MS non-fallers compared to trunk acceleration variability measures.

Methods: Persons with MS (age 22-60) were separated into MS fallers (2 or more falls in the previous 6-months; n=26) and MS non-fallers (no fall history; n=26). All subjects walked on a treadmill at self-selected pace for 3-minutes while wearing inertial sensors on their sternum and right ankle. Root mean square (RMS) and sample entropy (SaEn) were calculated from acceleration time series in the sagittal plane. To examine relationships between the trunk and feet, the gait stability index was calculated as the ratio of trunk acceleration variability to foot acceleration variability. Receiver operating characteristic curves were constructed for trunk and gait stability index variables, and the area under the curve (AUC) was calculated to assess sensitivity of these variables in separating MS fallers from MS non-fallers.

Results: MS fallers walked slower compared to MS non-fallers. The gait stability index was significantly higher in MS fallers compared to MS non-fallers for RMS ($p=0.036$) and SaEn ($p=0.004$) in the sagittal plane. There were no significant differences found between fallers and non-fallers for the trunk variability measures. The gait stability index showed moderate separation between groups for RMS (AUC=0.709) and SaEn (AUC=0.772). The trunk variability measures demonstrated poor separation between groups for RMS (AUC=0.684) and SaEn (AUC=0.597).

Discussion: The gait stability index in the sagittal plane can separate MS fallers from MS non-fallers more sensitively than trunk acceleration variability measures. Examining relationships between upper and lower segments may allow for a better understanding of whole-body stability rather than only studying movement of a single segment such as the trunk. The gait stability index used in the current study would be of particular interest for predicting persons at risk of future falls. Additionally, a sensitive measure of fall risk could be used to monitor progression of disease, efficacy of treatments, or predict fall risk in real time during daily life.

9 Appendix B: Calculation of variability measures

9.1 Data preparation

The raw acceleration time series were exported to Matlab (MATLAB version R2013b, The MathWorks, Inc., Natick, Massachusetts, USA) and were initially translated from local 3-dimensional Cartesian coordinates to resultant frontal and sagittal plane time series. These resultant frontal and sagittal plane time series were not aligned to the global anatomical planes, but only local to the individual sensors. The frontal plane time series was formed from the resultant of the X and Y acceleration time series, while the sagittal plane time series was formed from the resultant of the X and Z acceleration time series (Figure 9.1). All subsequent processing took place on the resultant frontal and sagittal acceleration time series. Matlab code for approximate entropy, sample entropy, and Lyapunov exponents was adapted from code developed by John McCamley and the University of Nebraska Omaha Center for Research in Human Movement Variability [1, 2]. For accurate analysis of the variability and complexity within the time series, data was left unfiltered [3].

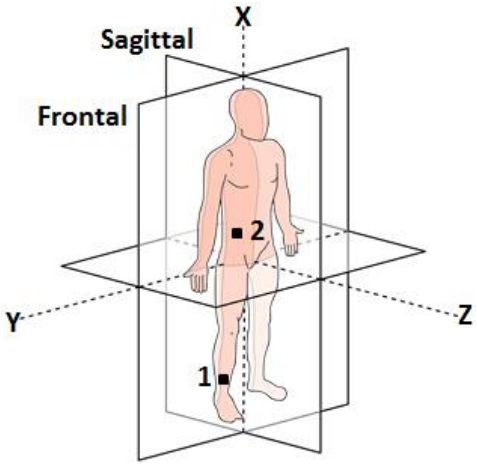


Figure 9.1. Alignment of axes from inertial sensors 1 (lumbar sensor) and 2 (right ankle sensor) with anatomical planes.

9.2 Calculation of linear variability measures

Range: A custom Matlab program was used to calculate the range of both the frontal and sagittal plane unfiltered acceleration time series. Range was used to quantify the absolute spread of the acceleration time series recorded during the trials.

$$Range_{Frontal/Sagittal} = Max(Acc_{Frontal/Sagittal}) - Min(Acc_{Frontal/Sagittal}) \quad \text{Eq. (1)}$$

Root Mean Square: A custom Matlab program was used to calculate the root mean square (RMS) of both the frontal and sagittal plane unfiltered acceleration time series. RMS was used to quantify the dispersion of the acceleration time series recorded during the trials.

$$RMS_{Frontal/Sagittal} = \sqrt{\frac{\sum Acc_{Frontal/Sagittal}{}^2}{N}} \quad \text{Eq. (2)}$$

9.3 Calculation of nonlinear variability measures

Sample Entropy: A custom Matlab program was used to calculate sample entropy (SaEn) and of both the frontal and sagittal plane unfiltered acceleration time series. SaEn(*m*, *r*, *N*) quantifies the entropy in a time series consisting of *N* data points, and is defined as the negative natural logarithm of the probability that a vector, or sequence, of data points of length, *m*, would repeat itself at *m*+1 [1]. Time lag, τ, is not typically included in entropy algorithms as τ=1 is typically sufficient [1, 4]. However, it was appropriate in the current study to use a time lag was to account for the accelerometers' high sample rates, differences in relative accelerations and magnitudes between the sensor at the foot and the sensor at the trunk, and to quantify the complexity of the signal due to nonlinear processes in the system [4]. The time lag was found by using the first minimum found by the average mutual information (AMI) algorithm [5]. Further details on the AMI algorithm can be found in the appendix. The principle behind finding the appropriate time lag is that a data point should have new information compared to the previous data point, but the points should not be so far separated from each other that they are completely independent of each other.

Given the raw acceleration time series, a set of *m*-length vectors, X_i was created such that the first vector contained data points 1 through *m*, as shown in Eq. (3). X_j was similarly created

as shown in Eq. (4). Comparisons were then made against each *m*-length vector, X_i and X_j for j=i+1, for the length of the time series.

$$X_i = (x_i, x_{i+\tau}, x_{i+2\tau}, \dots, X_{i+(m-1)\tau}) \quad \text{Eq. (3)}$$

$$X_j = (x_j, x_{j+\tau}, x_{j+2\tau}, \dots, X_{j+(m-1)\tau}) \quad \text{Eq. (4)}$$

If the two vectors being compared fell within a predetermined tolerance level, $\pm r$*standard deviation, the vectors were considered to be alike. The sum of the total number of alike vectors was then divided by *N*-*m*+1 and called *B*. The entropy algorithms then repeated this process but increased the vector length to *m*+1, and this subset was called *A*. SaEn was then calculated as shown in Eq. (6).

$$SaEn(m, r, N, \tau) = -\ln\left(\frac{A}{B}\right) = -\ln\left(\frac{\sum_{i=1}^{n-m\tau} A_i}{\sum_{i=1}^{n-m\tau} B_i}\right) \quad \text{Eq. (6)}$$

A tolerance coefficient of *r*=0.2 was used in this study, making the tolerance level 0.2*standard deviation, which is a general standard for entropy analysis. However, when using entropy measures, especially with continuous and cyclic time series data, it is important to examine the relative consistency of the analysis [6]. To check for relative consistency, the analysis was also run for vector lengths *m*=2 and *m*=4, as well as for tolerance coefficients *r*=0.15 and *r*=0.25. A perfectly regular and periodic time series such as a sine wave will result in a SaEn value of 0, and a random time series such as white noise will result in a SaEn value toward infinity.

Lyapunov Exponent: Local dynamic stability of the acceleration time series were assessed using the maximum finite-time Lyapunov exponent (λ_{max}) found via Wolf's algorithm [2]. The first step required when calculating local dynamic stability is the reconstruction of the state space *Y*(t). *Y*(t) is a function of the time series data *x*(t) which requires two main input parameters of time lag τ and an embedding dimension *n*, such that:

$$Y(t) = [x(t), x(t+\tau), x(t+2\tau), \ldots, x(t+(n-1)\tau)] \quad \text{Eq. (7)}$$

Time lag is again found through the use of the AMI function, while the embedding dimension is found using the false nearest neighbors (FNN) approach [7]. Further details regarding the FNN algorithm can be found in the appendix.

The time series were then unfolded into the newly reconstructed state spaces, and λ_{max} was then calculated for each time series. λ_{max} measures the rate at which nearby orbits converge or diverge. The algorithm first chooses a random initial point and follows the subsequent points, creating a reference trajectory. The nearest neighboring vector is then selected which follows a second trajectory. The distance between these two vectors are $L(t_0)$ and $L'(t_1)$ after a given time evolution of t_1. A new nearest neighboring vector is found nearest to the point on the reference trajectory at t_1. $L(t_1)$ is the distance between the reference trajectory and this nearest vector. This process is repeated until the reference trajectory has passed over the entire data set, with *M* being the total number of replacement steps. Then, λ_{max} is then calculated by Eq. (8):

$$\lambda_1 = \frac{1}{t_M - t_0} \sum_{k=1}^{M} \log_2 \frac{L'(t_k)}{L(t_{k-1})} \quad \text{Eq. (8)}$$

The process is then repeated once for each embedding dimension, until you have a set of λ_m, one for each embedding dimension. The maximum exponent is then taken as the largest λ from this set. An exponent $\lambda > 0$ indicates exponential growth or divergence, $\lambda = 0$ indicates a marginally stable state, and $\lambda < 0$ indicates exponential decay or convergence.

9.4 Algorithms used for variability analysis parameter selection

Algorithms for average mutual information (AMI) and false nearest neighbors (FNN) were developed by members of the University of Nebraska Omaha Center for Research in Human Movement Variability.

9.4.1 Average Mutual Information

The time lag was found by using the first minimum found by the average mutual information (AMI) algorithm. The principle behind finding the appropriate time lag is that a data point should have new information compared to the previous data point, but the points should not be so far separated from each other that they are completely independent of each other. The AMI algorithm is based around Eq. (4), where *k* is a variable time lag from 0 to 100, $P(x_t)$ is the probability of observing point x_t, $P(x_{t+k})$ is the probability of observing point x_{t+k}, and $P(x_t,x_{t+k})$ is the probability of observing point x_t and x_{t+k}.

$$I(k) = \sum_{t=1}^{n} P(x_t, x_{t+k}) \log_2 \frac{P(x_t,x_{t+k})}{P(x_t)P(x_{t+k})} \qquad \text{Appendix Eq. (1)}$$

The algorithm iterates through *k* and plots the results as shown in Figure 9.2, and the time lag is selected by identifying the first minimum average mutual information in the plot.

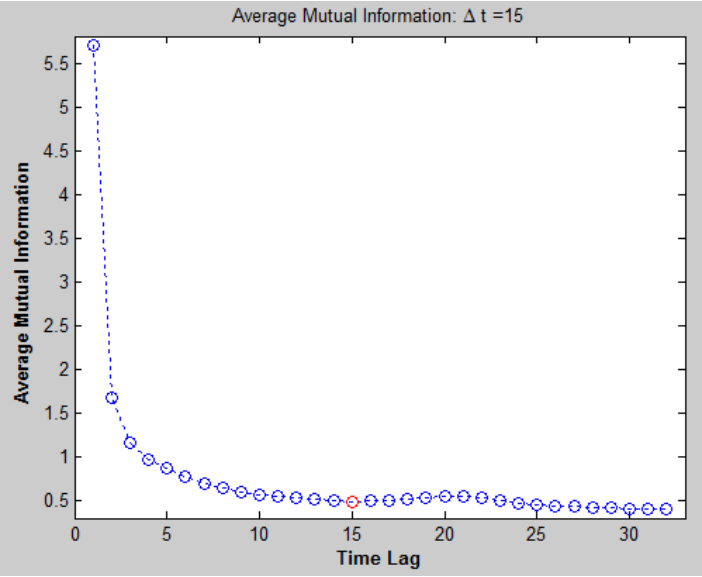


Figure 9.2. Depicted here is an example plot of average mutual information as a function of time lag. For this time series, the appropriate time lag is found to be 15.

9.4.2 False Nearest Neighbors

The embedding dimension was found using the false nearest neighbors (FNN) approach. FNN are defined as sets of points that appear very close at dimension n=k, but not n=k+1 [7], a simple representation of this can be seen in Figure 9.3.

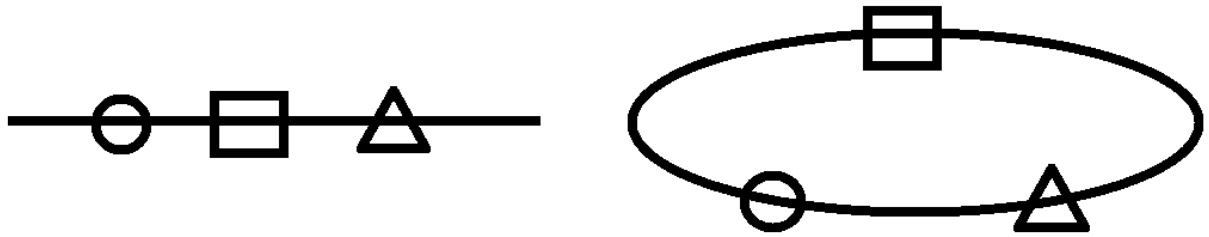


Figure 9.3. An illustration of the concept of false nearest neighbors. In 2-demensional space (left), it appears the square is the nearest neighbor to the circle. However, in 3-dimensional space, it is apparent that the triangle is in fact the nearest neighbor to the circle.

The FNN algorithm takes two sequential points in dimension *d* and calculates the distance between a vector and its nearest neighbor in the *d* dimensional space (Eq. 9). The algorithm then moves up to one higher dimensional space *d*+1 and calculates the distance between the same two vectors again (Eq. 10).

$$\|V(t) - V^{NN}(t)\| \qquad \text{Appendix Eq. (2)}$$

$$\left\|\hat{V}(t) - \hat{V}^{NN}(t)\right\| \qquad \text{Appendix Eq. (3)}$$

If they are true neighbors, the distances will be similar in both dimensional spaces. A ratio is taken of the differences in the distances, and if the ratio is beyond a preselected tolerance R_{tol}, the vector is a false nearest neighbor (Eq. 11).

$$\frac{\|\hat{V}(t)-\hat{V}^{NN}(t)\|^2-\|V(t)-V^{NN}(t)\|^2}{\|V(t)-V^{NN}(t)\|} > R_{tol}$$ Appendix Eq. (4)

The algorithm continues to cycle through dimensions 1 through 14, recording the percentage of false nearest neighbors, and plots each result. The embedding dimension is taken as the dimension at which %FN falls to approximately zero.

9.5 Matlab code used in the current study:

9.5.1 Code to calculate root mean square and range

```
%Root mean square and range
%-----------------------RMS--Range--------------------
clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '\']);

files=dir([directory_name,'*dat']);

if isempty(files)
    msgbox('No raw files in this directory');
end

for i=1:length(files)
    filename = [];
    filename = [filename; files(i).name]
    data=load([directory_name filename]);

RMSacc(i) = rms(data);
rangeAcc(i) = range(data);
end

%save, filename
        name = char(files.name);
        label = char('Filename', 'RMS', 'Range');
        c = cellstr(label);
        R = [RMSacc', rangeAcc'];
        results = [c'; cellstr(name), num2cell(R)];

       % xlswrite('RMS_Range',results);
```

```
user = getenv('USERNAME');

cd(['C:\Users\', user, '\Desktop'])

clc
disp('Writing results...')

xlswrite('RMS_Range',results)

close all

disp('Results written to the desktop as RMS_Range.xls')
```

9.5.2 Code to calculate average mutual information and false nearest neighbors

```
%Step 2
%Sample main function to obtain time delay and embedding
dimension
%Last Edited: Jordan Craig 7/2/15
clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '\']);
files=dir([directory_name,'*.dat']);

namer = struct2cell(files);

if isempty(files)
    msgbox('No raw files in this directory')
end
if isempty(files)
    msgbox('No raw files in this directory')
end

for i = 1:length(files)

    clearvars -except allDimTau namer i directory_name

    filename=char(namer(1,i));
    data=load([directory_name filename]);
```

```
    L=32; % window size for average mutual information
    MaxDim=14; Rtol=15; Atol=2; %parameters to obtain embedding
dimension

    figure(i)
    [tau,v_AMI]=AMI(data, L); %Find the first minimum average
mutual information

    [FN,dim] = FNN(data,tau,MaxDim,Rtol,Atol); %Find embedding
dimension

    %AMI_plot(tau,v_AMI,L ) %Plot average mutual information

    %FN_plot(FN,dim,MaxDim) %Plot the percentage of false
nearest neighbors

    allDimTau{i,1} = filename;
    allDimTau{i,2} = tau;
    allDimTau{i,3} = dim;

end

user = getenv('USERNAME');
cd(['C:\Users\', user, '\Desktop'])
clc
disp('Writing results...')
xlswrite('DimTau_Results',allDimTau)
%close all
disp('Results written to the desktop as DimTau_Results.xls')

function [tau,v_AMI]=AMI(data, L)

%L = 32; %maximal lag -- arbitrarly selected, must be much
smaller than length(data)

N=length(data);
bins=128;   %number of bins used for histogram calculation

epsilon = eps;      %or use epsilon = 1e-10;

data = data - min(data);       % making all the data points
positive
data = 1+ floor(data/(max(data)/(bins-epsilon)));  %scaling the
data
v=zeros(L,1);   %create a zero vector
overlap=N+1-L;
```

```
increment= 1/overlap;
one = ones(overlap,1); %create a column vector with all elements
being one

% MUTUAL INFORMATION
% I (time_lag) = sum [ p(x(t), x(t + time_lag))*log[(p(x(t),p(x
+ time_lag))/p(x(t))*p(x(t+time_lag))]

%find probability p(x(t))= pA
pA = sparse (data(1:overlap),one,increment);
%e.g. when overalp = N+1-L = 6001+1-32= 5970,
max(data(1:overlap))=129,
%creaing a histogram with (129-1) bins
% sum(pA)= 1 --> 100 % in total

for lag = 0: L -1
    %find probablity p(x(t+time_lag))=pB, sum(pB)=1
    pB = sparse(one, data(1+lag:overlap+lag), increment);
    %find joing probability p(A,B)=p(x(t),x(t+time_lag))
    pAB =
sparse(data(1:overlap),data(1+lag:overlap+lag),increment);
    [A, B, AB]=find(pAB);
    v(lag+1)=sum(AB.*log2(AB./(pA(A).*pB(B'))));  %Average
Mutual Information
end

v_AMI=v;
%Take time_lag when 1st min(I(time_lag))occurs for values of
time_lag near
%this minimum, the coordinate system produced by time delay
vector is
%esentially as good as that of the time_lag whih is the actual
1st min(I(time_lag))
for i = 1: length(v)-1
      if (find((v(i)<v(i+1))&&(v(i)<v(i-1)))) == 1
          x(i)=i;
    end
end

A = sparse(x);
A= find(A);
tau = A(1);   % tau = 1st min(I(time_lag))


function [FN,dim] = FNN(data,tau,MaxDim, Rtol,Atol )
```

```
% Determine the embedding dimension for a time series using the
false
% nearest neighbors
% References:   "Determining embedding dimension for phase-space
reconstruction using
% a geometrical construction", M. B. Kennel, R. Brown, and
H.D.I. Abarbanel,
% Physical Review A, Vol 45, No 6, 15 March 1992, pp 3403-3411.
% Inputs:
% data:     a time series
% tau:      time delay
% MaxDim:   maximum embedding dimension
% Rtol:     threshold for the first criterion
% Atol:     threshold for teh second criterion
% PerFFNs:  Threshold for percentage false nearest neighbors

n=length(data)-tau*MaxDim;  % # of data points to be used
RA=std(data); %the nominal "radius" of the attractor

data=data';
z = data(1:n);
y = [];
FN = [];

global yq m_search L_done pqd pqr pqz b_upper b_lower sort_list
node_list

m_search = 2; % just search for the nearest point; the closest
will be yq
% itself and the next its neighbor

indx=[1:n];

for dim = 1:MaxDim
    y = [y; z];
    z = data(1+tau*dim:n+tau*dim);
    L = zeros(1,n);
    %fprintf('Partitioning data for dim = %d\n',dim)
    kd_part(y, z, 512); % put the data into 512-point bins <--
this needs optimization
    %fprintf('Checking for false nearest neighbors\n')

    for i = 1:length(indx)
        yq = y(:,indx(i)); % set up the next point to check
        % set up the bounds, which start at +/- infinity
        b_upper = Inf*ones(size(yq));
        b_lower = -b_upper;
```

```
        % and set up storage for the results
        pqd = Inf*ones(1,m_search);
        pqr = [];
        pqz = [];
        L_done = 0;
        kdsearch(1); % start searching at the root (node 1)
        distance = pqz(1) - pqz(2);
        if abs(distance) > pqd(2)*Rtol
            L(i) = 1;
        end
        if sqrt(pqd(2)^2+distance^2)/RA > Atol
            L(i) = 1;
        end
    end
    FN = [FN sum(L)/n];
end

dE=FN(:,1:length(FN))';
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%
for i = 2:13
    if (dE(i)==0)||((dE(i-1)>dE(i)&&(dE(i)< dE(i+1))))
        dim(i)= i;
        i=i+1;
    else
        i=i+1;
    end
end
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%
dim=[];
for i = 1: 13
    %if dE(i)-dE(i+1)<=0
    if dE(i)-dE(i+1)<=0.001
        dim(i) = i;
    end
end
A=sparse(dim);
A=find(A);
dim=A(1);
```

9.5.3 Code to calculate sample entropy

```
%Last editted: Jordan Craig 8/11/15
```

```
%Entropy Step 3
%------------------------Sample Entropy-----------------------
clear all
close all
clc

directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '\']);

files=dir([directory_name,'*dat']);

if isempty(files)
    msgbox('No raw files in this directory');
end

[tauVal, tauName] =
xlsread([directory_name,'DimTau_Results.xls']);

% Entropy inputs (m = vector length; R = tolerance -->
R*StD(data))
m = 3;
R = 0.2;

for i=1:length(files)
    filename = [];
    filename = [filename; files(i).name]
    data=load([directory_name filename]);
    varTau = tauVal(i);
    tauUsed(i) = varTau;

%Sample  for original time series
SE(i) = SampEntHPL(data, m, R, varTau);

end

%save filename, SaEn of original data, Success rate A0, A1
        name = char(files.name);
        label = char('Filename', 'sEnt', 'Tau Used', 'RMS');
        c = cellstr(label);
        R = [SE', tauUsed'];
        results = [c'; cellstr(name), num2cell(R)];

       % xlswrite('Sample_Entropy Entropy',results);

user = getenv('USERNAME');

cd(['C:\Users\', user, '\Desktop'])
```

```
 clc
 disp('Writing results...')

 xlswrite('Sample_Entropy',results)

 close all

 disp('Results written to the desktop as Sample_Entropy.xls')


function SE = SampEnt(data, m, R, varTau)
 % Function to find Sample Entropy using the method described by
Richman et
 % al. 2000
 % J McCamley 7/16/2015
% Editted by Jordan Craig 8/11/15


 % Define R as r times the standard deviation
 r = R * std(data);
 u = data;
 N = length(u);
 tau = varTau;

 %Jordan Craig Added time delay sections - fall 2015
 for i = 1:N-m*tau
     for j = 1:N-m*tau
         for k = 1:m
             dij(k) = abs(u(i+((k-1)*tau))-u(j+((k-1)*tau)));
         end
         di(j) = max(dij);
     end
     d = find(di<=r); % find the vectors that are less than "r"
distant from one another
     nm = length(d)-1; % subtract the self match
     Bm(i) = nm/(N-(m*tau)-1);
 end
 Bmr = sum(Bm)/(N-(m*tau));

 for i = 1:N-m*tau
     for j = 1:N-m*tau
         for k = 1:m+1
             dij(k) = abs(u(i+((k-1)*tau))-u(j+((k-1)*tau)));
         end
         di(j) = max(dij);
     end
```

```
     d = find(di<=r); % find the vectors that are less than "r"
distant from one another
     nm = length(d)-1; % subtract the self match
     Am(i) = nm/(N-(m*tau)-1);
 end
 Amr = sum(Am)/(N-(m*tau));

 B = (((N-(m*tau)-1)*(N-(m*tau)))/2)*Bmr;
 A = (((N-(m*tau)-1)*(N-(m*tau)))/2)*Amr;
 SE = -log(A/B);
 End
```

9.5.4 Code to calculate Lyapunov Exponent

```
% Code to find the Lyapunov exponent for a selected data series
using the
 % Wolf algorithm and input values of Tau and Embedding
Dimension
 % John McCamley - 7/16/2015
 % For this code to run it requires the files in the folder
"LyE_Wolf" to
 % be in the Matlab path
 % Editted by Jordan Craig - 10/14/2015
 % To run batch folders with xls doc assigning tau

 clear all
 close all
 clc

 directory_name=uigetdir(pwd,'Select data directory');
 directory_name=([directory_name '\']);

 files=dir([directory_name,'*dat']);

 if isempty(files)
     msgbox('No raw files in this directory');
 end

 [tauVal, tauName] =
xlsread([directory_name,'DimTau_Results.xls']);

 % input embedding dimension for batch
 input1 = 'Enter the embedding dimension for this data? ';
```

```
 dim = input(input1);

 for i=1:length(files)
     filename = [];
     filename = [filename; files(i).name]
     data=load([directory_name filename]);
     varTau = tauVal(i);
     tauUsed(i) = varTau;

 %LyE
 LyE(i)=Lyapunov(data,dim,varTau);

 end

 %save / output .xls doc
         name = char(files.name);
         label = char('Filename', 'LyE', 'Tau Used');
         c = cellstr(label);
         R = [LyE', tauUsed'];
         results = [c'; cellstr(name), num2cell(R)];


 user = getenv('USERNAME');

 cd(['C:\Users\', user, '\Desktop'])

 clc
 disp('Writing results...')

 xlswrite('LyE_Wolf_Results',results)

 close all

 disp('Results written to the desktop as LyE_Wolf_Results.xls')


function LyE=Lyapunov(X,dim,tau)

 % dim:  embedding dimension
 % tau: time lag
 % DT: time between data samples required only for normalization
of the
 %      exponent
 % A: relative accuracy of the data below which noise is
expected to
 %     dominate
```

```
 % SCALMX: length scale on which the local structure of
attractor is no
 %          longer being probe
 % n: number of sample intervals over which each pair of points
is followed
 %    before a new pair is chosen.  If n is too large teh
trajectories get too
 %    far apart and the exponential divergence of the orbit is
lost.
 % IND: initial points to fiducial trajectory


 %change paramters here

 DT=1;
 A= 10^(-4);
 SCALMX=(max(X)-min(X))/10;
 n=3;
 IND=1;

 LyE=LyE_Wolf(X,dim,tau,DT,A,SCALMX,n,IND);



function [x,y] = embed(z,v,w)

 % [x,y] or x= embed(z,lags) or embed(z,dim,lag)
 % embed z using given lags or dim and lag
 % embed(z,dim,lag) == embed(z,[0:lag:lag*(dim-1)])
 % negative entries of lags are into future
 %
 % If return is [x,y], then x is the positive lags and y the
negative lags
 % Order of rows in x and y the same as sort(lags)
 %
 % defaults:
 %  dim = 3
 %  lag = 1
 %  lags = [0 1 2]; or [-1 lags] when two outputs and no
negative lags


 % Copyright (c) 1994 by Kevin Judd.
 % Please see the copyright notice included in this distribution
 % for full details.
 %
 % NAME embed.m
```

```
%   $Id$


if nargin==3
  v= 0:w:w*(v-1);
end;
if nargin==1
  v= [0 1 2];
end
if nargout==2 & min(v)>=0
  v= [-1 v];
end
lags= sort(v);

dim = length(lags);

[c,n] = size(z);
if c ~= 1
  z = z';
  [c,n] = size(z);
end
if c ~= 1
  error('Embed needs a vector as first arg.');
end

if n < lags(dim)
  error('Vector is too small to be embedded with the given
lags');
end


w = lags(dim) - lags(1);           % window
m = n - w;                    % Rows of x
t = (1:m)  + lags(dim);            % embed times

x = zeros(dim,m);

for i=1:dim
  x(i,:) = z( t  -  lags(i) );
end

if nargout==2
  id= find(v<0);
  y= x(id,:);
  id= find(v>=0);
  x= x(id,:);
end;
```

```
function ZLAP=LyE_Wolf(X,dim,tau,DT, SCALMN, SCALMX, EVOLV,IND)

 [r c]=size(X);
 if c > r
     X=X';
 end

 SUM=0.0;  % Sum holds running exponent estimate sans 1/time;
 ITS=0; % total number of propagation steps

 NPT=length(X)-dim*tau-EVOLV;  %Calculate useful size of data

 %Find nearest neighbor to first data point
 DI=1.e38;

 %Dont take point too close to fiducial point

 for i=11:NPT
     %Compute separation between fiducial point and canidate
     D=0;
     for j=1:dim
         D=D+(X(IND+(j-1)*tau)-X(i+(j-1)*tau))^2;
     end
     D=sqrt(D);

     %Store the best point so far but no closer than noise scale
     if (D <= DI) && (D >= SCALMN)
         DI=D;
         IND2=i;
     end
 end

 while (IND < NPT)
     %get coordinates of evolved points
     PT=GetCoordinate(X,IND,IND2,EVOLV,dim,tau);
     PT1=PT(:,1)';
     PT2=PT(:,2)';

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
     %Plot
     %SensitveDependenceIC(X,dim,tau,IND,IND2,EVOLV)

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

```
     %compute final separation between pair, update exponent
     DF=0;
     for j=1:dim
         DF=DF+(PT1(j)-PT2(j))^2;
     end
     DF=sqrt(DF);

     ITS=ITS+1;
     SUM=SUM+log(DF/DI)/(EVOLV*DT);

     ZLAP=SUM/ITS;

     %Look for replacement point
     %ZMULT is multiplier of SCALMX when go to longer distances
     INDOLD=IND2;
     ZMULT=1;
     ANGLMX=0.3;
     THMIN=3.14;

     %Search over all points
     [DII IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1,
PT2,SCALMX, ZMULT, SCALMN,DF,ANGLMX,INDOLD);

     IND=IND+EVOLV;
     DI=DII;
 end
 ZLAP;



function [DII, IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1,
PT2,SCALMX, ZMULT, SCALMN, DF,ANGLMX,INDOLD)

 THMIN=3.14;
 NPT=length(X)-dim*tau-EVOLV;
 for i=1:NPT
     III=abs(i-(IND+EVOLV));
     if (III >= 10)
         DNEW=0;
         for j=1:dim
             DNEW=DNEW+(PT1(j)-X(i+(j-1)*tau))^2;
         end
         DNEW=sqrt(DNEW);

         %look further away than noise scale, closer than
ZMULT*SCALM
         if (DNEW <= ZMULT*SCALMX)&&(DNEW >= SCALMN)
```

```
            %Find angular change old to new vector
            DOT= sum((PT1'-X(i+((1:dim)-1)*tau)).*(PT1'-PT2'));
            CTH=abs(DOT/(DNEW*DF));
            if (CTH > 1.0)
                CTH=1.0;
            end
            TH=acos(CTH);
            %Save point with smallest angular change so far
            if (TH <= THMIN)
                THMIN=TH;
            %end
            DII=DNEW;
            IND2=i;
            end
        end
    end
 end

  if (THMIN >= ANGLMX)
      [DII, IND2]=LookLongerDistance(X, dim, tau, IND, EVOLV,
PT1, PT2,SCALMX, ZMULT, SCALMN,DF, ANGLMX,INDOLD);
  end



function PT=GetCoordinate(X,IND,IND2,EVOLV,dim,tau)

 if min((length(X)>IND+EVOLV+((1:dim)-1)*tau))&&
min((length(X)>IND2+EVOLV+((1:dim)-1)*tau))
     PT1=[X(IND+EVOLV+((1:dim)-1)*tau)]';
     PT2=[X(IND2+EVOLV+((1:dim)-1)*tau)]';
     PT=[PT1' PT2'];
 else
     disp('Exceeds the length of X')
 end


function [DII, IND2]=LookLongerDistance(X, dim, tau, IND, EVOLV,
PT1, PT2,SCALMX, ZMULT, SCALMN,DF, ANGLMX,INDOLD)

 %Can't find a replacement -- look at longer distances
 ZMULT = ZMULT+1;
 if (ZMULT<5)
     [DII,IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1,
PT2,SCALMX, ZMULT, SCALMN,DF,ANGLMX,INDOLD);
     %disp('here1')
 else
```

```
     % No replacement at 5*SCALE, double search angle, reset
     % distance
     ZMULT=1.0;
     ANGLMX=2*ANGLMX;
     if (ANGLMX < 3.14)
         [DII,IND2]=GetNewPt(X, dim, tau, IND, EVOLV, PT1,
PT2,SCALMX, ZMULT, SCALMN,DF,ANGLMX,INDOLD);
     else
         IND2=INDOLD+EVOLV;
         DII=DF;
     end
 end
```

9.6 Analyzing minimum number of short overground bouts

```
% % Want to get R^2 (from R) from a correlation between estGSI
vs actualGSI.
% % Each correlation will be for a specific number of bouts in
the est.
% % Each datapoint will be one subject (x = estGSI, y =
actualGSI).
% % Jordan Craig Spring 2018


clear all
close all
clc


directory_name=uigetdir(pwd,'Select data directory');
directory_name=([directory_name '/']);

% Pull in Names (col A) and GSI Data (Col F) from the 2 xls
files

%Names
%[~,allFroNames] =
xlsread([directory_name,'RMS_Fro.xlsx'],'A:A');
[~,allSagNames] =
xlsread([directory_name,'SaEn_Sag.xlsx'],'A:A');
%Data
%allFroGSI = xlsread([directory_name,'RMS_Fro.xlsx'],'F:F');
allSagGSI = xlsread([directory_name,'SaEn_Sag.xlsx'],'F:F');
```

```
% Create Struct of individual subj and their fro and sag GSIs
over bouts

c = 1;
j = 0;


for i=1:length(allSagGSI)

    %subj.num = c;
    j = j+1;
    count(c) = j;

    if i+1 > length(allSagGSI)
        c = c;
        %test=3
    elseif
strcmp(allSagNames{i}(1:15),allSagNames{i+1}(1:15))==1
        c = c;
        %test=1
    elseif
strcmp(allSagNames{i}(1:15),allSagNames{i+1}(1:15))==0
        c = c+1;
        j = 0;
        %test=2
    end

end

%minimum number of bouts
minBouts = min(count);

clear i

for n = 1:1000

    clearvars -except minBouts allSagNames allSagGSI
allBoutRSquareSag n dataStruct count
    c = 1;
    j = 0;

% Need to get the GSI data into the correct cells -------- \/
%First subj
dataStruct.('sagSub1') = allSagGSI(1:count(1));

    mix = randperm(count(1));
    tempVect = dataStruct.('sagSub1')(:,1);
```

```
    dataStruct.('sagSub1')(:,1) = tempVect(mix);

    for j = 1:count(1)
        dataStruct.('sagSub1')(j,2) =
mean(dataStruct.('sagSub1')(1:j,1));
    end
actualGSI(1) = dataStruct.('sagSub1')(end,2);

for k = 1:minBouts
    estGSI(1,k) = dataStruct.('sagSub1')(k,2);
end

subLabels{1} = ['sagSub1'];

%Rest of subjs
for i = 1:length(count)-1

    subLabels{i+1} = ['sagSub' num2str(i+1)];

    tempCount = count(1:i);
    tempCount2 = count(1:i+1);
    dataStruct.(subLabels{i+1}) =
allSagGSI((sum(tempCount)+1):(sum(tempCount2)));

    mix = randperm(count(i+1));
    tempVect = dataStruct.(subLabels{i+1})(:,1);
    dataStruct.(subLabels{i+1})(:,1) = tempVect(mix);

    for j =
1:length(allSagGSI((sum(tempCount)+1):(sum(tempCount2))))
        dataStruct.(subLabels{i+1})(j,2) =
mean(dataStruct.(subLabels{i+1})(1:j,1));
    end

    actualGSI(i+1) = dataStruct.(subLabels{i+1})(end,2);

    for k = 1:minBouts

        estGSI(i+1,k)=dataStruct.(subLabels{i+1})(k,2);

    end
end

clear i j k


for k = 1:minBouts
```

```
    tempCorr = corrcoef(estGSI(:,k),actualGSI);
    boutCorrSag(k) = tempCorr(1,2);
    boutRSquareSag(k) = (tempCorr(1,2))^2;
end

allBoutRSquareSag(n,:) = boutRSquareSag;

end

meanAllBoutRSquareSag = mean(allBoutRSquareSag,1);

for i = 1:length(boutCorrSag)-1
    improvementSag(i) = (meanAllBoutRSquareSag(i+1) -
meanAllBoutRSquareSag(i))/meanAllBoutRSquareSag(i);
    if improvementSag(i)>0.01
        %continue
    elseif improvementSag(i) <= 0.01
        i
    end
end
```

10 Appendix C: Recruitment materials

10.1 Recruitment Flyer

VOLUNTEERS NEEDED FOR WALKING STUDY

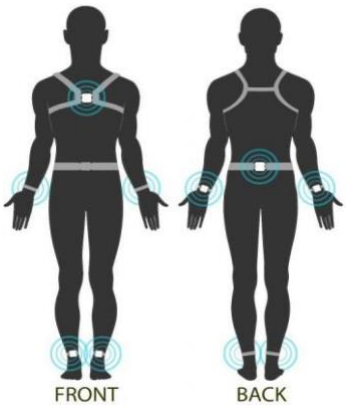
This study is being conducted in the Human Performance Laboratory at the Landon Center on Aging (KUMC). We aim to establish a clinical testing protocol for identification of walking problems and fall risk. Compensation will be provided.

Who are we looking for?

Persons with Multiple Sclerosis, age 20-60 years.

1. Must be able to walk for at least 25 feet without any aid.
2. No symptom exacerbations within previous 60 days.
3. No significant musculoskeletal disorders, vestibular problems, or orthopedic surgeries in the past.
4. Not currently taking Ampyra or Dalfampridine medications.

What will you be asked to do?



1. Participate in a testing session lasting about 2 hours in the Human Performance Laboratory at the Landon Center on Aging (KUMC).
2. Wear non-invasive wireless sensors and motion capture markers to track movement.
3. Walk on a treadmill at a variety of speeds – walking for 90 seconds at a time with breaks in-between.
4. Walk on an over-ground pathway for 4-minutes.

For more information contact:

Jordan Craig
(913) 588-0624
(913) 588-6372
jcraig2@kumc.edu
Landon Center on Aging
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160
Phone: (913) 588-1203
Fax: (913) 588-1201

10.2 Recruitment call script

"Hello [participant name], this is [your name] from the Human Performance Lab at the KU Medical Center. I'm calling you because you have participated in previous studies with our lab looking at walking and balance in MS. Our lab is working on a walking study where we have participants come in and walk on a treadmill for a total of about 2 hours. The entire visit will take no longer than 2 hours."

- **If VM**: "If that is something you would be interested in participating in, please give us a call at 913-588-0624. Thanks, have a great day."
- **If Person**: "Would that be something you may be interested in participating in?"

[They respond yes or no]

- If yes, continue down script
- If no, thank them for their time and end the conversation.

"Is it okay if I ask you a few screening questions first to see if you qualify for the study?

[They respond. **Go through questions to ask 4024 volunteers.** We want to be sure they will be able to finish the testing safely. This should be caught by the original exclusion criteria, but this is to double check.]

"Great, then it looks like you qualify for our study. We test from 9-5 Monday, Wednesday, Friday and the testing requires a 2-hour block of time. So the earliest you could schedule a collection would be 9am, and the latest would be 3pm. Are there any days or times during the week that would work best for you?"

[They respond. You look at the calendar. If they are especially indecisive, pick out a day for them. Ensure there are no conflicts on any of the calendars and that at least two people will be working at the time of the appointment. Write the date and time down on scratch paper immediately in case you can't add it quickly enough to the calendar.]

"Okay, I've got you down for [date and time]. And may a take down a phone number to reach you at?

[They respond, take down their number.]

"Okay, we're all set then. I will see you on [date and time]. If you have any questions, please call us at 913-588-0624. If you need to reschedule or cancel, please call at least one day in advance if possible. Alright, thank you."

10.3 Phone screening

MS Phone Screening

1. What is your age?
   *Must be 20 – 60
2. Are you currently taking Ampyra or Dalfampridine?
   *Can't be taking these

3. Have you had any recent symptom exacerbations? If yes, then when approximately?
   *Can't have any within 60 days

4. Do you wear an orthotic inside or outside? AFO?
   a. How often do you use the AFO and can you walk without it?
   *Must be able to walk without it

   b. Do you walk with a cane/walker always or only in public?
   *Must be able to walk without it

   c. Can you walk 25 feet without any kind of support?
   *Must be able to do so

5. Do you have any sort of orthopedic problem? Arthritis, joint replacements or pins in the body?
6. Do you have any vestibular problems? Any inner ear or balance disorders?
7. Are you diabetic?
   *Have you ever been diagnosed with diabetic neuropathy?

8. Are you color blind?
9. Do you have any significant vision problems?

10.4 MS recruitment email

Volunteers with multiple sclerosis are needed to serve as test subjects in a study examining walking in persons with multiple sclerosis. Male and female volunteers with multiple sclerosis between the ages of 20-60 years of age are needed. Volunteers should be free from lower extremity orthopedic problems such as arthritis or ligament/tendon injuries (i.e. ACL injuries or meniscus tears) and free from any other neurological or vestibular problems. This is a one-visit study that will last approximately 2 hours and you will be compensated for your time. We will measure your walking using a three-dimensional motion capture system. There is no invasive testing involved, i.e. no blood draws or similar tests.

If you would like to participate in this study, please contact Jordan Craig in the Human Performance Lab at jcraig2@kumc.edu

Or by phone:

Human Performance Lab – 913-588-0624

Adam Bruetsch (lab associate) – 913-588-6372

PI for this study is Jessie Huisinga, PhD

11 Appendix D: Testing Materials

11.1 Informed consent

Study Title: Segmental control during walking in young and aging populations

SUBJECT CONSENT FORM

TITLE Segmental control during walking in young and aging populations

INTRODUCTION
You are being asked to join a research study. Participating in research is different from getting standard medical care. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read it carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) with Dr. Jessie Huisinga as the researcher. About 200 people will be in the study at KUMC.

Why am I being asked to take part in this study?
You are being asked to take part in this study because you are either a) a healthy young adult b) a healthy elderly adult c) a fall-prone elderly adult d) a patient with multiple sclerosis e) a patient with Parkinson's disease.

Why is this study being done?
The purpose of this line of research is to develop a method of measuring stability and fall risk in individuals during walking that may be implemented in a clinical or real world environment. With this study, we are using wireless sensors to measure movement at the trunk and at the foot during walking on a treadmill at different speeds and under different sensory conditions in healthy adults and fall-prone populations.

What is being tested in this study?
The walking parameters (variability of foot and trunk accelerations) of healthy and fall-prone adults are tested during the course of the study.

How long will I be in the study?
This is a one-time study and does not involve a long term follow up. If you qualify and agree to participate in the study, your visit will last for approximately 2 hours in the Human Performance Laboratory at the Landon Center on Aging.

What will I be asked to do?

Demographic Information
We will measure your height and weight and ask you for details regarding your previous and current health status.

Physical Function Tests
Study personnel will attach wireless sensors to your wrists, ankles, sternum (breastbone), and lower back. You will be attached via a harness to a system that supports body weight. Data collection protocol involves the following parts:

1. You will perform a number of trials of walking at different walking speeds on a treadmill ranging from slow to fast pace in order to measure your walking parameters.
2. You will perform a number of trials of walking on a treadmill while wearing specialized footwear and eyewear designed to alter your sensation and vision.
3. You will perform a standardized clinical walking assessment which requires you to walk overground for a specific length of time.
4. Healthy control subjects will walk overground for a short distance while wearing specialized footwear designed to alter your sensation.

For MS Patients: You will stand on a surface which moves forward and backward in order to measure your muscle response.

Questionnaires
You will fill out questionnaires related to your perceived fatigue, walking ability, and balance performance.

You might be embarrassed by some of the questions the researchers ask you. You are free not to answer any questions.

What are the possible risks or discomforts?
The study may cause injury or other problems. The researchers will be checking your medical information during the study to watch for any injury. However, you should tell the research team about anything that is bothering you or any recent changes in your health. The researchers may be able to take steps to reduce possible injury. You may experience none, some, or all of the injuries or problems listed below. There may be other problems that are not yet known.

1. You may experience fatigue, sweating, and breathlessness due to the walking tasks. These risks are minimal. You may take a break at any time if rest is needed.
2. You may experience muscle soreness the following day due to the

walking tasks and wearing a harness. These risks are minimal.

Are there benefits to being in this study?
You will not benefit from this study. Researchers hope that the information from this research study may be useful in understanding stability during walking, and further understanding how to identify persons at risk of falls.

Will it cost anything to be in the study?
You will not be charged for being in the study.

Will I get paid to participate in the study?
For participating in the study, you will be reimbursed for your visit to the laboratory. Your rate of reimbursement for your visit will be $50.
You will be given a ClinCard, which works like a debit card. After a study visit, payment will be added onto your card by computer. The money will be available within 1 business day. You can use the ClinCard at an ATM or at a store. No one at KUMC will know where you spent the money.
You will be given one card during the study. If your card is lost or stolen, please call (866) 952-3795.
Your personal information will be kept on a secure computer. It will be removed from the computer after the study is over and the money on the card has been used. Your information will not be shared with other businesses. It will be kept completely confidential. If a commercial product is developed from this research, the profits will belong to the study sponsor. There are no plans to provide financial payment to you should this occur.

The KUMC Research Institute will be given your name, address, social security number, and the title of this study to allow them to set up the ClinCard system for your study payments. Study payments are taxable income. A Form 1099 will be sent to you and to the Internal Revenue Service if your payments are $600 or more in a calendar year.

What happens if I get hurt or sick during in the study?
If you experience harm or have any other problem during this study, you should immediately contact Dr. Jessie Huisinga at 913-945-7465. A member of the research team will decide what type of treatment, if any, is best for you at that time."

If any injury or illness happens to you as a direct result of being in this study, the sponsor of this study will provide medical treatment at no cost to you. Treatment may include first aid, emergency care and follow-up care, as needed. Payments will not be offered for other expenses (such as time off work, lost wages, childcare, etc.) You do not give up any legal rights by signing this form.

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state

law or the Kansas Tort Claims Act may allow payment to persons who are injured in research at KUMC.

Do I have to be in the study?
Being in research is voluntary. You can choose whether or not to participate. Even if you decide not to join the study, you can still come to KUMC for services and treatment.

What other choices do I have?
You can choose not to be in the study.

How will my privacy be protected?
The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

Can I stop being in the study?
You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Jessie Huisinga, The mailing address is Dr. Jessie Huisinga, University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 1005, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The researchers will stop collecting any additional information about you about you unless they need information about a side effect of the study. They may use and share information that was gathered before they received your cancellation.

Could my participation be stopped early?
This study might be stopped, without your consent, by the investigator or by the sponsor. Your participation also might be stopped by the investigator or by the sponsor if it is in your best interest or if you do not follow the study requirements.

Who can I talk to about the study?
Before you sign this form, Dr. Jessie Huisinga or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write to the Human Subjects Committee at Mail Stop #1032,

CONSENT

Dr. Jessie Huisinga or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.
You will be given a signed copy of the consent form to keep for your records.

_____
Print Participant's Name

_____ _____ _____
Signature of Participant Time Date

_____
Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

OPTIONAL STORAGE OF DATA FOR FUTURE USE

Purpose: You are being asked to allow storage of the information collected for this study, to be used in future research related to studying walking and balance in different clinical populations. If you agree, we will keep the information you provided for this study in a secure database at KUMC. Only authorized persons will have access to the information. The information may be kept indefinitely.

What is involved? Your information might be combined with results from our other studies to learn more about walking and balance control. It might also be shared with other researchers who are studying similar topics. If we share your study information with other researchers, we will remove any items that directly identify you.

How will information about me be kept private? The information about uses and disclosures of your personal information in the main study also applies to the information saved for future research related to walking and balance control. Giving permission to store your study information is entirely optional. You can still be in the main study even if you decide not to provide your information for future research.

What are possible risks? The main risk of this optional research is possible loss of privacy and confidentiality. We will take reasonable precaution to reduce this risk. No additional risks are expected from research being conducted on your information because confidentiality will be protected. You will not directly benefit from the future research, but it may help researchers learn more about their study.

If you say yes to storing your study information and change your mind later, please contact the study team at the address listed in the main consent form. They will stop using your information at that time.

Please mark your choice “Yes” or “No” below. If you have any questions you can talk to Dr. Jessie Huisinga or the study team.

Yes, I agree to allow Dr. Jessie Huisinga to store my study information for future research

No, I do not agree to allow Dr. Jessie Huisinga to store my study information for future research

_____
Print Participant’s Name

_____ _____ _____
Signature of Participant Time Date

_____
Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

Please indicate below if you would be interested in participating in future research studies conducted in the Human Performance Laboratory at KUMC.

_____I give permission for a member of the Human Performance Laboratory to contact me in the future for possible participation in a research study.

_____I do not wish to be contacted by any members of the Human Performance Laboratory about future research opportunities.

_____
Print Participant's Name

_____ _____ _____
Signature of Participant Time Date

_____
Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

11.2 Run sheet

4024 Sensory Run Sheet

Subject ID: _____ **Subject Name:** _____ **Study Date:** _____

Height (cm): _____ **Weight (lbs):** _____

Falls in previous 12 months: _____ in previous 6 months: _____

Fall: Unexpected event in which the participants come to rest on the ground, floor, or lower level.

Filenames: @@4024_##

i. @@ = HC / MS / PD
ii. ## = Subject number

25 foot walk times (sec): _____ _____ _____

Test glasses and foam shoes

Subjects will walk back and forth along 25ftw pathway with each of these

*** MS ONLY – VIBRATRON TEST

LEFT FOOT _____

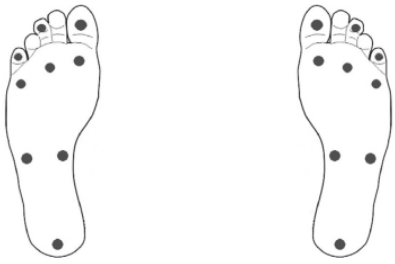
Vibration Level		A	B
	A		
	A		
	B		
	A		
	B		
	B		
	B		
	B		
	A		
	B		
	B		
	A		
	A		
	A		
	A		

RIGHT FOOT _____

Vibration Level		A	B
	A		
	A		
	B		
	A		
	B		
	B		
	B		
	B		
	A		
	B		
	B		
	A		
	A		
	A		
	A		

*** MS ONLY – MONOFILAMENT TEST

- Press monofilament (enough for it to bend) against top surface of foot, proximal to first MTP. Subject raises hand when they feel pressure, lowers hand when they don't feel pressure.
- Start with heaviest monofilament and decrease until subject fails test at any point on foot. Write down weight of monofilament.



RIGHT FOOT _____ **LEFT FOOT** _____

SUBJECT CHANGES INTO SINGLET

4 MINUTE OVERGROUND WALK – NORMAL SPEED

LEAD: Place Opal Sensors

(2) Foot – dorsal side/top of foot
(2) Ankle – lateral side of ankles
(1) Lower back – lumbar area, not waist
(1) Sternum

MOBILITY LAB: Turn on Opal External Sync

View > Motion Studio View > Stream

- ☐ **Opal Filename**: @@4024_##OG
- ☐ **Set mobility lab timer to 4 min (240 s)**

Test: Subject walks back and forth over walkway for 4 minutes at self-selected preferred walking speed. [illegible] distance covered in final bout with tape measure.

Distance covered in final partial bout **_____m**

Note: One "bout" is one length of the walkway (not round trip).

Place Markers – 33 Total

*placed on actual anatomical landmarks

Right			Left		
☐ Back of Heel	☐ Lower Shank		☐ Back of Heel	☐ Lower Shank	
☐ Medial MTP*	☐ Mid-shank		☐ Medial MTP*	☐ Mid-shank	
☐ Lateral MTP*	☐ Medial Knee*		☐ Lateral MTP*	☐ Medial Knee*	
☐ Heel	☐ Lateral Knee*		☐ Heel	☐ Lateral Knee*	
☐ Top of Foot	☐ Lower Front Thigh		☐ Top of Foot	☐ Lower Front Thigh	
☐ Medial Ankle*	☐ Mid-thigh		☐ Medial Ankle*	☐ Mid-thigh	
☐ Lateral Ankle*			☐ Lateral Ankle*		

[illegible]

Take Measurements

CIRCUMFERENCE	Left	Right	LENGTH	Left	Right
Upper thigh	_____	_____	ASIS to G. troch	_____	_____
Lower thigh	_____	_____	Thigh (troch – knee)	_____	_____
Upper shank	_____	_____	Shank (knee – mal)	_____	_____
Lower shank	_____	_____	Mal to floor	_____	_____
Foot (MTP)	_____	_____	Foot (heel-toe)	_____	
BREADTH			ASIS	_____	
Knee	_____	_____			
Ankle	_____	_____			
Foot	_____	_____			

Static Model Pose (33 Markers, 2 Trials)

1. **CORTEX**
   - Change file name
     - @@4024_##**cal_R1**
     - @@4024_##**cal_L1**
   - ***Add*** **Static Marker Set**
   - Capture the pose
   - After each trial:
     Post Process **Mode >** ***Quick ID***, ***Create Template***

2. **LEAD: Remove All Medial Markers (6 Total)**

Right	Left
Medial Knee*	Medial Knee*
Medial Ankle*	Medial Ankle*
Medial MTP*	Medial MTP*

Dynamic Model Pose (27 Markers, 1 Trial)

1. **CORTEX**
   - Change file name:
     - **Model1**
   - ***Add*** **Dynamic Marker Set**
   - Record just long enough to capture the pose
   - ***Post Process*** **Mode >** ***Quick ID***, ***Create Template***

***MS ONLY – POSTURAL PERTURBATION

EMG: Remove from dock. Turn on.
- Trigno Control Utility > *Start*

LEAD:
1. Set up the treadmill + marker
2. Place EMG sensors
   - Bilateral tibialis anterior
   - Bilateral gastrocnemius
3. Remove lateral thigh markers

LAPTOP: Woodway
1. Initialize treadmill (start and stop it)
2. Click lightning bolt to load test
   - test6cm_30mPERc2.ert

CORTEX: Change sample frequencies
- *Cameras* Tab > Frame rate = 120 frames per second (Hz)
- *Analog* Tab > Multiple of Frame Rate = 15 Current Sample Rate = 1800 Hz
- *Recording settings* = 5 seconds
- [illegible]
  - Autoscale > Right click

MOBILITY LAB:
- Start streaming OPALS

VIDEO CAMERA: Record

Data collection systems:
- [illegible]Hz
- Analog Inputs (EMG)[illegible]Hz

TEST: Postural perturbations – 5 seconds, Condition 4
MS subjects should be in the harness which is attached to the ceiling

Forward Translation	1	@@4024_##C4t1	Backward Translation	1	@@4024_##C4t4
	2	@@4024_##C4t2		2	@@4024_##C4t5
	3	@@4024_##C4t3		3	@@4024_##C4t6

DETERMINE PREFERRED PACE

LEAD:
Set up the treadmill

LAPTOP: Woodway
Initialize treadmill (start and stop it)

Fall-prone subjects should be in the harness which is attached to the ceiling
Increase treadmill speed until subject reports the speed feels comfortable: _____(m/s)

Increase treadmill speed until the subject reports the speed is "faster than they would prefer to walk"; record this speed

3 faster paces (m/s): _____ _____ _____

Decrease treadmill speed until the subject reports the speed is "slower than they would prefer to walk"; record this speed

3 slower paces (m/s): _____ _____ _____

Preferred pace: _____(m/s)

TREADMILL WALKING – SPEEDS

Subjects may rest between trials as necessary, subjects may hold rails during speed changes

MOBILITY LAB: Set sensors to record 3 minutes (180 seconds)

TEST: Treadmill walking – 3 minutes at each of the 5 speeds (randomize order)

RESTS: Subjects will take a mandatory 3-minute rest between each trial, during which they can complete the questionnaires.

% preferred pace		Treadmill speed	Filename	Random order
Slow	80%		4024@@##TWt1	
	90%		4024@@##TWt2	
Preferred	100%		4024@@##TWt3	
	110%		4024@@##TWt4	
Fast	120%		4024@@##TWt5	

Subjects should take a seated 5 minute rest before beginning altered sensory conditions

QUESTIONNAIRES (completed during rests)

- Activities-specific Balance Confidence Scale **(ABC)**
- Falls Efficacy Scale – International **(FES-I)**
- ******MS only:*** 12-Item Multiple Sclerosis Walking Scale **(MSW12)**
- ******MS only:*** Self-rated EDSS **(S-EDSS)**

TREADMILL WALKING – ALTERED SENSORY

MOBILITY LAB: Set sensors to record 3 minutes (180 seconds)

TEST: Treadmill walking – 3 minutes at preferred pace (from above) for each trial

REST: Subjects will take a mandatory 3-minute rest between the two conditions

Condition	Filename
Vision	4024@@##TWv
Somatosensory	4024@@##TWs

Vision condition: Subjects wear specialized eyewear with lenses to shift visual field for the entire duration of the trial
Somatosensory condition: Subjects wear specialized footwear with foam on soles to alter somatosensory feedback from feet for the entire duration of the trial

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EXPORT DATA (copy + paste)

DESKTOP

- FROM: Desktop > 4024 Study > Subject Folder
- TO: Desktop Shortcut: S drive > 4024 Study > … > Subject Folder

MOBILITY LAB

- FROM: Desktop Shortcut: MobilityLabProject > copy all files of that subject
- TO: Desktop Shortcut: 4024 Study > … > Subject Folder > Create new folder: “Mobility Lab Sync”

11.3 Subject inclusion criteria

Healthy young adults will be 20 to 60 years old, free from any orthopedic or neurological disease; Persons with MS will be 20 to 60 years old, have relapsing remitting MS, score <5 on the Kurtzke Expanded Disability Status Scale (EDSS), and will not be taking fampridine since it has been shown to specifically affect gait [8]. MS subjects will be considered fall-prone if they self-report two or more falls in the past year and will also be free of any orthopedic or neurological disease.

Exclusion Criteria:

a. Unable to give informed consent.
b. Are pregnant, breastfeeding or within 3 m post-partum at initiation of the study.
c. Are unable to walk without the use of assistive devices.
d. Have any other disability that would affect balance and/or mobility.
e. Have any other neurological or neurodegenerative disorder that would affect balance and/or mobility.
f. Vulnerable: no vulnerable subjects will be included.
g. Patients with any other clinical finding or co-morbid condition which would make exercise unsafe, or reason that in the opinion of the PI deems the patient unsuitable for enrollment into the study. Examples of such conditions include the following:
    - Current Diagnosis of Peripheral Arterial Disease with claudication
    - Diagnosed diabetic neuropathy
    - Chest pain or angina
    - Congestive heart failure, decompensated
    - Cardiac dysrhythmia, symptomatic
    - Uncontrolled hypertension
    - Uncontrolled asthma
    - Actively symptomatic COPD
    - Shortness of breath at rest or with mild exertion
    - Dizziness or syncope
    - Major ankle edema
    - Known heart murmur indicative of heart disease

11.4 References - Appendix

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4. Kaffashi, F., et al., *The effect of time delay on Approximate & Sample Entropy calculations.* Physica D: Nonlinear Phenomena, 2008. **237**(23): p. 3069-3074.
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7. Kennel, M.B., R. Brown, and H.D. Abarbanel, *Determining embedding dimension for phase-space reconstruction using a geometrical construction.* Physical review A, 1992. **45**(6): p. 3403.
8. Goodman, A.D., et al., *Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial.* The Lancet, 2009. **373**(9665): p. 732-738.