GAIT VARIABILITY IN PERSONS WITH MULTIPLE SCLEROSIS

BY

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THESIS

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ABSTRACT

This thesis contains three investigations examining gait variability in people with multiple sclerosis (MS), which is a neurological disease that can result in significant walking impairment. Gait variability, i.e. fluctuations in the mechanics and kinematics of steps during walking, has been associated with motor control function, stability and falls in other populations but has not been thoroughly documented in people with MS. In this thesis, gait variability is documented in different samples of people with MS using a variety of metrics. The first investigation examines differences in variability of spatiotemporal gait parameters between people with MS and healthy controls and associations between variability of spatiotemporal gait parameters and disability in MS. The second investigation determines variability of lower-limb joint and segment angles at various walking speeds in MS. The third investigation documents a novel metric for quantification of footfall placement variability and subsequent associations between footfall variability and fall history in MS. Results herein include greater variability of step length, step time, and footfall placement variability in people with MS compared to controls, decrease in ankle angle variability with increasing walking velocity in MS, and that increased footfall placement variability, indexed by a novel metric, separates recurrent and non fallers with MS. Additional research into gait variability in MS is warranted to further evaluate differences between MS and controls as well as to investigate underlying factors that may drive gait variability in MS.

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CHAPTER 1

INTRODUCTION

1.1 Introduction to Gait Variability in MS

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States and an estimated 2.5 million people world-wide[1]. MS involves demyelination, axonal loss, and formation of lesions in the CNS that distort and disrupt action potential conduction[2]. These effects manifest themselves in various symptoms including, but not limited to, sensory, cognitive, balance, and gait impairment[1]. MS generally does not affect life expectancy but does lead to progressive disability, which results in a lower quality of life[3,4], in large part due to changes in mobility. 70% of persons with MS report gait impairment as the most challenging aspect of the disease[5]. Half of people with MS require assistive devices for ambulation within the first 15 years of the disease[6].

Gait impairment in MS is well documented[7]. Individuals with MS walk slower, with reduced cadence and step length and spending a greater percent of the gait cycle in double-support compared to healthy controls[8-10]. Gait impairment in MS is multi-faceted. Fatigue[11,12], reduced leg muscle strength[13,14], and spasticity[15] have all been associated with gait impairment in MS. Gait impairment increases with increasing disability[9,16], commonly indexed in MS by the Expanded Disability Status Score (EDSS)[17]. EDSS ranges from 0 (normal neurological exam) to

10 (death due to MS), with EDSS>4.5 representing individuals with significant walking impairment.

Gait impairment in MS is measured in a variety of ways[18,19]. Clinically, gait is typically assessed through timed performance tests such as the timed 25-foot walk, 2-minute, and 6-minute walks[19]. In research, gait is additionally measured with motion capture systems[8,11,16] and instrumented walkways[9,10,12] that provide information about the mechanics of walking to compliment the results of timed performance tests.

Variability is inherent to biological function (e.g. heartbeat, respiration), including gait. It is maintained that a certain level of variability is indicative of health in most biological systems[20]. Too much variability may indicate that deviations are not corrected by the system which can lead to instability. Meanwhile, too little variability can indicate that a system is overly rigid and potentially unable to respond to perturbations[21]. It has also been suggested that gait variability may potentially be more sensitive to dysfunction than mean gait parameters[20].

Gait variability is a facet of walking behavior that has been garnering more scientific scrutiny in recent years[22]. The presence of pathology can cause changes in gait variability because of its impact on motor function and control[21]. Gait variability has been associated with instability and falls in populations with neurological deficiencies including the elderly[23-26], Alzheimer's[27], and Parkinson's disease[28]. Others have used gait variability to investigate impact of and recovery from various injuries. Researchers have examined changes in gait variability arising from serious knee surgeries such as ACL repair[29] and total knee replacement[30]. Gait variability has also been

studied as evidence of different motor control strategies arising from various forms of dysfunction. For example, one report investigated gait variability as a marker for different control strategies in children with Down Syndrome versus children with traditional development[31]. Others have looked at gait variability in connection to specific areas of impairment in the central nervous system[32], persistent versus anti-persistent control variables in healthy gait[33], and the impact of training on gait variability in runners[34].

Gait variability has been quantified with a variety of metrics, including quantification of both magnitude of variability as well structure of variability in time. Traditionally, variability is defined in simple terms such as standard deviation[26,30,35,36] or coefficient of variation[23-25,27,32,34] (CV=100%*SD/mean). Metrics such as standard deviation and CV provide information regarding variability magnitude. Other metrics have also been used to quantify the structure of gait variability, including detrended fluctuation analysis[33,37], Lyapunov exponents[29,30], uncontrolled manifold analysis[31], approximate entropy[38,39], and analysis of gait phase portraits using adapted posturographic measures[40,41]. Structure of variability refers to how variability fluctuates in time, rather than the magnitude. Selection of the proper metric for gait variability depends on the specific research question and timescale of interest.

Despite growing interest in gait variability in the research community, there has been limited documentation of gait variability in MS. It has been demonstrated that persons with MS demonstrate greater variability of step length[42], step time and single-support time[10] than healthy controls. One study showed that people with MS have elevated variability of hip, knee, and ankle angles[36]. Another study also demonstrated that cane use causes reduction in gait variability in

persons with MS[43]. Overall, contributing factors and clinical significance of gait variability in MS remain unclear. Further documentation of gait variability in people with MS is warranted.

In this thesis, three investigations regarding gait variability in MS are presented. In addition to looking at differences between people with MS and healthy controls, each study addresses a distinct research question and focuses on a distinct method for quantifying gait variability. The first study examines correlations between gait variability and disability in MS. The second investigates variability of lower limb joint and segment angles through phase portraits of gait at different walking speeds. The final study utilizes a novel metric for quantifying footfall placement variability and examines subsequent associations between footfall placement variability and falls in people with MS.

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CHAPTER 2

GAIT VARIABILITY AND DISABILITY IN MULTIPLE SCLEROSIS

2.1 Abstract

The purpose of this investigation was to examine variability of spatiotemporal gait parameters in people with multiple sclerosis (MS). Although gait variability is clinically relevant in various populations, there is limited documentation of gait variability in MS. Eighty-eight individuals with MS (age 52.4 ± 11.1, 83% female) and 20 healthy controls (age 50.9 ± 8.7, 80% female) participated in this investigation. Participants with MS underwent a brief neurological exam to determine Expanded Disability Status Scale (EDSS) and all participants performed two self-paced walking trials on a 7.9 meter GAITRite^{TM} electronic walkway. Gait variability was indexed by calculating coefficient of variation (CV=SD/mean) for step time, step length, and step width for each participant. Step length and step time variability were both significantly greater in the MS group compared to healthy controls ($p<0.05$). Disability, indexed by EDSS, was positively correlated with step length CV ($\rho=0.57$, $p<0.05$) and step time CV ($\rho=0.40$, $p<0.05$) and negatively correlated with step width CV ($\rho=-0.35$, $p<0.05$) in persons with MS. Gait variability is altered in MS as a function of disability status, and researchers should consider the consequences and potential techniques to target altered gait variability in MS.

2.2 Introduction

Multiple sclerosis (MS) is a prevalent, autoimmune disease that affects an estimated 400,000 American adults and 2.5 million adults world-wide. MS results in demyelination and loss of axons in the central nervous system. Such CNS damage manifests as muscle weakness, sensory loss, and ataxia, and such changes might be associated with walking or gait impairment[1]. Disability increases with MS and is typically indexed by the Expanded Disability Status Scale[2] (EDSS).

Gait impairment is one of the most frequent consequences of MS, and walking dysfunction is considered by the majority of patients as the most challenging, life-altering aspect of the disease[3]. Persons with MS walk slower, taking shorter, wider, and slower steps, and spend a greater percent of the gait cycle in double-support compared to healthy controls[4-6], even early in the disease course[7,9]. Such changes in gait have been directly associated with disability status as a marker of disease progression[6,10].

In addition to demonstrating different average spatiotemporal parameters of gait, there is some evidence that persons with MS have elevated gait variability compared to controls. For example, one study reported that persons with MS exhibit greater kinematic variability at the hip, knee, and ankle during ambulation than healthy controls[11]. Other studies have reported that persons with MS who had mild impairment demonstrate greater variability of step time and single-support time[7] and step length[8] than age and gender matched controls. Additionally, there is some preliminary evidence based on a small sample (n=10) that gait variability increases with

disability in MS[12]. That study demonstrated that persons with MS with walking impairment (EDSS>4.0) had greater variability of stride length compared to healthy controls, but individuals without walking impairment (EDSS≤4.0) did not[12].

Gait variability (i.e. fluctuations in gait parameters between steps) is predictive of mobility impairment and falls in older adults and other neurological populations[13-15]. Further, movement variability is a marker of motor control function and is potentially more sensitive to dysfunction than average parameters[16]. Consequently, documentation of gait variability as a function of disability is a first step towards investigating the clinical relevance of gait variability in MS.

In this investigation, we examined differences in variability of spatiotemporal gait parameters between persons with MS and healthy controls as well as associations between gait variability and disability level in persons with MS. We hypothesize that gait variability would be elevated in persons with MS compared to controls. Secondly, we hypothesize that gait variability would be positively correlated with disability in MS, as indexed by the EDSS.

2.3 Methods

The procedures for this investigation were approved by the local Institutional Review Board and all participants provided informed consent prior to data collection.

Persons with and without MS participated in this investigation. Inclusion criteria for participants with MS required a neurologist-confirmed diagnosis, the ability to walk without or with an

assistive device (e.g. a cane or walker) and be relapse-free for at least 30 days prior to testing. Inclusion criteria for controls required no gait impairment, no assistive device use, and no medical condition such as neurological or cardiovascular disease. Upon arrival at the testing facility, participants with MS underwent an examination by a neurologist to generate an EDSS score[2].

To determine variability in spatiotemporal gait parameters, all participants performed two walking trials across a 7.9 meter GAITRite™ (CIR Systems Inc., Haverton, PA, USA) electronic walkway at self-selected, comfortable speed. Variability of step length, step width, and step time were indexed by the coefficient of variation (CV). The CV of each parameter was calculated individually for each pass over the GAITRite™; those values were then averaged within a participant to produce an overall CV for each parameter.

Statistical analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). An independent samples t-test was used to determine group differences between MS and controls in age and gait variability, while a Mann-Whitney U test determined group differences in gender distribution. Spearman correlations were performed between gait variability, EDSS, and age. Partial correlations were performed between gait variability and EDSS while controlling for age. Significance was assumed for $p<0.05$.

2.4 Results

Eighty-eight participants with MS and 20 healthy controls participated in this investigation (Table 2.1). There were no differences between groups in age or gender distribution ($p>0.05$). The MS group had an average age of 52.4 years, average duration of MS of 11.8 years, and median EDSS score of 4.5. Furthermore, 83% of the MS group was female, 32% used unilateral assistive devices, and 6% used bilateral assistive devices. The control group had an average age of 50.9 years and 80% of the group was female. None of the control group utilized an assistive device for walking.

Step length and step time variability were significantly greater in MS versus controls ($p<0.001$). However, there was no significant difference in step width variability between MS and controls (Table 2.2). The MS group exhibited average step length variability of 5.1%, step time variability of 4.7%, and step width variability of 19.2%. The control group demonstrated step length variability of 2.0%, step time variability of 1.8%, and step width variability of 18.5%.

EDSS was significantly correlated to step length variability ($\rho=0.57$, $p<0.001$), step time variability ($\rho=0.40$, $p<0.001$), and step width variability ($\rho=-0.35$, $p=0.001$) in MS (Table 2.3). Age was significantly correlated to step length variability ($\rho=0.37$, $p<0.001$) and step time variability ($\rho=0.22$, $p=0.04$), but not step width variability ($p>0.05$). Given that age was related to gait variability in our sample and that gait variability has been previously associated with advanced aging[10], we examined correlations between gait variability and EDSS while controlling

for age. While controlling for age, EDSS remained significantly correlated to all three CV parameters (r_p ranging -0.26 to 0.42, p ranging <0.001 to 0.014).

2.5 Discussion

People with MS have gait impairment[1-10]. Gait impairment in MS has been quantified by mean spatiotemporal gait parameters, but less so by variability in those parameters. There is limited documentation of gait variability in MS[7,12,13,23]. This investigation examined differences in gait variability between a larger group of persons with MS, including a wide range of disability levels, and healthy controls. Additionally, we expanded on previous reports by examining the correlation between disability (EDSS) and gait variability in ambulatory persons with MS who had a wide range of disability status. The major findings of this study were: (1) persons with MS have greater variability of step length and step time than healthy controls, (2) variability of step length and step time had a significant positive association with disability status, and (3) step width variability had a significant negative association with disability status in MS.

The first observation in this investigation was that the MS group had significantly greater variability of step length and step time than the healthy control group (Table 2.2). Previous work[7] showed significantly greater variability (CV) of step time in persons with MS with minimal disability versus controls, but no difference in variability of step length or step width. Another study reported differences in step length between persons with MS with minimal disability and controls[8]. Others[12] report increased stride length variability (CV) in persons with MS with EDSS>4.0 than healthy controls, but no difference in step width variability. Our results

are congruent with both [7] and [12] in that we found no difference between MS and controls in step width variability. Concerning step time variability, our results are congruent with [7], who also reported greater CV of step time in MS versus controls. Our assertion that step length variability is greater in MS versus controls is congruent with [8], however [7] reports no differences in step/stride length. The difference in observations is possibly due to the inclusion of individuals with greater disability in our sample. We have shown that step length variability correlates positively with EDSS, therefore the presence of individuals with EDSS>4.0 could explain the greater variability of step length in our MS sample. Increased variability of step length in persons with MS with greater disability is consistent with [12], who reported a difference in stride length CV between persons with MS with EDSS>4.0 and controls, but no difference in persons with MS with EDSS<4.0 and controls.

A novel observation of this investigation is that variability of step length and step time correlated positively with disability in MS; i.e. persons with greater disability exhibit greater step length variability and step time variability (Table 2.3). These associations remained significant when controlling for age, confirming that the change in variability in persons with MS is indeed associated with disability, and not age per se.

Previous work demonstrated that persons with mild disability with MS had higher gait variability (CV of step time and single support time) than age and gender matched controls[7]. The CV values in [7], which considered only persons with MS with minimal gait impairment, were 2.8, 2.6, and 21.8 % for step length CV, step time CV, and base of support CV, respectively. Although these values are lower than the results of the current investigation (Table 2.2), the difference most

likely arises from greater average EDSS in our sample (Table 2.1). Additionally, in an investigation of gait variability in elderly people, others[13] reported step length, time, and width CV's that were similar to the values reported in this study, including the greater amplitude of step width variability.

There are several possible explanations why step length and step time variability are related to disability in persons with MS. Recently, it has been demonstrated that muscle quality (ratio of muscle strength to lean muscle mass, i.e. functional muscle strength) is associated with gait variability in healthy older adults[20]. Given that persons with MS have decreased muscle strength and that muscle strength is related to gait impairment[18], declines in muscle strength and/or muscle quality as a function of disability may contribute to gait variability in MS. Another potential explanation for the increase in gait variability in more disabled individuals is an increase in noise in the neuromuscular system. This is based on models that demonstrate an increase in neuromuscular noise leads to increased gait variability[21]. If elevated neuronal damage due to MS in more disabled individuals results in increased neuromuscular noise, this may be associated with increased gait variability in those individuals. Lastly, depression contributes to increased gait variability in Parkinson's disease[13]. Given that depression in MS increases with disability[22], it could also be a contributor to increased gait variability in more disabled individuals with MS. Future work needs to examine muscle strength, neuromuscular noise, depression, and other potential factors that could drive gait variability in persons with MS.

In contrast to step length and step time variability, step width variability was negatively related to disability level (Table 2.3). A possible explanation for decreased step width variability in more

disabled individuals is their use of assistive devices, i.e. canes and walkers. One report asserts that the use of a cane leads to significant gait improvement within an individual in persons with MS, including reduction in stride and swing time CV[23]. [23] did not report on step width variability, though it may also be impacted by assistive device use. In our study, 37.5% of participants used an assistive device, with 5.7% using bilateral support (e.g. walkers) (Table 2.1). Use of these assistive devices, especially walkers, considering the potential limitations they put on mediolateral motion, could explain reduced step width variability in individuals with MS with greater disability. Another possible explanation is that since individuals with greater disability had greater average step width, they are closer to their stability boundary in the mediolateral direction, limiting their potential range of motion in that direction and reducing step width variability.

Our results highlight differences between the association of step length and step time variability and disability compared to step width variability and disability in persons with MS. Step length and step time variability increased with disability, while step width variability decreased as a function of disability. Additionally, there is a difference in magnitude between step time and length CV and step width CV. Step width CV was ~20% for persons with MS while step length CV and step time CV values were ~5%. The 4-fold increase in magnitude of step width variability suggests that the mediolateral plane is less tightly controlled than other parameters, which has been demonstrated in postural control literature[24]. A potential explanation for these observations is the possibility that mediolateral and anterior-posterior plane gait parameters are controlled by different neural pathways that could be differently influenced by disability[25,26].

The clinical significance of gait variability in MS is unclear. Gait variability has been associated with fall risk in other clinical populations[13-14]. Previous research[13] showed that altered step width variability is related to falls history in the elderly. Given that one of the factors contributing to falls in MS is disability[27,28] and that the current results demonstrate an association between step width variability and disability, it is possible that gait variability may be connected to falls in persons with MS. Associations between gait variability and falls in persons with MS warrant further investigation.

A potential limitation of this investigation is its cross-sectional nature. Intra-individual changes in gait variability were not recorded as disability changed in a given individual over time. A second potential limitation was the relatively small number of steps collected to determine gait variability. Previous research has reported on variability of spatiotemporal parameters over similar time series[11,22], however some research has suggested that a greater number of steps are needed to investigate gait variability in certain situations[29]. Further research is warranted to investigate thresholds for reliable studies on gait variability in persons with MS.

In summary, results of the current investigation illustrate that persons with MS have greater variability of step length and step time than individuals without MS. Additionally, step length and step time variability correlate positively with disability while step width variability correlates negatively with EDSS. Potential reasons for altered gait variability in MS include declines in muscle strength and muscle quality as well as the influence of depression, assistive device use, and the impact of a mediolateral stability boundary on gait variability. Future investigations into the contributing factors and consequences of gait variability in MS are warranted.

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2.7 Tables

Table 2.1. Baseline characteristics for MS and control groups are reported. The MS and control groups were not significantly different in age or gender composition.

		MS (N=88)	**Controls (N=20)**
Age [years]	Mean (SD) Range	52.4 (11.1) 30-78	50.9 (8.7) 31-62
MS duration [years]		11.8 (9.9) 0-43	N/A
EDSS [-]	Mean (IQR) Range	4.5 (3.0) 2.0-6.5	N/A
Gender [% female]		83.0	80.0
Unilateral assist [% users]		31.8	0.0
Bilateral assist [% users]		5.7	0.0

Table 2.2. Coefficient of variation of spatiotemporal gait parameters is reported (standard deviation) for MS and control groups. The p-value reflects the statistical difference between groups from an independent samples t-test. Significance was assumed for $p<0.05$.

	MS	**Control**	**p**
Step length CV [%]	5.1 (2.7)	2.0 (0.8)	*<0.001*
Step time CV [%]	4.7 (2.4)	1.8 (0.5)	*<0.001*
Step width CV [%]	19.2 (11.9)	18.5 (5.2)	0.803

Table 2.3. Spearman-rho correlation results between EDSS, age, and CV of step length, step time, and step width in the MS group are reported. Partial correlations between EDSS and CV parameters while controlling for age are also reported.

	Spearman-rho				**Partial**	
	EDSS		**Age**		**EDSS**	
	ρ	*p* (2-tailed)	ρ	*p* (2-tailed)	ρ	*p* (2-tailed)
Age	.440	<0.001	-	-	-	-
Step length CV	.572	<0.001	.374	<0.001	.421	<0.001
Step time CV	.401	<0.001	.219	0.040	.339	0.001
Step width CV	-.350	0.001	-.066	0.543	-.263	0.014

CHAPTER 3

VARIABILITY OF LOWER-LIMB JOINT AND SEGMENT ANGLES IN MS GAIT

3.1 Abstract

Multiple sclerosis (MS) is a neurological disease that often results in gait impairment. It has been suggested that gait variability, i.e. fluctuations between steps during walking, is potentially more sensitive to dysfunction than average gait parameters. However, gait variability in MS has not been documented thoroughly. In this investigation, 14 individuals with MS and 10 controls walked at 75%, 100%, and 125% of their preferred walking speed on a treadmill. Gait variability was quantified by standard deviation of lower-limb joint and segment angles as well as by phase portrait (segment angle versus angular velocity) analysis. Persons with MS exhibited a significant change in variability of the ankle joint and thigh segment as walking speed increased. The control group exhibited greater variability of the foot segment than the MS group, which was surprising given previous documentation of increased gait variability in MS compared to controls. Future research is needed to adequately document differences between persons with MS and controls in kinematic gait variability as well as to understand the underlying factors that drive gait variability and changes in gait variability due to walking speed in MS.

3.2 Introduction

Multiple sclerosis (MS) is an autoimmune disease that results in damage to the central nervous system. In MS, myelin is destroyed, resulting in damage to axons, distortion of signal transduction, and formation of scar tissue. MS affects approximately 400,000 Americans and more than 2 million people world-wide. The disease is 2-3 times more prevalent in women than men and is typically diagnosed between the ages of 20-50[1]. MS has a variety of symptoms including gait impairment, commonly considered the most impactful aspect of the disease[2].

Gait impairment in MS has been well documented and is reflected in changes to spatiotemporal gait parameters as well as gait kinematics. Individuals with MS have been shown to walk slower, with reduced step/stride length and cadence, and increased time in the double-support phase of the gait cycle[3-7]. Persons with MS also exhibit altered lower-limb kinematic patterns than healthy individuals. Persons with MS have been shown to have different angular positioning of the lower limbs at heel strike and toe off and reduced range of motion during ambulation compared to healthy controls[5-7].

In addition to changes in the values of spatiotemporal and kinematic gait parameters in persons with MS, it has been demonstrated that persons with MS exhibit greater gait variability than healthy individuals. Gait variability refers to fluctuations in gait parameters between steps during ambulation. Previous reports demonstrated that persons with MS with minimal disability have larger variability of step and single-support time[8] and step length[9] than individuals without MS. One study reported a greater standard deviation of ankle, knee, and hip angles in persons with

MS compared to healthy controls[10]. Overall, however, there is limited documentation of variability of gait kinematics in persons with MS.

Once dismissed as simply signal noise, there has been increasing research exploring the meaning and clinical implications of physiological signal variability. It has been suggested that gait variability is potentially more sensitive to dysfunction than mean parameters due to connections between variability and motor control function[11]. Gait variability has been associated with falls in elderly individuals and other populations with neurological deficits[12-14]. Others have looked at gait variability as a way of examining the impact of injuries and compensation injuries[15] as well as a way to monitor injury recovery[16].

The purpose of this investigation was to examine changes in variability of lower-limb joint and segment angles in persons with MS compared to healthy controls.

3.3 Methods

Inclusion criteria for the MS group included a diagnosis of MS, age 18-64, and the ability to walk on a treadmill for 2 minutes. Healthy control subjects also participated and were screened for neurological disease, orthopedic surgery or other major lower limb injuries, and major cardiac problems. Procedures for this investigation were approved by the local Institutional Review Board.

After consenting to the study, participants completed 3 walking trials on a treadmill at various speeds. Prior to the first trial, the participants provided feedback to a researcher who adjusted the treadmill speed to the participant's comfortable walking pace. The first trial was then collected at that self-selected speed, followed by trials of 125% and 75% of the self-selected speed. The order of the "fast" and "slow" trials was randomized. Trials were 30 seconds long. Participants were permitted to use handrails of the treadmill (directly in front of them) during the trials if they so desired, but no assistive devices. Multiple walking speeds were recorded in order to examine the impact of changing speeds on gait variability. It has been demonstrated in healthy young individuals that magnitude of gait variability decreases as walking speed increases from 80-120% of an individual's comfortable walking speed[17].

Kinematic data were collected at 100 Hz using a 9-camera motion capture system including Eagle Digital Cameras and Cortex 1.14 software (MotionAnalysis Co., Santa Rosa, CA, USA). Participants were outfitted with reflective markers that were placed on their right side, located at the anterior superior iliac spine (hip), femoral lateral epicondyle (knee), lateral maleolus (ankle), calcaneus (heel), and 1st metatarsal head (toe). Using these markers, five sagittal plane segment and joint angles were defined: the thigh, shank, foot, knee, and ankle. Marker data were filtered with a low-pass Butterworth filter at a cutoff frequency of 10 Hz prior to data analysis.

Variability of joint and segment angles was quantified by the average standard deviation across the gait cycle, which was calculated by averaging the standard deviation across all strides at 1% increments of the gait cycle[10]. Segment variability was indexed additionally using a method to quantify cycle-to-cycle gait variability based on segment angle phase portraits[15] (segment angle

versus angular velocity). In segment phase portraits (Figure 3.1), the centroid of the shape created by each individual gait cycle was calculated; variability was quantified by the motion of that centroid point between consecutive gait cycles. Centroid motion was quantified by two metrics that arise from posturography: (1) 95% confidence ellipses for the area encompassing centroid points, and (2) the summation of the distance between consecutive centroid points (i.e. centroid path length). For this investigation, the path length was normalized by the number of gait cycles taken by each participant. To include as much data as possible for analysis, we chose to include as many gait clcyes as possible for each individual and then normalize the path length results by that number of gait cycles. This is different from the original method in [15], in which the same number of gait cycles was analyzed for each participant.

Statistical analysis of results was performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Differences in age, and average walking speed between the MS and control groups were analyzed using an independent samples t-test. Differences between groups in gender distribution were analyzed using a Mann-Whitney U test. Gait variability metrics were placed into a mixed-model repeated measures ANOVA with group (MS vs. control) as the between subjects factor and speed as the within subjects factor. Significance was assumed for $p<0.05$.

3.4 Results

Fourteen persons with MS (age 46.1 ± 10.8, 11 female / 3 male) and 10 healthy controls (age 50.6 ± 12.0, 8 female / 2 male) participated in this investigation. The average walking speeds and number of steps taken at each walking speed by the MS and control groups were not statistically

different (Table 3.1). Additionally, there were no differences between the MS and control groups in age and gender composition ($p>0.05$).

Table 3.2 reports standard deviations of ankle, knee, thigh, shank, and foot angles for MS and controls and the results of repeated measures analysis on those parameters. MS and controls both displayed significant change in ankle angle standard deviation due to speed ($p=0.007$ for MS, $p=0.042$ for controls). Additionally, the control group had a significant speed effect on knee ($p=0.037$) and foot angle ($p=0.026$). There was no significant difference between groups for standard deviation of any joint or segment angle, nor any significant group by speed interaction ($p>0.05$).

Table 3.3 reports segment variability, quantified by the motion of centroids of the shapes produced by each gait cycle in segment angle phase portraits. Five out of 14 participants with MS demonstrated an outlying value for at least one metric of phase portrait variability. Outlying values were removed from analysis. There was no significant speed, group, or group by speed interaction effect in centroid path length for the thigh, shank, or foot segment ($p>0.05$). 95% confidence ellipse results suggested that the MS group had significantly lower variability of the foot than healthy controls ($p=0.020$). Additionally, the MS group demonstrated a significant speed effect for thigh variability ($p=0.037$), also indexed by the 95% confidence ellipse for centroid motion.

3.5 Discussion

The objective of this study was to examine differences in kinematic gait variability between persons with MS and healthy controls over a range of walking speeds. A major finding of this investigation was that the MS group demonstrated a significant effect of speed on gait variability at the ankle joint (indexed by standard deviation) and at the thigh segment (indexed by 95% confidence ellipse in phase portrait analysis) (Table 3.2). Increasing walking speed caused individuals with MS to exhibit decreased standard deviation of ankle angle, which was a pattern that was similar to the control group in this study and has basis in previous research. Gait variability has been found to decrease in magnitude (coefficient of variation) as a result of increasing gait speed in healthy individuals[17]. The observation that gait variability significantly changed as a function of walking speed is important for future research on gait variability in MS. Future studies on gait variability in MS should document walking speed and should consider the potential impact of preferred walking speed on gait variability in their observations.

Concerning variability of leg segment angular movements, there were limited differences between MS and controls. There were no significant differences between MS and controls in standard deviation of the angular motion of the thigh, shank, or foot (Table 3.2). However, phase portrait analysis yielded a significant difference between the MS and control groups for motion of the foot segment (Table 3.3). The MS group had significantly lower variability of foot motion as indexed by the 95% confidence ellipse than the control group ($p=0.02$). Lower movement variability at the foot is a surprising result, given that previous reports have only documented greater gait variability in MS compared to controls[8-10,18]. One potential explanation for the lower

variability at the foot in MS versus controls could be reduced range of motion at the ankle, which has been demonstrated previously in MS[5].

It is possible that standard deviations and phase portrait metrics measure different aspects of gait variability. This is evidenced by finding reduced variability of foot motion in the MS group through phase portrait analysis while there was no difference in standard deviation of foot angle. Also, standard deviation was sensitive to changes in speed in MS while no phase portrait metrics had a significant speed effect. An explanation for the discrepancy may be that phase portrait analysis truly measures cycle-to-cycle variability in that each gait cycle is reduced to one centroid point and variability is quantified by only those 15-25 centroid points. Standard deviation analysis took into consideration the average standard deviation across all 100 points of each gait cycle as well as the average across the total number of cycles. In that way, standard deviation analysis is more of a combination of within-stride and between-stride variability while phase portrait variability is purely between-stride.

Overall, we detected few differences in gait variability between MS and controls. This was unexpected given that previous research reported elevated variability of spatiotemporal parameters[8,9,18] in persons with MS. It was particularly surprising that we found no difference between MS and controls in standard deviation of knee and ankle angles because it has been reported in previous literature[10]. Comparison of our results to [10] reveals that we report very similar values for knee and ankle standard deviation in MS. We report standard deviations of 2.7 ± 2.1 degrees at the knee and 1.4 ± 0.7 degrees at the ankle in our MS group at comfortable pace.

These values are very close to the standard deviation values in MS in [10] of 2.7 ± 0.8 degrees at the knee and 1.5 ± 0.4 degrees at the ankle.

There are several possible explanations for the differences in our results concerning knee and ankle standard deviation compared to [10]. First of all, we reported greater variability within our group than [10], which could result in less statistical difference between our MS and control groups. Second, although both reports use the same method for reporting joint angle standard deviation, there were other methodological differences. Our study measured variability during walking on a treadmill while [10] determined gait variability from non-consecutive over-ground strides. The presence of the treadmill itself, including hand rails, and the differences between a moving belt and over ground walking can cause changes in gait[19]. A third possible difference between our study and [10] was the walking speed of the participants. The MS group in our study walked at the same self-selected speed as the control group. Walking speed was not reported in [10], but it is expected that their MS group walked at a slower speed than their control group[3,4,6,7], which could have contributed to the group differences they report in gait variability. Given that we have shown significant changes in gait variability due to walking speed in MS, future studies should consider the potential influence of walking speed on their research question. A future, potentially larger study should re-examine differences between MS and controls in joint angle standard deviation and other gait variability metrics.

Surprisingly, the MS and control groups did not differ significantly in walking speed or number of steps in each 30 second trial. This result is surprising because it is well established that people with MS walk with reduced velocity and cadence[3,4,6,7]. A possible explanation for the lack of

differences in velocity is the presence of the treadmill itself. Participants in the MS group were allowed to use the handrails of the treadmill, which could have allowed them to feel comfortable walking a higher speed. No control participant used the handrails, so there was no impact of additional stability on the control group.

There were limitations of this investigation. The biggest limitation was the small sample size (N=14 with MS, 10 controls). Statistical significance may be over or under-estimated in analyses with small sample sizes and statistical power of current observations is low. Second, walking trials were performed on a treadmill, which can cause alterations from a person's normal over-ground gait[19]. Third, gait trials were limited to 30 seconds, limiting the number of gait cycles available for variability analysis. It has been suggested that a greater number of strides should be collected to accurately measure gait variability[20], although other publications have documented gait variability using similar timescales to this investigation.

Looking forward, the results of this investigation should caution future researchers to fully consider the effects of their methodology on preferred walking speed, which affects gait variability. Varying results between phase portrait analysis and standard deviation analysis of lower-limb segment motion suggests that phase portrait analysis and traditional metrics are sensitive to different things. Concerning variability of joint motion, future work is warranted to clarify potential differences between persons with MS and healthy controls for standard deviation of lower limb joint angles. Future examination of the factors driving gait variability and changes in gait variability due to speed in MS is warranted.

3.6 References

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3.7 Figures

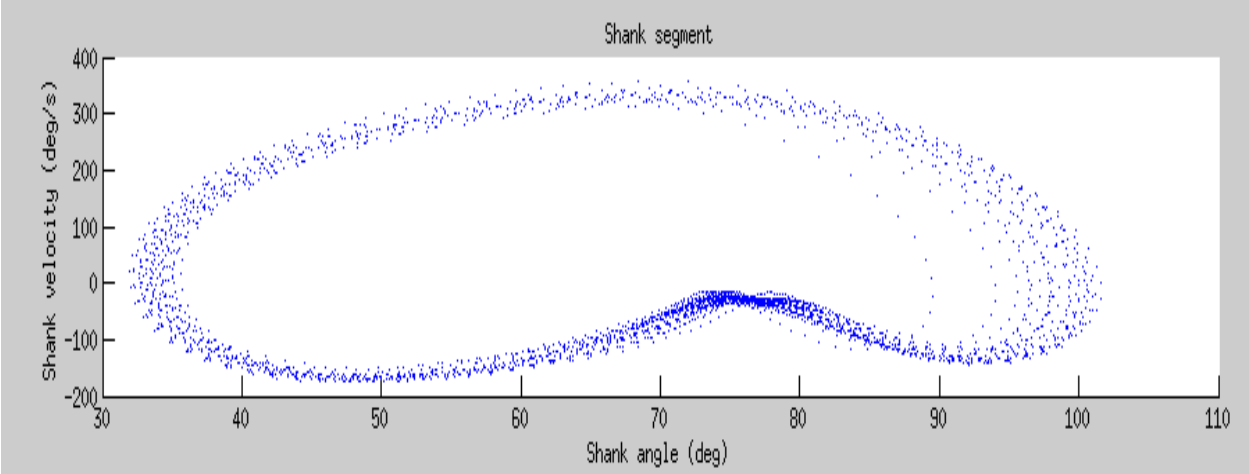

Figure 3.1. An example of a shank segment phase portrait. Each gait cycle produces one "loop" in the phase portrait, which dictates one centroid point. Gait variability is indexed by measurements of the motion of centroid points from cycle to cycle.

3.8 Tables

Table 3.1. Walking speed and the number of steps analyzed at each speed are reported for the MS and control groups. Gait was analyzed at 75%, 100%, and 125% of each individual's self-selected, comfortable walking speed. There were no significant differences between groups for speed or step counts.

		Walking Speed		
		Slow	Comfortable	Fast
Treadmill speed [km/hr]	MS	1.3 ± 0.6	1.8 ± 0.8	2.2 ± 1.1
	Controls	1.5 ± 0.5	2.0 ± 0.7	2.5 ± 0.8
Number of steps (right leg)	MS	19.4 ± 4.1	22.9 ± 4.5	24.6 ± 5.3
	Controls	22.0 ± 3.8	26.0 ± 2.4	28.1 ± 3.4

Table 3.2. Standard deviations of leg joint and segment angles are reported at each walking speed for the MS and control groups. Repeated measures analysis of speed, group, and group by speed interactions are also shown, with significance assumed for $p<0.05$.

Joint/segment angle		**Standard deviation [degrees]**			**Repeated measures interactions [p]**		
		Slow	Comfortable	Fast	Speed	Group	Group x Speed
Ankle	MS	2.0 ± 1.2	1.4 ± 0.7	1.4 ± 0.6	*0.007*	0.947	0.841
	Controls	1.9 ± 0.8	1.5 ±0.5	1.4 ± 0.8	*0.042*		
Knee	MS	3.2 ± 2.6	2.7 ±2.1	2.2 ± 1.4	0.093	0.255	0.747
	Controls	2.4 ± 0.8	1.8 ± 0.6	1.7 ± 0.8	*0.037*		
Thigh	MS	2.3 ± 2.4	2.2 ± 2.3	1.8 ± 1.7	0.251	0.239	0.649
	Controls	1.5 ± 0.5	1.2 ± 0.5	1.2 ± 0.8	0.314		
Shank	MS	2.6 ± 2.2	2.3 ± 2.2	2.0 ± 1.9	0.133	0.365	0.948
	Controls	2.0 ± 0.8	1.6 ± 0.5	1.4 ± 0.7	0.053		
Foot	MS	2.6 ± 2.4	2.4 ± 2.6	2.3 ± 2.1	0.505	0.593	0.619
	Controls	2.4 ± 1.0	1.9 ± 0.6	1.7 ± 0.7	*0.026*		

Table 3.3. Variability of the thigh, shank, and foot segments as deduced from segment angle phase portrait analysis is reported. Repeated measures analysis of speed, group, and group by speed interactions are also shown, with significance assumed for $p<0.05$.

Segment		**Centroid path length / # steps ($x10^3$)**			**Repeated measures interactions [p]**		
		Slow	Comfortable	Fast	Speed	Group	Group x Speed
Thigh	MS	15.5 ± 4.4	14.6 ± 4.5	16.6 ± 4.8	0.594	0.694	0.179
	Controls	19.5 ± 8.5	14.8 ± 4.8	14.7 ± 6.8	0.095		
Shank	MS	22.5 ± 11.1	21.4 ± 14.0	17.3 ± 4.3	0.251	0.881	0.369
	Controls	24.9 ± 10.5	17.9 ± 5.1	19.8 ± 12.7	0.199		
Foot	MS	19.4 ± 6.3	20.1 ± 13.7	17.4 ± 4.7	0.687	0.095	0.168
	Controls	29.6 ± 11.1	20.5 ± 4.5	24.0 ± 14.8	0.067		
		Centroid 95% ellipse area ($x10^3$)			**Repeated measures interactions [p]**		
Thigh	MS	6.8 ± 3.1	3.4 ± 1.4	5.2 ± 2.5	*0.037*	0.417	0.613
	Controls	6.9 ± 3.6	5.8 ± 6.2	8.8 ± 14.3	0.645		
Shank	MS	10.1 ± 5.8	9.2 ± 5.0	8.5 ± 3.0	0.618	0.090	0.280
	Controls	19.6 ± 15.9	12.7 ± 7.2	10.8 ± 11.7	0.164		
Foot	MS	8.2 ± 4.4	7.4 ± 3.0	8.7 ± 3.8	0.640	*0.020*	0.117
	Controls	18.9 ± 13.9	11.0 ± 3.5	12.9 ± 8.0	0.092		

CHAPTER 4

A NOVEL METRIC OF FOOTFALL VARIABILITY AND FALL HISTORY IN MULTIPLE SCLEROSIS

4.1 Abstract

Fifty percent of persons with multiple sclerosis (MS) fall in a given year. The purpose of this investigation was to determine associations between gait variability, including a new method for quantifying footfall placement variability, and fall history in people with MS. 47 individuals with MS and 20 healthy controls participated in this investigation. Individuals with MS were placed into two groups based on self-report fall history: recurrent (2+ falls in previous year) and non (-falls in previous year) fallers. Gait variability was quantified in both MS groups and healthy controls in two ways. One method was to calculate the coefficient of variation (CV) of step length, step width, and step time. Additionally, footfall variability (FV) was quantified by a novel metric that determined the order of Fourier series (i.e. the number of sine and cosine terms) necessary to accurately fit a pattern of footfall center of pressure coordinates from a 7.9 meter walk. While there were no differences between MS fall groups in traditional variability metrics (CV), the recurrent fallers group had significantly greater footfall variability (FV=7.0 ± 1.5) than the non fallers with MS (FV=5.8 ± 2.2). The current observations indicate that footfall variability is related to fall history in people with MS, but that associations between gait variability and falls in MS are not captured by traditional gait variability metrics. However, further investigation to evaluate the reliability of this novel method for quantifying footfall variability is warranted.

4.2 Introduction

Multiple sclerosis (MS) is an autoimmune disease that causes damage to the central nervous system. Symptoms of MS include gait, balance, cognitive, and sensory impairment. Given that all of these symptoms have been linked to falls in other clinical populations[1-4], it is not surprising that persons with MS are at elevated risk of falling. Previous research has shown that up to 50% of persons with MS report falling over a 6-12 month time period[5-8]. The incidence varies in the literature with reports that from 33-79% of fallers with MS are recurrent fallers (2+ falls in the previous year)[6,8,9]. Moreover, greater than 50% of falls in persons with MS are injurious[7,10]. Consequently, it is paramount to understand factors related to falls in MS so that appropriate interventions can be designed and implemented.

A number of factors have been linked to falls in MS including disability status, reduced postural control, gait impairment, muscle weakness, and use of assistive devices[5-12]. Clinically, performance tests (e.g. Berg Balance Scale, Timed Up and Go, Dynamic Gait Index) and self report measures (e.g. Activities-specific Balance Confidence, Dizziness Handicap Inventory, and 12-item Multiple Sclerosis Walking Scale) have been used to assess walking and balance deficiencies and falls in MS[11,13,14]. However, there has been a limited amount of research documenting subjective, quantitative measures of walking and balance and their associations with falls in MS[6,8].

One quantitative characteristic of walking behavior that has been found to be related to stability and falls in other clinical populations[15-18] is gait variability. For instance in elderly adults, very

high or very low step width variability was associated with falling in the previous year while moderate step width variability was not[16]. Additionally, a linear association has been demonstrated between variability of step length and double-support phase and incidence of multiple falls in the elderly[17]. Recurrent falls were also associated with variability of gait speed, cadence, and step time[17]. However, associations between gait variability and falls in persons with MS remain unknown.

People with MS exhibit greater variability of kinematic movement[19] and spatiotemporal gait parameters than healthy controls[20-22]. Gait variability has been documented in MS using mostly magnitude metrics such as standard deviation[19,20] (SD) and coefficient of variation[21,23,24] (CV). In this investigation, a novel method for quantifying gait variability is introduced that examines variability of footfall placement during a short walk. Variability of footfall placement is potentially more holistic than typical magnitude metrics because it quantifies variability in the anterior-posterior (AP) and mediolateral (ML) planes simultaneously. While the method in this investigation is novel, footfall placement variability has been studied previously in walking and balance analysis of individuals in clinical populations[25]. Previous research found associations between variability of footfall location relative to an individual's center of mass and traditional balance tests such as the Berg Balance Scale and Dynamic Gait Index in individuals recovering from spinal cord injury[25].

The purpose of this investigation was to examine associations between fall history and gait variability in persons with MS using traditional metrics as well as a novel analysis of footfall placement variability. Based on previous reports showing elevated gait variability in MS[19-22], we

hypothesize that persons with MS will demonstrate greater gait variability than controls. We further hypothesize that recurrent fallers with MS will exhibit greater gait variability, including footfall variability, than non fallers with MS.

4.3 Methods

All individuals provided informed consent prior to participation. Procedures for this investigation were approved by the local Institutional Review Board.

Inclusion criteria for participants with MS required a neurologist-confirmed diagnosis of MS, the ability to walk (with or without assistive devices), and having been relapse free for 30 days prior to testing. Inclusion criteria for healthy controls required no falls in the previous year, neurological disease, cardiac problems, or other serious health concerns. Participants with MS were placed into two groups based on self-reported fall history: recurrent fallers (2+ falls in the previous year) and non fallers (0 falls in the previous year). Participants reporting 1 fall were excluded from analysis because of the uncertainty regarding the circumstances of individual falls.

Upon arrival, participants with MS underwent examination by a neurologist to determine Expanded Disability Status Scale[26] (EDSS). Then, all participants performed two walking trials across a 7.9 meter GAITRite™ electronic walkway (gait mat) at their self-selected comfortable speed. Participants walked with shoes on, with or without using assistive devices (e.g. canes,

walkers). Walking trials began 1 meter in front of the gait mat and concluded 1 meter behind the gait mat in order to measure only steady-state walking.

Gait variability was indexed using two methods: first, the coefficient of variation (CV= standard deviation/mean) of step time, step length, and step width was calculated. Second, gait variability was indexed by a novel metric that quantified variability of the footfall placement in the AP-ML plane.

The footfall pattern from each individual pass over the gait mat was captured by examining the coordinates of the center of pressure (COP) during multiple footfalls in a single walk. To quantify variability of the footfall placement, the sequence of footfall patterns was fit with a Fourier series of sine and cosine waves using MATLAB R2010a (MathWorks, Inc., Natick, MA, USA), following the form:

$$y = \sum_{i=1}^{n} [A_i * \sin(i * \omega * \pi * x) + B_i * \cos(i * \omega * \pi * x)], \qquad (4.1)$$

where *y* is the COP coordinate in the ML plane, *x* is the COP coordinate in the AP plane, *n* is the series order, ω is frequency, and A_i, B_i are constants. Beginning with a first order series, each footfall sequence was fit with Fourier series of increasing order until the error between the fitted curve and the footfall pattern was less than a threshold value (Figures 4.1 – 4.3). Five percent error was tolerated because the purpose of this analysis was to analyze overall footfall locations, not to model the shape of COP motion within individual footfalls.

In this paradigm, footfall variability (FV) is defined as the order of Fourier series required to best fit a given footfall sequence. Larger FV values (i.e. number of terms in the series) indicate greater variability of footfall placement. FV values range from 1 to 9. An ideal footfall pattern (i.e. minimal variability in step length or step width and drift of the center of mass) would result in FV=1. However, a certain level of variability is healthy in biological systems[27] therefore even healthy individuals may demonstrate FV values greater than 1. The maximum FV value was 9 because the Fourier fit function in MATLAB (fit(X,Y,'fourier')) has a maximum possible order of 8. Therefore, any footfall output that had error greater than the threshold value with an 8^{th} order series was assigned FV=9.

For each participant, gait variability was quantified for both walks over the gait mat individually. Those values were then averaged to produce average CV and FV values for each participant over the two trials. These average values were used in statistical analysis.

Statistical analysis was performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). A one-way ANOVA was used to assess group differences in gait variability and age between recurrent fallers with MS, non fallers with MS, and healthy controls. Subsequently, Least Significant Difference post hoc analysis was performed. Group differences in gender distribution were assessed by a Kruskal-Wallis test. Significance was assumed for $p<0.05$.

4.4 Results

Forty-seven people with MS participated in this investigation. Six individuals who reported falling one time in the previous year were removed from analysis. Twenty-two individuals with MS reported falling 0 times in the previous year (average age 51.2) while 19 reported falling two or more times in the previous year (average age 54.4). Twenty healthy controls (same control group as chapter 2) were also analyzed (average age 50.9). Participant characteristics including age, gender, walking speed, and disability status are reported in Table 4.1. There were no differences between the three groups in age or gender distribution ($p>0.05$). The recurrent fallers group had significantly greater EDSS (EDSS=4.9) than the non fallers with MS (EDSS=3.9) ($p=0.034$). Non fallers with MS walked at a speed of 1.1 m/sec, which was significantly faster than recurrent fallers with MS, who walked at 0.9 m/sec ($p=0.018$). The control group walked at a speed of 1.50 m/sec, which was significantly faster than both MS groups ($p\leq0.001$).

Gait variability, including CV of step width, step length, and step time and footfall variability (FV) are reported in Table 4.2 for both MS groups and controls. There were no significant differences between MS groups in CV of step width, length, or time ($p>0.05$). Also, there were no differences between MS groups and the control group in step width CV ($p>0.05$). However, both MS fall groups demonstrated greater footfall variability ($p<0.001$), step length CV ($p\leq0.016$), and step time CV ($p\leq0.006$) than the control group. Footfall variability for recurrent fallers with MS was FV=7.0 ± 1.6, which was significantly greater ($p=0.043$) than non fallers with MS, who recorded FV=5.8 ± 2.2. Both MS groups had significantly greater FV than controls, who recorded FV=1.3 ± 0.5.

4.5 Discussion

The most important outcome of this investigation was that footfall variability, quantified using a novel methodology, is greater in recurrent fallers with MS compared to non fallers with MS, while traditional metrics of gait variability were not able to distinguish any difference. Previous reports[16-18] have found associations between gait variability and falls in the elderly, indexed using traditional metrics such as CV of spatiotemporal parameters. However, there were no differences between MS fall groups in CV of step length, step time, or step width in the current investigation. The lack of differences between fall groups in the current sample based on a simple variability metric such as CV demonstrates the value of the novel methodology for footfall variability.

Variability of step length and step width contribute to footfall variability in the current method in that fluctuations in step length or step width cause an individual's footfall pattern to move away from a simple sinusoid. However, CV of spatiotemporal gait parameters did not distinguish fall groups. This result was surprising because previous reports in other clinical populations found relationships between traditional variability metrics and falls[16-18]. This indicates that the additive effects of step length and step width variability, quantified by FV, may be more sensitive to falls than individual spatiotemporal gait parameters. In addition to variation of step length and width, a third potential contributor to footfall variability is an individual's ability to walk straight. This facet of gait variability is not captured by typical analysis of spatiotemporal gait parameters, but is encompassed in the current method. Drifting from side to side during ambulation causes deviation in an individual's footfall pattern away from a simple sinusoid. An inability to walk

straight could arise from sensory and balance impairment in MS, which are also related to falls in MS[8].

Examination of the physical meaning of footfall variability yields a logical connection between FV and falls. Increased footfall variability indicates reduced control over the placement of an individual's steps during walking. This could lead to falling in multiple ways. First, an individual with high footfall variability may be more likely to have a step land in an unstable location that could cause the center of mass to leave the base of support, resulting in a fall. Second, lack of control of where your steps land, reflected by increased footfall variability, could result in lower ability to avoid obstacles that could result in tripping.

Differences in gait variability between fall groups and healthy controls were also assessed using traditional parameters as well as footfall variability. Both recurrent and non fallers with MS demonstrated greater FV, step length CV, and step time CV than controls, but showed no differences in step width CV. These results are congruent with previous reports that show increased gait variability in people with MS compared to healthy controls[19-22]. There are several possible explanations for increased gait variability, including footfall variability, in persons with MS compared to controls. Increases in spasticity[28] and fatigue[29] and declines in muscle strength[30] have been previously associated with gait impairment in MS and could be related to elevated gait variability[31]. Specific relationships between gait variability and underlying factors warrant future investigation.

The results of the current study are also congruent with previous literature on gait and falls in MS. Both MS groups walked slower than controls[21,32,33]. The recurrent fallers with MS walked significantly slower than the non fallers with MS. This reflects more impaired gait in the recurrent fallers group, which is congruent with previous literature associating gait impairment with falls in MS[6,8]. In addition to footfall variability, disability status (EDSS) distinguished recurrent from non fallers with MS. This is also congruent with previous reports[5,8] that showed associations between disability status and falls in MS. It has been reported that approximately 50% of people with MS fall in a given year[5-8]. In our sample, 53% of individuals (25/47) reported at least 1 fall in the previous 12 months. Of the persons with MS who reported falling in our sample, 76% (19/25) were recurrent fallers, which is also congruent with previous literature reporting 33-79% of fallers with MS are recurrent fallers[6,8,9]. Overall, this suggests that our MS sample was representative of the MS population.

There are limitations to the current study. First of all, footfall variability was quantified using a novel metric. While the current observations demonstrate the potential for the FV method to distinguish fallers from non fallers with MS, future work must be done to assess the reliability of this metric. A second limitation of this study was its cross-sectional nature, which included fall history being self reported. If the current method for quantifying FV is proven to be valid and reliable, a prospective study should be performed to assess the potential value of FV as a predictive measure for falls in MS.

In summary, footfall variability is elevated in MS compared to controls and recurrent fallers with MS demonstrate greater footfall variability than non fallers with MS. The novel method used for

quantifying footfall variability requires further testing to determine reliability. However, the lack of differences between fall groups in variability of spatiotemporal gait parameters reinforces the need to develop new tools for analyzing gait variability. Potential mechanisms and underlying factors driving gait variability in MS should also be investigated.

4.6 References

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4.7 Figures

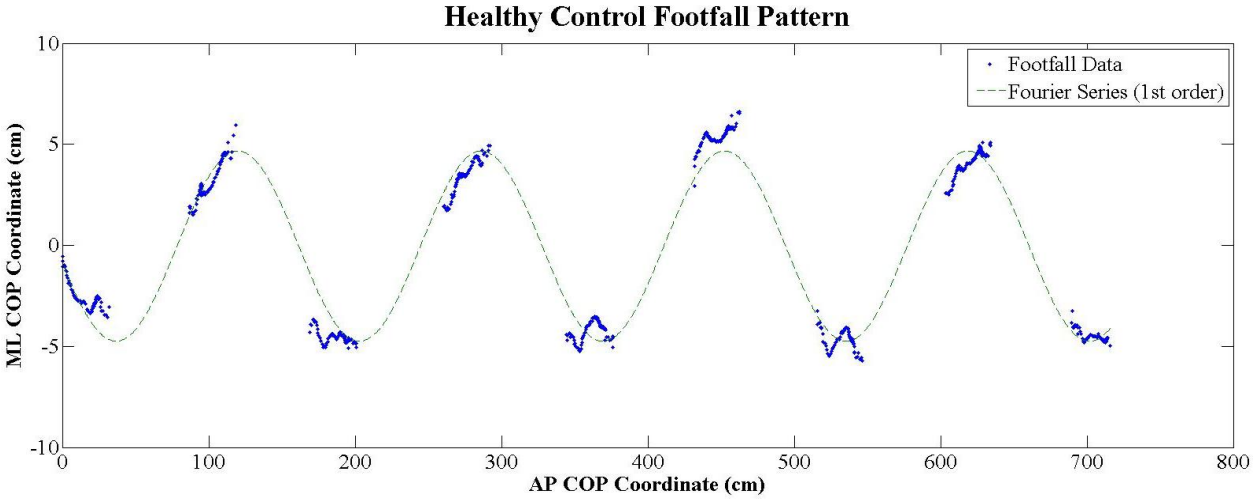

Figure 4.1. COP coordinates of each footfall from a healthy control participant's walking trial (left to right) are shown. This footfall pattern was best fit with a 1st order Fourier series (FV=1).

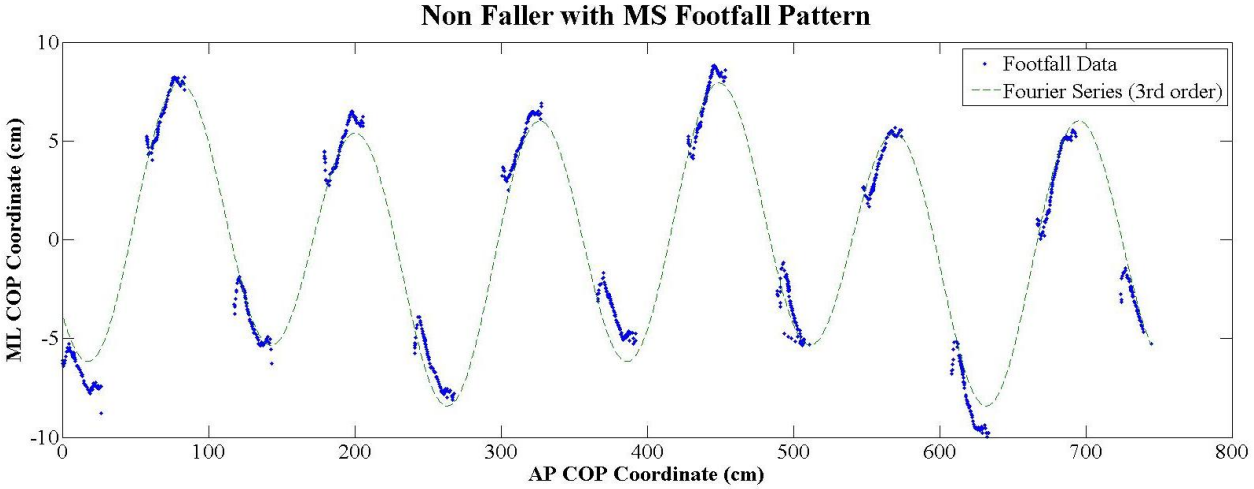

Figure 4.2. An example of a non faller with MS' footfall pattern is shown (walking left to right), which was best fit with a 3rd order Fourier series (FV=3).

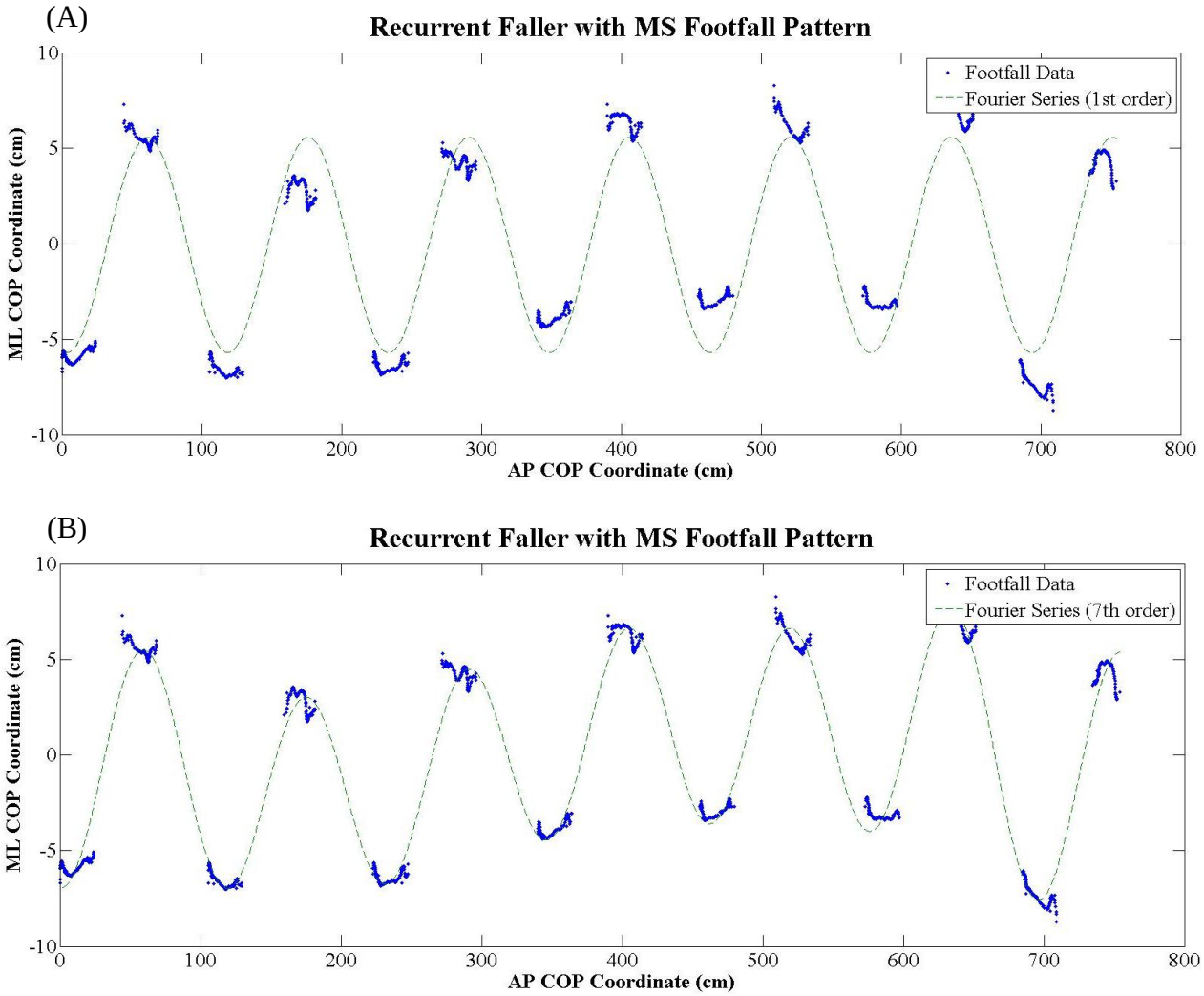

Figure 4.3. A recurrent faller with MS' footfall pattern is shown with (A) a 1st order Fourier series fit, which did not adequately capture footfall placement, and (B) a 7th order Fourier series (FV=7), which was considered to be the best fit.

4.8 Tables

Table 4.1. Participant characteristics for both MS fall groups and controls.

	Non Fallers w/ MS	**Recurrent Fallers w/ MS**	**Controls**
N	22	19	20
Age [years]	51.2 ± 12.1	54.4 ± 9.8	50.9 ± 8.7
Gender [F / M]	21 / 1	15 / 4	16 / 4
EDSS [-]	3.9 ± 1.5	4.9 ± 1.3	-
Walking speed [m/sec]	1.1 ± 0.3	0.9 ± 0.3	1.5 ± 0.1

Table 4.2. Gait variability results for both MS fall groups and controls. Coefficient of variation (CV) of step width, step length, and step time and footfall variability (FV) are reported. Results of the one-way ANOVA are also reported. Superscript a, b, and c denote specific group differences from post hoc analysis.

	Non Fallers w/ MS	**Recurrent Fallers w/ MS**	**Controls**	**F(2,48), p**
Step width CV [%]	21.2 ± 10.3	21.8 ± 17.4	18.2 ± 12.6	0.291, 0.749
Step length CV$^{a\,b}$ [%]	4.6 ± 3.0	6.0 ± 3.3	1.9 ± 0.7	7.024, 0.002
Step time CV$^{a\,b}$ [%]	4.5 ± 2.5	5.6 ± 3.4	4.4 ± 3.0	7.376, 0.002
FV$^{a\,b\,c}$ [-]	5.8 ± 2.2	7.0 ± 1.6	1.3 ± 0.5	34.612, <0.001

a - Difference between non fallers and controls, b – Difference between recurrent fallers and controls, c - Difference between MS fall groups ($p<0.05$).

CHAPTER 5

CONCLUSION

5.1 Summary and future directions

In summary, the purpose of the investigations contained within this thesis was to address unanswered questions concerning gait variability in persons with multiple sclerosis (MS). While there have been previous studies documenting gait variability in MS[1-5], they do not provide a complete picture. The current investigations provide additional documentation to existing work on gait variability in MS compared to healthy controls and address several unanswered questions about gait variability in MS.

Previous reports on gait variability in MS report that persons with MS have elevated variability of step and single-support time[1], step length[4], and hip, knee, and ankle angles[2] compared to healthy controls. Concerning variability of spatiotemporal gait parameters, our results (Chapter 2) were congruent with previous reports[1,4] demonstrating that people with MS have greater variability of step length and step time than healthy controls. In that investigation, we had a sample size (N=88 with MS) that was much greater than the previous reports[1,4] using similar metrics (N = 9 and 43 people with MS). Our investigation also included people with MS with a wider range of disability status than previous reports[1,4]. Our results (Chapter 3) concerning variability of leg joint angles were not congruent with the previous literature[2] who demonstrated greater variability of hip, knee, and ankle angle in MS compared to controls. Our results, using

the same metric (standard deviation), showed similar values for standard deviation of knee and ankle angles in the MS group, but we showed no differences between the MS and healthy control groups.

The first novel question addressed in this thesis was the role of disability status (Expanded Disability Status Scale[6], EDSS) in variability of spatiotemporal gait parameters in persons with MS (Chapter 2). A previous study[3] demonstrated that a small group (N=5) of people with MS with EDSS<4.0 had significantly less variability of stride length than a similarly sized group of people with MS with EDSS≥4.0. We expanded that result in much a larger sample (N=88) to show that variability of step length as well as step time correlate positively to EDSS. We also demonstrated that step width variability correlates negatively to EDSS, where the previous report[3] found no differences in step width variability between MS disability groups.

A second novel question concerning gait variability in MS that was addressed was the role of walking speed in gait variability (Chapter 3). We demonstrated that people with MS experience a significant change in variability at the ankle as they increase their walking speed from 75% of their preferred speed to 125% of their preferred speed. This pattern of change was similar to previous research[7] that demonstrated that people without MS experience reductions in magnitude of gait variability as walking speed is increased.

We also examined potential connections between gait variability and fall history in MS. Gait variability has been previously linked to falls in other populations[8-11], but not in MS. In chapter 4, it was demonstrated that recurrent fallers with MS exhibit greater variability of the placement

of their footfalls than non fallers with MS and healthy controls. This report utilized a novel metric that quantified footfall variability by the number of harmonic terms required to accurately map the AP-ML position of footfalls. The reliability of this method and the associations between footfall variability, indexed in this way, and other gait variability metrics should be investigated in the future.

Despite the novel observations reported in this thesis, important questions concerning gait variability in MS remain. As previously stated, the reliability and validity of methods for quantifying footfall placement variability need to be evaluated. Also, a larger study should be done to re-examine differences between people with MS and healthy controls with regards to variability of joint angles in the legs. Future investigations should also explore relationships between gait variability and other factors that have been related to gait impairment in MS such as fatigue[12,13], muscle weakness[14,15], and spasticity[16].

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