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Differential Effects of Reduced Foot Sole Sensitivity and Nerve Conduction Velocity on Postural Control and Functional Gait

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DIFFERENTIAL EFFECTS OF REDUCED FOOT SOLE SENSITIVITY AND NERVE CONDUCTION VELOCITY ON POSTURAL CONTROL AND FUNCTIONAL GAIT

by

KELSEY LEWIS

Under the Direction of Li Li

ABSTRACT

INTRODUCTION: Peripheral neuropathy is characterized by a loss of foot sole sensitivity and slowed nerve conduction velocity. Individuals with peripheral neuropathy have decreased postural control ability and functional gait performance. No research was found that differentiated the effects of the main symptoms of peripheral neuropathy on postural control and functional gait. PURPOSE: The purpose of this study was to assess the differential effects of reduced foot sole sensitivity and slowed nerve conduction velocity on postural control and functional gait. METHODS: Two main clinical symptoms, H-index and foot sole sensitivity were evaluated among 35 participants. Outcome variables are the center of pressure standard deviation in the anteroposterior direction (SD_{AP}) and the center of pressure average velocity (V_{avg}) during 30 seconds eyes open quiet standing, 6-minute walk distance (6MWD), and timed-up-and-go duration (TUG). RESULTS: Participants were separated into three groups symptomologically: Less affected (LA, 73±2 years old, 68.4±3.5kg, 1.62±0.02m, H-index: 89.7±3.4, range 78.0-109.4, cm^2/ms^2, Foot sole sensitivity score: 8.6±0.5, range 6-10), moderately affected (MA, 74±2 years old, 77.2±4.1kg, 1.65±0.02m, H-index: 60.2±3.4, range 42.8-76-6, cm^2/ms^2, Foot sole sensitivity score: 8.7±0.5, range 6-10), and severely affected (SA, 73±1 years old, 95.2±6.5kg, 1.73±0.03m, H-index: 61.8±2.1, range 45.6-75.5, cm^2/ms^2, Foot sole sensitivity score: 2.2±0.6, range 0-5). Multivariate analysis revealed significant group differences ($p<.05$), where post-hoc showed significant differences between LA and SA in V_{avg} ($F_{4,30}=3.752$, $p=0.014$). A discriminant analysis revealed that V_{avg} was the primary determinant and 6MWD and TUG were secondary determinents to the separation between the groups. Further analysis demonstrated that the severity of the disease mediates the relationship between the clinical symptoms and functional performance. The affect of foot sole sensitivity on functional

performance was very different for people within the LA and MA group. People in the MA group had much lower H-index values indicating slower nerve conduction velocity even though foot sole sensitivity of both groups was within the same range. On the other hand, the affect of nerve conduction velocity, measured by H-index, on postural control-related variables (SD_{AP} and V_{avg}) were foot sole sensitivity dependent. CONCLUSION: Peripheral neuropathy negatively affects postural control and functional gait. The severity of the disease mediates the specific effects on postural control and functional gait. Understanding the differential effects of the symptoms may help to design specifically tailored rehabilitation protocols.

INDEX WORDS: Peripheral neuropathy, H-index, Foot sole sensitivity, Postural control, Functional gait, Nerve conduction velocity

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CHAPTER 1

INTRODUCTION

Peripheral Neuropathy (PN) is a degenerative disease that mainly affects the peripheral sensory nerve (Li, Zhang, & Dobson, 2019; Martyn & Hughes, 1997). PN may be caused by diabetes mellitus, human immunodeficiency virus, or chemotherapy (Watson & Dyck, 2015). Millions of people are affected by this disease and may have positive (e.g., burning, tingling, allodynia, and hyperalgesia) or negative symptoms (e.g., loss of tactile sensation, proprioception, and temperature sensitivity)(Centers for Disease Control and Prevention, 2020). Common complications of PN are neuropathic pain and diabetic foot (Garcia-Morales et al., 2011; Smith & Torrance, 2012). The symptoms and/or complications negatively affect quality of life (Li & Hondzinski, 2012), the ability to complete activities of daily living, and sense of independence (Resnick et al., 2002). Older individuals with PN are at a higher risk of falling (Wallace et al., 2002). The leading reason for hospital or nursing home admissions in this population are fall related injuries, such as fractures or traumatic brain injuries (Pfortmueller et al., 2014). Repeated fall events can lead to an accumulation of medical costs (Pfortmueller et al., 2014). This population is at a higher risk of falling for many reasons, one of which is due to the inability to detect and delayed response to perturbations (Pfortmueller et al., 2014).

Postural control is the ability to maintain ones center of pressure within their base of support by detecting perturbations and correcting movements that potentially lead to falls (Li et al., 2019). This ability is important for maintaining postural control during quiet stance, functional gait, and in response to perturbations (Anson et al., 2017). Types of tactile receptors include Merkel's cells, Pacinian corpuscles, Meissner's corpuscles, and Ruffini endings and their presence on the sole of the foot contributes greatly to maintaining postural control during quiet standing (Kars, Hijmans, Geertzen, & Zijlstra, 2009). Previous research has shown that individuals with PN had a decreased postural control capacity, defined by average sway velocity and area, impaired functional gait evident by a shortened 6-minute walk distance (6MWD), and a longer timed-up-and-go duration (TUG) (Zhang, Manor, & Li, 2015). Researchers have investigated the differences in postural control among older individuals with and

without PN and reported that there is an increase in postural sway in people with PN (Kars et al., 2009; Lafond, Corriveau, & Prince, 2004; Toosizadeh, Mohler, Armstrong, Talal, & Najafi, 2015). It has also been shown that there is an inverse relationship between sway magnitude and H-index (Chen & Zhou, 2011; Nardone, Grasso, & Schieppati, 2006). H-index is a normalized measure of an individual's nerve conduction velocity. Individuals with PN have been observed to walk slower, and with greater magnitudes of variability (Manor, Wolenski, & Li, 2008; Zhang et al., 2015).

The pathological components of PN, reduced foot sole sensitivity and nerve conduction velocity, may affect postural control and functional gait differently depending on the stage of the disease (Fulk, Robinson, Mondal, Storey, & Hollister, 2010). The neural pathway for active control of stance and walking includes five different components: information from the sensory receptors; ascending signal to the central nervous system; information processing in the central nervous system; descending signal to muscles; and finally, the translation of the signal to the alpha motor neuron. PN affects feedback control mainly through the reduction in foot sole sensitivity and insensitivity to postural perturbations (Li et al., 2019; Zhang & Li, 2013). PN affects the efferent pathway by demyelination, leading to slower nerve conduction velocity. This in turn influences the speed at which an individual reacts to detected perturbations (Bonnet & Lepeut, 2011) and the completion of functional gait tests (Lange-Maia et al., 2016). These pathological components of PN have been investigated, either isolated or combined, and it has been determined that individuals with PN have decreased postural control and impaired functional gait. However, no research was found that addresses the differential effects of each component on postural control and functional gait in adults over the age of 65 years.

Therefore, the purpose of this study was to assess the differential effects of reduced foot sole sensitivity and nerve conduction velocity on postural control and functional gait. It was hypothesized that reduced foot sole sensitivity and slowed nerve conduction velocity will affect postural control and functional gait differentially. It was further hypothesized that the relationship between the dependent variables and reduced foot sole sensitivity or slowed nerve conduction velocity will be significantly different depending on the severity of the disease.

CHAPTER 2

METHODS

Prior to participant recruitment, this study was approved by the Institutional Review Board at Georgia Southern University. Thirty-eight participants were recruited from the local community and briefed about the testing procedures. Individuals were able to participate in the study if they met the following inclusion criteria: 1) over the age of 65 years old; 2) able to stand for a minimum of 5 min; 3) able to walk unassisted for at least 6 min; 4) did not have a history or evidence of central nervous system dysfunction; 5) did not have foot sole ulcers; 6). did not have a cardiac pacemaker implant; and 7). did not answer “yes” to any of the follow-up questions on the Physical Activity Readiness Questionnaire plus (PAR-Q+) and did not participate in any type of exercise.

At the beginning of the testing session, required forms and assessments were completed, including informed consent, medical history, and a PAR-Q+. Anthropometric data (i.e., age, sex, height, body mass) were also collected. Then foot sole sensitivity, Hoffmann reflex, postural control, and functional gait were tested.

Foot sole sensitivity was assessed using a 5.07-gauge Semmes-Weinstein monofilament (North Coast Medical, Inc, Morgan Hill, CA, USA) according to established protocol (Manor, Doherty, & Li, 2008). Testing sites included the hallux, bases of first and fifth metatarsals, midsole, and heel. This method has been used in this population and has been deemed reliable (Manor, Doherty, et al., 2008).

Hoffmann reflex test was conducted in a standing position. A surface electromyography (EMG) electrode (Trigno Wireless EMG System; Delsys Inc., Massachusetts, USA) was placed on the lateral gastrocnemius on the declared dominant leg of the participant, according to established protocal (SENIAM, 2020). The confirmative answer to the question, “what foot would you kick a ball with?” established leg dominance. Prior to placement, the skin was cleaned with an alcohol prep pad and shaved with a disposable razor, if necessary. After EMG surface electrodes were placed, a 5 cm × 8 cm anode and 2 cm diameter cathode were placed over the patella and popliteal fossa, respectively (Figure 1). Nerve conduction velocity was represented by the H-index, which considers body height in the conduction

velocity test results . The latency between the onsets of the M- (T_M) and H-wave (T_H) (ms) and the height (cm) of the individual was used to calculate the lateral gastrocnemius H-index (Equation 1).

$$\text{H-index} = \left(\frac{Height\ (cm)}{T_M - T_H}\right)^2 \times 2 \quad (1)$$

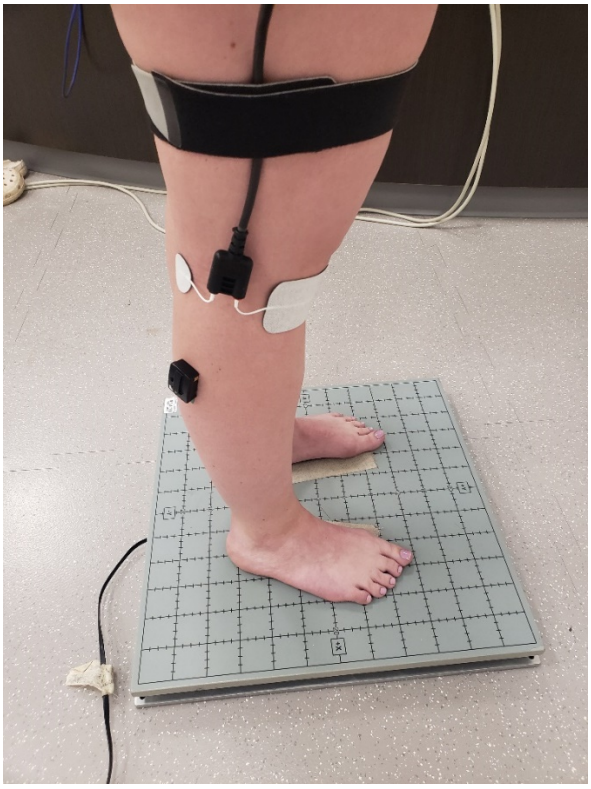


Figure 1. Electromyography placement on the lateral gastrocnemius. Electrical stimulation electrodes placed over the patella (Anode) and the popliteal fossa (Cathode).

During the process of setting up the recruitment curve, the participant stood with feet about shoulder-width apart, arms relaxed by their side, wore noise-canceling headphones, and was instructed to stare at a visual point that was set at eye level. A 500 µs square-pulse single stimulus was delivered to the tibial nerve by an electrical nerve stimulator (Digitimer model DS7A, Digitimer Ltd., Welwyn Garden City, England). Stimulation intensity began at 5 mA and increased in small increments of 2 mA until 65 mA was reached. Stimulation intervals were separated by 10 s. There was a 10 min rest following the Hoffman's reflex test before the postural control assessment. Reliability of H-index for this position has

been deemed “good” (unpublished data). The recruitment curve was imperative to determine the maximum M- and H- waves. Maximum amplitude was measured from peak to peak. The M-waves typical behavior is a gradual increase in amplitude, whereas the pattern of the H-wave is a gradual increase in amplitude, then it reaches a plateau (Chen & Zhou, 2011). The intensity at which maximum H-wave occurred was used to determine the latency period.

Postural control was assessed using an Accusway force plate (AMTI, Watertown, MA, USA) at a sampling rate of 1,000 Hz. Data were collected using the AMTI Netforce Software. Participants stood with their heels 10 cm apart with feet 10^{o} abducted for 30 s with their eyes opened (Manor, Doherty, et al., 2008). Postural control variables were the standard deviation of center of pressure movement in the anterior-posterior direction (SD_{AP}) and the average velocity of the center of pressure movement (V_{avg}).

Functional gait was assessed using the 6MWD and the TUG tests. The 6MWD test, cones were placed 30 m apart, as well as taped markers every meter along a brightly lighted hallway. Participants were instructed to walk at a self-selected pace between the cones for six min. The distance covered in six min was recorded to the nearest meter (Manor, Doherty, et al., 2008). The TUG test consisted of having the participant begin seated with their back against an armchair. The participant was instructed to stand up from the chair, walk around a cone that was set 3 m away and back to the seated position. Three meters was determined from the front edge of the chair, and the timer started when the participant initiated movement and stopped when the participant sat against the back of the armchair (Manor, Doherty, et al., 2008). A total of 3 trials were conducted, and the average duration was used in the analysis.

Statistical analysis was performed using SPSS 25 (IBM, Armonk, NY). The differential effects of reduced foot sole sensitivity and H-index on postural control (SD_{AP} & V_{avg}) and functional gait (TUG & 6MWD) were assessed using a one-way multivariate analysis of variance (MANOVA), discriminant analysis, and multiple univariate analysis of variance (ANOVA).

To understand the magnitude that each dependent variable contributed to the separation between groups the MANOVA was followed up with a discriminant analysis. There were 35 observations included

in the discriminant analysis. Entry level value for the analysis was set to 0.05, and the removal value was set to 0.01. Alpha level for all statistical tests was set at 0.05.

After a significant MANOVA, multiple ANOVAs with Least Significant Difference (LSD) post-hoc tests were conducted to observe what dependent variable was significantly different between the groups. Effect sizes were determined using Cohen's d ($Cohen's\ d\ = \frac{|M_2 - M_1|}{SD_{pooled}}$), where M_1 and M_2 are the group means, and SD_{pooled} is the pooled standard deviations of both groups. The criteria for evaluating effect size were $d < 0.2$, $0.2 \leq d < 0.5$, $0.5 \leq d < 0.8$, and $d \geq 0.8$ for very small, small, medium, and large, respectively.

To assess the relationship between the main clinical symptoms and the postural control and functional gait variables, Pearson product correlations were run within each group. The correlation coefficients of each group within the variables being assessed were compared using 95% confidence intervals (CI) (Li & Caldwell, 1999). The correlation was deemed significantly different from zero if the CI range did not cross zero.

CHAPTER 3

RESULTS

Thirty-eight participants (19 females; 19 males) were recruited for this study. Three individuals (1 female; 2 males) were excluded from the data analysis due to the inability to identify the onset of the M- and H-waves in their lateral gastrocnemius muscles.

Table 1. Means and Standard Errors of the Mean for Individual Group Characteristics

Group	LA (range)	MA (range)	SA (range)
Age (Years old)	73±2 (65-81)	74±2 (67-84)	73±1 (66-81)
F/M (N)	7F/3M	7F/5M	4F/9M
Body Mass (kg)	68.4±3.5 (45-81)	77.2±4.1 (51-100)	95.2±6.5 (65-140)
Height (m)	1.62±0.02 (1.53-1.71)	1.65±0.02 (1.55-1.78)	1.73±0.03 (1.55-1.88)
BMI (kg/m^2)	26.1±1.4 (18.2-32.1)	28.2±1.2 (21.3-33.3)	31.3±1.4 (22.6-40)
H-Index (cm^2/ms^2)	89.7±3.4 (78.0-109.4)	60.2±3.4 (42.8-76.6)	61.8±2.1 (45.6-75.5)
Foot Sole Sensitivity	8.6±0.5 (6-10)	8.7±0.5 (6-10)	2.2±0.6 (0-5)

Note. LA: Less Affected group, MA: Moderately affected group, SA: Severely affected group

Participants were grouped based on the severity of reduced foot sole sensitivity and slowed conduction velocity to study the differential effects of the two most significant movement related symptoms on postural control and functional gait. Participants were first grouped based on their foot sole sensitivity scores, 0-5 and 6-10. The group with more severe sensation loss (0-5) had a maximum H-index at just below 78 cm^2/ms^2. The groups were then further subdivided for those with less foot sole sensitivity loss (6-10) into two groups based on their H-index scores: less and greater than 78 cm^2/ms^2. This created three groups. Group 1 was less affected (LA) by the pathology (foot sole sensitivity 6-10, H-index ≥ $78cm^2/ms^2$); Group 2 was moderately affected (MA) by the pathology (foot sole sensitivity 6-10, H-index < $78cm^2/ms^2$); and Group 3 was severely affected (SA) by the pathology (foot sole sensitivity 0-5, H-index < 78 cm^2/ms^2). Anthropometrics and average H-index and foot sole sensitivity scores for each group are presented in Table 1.

According to the One-way MANOVA analysis there was a significant difference between the groups ($F_{4,30}$=3.752, p=0.014, partial η^2=0.333). The discriminant analysis revealed that the centroid locations of each group had the most separation for the linear discriminant function 1. In contrast, there was not a significant separation with linear discriminant function 2 (Figure 2). The primary determinant for this separation was $V_{avg,}$ along with the 6MWD and TUG contributing as the secondary determinants for linear discriminant function 1 (See Table 2 for more details).

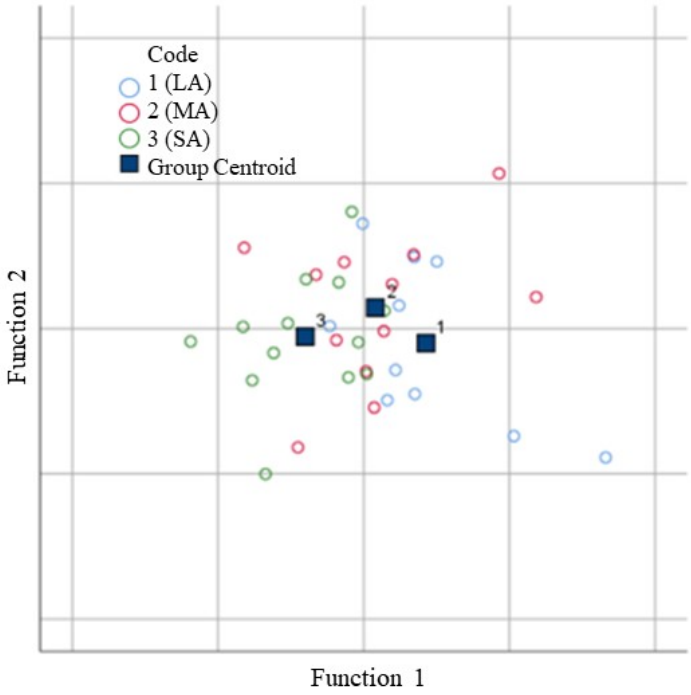


Figure 2. Graphical representation of the separation between the groups based on their centroid location. The discriminant analysis revealed that the greatest separation between the least affected (LA) & severely affected (SA) were for the linear discriminant function 1, whereas minute separation was observed for linear discrimination function 2.

Table 2. Results of Discriminant Function Analysis

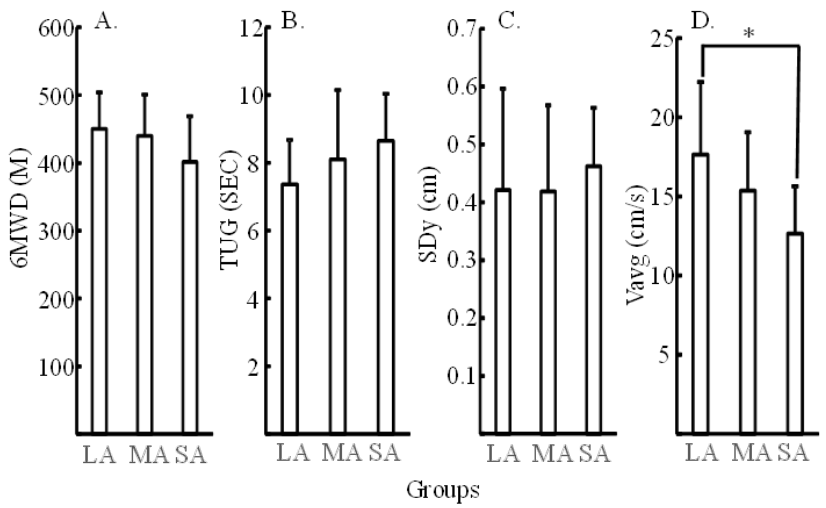
	Structure Matrix
	Correlation Coefficients with Linear Discriminant
Variables	Function 1
V_{avg}	0.816*
6MWD	0.498*
TUG	-0.459*
SD_{AP}	-0.192

Note. V_{avg}: Average velocity of the center of pressure movement, 6MWD: 6-minute walk distance, TUG: Timed-up-and-go, SD_{AP}: Standard deviation of the center of pressure movement in the anterior-posterior direction, Wilk's Lambda = 0.635, p=0.086; *denote significant contributors.

Multiple univariate one-way ANOVAs with a LSD adjustment was performed after a significant MANOVA. There was a significant difference observed for V_{avg} (F_2=5.344, p=0.010, partial η^2 =0.250). There were no statistically significant differences observed for SD_{AP} (F_2=0.370, p=0.694 partial η^2=0.023), 6MWD (F_2=2.098, p=0.139, partial η^2=0.116), and TUG (F_2=1.749, p=0.190, partial η^2=0.099).

Pairwise comparisons using LSD post-hoc analysis were conducted for the postural control and functional gait parameters (See Figure 3A-D for more details). Significant differences were observed between groups LA and SA for V_{avg} (p=0.003, d=1.291). Effect sizes were calculated for each of the pairwise comparisons and results are displayed on the right panel of Figure 3. Very small effect sizes were observed between LA and MA (d=0.172) for 6MWD, SD_{AP} (d=0.019). Small effect sizes were observed between LA and MA (d=0.415), and MA and SA (d=0.290) for TUG, LA and SA (d=0.280) and MA and SA (d=0.329) for SD_{AP}. Medium effect sizes were observed for LA and SA (d=0.792), MA and

SA (*d*=0.601) for 6MWD, as well as LA and MA for V_{avg}. Large effect sizes were observed for LA and SA (*d*=0.888) for TUG, LA and SA (*d*=1.291), and MA and SA (*d*=0.803) for V_{avg}.



Cohen's d		
	LAvsMA	0.172
6MWD	LAvsSA	0.792
	MAvsSA	0.601
	LAvsMA	0.415
TUG	LAvsSA	0.888
	MAvsSA	0.290
	LAvsMA	0.019
SD_{AP}	LAvsSA	0.280
	MAvsSA	0.329
	LAvsMA	0.552
Vavg	LAvsSA	1.291*
	MAvsSA	0.803

Figure 3A-D. Means and Standard Errors of the Means of the functional gait (A, B) and postural control (C, D) variables. LA, MA, and SA denote for the less, moderately, and severely affected groups, respectively. A. 6MWD: 6-minute walk distance, B. TUG: Timed-up-and-go, C. SD_{AP}: Standard deviation of the center of pressure movement in the anterior-posterior direction, and D. V_{avg}: Average velocity of the center of pressure movement. Pairwise comparison Cohen's d are listed to the right of the figures. It is categorized based on the following: very small (d <0.2), small (0.20 ≤ d <0.50), medium (0.50 ≤ d <0.80) and large (d ≤0.80) *indicates significant differences (p<0.05).

The relationship between foot sole sensitivity, H-index, and the dependent variables for all three groups are presented in Figures 4 and 5. The correlation was deemed significant if the 95% CI did not cross zero. See Table 3 for detailed results. The list of significant correlations with foot sole sensitivity observed includes, Group LA & SA: 6MWD; Group LA & MA: TUG; Group LA: SD_{AP}; and Group MA: V_{avg}. Significant correlations with H-index were observed from: Group LA & MA: 6MWD; Group LA & MA: TUG; and Group MA and SA: V_{avg}.

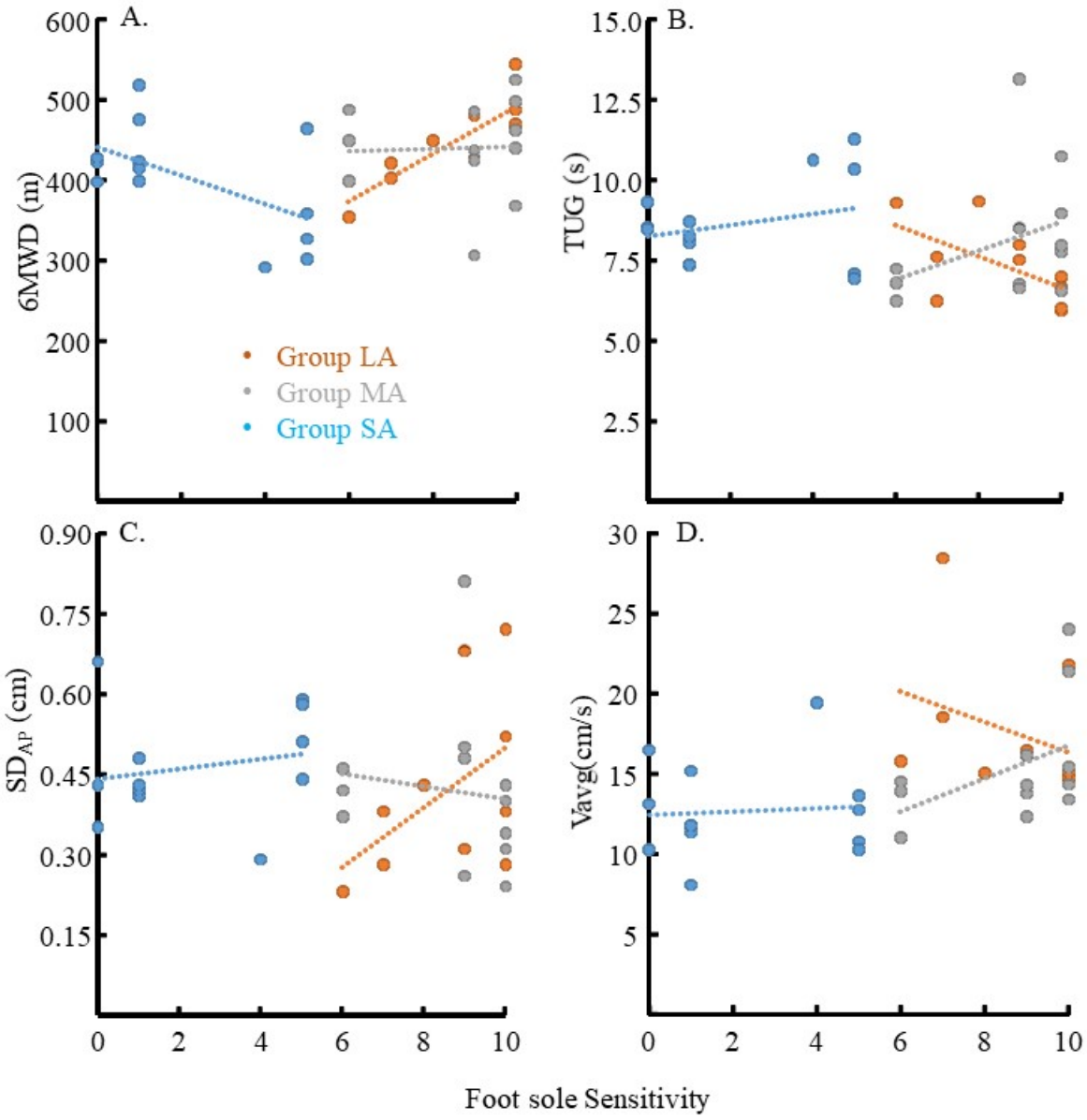


Figure 4A-D. Pearson product correlation for Foot Sole Sensitivity and Dependent Variables. Functional gait variables are presented in A& B, postural variables in C & D. A. 6MWD: 6-minute walk distance, B. TUG: Timed-up-and-go, C. SD_{AP}: Standard deviation of the center of pressure movement in the anterior-posterior direction, and D. V_{avg}: Average velocity of the center of pressure movement. Groups were LA (less affected), MA (moderately affected), and SA (severely affected).

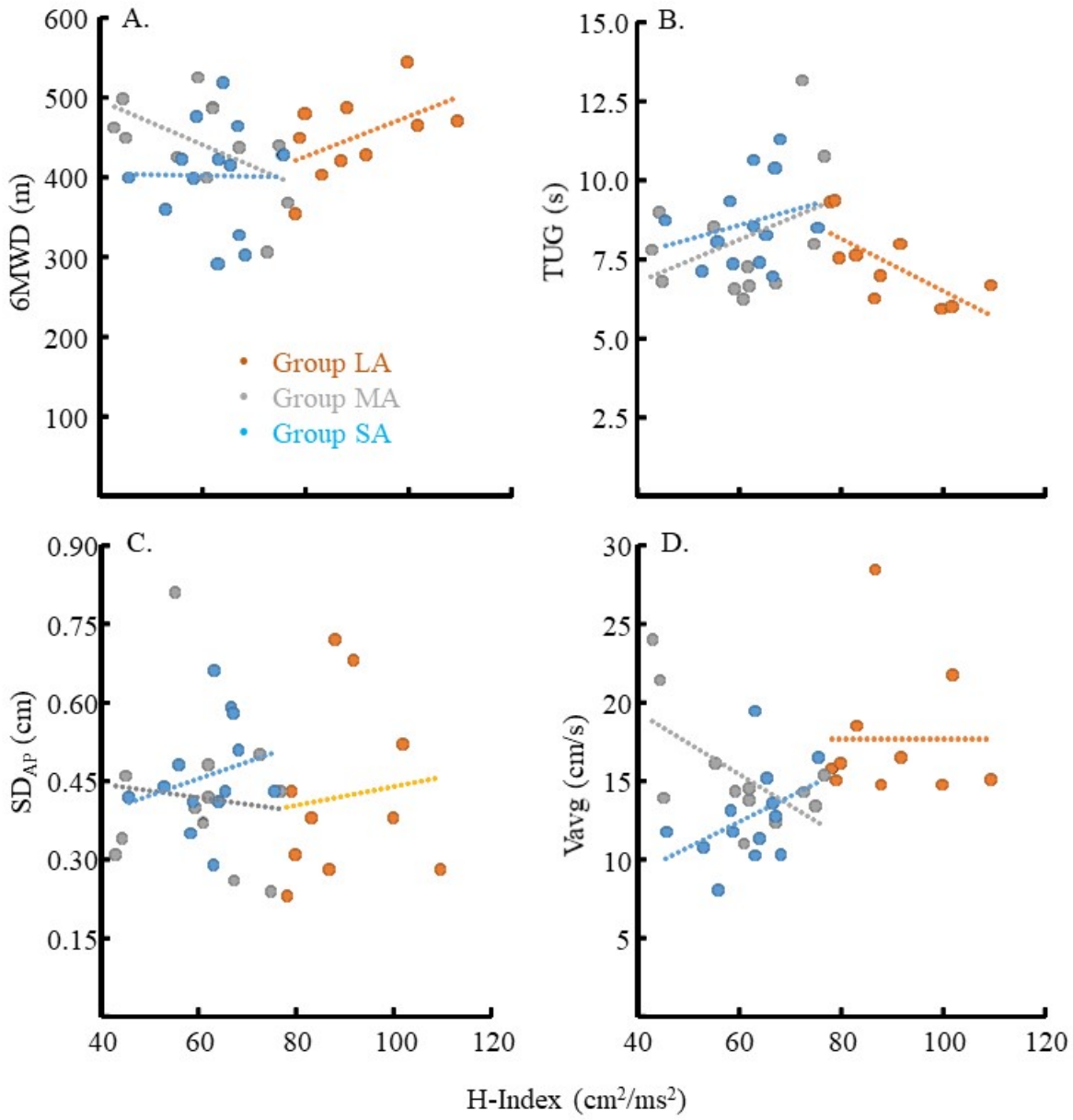


Figure 5A-D. Pearson product correlations between H-index and Dependent Variables. Functional gait variables are presented in A & B, postural variables in C & D. A. 6MWD: 6-minute walk distance, B. TUG: Timed-up-and-go, C. SD_{AP}: Standard deviation of the center of pressure movement in the anterior-posterior direction, and D. V_{avg}: Average velocity of the center of pressure movement. Groups were LA (less affected), MA (moderately affected), and SA (severely affected).

Table 3. Linear Relationship between Functional Gait and Postural Variables and Foot Sole Sensitivity and H-index

		Foot Sole Sensitivity		H-index	
	Group	**R**	**95% CI**	**R**	**95% CI**
6MWD	LA	0.860*	0.737,0.927	0.523*	0.229,0.729
	MA	0.044	-0.294,0.372	-0.535*	-0.737,-0.245
	SA	-0.569*	-0.758,-0.290	-0.012	-0.344,0.323
TUG	LA	-0.588*	-0.770,-0.316	-0.716*	-0.502,-0.847
	MA	0.364*	0.036,0.622	0.381*	0.055,0.634
	SA	0.274	-0.065,0.556	0.243	-0.098,0.533
SDY	LA	0.498*	0.198,0.713	0.116	-0.226,0.433
	MA	-0.131	-0.444,0.212	-0.100	-0.419,0.242
	SA	0.199	-0.143,0.499	0.242	-0.099,0.532
VAVG	LA	-0.326	-0.595,0.007	0.000	-0.333,0.333
	MA	0.466*	0.158,0.692	-0.622*	-0.791,-0.364,
	SA	0.069	-0.271,0.393	0.412*	0.091,0.655

Note. LA: Less affected group, MA: Moderately affected group, SA: Severely affected, 6MWD: 6-minute walk distance, TUG: Timed-up-and-go, SD_{AP}: Standard deviation of the center of pressure movement in the anterior-posterior direction, V_{avg}: Average velocity of the center of pressure movement R: Correlation coefficient, 95% CI: 95% Confidence Interval. * indicates that the correlation coefficient is significantly different from zero.

CHAPTER 4

DISCUSSION/CONCLUSION

The purpose of this study was to assess the differential effects of reduced foot sole sensitivity and nerve conduction velocity on postural control and functional gait. The first hypothesis was partially supported because the clinical symptoms affected postural control and functional gait differentially. SA individuals differed primarily in V_{avg} compared to LA individuals. However, functional gait variables were secondary contributors to the separation between the groups. The second hypothesis was partially supported as the clinical and outcome measures depended on the severity of the disease. An increase in pathology negatively affected functional gait for LA and these relationships were only consistently significant within LA. Inconsistent trends were observed as only one of the clinical measures significantly affected one of the outcome measures. For example, H-index affected 6MWD of LA negatively, but the same relationship had the opposite trend in MA. For another example, reduced H-index, but not foot sole sensitivity, negatively affected V_{avg}. Finally, V_{avg} reacted to the clinical declines differently within MA. Decreased V_{avg} was associated with decreased foot sole sensitivity, but increased V_{avg} was significantly related to decreased H-index.

The results of the determinant analysis showed that V_{avg} is the primary determinent that separates LA from SA, whereas the functional gait parameters only served as secondary determinants. This meant that disease progression affected postural control more than functional gait and supports the Zhang and Li results (Zhang & Li, 2013). They suggested that postural control heavily relies on feedback control where functional gait is mainly controlled through feedforward mechanisms (Zhang & Li, 2013). PN mainly affects foot sole sensitivity and sensory nerves, which affects the feedback control more than the feedforward control. Furthermore, a significant negative relationship between V_{avg} and H-index among MA found here is similar to what Zhang and colleagues (2015) reported. However, this relationship was not observed for SA, which was similar to the mean of the PN group in their study. A potential reason for this difference may be that the H-index was recorded in the prone position in their study, but in standing

in ours. Position changes have been shown to influence Hoffmann reflex (Alrowayeh, Sabbahi, & Etnyre, 2011; Tokuno, Garland, Carpenter, Thorstensson, & Cresswell, 2008).

We have separated the two main symptoms of PN: foot sole sensitivity and nerve conduction velocity, to study their differential effects on postural control and functional gait. No studies were found that studied differential effects in this way. For instance, nerve conduction velocity of MA was much lower compared to LA, whereas foot sole sensitivity was reduced comparing MA to SA. When the variables are compared between groups and evaluated, a significant difference in V_{avg} was observed between LA and SA. In conjunction with the discriminant analysis, this difference implies that as the severity of the disease increases, postural control is the main factor that separates LA from SA.

Furthermore, the differential influences of the two symptoms became apparent with our way of grouping the participants. For example, foot sole sensitivity for LA and MA were in similar range (6-10), but its correlation with V_{avg} behaved oppositely. Reduction of foot sole sensitivity was significantly associated with decreasing V_{avg} in MA, but with increasing V_{avg} in LA, although the latter association was not significant. This difference might be related to MA having a much lower nerve conduction velocity than LA. Without the conduction velocity reduction (LA), V_{avg} would increase with the reduction of foot sole sensitivity (Wang & Lin, 2008). However, with the reduced conduction velocity (MA), movement control strategy and adaptation to the loss of foot sole sensitivity could be very different. This phenomenon, that H-index mediated the relationship between functional outcomes and foot sole sensation can be seen on the right side of all four Figure 4 panels (A-D). Mediatation was apparent as LA and MA correleations were opposite. The H-index mediated relationship between foot sole sensitivity and functional movements (both postural control and functional gait) has not been found in the literature.

Nerve conduction velocity between MA and SA had a similar range (H-index was roughly in the 40 – 78 cm^2/ms^2 range), and its correlation with V_{avg} was different between groups. A decreased H-index was significantly correlated with the increase of V_{avg} in MA. This negative correlation has been reported in the literature (Zhang et al., 2015). However, within SA, nerve conduction velocity decrease was significantly correlated with V_{avg} increase. These two significant relationships indicate a foot sole

sensitivity mediated relationship between nerve conduction velocity and postural control since foot sole sensitivity was different between MA (6-10) and SA (0-5). However, we did not observe foot sole sensitivity mediated relationships between H-index and functional gait in MA and SA, where both were in the same direction albeit not all were significant.

Based on the observations from Figures 4 and 5, nerve conduction velocity meditates the relationship between foot sole sensitivity and both postural control and functional gait, where foot sole sensation only mediates the relationship between H-index and postural control, but not that of functional gait.

PN is a progressive disease and its adverse effects on postural control and functional gait increases. If we are able to understand the reasons for PN-related movement disorders (e.g., loss foot sole sensitivity or slowed nerve conduction velocity) then training programs can be adjusted or tailored accordingly. Our results showed that the improvement in foot sole sensation can positively affect postural control and functional gait when there is not a reduction in nerve conduction velocity, however, when there is already a reduction in H-index an improvement in foot sole sensitivity does not have the same effect. The results from this study show that early intervention may be critical to reduce or reverse the effects of PN on postural control and functional gait. Specific types of exercises have been shown to influence the clinical symptoms of neuropathy positively. For instance, Tai Chi has been shown as a successful early intervention for individuals who have a moderate reduction in foot sole sensitivity. It has been reported that foot sole sensitivity and functional gait, both 6MWD and TUG improved after 24 weeks of modified Tai Chi training (Li & Manor, 2010). However, their study did not measure H-index. Otherwise, it could be suggested that there was an increase in H-index as well, based on the positive correlation observed in LA between H-index and 6MWD. Other studies have investigated the benefits of resistance and aerobic exercises (Dixit, Maiya, & Shastry, 2014; Kruse, Lemaster, & Madsen, 2010; Singleton, Smith, & Marcus, 2015) as well as postural control training (Powell-Cope, Quigley, Besterman-Dahan, & Lind, 2014) for this population. Exercise can positively affect postural control capacity and functional gait. Older adults are encouraged to participate in exercise because it can help

decrease the chances of a fall and interrupt the progression of the disease (Pfortmueller et al., 2014). Our results support the notion that exercise can help reverse the vicious cycle of PN brought to people and improve their quality of life (Li & Hondzinski, 2012).

There are a few limitations to this study. For example, individuals recruited were either healthy or diagnosed with diabetes, diabetic neuropathy, or idiopathic neuropathy. The presence of diabetes potentially affects the vestibular system biologically (D'Silva, Lin, Staecker, Whitney, & Kluding, 2016). We do not know the contribution of vestibular system deterioration to our postural control tests. Timing of the day sensitivity and the number of steps taken have been shown to impact foot sole sensitivity (Alfuth & Rosenbaum, 2011), but was not controlled in our protocol. Factors that could affect the results of Hoffman's reflex, but were not controlled are the following: postural anxiety, fatigue, possible oligosynaptic spinal cord pathways (Chen & Zhou, 2011). We also did not record current medication intake and understand that participants may have been taking medications that are related to falling (Stolze et al., 2004). Those factors need to be better controlled in future studies. However, these factors were not likely to have a systematic effect on our observations due to the randomized nature of our data collection process.

Ankle joint proprioception and leg strength have been reported to affect functional gait among people with PN (Li et al., 2019; Manor, Doherty, et al., 2008). Future research should compare the influences of ankle joint proprioception and leg strength with impacts of the clinical outcome measures on functional gait among this population. This comparison can help us to understand the influence of PN progression on strength and ankle joint proprioception. Furthermore, a more thorough investigation of PN severity and extensive postural control ability (i.e., tandem walking or berg balance tests) is suggested to understand the severity of PN and dynamic postural control. The addition of more challenging tasks combined with the effects of the deterioration of Hoffman's reflex outcomes will give us more information on the influence of PN on movement control (Richardson, Thies, DeMott, & Ashton-Miller, 2004a, 2004b). H- and M-wave ratio has been shown to behave differently in different populations and positions (Alrowayeh et al., 2011; Angulo-Kinzler, Mynark, & Koceja, 1998; Capaday & Stein, 1986).

Studying the H/M ratio can give insight to neural adaptations that may be occurring as a result of PN (Angulo-Kinzler et al., 1998; Li et al., 2019).

CONCLUSION

Postural control and functional gait are impaired in individuals with PN because of the loss of foot sole sensitivity and slowed nerve conduction velocity. This study aimed to better understand the differential effects of the two main clinical symptoms of the disease on postural control and functional gait in older adults. We have observed that PN negatively impacts postural control and functional gait. The differential effects of reduced foot sole sensitivity and slowed nerve conduction velocity on postural control and functional gait were severity dependent. A deeper understanding of the impact of the clinical measures on postural control and functional gait can help us tailor rehabilitation and training programs specifically to people at different stages of the disease for optimal results.

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APPENDIX A: PROPOSAL DOCUMENT

Diabetic Neuropathy and Quality of Life

Diabetes Mellitus and Quality of Life

Over 23.1 million people are currently diagnosed with diabetes mellitus, with 25.2% being older adults over 65 years old (CDC, 2019). Diabetes Mellitus is an overarching group of diseases that are characterized by a defect in insulin secretion or insulin action that leads to hyperglycemia. Insulin action can be a result of inadequate insulin secretion and/or diminished tissue responses to insulin at many different points of the hormone pathway (American Diabetes Association, 2013; Kerner & Brückel, 2014). The pancreatic beta cells in people with diabetes are destroyed, which leads to insulin deficiency (American Diabetes Association, 2013; Kerner & Brückel, 2014). Hypoglycemia symptoms include polyuria (an abnormal production large amount of diluted urine), polydipsia (abnormally thirsty), weight loss, occasionally polyphagia (excessive hunger), and blurred vision (American Diabetes Association, 2013; Kerner & Brückel, 2014). There are two main types of diabetes. Type 1 diabetes is defined as an absolute deficiency of insulin secretion and affects 5-10% of the population, whereas Type II diabetes affects 90-95% of the population (American Diabetes Association, 2013; Zheng, Ley, & Hu, 2018). Type II Diabetes is defined as insulin resistance and inadequate compensatory insulin secretory response (American Diabetes Association, 2013). Risk factors for type II diabetes, the most common type of diabetes, are excess adipose tissue around the abdomen, obesity indicated by a high body mass index, age, physical inactivity, or ambient air pollution, or some medications (American Diabetes Association, 2013; Zheng, Ley, & Hu, 2018). When diagnosing individuals with diabetes mellitus, plasma glucose or HbA1c levels are tested. The following is the set criteria: HbAlc ≥ 6.5%(≥ 48mmol/mol), random plasma glucose ≥ 200mg/dl (≥ 11.1 mmol/l), fasting plasma glucose ≥ 126mg/dl (≥7.0mmol/dl), or OGTT 2-hour glucose in venous plasma ≥ 200mg/dl (≥ 11.1 mmol/l) (Kerner & Brückel, 2014). Long term effects of type II diabetes include increased risk of musculoskeletal, cardiovascular, hepatic, or digestive disorders as well as an increase in liver, pancreas, endometrium cancers and comorbidities such as non-

alcoholic fatty liver disease, obstructive sleep apnea, depression, infection, or neuropathy (Zheng et al., 2018).

Individuals with diabetes have an average of 8 years of reduction in their lifespan and exhibit a decreased quality of life (QoL) (Zheng et al., 2018). Diabetic foot ulcers and other diabetic complications are related to the reduced quality of life and increased medical expenses. Previous research has shown that age, presence of type II diabetes, increase the severity of the ulcers, lesion progression, the number of ulcers contributes to a decrease in the physical and psychological function (Garcia-Morales, Lazaro-Martinez, Martinez-Hernandez, Aragón-Sánchez, Beneit-Montesinos, & González-Jurado, 2011). The diabetic foot has been shown to have a greater impact on QoL when compared to the impact of neuropathy and pain symptoms. This condition may affect QoL because the treatment for diabetic foot includes staying off the affected foot which impairs mobility and ability to perform activities of daily living, and severe impairment may lead to quitting jobs and increasing psychological and social impact (Garcia-Morales et al., 2011).

Peripheral Neuropathy and Quality of Life

Peripheral neuropathy is a heterogeneous and symmetric condition with the defining characteristic of damaged axons and/or myelin of ≥ 1 peripheral nerve (Li, Zhang, & Dobson, 2018). PN may be caused by diabetes mellitus, human immunodeficiency virus, chemotherapy, or dysproteinemia disorders (Watson & Dyck, 2015). Individuals with PN may be asymptomatic; however, some may experience positive symptoms such as sensations of burning, tingling, prickling, and amplified response to pain, as well as negative symptoms like loss of tactile sensation, proprioception, loss of muscle strength, and temperature sensitivity (Li, & Manor, 2010; Timar et al., 2016; Azhary, Muhammad, Minal, Arshad, & Mounzer, 2015). This degradation of sensory feedback progress in a distal to the proximal manner (Li et al., 2018; Richardson, Ching, & Hurvitz, 1992; Davies, Brophy, Williams, & Taylor, 2006; Ghanavati, Yazdi, Goharpey, & Arastoo, 2012). Individuals with peripheral neuropathy also exhibit bilateral deficits in the absence of ankle reflexes, insensitivity to touch, vibration, and position (Mold,

Vesely, Keyl, Schenk, & Roberts, 2004) and loss of sensation in their feet (Dros, Wewerinke, Bindels, & Weert, 2009).

Two-thirds of individuals with PN may experience neuropathic pain (Girach et al., 2019), which is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Smith & Torrance, 2012). For example, neuropathic pain can be a resultant of allodynia, or associated comorbidities such as depression, anxiety, and sleep disturbances (Watson & Dyck, 2015; Davies et al., 2006). This pain increases health care facilities usage which increases medical expenses, increases personal financial burden because of the inability to work (Smith & Torrance, 2012; Girach et al., 2019). Risk factors for neuropathic pain are older age, female sex, manual occupation, inability to work, rural environment, and lower education level (Smith & Torrance, 2012). Also, individuals with PN may not be able to perform ADLs or tasks they previously did (Ghanavati et al., 2012).

A series of tests may be performed to diagnose PN and DPN. These include vibration perception, application of warmth and cold, and nerve conduction velocity studies. Monofilament testing, using Semmes-Weinstein calibrated monofilaments, is typically used as an inexpensive way to quantify reduced foot sole tactile sensation (Dros et al., 2009). The most common monofilament used to diagnose reduced foot sole sensation is 4.17, 5.07, and 6.10 (Dros et al., 2009). For this test, the monofilament wire contacts different parts of each foot three times. These areas are hallux, first and fifth metatarsal, midsole, and heel. Scoring for this test follows a standard protocol (Li & Manor, 2010). Nerve conduction velocity (NCV) testing is the lead assessment for diagnosing PN. Using the height of the individual divided by the onset of the maximum M-wave (M_{Max}) and H-wave (H_{Max}), the NCV can be calculated. NCV is reduced in individuals with PN and DPN. When an individual has diabetes, there may be an added effect of delayed muscle activation (Bonnet & Lepeut, 2011; Li et al., 2018). The amplitude of the M and H waves may suggest that demyelination or axonal degeneration has occurred (Boulton et al., 2005). For example, a lower amplitude may indicate axonal damage, whereas prolonged latency and slow conduction velocity may suggest demyelination (Azhary et al., 2015). The reduction in amplitude has been linked to impaired

glycemic control, abnormal sensation, decreased QoL (Li et al., 2018). The severity of peripheral neuropathy can be quantified using NCV and monofilament testing scores.

A research study in the United Kingdom determined that individuals with neuropathic pain, their health-related QoL is severely affected in comparison to those without neuropathic pain. QoL was assessed using the Short form 36 general health questionnaire. Another systematic review evaluated the role neuropathic pain plays in individuals with different causes, including diabetic neuropathy. Out of the 19 tools that were used to assess QoL, 34.8% used the SF-36 form to determine that QoL was severely impacted by neuropathic pain (Girach et al., 2019).

Diabetic Neuropathy and Quality of life

Out of the individuals diagnosed with diabetes, it is estimated that about one-half have peripheral neuropathy as a result (CDC, 2019). Diabetic Neuropathy (DPN) is a common progressive type of peripheral neuropathy that is the result of long-term diabetes (Kim et al., 2014; Eftekhar-Sadat, Azizi, Aliagharzadeh, Toopchizadeh, & Ghojazadeh, 2015). DPN is diagnosed when all other causes have been ruled out (Boulton et al., 2005). DPN can also be described as a long-term diabetic complication (Van Acker et al., 2009). Risk factors for DPN include: older age, sustained duration of diabetes, poor glycemic control, gender, height, insulin therapy, smoking status, obesity, alcohol consumption, high body mass index, elevated systolic blood pressure, high triglyceride levels, low HDL cholesterol, or presences of peripheral vascular disease, retinopathy or nephropathy (Van Acker et al., 2009; Davies et al., 2006). Out of the individuals diagnosed with DPN, 10-20% require some treatments for their symptoms (Van Acker et al., 2009). Individuals who have type II diabetes may experience painful DPN more often than people with type 1 diabetes (Van Acker et al., 2009). If left untreated, complications such as diabetic foot, infections, foot ulcers, bone deformities, stiffened tendons, ligaments, and plantar soft tissue, reduced flexibility may occur (Bonnet & Lepeut, 2011; Van Acker et al., 2009).

In addition to the previous PN tests mentioned, diagnosis of diabetic neuropathy may be made if the pain affects both lower limbs, is worse at night, not related to exertion, and not caused by other conditions (Davies et al., 2006).

Symptoms can last for many years thus continuously negatively impacting QoL. Individuals with DPN experience a significantly higher financial burden because of the increased usage of medical facilities, medications, procedures, or interventions. An individual may be negatively impacted personally or socially (Smith & Torrance, 2012). The amount of negative impact on QoL is different between individuals depending on the presence of painful diabetic neuropathy. Davies and colleagues (2006) conducted a survey investigating the impact painful diabetic neuropathy has on QoL. It was concluded that there was a correlation between severity and QoL when compared to individuals without neuropathic pain (Davies et al., 2006). This condition puts a burden on individuals with diabetic neuropathy because treatment is sparse, and expenses accumulate (Davies et al., 2006).

Compromised postural control capacities during activities of daily living (ADLs), fear of falling, or increased financial burden may also affect QoL (Li et al., 2002; Najafi et al., 2010; Timar et al., 2016). Avoidance of activities may lead to muscle atrophy, decreased lower body muscle strength, mobility, and physical functioning (Li et al., 2003). A research study conducted by Li and colleagues (2002) evaluated the relationship between fear of falling and functional ability in elder adults (age > 70 years old) and determined that fall-related self-efficacy acted as the mediator for this relationship (Li et al., 2002). It has been shown that individuals who have higher levels of fear are more likely to have decreased functional ability performance and reduced quality of life (Li et al., 2003) and are more likely to avoid other social and physical activities thus a decline in physical and mental health (Li et al., 2003). In the elderly population, the leading cause of hospital and emergency room admissions were due to unintentional falls, in which 87% result in fractures (Wallace et al. 2002). The risk of falling increases in elders with diabetes and peripheral neuropathy by 15% when compared to individuals without neuropathy (Wallace et al., 2002). Hospital stays in this population are longer, which causes summation of hospital expenses. In the

year 2000, the direct medical costs and productivity loss total in older adults was 31 billion dollars (Stevens et al., 2006), which contribute to the increased financial burden for the health care system.

Individuals with diabetes or DPN may have evidence of a decline in somatosensory, visual, and vestibular function, metabolic muscle function (Hewston & Deshpande, 2016). These aspects play a role in the increased risk of falling in this population (Hewston & Deshpande, 2016) as well as the reoccurrence of falls (Lafond, Corriveau, & Prince, 2004). These characteristics of diabetic neuropathy can affect an individual's quality of life by increasing fear of falling, anxiety, depression, loss of mobility, and independence (Benbow et al., 1998; Najafi et al., 2010). Pain-related reduction of Qol occurs in almost 10% of this population (Benbow et al., 1998).

Diabetic Neuropathy and Postural Control

Postural Control Mechanisms

Increased risk of falling can be associated with poor postural control and can be assessed using quiet standing (Lafond et al., 2004). Postural control involves the musculoskeletal and neural systems, and describes the ability to maintain, correct, or achieve Stable postural control during any activities (Li et al., 2018). Stable postural control describes the ability to maintain an individual's center of mass within their base of support (Palmieri et al., 2002). During a quiet stance, the body naturally sways in an inverted pendulum motion (Li et al., 2018). Since the body is a multilinked system, it uses ankle or hip strategies to maintain the center of mass within the base of support in the anteroposterior and mediolateral directions, respectively (Bonnet & Lepeut, 2011). Analysis of the center of pressure 95% sway area and sway velocity can be used to describe the postural control behavior (Toosizadeh, Mohler, Armstrong, Talal, Majafi, 2015). Postural sway measures the magnitude and direction of an individual's center of pressure moves (Palmieri, Ingersoll, Stone, & Krause, 2002). The center of pressure is defined as the vertical projection of an individual's center of mass and can explain the force distribution occurring at the ground level (Chen & Zhou, 2011; Winter, 1995). The direction in which individual sways can give

insight to what adaptive strategy is being used. For instance, for smaller sway magnitude in the anteroposterior direction can be associated with the ankle strategy, whereas sway in the mediolateral direction is an indicator of hip strategy (Winter, 1995). During postural control, different systems help the individual maintain their stability, or center of pressure within their base of support (Chen & Zhou, 2011).

The vestibular, visual, and somatosensory systems contribute sensory information to help maintain postural control stability (Hewston & Deshpande, 2015; Lafond et al., 2004; Bonnet & Lepeut, 2011). The vestibular systems' role is to provide information regarding the head's position and the spatial orientation (Hewston & Deshpande, 2016). The somatosensory system provides information about where the body's segments are relative to each other. This system includes proprioception and cutaneous sensation. Proprioception includes muscle spindles, Golgi tendon organs, and joint receptors, and they are responsible for detecting changes in movement and sending the information to the central nervous system (Chen & Zhou, 2011). For postural stability, the proprioception and cutaneous receptors at the legs and bottom of the feet have been shown to contribute significantly (Bonnet & Lepeut, 2011; Eftekhar-Sadat et al., 2015). Cutaneous receptors can detect pressure, mechanical stimuli, temperature, and pain. Each receptor provides feedback that allows the body to adjust to any changes in body position (Chen & Zhou, 2011). The primary tactile receptors in the skin are Merkel's cell, Pacinian corpuscles, Meissner's corpuscles, and Ruffini endings (Li et al., 2018). Visual input plays a vital role due to being able to provide feedback about contextual clues and surrounding movements (Chen & Zhou, 2011).

The central nervous system coordinates the control of posture and movements (El Bardawil et al., 2013). The coordinative mechanisms include the cerebral motor cortex which generates the motor commands, cerebellum that plays a role in postural and locomotion control, and then the basal ganglia and brainstem control autonomic and voluntary movements (Chen & Zhou, 2011). Type 1a and type 11a afferent pathways innervate different receptors. Type Ia afferent innervates primary afferents of the muscle spindles, whereas type II afferent innervate secondary afferents of the muscle spindles and

mechanoreceptors (Zhang, Manor, & Li, 2015). Electrical stimulation and electromyography have been used to gain insight into the nerve signaling.

Postural control can be used to measure stability impairments in individuals susceptible to deteriorated stability performance. Age, neurological, or musculoskeletal disorders have been shown to impact postural control abilities (Palmieri et al., 2002). Understanding how diabetes, peripheral neuropathy, and diabetic neuropathy affect postural control can help gain insight on postural control performance, thus fall risks.

Diabetes and Postural Control

People with diabetes have been shown that individuals over the age of 60 years old who are diagnosed with diabetes are 2.5 times more likely to fall when compared to nondiabetics (Wallance et al., 2002). Postural control performance is negatively impacted by diabetes (Fulk et al., 2010). Fulk and colleagues (2010) concluded that individuals with diabetes and no peripheral neuropathy had more trouble reacting to small postural perturbations (Fulk et al., 2010). It was suggested that the reason for this is due to the vestibular system is affected by the change in blood glucose and insulin levels. People with diabetes are 2.3 times more likely to have trouble with detecting postural disturbances because there is an impairment in the translation of information regarding body position and spatial awareness (Chen & Zhou, 2011; Hewston & Deshpande, 2016; Fulk et al., 2010). However, hypoglycemia, a symptom of diabetes have been shown to damage sensory nerve fibers, thus hindering the somatosensory system's feedback (Hewston & Dashpande, 2016), affect the circulatory system of the retina, cause inflammation and reduced sensitivity in the metabolic vasculature in the inner ear, impact mechanical and metabolic muscle function due to impaired glucose regulation (Hewston & Deshpande, 2016; Toosizadeh et al., 2015). Impaired metabolic muscle function hinders the ability to increase muscle strength. Thus people with diabetes have been shown to have trouble performing ADLs because of the decreased muscle strength (Toosizadeh et al., 2015). Schwartz and colleagues tested muscular strength and tandem balance in women over the age of 67 who had diabetes and/or peripheral neuropathy and determined that this

population was at a higher risk of falling due to instability and decreased muscle strength (Schwartz et al., 2002).

Studies have investigated postural control in individuals with diabetes. However, some have neglected to include how they screened for neuropathy, or they combined DPN and diabetes into the same group. When DPN was included, this group exhibited greater sway area and velocity than individuals with diabetes without neuropathy and healthy controls. When diabetes was isolated to its group and compared to the healthy control, there was a significant difference between healthy control and people with diabetes when examining quadriceps muscle strength, greater sway and worse sensory-motor function test scores (Bonnet, Carello, Turvey, 2009).

Neuropathy and Postural Control

Individuals with PN facing postural control challenges (Winter, 1995). Because of this, individuals with PN are at a higher risk of falling and reduced mobility. PN is associated with reduced postural control ability and walking speed (Schwartz et al., 2002). During postural control assessments, individuals with PN exhibit increased postural sway magnitude. Greater sway may be due to the lack of ability to react to position changes due to the diminished proprioceptive and cutaneous sensory receptors (Li et al., 2018).

During postural control and functional mobility, ankle joint proprioception, and tactile sensitivity have been shown to play a critical role (Li et al., 2018; Menz, Morris, & Lord, 2005). Ankle proprioception has been previously defined as a “specialized variation of the touch sensory modality, which includes joint movement and joint position movements” (Zhang et al., 2014). Reduced ankle joint proprioception leads to increased fall risk, decreased distance covered during the 6MWD and longer TUG durations (Li & Manor, 2010; Zhang & Li, 2014; Zhang, Holmes, & Li, 2014).

Diabetic Neuropathy and Postural Control

Wallance and colleagues evaluated the incidence of falls, as well as the reason for an increase in falls in older adults. They observed that individuals with diabetic neuropathy had an increased risk of falling due to loss of foot sole sensation. Another study by Cavanagh and colleagues, determined that DPN individuals were 15 times more likely to experience fall-related injuries. It has been shown that falls are more common in individuals with diabetic neuropathy, specifically type II diabetes, due to the increase in postural sway and difficulties with sensory input (Fulk, Robinson, Mondal, Storey, & Hollister, 2010; Hewston & Deshpande, 2016). It has also been noted that individuals with diabetes have an increased postural sway, decreased peripheral sensory and motor pathways, and abnormal neuromuscular responses to postural disturbances and walking (Fulk et al., 2010). The reduction of postural control could be due to loss of somatosensory input, loss of pressure perception, decrease in ankle joint position sense, slower reaction time, or decreased muscle strength that is a result from peripheral neuropathy and diabetic complications (Fulk et al., 2010; Hewston & Deshpande, 2016; Richardson et al., 1992). PN has also been shown to lead to muscle atrophy in the foot, which can compromise bone structure (Richardson et al., 1992).

Individuals with diabetic sensory neuropathy and the inaccuracy of proprioception feedback have a larger sway area magnitude and sway velocity (Lafond et al., 2004). Also, the center of pressure measurements are highly correlated to the increased severity of peripheral neuropathy and not necessarily of the diabetes mellitus (Lafond et al., 2004). Yamatoto and colleagues (2001) evaluated the center of pressure average area and velocity in individuals with diabetic neuropathy and concluded that the average area and velocity was 245% and 159% percent higher, respectively (Yamatoto et al., 2001). Another study using wearable technology determined that individuals with diabetic neuropathy have an increase in the center of mass sway by 98% and 245% during eyes open and closed conditions, respectively (Najafi et al., 2010). It has also been observed that individuals with diabetes have an increased rate of postural sway. One study reported that the rate of sway was about 49% higher individuals who have diabetic

neuropathy (Toosizadeh et al., 2015) and the increase was explained through reduced muscle strength, and lack of sensory feedback. Toosizadeh and colleagues also evaluated quiet stance performance in individuals with diabetic neuropathy and determined that the DPN group had a significantly higher body sway in the eyes open (about 74%) and eyes closed (about 87%) condition (Toosizadeh et al., 2015).

Neural Adaptations studied using Hoffman's reflex mechanisms

Hoffman's reflex mechanisms

Neurological adaptations can be investigated through understanding two types of monosynaptic reflexes; stretch reflex and Hoffman's reflex (H-reflex). Anytime there is a change in the length of a muscle, the muscle spindle detects this and sends a signal via afferent neurons to the spinal cord. The neuron synapses on the efferent excitatory neuron, causing the signal to travel to the muscle. Once the signal reaches the muscle, it causes the muscle to contract.

H-reflex is like the stretch reflex because it travels the same neural pathway; however, the muscle contraction is the result of electrical stimulation, not the change in the muscle spindles. H-reflex is a valuable tool in understanding the electrical synaptic transmission of the neuromuscular system and can be used to understand presynaptic and postsynaptic inhibition (Palmieri, Ingersollt, & Hoffman, 2004; Gajewski & Mazur-Różycka, 2016; Chen & Zhou, 2011). One of the most common muscles used for eliciting H-reflex is the soleus, which is innervated by the tibial nerve. A stimulation is introduced into the mixed nerve and the response of this stimulation, i.e., H-reflex, is measured using electromyography (Chen & Zhou, 2011). At low intensities, the signal travels toward the spinal cord via afferent sensory neuron then synapses on the efferent alpha motor neuron, causing the muscle to contract. The EMG signals recorded related to this muscle contraction is called the H-wave. The H-wave can describe the recruitment behavior of the afferent neurons. Typically, type 1a afferent neurons are recruited first due to the decreased excitability threshold and larger diameter (Palmieri et al., 2004; Gajewski et al., 2017). If the signal from the 1a afferent neuron is strong enough, an excitatory postsynaptic potential will occur on

the alpha motor neuron causing the neurotransmitter acetylcholine to release into the neuromuscular junction. The release of neurotransmitters causes muscle fibers to depolarize, thus causing muscle contraction. When the stimulation intensity is high enough, the electrical stimulation will directly elicit muscle contraction, and the muscle response or M-wave is recorded by EMG (Palmieri et al., 2004; Gajewski et al., 2017). H-wave and M-wave are different due to the distance the signal has to travel before its tracing is seen on the EMG. The time it takes to show up is referred to as the latency period. Latency periods for the H-wave and M-wave are 30 milliseconds and 4 to 5 milliseconds, respectively (Palmieri et al., 2004; Gajewski et al., 2017).

A common method for determining an individual's maximum H and M-wave is through a recruitment curve. This curve can be determined using the following procedure. The stimulation starts at a low intensity and gradually increases stimulation until a maximum M-wave (M_{Max}) is determined. Usually, stimulation current is increased in 1.2 to 2.5 milliamps (mA) increments (Chen & Zhou, 2011; Palmieri et al., 2004; Gajewski et al., 2017). As stimulation increases the magnitude of the H and M-wave increases because of the increase in motor unit recruitment. H-wave will gradually increase as stimulation increases but will reach a peak and then begin to decrease. The reduction of H-wave peak magnitude is due to the antidromic collision of the electrical activity that is traveling to and from the spinal cord along the same pathway. Antidromic collisions can be described by Newton's first law. A decrease is observed when the signal traveling to the spinal cord is greater than the electrical activity traveling from the spinal cord. In contrast, the M-wave will continue to increase as stimulation increases until a plateau is observed. At this plateau, all motor units that innervate the muscle have been recruited (Palmieri et al., 2004; Gajewski et al., 2017).

H_{max} represents the estimated maximum number of motor neurons that can be activated from a reflex at a specific time and can be useful in describing an individual's central fatigue. M_{max} represents the maximal motor neuron activation and can describe the level of an individual's peripheral fatigue (Palmieri et al., 2004; Gajewski et al., 2017). After the maximum H-wave (H_{max}) and M_{max} are determined from the

recruitment curve, it can be normalized through the use of the M_{max}/H_{max} ratio, which gives the proportion of motor neurons recruited during the reflex to the entire number of motor units in that muscle's motor neuron pool (Palmieri et al., 2004; Gajewski et al., 2017). It can also be used to measure the modifications made by the central nervous system (Zhang et al., 2014).

H-index is used as a diagnostic tool in individuals with peripheral neuropathy. This measurement takes into account the onset of the H- and M-wave and the height of the individual and can calculate the nerve conduction velocity of the entire reflex arc (Zhang et al., 2014).

Hoffman's Reflex and Postural Control

Hoffman's reflex has been used in different populations, positions, and as a dependent variable in postural control evaluations and training interventions. An inverse relationship has been suggested in healthy adults between postural sway magnitude and H-reflex magnitude, as well as a greater H_{max}/M_{max} ratio with COP displacement in the anterior direction (Chen & Zhou, 2010). Zhang and colleagues (2015) investigated the postural control behavior in individuals with peripheral neuropathy. A series of tests, such as H-reflex, ankle joint proprioception, TUG, and 6MWD were conducted. It was determined that there was a relationship between postural control and H-reflex, as well as a relationship between reduced foot sole sensation and 6MWD. This study indicated that individuals with PN have reduced H-reflex.

During standing, the H-reflex amplitude is greater in the soleus when compared to the gastrocnemius, but the H-/M-ratio is similar between these muscles. Greater muscle activation changes the H-reflex. The reaction of H-reflex to muscle activation is evident with the increased amplitude from prone to standing, and throughout the gait cycle (Makihara, Segal, Wolpaw, & Thompson, 2011).

Nardone and colleagues investigated various neuropathies; diabetic neuropathy and Charcot-Marie-tooth (CMT) disease and evaluated postural control ability under static and dynamic conditions. The population consisted of 20 healthy participants (age: 29-77 years), 14 diabetic neuropathy (age: 43-77 years), and Charcot-Marie-Tooth disease (Type 1: 32-63 years, Type 2: 18-61 years). They reported that

diabetic neuropathic individuals were generally unstable during the static quiet stance, but individuals with CMT were stable. The difference was evident in the inverse relationship between the increasing sway area and decreasing conduction velocity. Researchers concluded that the feedback for the leg muscles was type 1a afferent input.

Hoffman's Reflex and Postural Control among people with Diabetic Neuropathy

When evaluating Hoffman's reflex and postural control among people with DPN, supplement assessments of foot sole sensation and ankle proprioception should be included (Zhang et al., 2014). These assessments can give insight on neuroplastic changes that may be occurring within the central nervous system. A typical neural adaptation is sensory reweighting. The adaptation occurs when one sensory stimulus begins to compensate for a weakened or nonexistent stimulus (Li et al., 2018). It has been observed that individuals with PN exhibit decreased H-index, increased postural sway, and impaired functional mobility.

Previous studies have investigated the relationship between DPN and H-reflex. Dixit and colleagues were able to determine indirectly that sensory reweighting occurred after eight weeks of aerobic training. Another study conducted by El Bardawil et al. (2013) evaluated the relationship between a motor control test of postural responses and electrophysiology of the peripheral nerves. In this study, individuals with type 2 diabetes and some with neuropathy were evaluated. It was concluded that impaired peripheral nerve function played a role in postural instability. Instability in individuals with DPN has thought to be because of PN itself. The effect PN has on postural control instability is evident through the central nervous system. For instance, instability may be due to lack of accurate proprioceptive feedback, impairment of ankle strength, postural recovery and walking stability in people with diabetes (El Bardawil et al., 2013).

Based on previous literature, it has been concluded that postural control is impaired in individuals with diabetes, peripheral neuropathy, and diabetic neuropathy. The key reason for postural instability in

diabetes is muscle weakness, whereas postural instability in neuropathic individuals was due to reduced foot sole sensation. When Hoffman's reflex is included, the neuroplasticity of the central nervous system can be investigated. Individuals with diabetes were unstable due to motor deficiency, which leads to no change in H-reflex and individuals with neuropathy; however, lead to an enhanced H-reflex.

Purpose

Therefore, the purpose of this study is to examine the accumulated effects of diabetic neuropathy on neuroplasticity and postural control. It is hypothesized that individuals with DPN will exhibit a greater postural sway and decreased H-reflex. The secondary purpose is to examine the influence of ankle joint proprioception and reduced foot sole sensation on functional ability and postural performance. It is hypothesized that individuals with reduced ankle joint proprioception and reduced foot sole sensation will have decreased postural performance and functional ability. The tertiary hypothesis is to determine if a relationship between Hoffman's reflex (i.e H-/M-ratio, H-index) and postural control-related parameters (COP_{sway}, COP magnitude, COP velocity) exists. It is hypothesized that individuals with increased severity of neuropathy will have a depressed H-reflex and worsened postural control ability.

Methods

Participants:

We will recruit four groups of older adults who are either healthy or physician-diagnosed with idiopathic neuropathy, diabetes, or diabetic neuropathy. This study aims to recruit 15 individuals for each group. Participants will be recruited from the local community through snowball methods. Participants in each of the four groups must be 65 years or older, able to walk unassisted for at least 6 minutes and stand for a minimum of 2 minutes.

Participants will be excluded if they have a history or evidence of central nervous system dysfunction, trauma and/or disease that significantly affects their posture and mobility control, evidence of foot sole ulcers, evidence of cardiac pacemaker, or answer "yes" to one or more of the follow-up

questions on the Physical Activity Readiness Questionnaire plus (PAR-Q+) and do not exercise regularly. The Institutional Review Board at Georgia Southern University has approved this project. Prior to data collection, signed informed consent would be obtained from each participant after the experimental protocol is thoroughly explained and all questions have been satisfactorily answered.

Experiment Protocol:

Testing will occur on two different occasions separated by at least 24 hours in the Biomechanics Lab. The first session of testing will include the completion of all paperwork and testing cutaneous sensitivity, proprioception, leg strength, and functional mobility. Dependent variables are monofilament testing score, ankle joint repositioning error, knee peak extensor peak torque, 6-minute walking distance, and timed-up-and-go duration. The second day of testing will include the Hoffman's reflex (H-reflex) test and postural control assessment. H-reflex is a valuable tool in understanding the electrical synaptic transmission of the neuromuscular system and can be used to estimate the alpha motor neuron excitability in the monosynaptic neural pathway (Palmeiri, Ingersollt, & Hoffman, 2004; Gajewski & Mazur-Różycka, 2017). Dependent variables are H-/M-wave ratio, H-index, anteroposterior postural sway, mediolateral postural sway, postural sway velocity, and entropy. Electrical stimulation can yield a maximum M-wave, which is representative of the maximal muscle activation and can describe the level of an individual's peripheral fatigue. Whereas, H_{max} represents the estimated maximum number of motor neurons that can be activated from a reflex at a given time and can be useful in describing an individual's central fatigue (Palmeiri et al., 2004; Gajewski et al., 2017).

On their first visit to the Biomechanics Lab, the participants will be given an overview of the research study and have the opportunity to ask any questions. Signatures for the informed consent will be obtained before any supplement paperwork is collected, such as the Physical Activity Readiness Questionnaire Plus (PAR-Q+), Visual Analogue Score (VAS), Health-Related Quality of Life (SF-36) questionnaire, and participant information form. Once the paperwork is completed, anthropometric data will be collected (i.e., sex, height, body mass, and disease status and duration).

Cutaneous sensitivity will be assessed using a 5.07-gauge Semmes-Weinstein monofilament (North Coast Medical, Inc, Morgan Hill, CA, USA) according to the established protocol (Manor, Doherty, & Li, 2008). Testing sites include the heel, midsole, bases of first/fifth metatarsals and hallux. This method has been used in this population and has been deemed reliable (Manor, et al., 2008).

Ankle joint proprioception will be assessed using the Biodex 3 dynamometer (Biodex Medical System, Inc, Shirley, NY, USA) and protocol established by Zhang and Li (2014). The participant's ankle will be positioned in the target position of 5 degrees plantarflexion for 10 seconds in which the participant will be instructed to close their eyes and concentrate on how their ankle feels. Then the ankle joint will be moved to start from the neutral position (i.e., 0 degree) at 1 degree per second toward the targeted position. Using the handheld trigger button, participants will stop the motion of the machine when they believed their ankle had reached the target position. The error of repositioning will be recorded and the test will be repeated three times. The participant will not know the velocity setting for this test.

Knee joint extensor peak torque will be measured at 60 degrees per second using the Biodex. Three repetitions will be performed. Participants will be instructed to exert maximum effort on the third repetition. The highest peak torque value will be recorded (Manor et al., 2008).

A six-minute walk distance test will be used to assess the endurance component of functional mobility. Cones will be placed 30 meters apart, as well as taped markers every meter. Participants will be instructed to walk at a self-selected pace back and forth for 6 minutes. The verbal cue will be "Three, two, one, go," and the timer will start when the participant initiates movement. The distance covered in 6 minutes will be recorded to the nearest meter (Manor et al., 2008).

Timed-up-and-go (TUG) test will be conducted to measure the agility aspect of functional mobility. The participant will be begin seated with their back against an armchair. The participant will stand up, walk 3 meters, turn around, and walk back 3 meters and sit back down in the armchair. Three

meters will be determined from the front edge of the chair, and the timer will start when the participant initiates movement and stop when the participant sits against the back of the chair (Manor et al., 2008). A total of 3 trials will be conducted and all trials will be used in the analysis.

Day two of testing will begin with the Hoffman's reflex test to establish the maximum M- and H-wave in the prone and standing position, followed by a postural control assessment. Surface electromyography (EMG) electrodes (Trigno Wireless EMG System; Delsys Inc., Massachusetts, USA) will be placed on the soleus (Sol), medial gastrocnemius (MG), and lateral gastrocnemius (LG) on the declared dominant leg of the participant, and according to SENIAM recommendations. Leg dominance will be established using the question, "what foot would you kick a ball with?" Prior to placement, the skin will be prepared by wiping the area with alcohol prep pads and shaving the area with a disposable razor. After EMG surface electrodes are placed, a 5cm×8cm anode and 2 centimeters (cm) in diameter cathode will be placed over the patella and popliteal fossa, respectively.

To establish the maximum M-wave, the participant will lie in the prone position, and stimulation intensity will begin at five microamps (mA) and increase in small increments of 2 mA until 60 mA is reached. Stimulation intervals will be separated by 10 seconds. A 500-microsecond square-pulse single stimulus delivers the stimulation on the tibial nerve by an electrical nerve stimulator (Digitimer model DS7A, Digitimer Ltd., Welwyn Garden City, England).

The establishment of the maximum M-wave will be repeated in the standing position. The M-/H-wave ratio and H-index for each position will be used in the analysis. H-index takes into account the duration of the onset of the M-wave (T_M) and the H-wave (T_H). There will be at least ten minutes of rest between tests.

Postural control will be assessed using an Accusway force plate (AMTI, Watertown, MA, USA). Participants will stand with their heels 10 centimeters apart and their feet 10 degrees adducted. Two 30-second trials of quiet standing eyes open and eyes closed with 45 seconds of rest in between trials will

occur (Manor et al., 2008). The testing order will be counterbalanced. The center of pressure will be collected at a sampling rate of 1,000 hertz (Hz) using the AMTI Netforce Software. Postural control variables will be 95% center of pressure (COP) area, velocity, and entropy in the mediolateral and anteroposterior directions.

Data Analysis:

Outcome variables are sensitivity scores, repositioning error scores, knee peak torque scores, total distances of 6MW, and TUG durations. From Hoffman's reflex tests, the dependent variables are M_{Max}-/H_{Max}-wave ratio and H-index. Maximum M- and H-wave will be determined using peak to peak amplitude. H-index = $([\frac{Height\ (cm)}{(T_H - T_M)}]^2 \times 2)$. Postural control variables are 95% center of pressure (COP) area, velocity, and entropy in the mediolateral and anteroposterior directions. Sample entropy $=-log(\frac{(\sum A_i)}{(\sum B_i)})$or -log$\frac{A}{B}$, with A_i being the number of matches of length m+1 with its ith template, and B_i as the number of matches of length m with ith template.

Statistical Analysis:

Statistical analysis will be performed using SPSS 25 (IBM, Armonk, NY). Normality will be assessed using Shapiro-Wilks, and skewness and kurtosis. If the *p*-value from the Shapiro-Wilks test is greater than 0.05 the data will be deemed nonparametric. If the *p*-value is less than 0.05 than the data will be deemed parametric. If the ratio between skewness and kurtosis is less than 1.96 the data are parametric. If the ratio is greater than 1.96 the data will be deemed nonparametric.

Differences for all outcome variables among each group will be assessed using Analysis of Variance (ANOVA). A one-way ANOVA will be conducted for parametric data. If the data is nonparametric, Friedman's Two-way ANOVA will be conducted. To compare the effects of peripheral neuropathy on the postural control-related variables, an ANCOVA will be conducted using the M-/H-wave ratio and H-index as covariates. The alpha level will be set at 0.05. Specific group differences will

be determined using a Bonferroni post-hoc test if significant ANOVA results were observed. Effects sizes will be determined using Cohen's d. Cohen's d=$\left(\frac{M_1-M_2}{S}\right)$, where S is the standard deviation of the control group, M_1 is the mean of the control group and M_2 is the mean of the experimental group. The criteria for the effect size are $0.2<d\leq0.5$ is small, $0.5<d\leq0.8$ is medium, and >0.8 will be considered large.

To assess the relationship between peripheral neuropathy variables and postural control variables, correlation assessments will be conducted. If data are parametric, Pearson's Product Moment Correlation will be calculated; otherwise a Spearman's Rho correlation will be calculated.

Expected Results

The dependent variables of interest are monofilament testing score, ankle joint repositioning error, knee peak extensor peak torque, 6-minute walking distance, timed-up-and-go duration, H-/M-wave ratio, H-index, anteroposterior postural sway, mediolateral postural sway, postural sway velocity, and entropy. Therefore, the purpose of this study is to examine the accumulated effects of diabetic neuropathy on neuroplasticity and postural control. It is hypothesized that individuals with DPN will exhibit a greater postural sway and decreased H-reflex. I expect to see an increase in anterior-posterior COP sway in all participants (Laughton et al., 2002; Eftekhar-Sadat et al., 2015). Since diabetes does not affect H-reflex, but PN does. I expect to see a decreased H-reflex when compared to the PN group. The secondary purpose is to examine the influence of ankle joint proprioception, leg strength and foot sole sensation on functional ability and postural control performance. It is hypothesized that individuals with reduced ankle joint proprioception and reduced foot sole sensation will have decreased postural control performance and functional ability. For individuals who have greater sway in the mediolateral direction, they will exhibit reduced foot sole sensation, and ankle joint proprioception (Bonnet & Lepeut, 2011). The tertiary hypothesis is to determine if a relationship between Hoffman's reflex (i.e., H-/M-ratio, H-index) and postural control parameters (COP_{sway}, COP magnitude, COP velocity) exists. It is expected that there will a greater H-/M-ratio when compared to COP displacement (Chen & Zhou, 2010). Then individuals with

more severe neuropathy, evident by reduced foot sole sensation and ankle joint proprioception, decreased leg strength, and decreased functional ability, will have a slower nerve conduction velocity (H-index).

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APPENDICES B: STATISTICAL OUTPUT

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  /EMMEANS=TABLES(Code) COMPARE ADJ(LSD)
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General Linear Model

Notes

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	Weight	<none>
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	N of Rows in Working Data File	35
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	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		GLM @6MWDM TUGSEC SDycmEO VavgcmsEO BY Code /METHOD=SSTYPE(3) /INTERCEPT=INCLUDE /POSTHOC=Code(LSD) /EMMEANS=TABLES(Code) COMPARE ADJ(LSD) /PRINT=DESCRIPTIVE ETASQ /CRITERIA=ALPHA(.05) /DESIGN= Code.
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Between-Subjects Factors

		N
Code	1.00	10

2.00	12
3.00	13

Descriptive Statistics

	Code	Mean	Std. Deviation	N
6MWD (M)	1.00	450.1000	52.15458	10
	2.00	440.1667	60.70320	12
	3.00	401.6923	67.25621	13
	Total	428.7143	62.99747	35
TUG (SEC)	1.00	7.3600	1.26069	10
	2.00	8.1000	2.03157	12
	3.00	8.6308	1.40913	13
	Total	8.0857	1.65087	35
SDy (cm) EO	1.00	.4210	.16941	10
	2.00	.4183	.14868	12
	3.00	.4615	.10164	13
	Total	.4351	.13719	35
Vavg (cm/s) EO	1.00	17.6540	4.36141	10
	2.00	15.3508	3.70299	12
	3.00	12.6531	2.99480	13
	Total	15.0069	4.10586	35

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	.997	2248.216[b]	4.000	29.000	.000

	Wilks' Lambda	.003	2248.216[b]	4.000	29.000	.000
	Hotelling's Trace	310.099	2248.216[b]	4.000	29.000	.000
	Roy's Largest Root	310.099	2248.216[b]	4.000	29.000	.000
Code	Pillai's Trace	.380	1.760	8.000	60.000	.103
	Wilks' Lambda	.635	1.845[b]	8.000	58.000	.087
	Hotelling's Trace	.549	1.922	8.000	56.000	.075
	Roy's Largest Root	.500	3.752[c]	4.000	30.000	.014

Multivariate Tests[a]

Effect		Partial Eta Squared
Intercept	Pillai's Trace	.997
	Wilks' Lambda	.997
	Hotelling's Trace	.997
	Roy's Largest Root	.997
Code	Pillai's Trace	.190
	Wilks' Lambda	.203
	Hotelling's Trace	.215
	Roy's Largest Root	.333

a. Design: Intercept + Code

b. Exact statistic

c. The statistic is an upper bound on F that yields a lower bound on the significance level.

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F

Corrected Model	6MWD (M)	15639.807[a]	2	7819.903	2.098
	TUG (SEC)	9.131[b]	2	4.566	1.749
	SDy (cm) EO	.014[c]	2	.007	.370
	Vavg (cm/s) EO	143.517[d]	2	71.759	5.344
Intercept	6MWD (M)	6413513.465	1	6413513.465	1720.373
	TUG (SEC)	2229.975	1	2229.975	854.277
	SDy (cm) EO	6.502	1	6.502	332.691
	Vavg (cm/s) EO	8009.965	1	8009.965	596.566
Code	6MWD (M)	15639.807	2	7819.903	2.098
	TUG (SEC)	9.131	2	4.566	1.749
	SDy (cm) EO	.014	2	.007	.370
	Vavg (cm/s) EO	143.517	2	71.759	5.344
Error	6MWD (M)	119295.336	32	3727.979	
	TUG (SEC)	83.532	32	2.610	
	SDy (cm) EO	.625	32	.020	
	Vavg (cm/s) EO	429.657	32	13.427	
Total	6MWD (M)	6567793.000	35		
	TUG (SEC)	2380.920	35		
	SDy (cm) EO	7.267	35		
	Vavg (cm/s) EO	8455.376	35		
Corrected Total	6MWD (M)	134935.143	34		
	TUG (SEC)	92.663	34		
	SDy (cm) EO	.640	34		
	Vavg (cm/s) EO	573.174	34		

Tests of Between-Subjects Effects

Source	Dependent Variable	Sig.	Partial Eta Squared
Corrected Model	6MWD (M)	.139	.116
	TUG (SEC)	.190	.099
	SDy (cm) EO	.694	.023
	Vavg (cm/s) EO	.010	.250
Intercept	6MWD (M)	.000	.982
	TUG (SEC)	.000	.964
	SDy (cm) EO	.000	.912
	Vavg (cm/s) EO	.000	.949
Code	6MWD (M)	.139	.116
	TUG (SEC)	.190	.099
	SDy (cm) EO	.694	.023
	Vavg (cm/s) EO	.010	.250
Error	6MWD (M)		
	TUG (SEC)		
	SDy (cm) EO		
	Vavg (cm/s) EO		
Total	6MWD (M)		
	TUG (SEC)		
	SDy (cm) EO		
	Vavg (cm/s) EO		
Corrected Total	6MWD (M)		
	TUG (SEC)		
	SDy (cm) EO		
	Vavg (cm/s) EO		

a. R Squared = .116 (Adjusted R Squared = .061)

b. R Squared = .099 (Adjusted R Squared = .042)

c. R Squared = .023 (Adjusted R Squared = -.039)

d. R Squared = .250 (Adjusted R Squared = .204)

Estimated Marginal Means

Code

Estimates

Dependent Variable	Code	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
6MWD (M)	1.00	450.100	19.308	410.771	489.429
	2.00	440.167	17.626	404.264	476.069
	3.00	401.692	16.934	367.198	436.186
TUG (SEC)	1.00	7.360	.511	6.319	8.401
	2.00	8.100	.466	7.150	9.050
	3.00	8.631	.448	7.718	9.544
SDy (cm) EO	1.00	.421	.044	.331	.511
	2.00	.418	.040	.336	.501
	3.00	.462	.039	.383	.541
Vavg (cm/s) EO	1.00	17.654	1.159	15.294	20.014
	2.00	15.351	1.058	13.196	17.505
	3.00	12.653	1.016	10.583	14.723

Pairwise Comparisons

Dependent Variable	(I) Code	(J) Code	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b] Lower Bound
6MWD (M)	1.00	2.00	9.933	26.143	.706	-43.318
		3.00	48.408	25.682	.069	-3.905
	2.00	1.00	-9.933	26.143	.706	-63.185
		3.00	38.474	24.442	.125	-11.313
	3.00	1.00	-48.408	25.682	.069	-100.720
		2.00	-38.474	24.442	.125	-88.262
TUG (SEC)	1.00	2.00	-.740	.692	.293	-2.149
		3.00	-1.271	.680	.071	-2.655
	2.00	1.00	.740	.692	.293	-.669
		3.00	-.531	.647	.418	-1.848
	3.00	1.00	1.271	.680	.071	-.113
		2.00	.531	.647	.418	-.787
SDy (cm) EO	1.00	2.00	.003	.060	.965	-.119
		3.00	-.041	.059	.496	-.160
	2.00	1.00	-.003	.060	.965	-.125
		3.00	-.043	.056	.446	-.157
	3.00	1.00	.041	.059	.496	-.079
		2.00	.043	.056	.446	-.071
Vavg (cm/s) EO	1.00	2.00	2.303	1.569	.152	-.893
		3.00	5.001*	1.541	.003	1.861
	2.00	1.00	-2.303	1.569	.152	-5.499

		3.00	2.698	1.467	.075	-.290
	3.00	1.00	-5.001*	1.541	.003	-8.140
		2.00	-2.698	1.467	.075	-5.686

Pairwise Comparisons

Dependent Variable	(I) Code	(J) Code	95% Confidence Interval for Difference Upper Bound
6MWD (M)	1.00	2.00	63.185
		3.00	100.720
	2.00	1.00	43.318
		3.00	88.262
	3.00	1.00	3.905
		2.00	11.313
TUG (SEC)	1.00	2.00	.669
		3.00	.113
	2.00	1.00	2.149
		3.00	.787
	3.00	1.00	2.655
		2.00	1.848
SDy (cm) EO	1.00	2.00	.125
		3.00	.079
	2.00	1.00	.119
		3.00	.071
	3.00	1.00	.160
		2.00	.157

Vavg (cm/s) EO	1.00	2.00	5.499
		3.00	8.140
	2.00	1.00	.893
		3.00	5.686
	3.00	1.00	-1.861
		2.00	.290

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Multivariate Tests

	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Pillai's trace	.380	1.760	8.000	60.000	.103	.190
Wilks' lambda	.635	1.845[a]	8.000	58.000	.087	.203
Hotelling's trace	.549	1.922	8.000	56.000	.075	.215
Roy's largest root	.500	3.752[b]	4.000	30.000	.014	.333

Each F tests the multivariate effect of Code . These tests are based on the linearly independent pairwise comparisons among the estimated marginal means.

a. Exact statistic

b. The statistic is an upper bound on F that yields a lower bound on the significance level.

Univariate Tests

Dependent Variable	Sum of Squares	df	Mean Square	F	Sig.

6MWD (M)	Contrast	15639.807	2	7819.903	2.098	.139
	Error	119295.336	32	3727.979		
TUG (SEC)	Contrast	9.131	2	4.566	1.749	.190
	Error	83.532	32	2.610		
SDy (cm) EO	Contrast	.014	2	.007	.370	.694
	Error	.625	32	.020		
Vavg (cm/s) EO	Contrast	143.517	2	71.759	5.344	.010
	Error	429.657	32	13.427		

Univariate Tests

Dependent Variable		Partial Eta Squared
6MWD (M)	Contrast	.116
	Error	
TUG (SEC)	Contrast	.099
	Error	
SDy (cm) EO	Contrast	.023
	Error	
Vavg (cm/s) EO	Contrast	.250
	Error	

The F tests the effect of Code . This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

Post Hoc Tests

Code

Multiple Comparisons

LSD

Dependent Variable	(I) Code	(J) Code	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound
6MWD (M)	1.00	2.00	9.9333	26.14312	.706	-43.3185
		3.00	48.4077	25.68201	.069	-3.9048
	2.00	1.00	-9.9333	26.14312	.706	-63.1851
		3.00	38.4744	24.44243	.125	-11.3132
	3.00	1.00	-48.4077	25.68201	.069	-100.7202
		2.00	-38.4744	24.44243	.125	-88.2620
TUG (SEC)	1.00	2.00	-.7400	.69179	.293	-2.1491
		3.00	-1.2708	.67958	.071	-2.6550
	2.00	1.00	.7400	.69179	.293	-.6691
		3.00	-.5308	.64678	.418	-1.8482
	3.00	1.00	1.2708	.67958	.071	-.1135
		2.00	.5308	.64678	.418	-.7867
SDy (cm) EO	1.00	2.00	.0027	.05986	.965	-.1193
		3.00	-.0405	.05880	.496	-.1603
	2.00	1.00	-.0027	.05986	.965	-.1246
		3.00	-.0432	.05597	.446	-.1572
	3.00	1.00	.0405	.05880	.496	-.0792
		2.00	.0432	.05597	.446	-.0708
Vavg (cm/s) EO	1.00	2.00	2.3032	1.56894	.152	-.8927
		3.00	5.0009*	1.54127	.003	1.8615

	2.00	1.00	-2.3032	1.56894	.152	-5.4990
		3.00	2.6978	1.46688	.075	-.2902
	3.00	1.00	-5.0009*	1.54127	.003	-8.1404
		2.00	-2.6978	1.46688	.075	-5.6857

Multiple Comparisons

LSD

			95% Confidence Interval
Dependent Variable	(I) Code	(J) Code	Upper Bound
6MWD (M)	1.00	2.00	63.1851
		3.00	100.7202
	2.00	1.00	43.3185
		3.00	88.2620
	3.00	1.00	3.9048
		2.00	11.3132
TUG (SEC)	1.00	2.00	.6691
		3.00	.1135
	2.00	1.00	2.1491
		3.00	.7867
	3.00	1.00	2.6550
		2.00	1.8482
SDy (cm) EO	1.00	2.00	.1246
		3.00	.0792
	2.00	1.00	.1193
		3.00	.0708
	3.00	1.00	.1603

		2.00	.1572
Vavg (cm/s) EO	1.00	2.00	5.4990
		3.00	8.1404
	2.00	1.00	.8927
		3.00	5.6857
	3.00	1.00	-1.8615
		2.00	.2902

Based on observed means.

The error term is Mean Square(Error) = 13.427.

*. The mean difference is significant at the .05 level.

```
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Discriminant

Notes

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Syntax		DISCRIMINANT /GROUPS=Code(1 3) /VARIABLES=@6MWDM TUGSEC SDycmEO VavgcmsEO /ANALYSIS ALL /METHOD=WILKS /FIN=0.05 /FOUT=0.01 /PRIORS EQUAL /HISTORY /STATISTICS=MEAN STDDEV CORR TABLE CROSSVALID /PLOT=COMBINED /CLASSIFY=NONMISSING POOLED.
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Excluded	Missing or out-of-range group codes	0	.0
	At least one missing discriminating variable	0	.0

	Both missing or out-of-range group codes and at least one missing discriminating variable	0	.0
	Total	0	.0
Total		35	100.0

Group Statistics

Code		Mean	Std. Deviation	Valid N (listwise)	
				Unweighted	Weighted
1.00	6MWD (M)	450.1000	52.15458	10	10.000
	TUG (SEC)	7.3600	1.26069	10	10.000
	SDy (cm) EO	.4210	.16941	10	10.000
	Vavg (cm/s) EO	17.6540	4.36141	10	10.000
2.00	6MWD (M)	440.1667	60.70320	12	12.000
	TUG (SEC)	8.1000	2.03157	12	12.000
	SDy (cm) EO	.4183	.14868	12	12.000
	Vavg (cm/s) EO	15.3508	3.70299	12	12.000
3.00	6MWD (M)	401.6923	67.25621	13	13.000
	TUG (SEC)	8.6308	1.40913	13	13.000
	SDy (cm) EO	.4615	.10164	13	13.000
	Vavg (cm/s) EO	12.6531	2.99480	13	13.000
Total	6MWD (M)	428.7143	62.99747	35	35.000
	TUG (SEC)	8.0857	1.65087	35	35.000
	SDy (cm) EO	.4351	.13719	35	35.000
	Vavg (cm/s) EO	15.0069	4.10586	35	35.000

Pooled Within-Groups Matrices

		6MWD (M)	TUG (SEC)	SDy (cm) EO	Vavg (cm/s) EO
Correlation	6MWD (M)	1.000	-.721	.033	-.075
	TUG (SEC)	-.721	1.000	.066	.050
	SDy (cm) EO	.033	.066	1.000	-.208
	Vavg (cm/s) EO	-.075	.050	-.208	1.000

Analysis 1

Stepwise Statistics

Variables Entered/Removed[a,b,c,d]

		Wilks' Lambda						
						Exact F		
Step	Entered	Statistic	df1	df2	df3	Statistic	df1	df2
1	Vavg (cm/s) EO	.750	1	2	32.000	5.344	2	32.000
2	6MWD (M)	.666	2	2	32.000	3.491	4	62.000
3	TUG (SEC)	.642	3	2	32.000	2.482	6	60.000
4	SDy (cm) EO	.635	4	2	32.000	1.845	8	58.000

Variables Entered/Removed[a,b,c,d]

	Wilks' Lambda	
	Exact F	
Step		Sig.
1		.010
2		.012

3	.033
4	.087

At each step, the variable that minimizes the overall Wilks' Lambda is entered.[a,b,c,d]

a. Maximum number of steps is 8.

b. Minimum partial F to enter is 0.05.

c. Maximum partial F to remove is 0.01.

d. F level, tolerance, or VIN insufficient for further computation.

Variables in the Analysis

Step		Tolerance	F to Remove	Wilks' Lambda
1	Vavg (cm/s) EO	1.000	5.344	
2	Vavg (cm/s) EO	.994	5.072	.884
	6MWD (M)	.994	1.942	.750
3	Vavg (cm/s) EO	.994	4.843	.849
	6MWD (M)	.479	.964	.683
	TUG (SEC)	.481	.568	.666
4	Vavg (cm/s) EO	.952	4.409	.829
	6MWD (M)	.474	.983	.679
	TUG (SEC)	.473	.604	.662
	SDy (cm) EO	.940	.145	.642

Variables Not in the Analysis

Step		Tolerance	Min. Tolerance	F to Enter	Wilks' Lambda
0	6MWD (M)	1.000	1.000	2.098	.884
	TUG (SEC)	1.000	1.000	1.749	.901

	SDy (cm) EO	1.000	1.000	.370	.977
	Vavg (cm/s) EO	1.000	1.000	5.344	.750
1	6MWD (M)	.994	.994	1.942	.666
	TUG (SEC)	.998	.998	1.510	.683
	SDy (cm) EO	.957	.957	.093	.745
2	TUG (SEC)	.481	.479	.568	.642
	SDy (cm) EO	.957	.952	.094	.662
3	SDy (cm) EO	.940	.473	.145	.635

Wilks' Lambda

Step	Number of Variables	Lambda	df1	df2	df3	Exact F Statistic	Exact F df1	Exact F df2
1	1	.750	1	2	32	5.344	2	32.000
2	2	.666	2	2	32	3.491	4	62.000
3	3	.642	3	2	32	2.482	6	60.000
4	4	.635	4	2	32	1.845	8	58.000

Wilks' Lambda

Step	Exact F Sig.
1	.010
2	.012
3	.033
4	.087

Summary of Canonical Discriminant Functions

Eigenvalues

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	.500[a]	91.1	91.1	.577
2	.049[a]	8.9	100.0	.216

a. First 2 canonical discriminant functions were used in the analysis.

Wilks' Lambda

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	.635	13.828	8	.086
2	.953	1.455	3	.693

Standardized Canonical Discriminant Function Coefficients

	Function 1	Function 2
6MWD (M)	.420	1.270
TUG (SEC)	-.198	1.240
SDy (cm) EO	-.015	-.474
Vavg (cm/s) EO	.854	-.190

Structure Matrix

	Function 1	Function 2

Vavg (cm/s) EO	.816*	-.124
6MWD (M)	.498*	.376
TUG (SEC)	-.459*	.284
SDy (cm) EO	-.192	-.311*

Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions

Variables ordered by absolute size of correlation within function.

*. Largest absolute correlation between each variable and any discriminant function

Functions at Group Centroids

	Function	
Code	1	2
1.00	.854	-.201
2.00	.159	.288
3.00	-.804	-.112

Unstandardized canonical discriminant functions evaluated at group means

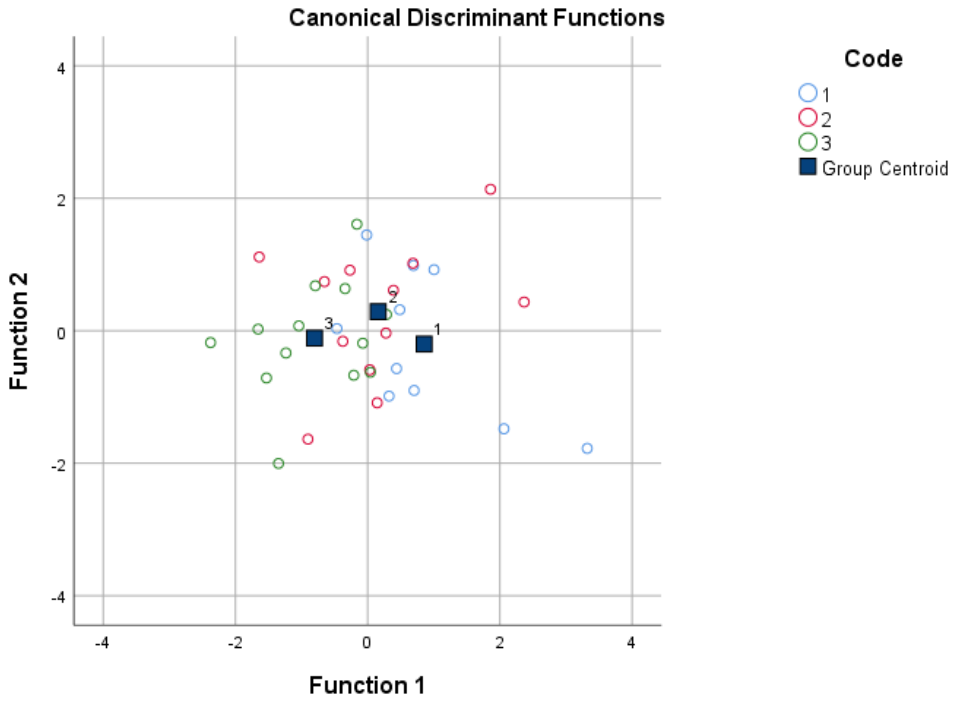
Classification Statistics

Classification Processing Summary

Processed		35
Excluded	Missing or out-of-range group codes	0
	At least one missing discriminating variable	0
Used in Output		35

Prior Probabilities for Groups

		Cases Used in Analysis	
Code	Prior	Unweighted	Weighted
1.00	.333	10	10.000
2.00	.333	12	12.000
3.00	.333	13	13.000
Total	1.000	35	35.000



Classification Results[a,c]

			Predicted Group Membership			
		Code	1.00	2.00	3.00	Total
Original	Count	1.00	5	4	1	10
		2.00	2	6	4	12
		3.00	1	4	8	13
	%	1.00	50.0	40.0	10.0	100.0
		2.00	16.7	50.0	33.3	100.0
		3.00	7.7	30.8	61.5	100.0
Cross-validated[b]	Count	1.00	3	6	1	10
		2.00	5	3	4	12
		3.00	2	4	7	13
	%	1.00	30.0	60.0	10.0	100.0
		2.00	41.7	25.0	33.3	100.0
		3.00	15.4	30.8	53.8	100.0

a. 54.3% of original grouped cases correctly classified.

b. Cross validation is done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.

c. 37.1% of cross-validated grouped cases correctly classified.

APPENDICES C: IRB DOCUMENTS

Georgia Southern University
Office of Research Services & Sponsored Programs

Institutional Review Board (IRB)

Phone: 912-478-5465
Fax: 912-478-0719
IRB@GeorgiaSouthern.edu
Veazey Hall 3000
PO Box 8005
Statesboro, GA 30460

To: Lewis, Kelsey; Sun, Mengzi; Li, Li

From: Office of Research Services and Sponsored Programs

Initial Approval Date: 11/11/2019

Expiration Date: 10/31/2020

Subject: Status of Application for Approval to Utilize Human Subjects in Research – **Full Board Review**

After a review of your proposed research project numbered **H20076**, and titled **"Neural Plasticity of Posture Control and Motor Control among People with Peripheral Neuropathy,"** it appears that (1) the research subjects are at minimal risk, (2) appropriate safeguards are planned, and (3) the research activities involve only procedures which are allowable. You are authorized to enroll up to a maximum of **60** subjects.

There are human subjects incentives in this project in the amount of **$ 25 gift cards**. This project has been approved as **a named** data collection. If University or sponsored funds are used to pay incentives please refer to the Human Subjects Incentive Policy and Human Subjects Incentive Disbursement and Reconciliation Form.

Therefore, as authorized in the Federal Policy for the Protection of Human Subjects, I am pleased to notify you that the Institutional Review Board has approved your proposed research.

Description: The purpose of this research is to examine the relationship between Hoffman-reflex and postural control, gait, functional mobility, cutaneous sensation, ankle joint proprioception, leg strength, and foot sole pressure distribution among patients with idiopathic neuropathy, diabetic neuropathy, diabetes, and compared to a control group.

If at the end of this approval period there have been no changes to the research protocol; you may request an extension of the approval period. In the interim, please provide the IRB with any information concerning any significant adverse event, **whether or not it is believed to be related to the study**, within five working days of the event. In addition, if a change or modification of the approved methodology becomes necessary, you must notify the IRB Coordinator **prior** to initiating any such changes or modifications. At that time, an amended application for IRB approval may be submitted. Upon completion of your data collection, you are required to complete a *Research Study Termination* form to notify the IRB Coordinator, so your file may be closed.

Sincerely,

Eleanor Haynes
Compliance Officer

GEORGIA SOUTHERN UNIVERSITY

OFFICE OF RESEARCH INTEGRITY

Institutional Review Board (IRB)

Application for Research Approval – Expedited/Full Board

Please submit this protocol to IRB@georgiasouthern.edu in a single email; scanned signatures and official Adobe electronic signatures are accepted. Applications may also be submitted via mail to the Georgia Southern University Office of Research Integrity, PO Box 8005.

Principal Investigator	
PI's Name: Kelsey Lewis	Phone: (904)445-0506
Email: kl06040@georgiasouthern.edu (Note: Georgia Southern email addresses will be used for all correspondence.)	Department: College of Health and Kinesiology College: WCHP
Primary Campus: X Statesboro Campus Armstrong Campus Liberty Campus	
X Faculty Doctoral Specialist X Masters Undergraduate Other:	
Georgia Southern Co-Investigator(s)	
Co-I's Name(s): Mengzi Sun(F), Li Li (F) (By each name indicate: F(Faculty), D(Doctoral), S(Specialist), M(Masters), U(Undergraduate), O(Other))	Email: mengzisun@georgiasouthern.edu. lili@georgiasouthern.edu (Note: Georgia Southern email addresses will be used for all correspondence.)
Personnel and/or Institutions Outside of Georgia Southern University involved in this research:	
	Training Attached IRB Approval Attached intent to rely on GS
	Training Attached IRB Approval Attached intent to rely on GS

For Offi

Project Information
Title: Neural Plasticity of Posture Control and Motor Control among People with Peripheral Neuropathy
Number of Participants (Maximum) 60
Will you be using monetary incentives (cash and/or gift cards)? X Yes No *Will be compensated with a $25 gift card
Funding Source: Federal State Private Internal GS (enter source below) X Self-funded/non-funded Funding Agency/ GS Source: Grant Number: Grant Title: Same as above Enter here:
Compliance Information
Do you or any investigator on this project have a financial interest in the Participants, study outcome, or project sponsor? (A disclosed conflict of interest will not preclude approval. An undisclosed conflict of interest will result in disciplinary action.). Yes (No) (If yes attach disclosure form)

Certifications
I certify that the statements made in this request are accurate and complete, and if I receive IRB approval for this project, I agree to inform the IRB in writing of any emergent problems or proposed procedural changes. I agree not to proceed with the project until the problems have been resolved or the IRB has reviewed and approved the changes. It is the explicit responsibility of the researchers and supervising faculty/staff to ensure the well-being of human participants. At the conclusion of the project I will submit a report. A report must be submitted no later than 12 months after project initiation. Kelsey Lewis 8/27/19

Institutional Review Board (IRB)

Application for Research Approval – Expedited/Full Board

Signature of Primary Investigator Date 8/27/19

Mengzi Sun

Signature of Co-Investigator(s) Date

By signing this cover page I acknowledge that I have reviewed and approved this protocol for scientific merit, rational and significance. I further acknowledge that I approve the ethical basis for the study.

If faculty project, enter department chair's name; if student project, enter research advisor's name: Dr. Li Li

Signature of Department Chair or Research Advisor Date 8/27/19

Institutional Review Board (IRB)

Application for Research Approval – Expedited/Full Board

Compliance Information	
Please indicate which of the following will be used in your research: (applications may be submitted simultaneously)	
☒ Human Participants ☐ Care and Use of Vertebrate Animals (Submit IACUC Application) ☐ Biohazards (Submit IBC Application)	
Please indicate if the following are included in the study (Check all that apply):	
☐ Survey delivered by email to .georgiasouthern.edu addresses ☐ Deception ☐ Prisoners ☐ Children ☐ Individuals with impaired decision making capacity, or economically or educationally disadvantaged persons	☐ Video or Audio Recordings ☐ Human Participants Incentives ☒ Medical Procedures, including exercise, administering drugs/dietary supplements, and other procedures, or ingestion of any substance
Is your project a research study in which one or more human Participants are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. See the IRB FAQ for help with the definition above. ☐ Yes ☒ No If yes, attach Good Clinical Practice (GCP) CITI training appropriate to the project.	

Instructions: Please respond to the following as clearly as possible. The application should include a step by step plan of how you will obtain your Participants, conduct the research, and analyze the data. Make sure the application clearly explains aspects of the methodology that provide protections for your human Participants. Your application should be written to be read and understood by a general audience who does not have prior knowledge of your research and by committee members who may not be expert in your specific field of research. Your reviewers will only have the information you provide in your application. Explain any technical terms, jargon or acronyms.

1. Personnel

Please list any individuals who will be conducting research on this study. Also, please detail the experience, level of involvement in the process, and the access to information that each may have.

- Kelsey Lewis B.S Exercise Science, Research/Teaching assistant for Biomechanics Lab, MS Kinesiology Candidate
  - O Principal Investigator
  - O Will have access to participants' personal information including contact information and data.
  - O Oversee scheduling of participants
  - O Will be responsible for the collection and testing of experimental data
  - O Will be responsible for data analysis
- Mengzi Sun: Doctoral student in the Beijing Sport University
  - O Co-Investigator
  - O Will be responsible for making appointments with participants
  - O Will have access to participants' personal information and data.
  - O Will be responsible for the collection and testing of experimental data
  - O Will be responsible for data analysis
  - O Ms. Mengzi Sun will be administering the stimulation during all trials.
- Li Li PhD: Research Professor in the Department of Health Sciences and Kinesiology
  - O Advisor
  - O Will be responsible for making appointments with participants, accessing participants' personal information and data.

O Will help collect experiment data
O Will be responsible for data analysis

All 3 researchers are experienced with Biomechanics Research Data Collection in the Biomechanics Lab. Also Dr. Li has 20 years of experience working with electric stimulation with human participants, specifically this population. He has taught the other researchers proper electrical stimulation procedures and they have practiced multiple times how to administer the electrical stimulation. Pilot data collections have been conducted for the last 2 months.

2. Purpose

A. Briefly describe in one or two sentences the purpose of your research.

The purpose of this research is to examine the relationship between Hoffman-reflex and postural control, gait, functional mobility, cutaneous sensation, ankle joint proprioception, leg strength, and foot sole pressure distribution among patients with idiopathic neuropathy, diabetic neuropathy, diabetes, and compared to a control group. The goal of this study is to examine the adaptability of the spinal reflex with the changes in posture and movement among people with sensory and motor function deficits.

B. What questions are you trying to answer in this project? Please include your research question in this section. The jurisdiction of the IRB requires that we ensure the appropriateness of research. It is unethical to put participants at risk without the possibility of sound scientific results. For this reason, you should be very clear about how participants and others will benefit from knowledge gained in this project.

1. What is the repeatability of Hoffman's reflex tests during locomotion?
2. Is there a relationship between Hoffman's reflex and postural control? If is, how does it different between the four groups?
3. How does Hoffman's reflex affects different phases of locomotion with four groups population?

C. Provide a brief description of how this study fits into the current literature. Have the research procedures been used before? How were similar risks controlled for and documented in the literature? Have your instruments been validated with this audience? Include citations in the description. Do not include dissertation or thesis chapters.

Peripheral neuropathy is a neurodegenerative disease that damages the peripheral nervous system in a distal to proximal fashion (Martyn, Hughes, 1997). Patient often exhibit neural impairments and associated abnormal sensation such as tingling. pricking, chilling, burning or numb sensation on the skin.(Richardson, 2002). Cutaneous sensation such as pressure, temperature or pain, plays an important role in posture control (Nurse, Niggs, 2001). Lower extremities proprioception information is believed to contribute to motor control (Lentell et al., 1995). Proprioception sensory sources are able to detect body displacement as a result of stretch in the muscle spindles, or golgi tendon organs. When a stretch in the receptors in the muscle is detected, a stimulus is sent to the spinal cord through the use of type 1a afferent neurons which synapse on an interneuron or alpha motor neuron in the spinal cord. If the stimulus is strong enough to create an action potential in the alpha motor neuron, the resulting action is the contraction of the muscle. Therefore, the speed of nerve conduction and α-motoneuron pool excitability are important indicators for studying posture control and gait. In former research, the importance of Hoffman's index for posture control has been confirmed with individuals that have poor cutaneous sensation (Zhang, Manor, Li, 2015). It was reported that Hoffman's index acted as a mediator between average sway velocity and group. However, Hoffman's index is different from the parameters that will be assessed in this study. Hoffman's index takes into account the height of the individual and difference in times of onsets of the M-wave and H-wave. In this study, comparisons will be made between the ratio of the maximum M wave and maximum H wave and the center of pressure magnitude, direction, and velocity. In addition, the role and regulation of Hoffman's reflex in gait is not clear with peripheral neuropathy and diabetes. To the researchers' knowledge of the role and regulation of Hoffman's reflex in gait and posture is not clear in individuals with peripheral neuropathy or diabetes, or both. So, in this study, we will focus on the relationship between Hoffman-reflex and balance, gait,

functional mobility, cutaneous sensation, ankle joint proprioception, leg strength, foot sole pressure distribution as well as to enhance understanding of spinal reflex plasticity.

There are minimal risks involved for participants. All measures are noninvasive. In former experiments, all instruments were used for this population, and had been validated for safe use. All participants will be told of their right to withdraw at any time with no penalty.

1. Burke, D. (2016). Clinical uses of H reflexes of upper and lower limb muscles. *Clinical Neurophysiology Practice*, *1*, 9-17.
2. Lentell, G., Baas, B., Lopez, D., McGuire, L., Sarrels, M., & Snyder, P. (1995). The contributions of proprioceptive deficits, muscle function, and anatomic laxity to functional instability of the ankle. *Journal of Orthopaedic & Sports Physical Therapy*, *21*(4), 206-215.
3. Martyn, C. N., & Hughes, R. A. (1997). Epidemiology of peripheral neuropathy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *62*(4), 310.
4. Nurse, M. A., & Nigg, B. M. (2001). The effect of changes in foot sensation on plantar pressure and muscle activity. *Clinical Biomechanics*, *16*(9), 719-727.
5. Richardson, J. K. (2002). Factors associated with falls in older patients with diffuse polyneuropathy. *Journal of the American Geriatrics Society*, *50*(11), 1767-1773.
6. Zhang, S., Manor, B., & Li, L. (2015). Hoffman's index is important for postural control for people with impaired foot sole sensation. *PloS one*, *10*(3), e0121847.

3. Outcome

Please state what results you expect to achieve. Who will benefit from this study? How will the participants benefit (if at all)? Remember that the participants do not necessarily have to benefit directly. The results of your study may have broadly stated outcomes for a large number of people or society in general.

Through this study, the research team will be able to observe valuable characteristics of the patterns of neuromuscular coordination in people with peripheral neuropathy and diabetes. This project will attempt to fill the gap in the study of peripheral neuropathy and diabetic neuropathy, and hope to provide a theoretical basis for the exercise and rehabilitation of patients with idiopathic peripheral/diabetic neuropathy to improve the overall health of the patient.

4. Describe Your Participants

A. Maximum number of participants

60

B. Briefly describe the study population.

Both male and female older participants will be recruited for this study. Four groups: idiopathic neuropathy, type II diabetes, diabetic neuropathy, and healthy controls. 15 people per group.

C. Applicable inclusion or exclusion requirements (ages, gender requirements, allergies, etc.)

Inclusion criteria: (1) Age 65 years old and older; (2) one of the conditions: healthy, or neurologist diagnosed idiopathic neuropathy, or type II diabetes, or diabetic neuropathy; (3) able to walk on the treadmill for at least 5 continuous minutes; and (4) Willing to participate in the study. (5) Must be able to read English

Exclusion criteria: (1) History or evidence of central nervous system dysfunction; (2) Trauma and disease that significantly affect posture and mobility control; (3) Evidence of foot sole ulcers; (4) Evidence of cardiac pacemaker; and (5) Less than a score of 24 on the Mini-Mental State Exam (MMSE) (6) Answering "yes" to one of more of the follow up questions in the Physical Activity readiness Questionnaire plus (PAR-Q+) will lead to exclusion from participation. This is the standard laid out on the PAR-Q+ form.

Institutional Review Board (IRB)

Application for Research Approval – Expedited/Full Board

D. *How long will each subject be involved in the project? (Number of occasions and duration)*

Two 2-hour testing sessions will be completed per each participant.

5. Recruitment

Describe how Participants will be recruited. (Attach a copy of recruitment emails, flyers, social media posts, etc.) DO NOT state that Participants will not be recruited.

Dr. Li is teaching a local senior Tai Chi class for the last 4 years. He will distribute the flyers among his class and encourage the practitioners to contact their acquaintances who may qualify for the study. Then snowball methods will follow.

The flyer will include inclusion and exclusion criteria as well as the contact information of the principal investigator.

6. Incentives

A. *Are you compensating your Participants with money, course credit, extra credit, or other incentives?*

☒ Yes ☐ No

B. *If yes, indicate how much and how they will be distributed.*

$25 gift card per person per day. The gift card recipient will sign a form to show they received it.

C. *Describe if and how you will compensate Participants who withdraw from the project before it ends and any exclusion criteria from compensation.*

Participants are compensated each session attended. No further compensation will be provided if they withdraw from the study.

7. Research Procedures and Timeline

A. *Outline step-by-step what will happen to participants in this study (including what kind of experimental manipulations you will use, what kinds of questions or recording of behavior you will use, the location of these interactions). Focus on the interactions you will have with the human Participants. Specify tasks given as attachments to this document.*

Testing will consist of two testing days for two hours each. There will be at least 48 hours between the testing sessions. One experimenter will meet the participant in the parking lot at their arrival and escort them to the Biomechanics Lab at the beginning of each session and escort them back to their car after the end of each session.

Prior to testing all participants will be instructed to come to the lab wearing comfortable clothing, for which they are able to walk and provide easy access to the lower right leg, and comfortable walking shoes.

Day One:

The participant will come into the Biomechanics Lab. They will be given an overview of the research and have the opportunity to ask any questions. After all of the questions answered satisfactorily, the signed Informed Consent Form will be obtained before any supplement information is collected. Supplement information includes: Physical Activity Readiness Questionnaire Plus (PAR-Q+), Visual Analogue Score (VAS), Health Related Quality of Life (SF-36) questionnaire, Mini-Mental State Exam (MMSE), and a participant Medical History sheet. Also the participants will be ensured that all personal information will be kept confidential. The questionnaires (VAS and SF-36) will be used in the analysis to correlate with functional data and aid as a

potential explanation to the observations. The MMSE will be used to determine the mental state of the participants and they will be excluded from the study with a score less than 24.
After all forms are completed and all inclusion criteria are met, the participant's height and weight will be taken and recorded using a Detecto Scale (Weigh Beam Stainless Steel, Missouri, USA). Testing will start with testing the participant's cutaneous sensation. The test will be performed by having the participant's laying down with their backs against the treatment table. Sensitivity will be assessed with a 5.07-gauge Semmes-Weinstein monofilament (North Coast Medical, Inc, Morgan Hill, CA, USA). Testing sites include the heel, mid-sole, bases of first/fifth metatarsals and hallux. A score of "1"is given when a "yes" response accompanied the detected pressure, whereas a "no" response is given a score of "0." Each site is tested 3 times. Then the score from each site is added. If the total score is 2 or greater, the site will be reassigned a one. If the site receives a total score of 0 or 1 the site will be reassigned to a 0. For example, if the participant says "yes" twice, and "no" once at the same site, that site will be given an overall score of 1. Vice versa, if the participant said "no" twice and "yes" once that site would be reassigned a 0. Then the reassigned scores will be added and will be between 0 and 5. This method has been used in this population and the method is deemed reliable. The sensitivity score will be used as descriptive data.
To test ankle joint proprioception, participants will sit in a Biodex (System 4 Pro; Biodex Medical Systems., New York, USA) chair reclined at 70 degrees with legs parallel to the ground. Ankle joint proprioception will be tested by repositioning the ankle joint at 5 degrees plantarflexion from neutral position. Participants' ankle joint will be moved to the targeted position (5 degrees), held for 10 seconds and then moved back toward the neutral position. Then the ankle joint will be moved from the neutral position at 1 degrees per second toward the targeted position. Participants will be asked to stop the motion of the machine when they believed their ankle reached the target position by pressing a hand-held trigger button. The error of repositioning will be recorded and the test will be repeated three times.
The next test will be conducted only if the participant is rested and okay with moving on. The participant will verbally confirmed that they are rested enough to move on. Knee joint extensor peak torque will be measured at 60 degrees per second using the Biodex. The participant will warm up by performing the knee extension and knee flexion movement (similar to a swinging motion) to get used to the machine. One trial (3 repetitions) will occur with the participant being encouraged to exert maximum effort for each repetition and peak torque will be recorded with 10-second break between each repetition. The maximum torque of the three repetitions will be recorded. Once testing is completed, the participant will rest for 5 minutes before continuing to the functional mobility testing. The participant will be asked before moving on if they are rested enough, and more time will be granted if they do not feel like they are rested. The participant will verbally confirmed that they are rested enough to move on.
Functional mobility testing includes the six minute walk distance test (6MWD) and the timed-up-and-go test (TUG). Participants will start with the 6MWD in a well lit hallway. The testing area that is 30 meters long and has cones placed at each end as well as taped markers every meter. The researcher will instruct the participant to walk at a comfortable pace for 6 minutes, using the verbal cue "Three, two, one, go" the time will begin. They will be encouraged to continue and avoid sitting. The researcher will not walk with the participant, but will be standing in the middle of the testing area and spotters will be around the testing area for extra safety. The distance they cover in 6 minutes will be recorded to the nearest meter and used for further analysis. If at anytime the participant is dizzy, nauseous, or uncomfortable testing will cease immediately. After a 10 minutes or longer break, if verbally needed, the next test will be TUG and it measures the time it takes the participant to stand up from an armchair and walk 3 meters, turn, and walk back 3 meters and sit back down in the armchair. Three meters will be determined from the front edge of the chair and the timer will start when the participant initiates movement and stop when the participant sits against the back of the chair.
To prepare the participant for the second day of the walking test, the participant will walk on the treadmill at a self selected pace for 5 minutes if they are not used to walking on treadmills and to familiarize themselves to this

piece of equipment. A spotter will be located behind the participant on the treadmill whenever they are walking on the treadmill. The treadmill also has handrails and an emergency stop button for safety.

Day Two:
The next set of testing involves Hoffman's Reflex, postural control, and gait.
Surface electromyography (EMG) electrodes (Trigno Wireless EMG System; Delsys Inc., Massachusetts, USA) will be placed on the contracted muscle belly of three muscles of right leg; soleus (Sol), medial gastrocnemius (MG), lateral gastrocnemius (LG). Before placement, the skin will be shaved using disposable one-time use razors and cleaned with alcohol pads. The disposable razor will be discarded in a sharps container after each use. A new razor will be used for each participant. Verbal consent will be received before shaving the area. If the participant does not allow the researcher to shave the area they will be excused from the study. Also we will ask the participants if they are allergic to alcohol prep pads and any kind of adhesive (i.e tape or gel). The participants will be excluded from the study as well if they answer "yes". After EMG electrodes are placed, the optimal site of tibial nerve stimulation will be determined using a hand-held electrode that comes with the stimulator (Digitimer model DS7A, Digitimer Ltd., Welwyn Garden City, England) using the criterion that soleus Ia afferents could be selectively stimulated at low stimulation intensities. Once the site is determined, disposable electrodes that are 2 centimeters (cm) in diameter cathode (negative electrode) on the skin in the popliteal fossa (located at the back of the knee) and 5cm×8cm anode (positive electrode) placed over the patella (knee cap) will be placed respectively. There will be four testing periods for the Hoffman's Reflex test. The first period will consist of determining the standard stimulation level for calculation Hoffman's index and M/H ratio. The following three period we apply the standard stimulation level to prone, standing, and walking (locomotion).
In the first period, we will find the standard stimulation level as the 15% of stimulation level association with the maximum M wave in prone.
Hoffman's reflex will be assessed while the participant is laying on their stomach (prone), as well as when they are standing and walking. In the prone test, participants will be lying face down on a treatment table. They will be laying straight and have their arms by their side. The Hoffman's reflex is elicited by a 500-microsecond square-pulse single stimulus (Digitimer model DS7A, Digitimer Ltd., Welwyn Garden City, England). **The FDA safety approval number of stimulator device is K051357 and the FDA indication for use approval document is attached as well as the manual (including all safety precautions).** Stimulation will start at 5milliamps (mA) and increase in small increments (2mA) until maximum M-wave is reached. Approximately 30 stimuli will be collected at each test, between each stimulation there will be at least 10 seconds with a gradual increase in amplitude (2mA). During the process, the participants will be instructed to limit talking, movement, and to relax as much as possible. Noise canceling headphones will be used, and cleaned with dawn dish detergent after every use. The use of the stimulator is safe to use on humans and all safety protocols will be enforced. If at any time the participant feels uncomfortable, or no longer wants to proceed, testing will stop immediately. The right to withdraw without penalty will be addressed in the informed consent, and the research team will ensure that the participant understands this.
After the first period of testing, the standard level of stimulation will be administered for the prone test in which the M and H waves observed will be recorded. After this test, the participant will rest for 10 minutes or longer at the participants request.
To test Hoffman's reflex while standing the standard stimulation will be administered and the M and H wave observed will be recorded for further analysis. In this test, the participant will be instructed to stand with their feet shoulder width apart and arms by their side relaxed. They will look at a visual point ahead and instructed to continue staring at that during the test. During the standing trial, a researcher will be within arms reach in case the participant loses their balance during the test. After this test, the participant will rest for 10 minutes. More rest time will be given if requested. The participant will verbally confirmed that they are rested enough to move on.
For the postural control assessment, participants will begin by standing on a force plate (AccuSway, AMTI, Watertown, MA, USA) with their heels 10 centimeters apart and their feet 10 degrees adducted. They will remain

standing for 30 seconds for 1 trial of each condition; eyes open and eyes closed. The order of testing will be counterbalanced. A 45 seconds break will be given between the trials. More time will be given if the participant feels they are not ready. This method of testing posture has been deemed reliable in this population through test-retest reliability (Manor et al, 2008). The center of pressure position-time profile will be collected using Vicon Software (Vicon Motion Systems Ltd., Oxford Metrics, UK). This data will be used later to calculate all postural control variables, including center of pressure range of motion in the front-back and side-to-side direction, velocity, and approximate entropy.
After the postural control assessment, the participant will rest for 5 minutes before continuing to the treadmill for the walking test. The participant will verbally confirmed that they are rested enough to move on. To measure the kinematics during the walking test, the XSENS system (Awinda; XSENS., Enschede, Netherlands) will be used. XSENS sensors will be placed using velcro straps issued by the company according to the XSENS manual. Sensors will be placed bilaterally on the feet, lower (inner mid shin) and upper leg (outside of the mid-thigh), pelvis (top of tailbone). Once the XSENS sensors are placed, the participant's segment will be measured using a tape measurer issued by the company and entered into the XSENS system. This contributes to the biomechanical model that will be made for the individual. After taking the measurements, the participant will then be instructed to stand with feet shoulder width apart and hands by their side with palms facing in (neutral pose). The participant will then be instructed look forward and hold still in this neutral pose until instructed to look forward and walk. Then they will be instructed to turn and walk back to where they started and pause in the neutral pose. Once completed this concludes the calibration process for XSENS. Kinematic data of the lower body will be collected using the XSENS software.
In the test of Hoffman's reflex in the walking, the standard level of stimulation will be administered and the M and H waves will be recorded. Hoffman's reflex will be collected during the three phases of the gait cycle at the beginning, middle, and end of the stance phase (when the right foot is in contact with the ground). Additionally, Hoffman's reflex will be tested in the middle of the swing phase (when the foot is off the ground). An electrical foot switch will be used to trigger the stimulator during the walking test. This footswitch will be taped under the right heel of the shoe. The footswitch is being used to detect heel-contact during walking. The participant will be walking on the treadmill at a self-selected speed for less than 5 minutes.
Foot sole pressure distribution will be measured by Novel Pedar system (Novel GmbH, Munich, Germany) which permits measurement of in-shoe pressure while walking on the treadmill.

Throughout the study, if participants feel tired, we will give them plenty of rest. More than this, the participants feel so terrible that can't finish the test, they will be excluded from this study. After all the tests, we will carefully tear off the tape without damaging the skin of the participants.

B. *Identify any activity included in the research description that will occur without modification regardless of the research effort. (E.g., A class exercise that is part of the normal course activities that is not altered for the research about which you will collect data or a team warm-up exercise session that is not altered for the study about which you will collect data.)*

Not Applicable

C. *Describe how legally effective informed consent will be obtained. Attach a copy of the consent form(s).*

The participants will review the informed content and be given an overview of the study. The researcher will ensure that the participants fully understand before any signatures are obtained.. They will sign before obtaining any personal information

D. *If minors are to be used, describe procedures used to gain consent of their parent (s), guardian (s), or legal representative (s), and gain assent of the minor.*

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☒ N/A or Explain:

E. *Describe all study instruments and whether they are validated. Attach copies of questionnaires, surveys, and/or interview questions used, labeled accordingly.*

Visual Analogue Scale (VAS) is a psychometric measuring instrument designed to document the characteristics of disease-related symptom severity in individual patients and use this to achieve a rapid classification of symptom severity and disease control (Flynn D, van Schaik P 2004). A VAS is usually a 10cm long horizontal line with verbal descriptors at each end to express the extremes of the feeling of pain. 0 score means no pain,10 score means unbearable pain (Erol, D. D, 2011).We will use it to assess peripheral neuropathy pain of participants (Langley G.B, Sheppeard H , 1984).

Flynn D, van Schaik P,van Wersch A (2004) . A comparison of multi-item likert and visual analogue scales for the assessment of transactionally defined coping. Eur J Psychol Assess.;20:49–58.

Erol, D.D.(2011). The analgesic and antiemetic efficacy of gabapentin or ergotamine/caffeine for the treatment of postdural puncture headache.Adv Med Sci. 56(1), 25-29.

Langley,G B. Sheppeard, H. Problems associated with pain measurement in arthritis: comparison of the visual analogue and verbal rating scales.Clin Exp Rheumatol. 2(3), 231-234.

Xsens MVN accuracy has been verified (Dinu D, Fayolas M, 2016). It can be used to collect kinematic data during slow walking.

Dinu D, Fayolas M, Jacquet M, et al (2016). Accuracy of Postural Human-motion Tracking Using Miniature Inertial Sensors[J]. Procedia Engineering, 147: 655-658.

Assessment of Hoffman's reflex in this population has been deemed reliable (Zhang, Holmes, Li, 2014).

Zhang, S., Holmes, M., & Li, L. (2015). Reliability of nerve function assessments for people with peripheral neuropathy. International Journal of Neuroscience, 125(3), 201-207.

DS7A stimulator's safety is recognized by the FDA. **The FDA safety approval number of stimulator device is K051357.** DS7A has proven to be highly reliable (Phadke C P, Robertson C T, 2012; Stowe A M, Hughes-Zahner L, 2008) . It is widely used in human scientific research (Querry R G, 2008; Lagerquist O, 2008;Walchli M, Tokuno C D, 2017; Andrews J C, 2015), and there are many studies of the elderly (Zhang S, Manor B,2015; Chen Y S, Zhou S,2015).

Phadke C P, Robertson C T, Condliffe E G, et al (2012). Upper-extremity Hoffman's reflex measurement post-stroke: reliability and inter-limb differences[J]. Clin Neurophysiol, 123(8): 1606-15.

Stowe A M, Hughes-Zahner L, Stylianou A P, et al (2008). Between-day reliability of upper extremity Hoffman's reflexes[J]. J Neurosci Methods, 170(2): 317-23.

Querry R G (2008). Synchronous stimulation and monitoring of soleus H reflex during robotic body weight-supported ambulation in Participants with spinal cord injury[J]. The Journal of Rehabilitation Research and Development, 45(1): 175-186.

Lagerquist O (2008), Collins D F. Stimulus pulse-width influences Hoffman's reflex recruitment but not H(max)/M(max) ratio[J]. Muscle Nerve,37(4): 483-9.

Walchli M, Tokuno C D (2017), Ruffieux J, et al. Preparatory cortical and spinal settings to counteract anticipated and non-anticipated perturbations[J]. Neuroscience, 365: 12-22.

Andrews J C, Stein R B, Roy F D (2015). Post-activation depression in the human soleus muscle using peripheral nerve and transcutaneous spinal stimulation[J]. Neurosci Lett, 2015, 589: 144-9.

Zhang S, Manor B, Li L(2015). Hoffman's index is important for postural control for people with impaired foot sole sensation[J]. PLoS One, 10(3): e0121847.

Chen Y S, Zhou S, Cartwright C (2015). Modulation of soleus Hoffman's reflex during shortening and lengthening muscle actions in young and older adults[J]. Chin J Physiol, 58(1): 9-18.

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Zhang, S., Holmes, M., & Li, L. (2015). Reliability of nerve function assessments for people with peripheral neuropathy. International Journal of Neuroscience, 125(3), 201-207.

Foot switch is used as a trigger for electrical stimulation during walking and is widely used in human research (Phadke, Chetan P,2016; Yukiko M PT, Richard L, 2012; Knikou M, Hajela N, 2011).
Phadke C P, Thompson F J, Kukulka C C, et al (2016). Soleus Hoffman's reflex Modulation After Motor Incomplete Spinal Cord Injury: Effects of Body Position and Walking Speed[J]. The Journal of Spinal Cord Medicine, 33(4): 371-378.
Yukiko Makihara, PT, Richard L, Segal PT (2012).Hoffman's reflex modulation in the human medial and lateral gastrocnemii during standing and walking. Muscle & Nerve.45(1),116-125.
Knikou M, Hajela N, Mummidisetty C K, et al (2011). Soleus Hoffman's reflex phase-dependent modulation is preserved during stepping within a robotic exoskeleton[J]. Clin Neurophysiol, 122(7): 1396-404.

Biodex Pro 3 will be used to measure torque. Biodex are scientifically acceptable and can be found in the literature with high reliability.This piece of equipment has been deemed reliable through test-retest reliability and valid against a criterion measurement of torque.
Drouin, J. M., Valovich-mcLeod, T. C., Shultz, S. J., Gansneder, B. M., & Perrin, D. H. (2004). Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. European journal of applied physiology, 91(1), 22-29.

Novel Pedar system has good reliability for the measurement of in-shoe pressures during walking (Boyd L A, Bontrager E L. 1997).
Boyd L A, Bontrager E L, Mulroy S J, et al (1997). The reliability and validity of the novel pedar system of in-shoe pressure measurement during free ambulation[J]. Gait & Posture, 1997, 5(2): 165-165.

F. Describe how you will protect the privacy of study participants.
Each participant will sign an informed consent with their legal name. After that, the name will be coded and used in the process of data collection, processing, analysis, writing, etc., and private information will not be leaked out.

8. Data Analysis

A. Briefly describe how you will analyze and report the collected data.
Analyses will be performed using SPSS 25.
Mean and Standard deviations of each group for all outcome variables will be calculated.

Power analysis was performed using G*Power for 80% power, one-way ANOVA, for three different outcome variables using data from previous research projects among similar populations.
Results: center of pressure 95% area: N=12 for each group; 6-minute walking distance: N=8 for each group; Stride duration variability when walking on the treadmill: N=9 for each group.
We will recruit 15 participants in each group.

1. Intraclass correlation coefficients (ICC) will examine the consistency of Hoffman's reflex test of walking. 95% confidence intervals of ICCs will be computed. ICC values below 0.60 will be considered poor and above 0.80 as high reliability.
2. All Hoffman's reflex variables (H-index and M/H Ratio) will be analyzed using a one way ANOVA to examine the differences among the groups. All the posture, gait, and mobility variables will be analyzed using one way ANCOVA using the Hoffman's reflex variables as a covariant.

Based on the assessment of normality using shapiro wilks and skewness and kurtosis, correlations will be run to examine the relationships between Hoffman-reflex and cutaneous sensation, proprioception, strength, foot sole pressure distribution, balance, gait, functional mobility (6MW, TUG). If the ratio between skewness and Kurtosis is more than 1.96 then the data will be deemed nonparametric. If the data are parametric, pearson's product moment correlations will be run. If the data are nonparametric, Spearman Rho correlations will be run.
Significance level will be set at 0.05 for the correlations, ANOVAs, as well as the ANCOVAs.
The questionnaires will be used in the analysis to correlate with functional data and aid as a potential explanation to the observations.

3. Three phases of gait (beginning, middle, end of stance phase) ×four groups (healthy, idiopathic, neuropathy, typeII diabetes, diabetes neuropathy) mixed-design ANOVA will examine the differences in Hoffman's reflex of different phases among the groups.

B. *What will you do with the results of your study (e.g. contributing to generalizable knowledge, publishing sharing at a conference, etc.)?*

The main goal of this project is to provide data for future thesis, presentations, publications, and grant applications.

C. *Include an explanation of how will the data be maintained after the study is complete. Specify where and how it will be stored (room number, password protected file, etc.)*

Signed Informed Consent Forms will be stored in Dr. Li's office in a locked cabinet. All digital data will be de-identified and stored on password-protected university computers and test computer for further anonymous use

D. *Student researchers must specify which faculty or staff member will be responsible for records after you have left the university.*

Dr. Li Li

E. *Anticipated destruction date or method used to render data anonymous for future use.*

☐ Destroyed 3 Years after conclusion of research (minimum required for all PIs)
☒ Other timeframe (min 3 years): 5
☐ Maintained for future use in a de-identified fashion. Method used to render it anonymous for future use: All digital data will be de-identified and stored on password-protected university computers and test computer for further anonymous use.

Note: Your data may be subject to other retention regulations (i.e. American Psychology Association, etc.)

Special Conditions

9. Risk

Even minor discomfort in answering questions on a survey may pose some risk to Participants. Carefully consider how the Participants will react and address ANY potential risks.

A. *Is there greater than minimal risk from physical, mental, or social discomfort?*

☐No

If no, Do not simply state that no risk exists. If risk is no greater than risk associated with daily life experiences, state risk in these terms.

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☒ Yes

If yes, describe the risks and the steps taken to minimize them. Justify the risk undertaken by outlining any benefits that might result from the study, both on a participant and societal level.

1. The participants will drive to campus by themselves. An investigator will wait for them in the parking lot and accompany them safely to the lab. After the experiment per day, the participants will be escorted by the researcher to the parking lot.
2. During the test of Hoffman's reflex, in order to reduce the discomfort of the subject with stimulation, we will reduce the stimulation intensity without affecting the test results, including lower current magnitude, lower pulse duration. In case the subject feels obvious unwell during the stimulation, we will stop immediately. The stimulator (Digitimer model DS7A, Digitimer Ltd., Welwyn Garden City, England) used has been deemed safe for the use of human research. **The FDA safety approval number of stimulator device is K051357 and the FDA indication for use approval document is attached as well as the manual (including all safety precautions).**
3. The participant will be informed that they may experience skin irritation or skin tear from electrode adhesives.
4. During the test of walking on the treadmill, in order to prevent the participants from fall or giving protection at the time of the fall, we have the following safeguards: 1) a spotter will be positioned behind the treadmill and will be there if the participant was to trip or lose the balance. The spotter will be capable of catching the participant in the event of this occurring. 2) The treadmill also has handle bars on the sides to provide extra support if the participant needs it. They will be allowed to grab the handlebars at any time. 3) The treadmill also has an emergency stop button that will cease the treadmill belt immediately when hit The participants will be told about the emergency stop as well as the safety protocols. 4) The participant will test in sport tennis shoes that will be either ones they bring or ones issued by the lab. This will create friction between the participant and the treadmill. 5) the participants walk at the self-speed which is generally slower. 6) A familiarization for treadmill walking will be conducted at the end of day 1 in preparation for the walking test on day 2.
5. During the test of functional mobility, the participants will walk on the ground according to the investigator's requirements. In order to prevent them from falling when walking and dizzy when standing up from a chair, we have the following safeguards: 1) the ground of the lab is non-slip and has a great fiction. 2) the participants wear sports shoes to prevent slipping. 3) Spotters will walk be positioned around the testing area.
6. During the posture assessment, a spotter will be used and will stand behind the participant within arms reach. This spotter will provide support in the event of the participant losing balance.

B. Will you be carrying out procedures or asking questions that might disturb your Participants emotionally or produce stress or anxiety? If yes, describe your plans for providing appropriate resources for Participants.

The participants will not be asked any questions that will induce stress of anxiety nor disturb my participants emotionally.

10. Research Involving Minors

A. Will minors be involved in your research?
☐ Yes ☒ No

B. *If yes, describe how the details of your study will be communicated to parents/guardians. Please provide both parental consent letters and child assent letters (or processes for children too young to read).*

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C. *Will the research take part in a school (elementary, middle, or high school)?*
☐ Yes ☒ No

D. *If yes, describe how permission will be obtained from school officials/teachers, and indicate whether the study will be a part of the normal curriculum/school process.*

☐ Part of the normal curriculum/school process
☐ Not part of the normal curriculum/school process

11. Deception

A. *Will you use deception in your research?*
☒ No Deception
☐ Passive Deception
☐ Active Deception

B. *If yes, describe the deception and how the subject will be debriefed. Include a copy of any debriefing materials. Make sure the debriefing process is listed in your timeline in the Procedures section.*

C. *Address the rationale for using deception.*

Be sure to review the deception disclaimer language required in the informed consent. Note: All research in which active deception will be used is required to be reviewed by the full Institutional Review Board. Passive deception may receive expedited review.

12. Medical Procedures

A. Does your research procedures involve any of the following procedures:
☒ Low expenditures of physical effort unlikely to lead to physical injury
☐ High expenditures of physical effort that could lead to physical injury
☐ Ingesting, injecting, or absorbing any substances into the body or through the skin
☐ Inserting any objects into bodies through orifices or otherwise
☐ Handling of blood or other bodily fluids
☐ Other Medical Procedures
☐ No Medical Procedures Involved

B. *Describe your procedures, including safeguards. If appropriate, briefly describe the necessity for employing a medical procedure in this study. Be sure to review the medical disclaimer language required in the informed consent.*

During the stimulation, the participant may feel discomfort. To minimize risk or discomfort, all precautions mentioned in the manual will be taken.
During all overground test, spotters will be located around the testing area. When using the Biodex, there is a safety emergency stop button that the participant will have access to and will be able to stop at any time.
During the posture assessment, a spotter will be used and will stand behind the participant within arms reach. This spotter will provide support in the event of the participant losing balance.
During the treadmill test, a spotter will be positioned behind the treadmill and will be there if the participant was to trip or lose the balance. The spotter will be capable of catching the participant in the event of this occurring. The treadmill also has handle bars on the sides to provide extra support if the participant needs it. They will be allowed to grab the handlebars at any time. The treadmill also has an emergency stop button that will cease the treadmill belt immediately when hit The participant will be told about the emergency stop as well as the safety protocols. Also the participant will test in athletic shoes which increases the friction between the participant and the treadmill.

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C. *Describe a medical emergency plan if the research involves any physical risk beyond the most minimal kind. The medical research plan should include, but not necessarily be limited to: emergency equipment appropriate for the risks involved, first rescuer actions to address the most likely physical risk of the protocol, further actions necessary for the likely risks.*

In the event of an emergency, 9-1-1 will be called and the emergency action plan will be activated.
Emergency action plan: participants with non-emergency injuries due to participation should be referred to their primary care doctor. In the event of an emergency that 911 will be called as the emergency action plan, no medical treatment will be performed by the investigators in any event.

Reminder: No research can be undertaken until your proposal has been approved by the IRB.

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CERTIFICATION OF INVESTIGATOR RESPONSIBILITIES

By signing the cover page, I agree/certify that:

1. I have reviewed this protocol submission in its entirety and I state that I am fully cognizant of, and in agreement with, all submitted statements and that all statements are truthful.

2. This application, if funded by an extramural source, accurately reflects all procedures involving human participants described in the proposal to the funding agency previously noted.

3. I will conduct this research study in strict accordance with all submitted statements except where a change may be necessary to eliminate an apparent immediate hazard to a given research subject.
    a. I will notify the IRB promptly of any change in the research procedures necessitated in the interest of the safety of a given research subject.
    b. I will request and obtain IRB approval of any proposed modification to the research protocol or informed consent document(s) prior to implementing such modifications.

4. I will ensure that all co-investigators, and other personnel assisting in the conduct of this research study have been provided a copy of the entire current version of the research protocol and are fully informed of the current (a) study procedures (including procedure modifications); (b) informed consent requirements and process; (c) anonymity and/or confidentiality assurances promised when securing informed consent (d) potential risks associated with the study participation and the steps to be taken to prevent or minimize these potential risks; (e) adverse event reporting requirements; (f) data and record-keeping requirements; and (g) the current IRB approval status of the research study.

5. I will not enroll any individual into this research study: (a) until such time that the conduct of the study has been approved in writing by the IRB; (b) during any period wherein IRB renewal approval of this research study has lapsed; (c) during any period wherein IRB approval of the research study or research study enrollment has been suspended, or wherein the sponsor has suspended research study enrollment; or (d) following termination of IRB approval of the research study or following sponsor/principal investigator termination of research study enrollment.

6. I will respond promptly to all requests for information or materials solicited by the IRB or IRB Office.

7. I will submit the research study in a timely manner for IRB renewal approval.

8. I will not enroll any individual into this research study until such time that I obtain his/her written informed consent, or, if applicable, the written informed consent of his/her authorized representative (i.e., unless the IRB has granted a waiver of the requirement to obtain written informed consent).

9. I will employ and oversee an informed consent process that ensures that potential research Participants understand fully the purpose of the research study, the nature of the research procedures they are being asked to undergo, the potential risks of these research procedures, and their rights as a research study volunteer.

10. I will ensure that research Participants are kept fully informed of any new information that may affect their willingness to continue to participate in the research study.

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11. I will maintain adequate, current, and accurate records of research data, outcomes, and adverse events to permit an ongoing assessment of the risks/benefit ratio of research study participation.

12. I am cognizant of, and will comply with, current federal regulations and IRB requirements governing human subject research including adverse event reporting requirements.

13. I will notify the IRB within 24 hours regarding any unexpected study results or adverse events that injure or cause harm to human participants.

14. I will make a reasonable effort to ensure that Participants who have suffered an adverse event associated with research participation receive adequate care to correct or alleviate the consequences of the adverse event to the extent possible.

15. I will notify the IRB prior to any change made to this protocol or consent form (if applicable).

16. I will notify the IRB office within 30 days of a change in the PI or the closure of the study.

***Faculty signature on the first page indicates that he/she has reviewed the application and attests to its completeness and accuracy**

GEORGIA SOUTHERN UNIVERSITY

COLLEGE OF Health and Human Sciences

DEPARTMENT OF Health Sciences and Kinesiology

Consent to participate in the following Study:

Title of Project: Neural Plasticity of Posture Control and Motor Control among People with Peripheral Neuropathy

Principal Investigator's Name: Kelsey Lewis **Phone:** (904)445-0506

Participant's Name: _____ **Date:** _____

Data Collection Location: Biomechanics Laboratory, Georgia Southern University Campus

The research team consists of doctoral and master candidates. This project is under the direction of Dr. Li Li. The goal of this study is to learn how diabetes and neuropathy affect the way we stand and walk.

In order to participate in this study, you should be able to read English, at least 65 years of age, currently healthy, or have been diagnosed with **peripheral neuropathy**, **diabetes**, or **diabetic neuropathy**; and you are able to walk on a treadmill for at least 5 continuous minutes. If you have any of the following, please notify the research team and unfortunately you will not be able to participate in this study: history or evidence neurological illnesses, or having trouble standing or walking for a short among time, evidence of foot sole ulcers, or have a pacemaker. You will also not be able to participate if you answer yes to any of the questions on the Physical Activity Readiness Questionnaire Plus that will follow the signing of this form as well as a score of less than 24 on the Mini-Mental State Exam. Let us know if any of these terms concern you.

There will be two days of testing for about two hours each time. We will walk with you from your car to the lab and back to your car after each session. At the very beginning, we will ask you to sign this form after addressing all the questions you may have. We will use a few more forms to ask you some information about yourself including if you are suffering from any levels of pain and your quality of life related to your health. All your information we collect will be coded and kept secure. If you agree to participate, the following tests will occur: foot sole numbness, ankle joint proprioception, leg strength, the capacity of walking and standing, and nerve conduction study.

On the first day, foot sole numbness will be tested using a thin monofilament; ankle joint proprioception will be tested to reposition your foot to a targeted position; leg strength will be tested when you kick your leg as hard as you could; walking capacity will be tested two different ways: how far you walk in six minutes, and how fast you can get up from a chair, walk three yards, turn and walk back. After resting a while, you will walk on a treadmill for five minutes and get ready for the next test session.

The second day of testing will include nerve conduction study of your leg, standing balance, walking, and foot sole pressure distribution. Nerve conduction will be tested with low levels of electrical stimulation to the nerve behind the knee and calf muscle reactions to the stimulation,

while you are laying a treatment table, standing, and walking on the treadmill. Electrodes will be placed on your calf, excessive hair will be shaved to improve conduction. Although rare, you might experience skin irritation or skin tear as a result of the electrode adhesive. Let us know if you are allergic to any adhesives or to alcohol prep pads and not able to participate. You will feel a slight pinch to the back of your knee and twitch of your calf during the nerve conduction study. The standing balance will be tested with your eyes open and closed for 30 seconds each. While walking on a treadmill, sensors will be placed on your leg to measure your movement and a different sensor in your shoe will measure the pressure underneath your feet.

You may be sore after each session. It should be minute and temporary. For the simulation tests, we are taking all precautions to ensure that you are not put at risk. When walking on the treadmill, handlebars are present as well as an emergency stop button that you can press at any time during the testing period. During the testing sessions, let us know if you feel any discomfort, we will immediately stop testing and refer you to your primary care physician if necessary. If you experience a non-emergency injury due to participation, you will be referred to your primary care doctor. In the event of an emergency, 9-1-1 will be called as the emergency action plan, no medical treatment will be performed by the investigator in any event. By signing this form you understand that medical care is available in the event of injury resulting from research but that neither financial compensation or free medical treatment is provided by the researchers or Georgia Southern University.

All data collected from this study and paperwork that you fill out will be kept in a locked cabinet in Dr. Li's office. Your identity will be kept confidential and will not be connected to the data. Your name will be coded after signing this form. All of your paperwork will be shredded by Dr. Li five years later after completion of this project. All digital data will be de-identified and stored on password-protected university computers for further anonymous use.

You have the right to ask questions and be answered. If you have questions about this study, please contact Kelsey Lewis at (904)445-0506 or Dr. Li at (912)478-8015. For questions concerning your rights as a research participant, contact the Georgia Southern University Institutional Review Board at 912-478-5465. You may end your participation at any time without penalty. To compensate for your time and travel expenses, we will issue a $25 gift card to you at the end of each testing session.

You will be given a copy of this consent form to keep for your records. This project has been reviewed and approved by the GSU Institutional Review Board under tracking number H20076.

Investigators:
Kelsey Lewis &Menzi Sun
1303 Hanner Fieldhouse
(904)445-0506 & (912) 541-0623
KL06040@georgiasouthern.edu
& mengzisun@georgiasouthern.edu

Faculty Advisor:
Li Li, Ph.D.
0107B Hollis Building
912-478-0200
lili@georgiasouthern.edu

Participant Signature _____ Date _____

I, the undersigned, verify that the above-informed consent procedure has been followed.

Investigator Signature _____ Date _____

DATA OWNERSHIP AND USE AGREEMENT

This Data Ownership and Use Agreement ("Agreement") is entered into this 6 day of November, 2019 between and among Kelsey Lewis, Mengzi Sun, Li Li (singularly "Researcher"; collectively, "Researchers"), and Georgia Southern University ("University") as set forth herein.

WHEREAS the Researchers have submitted a research project to the University's Institutional Review Board ("IRB") for required approval of research involving human subjects (the "Project");

WHEREAS Kelsey Lewis is a graduate student at the University, Mengzi Sun is a visiting scholar from China visiting the University, and Li Li is a faculty member at the University; and

WHEREAS the Project is expected to generate research data from the human subjects ("Data") that may be utilized for future research projects.

WHEREFORE, in consideration of the premises and the good and valuable consideration set forth herein, the Researchers and the University agree as follows:

1. All Data created from the Project shall be the property of the University. The Researchers shall have a limited, non-exclusive license to use the Data pursuant to the terms set forth in this Agreement. Data may not be used by any Researcher except pursuant to this Agreement.

2. The Data shall be deidentified at the conclusion of the Project and shall be in the custody of Li Li so long as he is an employee of the University. Any Researcher who uses the Data on future research projects shall maintain the confidentiality of the Data. In the event the Data is not completely deidentified, a Researcher who uses the data shall remove any identifying information.

3. No Researcher may release or otherwise disclose the Data to a third party without the prior written approval of the University. Any third party who is allowed to use the Data by the University shall be subject to the provisions set forth in this Agreement.

4. The Data collected may be used to support the capstone project of Kelsey Lewis and the doctoral dissertation of Mengzi Sun. Li Li will otherwise have the right of first publication from the Data. No Researcher shall otherwise share, publish or otherwise release any findings or conclusions derived from analysis of the Data without prior approval of the University. The Researchers agree to recognize each other's contributions and the University in all visual, verbal, and written disclosures of future research using the Data in accordance with the appropriate scholarly standards.

5. The Researchers agree to use the Data in compliance with all applicable laws and professional standards applicable to such research.

6. The Researchers shall store the Data in a password-protected file with adequate security controls in place and shall otherwise treat the Data as if personal identifiers were still attached.

Kelsey Lewis

Kelsey Lewis

Mengzi Sun

Mengzi Sun

GEORGIA SOUTHERN UNIVERSITY

Li Li

Li Li

By:_____

Title:_____

Participant Information

ID: _____

Sex (M/F): _____

Date of birth: _____

What foot would you kick a ball with ? Right or Left

Please check one of the following conditions you currently have:

☐Idiopathic Neuropathy

☐ Diabetes

☐ Diabetic Neuropathy

☐ None of the above

If you have checked one of the first three choices, how long have you had this condition? _____

Inclusion:

Are you able to read English?

Yes or No

Age 65 years old and older

Yes or No

Are you able to walk on the treadmill for 5 continuous minutes?

Yes or No

Exclusion:

Do you have a history or evidence of central nervous system dysfunction?

Yes or No

Have you had any Trauma or disease that significantly affects posture and mobility control?

Yes or No

Do you have any evidence of foot sole ulcers?

Yes or No

Do you have a cardiac pacemaker?

Yes or No

If you have answered yes to any of the exclusion questions, you are ineligible to participate in this study.

2019 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition ☐ OR high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it **does not limit your current ability** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION

If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for its records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at **www.eparmedx.com** before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

11-01-2018

2019 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. Do you have Arthritis, Osteoporosis, or Back Problems?

If the above condition(s) is/are present, answer questions 1a-1c — If **NO** ☐ go to question 2

1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	YES ☐ NO ☐
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	YES ☐ NO ☐

2. Do you currently have Cancer of any kind?

If the above condition(s) is/are present, answer questions 2a-2b — If **NO** ☐ go to question 3

2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and/or neck?	YES ☐ NO ☐
2b.	Are you currently receiving cancer therapy (such as chemotheraphy or radiotherapy)?	YES ☐ NO ☐

3. Do you have a Heart or Cardiovascular Condition? This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm

If the above condition(s) is/are present, answer questions 3a-3d — If **NO** ☐ go to question 4

3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
3b.	Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction)	YES ☐ NO ☐
3c.	Do you have chronic heart failure?	YES ☐ NO ☐
3d.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	YES ☐ NO ☐

4. Do you have High Blood Pressure?

If the above condition(s) is/are present, answer questions 4a-4b — If **NO** ☐ go to question 5

4a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
4b.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure)	YES ☐ NO ☐

5. Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes

If the above condition(s) is/are present, answer questions 5a-5e — If **NO** ☐ go to question 6

5a.	Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies?	YES ☐ NO ☐
5b.	Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness.	YES ☐ NO ☐
5c.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, **OR** the sensation in your toes and feet?	YES ☐ NO ☐
5d.	Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)?	YES ☐ NO ☐
5e.	Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future?	YES ☐ NO ☐

2019 PAR-Q+

6. Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome

If the above condition(s) is/are present, answer questions 6a-6b If **NO** ☐ go to question 7

6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
6b.	Do you have Down Syndrome **AND** back problems affecting nerves or muscles?	YES ☐ NO ☐

7. Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure

If the above condition(s) is/are present, answer questions 7a-7d If **NO** ☐ go to question 8

7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
7b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	YES ☐ NO ☐
7c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	YES ☐ NO ☐
7d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	YES ☐ NO ☐

8. Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia

If the above condition(s) is/are present, answer questions 8a-8c If **NO** ☐ go to question 9

8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments)	YES ☐ NO ☐
8b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	YES ☐ NO ☐
8c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	YES ☐ NO ☐

9. Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event

If the above condition(s) is/are present, answer questions 9a-9c If **NO** ☐ go to question 10

9a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	YES ☐ NO ☐
9b.	Do you have any impairment in walking or mobility?	YES ☐ NO ☐
9c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	YES ☐ NO ☐

10. Do you have any other medical condition not listed above or do you have two or more medical conditions?

If you have other medical conditions, answer questions 10a-10c If **NO** ☐ read the Page 4 recommendations

10a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months?	YES ☐ NO ☐
10b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	YES ☐ NO ☐
10c.	Do you currently live with two or more medical conditions?	YES ☐ NO ☐

PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

_____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.

2019 PAR-Q+

If you answered NO to all of the FOLLOW-UP questions (pgs. 2-3) about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

If you answered **YES** to **one or more of the follow-up questions** about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the **ePARmed-X+ at www.eparmedx.com** and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ **at www.eparmedx.com** before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact
www.eparmedx.com
Email: eparmedx@gmail.com

Citation for PAR-Q+
Warburton DER, Jamnik VK, Bredin SSD, and Gledhill N on behalf of the PAR-Q+ Collaboration. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). Health & Fitness Journal of Canada 4(2):3-23, 2011.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

Key References

1. Jamnik VK, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the effectiveness of clearance for physical activity participation; background and overall process. APNM 36(S1):S3-S13, 2011.
2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance; Consensus Document. APNM 36(S1):S266-s298, 2011.
3. Chisholm DM, Collis ML, Kulak LL, Davenport W, and Gruber N. Physical activity readiness. British Columbia Medical Journal. 1975;17:375-378.
4. Thomas S, Reading J, and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Canadian Journal of Sport Science 1992;17:4 338-345.

11-01-2018

SF-36 QUESTIONNAIRE

ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?
○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○ Somewhat worse now than one year ago
○ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking one block
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bathing or dressing yourself

◯Yes, Limited a Lot ◯Yes, Limited a Little ◯No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

◯Yes ◯No

Accomplished less than you would like

◯Yes ◯No

Were limited in the kind of work or other activities

◯Yes ◯No

Had difficulty performing the work or other activities (for example, it took extra effort)

◯Yes ◯No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

◯Yes ◯No

Accomplished less than you would like

◯Yes ◯No

Didn't do work or other activities as carefully as usual

◯Yes ◯No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

◯Not at all ◯Slightly ◯Moderately ◯Severe ◯Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

◯None ◯Very Mild ◯Mild ◯Moderate ◯Severe ◯Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

◯Not at all ◯A little bit ◯Moderately ◯Quite a bit ◯Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you been a very nervous person?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you felt calm and peaceful?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Did you have a lot of energy?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I am as healthy as anybody I know
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I expect my health to get worse
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

My health is excellent
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

https://clinmedjournals.org/articles/jmdt/jmdt-2-023-figure-1.pdf

Visual Analogue Score

ID:_____

1. What is your current level of pain? Please mark the appropriate location on the line below.

No pain **Unbearable Pain**

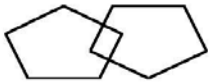
2. What is the maximum pain you have had over the past 24 hours? Please mark the appropriate location on the line below.

No pain **Unbearable Pain**

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.

GEORGIA SOUTHERN UNIVERSITY
WATERS COLLEGE OF HEALTH PROFESSIONS

Looking for Participants!!!

Thesis Volunteers needed to participate in a study examining the different aspects of Peripheral Neuropathy and Diabetes!

- This study is looking at the effect Peripheral Neuropathy and/or diabetes has on how strong your muscles are, sense of ankle movement, ability to maintain balance, and walking.
- Testing could consist of two days that may last about 2 hours each day
- Session One will include tests that assess how strong your leg muscle is, sense of ankle movement, and ability to move through daily living tasks.
- Session Two will consist of:
  - Measuring your muscle's ability to react to stimulation. You will receive low intensity stimulation through a noninvasive surface electrode and the muscle activity will be recorded. After this we will deliver the stimulation again when you are standing and walking.
  - Maintaining balance assessment: This consist of having you stand with your eyes open and eyes closed for 30 seconds
  - Walking test: This consist of having you walk on a treadmill for 5 minutes

Seeking individuals who have the following:

- Over the age of 65 years
- Currently healthy or have been diagnosed one of the following conditions: Idiopathic Neuropathy, Diabetes, OR Diabetic Peripheral Neuropathy
- Medical Clearance to walk for 10 minutes

To be included in this study you must be:

- Able to stand and walk unassisted
- Able to walk on a treadmill
- Not allergic to any alcohol prep pads or adhesives (tape/gel)
- Have had no issues managing your chronic medical condition
- Do not exhibit chest pain at rest, during daily activities of living, or exercising
- Have no history or evidence of Central Nervous System disorders
- Have no trauma or disease that affects your ability to move or stand
- Have no foot sole ulcers
- No cardiovascular condition
  - May be able to participate if you have medical clearance
- No cardiac pacemaker implant
- Do not lose balance because of dizziness
- Have not lost consciousness in the last 12 months
- In the past 12 months, you have not had any bone, joint or muscle, ligament or tendon problems that can be made worse by participating

Hanner Fieldhouse
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