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14. ABSTRACT

Aim The main objective of this proposal is to investigate the role of central mechanisms in motor fatigue and to unmask the alterations in the neural connectivity patterns underpinning central fatigue in PwMS.Specifically, we aim to 1a) determine the role of central mechanisms in motor fatigue in PwMS, 1b) impact of fatigue on mobility impairments and 2) to determine the neural correlates of central fatigue in PwMS.
Methods: Aim 1: Fatigue Assessment: PwMS and healthy controls are currently being recruited to participate in a fatiguing motor task involving a sustained contraction of plantarflexor (PF) muscles for 60 seconds. We are using the interpolated twitch technique to determine voluntary activation (VA) of the PF muscles. The decline in VA during motor task represents the inability of the central nervous system to maximally drive muscles for a sustained period and provides an index of central fatigue. We further relate this objective index of central fatigue to decline in the balance control during standing (pre- and post- fatigue test) and the fast six-minute walk test. We hypothesize that
1a: PwMS will exhibit significantly higher central fatigue during the performance of the fatiguing motor task,
1b: Fatigue will be related to the decline in balance control during standing and walking performance.
Aim 2: Neuroimaging: Resting-state functional MRI (RS-fMRI) is being collected in the participants from Aim 1 to investigate neural mechanisms underlying motor fatigue in PwMS. We hypothesize that 2) The severity of central fatigue in PwMS will be associated with increased functional connectivity among the cortico-striatal structures in the motor circuit of the basal ganglia.
Results and Conclusions: Preliminary findings are presented in this report.

15. SUBJECT TERMS

NONE LISTED

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1. INTRODUCTION:

Approximately 70-90% of people with multiple sclerosis (PwMS) experience difficulties initiating and/or sustaining physical activities (motor fatigue) daily. Though common, the mechanisms underlying motor fatigue are poorly understood. Furthermore, the research on the mechanisms and therapeutics of motor fatigue in PwMS has been impeded by reliance on subjective (self-reported) fatigue questionnaires. Therefore, an objective assessment of motor fatigue is crucial in MS for a more precise diagnosis, a clear understanding of underlying mechanisms, and the design of treatment and rehabilitation programs. Motor fatigue, also called performance fatigability, can be evoked by changes in the peripheral neuromuscular system or in the muscle itself (peripheral mechanisms) and in sites proximal to the peripheral nerves, including the spinal cord and brain (central mechanisms). *The main objective of this proposal was to investigate the role of central mechanisms in motor fatigue and to unmask the alterations in the neural connectivity patterns underpinning central fatigue in PwMS.*

2. KEYWORDS:

Multiple Sclerosis, Motor Fatigue, Neuroimaging, Inertial Sensors, Balance, Gait

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major task 1: Launch Study Activities (100% complete)
Subtask 1: Prepare Regulatory Documents and Research Protocol
Subtask 2: Prepare research protocols
Subtask 3: Training Personnel
Subtask 4: Research Essential Documents

Major Task 2: Recruitment and Testing
Subtask 1: Recruitment (100% complete)
Subtask 2: Data Collection and Management (100% complete)

Major Task 3: Data Analysis and Publications (100% complete)
Subtask 1: Data Analysis
Subtask 2: Data Dissemination

What was accomplished under these goals?

Major task 1: Launch Study Activities
Subtask 1: Prepare Regulatory Documents and Research Protocol

- Set up sub-award at OHSU (100% complete)
- Finalize consent form and human subject protocol; refine eligibly criteria, exclusion criteria, and screening protocol (100% complete)
- Prepare screening and testing forms for participant database (100% complete)
- Create a Redcap database to store screening and testing forms (100% complete)

- Prepare OHSU IRB-approved forms (100% complete)
- Prepare OHSU log to track payments of research subjects (100% complete)
- Set up iLab account for OHSU Imaging contract (100% complete)
- Obtain HRPO approval (100% complete)

Subtask 2: Prepare research protocols

- Prepare and test fatigue testing protocol (100% complete)
- Finalize and prepare a written protocol for neuroimaging (100% complete)

Subtask 3: Training Personnel

- Staff completes research compliance training (100% complete)
- Train RA's in data collection and protocol (100% complete)
- RA's take classes to use Epic to screen potential subjects for recruitment (100% complete)
- Order stimulation electrodes, EMG electrodes, etc. (100% complete)

Subtask 4: Research Essential Documents

- Submit IRB amendments, adverse events, and protocols as needed (100% complete)

Milestones Achieved: All Subtasks for Major Task 1 Complete

All launching study activities completed: All protocols finalized, research training complete, and the required IRB and HRPO approvals in place

Major Task 2: Recruitment and Testing

Subtask 1: Recruitment

- Prepare brochures for subject recruitment (100% complete)
- Contact referrals sources through OHSU MS clinics and lab database (100% complete)
- Phone/Online screening of subjects (100% complete)
- Phone Recruitment (100% complete)

Subtask 2: Data collection and Management

- Schedule participants (100% complete).
- Complete MRI data collection @ AIRC, OHSU (100% complete)
- Fatigue data collection (following MRI) using Biodex Dynamometer (100% complete).
- Balance assessment during standing task (pre-and post-fatigue test) and the fast six-minute walking test (6MWT) using APDM sensors (100% complete).
- Clinical data collection: Medical history, Sleep questionnaire, depression questionnaire, activity questionnaire, fall history, and subjective fatigue questionnaires. Screen and verify data on the server; check for accuracy (100% complete).

Milestones Achieved: All Subtasks for Major Task 2 Complete

Data collection for Specific Aim I is 100% complete: Objective assessment of central fatigue in MS and healthy controls.

Data collection for Specific Aim 2 is 100% complete: Neuroimaging correlates of fatigue in people with MS.

Major Task 3: Data Analysis and Publications

Subtask 1: Data Analysis

- Perform fatigue data analysis to evaluate an index of central fatigue (100% complete).
- Compare the incidence of central fatigue in PwMS vs. healthy controls (100% complete).
- Assess changes in balance control during standing pre-and post-fatigue and during the 6MWT from first to last minute (100% complete).
- Perform MRI data processing (100% complete), motion correction (100% complete), and functional connectivity analysis (100% complete).
- Assess neuro-correlates of central fatigue using resting state functional connectivity, specifically, the role of connectivity between cortico-striatal structures in central fatigue (100% complete).
- Compare the severity of central fatigue to the decline in the balance control (100% complete).
- Assess predictors of falls in mild to moderately involved PwMS based on instrumented balance and gait measures (100% complete)

Subtask 2: Data Dissemination

- Disseminate findings (abstracts, presentations, papers, DoD), including APTA, ACTRIMS, and MHSRS, and rehabilitation journals to share with clinicians (complete)
- Submit a manuscript describing the predictors of falls in mild to moderately involved PwMS based on instrumented mobility measures (Under Review).
- Submit a manuscript describing the fatigue protocol and preliminary findings (In preparation).
- Submit manuscript presenting findings on neuro-correlates on motor fatigue in MS. (In preparation).

Significant Results/ Key outcomes

The Institutional Review Board of Oregon Health & Science University approved this prospective cohort study. 26 PwMS and 26 Healthy Controls were enrolled and tested in this study. The investigation was conducted according to the principles expressed in the Declaration of Helsinki, and written informed consent was obtained from the participants.

The following is the summary of the main findings from the study:

Healthy Controls vs. PwMS

Demographics: Table 1 shows the demographic characteristics of healthy controls (n = 26; 19 females (F) and 7 males (M)) and PwMS (n = 26; 20 F and 6 M). No significant differences between the two groups were observed in age, weight, and height, Table 1.

Depression: The BDI-II is a widely used 21-item self-report inventory measuring the severity of depression in adolescents and adults. For example, individuals are asked to respond to each question based on two weeks rather than the one-week timeframe on the BDI. The BDI-II is widely used as an indicator of the severity of depression but not as a diagnostic tool, and numerous studies provide evidence for its reliability and validity across different populations and cultural groups. It has also been used in numerous treatment outcome studies and numerous studies with trauma-exposed individuals. In this study, PwMS scored significantly higher on BDI-II than healthy controls, Table 1.

Table 1. Demographics for healthy control and MS groups provided as mean (standard error).

Participants	Age	Gender (F/M)	Height	Weight	Depression	Weekly Activity	Global Sleep
Heathy Controls	41.0±2.4	19/7	167.3±2.4	155.2±5.7	3.7±1.2	46.0±3.8	5.4+0.6
People with MS	43.9±1.9	20/6	166.6±2.6	164.3±6.5	10.6±1.7	32.8±4.4	8.8±0.8
p value	0.3	n/a	0.9	0.3	0.0	0.0	0.0

Sleep: Sleep was assessed using Pittsburgh Sleep Quality Index (PSQI) in PwMS and healthy controls. In scoring the PSQI, seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality. The global sleep scores were significantly higher in MS group compared to healthy controls, indicating poor sleep quality in PwMS. The global sleep quality was significantly poor among PwMS. Specifically, PwMS scored significantly higher on daytime dysfunction and subjective sleep scores compared to healthy controls, reflecting poor sleep habits in the former group. In addition, habitual sleep efficiency was lower in PwMS (Table 2).

Table 2: Components of Pittsburg Sleep Quality Index.

Participants	Daytime Dysfunction	Habitual Sleep efficiency	Sleep Latency	Sleep Duration	Subjective Sleep Quality
Heathy Controls	0.7±0.2	79.7±1.9	0.9+0.2	0.7±0.1	0.6±0.1
People with MS	1.4±0.1	73.1±2.7	1.3±0.2	1.2±0.2	1.3±0.1
p value	0.00	0.05	0.15	0.06	0.00

Physical Activity Scores: There have been recent efforts toward creating a health contribution score from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) that reflects public-health guidelines for moderate-to-vigorous physical activity levels. On average, MS and healthy control group participants fell in the "active" category based on GLTEQ scale scoring, but healthy controls were significantly more active compared to PwMS (Table 1).

Fatigue Measures:

Motor Fatigue: The decline in force production during the sustained contraction task was 10.6% (±3.2) in healthy controls vs. 20.1% (±4).3 in PwMS, but no significant differences were observed (p=0.08).

Central Fatigue (Primary outcome measure; Aim 1): Central fatigue was defined as ≥10% decline in voluntary activation during the sustained contraction task. The sustained contraction data from 4 PwMS and 2 healthy controls was excluded from further analysis because these participants could not follow the protocol consistently. As we hypothesized, the incidence of central fatigue was significantly higher in PwMS compared to healthy controls in our cohort (67% vs. 13%, $p<0.00$).

Mobility Impairments (Secondary outcome measures**)**

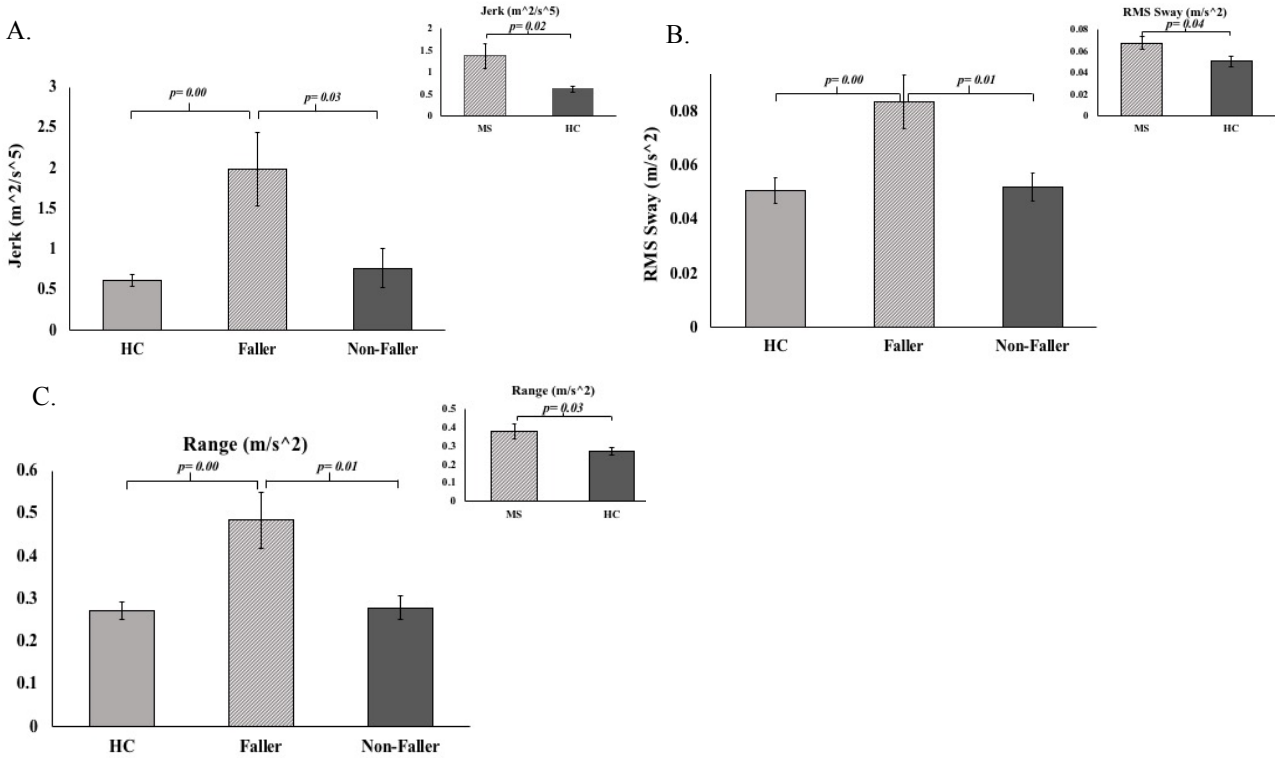
Instrumented Balance Testing: The main aim of this sub-study was to investigate if the instrumented postural sway measures that differentiate PwMS from healthy controls can characterize fallers in the MS group.

Methods: Twenty-two PwMS (age: 45 ± 10.16 yrs, EDSS < 4.5) and twenty age-matched healthy controls (age: 41 ± 13.27 yrs) participated in an instrumented postural sway test. Participants were instructed to stand on a firm surface for 30 seconds with eyes open, wearing a lumbar sensor (Opal, v1, APDM Inc., Portland, Oregon). Further, participants in the MS group were categorized as fallers (n=11) and non-fallers (n=11) based on prior history of falls. Independent t-tests were performed to determine which measures of instrumented postural sway differentiate healthy controls from PwMS. Then, the distinct sway deviations identified in the previous step were used to assess the mean differences between fallers and non-fallers in the MS group.

Results: PwMS performed significantly worse on the instrumented postural sway test compared to the healthy controls. Specifically, increased jerk (a measure of smoothness in motion), range, and the root mean square (RMS) of sway were observed in the MS group. Importantly, these postural sway abnormalities successfully differentiated fallers from non-fallers in the MS group. Compared to the non-fallers, sway measures (jerk, range, and RMS) were significantly higher in PwMS who reported falls in the past six months (Fig. 1).

Conclusions: Instrumented postural sway test may be important in identifying fallers in mild to moderately involved PwMS. The reported postural sway abnormalities indicate that PwMS, especially fallers, experience a significant decrease in postural stability that requires active and frequent postural corrections. In addition, these subtle differences in sway measures between the faller and non-faller cohorts may allow for early detection of falls, possibly aiding clinicians and researchers in mitigating the burden of falls placed on PwMS.

Fig. 1 Instrumented sway measures that discriminated fallers from non-fallers in the MS group.



Instrumented Gait Testing: The primary aim of this sub-project was to investigate if falls can be detected in PwMS using instrumented gait measures.

Methods: Participants performed a 6MWT wearing six-wireless inertial sensors. One sensor was positioned on the low back, two on the feet, one on the sternum, and two on the wrists. The sensors wirelessly transmitted raw data at 128 Hz to the laptop data collection using MobilityLab (v2, APDM Inc., Portland, Oregon). The different gait measures obtained from the sensor data were divided into the following categories:

1) *Spatiotemporal features of gait,* i.e., gait cycle duration, speed, double support, cadence, step duration, stride velocity, stride length, circumduction, toe-off angle, etc.
2) *Upper body control,* i.e., local dynamic velocity and arms range of motion and velocity.
3) *Postural transitions:* Turning analysis, i.e., turn duration, angle, velocity, and the number of steps.

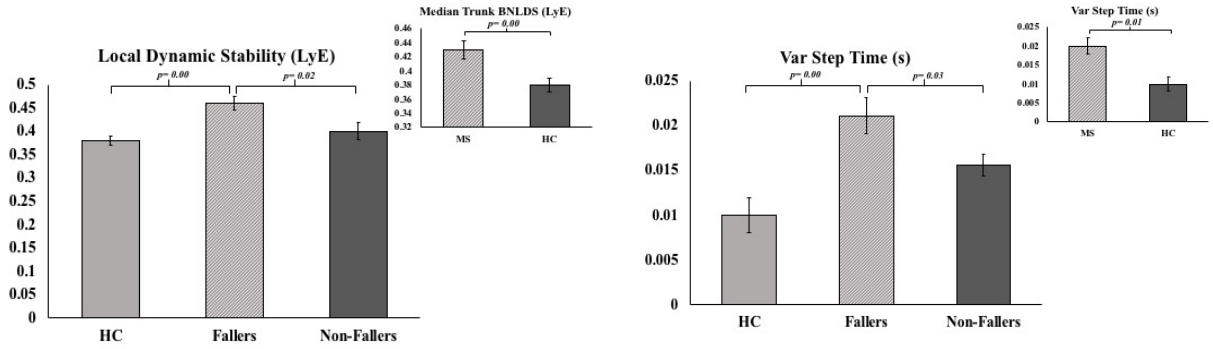
First, we investigated which gait measures differed between MS and healthy control groups (Step 1). Then, the distinct gait deviations identified from step 1 were used to discriminate fallers from non-fallers in the MS group. Participants in the MS group were categorized as fallers and non-fallers based on prior history of falls

Results: We found significant differences between various instrumented gait measures among MS and healthy controls (shown below in Table 3).

	Gait Measures	Multiple Sclerosis (mean ± SE)	Healthy Controls (mean ± SE)	p value
Spatiotemporal	Cadence (steps/min)	131.21 ± 2.67	142.18 ± 2.56	0.01
	Double Support (%GCT)	17.87 ± 0.85	13.71 ± 0.70	0.00
	Speed (m/s)	1.35 ± 0.05	1.62 ± 0.04	0.00
	Circumduction (cm)	2.83 ± 0.20	3.46 ± 0.23	0.04
	Stride Length (m)	1.23 ± 0.04	1.37 ± 0.02	0.00
	Early Swing Time (s)	0.39 ± 0.01	0.42 ± 0.01	0.04
	Late Swing Time (s)	0.47 ± 0.01	0.50 ± 0.01	0.03
	Mean Step Time (s)	0.46 ± 0.01	0.42 ± 0.01	0.01
	Variation in Step Time (s)	0.02 ± 0.001	0.01 ± 0.001	0.01
	Foot strike angle (degrees)	17.40 ± 0.85	20.17 ± 0.61	0.01
	Toe off angle (degrees)	37.65 ± 0.97	40.94 ± 0.68	0.01
Upper body Control	Lumbar Coronal ROM (degrees)	9.71 ± 0.70	11.86 ± 0.61	0.03
	Lumbar Transverse ROM (degrees)	11.77 ± 0.84	16.65 ± 1.47	0.01
	Local Dynamic Stability (λ)	0.43 ± 0.01	0.38 ± 0.01	0.00
Turns	Duration (s)	2.26 ± 0.10	1.93 ± 0.06	0.01
	Number of Turns (#)	22.09 ± 1.35	29.75 ± 0.84	0.00
	Turn Velocity (degrees/s)	193.13 ± 10.20	247.01 ± 12.46	0.00

The distinct gait measures shown in table 1 were used to differentiate fallers from non-fallers in the MS group. Among the above-instrumented gait measures, only local dynamic stability (upper body control measure) and Variation in step time (spatiotemporal measure) were different between fallers and non-fallers (Fig. 2).

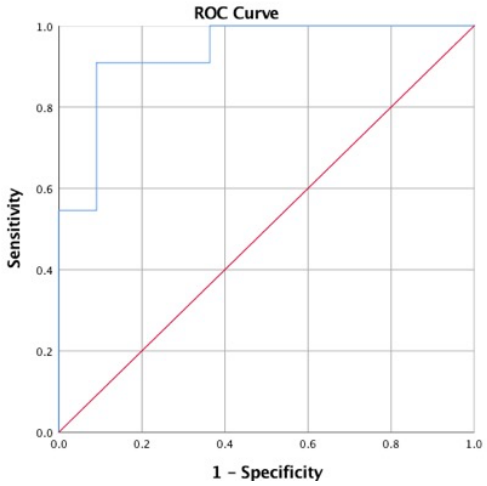
Fig. 2 Instrumented gait measures that discriminated fallers from non-fallers in the MS group.



Best model for fall prediction based on mobility impairments: The primary aim here was to identify the best model for fall prediction based on balance and gait impairments in PwMS.

Methods: For this sub-aim, both balance and gait variables significantly different between MS and healthy controls were classified as 'potential fall predictors' and carried into the analysis. To determine the best independent predictors of falling, forward and backward stepwise regression models were implemented to determine the best combination of mobility variables to predict fall frequency in PwMS.

Results: The final model was the same regardless of forward or backward steps based on the Area under the curve (AUC). The model included Sway Range and trunk local dynamic stability as the predictors of falls and yielded an AUC of 0.934 (Fig. 3).



Area Under the Curve				
Area	Std. Error	Asymptotic Sig.	Confidence Interval Lower Bound	Upper
0.934	0.053	0.001	0.831	1
Under the nonparametric Null hypothesis: true area = 0.5				

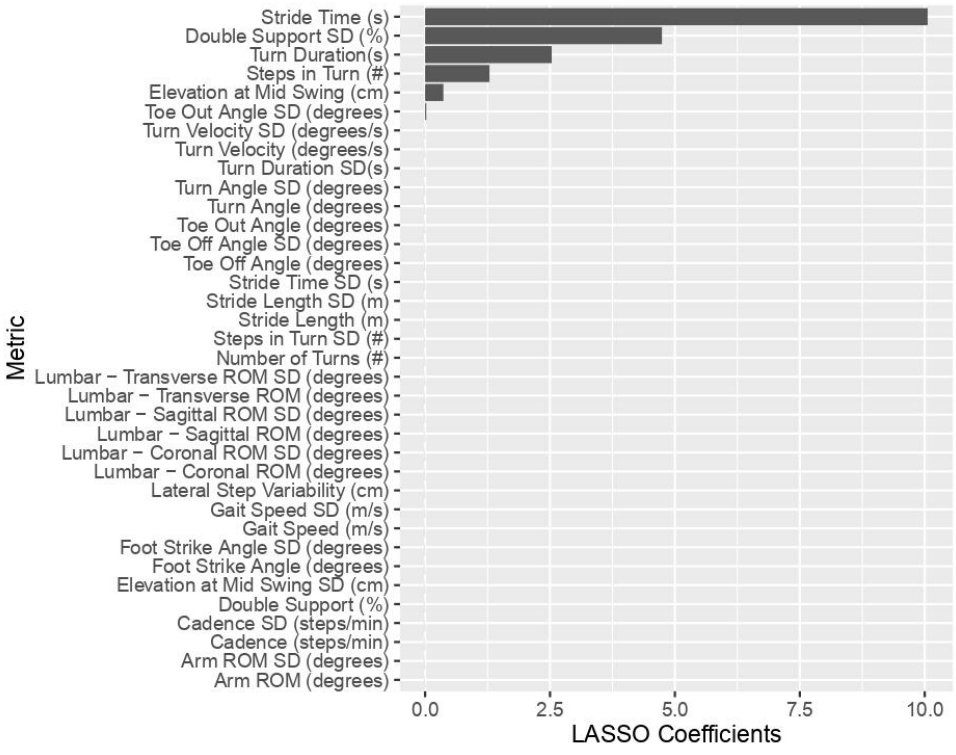
Investigation of the best combination of gait measures discriminating people with multiple sclerosis from healthy controls

Background and Aim: Stopwatch-timed tests or rating scales poorly capture Gait deficits in PwMS. Body-worn inertial sensors can detect gait abnormalities in people with MS who have normal walking speed.

Key challenges in using body-worn inertial sensors to monitor gait characteristics are excessive measures and a lack of consensus on the most useful measures for MS. This study aimed to determine the best combination of gait measures to discriminate MS from healthy controls.

Methods: We used two datasets: Study I (funded by DOD grant) for development and validation, and Study II: for independent test of the proposed model. Participants were instructed to complete the 6-minute walk test at their fastest speed to cover as much distance as possible by walking back-and-forth along a 20-m straight walkway (Study I) or a 15-m straight walkway (Study II). Subjects wore inertial sensors (Opals) attached to both feet, sternum and lumbar regions. LASSO (5-fold, cross-validated least absolute shrinkage and selection operator) was applied as a feature-selection method on 70% of the training dataset followed by logistic regression on the remaining 30% of Study I. To test the generalizability of the proposed model, it was applied to the Study II independent data. The area under the curve (AUC) of receiver operator characteristic (ROC) curves was used to evaluate the discriminate ability of the proposed model.

Results: From 36 gait measures, LASSO selected 6 measures from the training dataset: stride time, double support time standard deviations (%), turn duration, total number of turns, elevation at mid-swing, and toe-out angle standard deviation (Fig.4). Logistic regression with the above 6 gait measures resulted in AUC=1 (sensitivity=1 and specificity=1) when applied on the validation dataset (30% of Study I). The proposed model applied to an independent dataset (Study II) resulted in AUC=0.92 (sensitivity=0.89, specificity=1).



Conclusions: The best combination of gait measures for accurate classification of MS gait from healthy controls gait during the 6-minute walk test did not include gait speed. These findings pave the way for a better understanding of gait deficits in MS to support informed clinical decision-making about the status of the disease or effect of an intervention.

Development of algorithm to estimate walk distance using wearable sensors

Shah VV, Curtze C, Sowalsky K, Arpan I, Mancini M, Carlson-Kuhta P, El-Gohary M, Horak FB, McNames J. Inertial Sensor Algorithm to Estimate Walk Distance. *Sensors*. 2022; 22(3):1077. https://doi.org/10.3390/s22031077

Abstract: The "total distance walked" obtained during a standardized walking test is an integral component of physical fitness and health status tracking in a range of consumer and clinical applications. Wearable inertial sensors offer the advantages of providing accurate, objective, and reliable measures of gait while streamlining walk test administration. The aim of this study was to develop an inertial sensor-based algorithm to estimate the total distance walked using older subjects with impaired fasting glucose (Study I), and to test the generalizability of the proposed algorithm in patients with Multiple Sclerosis (Study II). All subjects wore two inertial sensors (Opals by Clario-APDM Wearable Technologies) on their feet. The walking distance algorithm was developed based on 108 older adults in Study I performing a 400 m walk test along a 20 m straight walkway. The validity of the algorithm was tested using a 6-minute walk test (6MWT) in two sub-studies of Study II with different lengths of a walkway, 15 m (Study II-A, n = 24) and 20 m (Study II-B, n = 22), respectively. The start and turn around points were marked with lines on the floor while smaller horizontal lines placed every 1 m served to calculate the manual distance walked (ground truth). The proposed algorithm calculates the forward distance traveled during each step as the change in the horizontal position from each foot-flat period to the subsequent foot-flat period. The total distance walked is then computed as the sum of walk distances for each stride, including turns. The proposed algorithm achieved an average absolute error rate of 1.92% with respect to a fixed 400 m distance for Study I. The same algorithm achieved an absolute error rate of 4.17% and 3.21% with respect to an averaged manual distance for 6MWT in Study II-A and Study II-B, respectively. These results demonstrate the potential of an inertial sensor-based algorithm to estimate a total distance walked with good accuracy with respect to the manual, clinical standard. Further work is needed to test the generalizability of the proposed algorithm with different administrators and populations, as well as larger diverse cohort.

Fatigue and its impact on balance & gait

Muscle Fatigue in PwMS impairs standing balance and gait. PwMS demonstrated a significant increase in the sway measures in the mediolateral direction after the fatiguing protocol ($p<0.05$), while healthy controls did not show any change (Fig. 5). The increase in trunk sway during quiet stance in PwMS after the fatigue of ankle plantar flexors are consistent with impaired control of postural sway and/or a decreased use of the ankle strategy and increased use of the hip strategy to control stance posture. No changes were observed in the spatiotemporal measures of gait after fatiguing protocol in either MS or control groups (Fig. 6). However, in PwMS, a significant increase in the transverse range of motion of trunk was observed after the fatiguing task (Fig. 6), indicating that the trunk control during walking may be a more sensitive measure of fatigue than the spatiotemporal features of gait.

- Trunk control during walking may be a more sensitive measure of fatigue than the spatiotemporal features of gait**.** No changes in the tempo-spatial measures of gait were observed after fatigue

testing, but PwMS showed the most significant changes in the trunk range of motion in the transverse plane (Fig. 7).

Fig. 5 Pre- and post-fatigue sway measures in healthy controls (blue) and PwMS (orange). * reflects a significant change in sway measures in the MS group after the fatiguing task.

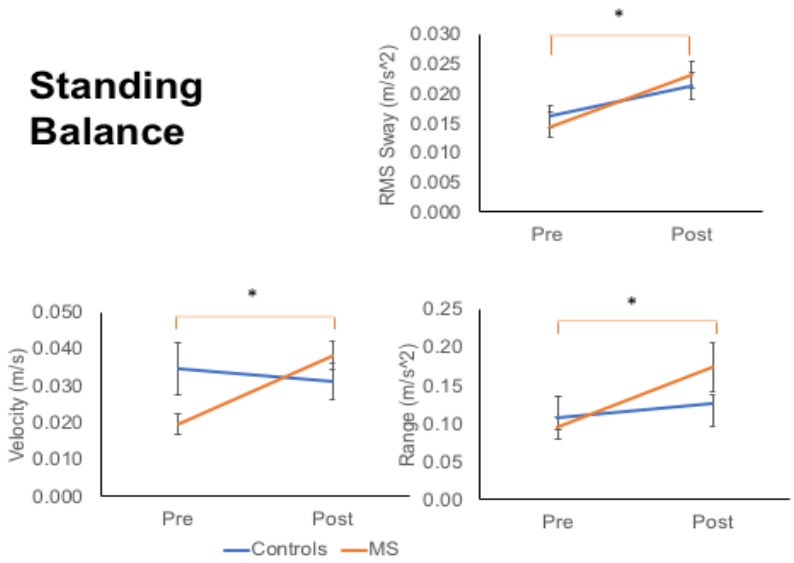


Fig. 6 Pre- and post-fatigue spatiotemporal measures of gait in healthy controls (blue) and PwMS (orange). * reflects a significant change in spatiotemporal features of gait in the MS group after the fatiguing task.

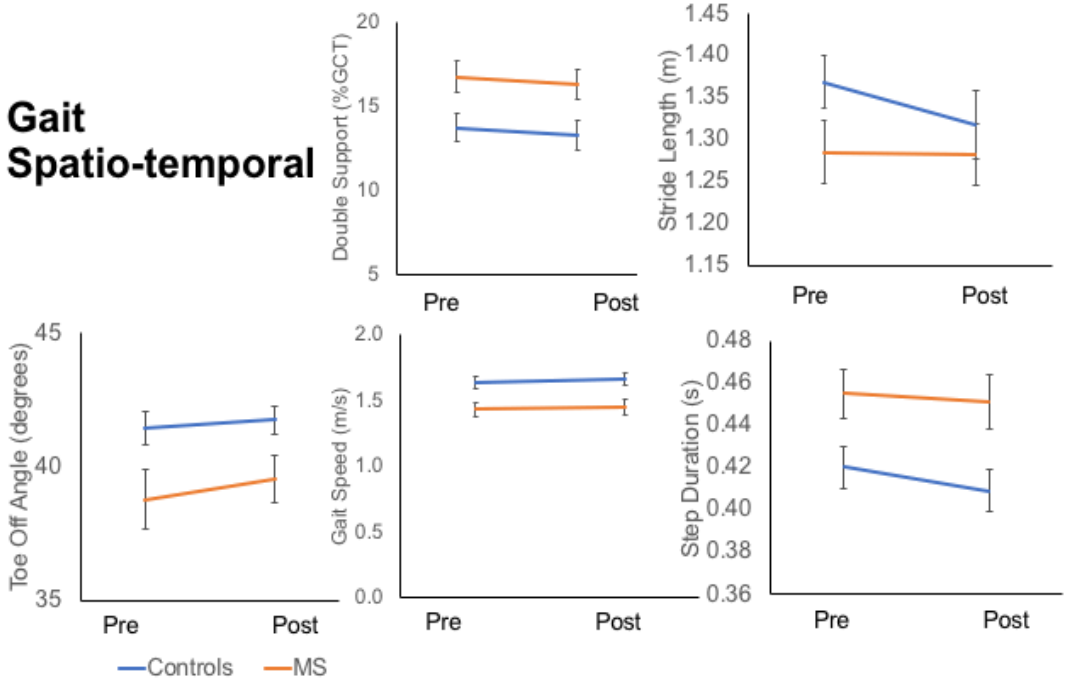
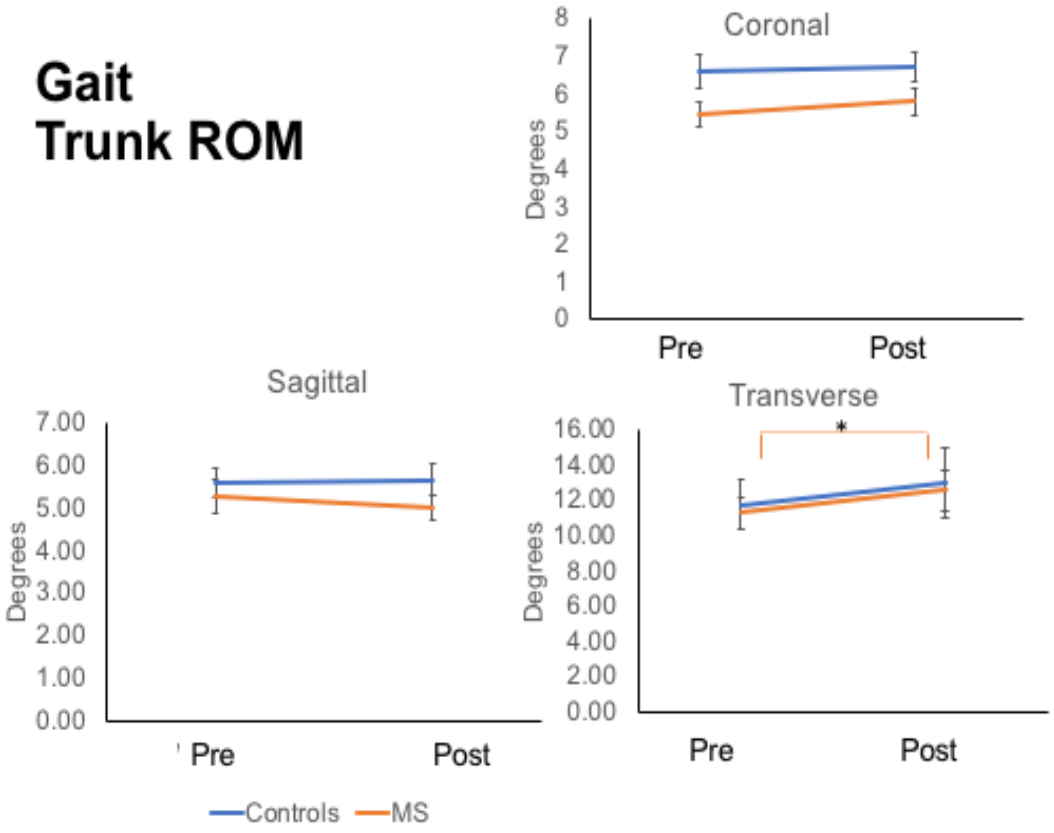


Fig. 7 Pre- and post-fatigue trunk ROM in healthy controls (blue) and PwMS (orange). * reflects a significant change in trunk ROM while walking in the MS group after the fatiguing task.



Neuro-correlates of fatigue (AIM 2)

rsfMRI data processing

We used the CONN-fMRI functional connectivity toolbox v18b (Whitfield-Gabrieli and Nieto-Castanon, 2012) (https://web.conn-toolbox.org/) in conjunction with SPM 12 (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm/) and MATLAB R2015 (The MathWorks, Inc., Natick, Massachusetts) to perform the functional connectivity analysis.

All structural and functional sequences were preprocessed using the CONN's default pipeline for volume-based analysis, as follows: 1) functional realignment and unwarping (subject motion estimation and correction); 2) functional center to (0,0,0) coordinates (translation); 3) functional slice-timing correction using ascending order (correction for inter-slice differences in acquisition time); 4) functional outlier detection (ART-based identification of outliers scans for scrubbing), using conservative settings (global-signal z-value threshold= 3 and subject-motion mm threshold= 0.5); 5) functional direct segmentation (simultaneous gray and white matter/cerebrospinal fluid [CSF] and normalization to MNI adopting default Tissue Probability Maps with target resolution= 2

mm; 6) structural center (0,0,0) to coordinates (translation); 7) structural segmentation (simultaneous gray and white matter/CSF and normalization to MNI space adopting default Tissue Probability Maps with target resolution= 1 mm; and 8) functional smoothing (spatial convolution with 8 mm full width half maximum Gaussian Kernel filter).

During preprocessing, the first four volumes of functional sequences were excluded from the analysis to obtain signal stabilization. After pre-processing, 11 functional sequences from MS-F group, 1 functional sequence from MS-NF group, and 5 functional sequences from healthy controls group were excluded due to insufficient amount of valid scans (< 3 min of total scans and < 90% of valid scans) to ensure data quality (Whitfield-Gabrieli and Nieto-Castanon, 2012, Yan et al., 2013).

CONN implements the CompCor (component-based noise correction method) for temporal and spatial preprocessing to remove confounds in the BOLD signal, such as physiological noise and head motion. BOLD data underwent a denoising process with a CompCor method (Chai et al., 2012), applying a band-pass filter (0.008 to 0.009 Hz), using a simultaneous band-pass approach (Hallquist et al., 2013) to reduce both noise effects and low-frequency drift, and linear regression of the following confounding effects: 5 parameters for CSF, 5 parameters for white matter, 12 parameters for realignment, and 113 parameters for artifact scrubbing (Whitfield-Gabrieli and Nieto-Castanon, 2012).

To conduct the seed-based ROI-to-ROI analysis to create the functional connectivity maps, we used the CONN's default atlas (23 ROIs described at the end of the report). The CONN's default atlas includes cortical and subcortical ROIs referred to as the Harvard Oxford atlas (Desikan et al., 2006) and cerebellar ROIs based on the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). In addition, a non-parametric two-sided multivoxel pattern analysis (MVPA) test was used. Since this was an exploratory analysis, we did not correct for multiple comparisons.

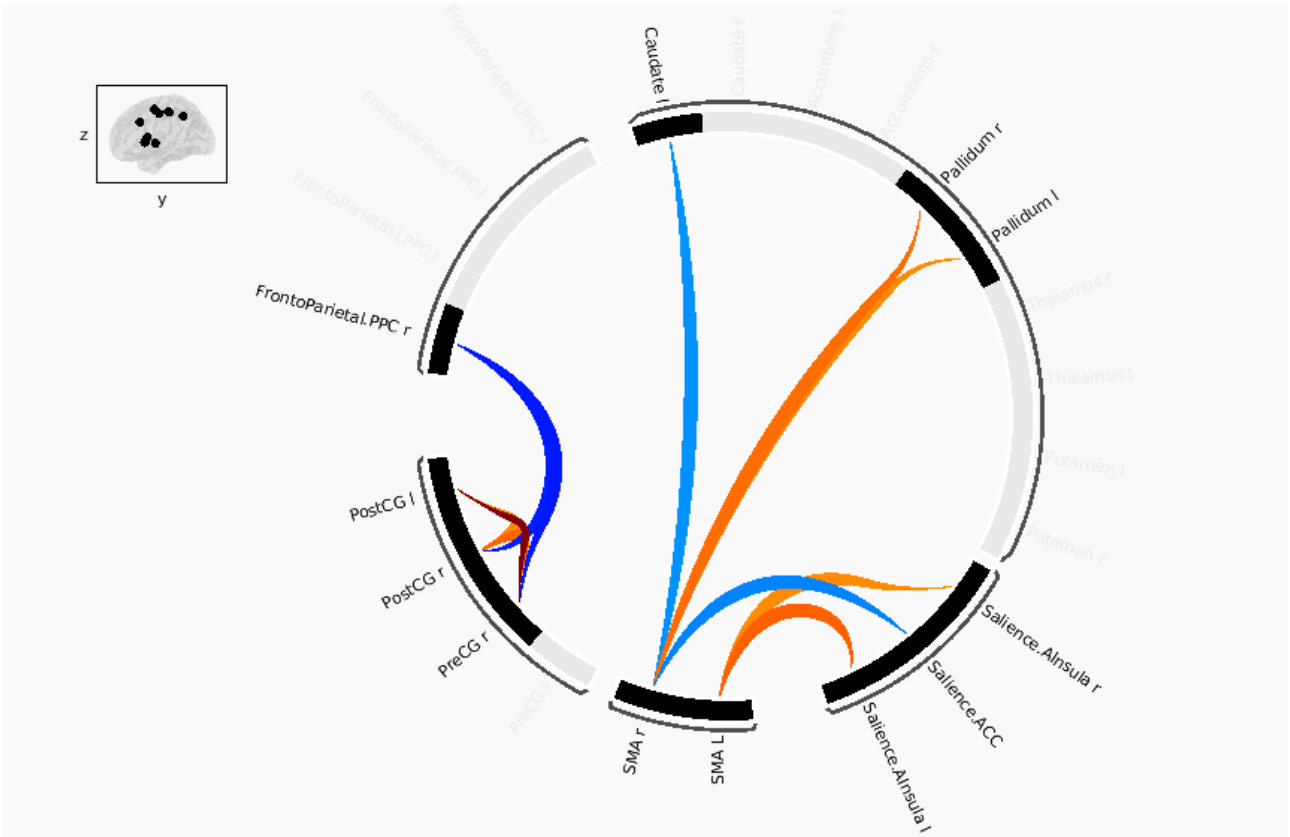
Participants

As described previously, central fatigue was defined as ≥10% decline in voluntary activation during the sustained contraction task, and based on this threshold, PwMS were divided into two groups: Fatigue (>10% decline in VA) vs. NoFatigue (<10% decline in VA)

Results

Contrast MS-F group > MS-NF group

Figure 8 shows that the ROI-to-ROI analysis detected significant differences in resting-state functional connectivity between MS-F and MS-NF groups. In our hypothesis, alterations in the cortico-striatal network resulting in effort–reward imbalance were proposed as a central feature of fatigue. As speculated, we identified functional decoupling between these regions. Specifically, our results showed significantly reduced rs-FC negative connectivity between caudate and SMA in fatigued PwMS. We also found alterations in the functional connectivity within cortical connections.



Analysis Unit	Statistic	p-unc	p-FDR
Cluster 1/15	F(2,52) = 5.79	0.005351	0.061651
Cluster 2/15	F(1,53) = 7.07	0.010329	0.061651
Cluster 3/15	F(2,52) = 4.79	0.012330	0.061651
Cluster 4/15	F(2,52) = 3.19	0.049366	0.185124

Fig. 8 illustrates strong functional connections between different ROIs and networks for the contrast MS-F group > MS-NF group. Blue line represents a strong negative connectivity and red lines represent strong positive connectivity.

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List of ROIs

1. atlas.PreCG r (Precentral Gyrus Right)
2. atlas.PreCG l (Precentral Gyrus Left)
3. Networks.Salience.ACC
4. networks.Salience.AInsula (L) (-44,13,1)
5. networks.Salience.AInsula (R) (47,14,0)
6. atlas.PostCG r (Postcentral Gyrus Right)
7. atlas.PostCG l (Postcentral Gyrus Left)
8. networks.FrontoParietal.LPFC (L) (-43,33,28)
9. networks.FrontoParietal.PPC (L) (-46,-58,49)
10. networks.FrontoParietal.LPFC (R) (41,38,30)
11. networks.FrontoParietal.PPC (R) (52,-52,45)
12. atlas.SMA r (Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex- Right)
13. atlas.SMA L(Juxtapositional Lobule Cortex -formerly Supplementary Motor Cortex- Left)
14. atlas.Thalamus r

15. atlas.Thalamus l

16. atlas.Caudate r

17. atlas.Caudate l

18. atlas.Putamen r

19. atlas.Putamen l

20. atlas.Pallidum r

21. atlas.Pallidum l

22. atlas.Accumbens r

23. atlas.Accumbens l

What opportunities for training and professional development has the project provided?

The research team members have had multiple opportunities to present the findings from this project at local and national conferences, including Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) meeting to meet and share our results with experts in the field of research. ACTRIMS is a community of leaders from the United States and Canada dedicated to treating and researching MS and other demyelinating diseases. Here's an article highlighting our work:

https://www.neurologylive.com/view/sway-test-differentiates-fallers-non-fallers-ms

This year, we are submitting an abstract on neuro-correlates of subjective fatigue to 2023 MHSRS meeting. In addition, we submitted an abstract to the International Society of Posture and Gait Research (ISPGR) world congress in July 2022, which was selected for a platform presentation. We also submitted an abstract to the 2021 Annual Meeting of The Consortium of Multiple Sclerosis Centers (CMSC) 2021. Our abstract was chosen to be presented during the Whitaker Platform Session, which is recognized for young and emerging scientists whose works are deemed to have substantial promise to increase the understanding of the pathophysiology, immunology, genetics and epidemiology of MS.

In addition, Dr. Horak, PI of the study, discussed findings from this study and mobility problems in other populations as an invited speaker in the following meetings: Northwest Portland Area Indian Health Board – "Gait and Balance in Aging Communities"; Portland, OR, Sept 2018; Workshop for Physical Therapists: Evaluation and Treatment of Balance Disorders, Vancouver, BC, Sept 2018; Digitial Biomarkers for Neurological Disorders, San Diego, November 2018; NIH Advisory Committee: Balance Disorders and their Rehabilitation, Washington DC, 2019; University of Michigan, Neurology Rounds: "Digital Biomarkers for Neurological Mobility Disability", Michigan, April 2019; Invited Public Lecture "What goes wrong with balance as we age and what to do about it" at OHSU, 2019; Teaching Lectures Balance Assessment and Rehabilitation for Neurological

Disorders National Parkinson Foundation Faculty Scholars, OHSU, August 2019; Video to train Foundation, Dec, 2020; Movement Disorders Journal Club "Balance Rehabilitation for Movement Disorders", Dept of Neurology, OHSU, Dec 2020.

In addition, Dr. Arpan, co-investigator of the study, presented the study protocol and preliminary findings at a meeting with the visiting members of the Biogen team in 2019. The goal of the meeting was to discuss non-invasive, objective, and sensitive measures of mobility impairments and fatigue in clinical trials.

How were the results disseminated to communities of interest?

The results have been disseminated to broad communities of interest, such as:

- Other scientists (ACTRIMS Meeting, ISPGR, upcoming DOD meeting)
- Clinician audience (OHSU Grand Rounds, OHSU MS Center Physician Group)
- Patient groups (Community Lab Tours)

What do you plan to do during the next reporting period to accomplish the goals?

We plan to finish the papers and apply for new funding based on these exploratory results.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
This project is allowing researchers in the area of multiple sclerosis to understand more about the role that central factors play in motor fatigue and how motor fatigue can further worsen balance deficits in this population. Furthermore, it is creating awareness in clinicians of the need to use more objective measurements of fatigue and mobility impairments. Subjective fatigue questionnaires only measure an individual's perception of fatigue and neglect the critical context of functional performance demands during daily life. Valid objective measurement of motor fatigue in the lower limb muscles involved in standing and functional movements and a precise understanding of its relationship with the altered brain connections has the potential to reveal the underlying pathophysiology of motor fatigue in MS. In future studies, we plan to explore the impact of rehabilitation interventions targeting central fatigue on the altered cortico-striatal connectivity in PwMS. Further, the investigation of motor fatigue's effects on balance control expands our understanding of the potential risks of falls and injuries during daily activities in PwMS. Our most recent publication has shown that the pitch at toe-off (reflecting less plantarflexion during the push-off phase of walking) is the single most influential predictor of future falls in PwMS.

What was the impact on other disciplines?
Our research team members continued meeting once per month with clinicians and physical therapists at OHSU MS center. We have found that these meetings allow an open discussion between researchers and clinicians to discuss research findings and work towards translating research knowledge into clinical practice. In addition, we work closely with members of the Developmental Cognition and Neuroimaging (DCAN) Lab at OHSU. DCAN lab specializes in using resting state functional connectivity magnetic resonance imaging to study the brain across development (from infancy to aging), in different disorders (ADHD, autism, Parkinson's Disease),

and across different species (humans, non-human primates and rodents). Our collaboration with DCAN lab is helping us explore ways to better characterize individual patients with MS using sophisticated neuroimaging tools. FIRMM (Framewise Integrated Real-time MRI Monitoring) software (for real-time movement monitoring in the scanner) developed by DCAN lab has allowed us to maximize the usage of MRI data collected from each participant enrolled in this study.

What was the impact on technology transfer?
The immediate impact on technology transfer is the presentation of our preliminary findings at various conferences, including ACTRIMS. ACTRIMS provides an annual forum for national and internationally experienced and newer clinicians and researchers to exchange information, debate current issues and discuss advances related to basic research and clinical issues in MS. The studies are helping transfer knowledge to other researchers that the instrumented measures, specifically trunk ROM may be a more sensitive measure of fatigue than the traditionally-used spatiotemporal gait features in a research setting. Further, our research is promoting digital measures for analyzing mobility dysfunction in PwMS and other balance-impaired populations. Also, our findings intend to encourage clinicians to use more objective measurements of fatigue and mobility impairments. The research team member, who presented this abstract at the conference, had been awarded an Educational Travel Grant by the ACTRIMS committee based on the scoring of our abstract.

Another impact this study is generating is in the area of home monitoring in PwMS. Dr. Horak, PI of the study, is assessing the benefits of continuous movement monitoring using wireless inertial sensors in the home settings in PwMS and comparing it to the gait metrics collected in the laboratory. It is believed that short walks in a research setting do not always reflect the actual functional mobility of patients in their everyday lives. In a research setting, people pay attention to their walking and tend to do their best, whereas in everyday life, people need to attend to other things while they walk, meaning that their automatic walking patterns are often more affected by their impairments. In addition, mobility can fluctuate over time due to many different factors, such as a patient's fatigue (as observed in our preliminary findings). Therefore, continuous monitoring of gait-related metrics on a daily basis could help to better assess the risk of falling in PwMS, allowing clinicians to gain insight into their patients both inside and outside of healthcare facilities. Our recent publication demonstrated the potential of passive monitoring of gait and turning in daily life in PwMS to identify those at future risk of falls.

What was the impact on society beyond science and technology?
Our team members attended the OHSU Brain Fair, an annual event held at the Oregon Museum of Science and Industry (OMSI). The fair is open to the public and people of all ages were present. Our research team members discussed issues around balance and gait in PwMS, performed demonstrations, and invited fair attendees to test their balance using our inertial sensors. Further, three high school students joined our research team as summer interns, which allowed them to learn about our study and complete an independent project which built their knowledge in MS, balance, and gait.

5. CHANGES/PROBLEMS:

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS: Publications, conference papers, and presentations

Journal publications.

Arpan I, Shah VV, McNames J, Harker G, Carlson-Kuhta P, Spain R, El-Gohary M, Mancini M, Horak FB. Fall Prediction Based on Instrumented Measures of Gait and Turning in Daily Life in People with Multiple Sclerosis. Sensors (Basel). 2022 Aug 9;22(16):5940. doi: 10.3390/s22165940. PMID: 36015700; PMCID: PMC9415310.

Shah VV, Curtze C, Sowalsky K, Arpan I, Mancini M, Carlson-Kuhta P, El-Gohary M, Horak FB, McNames J. Inertial Sensor Algorithm to Estimate Walk Distance. *Sensors*. 2022; 22(3):1077. https://doi.org/10.3390/s22031077

In preparation/under submission manuscripts:

1. Batista C, Penteado M Prewitt A, Mancini M, Horak F, Arpan I. Multiple Sclerosis-related subjective fatigue and alterations in functional connectivity of the brain.
2. Arpan I, Fino PC, Mancini M, Horak FB. Application of wearable inertial sensors to identify fall-risk predictors in people with multiple sclerosis.
3. Arpan I, Fino PC, Horak FB. Neuro-correlates of local dynamic stability in people with multiple sclerosis.

4. Arpan I, et al. Resting-state functional connectivity networks associated with motor fatigue in multiple sclerosis.

Books or other non-periodical, one-time publications.
Nothing to report

Other publications, conference papers and presentations.
Ishu Arpan, PhD, Vrutangkumar V Shah, PhD, Martina Mancini, PhD, Fay B Horak, PhD, Neurology, Oregon Health & Science University, Portland, OR. Feasibility of gait and turning measures in daily life for fall prediction in people with MS, Platform Presentation, ISPGR, Montreal, July 7, 2022.

Vrutangkumar V Shah, PhD, Fay B Horak, PhD and Ishu Arpan, PhD, Neurology, Oregon Health & Science University, Portland, OR. Best Combination of Gait Measures Discriminating Multiple Sclerosis from Healthy Controls Using Body-Worn Inertial Sensors, Whitaker Platform Series, 2021 CMSC Annual meeting, Orlando, Florida, October 25, 2021.

Amy Rude, Austin Prewitt, B.S., ATC, Fay Horak, PhD, PT, Ishu Arpan, PhD. Feasibility of Postural Sway Measures to Predict Falls in Multiple Sclerosis, ACTRIMS (virtual), February 25-27, 2021.

Prewitt A, McBarron G, Horak F, Arpan I. Muscle Fatigue In People With Multiple Sclerosis Impairs Standing Balance, ACTRIMS, Florida, February 27-29, 2020.

- **Website(s) or other Internet site(s)**

https://www.neurologylive.com/view/sway-test-differentiates-fallers-non-fallers-ms

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Nothing to report

- **Other Products**
  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Fay Horak
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	1-7704-5459
Nearest person month worked:	0.6
Contribution to Project:	Supervised and approved all study-related activities as discussed below.

Name: Ishu Arpan
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 1-7574-9591
Nearest person month worked: 0.5
Contribution to Project: Applied for the IRB amendments. Scheduled, screened, recruited, and tested study participants.

Name: Oscar Miranda Dominguez
Project Role: Collaborator
Researcher Identifier (e.g. ORCID ID): 2-3622-0166
Nearest person month worked: 0.2
Contribution to Project: Ensured quality of collected MRI data.

Name: Austin Prewitt
Project Role: Graduate student/ RA
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 0.5
Contribution to Project: Assisted in the scheduling, screening, and testing of study participants.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHART:
Add Quad Chart here (Appendices)

9. APPENDICES:

ACTRIMS 2021

Feasibility of Postural Sway Measures to Predict Falls in Multiple Sclerosis
Amy Rude, Austin Prewitt, B.S., ATC, Fay Horak, PhD, PT, Ishu Arpan, PhD

Background
People with multiple sclerosis (PwMS) are at a higher risk of falls since balance impairment is an early and common symptom in MS. Assessment of fall risk may be facilitated by measurements of postural sway, which reflects complex, sensorimotor, neural control of postural equilibrium that is affected by MS.

Objectives
To test whether the instrumented postural sway measures that differentiate PwMS from healthy controls (HC) also differentiate fallers from non-fallers with MS.

Methods
Twenty-two PwMS (age: 45 ± 10.16 yrs, EDSS < 4.5) and twenty age-matched HC (age: 41 ± 13.27 yrs) participated in an instrumented postural sway test. Participants were instructed to stand on a

firm surface for 30 seconds with eyes open wearing a wireless inertial sensor (Opal by APDM) on the lumbar spine. Participants in the MS group were categorized as fallers (n=11) or non-fallers (n=11) based on prior history of falls in the past 6 months. Independent t-tests were performed to determine which measures of instrumented postural sway differentiate healthy controls from PwMS. Then, the specific sway measures sensitive to MS were used to assess the mean differences between fallers and non-fallers in the MS group. The level of significance was set to $p<0.05$.

Results
PwMS performed significantly worse on the instrumented postural sway test compared to the healthy controls. Specifically, increased jerk (a measure of smoothness), range, and the root mean square (RMS) of sway were observed in the MS group. Importantly, these same postural sway abnormalities successfully differentiated fallers from non-fallers in the MS group. Compared to the non-fallers, sway measures (jerk, range and RMS) were significantly higher in PwMS who reported falls in the past six months.

Conclusion
A quick, simple instrumented postural sway test may be an important tool in identifying fallers in mild to moderately involved PwMS. The reported postural sway abnormalities indicate that PwMS, especially fallers, experience a significant decrease in postural stability reflected by increase size and jerkiness of sway. To better understand the pathophysiology of balance disorders in PwMS, future studies should relate abnormalities of postural sway to specific sensory, motor and cognitive impairments in PwMS.

Keyword:
Multiple Sclerosis, Instrumented Postural Sway, Falls, Biosensors

Muscle Fatigue in People with Multiple Sclerosis Impairs Standing Balance

Austin Prewitt, Grace McBarron, Sarah Chesley, Fay Horak, Ishu Arpan

Background
People with Multiple Sclerosis (PwMS) experience fatigue differently than those without MS due to axonal loss and demyelination[1, 2]. This fatigue may play a role in lack of balance control in PwMS. Poor balance control poses a serious health concern for PwMS, resulting in falls, limiting independence, and reducing quality of life.

Objectives
To test the effects of motor fatigue on static postural balance control and ambulatory gait in PwMS compared to healthy controls.

Methods
Eighteen PwMS and fifteen age-matched healthy control participants underwent a fatiguing protocol consisting of a sustained maximum voluntary contraction of plantarflexor (PF) muscles for one minute. PF muscles were chosen for the fatigue assessment as these muscles significantly contribute use of the ankle strategy to control standing posture. Standing balance data were collected immediately before and after implementing the fatiguing protocol using wearable sensors placed on the wrists, sternum, lumbar spine, and feet. Standing balance was measured for thirty seconds while standing with eyes-open on a firm surface and a foam surface.

Results
Increases in trunk sway during static postural sway tests were found in PwMS after the fatiguing task but not in healthy control subjects. Specifically, PwMS showed the greatest changes in trunk range of motion, velocity, jerk and the root mean square of the sway angle in the coronal plane after the fatiguing protocol ($p<0.05$), while healthy controls did not show any change.

Conclusion
The increase in trunk sway during quiet stance in PwMS after fatigue of ankle PF are consistent with impaired control of postural sway. This increase in trunk sway also indicates decreased use of the ankle strategy and increased use of the hip strategy to control stance posture, secondary to impaired posture sway control. This type of "truncal ataxia" in PwMS may reflect a shift to use of hip torque, rather than fatigued ankle torque, to control standing balance. Ensuing studies will investigate the effects of PF fatigue on balance control during gait and investigate neural correlates of fatigue in MS.

Keyword: Fatigue

Citations

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sensors

MDPI

Article

Inertial Sensor Algorithm to Estimate Walk Distance

Vrutangkumar V. Shah [1,*], Carolin Curtze [2], Kristen Sowalsky [3], Ishu Arpan [1], Martina Mancini [1], Patricia Carlson-Kuhta [1], Mahmoud El-Gohary [3], Fay B. Horak [1,3] and James McNames [3,4]

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Abstract: The "total distance walked" obtained during a standardized walking test is an integral component of physical fitness and health status tracking in a range of consumer and clinical applications. Wearable inertial sensors offer the advantages of providing accurate, objective, and reliable measures of gait while streamlining walk test administration. The aim of this study was to develop an inertial sensor-based algorithm to estimate the total distance walked using older subjects with impaired fasting glucose (Study I), and to test the generalizability of the proposed algorithm in patients with Multiple Sclerosis (Study II). All subjects wore two inertial sensors (Opals by Clario-APDM Wearable Technologies) on their feet. The walking distance algorithm was developed based on 108 older adults in Study I performing a 400 m walk test along a 20 m straight walkway. The validity of the algorithm was tested using a 6-minute walk test (6MWT) in two sub-studies of Study II with different lengths of a walkway, 15 m (Study II-A, n = 24) and 20 m (Study II-B, n = 22), respectively. The start and turn around points were marked with lines on the floor while smaller horizontal lines placed every 1 m served to calculate the manual distance walked (ground truth). The proposed algorithm calculates the forward distance traveled during each step as the change in the horizontal position from each foot-flat period to the subsequent foot-flat period. The total distance walked is then computed as the sum of walk distances for each stride, including turns. The proposed algorithm achieved an average absolute error rate of 1.92% with respect to a fixed 400 m distance for Study I. The same algorithm achieved an absolute error rate of 4.17% and 3.21% with respect to an averaged manual distance for 6MWT in Study II-A and Study II-B, respectively. These results demonstrate the potential of an inertial sensor-based algorithm to estimate a total distance walked with good accuracy with respect to the manual, clinical standard. Further work is needed to test the generalizability of the proposed algorithm with different administrators and populations, as well as larger diverse cohorts.

Keywords: 6MWT; inertial sensors; neurological disorders; 400 m walk test; 6MWD

Citation: Shah, V.V.; Curtze, C.; Sowalsky, K.; Arpan, I.; Mancini, M.; Carlson-Kuhta, P.; El-Gohary, M.; Horak, F.B.; McNames, J. Inertial Sensor Algorithm to Estimate Walk Distance. *Sensors* **2022**, *22*, 1077. https://doi.org/10.3390/s22031077

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1. Introduction

Walking is one of the most common and important daily activities for functional independence. Walking abnormalities are prevalent in elderly people and people with neurological disorders, leading to an elevated risk of falls and reduced quality of life [1–3]. Clinically, walking tests are widely used as standard assessments to identify and track impaired walking ability. Walking tests are usually performed either over a fixed time or over a fixed distance. Among the many measures used to quantify walking abnormalities like gait speed [4], the total distance walked is one of the most common measures to assess functional independence [5].

The six-minute walk test (6MWT) assesses distance walked over 6 min and is the most established outcome measure of aerobic capacity in clinical trials [5–7]. The 6MWT is an objective tool that is traditionally used in clinics to assess functional capacity in chronic obstructive pulmonary disease and congestive heart failure [6–8]. In addition, the 6MWT has been commonly used as a functional test of aerobic capacity and endurance [7–10], to monitor disease state [11], and to investigate an effect of an intervention [12]. The primary measure of a 6MWT is the 6-minute walk distance (6MWD), the total distance covered in 6 mins. The 6MWD is reduced by several types of diseases, including obstructive lung disease, heart failure, arthritis, neuromuscular disease, frailty, multiple sclerosis, and neurological disorders [13,14].

Although the 6MWT is easy to perform, it has some practical limitations. To start with, it is typically administered by trained personnel in a clinical setting. The test requires a dedicated corridor in a clinic, of length between 30 m and 50 m, and no shorter than 15 m^5. It does not consider the time it takes to turn, which could greatly influence the score, particularly with shorter laps and in neurological (like parkinsonism) or aging groups in which turning is specifically impaired. The test also requires an administrator to observe the test and note the distance, which, in turn, may lead to human error from a distance set-up mistake, error counting laps, or measuring the total distance improperly. Finally, patients need to visit the clinic where the test is performed, and hence the 6MWT is performed infrequently.

Recently, the use of wearable inertial sensors has made it possible to quantify mobility in the clinic and during daily life [15–21]. Wearable inertial sensors may be used to easily and accurately measure the total walking distance during a prescribed task. There is also the potential for collecting the 6MWT remotely in everyday settings; this has the benefit of a participant not having to be in a clinic/lab for testing and allows a prescribed walking test to be administered more frequently. Additionally, wearable inertial sensors show a potential to provide continuous monitoring of multiple and perhaps more sensitive variables of walking, which enables trends to be identified, making it easier to distinguish when health is deteriorating [22]. Furthermore, wearable sensors provide an opportunity to scale up multi-center clinical trials without an additional burden on clinical sites. Although there are many advantages of wearable inertial sensors, the adaptation in clinical settings is still limited due to lack of regulatory, ethical, infrastructure, training and standardization in data collection and analysis, and security challenges. As a first step to improve the standard clinical 6MWT, we present an objective, and validated algorithm for total distance walked from wearable sensors on the feet.

Various studies have used wearable sensors placed at different body parts to estimate the total distance walked during a walking test [23–35]. However, all of the commercial/custom algorithms used in these studies either require a priori information (age, height, weight) or calibration data to calculate the total distance walked. Furthermore, only one research group validated their proposed algorithm to calculate the total distance walked on independent cohorts with different protocols [28]. To overcome these limitations, here we present an objective, and validated algorithm for total distance walked from feet sensors that does not depend on anthropometric information or calibration to calculate the total distance walked. The main contribution of this study is to show how these zero-velocity (foot-flat) periods can be used to estimate the horizontal distance traveled and to provide an assessment of how well this matches the straight-line distance typically used as the reference measure in clinical studies. Specifically, we tested the validity and generalizability of our proposed distance-walked algorithm in two independent cohorts (see Study II). Study I (n = 108) with a fixed distance walk test (400 m) in subjects over 65-years-old was used to develop the algorithm, while Study II with a fixed time walk test (6MWT) was used to validate and test the generalizability of the proposed algorithm in patients with multiple sclerosis. Study II had two sub-studies with different lengths of walkways, 15 m (Study II-A, n = 24) and 20 m (Study II-B, n = 22), respectively.

2. Methods

2.1. Participants

Study I: 400 m fast walk with 20 m walkway (Algorithm Development Dataset). Older adults with impaired fasting glucose (IFG) were recruited on a convenience basis from the Portland VA Healthcare System (PORVAHCS). Inclusion criteria were: (a) ambulatory adults ≥65 years old with IFG, (b) sedentary, (c) weight-stable, (d) no walking aides, (e) no neurological conditions. Laboratory assessment was performed for fasting glucose to identify participants with IFG (100 mg/dL ≤ fasting glucose < 126 mg/dL). Exclusion criteria for Study I were medical conditions that are relative contraindications to metformin, increase the risk of major bleeding with muscle biopsies and affect muscle mass or performance measurements. The experimental protocol for Study I was approved by the Institutional Review Board of the PORVAHCS (#8860). All the participants provided informed written consent.

Impaired fasting glucose (>100 mg/dL) can be a precursor to diabetes mellitus (>126 mg/dL), which is associated with peripheral neuropathy, retinopathy, and peripheral artery disease that can impair gait at the time of diagnosis of diabetes. However, the population-based, Rotterdam study on 3019 adults showed that people with elevated fasting glucose had normal gait characteristics unlike those with diabetes, who had abnormal gait characteristics, so they can be considered an elderly control group [36].

Study II (A and B): A 6MWT with a 15 m Walkway (Algorithm Validation Dataset A) and a 20 m Walkway (Algorithm Validation Dataset B). As the objective of this study was to test the generalizability of the proposed algorithm, in addition to a fixed distance protocol (Study I: 400 m fast walk), we have included two sub studies (Study II: A and B) of a fixed time protocol (6MWT) with different walkway length.

People with Multiple Sclerosis (PwMS) and age-matched healthy controls (HC) were recruited on a convenience basis from the Oregon Health & Science University—MS Clinic and the local community. Inclusion and exclusion criteria were the same for both substudies of Study II (A and B). Inclusion criteria were ages 18–65 years, an absence of any orthopedic or neurologic problems other than Multiple Sclerosis (MS), and the ability to walk for 6 min without an assistive device. Exclusion criteria were MS exacerbation or the use of corticosteroids within 30 days of screening. Participants were instructed not to take caffeine in the morning of the testing and all testing was done between 10 am to noon. Additionally, PwMS were told not to take fatigue-related medication for 24 h before testing. The experimental protocol for Study II (A and B) was approved by the Institute Review Board of the Oregon Health & Science University (#15568 and #18714). All the participants provided informed written consent.

All the participants in both the studies (study I and II) gave written informed consent in accordance with the Declaration of Helsinki.

2.2. Data Collection

Inertial sensor placement for all studies. The subjects wore six inertial sensors (Opals by Clario—APDM Wearable Technologies, Portland, OR, USA) that included triaxial accelerometers, gyroscopes, and magnetometers. The sensor data were sampled at 128 Hz. The sensors were attached to the dorsum of both feet (Figure 1), wrists, sternum, and lumbar area. Only sensor data from the feet were used in this analysis.

Protocol for Study I (400 m walk test). Cones were placed on the floor 20 m apart and participants were instructed to walk 10 laps as fast as possible, making clockwise turns around the cones. The 400 m distance is considered a ground truth to compare the results with the total distance walked from the proposed algorithm.

Protocol for Study II (6MWT). Participants were instructed to complete the 6MWT at their fastest speed, aiming to cover as much distance as possible [37] by walking back-and-forth along a 15 m straight walkway (for Study II-A) and along a 20 m straight walkway (for Study II-B). The walkway had a start line, placed horizontally on the floor at the beginning, with smaller horizontal lines placed every 1 m to calculate a total distance walk. The

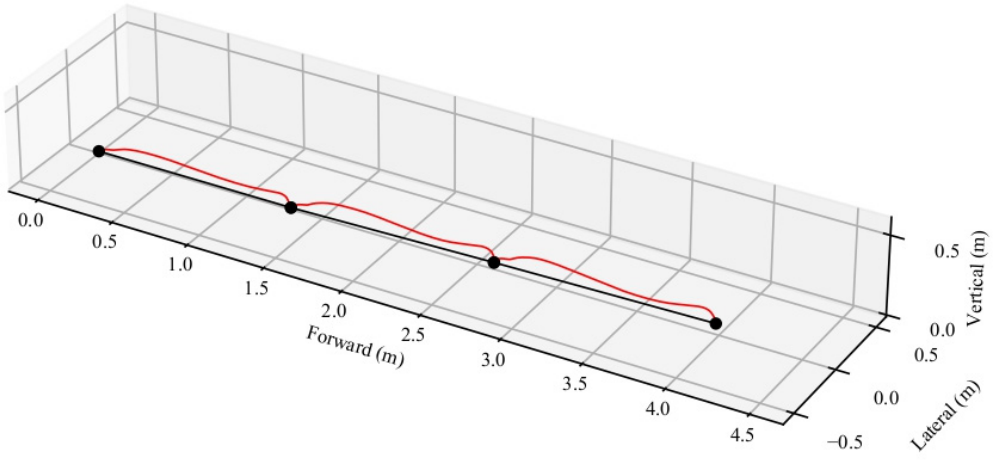
manually calculated total distance walked using a tape measure is considered a ground truth to compare the results with the total distance walked from the proposed algorithm.

Figure 1. Inertial sensor (Opal) placement on the foot dorsum.

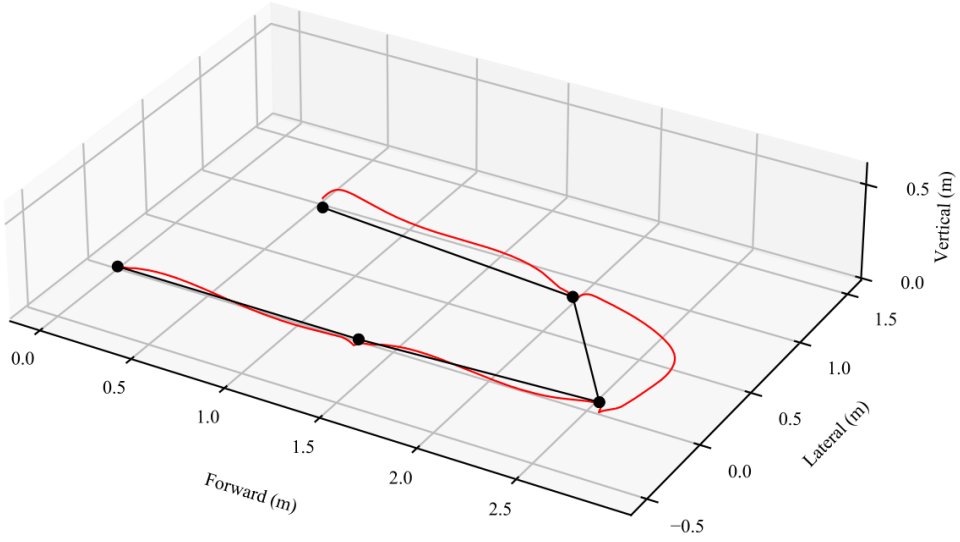
2.3. Total Distance Walked Algorithm

We used APDM's Mobility Lab algorithms that have been validated previously [38,39] to estimate the entire, three-dimensional trajectory of the foot, including its orientation in space. This is determined by first estimating the orientation of the sensors by fusing the rotational rate estimated by the gyroscopes with the gravitational component exhibited in the accelerometers using well-known methods [40–42]. This orientation can be used to express the accelerometer signals in an Earth reference frame so that the acceleration due to gravity can simply be subtracted. Estimates of the velocity and position can then be obtained directly by numerical integration, though any error in the acceleration estimates accumulates rapidly during this process. To help reduce this effect, the algorithm detects periods when the foot is in contact with the ground and the velocity of the sensors is known to be zero to update the velocity estimates. This approach is well known for using zero-velocity updates [40,42]. Once the spatial-temporal trajectories are known, we implemented further calculations to determine the horizontal distance traveled [43,44]. We calculated the forward distance traveled during each step as the change in the horizontal position from each foot-flat period to the subsequent foot-flat period. Specifically, let $\mathrm{v(t)} = [\mathrm{x(t)},\ \mathrm{y(t)},\ \mathrm{z(t)}]^T$ be a three-dimensional vector with the spatial coordinates in an Earth reference frame at each time t. In this coordinate frame, the last element of the vector represents the vertical axis based on the gravity vector determined from the accelerometer. If the foot is flat and still at time t_i during one zero-velocity period, and after the step the foot is flat and still again at another time t_{i+1}, then the horizontal distance traveled between these two points is calculated as $d_i = \sqrt{(x(t_{i+1}) - x(t_i))^2 + (y(t_{i+1}) - y(t_i))^2}$. The total horizontal distance traveled is then calculated as $d_{total} = \sum_{i=1}^{i=N-1} d_i$ where N is the number of periods when the foot was flat on the ground. Figure 2 illustrates the calculation of the total distance walked during a straight walk and turn while walking. The black dots show the position of one foot during the foot flat periods, the red trace shows the three-dimensional trajectory of the foot during each stride, and the black line segments show the forward, horizontal distance traveled during each of the three steps. The total walk distance calculation is performed separately for each foot. We report the final total walk distance as the average of the total walk distances estimated for each foot. The proposed algorithm only uses feet sensors to calculate the total distance walked. Another way to estimate the horizontal distance traveled is to calculate the velocity magnitude in the horizontal plane and then integrate it [45]. However, this will include the total curvature of

the foot trajectories between steps, which is larger than the straight-line distance used in current clinical assessments. This is also longer than the horizontal movement of the center of mass of the body which does not follow a horizontal path with as much curvature as the feet.



(**a**)



(**b**)

Figure 2. Example of walk trajectory used to calculate the total distance walked on a straight path (**a**) and with addition of a turn (**b**). The black dots show the position of the foot during the foot flat periods, the red trace shows the three-dimensional trajectory of the foot during each stride, and the black line segments show the horizontal distance traveled during each of the three strides. The total walk distance is then simply computed as the sum of walk distances for each stride.

2.4. Statistical Analysis

Study I. To investigate the percentage error in estimating the distance, we first subtracted the distance estimated by the proposed algorithm from a fixed distance of 400 m and then normalized it to 400 m to calculate the percentage error.

Study II. To investigate an error between a manually determined distance and a digital distance estimated by the proposed algorithm, we used an average absolute error rate ($100 * | \text{Distance}_{\text{manual}} - \text{Distance}_{\text{digital}} |_{\text{average}} / \text{Distance}_{\text{manual\_average}}$). Here, $\text{Distance}_{\text{manual}}$ is referring to the manually calculated total distance walked using a measurement tape

and $Distance_{digital}$ is referring to the objectively calculated total distance walked using the proposed algorithm. The agreement between the manually determined distance and the digital distance estimated by the proposed algorithm was also investigated using the Bland and Altman method [46], and the intraclass correlation coefficient (ICC), specifically ICC (2,1) [47]. All statistical analysis was performed using R Studio IDE Version 1.2.5019 software.

3. Results

Study I. A total of 108 older adults (age = 71.20 ± 5.11 years; height = 176.86 ± 6.43 cm, weight = 93.32 ± 14.73 kg) participated in this study. The proposed algorithm showed an average absolute error rate of 1.92%, resulting in a slight underestimation from 400 m. The mean (SD) absolute error between the digital (algorithm) and 400 m walking protocol distance was 7.68 m (SD = 5.45 m; min = 0.18 m; max = 28.81 m). Figure 3 shows the histogram of the true error ($distance_{digital}$—400 m) for all subjects.

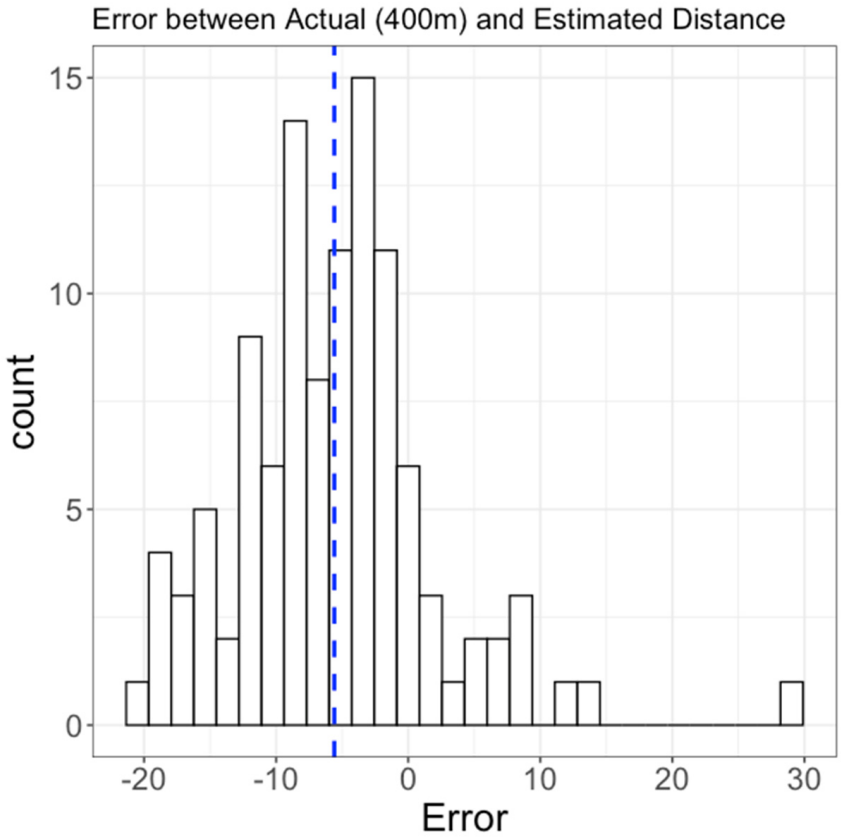


Figure 3. Histogram of error between 400 m and a total distance walked estimated by the proposed algorithm in 108 older adults (Study I). Vertical dashed line represents a mean of the histogram.

Study II-A. A total of 24 subjects (20 PwMS and 4 HC) participated in this study. The proposed algorithm showed an average absolute error rate of 4.17% with respect to an average manual distance, resulting in an overestimation compared to the manual distance. The average absolute distance error between the digital and manual distance was 19.77 m (SD = 14.40 m; min = 1.80 m; max = 64.24 m) for 6MWT over an average manual distance of 474.42 ± 97.31 m. Further, the agreement between walk distance from the proposed algorithm versus manual distance was excellent ($ICC_{(2,1)}$ [95% CI] = 0.97 [0.91–0.99]), with a bias of −10.50 [−19.94–−1.05] m, and upper and lower limits of agreement (LOA) of −54.34 [−70.71–−37.97], and 33.35 [16.98–49.73], respectively (Figure 4A).

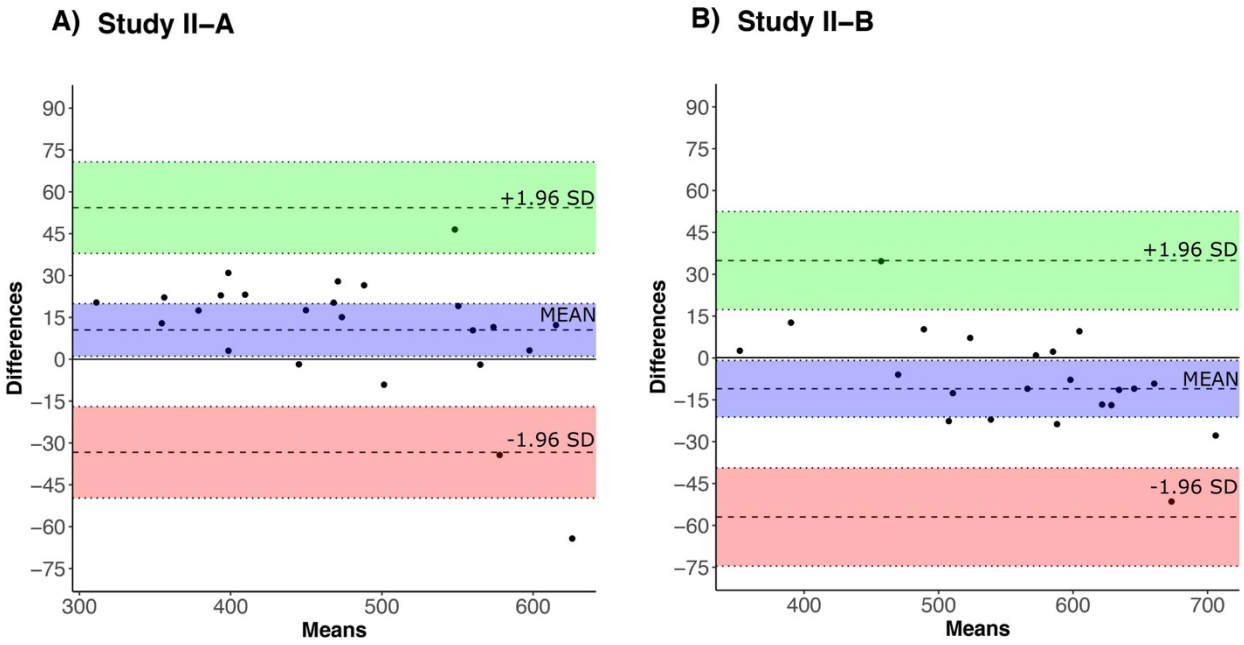


Figure 4. Bland-Altman plot for agreement between a manually calculated walk distance and walk distance estimates using the proposed algorithm for 6MWT in (**A**) Study II-A (15 m walkway distance) and (**B**) Study II-B (20 m walkway distance). Bias (mean), upper (+1.96 SD) and lower (−1.96 SD) limit agreement are represented by blue, green, and red colors, respectively.

Study II-B. A total of 22 subjects (9 PwMS and 13 HC) participated in this study. The proposed algorithm showed an average absolute error rate of 3.21% with respect to average manual distance resulting in a slight underestimation compared to the manual distance. The average absolute distance error between the digital (algorithm) and manual distance was 18.36 m (SD =18.79 m; min = 0.82 m; max = 83.85 m) for 6MWT over an average manual distance of 571.68 ± 103.24 m. Further, the agreement between walking distance from the proposed algorithm versus manual distance was excellent ($ICC_{(2,1)}$ [95% CI] = 0.97 [0.91–0.99]), with a bias of 11.16 [0.52–21.80] m, and upper and lower limits of agreement (LOA) of −35.87 [−54.34–−17.41], and 58.19 [39.73–76.65], respectively (Figure 4B).

4. Discussion

In this study, we tested the validity and generalizability of a new distance-walked algorithm using wearable sensors on the feet in two different cohorts. Study I (n = 108) with a fixed distance walk test (400 m) in subjects over 65-years-old was used to develop the algorithm, while Study II with a fixed time walk test (6MWT) was used to validate the proposed algorithm in patients with multiple sclerosis. Study II had two sub-studies with different lengths of walkways, 15 m (Study II-A, n = 24) and 20 m (Study II-B, n = 22), respectively. The proposed algorithm achieved an absolute error rate of 1.92% for Study I, 4.17% for Study II-A, and 3.21% for Study II-B.

Our proposed algorithm does not require any information about the subject's height, weight/age and does not need any calibration to calculate the total distance walked. In contrast, current commercial and custom algorithms rely on the availability of such information as a part of a calibration process [23–35]. Therefore, we believe this is a significant improvement.

400 m walk test. Our results for the 400 m walk test are more accurate and consistent with the findings in the literature. Specifically, one study investigated the accuracy of the total distance walked with pedometers for the 400 m-walk test [30]. From all of the ten pedometers, the minimum error was observed for Sportline 345 (SL345) with a mean ± SD error (not absolute) of 12 ± 8 m with respect to 400 m fixed distance. Comparing the results of SL345, our proposed algorithm showed an improvement in the accuracy with a

mean ± SD error of 6 ± 8 m. Both the pedometers and our proposed algorithm underestimated the total 400 m distance walked. Another study investigated the accuracy of the total distance walked during the 400 m-walk test with seven activity monitors [24]. Out of seven activity monitors, two overestimated the distance and the other five underestimated the 400 m distance. The authors reported a minimum error of 4.1 ± 8.1% for Fitbit Zip and Yamax CW-701 in contrast to our proposed algorithm that showed better accuracy (1.92%).

6-min walk test. Our results (average absolute error rate of 4.17% for Study II-A and 3.21% for Study II-B) are more accurate and consistent with the findings in the literature, albeit studies in the literature did not validate their algorithm in a separate cohort with a different protocol. Specifically, a recent study by Ata et al. [33] investigated the accuracy of the built-in iPhone distance-walked algorithm (with the iPhone placed in the hand) compared to the manually measured distance walked for the 6MWT in patients with peripheral artery disease. The authors found that the iPhone distance-walked algorithm overestimated distance with a bias of 43 ± 42%. In contrast, in the study by Juen et al. [35], the authors built a regression model from a smartphone and achieved an error of 5.87% for 6MWT. In a successive attempt, Juen et al. [34] further developed a machine learning model (using support vector machine algorithm) and achieved an error of 3.23% for 6MWT. To further improve the accuracy, Capela et al. [25] proposed an improved algorithm with a smartphone that achieved an average error of 0.12% for 6MWT. However, we recommend caution in interpreting the results as the authors used walkway length information to achieve this accuracy. Similarly, another study by Brooks et al. [28] developed a linear model of the distance-walked algorithm from smartphones and found an average error of 10%. Furthermore, when the same model was applied to two independent datasets, the authors found an average error of 10% (n = 33 in clinic) and 5% (n = 16 in home).

In Study II-B, we observed a single outlier where the calculated distance error was 83.85 m. This occurred in the subject who had the largest walk distance. Further investigation revealed that this was caused by the accelerations of the feet exceeding the bandwidth of the sensors, which was 48 Hz for the configured sample rate of 128 Hz. This was an unusual case because the subject was walking on a concrete floor, barefoot, at a rapid speed, with the sensors strapped firmly to the feet. The sensors were subjected to sharp acceleration impulses at the moments of foot strike and foot flat. This would not occur at the usual normal-paced walk, with more compliant flooring, or typical footwear designed to absorb this type of shock.

The average absolute error for Study II-A (15 m walkway) was 4.17%, and the average absolute error for Study II-B (20 m walkway) was 3.21%. On average, the algorithm slightly overestimated the distance in Study II-A and slightly underestimated the distance in Study II-B. We do not believe the bias was systematic, or that it was due to differences in the walkway distance. These are not large studies with hundreds of subjects, so it might just be due to the chance that one was overestimated and the other was underestimated. It might also relate to the length of the walkway and the effect of having some of the estimated distance include lateral distance during turns. However, the turns cannot be easily excluded because there are a variety of ways in which subjects approach a turn. For example, some subjects perform a pivot turn and rotate on the ball of their foot. Others will perform a broad turn in which they walk continuously in a semicircle without changing their pace. There is not an obvious, specific criterion that can be used to detect the beginning and completion of all turns to eliminate them from calculating the horizontal distance traveled from the sensors.

The proposed algorithm can be used even if the step detection algorithm produces false positives or false negatives. The algorithm calculates the distance traveled between stationary periods that correspond to the period when the foot is flat on the ground during the gait cycle. If a stationary period is not detected, the algorithm just calculates the distance traveled between stationary periods that are detected. This makes the algorithm insensitive to errors in step detection.

There are several limitations to the current study. First, our results were from a clinic test performed in the laboratory/controlled environment and should be repeated in an unsupervised environment. Second, we did not have the test-retest reliability of the total distance walked considering the participants' own fluctuations during a day. Third, we had only a single clinical site's data with three populations including patients with older adults with impaired fasting glucose, multiple sclerosis, and healthy control subjects. Future work is needed to validate the algorithm in a large multi-site clinical trial with test-retest reliability in different populations. Finally, the total distance traveled in turns may contribute to the errors in our studies, so one should be careful when comparing the results between studies with different walkway distances, which will necessarily change the number of turns included.

5. Conclusions

A novel algorithm was proposed to estimate the total distance walked using inertial sensors on feet. The walking distance algorithm was developed from 108 participants, and validated and tested for generalizability against different lengths of walkways in a total of 46 participants performing 6MWT. The results demonstrate the potential of an inertial sensor-based algorithm to estimate the total distance walked that can be used in a large clinical trial. Future work will validate the algorithm in remote settings with a large cohort of different populations.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Oregon Health & Science University (IRB #s: 18714, 10 May 2018; 8860, 12 March 2012).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: V.V.S., C.C., I.A., M.M. and P.C.-K. declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. The remaining authors declare the following financial interests/personal relationships, which may be considered potential competing interests: M.E.-G., F.B.H. and J.M. are employees of APDM Wearable Technologies—A Clario company, that may have a commercial interest in the results of this research and have a relationship with OHSU. Horak has also received honoraria from: British Columbia PT Association, Neuropore, Sanofi, Takeda, Adamas, Penn State University, University of Michigan, Stanford University, Johns Hopkins University. These potential conflicts of interest have been reviewed and managed by OHSU. K.S. is an employee of Clario—APDM Wearable Technologies.

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Fall Prediction Based on Instrumented Measures of Gait and Turning in Daily Life in People with Multiple Sclerosis

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Abstract: This study investigates the potential of passive monitoring of gait and turning in daily life in people with multiple sclerosis (PwMS) to identify those at future risk of falls. Seven days of passive monitoring of gait and turning were carried out in a pilot study of 26 PwMS in home settings using wearable inertial sensors. The retrospective fall history was collected at the baseline. After gait and turning data collection in daily life, PwMS were followed biweekly for a year and were classified as fallers if they experienced >1 fall. The ability of short-term passive monitoring of gait and turning, as well as retrospective fall history to predict future falls were compared using receiver operator curves and regression analysis. The history of retrospective falls was not identified as a significant predictor of future falls in this cohort (AUC = 0.62, $p = 0.32$). Among quantitative monitoring measures of gait and turning, the pitch at toe-off was the best predictor of falls (AUC = 0.86, $p < 0.01$). Fallers had a smaller pitch of their feet at toe-off, reflecting less plantarflexion during the push-off phase of walking, which can impact forward propulsion and swing initiation and can result in poor foot clearance and an increased metabolic cost of walking. In conclusion, our cohort of PwMS showed that objective monitoring of gait and turning in daily life can identify those at future risk of falls, and the pitch at toe-off was the single most influential predictor of future falls. Therefore, interventions aimed at improving the strength of plantarflexion muscles, range of motion, and increased proprioceptive input may benefit PwMS at future fall risk.

Keywords: home monitoring; instrumented gait and turning analysis; retrospective fall history; prospective falls; multiple sclerosis; pitch at toe-off

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1. Introduction

Multiple sclerosis leads to the disruption of neurological networks in the central nervous system, commonly affecting functions such as mobility, muscle strength, and coordination [1,2]. Impairments in any of these functions can contribute to the common occurrence of falling. A meta-analysis found that the prevalence of falls is about 56% in people with MS (PwMS), and around 37% of fallers are classified as frequent fallers [3–5]. Falling is a significant concern for PwMS due to an increased chance of injury and reduced physical and professional activities and societal participation [3,6]. Therefore, falls in MS are gaining increased attention in the scientific community, driving research on multivariate risk prediction models using prospective study designs to accurately predict and prevent future occurrences.

Impaired balance and gait are the most common causes of falls in PwMS [7–10]. Studies have shown that PwMS are more prone to falls during dynamic activities such as walking and turning, rendering quantitative investigation of balance dysfunction during walking and turning critical to identify fall-prone individuals. Wearable inertial sensors are sensitive

to early changes in balance control and can detect mobility dysfunction in PwMS earlier than conventional measures [11]. Furthermore, wearable technology can provide quantitative gait and turning assessments even in-home settings [12–16]. In PwMS, most falls are known to occur inside the home during general mobility without the execution of any other specific task. Hence, the investigation of gait and turning dysfunction in the home environment is crucial for our understanding of the environmental context of falls. Moreover, brief examinations of balance and gait in the clinic or research settings may not accurately reflect the actual functional mobility of patients in their everyday lives. Mobility can fluctuate due to many different factors, such as fatigue, medication, and environmental conditions, which are likely for a person with MS. Therefore, passive monitoring of mobility during daily life could help better assess the risk of falling in PwMS, allowing researchers and clinicians to gain insights about their patients both inside and outside of healthcare facilities.

While mobility dysfunction remains the center of investigation for future fall prediction and prevention studies, recent evidence suggests that clinical balance measures, in isolation, may be poor predictors of future fallers. A study by Cameron et al. advocates that a positive retrospective fall status of patients is the single most influential predictor of falls in PwMS [17]. Although this approach may seem simple, a downside of using fall history to predict fall risk is that it can only be implemented in those patients who have experienced at least one fall in the past, limiting its applicability in identifying those at risk of the first fall episode. Furthermore, the previous study only focused on clinical measures of disease severity, subjective balance, gait questionnaires, and a handful of objective clinical gait characteristics such as gait speed as predictors of future fallers in MS [17]. Therefore, multifactorial assessment including both fall history and quantitative measures of gait and turning in daily life may provide a better fall risk screening tool.

The objectives of this study were (1) to identify whether short-term passive monitoring of gait and turning (mobility) measures in daily life alone or in combination with a history of falls had the highest discriminative ability for predicting future fallers from non-fallers in PwMS, and (2) to assess the potential value of a multivariate prediction model that combined both subjective fall history and gait and turning measures in daily life in identifying those at risk of future falls.

2. Methods

This prospective cohort study was approved by the Institutional Review Board of Oregon Health & Science University. PwMS were recruited from the outpatient MS specialty clinics of the institution and surrounding community neurology clinics. The investigation was conducted according to the principles expressed in the Declaration of Helsinki, and written informed consent was obtained from the participants.

Inclusion criteria for the participants included: (1) confirmed diagnosis of relapsing-remitting or progressive MS, (2) mild-to-moderate MS-associated disability, (3) complaints about mobility, (4) capable of communicating with investigators and able to follow instructions, (5) able to walk independently without an assistive device, and (6) no other neurological or musculoskeletal disorder that could affect mobility other than MS.

Passive monitoring of gait and turning during daily life were assessed using the Opal instrumented socks (detailed description provided elsewhere [18]). This system enables continuous characterization of the quantity and quality of gait and turning during daily life activities using one Opal sensor on the waist and wireless inertial sensors embedded in the socks (prototype instrumented socks; APDM Wearable Technologies-A Clario Company, Portland, OR, USA; Figure 1). Each Opal sensor includes a tri-axial accelerometer, gyroscope, and magnetometer with a sampling rate of 128 Hz. The Opal is lightweight (22 g), has a battery life of 12 h, and includes 8 GB of storage and can record over 30 days of data.

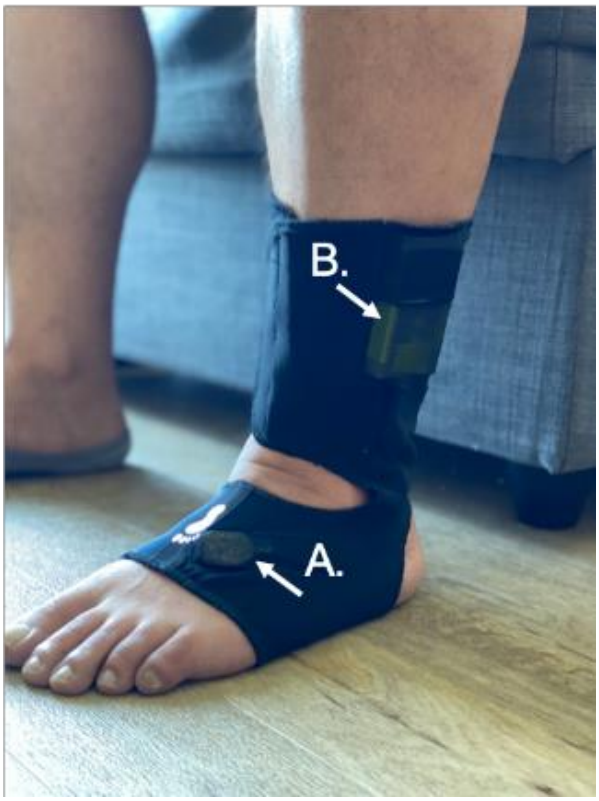

Figure 1. Participant wearing an instrumented sock, APDM prototype. The inertial sensor is located on top of the foot (**A**), and the main unit containing the battery in the socks is located in a second pocket just above the lateral malleolus (**B**). To maximize fit, the socks come in different sizes, and the Velcro attachment around the foot and ankle is adjustable to ensure a snug fit and that the sensor does not move on the foot while being worn.

During a baseline visit to the clinic, participants learned how to wear the instrumented socks on each foot and one Opal sensor over the lower lumbar area with an elastic belt for continuous monitoring of mobility. They were instructed to wear the sensors for at least 8 h/day and then take them off to charge each night for a week. Raw data were stored in the 8 GB internal memory of the sensors and uploaded to a secure cloud-based database server for analysis after being mailed back to investigators.

Gait and turning measures during daily life: The algorithms used for extracting spatial and temporal measures of gait and turning have been detailed previously [18]. Briefly, the daily life algorithm first searches for possible walking bouts and turns from inertial sensor data of the feet and lumbar using a time-domain approach. Potential walking bouts are defined as at least 3 consecutive steps, at least 3 s in duration, and the duration from one step to the next step is less than 2.5 s. Finally, each potential bout is processed with the commercial gait analysis algorithms included in Mobility Lab (APDM Wearable Technologies-A Clario Company [18,19]). To precisely estimate the orientation and position trajectory of each foot between quiet stance periods, we fused the information from the accelerometers and gyroscopes using the unscented Kalman filter. For the results reported in this paper, we only included stride pairs during periods of straight walking, and we excluded walking during turns. To detect and characterize each turn, we used the algorithm described in El-Gohary et al. 2013 [20]. Overall, 35 digital outcome measures of mobility were obtained as described previously [21]. Specifically, we had 9 measures of mobility for lower body, 4 instrumented measures for turning, and 3 measures of trunk (Supplementary Table S1). In addition to quantity measures of mobility, we had 3 measures of quality of gait characteristics in daily life. We also evaluated the variability of each measure from all the gait strides and turns (16 total variability measures) across the 7 days as the coefficient

of variation (CV) (standard deviation divided by the mean). The detailed description of the definition of mobility measure is given in Supplementary Table S1. For example, the pitch at toe-off is the plantar flexion angle of the foot relative to a level, horizontal surface at the time the foot leaves the floor at push-off during straight-ahead walking. With Opal sensors attached on top of the foot, the algorithms utilize the angular velocity of the foot to determine the change in angle from the time when the foot is flat to time the foot leaves the floor at push-off. The angular change from foot flat to time of toe-off, along with a kinematic model of the foot were used to estimate the pitch at toe-off.

Fall monitoring (retrospective and prospective): Participants were followed prospectively for a year for falls. Participants were instructed to make note of any falls and report the information during biweekly email surveys. A research assistant contacted participants (1) in cases of reported falls to find out the details or (2) if biweekly fall reports were not received. A fall was defined as "an event that results in coming to rest unintentionally on the ground or other lower-level" [22,23]. Subjects were classified as fallers if they had more than >1 fall in the 12-month period after home monitoring.

Statistical analysis: The Shapiro–Wilk test was used to test the normality of the data. Independent t-tests (or Mann–Whitney U-tests if not normally distributed) were used to compare between-group differences in fallers and non-fallers. Effect size was calculated using Cohen's d.

Fall prediction based on instrumented measures of mobility (Univariate Model): The area under the receiver operating characteristic (ROC) curve (AUC) was computed for each gait measure that discriminated fallers from non-fallers and ordered the measures from the highest to the lowest AUC value.

Fall prediction based on the history of falls (univariate model): The relationship between the history of falls and prospective falls was investigated using logistic regression analysis, and the AUC was computed.

Final prediction model based on fall history and daily mobility measures (multivariate model): Regression analysis was performed to identify the best prediction model for falls. The history of falls along with instrumented measures of mobility were used to generate the risk model for prospective falls.

3. Results

3.1. Demographics

Table 1 shows the demographic characteristics of non-fallers (n = 13; 11 females (F) and 2 males (M)) and fallers (n = 13; 10F and 3M). No significant differences between the non-faller and faller groups were observed in age, weight, height, disease duration, or Expanded Disability Status Scale (EDSS) (Table 1). Daily life mobility data were collected on average for 6 days (range: 2–8 days) for an average total duration of 52 h (range: 17–78 h). Notably, no differences were observed between the quantity of mobility measures among fallers and non-fallers (Table 1); only the quality of mobility measures discriminated PwMS at future fall risk from non-fallers, as described below.

3.2. Fall Prediction Based on Instrumented Measures of Mobility

On average, the fallers walked slower than non-fallers with smaller stride lengths and spent a significantly greater percentage of the gait cycle in double-limb support during walking (Table 2). Similarly, the percentage of swing phase during gait cycle was reduced in fallers (37%) compared to non-fallers (39%). In addition, fallers demonstrated a significantly smaller pitch angle (plantarflexion) of the foot at toe-off during walking and smaller turning angles compared to non-fallers (Table 2). The top instrumented measures of mobility discriminating fallers from non-fallers in PwMS were the pitch angle of the foot at toe-off, gait speed, stride length, swing (%), and double-support (%) (Table 3).

Table 1. Demographic features of the study population along with the quantity of mobility in daily life. Fallers were defined as people with MS who experienced more than 1 fall in the following year after their recruitment in the study.

		Faller/ Non-faller	N	Mean	Std. Error	*p* value
DEMOGRAPHIC FEATURES	Age (yrs)	Non-Fallers	13	49.2	2.4	0.1
		Fallers	13	49.1	3.5	
	EDSS (#)	Non-Fallers	13	4.3	0.23	0.8
		Fallers	13	4.2	0.18	
	Weight (lbs)	Non-Fallers	13	156.9	10.5	0.8
		Fallers	13	160.2	11.4	
	Height (cm)	Non-Fallers	13	170.2	2.2	1
		Fallers	13	170	3	
	Disease Duration (yrs)	Non-Fallers	13	13.8	2	0.4
		Fallers	13	16.8	2.9	
QUANTITY OF MOBILITY	Bouts/hour (#)	Non-Fallers	13	5.89	0.91	0.7
		Fallers	13	6.4	0.72	
	Strides/hour (#)	Non-Fallers	13	137.11	29	0.8
		Fallers	13	130.5	15.56	
	Turns/hour (#)	Non-Fallers	13	17.74	4.33	0.8
		Fallers	13	18.88	2.57	

Table 2. Differences among fallers and non-fallers in the instrumented gait and turning measures collected during the daily home monitoring.

Test Result Variable(s)		**N**	**Mean**	**Std. Error**	**95% Confidence Interval**		**Range**		***p* Value**	**Effect Size**
					Lower	**Upper**	**Min**	**Max**		**Cohen's d**
Pitch at Toe Off (°)	Non-Fallers	13	30.92	1.00	28.74	33.09	23.94	37.18	0.00	1.42
	Fallers	13	23.88	1.66	20.26	27.50	13.73	33.15		
Gait Speed (m/s)	Non-Fallers	13	1.08	0.03	1.01	1.16	0.90	1.26	0.01	1.05
	Fallers	13	0.89	0.06	0.76	1.03	0.40	1.31		
Stride Length (m)	Non-Fallers	13	1.22	0.03	1.15	1.30	1.00	1.41	0.01 [a]	0.99
	Fallers	13	1.06	0.06	0.93	1.18	0.68	1.40		
Double Support (%)	Non-Fallers	13	22.70	0.70	21.17	24.23	18.48	26.94	0.01	1.14
	Fallers	13	26.14	0.95	24.06	28.22	21.07	31.29		
Swing (%)	Non-Fallers	13	38.68	0.35	37.91	39.44	36.58	40.76	0.01	1.13
	Fallers	13	37.03	0.45	36.05	38.02	34.47	39.46		
Pitch at Initial Contact (°)	Non-Fallers	13	22.09	1.09	19.73	24.46	26.51	12.46	0.02 [a]	0.92
	Fallers	13	17.30	1.74	13.52	21.08	24.41	5.38		
Turn Angle (°)	Non-Fallers	12	88.79	1.40	85.71	91.87	79.03	95.58	0.04	0.87
	Fallers	13	82.55	2.43	77.25	87.86	63.36	97.65		

[a] The data for stride length and pitch at initial contact were not normally distributed. Therefore, the Mann–Whitney U-test was used to compare between-group differences between fallers and non-fallers.

Table 3. The area under the receiver operating characteristic (AUC) curves to classify the instrumented measures of mobility as predictors of future falls.

Test Result Variable (s)	Area	Std. Error [a]	Asymptotic Sig. [b]	95% Confidence Interval	
				Lower	Upper
Pitch at Toe Off (°)	0.85	0.080	0.003	0.690	1.000
Gait Speed (m/s)	0.78	0.096	0.017	0.595	0.969
Stride Length (m)	0.78	0.100	0.019	0.579	0.972
Double Support (%)	0.78	0.095	0.017	0.589	0.962
Swing (%)	0.78	0.094	0.017	0.598	0.966
Pitch at Initial Contact (°)	0.77	0.093	0.020	0.587	0.951
Turn Angle (°)	0.75	0.104	0.034	0.546	0.954

[a]. Under the nonparametric assumption. [b]. Null hypothesis: true area = 0.5.

3.3. Fall Prediction Based on the History of Falls

Retrospective fall status was not a significant predictor of prospective fall status in PwMS (AUC = 0.62, $p = 0.32$). The proportion of prospective fallers who did not have a history of falls in the past year was 46% (Figure 2).

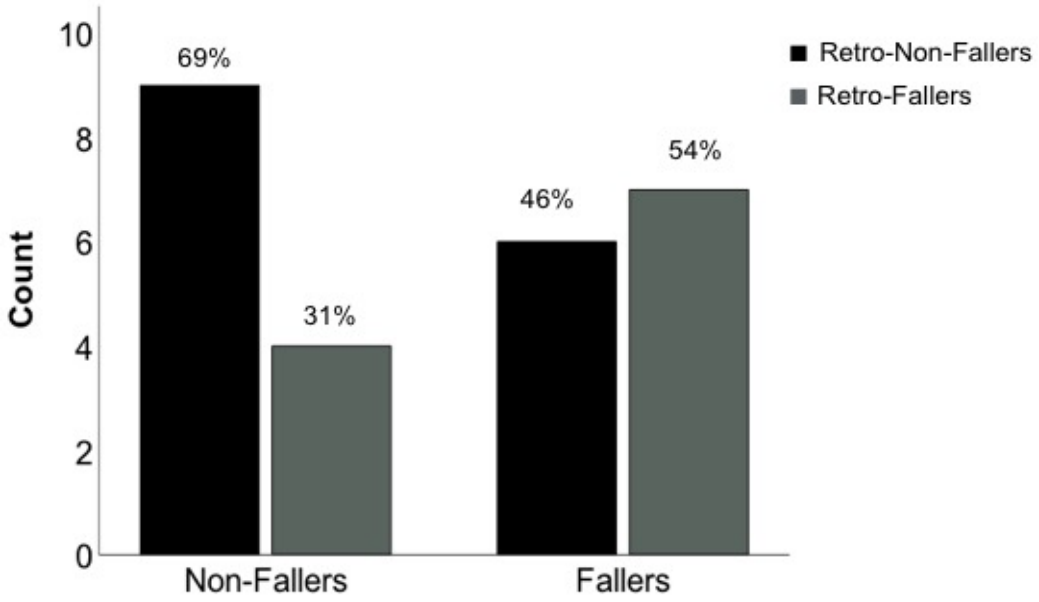

Figure 2. Percent of non-fallers and fallers predicted by retrospective fall history of 1 year.

Final prediction model based on fall history and daily mobility measures (multivariate model): When the instrumented gait measures discriminative of fallers from non-fallers (pitch at toe-off (°), gait speed (m/s), stride length (m), double-support (%), swing (%), pitch at initial contact (°), turn angle (°)) were entered along with the history of falls in the prediction model, a forward regression yielded a significant model consisting of only one gait variable, foot pitch at toe-off ($p < 0.01$). The discriminative ability of the final model to classify future fallers from non-fallers with the pitch at toe-off angle as a predictor was 86% (AUC = 0.86, $p < 0.002$, Figure 3).

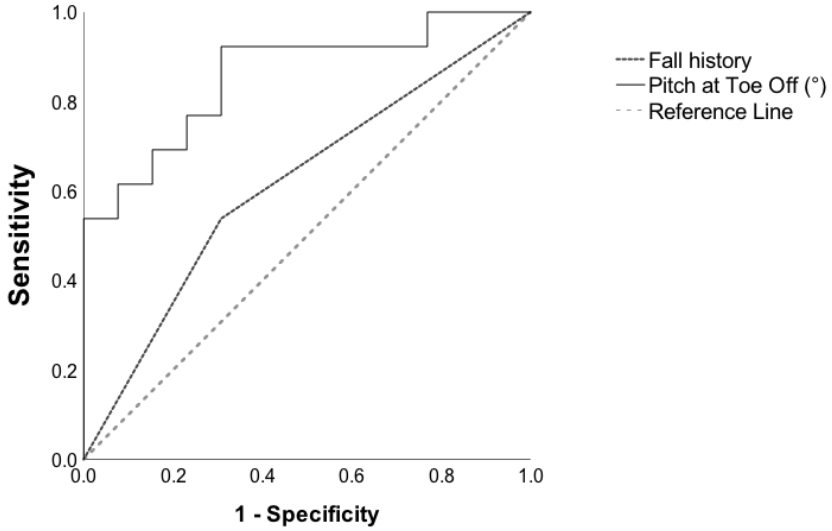

Figure 3. Receiver operating characteristic for fall history and pitch at toe-off angle to classify future fallers from non-fallers.

4. Discussion

The increasing use of wearable technologies in movement disorders is revolutionizing health care since it allows quantitative assessment of balance and gait disorders in supervised clinical, as well as unsupervised daily life environments [24,25]. To the best of our knowledge, this pilot study is the first longitudinal study investigating the future fall risk in PwMS based on instrumented gait and turning monitoring in daily life. Measures of both the quantity and quality of mobility in daily life were obtained; however, only quality of mobility discriminated fallers from non-fallers.

A key finding of the study was that the foot pitch at toe-off was the single most influential predictor of the future fall risk in our modest sample of PwMS. The pitch at toe-off is the angle of the foot as it leaves the floor at push-off during straight-ahead walking. In our study, fallers had a significantly smaller lower pitch at toe-off in comparison to non-fallers, reflecting reduced plantarflexion during the push-off phase of walking. In PwMS, the reduced plantarflexion can be attributed to either the weakness of the gastrocnemius–soleus muscles and/or decreased foot/ankle proprioceptive input during walking. Deficits in the ankle plantarflexion at the push-off phase of the gait cycle can reduce the forward propulsion of the body and swing initiation by the trailing leg, resulting in poor foot clearance during the swing phase and decreased walking speed [26–28]. Besides alterations in the gait cycle, there are both mechanical and energetic consequences of reduced ankle plantar flexion in human walking [27]. The decreased plantar flexion at toe-off can increase the mechanical loading borne by the leading leg at heel-strike and increase the metabolic cost of walking [26,27]. Therefore, fall prevention programs aimed at improving strength training of plantar flexor muscles, ankle range of motion, and increased proprioceptive feedback at the ankle may prove beneficial in improving the dynamic stability and metabolic cost of walking in PwMS.

In addition to the reduced pitch angle at toe-off, several alterations in the spatiotemporal features of gait were observed for PwMS at fall risk. Our results supported the evidence from previous studies that gait speed with a cut-off 1.0 m/s could represent a useful tool for identifying individuals who are at risk of falling [29]. At least 77% of fallers in this study had a gait speed of <1.0 m/s in their daily lives compared to only 31% of non-fallers. The reduced gait speed observed in fallers can be attributed to either plantar flexor deficits at toe-off (as discussed above) or to a cautious gait strategy adopted by fallers to maintain dynamic balance by walking slowly and taking shorter steps with more time in double-support [30–32].

The gait cycle can be divided into two primary phases: the stance and swing phases, which alternate for each lower limb. The initial contact of the foot with the ground marks the beginning of the stance phase. Fallers in this study demonstrated significantly lower pitch angles at the initial foot contact compared to non-fallers, reflecting reduced dorsiflexion at foot strike. This finding combined with the reduced PF during the push-off phase indicates that PwMS at fall-risk tend to shuffle [21,33] or drag their feet when they walk. In addition, we found that fallers spent a significantly greater percentage of the gait cycle in the stance phase, specifically double-limb support time. Since individuals at fall risk may have better control over their center of mass movement when both feet are in contact with the ground simultaneously, increasing the percentage of double-support period during walking may reflect a compensatory mechanism to stabilize the inefficient gait control. Importantly, similar alterations in gait patterns have been previously observed in elderly fallers versus non-fallers in clinical settings [31], supporting the idea that monitoring the deviations in these spatiotemporal variables of gait in daily life and/or clinical settings is crucial for distinguishing prospective fallers from non-fallers in community adults, as well as patient populations.

Besides alterations in gait patterns during straight walking, we also found significant differences in the turning angle among fallers and non-fallers in PwMS. Fallers had significantly smaller turning angles over the week of monitoring compared to non-fallers, indicating that fallers may avoid or find it difficult to control large turns. Alternatively, fallers may hesitate while turning such that hesitations >2 s would be counted as two, smaller turns. Overall, our findings demonstrate that only measures of the quality of gait were significant predictors of fall risk in PwMS, while the quantity of mobility was similar for fallers and non-fallers (Table 1).

Retrospective fall history was not a significant predictor of future falls in our cohort of PwMS, in contrast to the previous study [17]. This might be due to the small sample size of our study or the differences among methodologies to categorize fallers versus non-fallers across studies. We surveyed subjects via email every 2 weeks for their fall status, whereas most other studies had monthly fall diaries mailed, which increases the chance of missing falls.

The main limitation of our study is the small sample size, so it should be considered as pilot data for a larger study. However, the real-life mobility data collected from this study represent an important starting point to improve our knowledge on remote monitoring of gait in patients with MS. Second, we performed all mobility analyses by taking the mean of each measure for all the strides over a week for every participant and, thus, gave equal weight to each stride [21]. However, in reality, gait speed and other gait measures may vary among gait bouts of different lengths [16]. Hence, future studies are recommended to analyze the impact of bout length on each mobility measure and how gait bout length affects the discriminatory power of each mobility measure.

5. Conclusions

Our results demonstrated the potential of objective monitoring of gait and turning in daily life to identify those at the future risk of falls, even without a history of falls. Most of the gait impairments in fallers compared to non-fallers were consistent with a slower pace of gait as a decreased foot pitch angle at toe-off, slower gait speed, longer double-support time, and shorter stride length, and even smaller turn angles reflect a weaker or more cautious gait. Our finding of the decreased foot pitch angle at toe-off as a most critical predictor of falls may assist in future fall prevention by developing optimal interventions for this impairment, as well as by identifying PwMS in need of treatment to avoid falls.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/s22165940/s1, Table S1. Mobility measures and their definitions grouped by domains of mobility. Each domain is color-coded; Table S2. Instrumented gait and turning measures collected during the daily home monitoring that were not significantly different between fallers and non-fallers.

Author Contributions: Conceptualization, I.A., V.V.S., M.M. and F.B.H.; methodology, I.A., V.V.S., P.C.-K., M.M. and F.B.H.; software, J.M. and M.E.-G.; validation, J.M. and M.E.-G.; formal analysis, I.A.; investigation, I.A.,V.V.S., P.C.-K. and M.M.; resources, R.S., M.M. and F.B.H.; data curation, I.A., V.V.S., G.H., J.M. and M.E.-G.; writing, I.A; writing—review and editing, I.A., V.V.S., G.H., J.M., M.E.-G., M.M., R.S., P.C.-K. and F.B.H.; visualization, I.A. and M.M.; supervision, P.C.-K., M.M. and F.B.H.; project administration, G.H. and P.C.-K.; funding acquisition, I.A., M.M. and F.B.H. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Oregon Health & Science University ((#15578).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon request.

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Conflicts of Interest: I.A., G.H., M.M., R.S. and P.C.-K. declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. The remaining authors declare the following financial interests/personal relationships that may be considered potential competing interests: V.V.S., M.E.-G., F.B.H. and J.M. are employees of APDM Wearable Technologies—A Clario company, which may have a commercial interest in the results of this research and technology. This potential conflict has been reviewed and managed OHSU.

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Motor Fatigue in Multiple Sclerosis: Role of Central Mechanisms

Grant Number: MS170133
Award Number: W81XWH-18-1-0425

PI: Fay Horak **Org:** Oregon Health & Science University **Award Amount:** $230,995.00

Study/Product Aim(s)

The main objective of this proposal is to investigate the role of central mechanisms in motor fatigue and to unmask the neural network alterations underlying central fatigue in people with multiple sclerosis (PwMS).

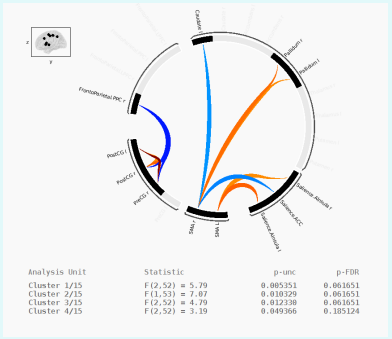
Specifically, we aim to 1a) Determine the role of central mechanisms in motor fatigue in PwMS. 1b) Determine the impact of motor fatigue on balance & gait. 2) Determine the neural correlates of central fatigue in PwMS.

Approach

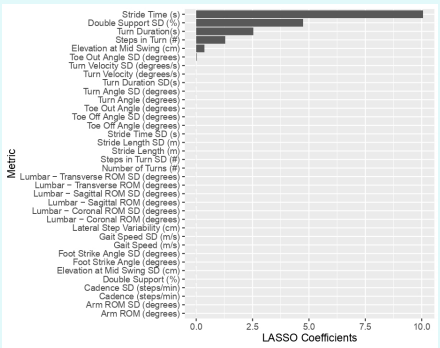
Aim 1: 30 PwMS & 30 healthy controls will participate in a fatiguing motor task involving a sustained contraction of plantarflexor (PF) muscles for 60 seconds. The interpolated twitch technique will be used to determine voluntary activation (VA) of the PF muscles. The decline in VA during task will provide an index of central fatigue. In addition to VA testing, subjects will participate in a standing task and a six minute walk test wearing six wireless intertial sensors (APDM Wearable Technologies, Portland, OR, USA) for objective assessment of balance and gait impairments.

Aim 2: Resting-state functional MRI (RS- fMRI) will be employed to investigate neural mechanisms underlying motor fatigue in PwMS

Neuroimaging



Balance & gait testing



Left panel illustrates strong functional connections between different ROIs and networks for the contrast MS-fatigue group > MS-Non-fatigued group. Blue line represents a strong negative connectivity and red lines represent strong positive connectivity. Right panel shows 6 gait measures (out of total 36 gait measures obtained from body-worn wireless inertial sensors) identified as best measures to differentiate MS from healthy controls.

Accomplishment: 1) People with MS (PwMS) had significantly higher decline in voluntary activation (measure of central fatigue) compared to healthy controls, 2) Significant changes in balance and gait were observed in PwMS after fatigue testing but not healthy controls, 3) Significant alterations cortico-striatal connectivity in resting state functional connectivity between fatigued vs non-fatigued PwMS.

Timeline and Cost

Activities CY	18-19	19-22
Major task 1: Launch Study Activities		
Major Task 2: Recruitment and Testing		
Major Task 3: Data Analysis & Publications		
Estimated Budget ($K)	$120,183	$110,812

Updated: Portland, OR; Dec 31, 2022

Goals/Milestones

CY18 Goal – Study set up and launch
- ☒ All IRB, finalize protocols, order and test all equipment
- ☒ HRPO approval

CY19-21 Goals – Subject recruitment and data collection
- ☒ Begin functional data collection and MRI data collection (Aims I and II)
- ☒ Submit IRB amendments, if needed
- ☒ Start functional (balance & gait as well as fatigue data) data analysis
- ☒ Start MRI data processing and movement correction

CY21-22 Goals – Complete all testing, analysis and dissemination of results
- ☒ Complete testing and Data Analysis
- ☒ Disseminate findings on mobility impairments
- ❑ Disseminate findings on neuroimaging

Budget Expenditure to Date
Projected Expenditure:$230,995
Actual Expenditure: $230,995