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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 Motor Fatigue, Postural Sway, Gait, Balance, Inertial Sensors, Neuroimaging, Falls					
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1. INTRODUCTION:

Approximately 70-90% of people with multiple sclerosis (PwMS) experience difficulties in initiating and/or sustaining physical activities (motor fatigue) during daily life. Though common, the mechanisms underlying motor fatigue are poorly understood. 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 for the design of treatment and rehabilitation programs. Motor fatigue, also referred to as 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 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.*

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Goals: To assess role of central mechanisms in motor fatigue & neuro-correlates of fatigue in MS

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 (80% complete)

Subtask 2: Data Collection and Management (80% complete)

Major Task 3: Data Analysis and Publications (76% 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 eligibility criteria, exclusion criteria and screening protocol (100% complete)
- Prepare screening and testing forms for subject database (100% complete)
- Create 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 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 class 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)

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 (Ongoing)
- Phone/Online screening of subjects (Ongoing)
- Phone Recruitment (Ongoing)

Subtask 2: Data collection and Management

- Schedule participants (82% complete).
- Complete MRI data collection @ AIRC, OHSU (80% complete)
- Fatigue data collection (following MRI) using Biodex Dynamometer (80% complete).
- Balance assessment during standing task (pre-and post-fatigue test) and during the fast six-minute walking test (6MWT) using APDM sensors (80% complete).
- Clinical data collection: Medical history, Sleep questionnaire, depression questionnaire, activity questionnaire, fall history and subjective fatigue questionnaires. Screen and verify data on server; check for accuracy (80% complete).

Major Task 3: Data Analysis and Publications

Subtask 1: Data Analysis

- Perform fatigue data analysis to evaluate an index of central fatigue (80% complete).
- Assess changes in balance control during standing pre-and post-fatigue and during the 6MWT from first to last minute (72% complete).
- Perform MRI data processing (72% complete), motion correction (72% complete), and functional connectivity analysis (0% complete).
- Assess neuro-correlates of fatigue (50% complete)
- Assess if the severity of central fatigue is correlated with functional connectivity among the cortico-striatal structures in the motor circuit of the basal ganglia (0% complete).
- Compare severity of central fatigue to the decline in the balance control (0% 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.
- Submit manuscript describing the predictors of falls in mild to moderately involved PwMS based on instrumented mobility measures (data analysis complete; manuscript to be submitted to Gait & Posture journal).
- Submit manuscript describing the fatigue protocol and preliminary findings (In preparation).
- Submit manuscript presenting findings on neuro-correlates on motor fatigue in MS. Processing of the neuroimaging data collected till date is complete.

Significant Results/ Key outcomes

The following summary of findings are preliminary and are subject to change on re-analysis with a complete dataset:

Demographics

There were no significant differences in age, weight and height between two groups in the study. The demographics data is provided in the Table 1 as mean $\pm$ standard error.

	Multiple Sclerosis (22)	Healthy Controls (20)
Age (yr)	44.7 $\pm$ 2.2	41.7 $\pm$ 3.0
F/M	17/5	13/7
Height (cm)	166.8 $\pm$ 2.3	168.0 $\pm$ 2.1
Weight (lbs)	165.7 $\pm$ 7.3	156.3 $\pm$ 6.5

Other subject characteristics

Sleep: Sleep was assessed was 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 the healthy controls, indicating poor sleep quality in PwMS.

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 levels of moderate-to vigorous physical activity. The total leisure activity scores were not significantly different between two groups. On average, participants in both MS and Healthy control groups fell in the “active” category in the basis of GLTEQ scale scoring (33.6 $\pm$ 4.6 vs 42.9 $\pm$ 4.2, $p=0.11$)

Mobility Impairments

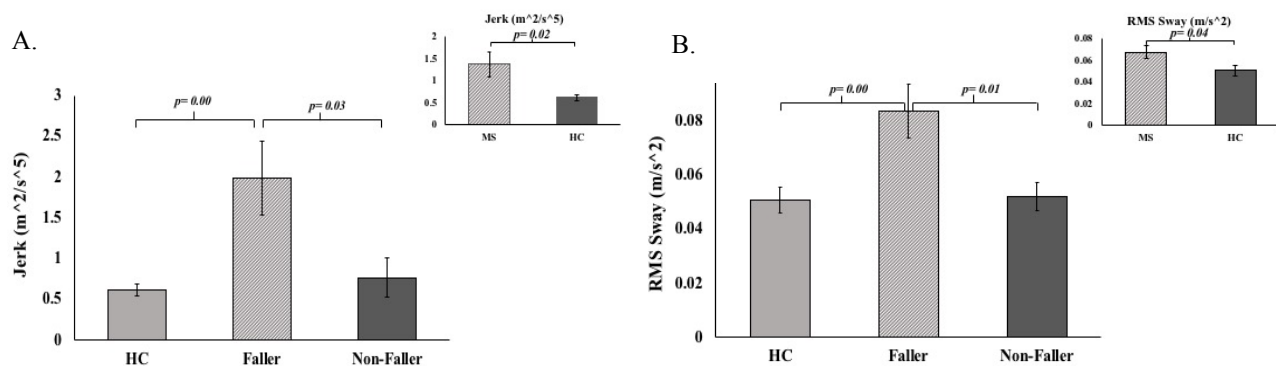
Instrumented Balance Testing: The main aim of this sub-study was to investigate if the instrumented postural sway measures that differentiate PwMS from healthy controls (HC) can characterize fallers in the MS group.

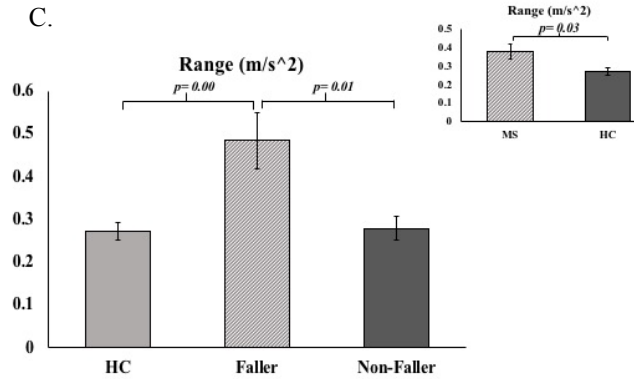
Methods: Twenty-two PwMS (age: 45 ± 10.16 yrs, EDSS < 4.5) and twenty age-matched HC (age: 41 ± 13.27 yrs) participated in an instrumented postural sway test. Participants were instructed to stand on a firm surface for 30 seconds with eyes open wearing a lumbar sensor (Opal, v1, APDM Inc., Portland Oregon). 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. 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 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 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 that requires active and frequent postural corrections. 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 transmitted raw data at 128 Hz wirelessly 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.

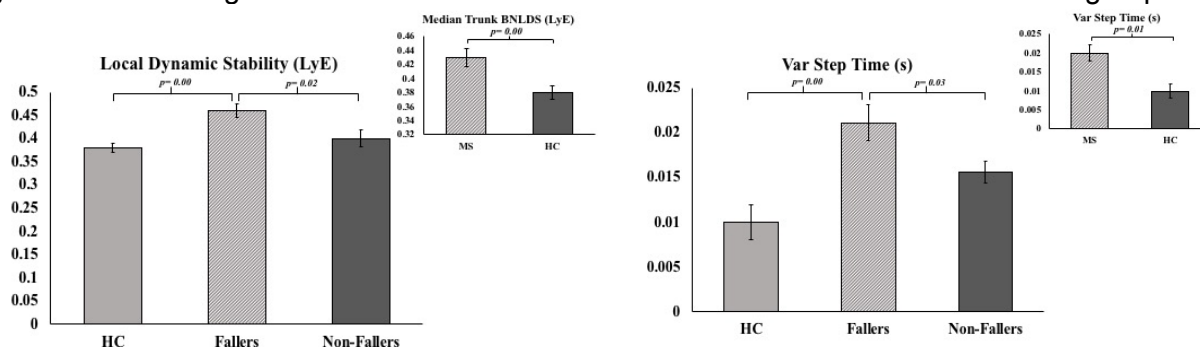
First, we investigated which gait measures were different between MS and healthy control groups (Step 1). Then, the distinct gait deviations identified from step 1 were used to discriminate fallers from non-fallers in the MS group. Participants in the MS group were categorized as fallers and non-fallers 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 2).

		Multiple Sclerosis (mean ± SE)	Healthy Controls (mean ± SE)	p value
Spatiotemporal	Gait Measures			
	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
Upper body Control	Toe off angle (degrees)	37.65 ± 0.97	40.94 ± 0.68	0.01
	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).

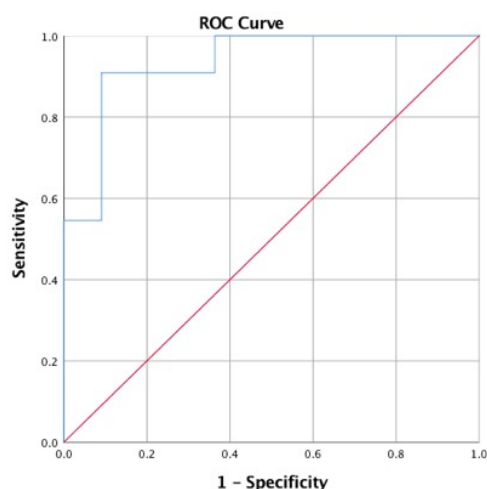
Fig. 2 Instrumented gait measures that discriminated fallers from non-fallers in the MS group.



- **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 that were significantly different between MS and healthy controls were classified as ‘potential fall predictors’ and carried into analysis. To determine the best independent predictors of falling, forward and backward step-wise regression models were implemented to determine the best combination of mobility variables that can predict fall frequency in PwMS.

Results: The final model was same regardless of forward or backward steps based on 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	
0.934	0.053	0.001	Lower Bound	Upper
Under the nonparametric				
Null hypothesis: true area = 0.5				

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

Background and Aim: Gait deficits in PwMS are poorly captured by stopwatch-timed tests or rating scales. 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 an excessive number of 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 HC subjects.

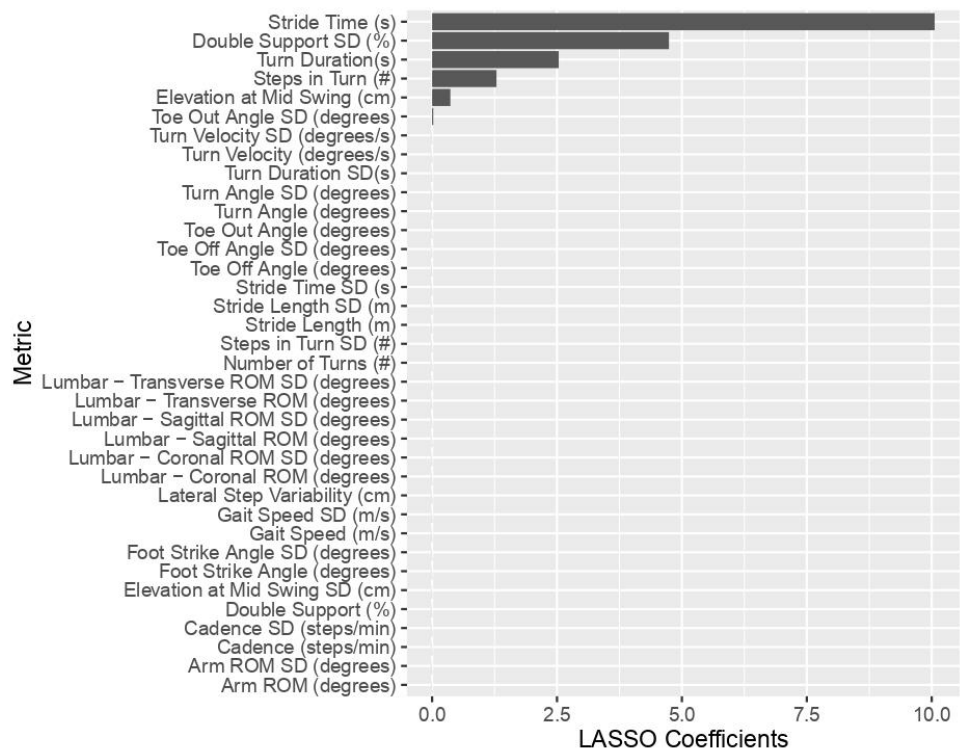
Methods: We used two datasets: Study I (funded by DOD grant) for development and validation, and Study II: for independent test of the proposed model. Participants were instructed to complete the 6-minute walk test at their fastest speed to cover as much distance as possible by walking back-and-forth 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 a totally 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 HC 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

- **Motor fatigue is significantly higher in PwMS:** The decline in force production during the sustained contraction task was 10% in healthy controls vs 42% in PwMS, indicating higher incidence of motor fatigue was higher in latter group.
- **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 fatigue of ankle plantarflexors 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 tempo-spatial measures of gait observed after fatigue testing but PwMS showed the greatest changes in 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 significant change in sway measures in MS group after fatiguing task.

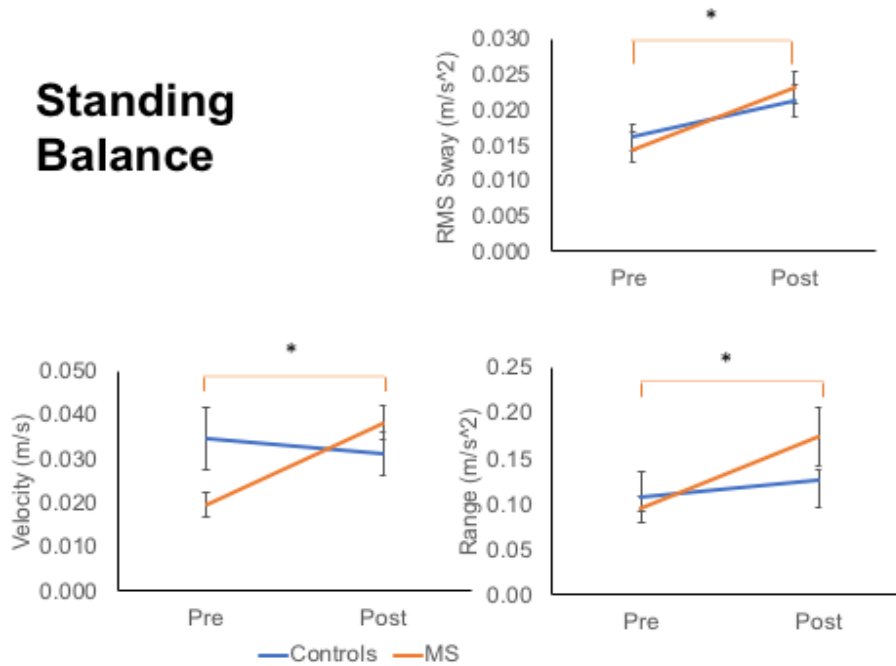


Fig. 6 Pre- and post-fatigue spatiotemporal measures of gait in healthy controls (blue) and PwMS (orange). * reflects significant change in spatiotemporal features of gait in MS group after fatiguing task.

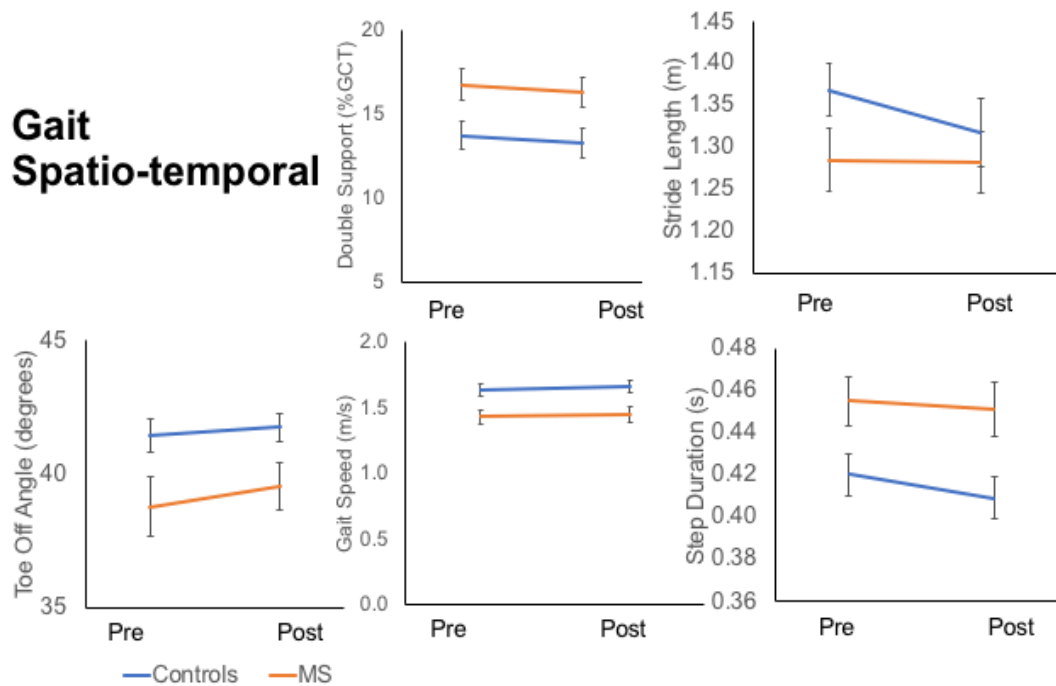
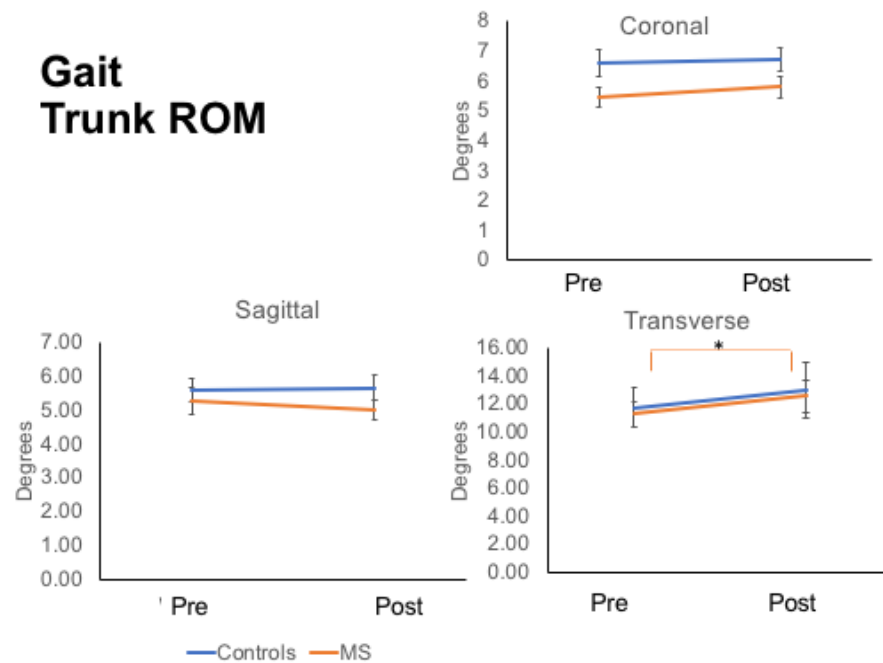


Fig. 7 Pre- and post-fatigue trunk ROM in healthy controls (blue) and PwMS (orange). * reflects significant change in trunk ROM while walking in MS group after fatiguing task.



Preliminary findings on neuro-correlates of fatigue

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 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 HC 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 (35 ROIs described at the end of report). The CONN' default atlas includes cortical and subcortical ROIs referred to the Harvard Oxford atlas (Desikan et al., 2006) and cerebellar ROIs based on the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). A non-parametric two-sided multivoxel pattern analysis (MVPA) test was used with p-corrected at the cluster level for $p < 0.05$.

Preliminary Results

Participants analyzed

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others. The modified fatigue impact scale (MFIS) questionnaire is the list of statements that describe the effects of fatigue in PwMS. We divided PwMS were divided into MS-fatigue (F) vs MS-no fatigue (NF) on basis of their subjective scores on the scale. For this preliminary analysis, 13 MS individuals with fatigue (MS-F group) and 10 individuals with MS and no fatigue (MS-NF group) were analyzed.

Contrast MS-F group > MS-NF group

Figure 8 shows that the ROI-to-ROI analysis detected significant connectivity between MS-F and MS-NF groups, as follow: i) a stronger negative connectivity ($F_{3,128}=6.35$, $P_{\text{FRD-corrected}}=0.009$) of the right and left SMA with the left caudate for the MS-F group compared with the MS-NF group; ii) a stronger positive connectivity ($F_{3,128}=5.22$, $P_{\text{FRD-corrected}}=0.019$) of the anterior cerebellar network with the left and right sensorimotor-lateral networks for the MS-F group compared with the MS-NF group; and iii) a stronger positive connectivity ($F_{3,128}=4.30$, $P_{\text{FRD-corrected}}=0.031$) of the right SMA with the left dorsal attention network for the MS-F group compared with the MS-NF group.

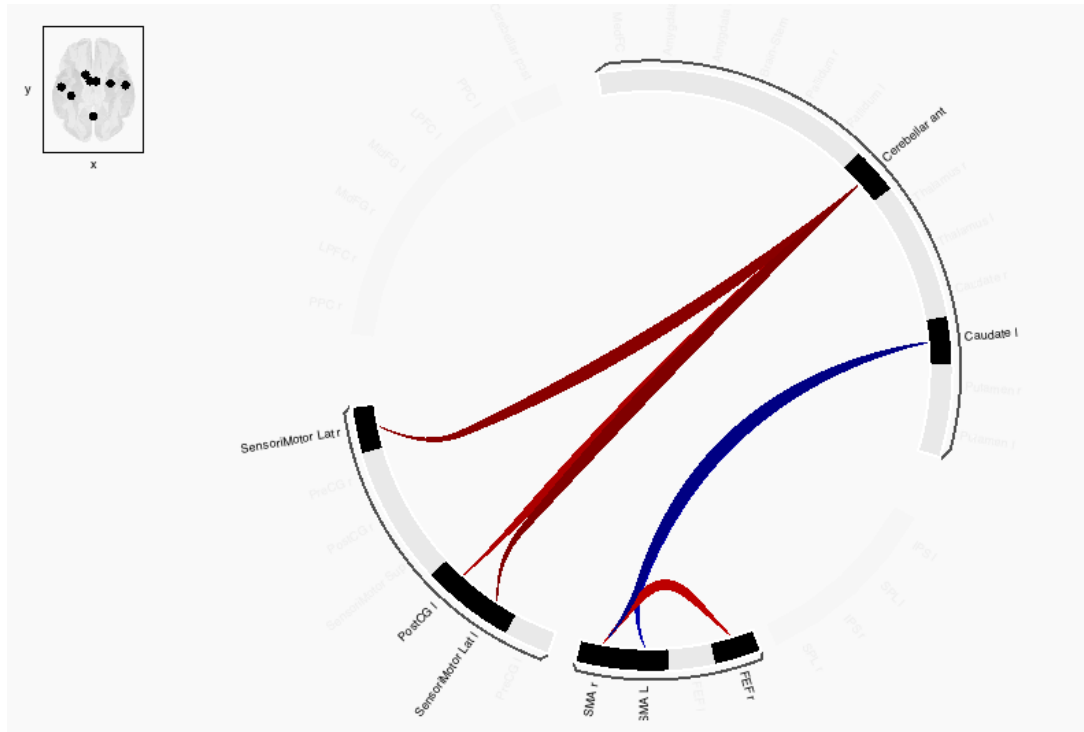
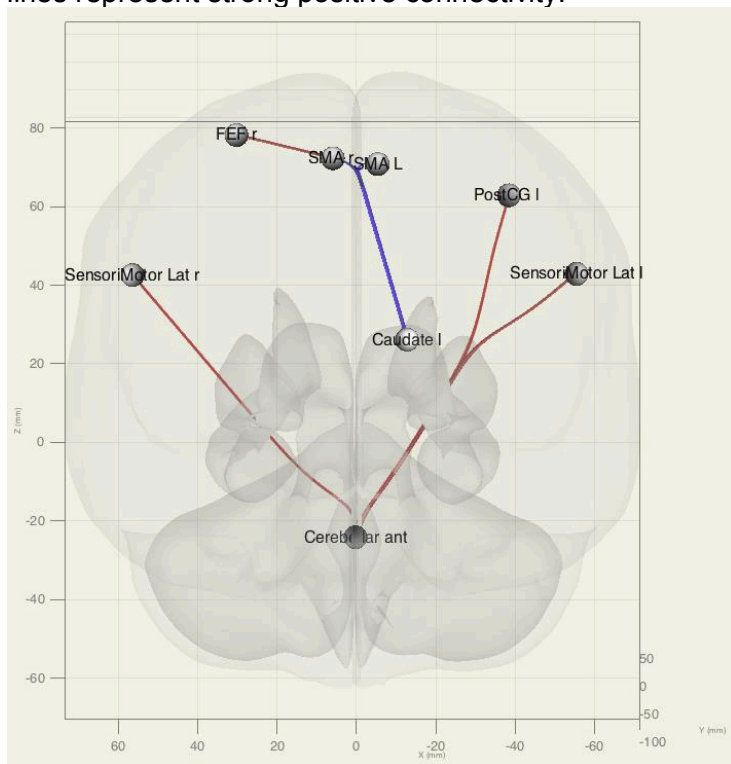


Figure 9 illustrates strong functional connections between different ROIs and networks for the contrast MS-F group > MS-NF group. Blue line represents a strong negative connectivity and red lines represent strong positive connectivity.



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

The members of research team have had the opportunity to present the preliminary findings from this project at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) meeting twice in order 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 who are dedicated to the treatment and research in MS and other demyelinating diseases. Here's an article highlighting our work:

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

We also submitted an abstract to the 2021 Annual Meeting of The Consortium of Multiple Sclerosis Centers (CMSC) in 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/or epidemiology of MS.

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; Digital 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 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)
- 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 recruitment and wrap up study in the next quarters. COVID-19 pandemic has impacted the conduct of human research studies at many levels due to a variety of challenges, such as quarantines, site closures, and travel limitations. At OHSU, we received an approval for our Return to Research plan at Level 2 (R2R) from the department of Neurology in late June 2019 and have made modifications since then (applied for R2R approval to the AIRC for MRI data collection and KCRB for functional data collection). The most recent modification was accepted 10/25/20. Under these provisions, our Balance Disorders Lab was allowed to resume some in-lab data collection with subjects at 2:1 ratio of research staff to participant in the following populations:

Low Risk Subjects (coming in at Level 2)

- Adult Healthy Controls

High Risk Subjects (not coming into lab until Level 1 operations)

- Healthy Older Adults (over the age of 65)
- Multiple Sclerosis Subjects

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 important 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. As we progress through the study, we hope that this project will yield a responsive new endpoint to measure the therapeutic response of medications/rehabilitation interventions targeting central fatigue with smaller, less expensive clinical trials. Further, the investigation of acute effects of motor fatigue on balance control is expanding our understanding of the potential risks of falls and injuries during daily activities in PwMS. Our preliminary results have shown that acute fatigue from one minute of sustained

contraction task impairs standing balance and gait in people with MS. If even a short-lived motor fatigue impairs balance in MS, it is essential for the rehabilitation therapists to make appropriate recommendations for safe and effective clinical rehabilitation practice as well as for fall prevention during activities of daily living.

What was the impact on other disciplines?

Our research team members have continued to meet once per month virtually (because of the Covid-19) with clinicians 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 are working closely with members of 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 primary impact on technology transfer is the submission of our preliminary findings to the ACTRIMS conference. ACTRIMS provides an annual forum for national and international experienced and newer clinicians and researchers to exchange information, debate current issues and discuss advances related to basic research and clinical issues in MS. We have this opportunity twice. Our first submission to the ACTRIMS was in the year 2019; the primary aim of that project was to help transfer knowledge to other researchers in the field in how trunk ROM may be a more sensitive measure of fatigue than the traditionally-used spatiotemporal features of gait in a research-setting and promote the use of this method for analyzing balance dysfunction in PwMS and other balance impaired populations (Appendices: Attachment 1). Also, our findings intended to encourage clinicians to use more objective measurements of fatigue and mobility impairments. The research team member, who presented this abstract was awarded an Educational Travel Grant by the ACTRIMS committee based on the scoring of our abstract.

We had other presentation at ACTRIMS 2021 was highlighted in Neurology Live (Appendices: Attachment 2).

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

The goal of this paper is to use the instrumented postural sway measures to characterize fallers in the MS group. Our findings show that the 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 that requires active and frequent postural corrections. 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.

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 monitoring of movement 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 about their patients both inside and outside of healthcare facilities. Based on these new results, we will focus on trunk control during daily life mobility to identify a sensitive measure of MS on daily life walking.

What was the impact on society beyond science and technology?

The members of our team attend 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. In past events, our team discussed issues around balance and gait in PwMS, performed demonstrations and invited fair attendees to test their balance using our inertial sensors. Further, since the beginning of the study, one high school student has joined our research team every summer as an internee, which provided them an opportunity to learn about our study. All students completed their independent projects related to this study, which built their knowledge in the area of MS, balance and gait.

5. CHANGES/PROBLEMS:

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

During Quarter 1-2, we encountered a delay in started study-related activities (i.e. screening, recruitment, testing final protocol etc.) due to pending HRPO approval. As a result of this delay, we are behind in some subtasks related to major task 1 till second quarter. The HRPO approval was obtained by the end of the second quarter and hence all study related activities, i.e., screening, recruitment, testing final protocol etc. were started in third quarter. To meet our target enrollment by the end of year 1, we started recruiting and testing ~2-3 subjects per week. As a result, we were very close to our target enrollment for year 1.

In year 2, the Covid-19 pandemic put a temporary halt on all the research-related activities. Even before the official closure, the new subject enrollment had slowed down significantly (no testing in the month of March) due to the fear about heightened risks of infection in our patient population. Therefore, we were granted a one-time, 12-month extension for our DOD Award to ensure we can reach our target goal by next year. We re-started subject enrollment and testing during late 2020 into early 2021. However, we couldn't reach our target goals in terms of recruitment and testing. We had to stop study related activities after July 2021 due to pending approval of another extension to test more subjects.

Changes that had a significant impact on expenditures

Due to delay in starting study-related activities till quarter 2, we did not spend the requested budget for the 1st year entirely. Our projected year 1 expenditure was \$120,075, and our actual year 1 expenditure was only \$94,365. More recently, repeated no-cost extensions of the grant due to Covid-related delays have impacted our budget.

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

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.

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. Arpan I, Fino PC, Mancini M, Horak FB. Application of wearable inertial sensors to identify fall-risk predictors in people with multiple sclerosis.
2. Arpan I, Fino PC, Horak FB. Neuro-correlates of local dynamic stability in people with multiple sclerosis.
3. Arpan I, Miranda-Domínguez O, Horak FB. Resting-state functional connectivity networks associated with fatigue in multiple sclerosis.

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

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: 1.5
 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: 0.6
 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: 0.8
 Contribution to Project: Assisted in the scheduling, screening, and testing study participants.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

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

Please Check Your Abstract One More Time.

Then scroll all the way down to the bottom of this page and click "Conclude Submission".

Best Combination of Gait Measures Discriminating Multiple Sclerosis from Healthy Controls Using Body-Worn Inertial Sensors

Vrutangkumar V Shah, PhD, Fay B Horak, PhD and Ishu Arpan, PhD, Neurology, Oregon Health & Science University, Portland, OR

Abstract Text:

Background: Gait deficits are common in Multiple Sclerosis (MS) but poorly captured by stopwatch-timed tests or rating scales. 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 an excessive number of measures and a lack of consensus on the most useful measures for MS.

Objectives: This study aimed to determine the best combination of gait measures to discriminate MS from healthy control (HC) subjects.

Methods: We used two datasets, Study I: for development and validation, and Study II: for independent test of the proposed model. Study I recruited 14 MS and 17 HC and Study II recruited 9 MS and 7 HC. 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. 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 a totally 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 HC 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.

Title:

Best Combination of Gait Measures Discriminating Multiple Sclerosis from Healthy Controls Using Body-Worn Inertial Sensors

Submitter's E-mail Address:

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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

1. Wolkorte, R., Heersema, D. J., & Zijdwind, I. (2016). Reduced Voluntary Activation During Brief and Sustained Contractions of a Hand Muscle in Secondary-Progressive Multiple Sclerosis Patients. *Neurorehabilitation and Neural Repair*, 30(4), 307–316. <https://doi.org/10.1177/1545968315593809>
2. Behm, David & St-Pierre, D.M.M. & Perez, D. (1996). Muscle inactivation: Assessment of interpolated twitch technique. *Journal of applied physiology* (Bethesda, Md. : 1985). 81. 2267-73. 10.1152/jappl.1996.81.5.2267.
3. Blenkinsop, G. M., Pain, M., & Hiley, M. J. (2017). Balance control strategies during perturbed and unperturbed balance in standing and handstand. *Royal Society open science*, 4(7), 161018. doi:10.1098/rsos.161018

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 m⁵. 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 foot 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 ($100 \text{ mg/dL} \leq \text{fasting glucose} < 126 \text{ mg/dL}$). 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 ($>100 \text{ mg/dL}$) can be a precursor to diabetes mellitus ($>126 \text{ mg/dL}$), 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 sub-studies 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 $\mathbf{v}(t) = [x(t), y(t), z(t)]^T$ 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 $d_{total} = \sum_{i=1}^{N-1} d_i$ 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.

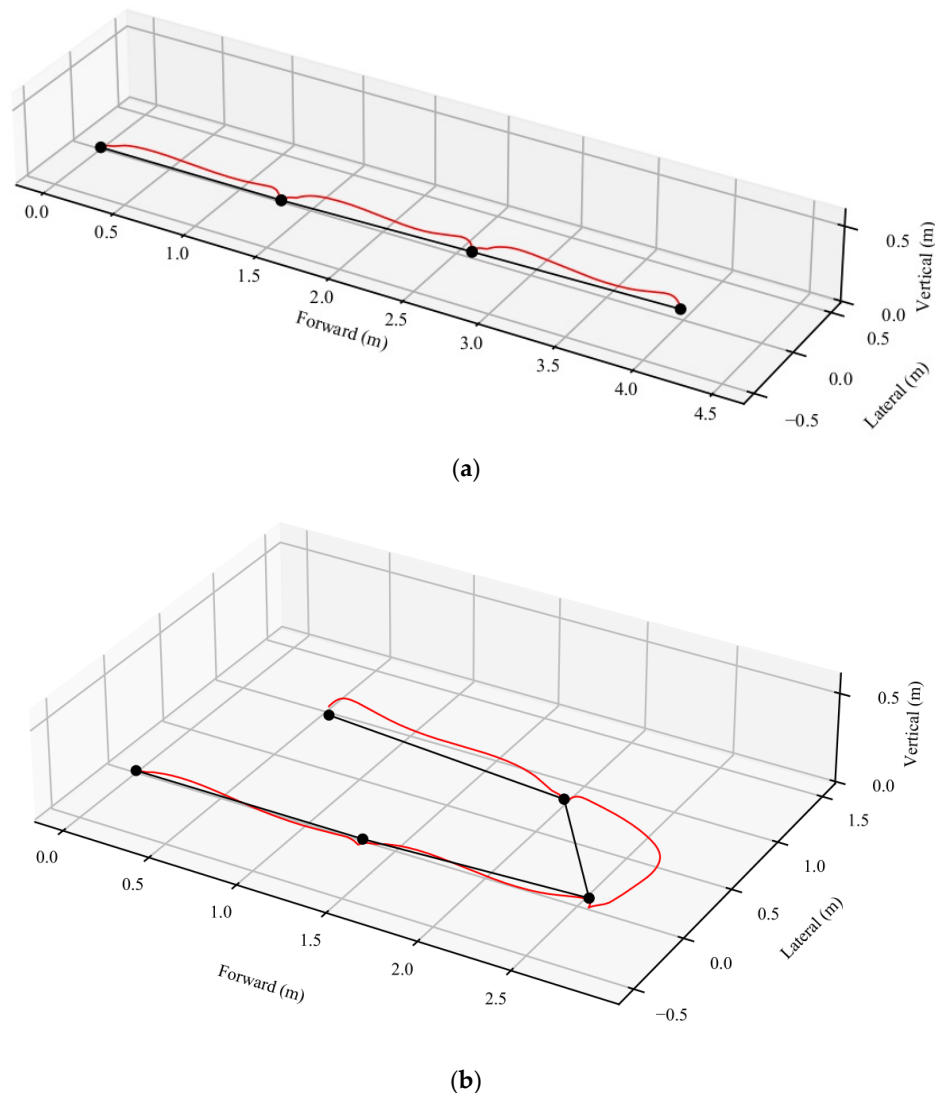


Figure 2. Example of walk trajectory used to calculate the total distance walked on a straight path (a) and with addition of a turn (b). The black dots show the position of the foot during the foot flat periods, the red trace shows the three-dimensional trajectory of the foot during each stride, and 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.

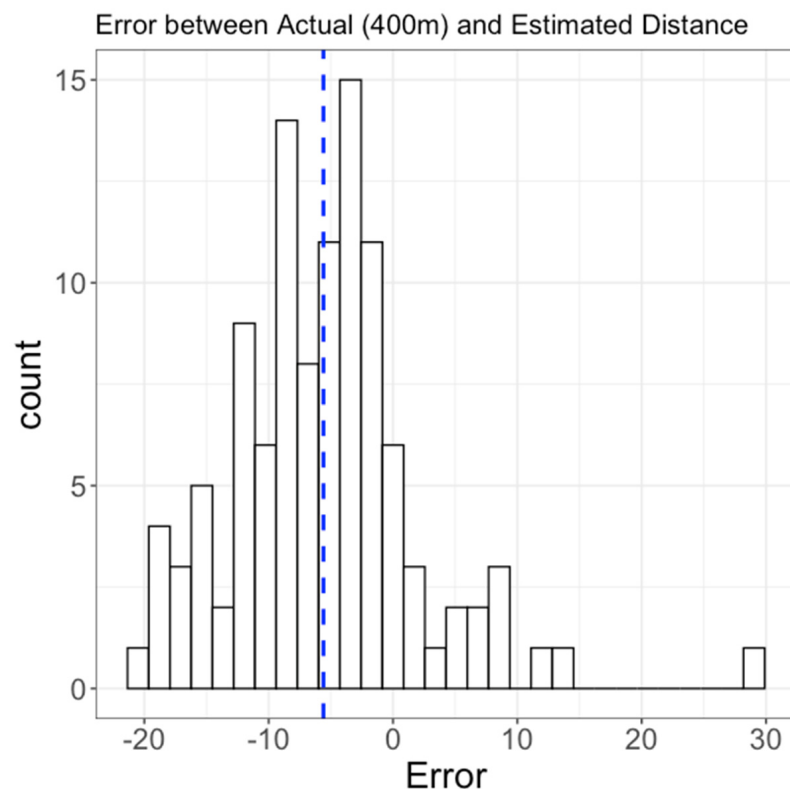


Figure 3. Histogram of error between 400 m and a total distance walked estimated by the proposed algorithm in 108 older adults (Study I). Vertical dashed line represents a mean of the histogram.

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).

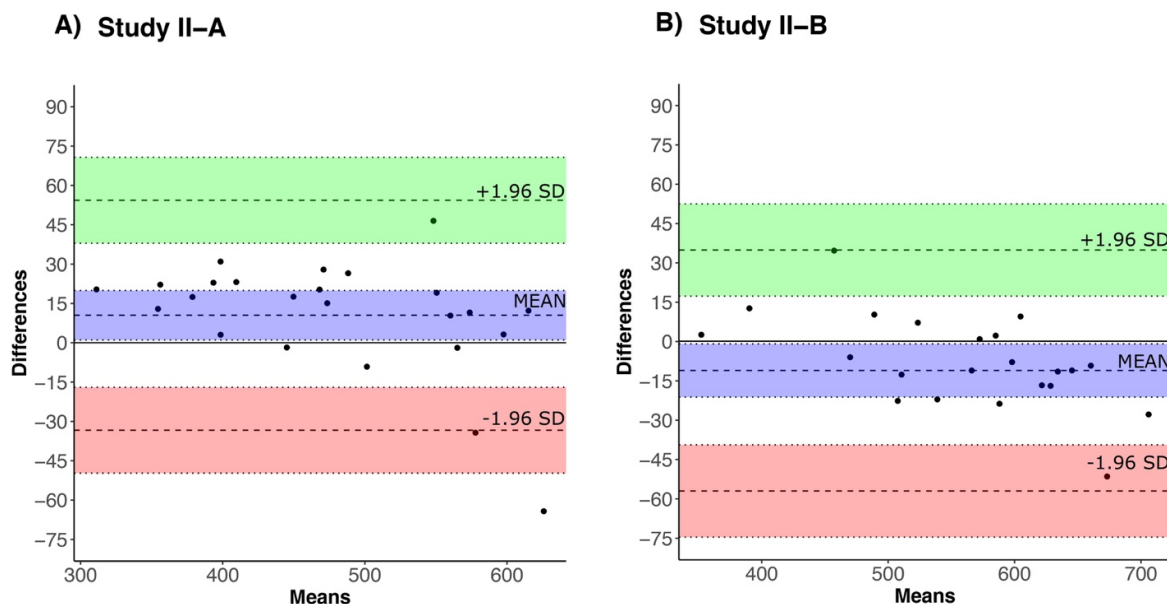


Figure 4. Bland-Altman plot for agreement between a manually calculated walk distance and walk distance estimates using the proposed algorithm for 6MWT in (A) Study II-A (15 m walkway distance) and (B) Study II-B (20 m walkway distance). Bias (mean), upper (+1.96 SD) and lower (−1.96 SD) limit agreement 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 ($ICC_{(2,1)} [95\% \text{ CI}] = 0.97 [0.91\text{--}0.99]$), 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 $\pm$ 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 $\pm$ 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 $4.1 \pm 8.1\%$ 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 $43 \pm 42\%$. 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 #: 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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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).

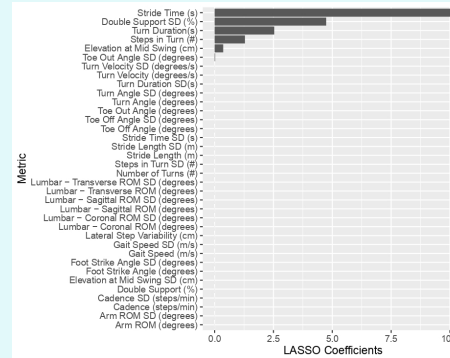
Specifically, we aim to 1a) Determine the role of central mechanisms in motor fatigue in PwMS. 1b) Determine the impact of motor fatigue on balance & gait. 2) Determine the neural correlates of central fatigue in PwMS.

Approach

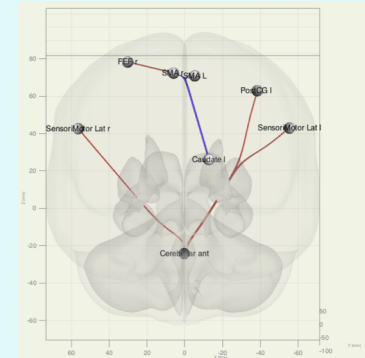
Aim 1: 30 PwMS & 30 healthy controls will participate in a fatiguing motor task involving a sustained contraction of plantarflexor (PF) muscles for 60 seconds. The interpolated twitch technique will be used to determine voluntary activation (VA) of the PF muscles. The decline in VA during task will provide 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 inertial sensors (APDM Wearable Technologies, Portland, OR, USA) for objective assessment of balance and gait impairments. Finally, objective index of central fatigue will be then related to decline in the balance control during standing (pre- and post-fatigue test) and the fast six-minute walk test.

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

Balance & gait testing



Neuroimaging



Left 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. Right 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.

Accomplishment: Preliminary results show that 1) Range and local dynamic stability are two best predictors of falls in mild to moderately involved people with MS, 2) Significant changes in balance and gait are observed in PwMS after fatigue testing but not healthy controls, 3) Differences in resting state functional connectivity between fatigued vs non-fatigued people with MS.

Timeline and Cost

Activities	CY	18-19	19-21
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

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

- ☐ Analyze results and disseminate findings

Comments: Recruitment, testing and analysis have begun, 48 people have completed testing.

Budget Expenditure to Date

Projected Expenditure: \$128,504

Actual Expenditure: \$125,283.29

Updated: Portland, OR; July 25, 2021