AWARD NUMBER: W81XWH-18-1-0425

TITLE: Motor Fatigue in Multiple Sclerosis: Role of Central Mechanisms

PRINCIPAL INVESTIGATOR: Fay Horak

CONTRACTING ORGANIZATION: Oregon Health & Science University 3181 SW Sam Jackson Park Rd, Portland, OR 97239

REPORT DATE: August 2020

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2020	Annual	01Aug2019-31Jul2020

4. TITLE AND SUBTITLE

Motor Fatigue in Multiple Sclerosis: Role of Central Mechanisms

5a. CONTRACT NUMBER W81XWH-18-1-0425

5b. GRANT NUMBER MS170133

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. Ishu Arpan, Dr. Fay Horak (PI)

E-Mail:

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, Oregon 97239

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: 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 1) determine the role of central mechanisms in motor fatigue in PwMS, 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, and 1b: Central 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.*

Status: We have screened a total of 109 subjects for participation in this study. Of those screened, a total of 43 subjects (20 healthy controls and 23 PwMS) have completed data collection for Aim 1 and Aim 2.

Findings to date: PwMS performed significantly worse on the instrumented postural sway and instrumented gait testing 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. The reported postural sway abnormalities indicate that PwMS, especially fallers, experience a significant decrease in postural stability that requires active and frequent postural corrections. Similarly, we found significant differences between various instrumented gait measures among MS and healthy controls, among which local dynamic stability (upper body control measure) and variation in step time (spatiotemporal measure) were different between fallers and non-fallers in the MS group. Regression analysis was implemented on both mobility measures (sway and gait) to determine the best combination of mobility variables that can predict fall frequency in PwMS. The final model included Sway Range and trunk local dynamic stability as the predictors of falls and yielded an AUC of 0.934. These findings may allow for early detection of falls, possibly aiding clinicians and researchers in mitigating the burden of falls placed on PwMS. In addition to mobility impairments, PwMS had higher incidence of motor fatigue than healthy controls. 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. 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. However, in PwMS, a significant increase in the transverse range of motion of trunk was observed after the fatiguing task, indicating that the trunk control during walking may be a more sensitive measure of fatigue than the spatiotemporal features of gait. These results were consistent with our findings of the gait impairments, wherein the local dynamic stability (a measure of trunk control) was more sensitive in differentiating fallers from non-fallers in PwMS. Together these results suggest that the upper body control is impaired in PwMS and it can worsen after the fatiguing tasks, further increasing the risks of falls in this population.

15. SUBJECT TERMS
Motor Fatigue, Neuroimaging, Postural Sway, Gait, Balance, Inertial Sensors, Falls

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT Unclassified	**b. ABSTRACT** Unclassified	**c. THIS PAGE** Unclassified	Unclassified	21	**19b. TELEPHONE NUMBER** *(include area code)*

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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 (75% complete)
Subtask 2: Data Collection and Management (72% complete)

Major Task 3: Data Analysis and Publications (50% 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 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 (75% complete).
- Complete MRI data collection @ AIRC, OHSU (72% complete)
- Fatigue data collection (following MRI) using Biodex Dynamometer (72% complete).
- Balance assessment during standing task (pre-and post-fatigue test) and during the fast six-minute walking test (6MWT) using APDM sensors (72% 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 (72% complete).

Major Task 3: Data Analysis and Publications

Subtask 1: Data Analysis
- Perform fatigue data analysis to evaluate an index of central fatigue (40% 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 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; data presented in the annual report).

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:

Summary of screening, enrolment and completion
Till date, 127 subjects have completed the pre-screening survey. Out of 127, 109 completed the screening process. Total 43 participants (23 MS & 20 Healthy Controls)have completed testing. 4 new MS participants and 1 healthy control filled the screening questionnaires since the research activities were halted in March 2020 due to the COVID-19 situation, hence these participants have not been enrolled in the study yet.

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

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

Other subject characteristics

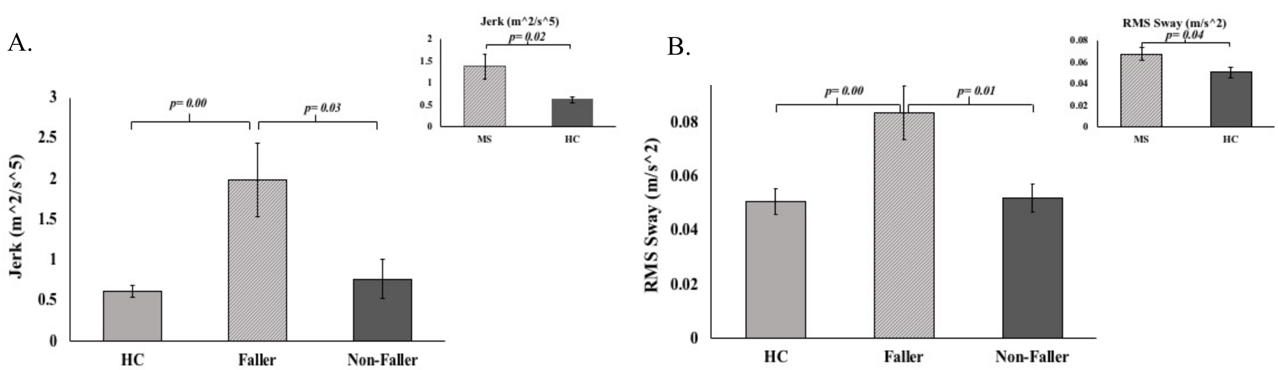
Sleep: Sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) in PwMS and healthy controls. In scoring the PSQI, seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores 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 ± 4.6 vs 42.9±4.2, p=0.11)

<u>Mobility Impairments</u>

Instrumented Balance Testing: The main aim of this sub-project 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.



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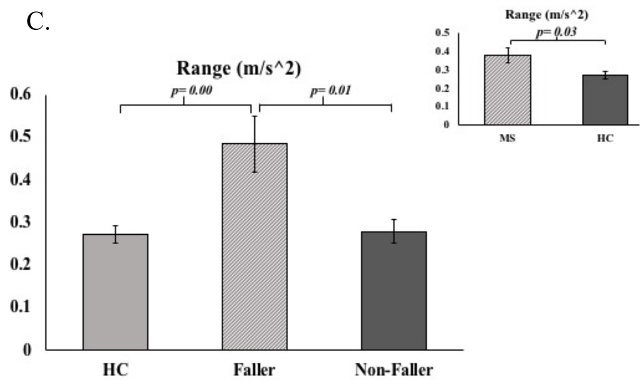


- **Instrumented Gait Testing:** The primary aim of this sub-project was to investigate if falls can be detected in PwMS using instrumented gait measures.

Methods: For this sub-project, all participants performed the 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 (v1, 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.

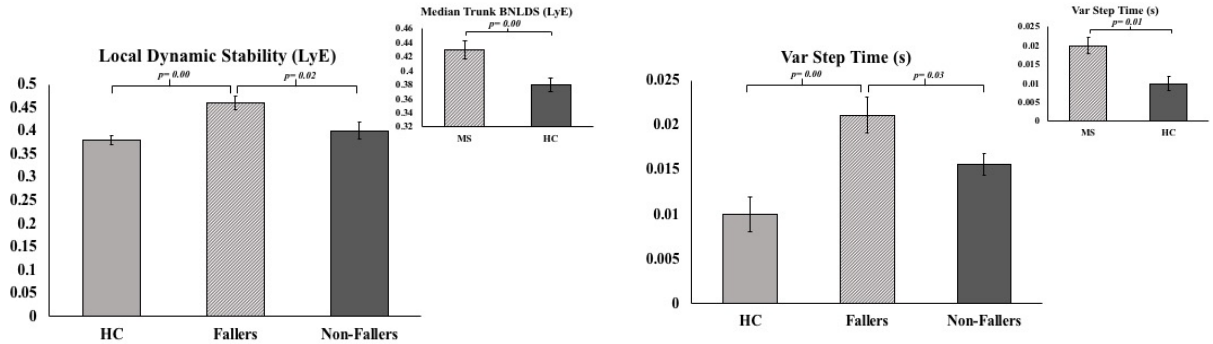
Results: We found significant differences between various instrumented gait measures among MS and healthy controls (shown below in Table 2).

Table 2: Differences in the instrumented gait parameters among MS and healthy controls.

	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 2 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).

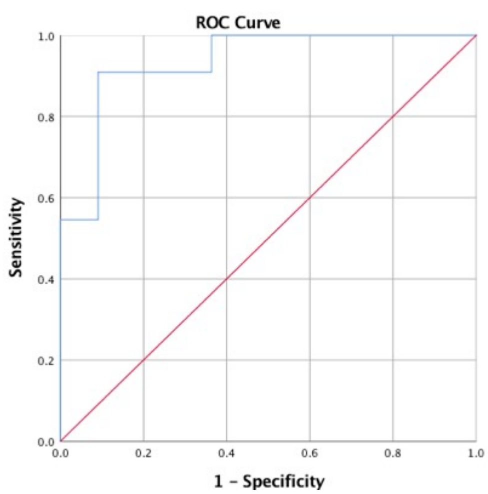
Fig. 2 Instrumented gait measures that discriminated fallers from non-fallers in the MS group.



- **Instrumented mobility-based predictive models of fall risk in PwMS:** The primary aim here was to identify the best model for fall prediction based on mobility 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).

  Fig. 3 Model consisting of two best predictors of falls, one variable (Range) from instrumented sway testing and one (Local dynamic stability) from instrumented gait testing.



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				

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 the 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. 4). 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. 5). 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. 6).

Fig. 4 Pre- and post-fatigue sway measures in healthy controls (blue) and PwMS (orange). * reflects significant change in sway measures win MS group after fatiguing task.

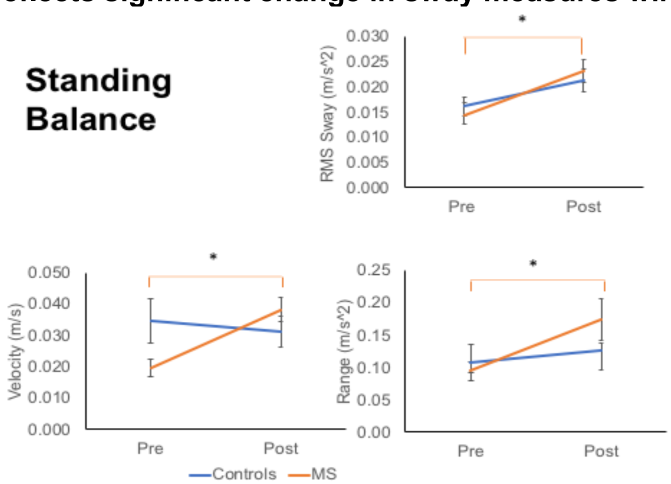


Fig. 5 Pre- and post-fatigue spatiotemporal measures of gait in healthy controls (blue) and PwMS (orange). * reflects significant change in spatiotemporal features of gait in MS group after fatiguing task.

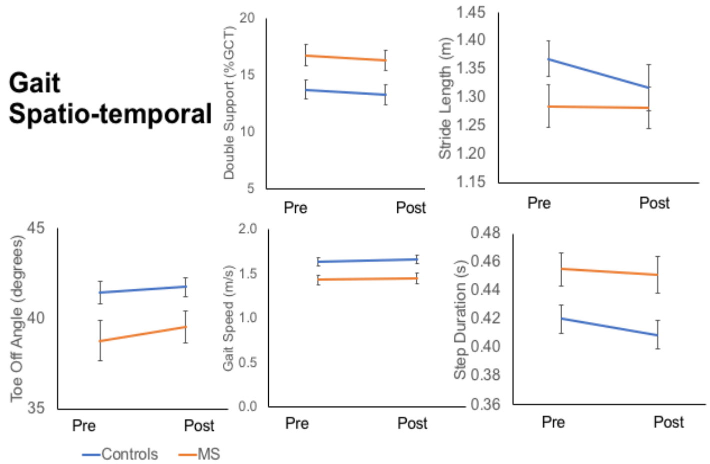
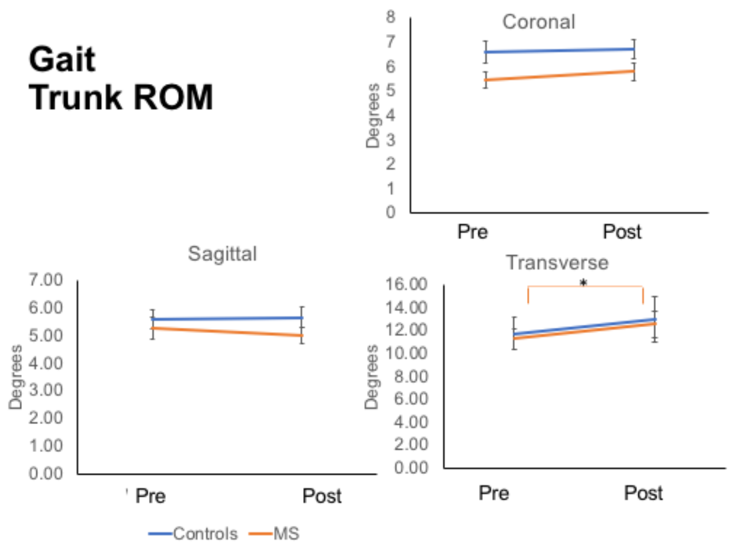


Fig. 6 Pre- and post-fatigue trunk ROM in healthy controls (blue) and PwMS (orange). * reflects significant change in trunk ROM while walking in MS group after fatiguing task.



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.

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 Physical Therapists Balance Disorders in Parkinson’s Disease National Parkinson’s Foundation, Minneapolis, Minn; Presentation “Wearable Technology for Home monitoring of Mobility”, Apple, Inc. August, 2020; Digital Gait Outcomes for MS Clinical Trials, Swanbio Discussion, September, 2020; Discussion, Advisory “Wearable Digital Sensors for MS clinical trials”, Uniqure Pharma, October 2020; “Balance and Gait objective measures for MS”, Larimor Pharma, November, 2020; Invited Webinar “Digital Technologies for Assessing Patient Functioning in Multiple Sclerosis Clinical Trials SCA and ARCA and Ataxia Global Conference”, December, 2020; Invited Webinar “Wearable Sensors Link Gait and Balance to Severity of Spinocerebellar Ataxia National Ataxia” 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. Our University was officially closed for non-essential research activities on March 8, 2020. 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.

At OHSU, we received an approval for our Return to Research plan at Level 2 (R2R) from the department of Neurology in late June 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 a 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

Though we were approved to restart testing at the AIRC for MR data collection, we did not receive approval to resume research activities in the KCRB (where we collect our functional data), as their R2R plan was only allowing 1:1 ratio of research staff to participant at research level 2. Since our study needs at least two research staff members for the functional data collection, we needed an exception request to be evaluated by the Clinical Research Taskforce. Once approved, we were hoping to restart testing healthy controls in December, 2020. However, our plans to restart testing again hit a roadblock when due to the sudden spike in the COVID-19 cases in the month of November, OHSU moved back to the Level 3 research operations on 11/18/2020. Therefore, our exception request for resuming functional testing at KCRB wouldn't be considered till OHSU moves to Level 2 research operations again. Till then, there will be a focus placed on data analysis and the dissemination of research findings through reports, conference presentations and manuscripts. Data analysis, so far, have been focused on the functional data. We were hoping to initiate MR data analysis once the data collection was completed for all subjects (Major Task II). However, because of the uncertainty in the timeline of restarting research operations in the wake of Covid-19, we have started the resting-state functional data analysis (using the subset MR data collected till date). Thus, in the next quarterly reporting period, we will have preliminary findings related to neuroimaging aim of the study.

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 the 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 are 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 have submitted another abstract to the ACTRIMS this year (Appendices: Attachment 2). 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?

In the years 2019 and 2020, members of our team 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. Members of our research team discussed issues around balance and gait in PwMS, performed demonstrations and invited fair attendees to test their balance using our inertial sensors. Further, two summer students joined our research team in the years 2019 and 2020 as summer interns (one still active), which provided them an opportunity to learn about our study. Both 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 have re-started subject enrollment and waiting for OHSU to move back to Level 2 research operations for restarting subject testing.

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. In the year 2, study related activities were halted in the wake of Covid-19 pandemic. Therefore, we had $51,233 left as the available balance by the end of June 2020.

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.**

Published manuscripts: Nothing to report

In preparation manuscripts:

1. Arpan I, Fino PC, Mancini Martina, Horak FB. Fall prediction in people with Multiple Sclerosis based on instrumented mobility testing (Gait & Posture Journal).
2. Arpan I, Fino PC, Miranda-Domínguez O, 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.
Prewitt A, McBarron G, Horak F, Arpan I. Muscle Fatigue In People With Multiple Sclerosis Impairs Standing Balance, ACTRIMS, Florida, February 27-29, 2020.

Rude A, Prewitt A, Horak F, Arpan I Feasibility of Postural Sway Measures to Predict Falls in Multiple Sclerosis, ACTRIMS Forum 2021, taking place online, February 25-27, 2021

- **Website(s) or other Internet site(s)**
  Nothing to report

- **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: 4.5
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: Grace McBarron
Project Role: Research assistant
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 0.2
Contribution to Project: Assisted in the scheduling, screening, and testing study participants.

Name: Austin Prewitt
Project Role: Graduate student/ RA
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 1.8
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.

9. APPENDICES:

Abstract for ACTRIMS 2020

Muscle Fatigue in People with Multiple Sclerosis Impairs Standing Balance

Austin Prewitt, B.S., ATC, Grace McBarron, B.S., Sarah Chesley, Fay Horak, PhD, PT, Ishu Arpan, PhD

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., & Zijdewind, 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

Abstract for 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

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).

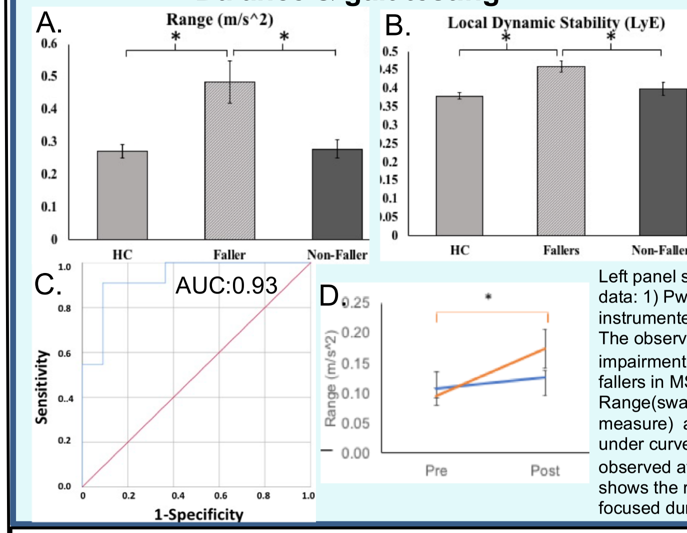
Specifically, we aim to 1a) Determine the role of central mechanisms in motor fatigue in PwMS. 1b) Determine the impact of motor fatigue on balance & gait. 2) Determine the neural correlates of central fatigue in PwMS.

Approach

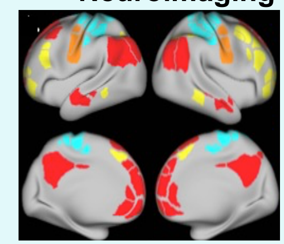
Aim 1: 30 PwMS & 30 healthy controls will participate in a fatiguing motor task involving a sustained contraction of plantarflexor (PF) muscles for 60 seconds. The interpolated twitch technique will be used to determine voluntary activation (VA) of the PF muscles. The decline in VA during task will provide an index of central fatigue. This 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 the preliminary findings from the mobility data: 1) PwMS performed significantly worse on the instrumented postural sway & 6MWT compared to controls. The observed postural sway abnormalities and gait impairments successfully differentiated fallers from non-fallers in MS group (A,B). 2) Regression analysis yielded Range(sway measure) and Local dynamic stability (gait measure) as the best predictors of falls and yielded an area under curve of 0.93 (C). 3) Balance & gait changes were observed after fatiguing task in PwMS only. Right panel shows the resting-state functional networks that will be focused during neuroimaging analysis.

Accomplishment: Preliminary results show that 1) Range and local dynamic stability are two best predictors of falls in mild to moderately involved PwMS, 2) Incidence of motor fatigue is higher in PwMS, & 3) Changes in instrumented mobility measures are observed in PwMS after fatigue testing but not healthy controls.

Timeline and Cost

Activities CY	18-19	19-20
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; December 15, 2020

Goals/Milestones

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

CY19 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

CY20 Goal – Complete all testing, analysis and dissemination of results: Impacted due to COVID-19 pandemic.

CY21 Goal – Restart and complete all testing. Finalize MR data analysis and compare it to the functional data
❑ Analyze results and disseminate findings

Comments: 43 people (20 healthy controls and 23 PwMS) have completed testing. 4 new participants have been enrolled in the study, who will be tested as soon restrictions on the non-essential research activities are removed at OHSU.

Budget Expenditure to Date
Projected Expenditure:$128,504 Actual Expenditure: $77,271