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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

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Fort Detrick, Maryland 21702-5012

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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 65 subjects for participation in this study. Of those screened, a total of 34 subjects (16 healthy controls and 18 PwMS) have been enrolled and a total of 28 have completed data collection for Aim 1 and Aim 2.

Findings to date: PwMS had higher incidence of motor fatigue than healthy controls. Further, 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.

15. SUBJECT TERMS

Motor Fatigue, Neuroimaging, Postural Sway, Gait, Balance, Inertial Sensors

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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.* Furthermore, motor fatigue can worsen the balance and gait impairments in PwMS. Therefore, *we also plan to investigate the effects of motor fatigue on balance control during standing and walking in MS.*

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major task 1: Launch Study Activities (100% complete)

Subtask 1: Prepare Regulatory Documents and Research Protocol

Subtask 2: Prepare research protocols

Subtask 3: Training Personnel

Subtask 4: Research Essential Documents

Major Task 2: Recruitment and Testing

Subtask 1: Recruitment (57% complete)

Subtask 2: Data Collection and Management (47% complete)

Major Task 3: Data Analysis and Publications (25% 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)

Milestones Achieved: All Subtasks for Major Task 1 Complete

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

Major Task 2: Recruitment and Testing

Subtask 1: Recruitment

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

Subtask 2: Data collection and Management

- Schedule participants (35-40% complete).
- Complete MRI data collection @ AIRC, OHSU (33% complete)
- Fatigue data collection (following MRI) using Biodex Dynamometer (33% complete).
- Balance assessment during standing task (pre-and post-fatigue test) and during the fast six-minute walking test (6MWT) using APDM sensors (33% 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 (33% complete).

Milestones Achieved: All Subtasks for Major Task 2 Complete

Data collection for Specific Aim I is 33% complete: Objective assessment of central fatigue and mobility impairments in 30 people with MS versus 30 controls.

Data collection for Specific Aim 2 is 33% complete: Neuroimaging correlates of fatigue in people with MS.

Major Task 3: Data Analysis and Publications

Subtask 1: Data Analysis

- Perform fatigue data analysis to evaluate an index of central fatigue (20% complete).
- Assess changes in balance control during standing pre-and post-fatigue and during the 6MWT from first to last minute (33% complete).
- Perform MRI data processing (33% complete), motion correction (33% 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).

Subtask 2: Data Dissemination

- Disseminate findings (abstracts, presentations, papers, DoD), including APTA, ACTRIMS and MHSRS and rehabilitation journals to share with clinicians (One abstract submission to ACTRIMS)
- Submit manuscript describing the fatigue protocol and preliminary findings (In preparation).
- Submit manuscript presenting balance and gait data in relation to fatigue (Data analysis ongoing).
- Submit manuscript presenting findings on neuro-correlates on motor fatigue in MS (In preparation).

Significant Results/ Key outcomes

Summary of screening, enrolment and completion:

We have screened a total of 65 subjects for participation in this study. Of those screened, a total of 34 subjects (16 healthy controls and 18 PwMS) have been enrolled and a total of 28 have completed data collection for Aim 1 and Aim 2.

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

	Healthy Controls	People with MS
Age	39±13 (yrs)	43±10 (yrs)
Gender	5M/11F	1M/11F
Weight	152±24 (lbs)	162±41 (lbs)
Height	5.5±0.4 (ft)	5.4±0.3 (ft)
MFIS (Total Score)	NA	35±23
Physical		16±10
Cognitive		17±11
Psychosocial		3±2

*MFIS: Modified Fatigue Impact Scale

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

- **Motor fatigue:** 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.
- **Balance and Gait:** No differences in pre-fatigue sway measures were observed among healthy controls and MS groups. But, PwMS had higher double support time and step duration, and lower toe-off angle, gait speed, swing, and stride length compared to healthy controls, all indicating slower walking in the MS group. Moreover, pre-fatigue trunk coronal ROM was lower in PwMS.
- **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. 1). 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. 2). However, in PwMS, a significant increase in the transverse range of motion of trunk was observed after the fatiguing task (Fig. 3), 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. 3).

Fig.1 Pre- and post-fatigue sway measures in healthy controls (blue) and PwMS (orange). * reflects a significant change in sway measures in MS group after fatiguing task.

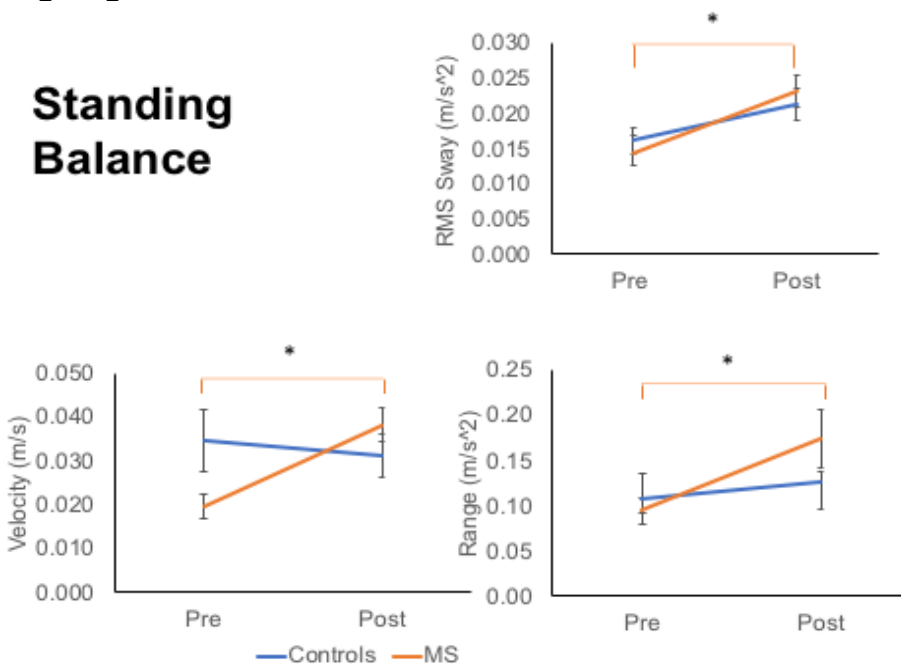


Fig. 2 Pre- and post-fatigue spatiotemporal measures of gait in healthy controls (blue) and PwMS (orange). * reflects a significant change in spatiotemporal features of gait in MS group after fatiguing task.

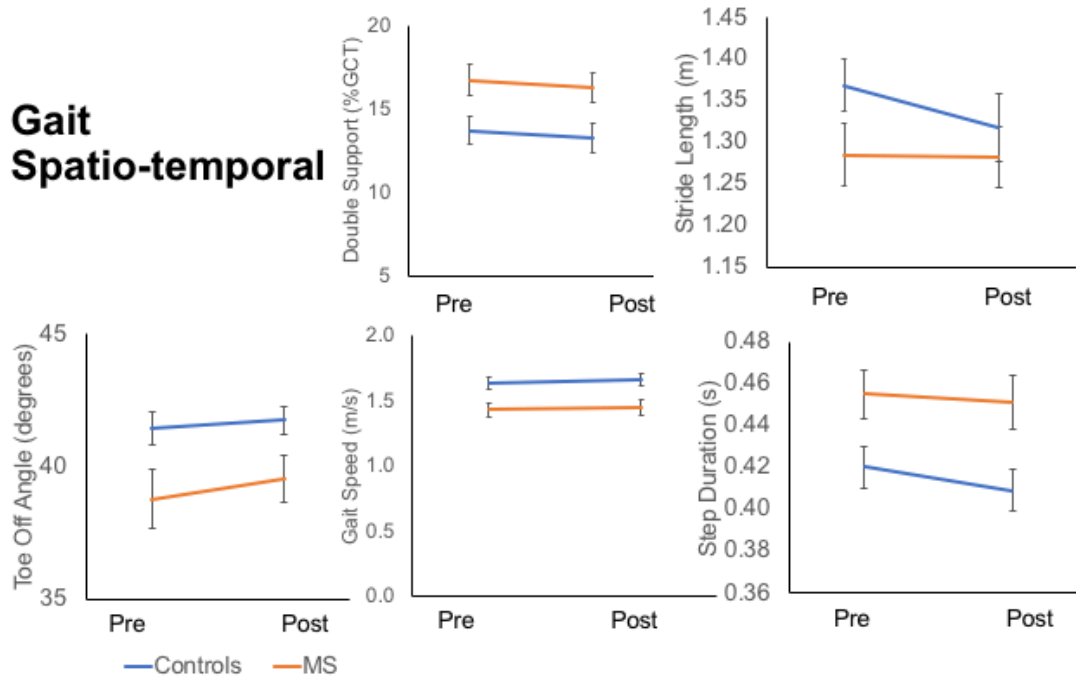
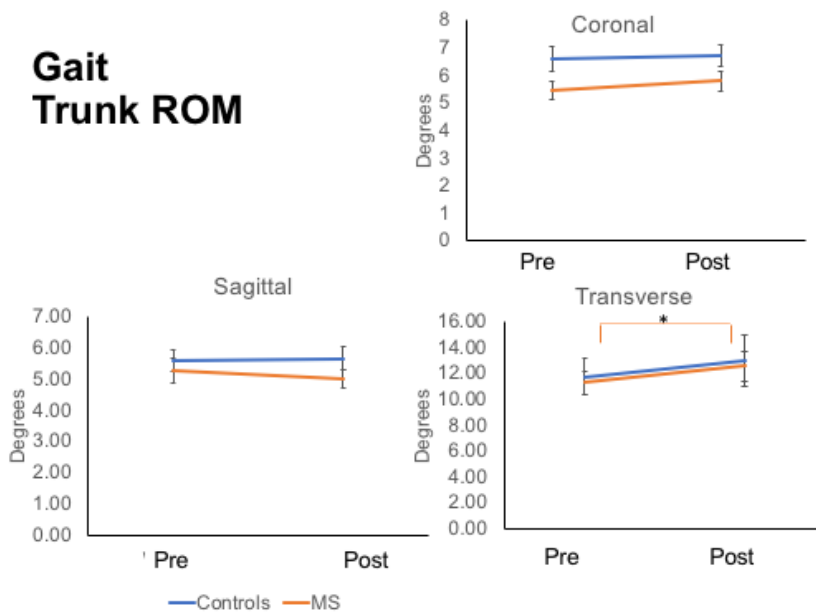


Fig.3 Pre- and post-fatigue trunk ROM in healthy controls (blue) and PwMS (orange). * reflects a significant change in trunk ROM while walking in MS group after fatiguing task.



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

The members of research team will have opportunity to present the preliminary findings from this project at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS, 2020) meeting 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 balance and gait problems in PwMS as an invited speaker in the following meetings: 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; Workshop for Physical Therapists: Evaluation and Treatment of Balance Disorders, Vancouver, BC, Sept 2018; Northwest Portland Area Indian Health Board – “Gait and Balance in Aging Communities”; Portland, OR, Sept 2018; and Neuropore, Inc, Digital Biomarkers for Neurological Disorders, San Diego, November 2018.

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. The goal of the meeting was to discuss non-invasive, objective and sensitive outcome 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 in the next quarters. Following this, there will be a focus placed on data analysis and the dissemination of research findings through reports, conference presentations and manuscripts. Analyses of data (so far) have primarily focused on 1) measuring the decline in motor task performance (a measure of motor fatigue), and 2) pre- and post-fatigue changes in balance and gait. Our next steps are: 1) to determine the role of central mechanisms in motor fatigue by analyzing changes in voluntary activation (a measure of central fatigue) during the fatiguing task, and 2) to determine if the changes in balance and gait after fatigue testing are related to the decline in voluntary activation. In addition, once we have completed the neuroimaging data collection for all subjects (Major Task II), we will be able to initiate analyses on the MRI data. Thus, in the next reporting period, we will have finalized our analysis for Aim I, and begin analysis of Aim II.

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 with clinicians and physical therapists at OHSU MS center. We have found that these meetings allow an open discussion between researchers and clinicians, to discuss research findings, and work towards translating research knowledge into clinical practice. In addition, we work closely with members of 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 (Framework 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. The paper aims 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. Also, our findings intend to encourage clinicians to use more objective measurements of fatigue and mobility impairments. The research team member, who will be

presented this abstract at the conference, had been awarded an Educational Travel Grant by the ACTRIMS committee based on the scoring of our abstract.

Another impact this study is generating, is in the area of home monitoring in PwMS. Dr. Horak, PI of the study, is assessing the benefits of continuous 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 March 2019 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, a high school student joined our research team as a summer internee, which provided her an opportunity to learn about our study and complete an independent project which built her 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 are very close to our target enrollment for year 1.

Further, at the end of year 1, we noticed that subjects in our healthy control group were younger (not statistically significant) than those in the MS group. Therefore, in Yr2, we will focus primarily on the enrollment of older control subjects (and/or recruit young people with MS).

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 \$120,183, and our actual year 1 expenditure was only \$94,365.

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, Horak FB. Neuro-correlates of local dynamic stability in people with multiple sclerosis.
2. 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.

- **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: 1.8
 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: 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:

Please refer to the attached Quad Chart at the end of the report.

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., & 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

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)

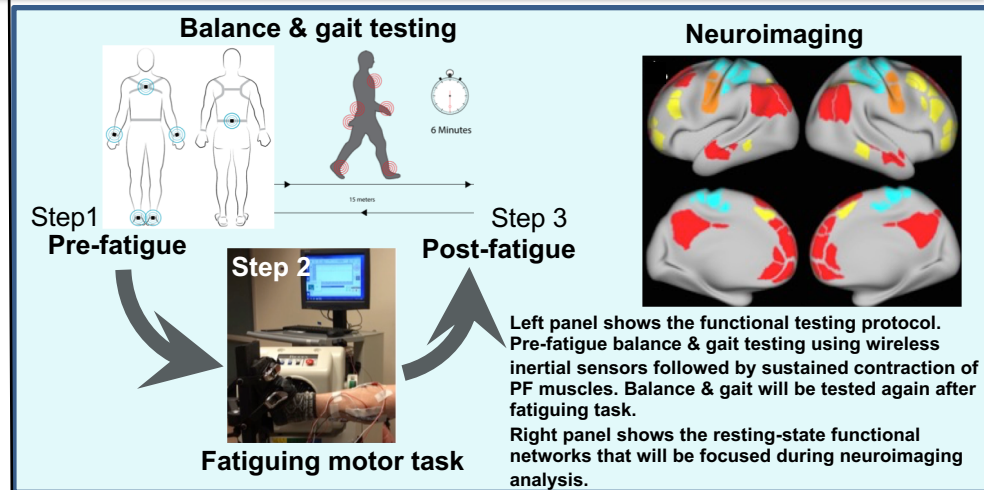
The main objective of this proposal is to investigate the role of central mechanisms in motor fatigue and to unmask the neural network alterations underlying central fatigue in people with multiple sclerosis (PwMS).

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



Accomplishment: Preliminary results show that the incidence of motor fatigue is higher PwMS than health controls. Further, significant changes in balance and gait 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; Jan 21, 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

- Analyze results and disseminate findings

Comments: Recruitment and testing have begun, 5 people are now enrolled in the study

Budget Expenditure to Date

Projected Expenditure: \$120,183

Actual Expenditure: \$94,365