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TITLE: Effects of Exercise on Glymphatic Functioning and Neurobehavioral Correlates in Parkinson's Disease

PRINCIPAL INVESTIGATOR: Daniel O. Claassen, MD, MS

CONTRACTING ORGANIZATION: Vanderbilt University Medical Center  
Nashville, TN

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<b>13. SUPPLEMENTARY NOTES</b> None.					
<b>14. ABSTRACT</b> This study is designed to measure the change in patients diagnosed with Parkinson's disease (PD) before, during and after a 12-week exercise program. The focus of this study is the glymphatic system. The glymphatic system is a recently discovered novel waste clearance pathway, in patients with Parkinson's Disease (PD). The glymphatic system acts as a waste-clearance system in the brain of vertebrate animals. The glymphatic system has been proposed in which new clearance pathways involving communication between paravascular spaces, interstitial fluid, and ultimately meningeal and dural lymphatic vessels exists, and we have provided evidence that this system may be dysfunctional in patients with Parkinson's disease with cognitive disorders. Early research suggest glymphatic function increases following exercise, this response is believed to clear beta-amyloid in the brain and may mediate the neurobehavioral response to exercise in PD. This study will use cognitive exams, neurological exams as well as specialized imaging to record data points and evaluate the glymphatic function after exercise.					
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**INTRODUCTION:** This study is designed to measure the change in patients diagnosed with Parkinson's disease (PD) before, during and after a 12-week exercise program. The focus of this study is the glymphatic system. The glymphatic system is a recently discovered novel waste clearance pathway, in patients with Parkinson's Disease (PD). The glymphatic system acts as a waste-clearance system in the brain of vertebrate animals. The glymphatic system has been proposed in which new clearance pathways involving communication between paravascular spaces, interstitial fluid, and ultimately meningeal and dural lymphatic vessels exists, and we have provided evidence that this system may be dysfunctional in patients with Parkinson's disease with cognitive disorders. Early research suggest glymphatic function increases following exercise, this response is believed to clear beta-amyloid in the brain and may mediate the neurobehavioral response to exercise in PD. This study will use cognitive exams, neurological exams as well as specialized imaging to record data points and evaluate the glymphatic function after exercise.

**KEYWORDS:** Parkinson's, glymphatics, CSF flow, amyloid-beta, MRI, PET, exercise

## **ACCOMPLISHMENTS:**

### **What were the major goals of the project?**

Our primary goal of the project is to evaluate the glymphatic functioning and beta-amyloid burden response to a 12-week community-based exercise program in PD patients.

Aim 1: Quantify the association between glymphatic functioning, beta-amyloid burden, and neurobehavioral dysfunction in PD.

Aim 2: Assess the degree to which neuroimaging-based response to exercise mediates clinical improvement in PD.

Aim 3: Evaluate whether the association between glymphatic functioning, beta-amyloid burden, and neurobehavioral dysfunction in PD differs between cognitively healthy and cognitively impaired PD phenotypes.

Ai 4: Determine differences between cognitively healthy and cognitively impaired PD phenotypes

### **What was accomplished under these goals?**

During this reporting period we completed study startup, including finalizing neuroimaging scan protocols, training research coordinators on data collection, and assembling all assessment materials. We initiated enrollment and successfully recruited 2 patients for participation, prior to COVID-19 restrictions pausing recruitment, which was within our targeted timeline. After a pause in research efforts, we will have enrolled another 2 subjects into the study by the end of this reporting period. Baseline assessments were completed for all subjects, including a screening, MRI and PET scan, neurological exam, and in-depth cognitive assessments. Due to COVID-19 restrictions, research efforts were paused and are slowly being brought back in. We were able to complete the final study visit for one participant and are analyzing those preliminary results, and one is due for a follow up within the next reporting period.

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

During this annual reporting period, we hired and trained a full-time study coordinator to support this project. One of the Co-Investigators (Ciaran Considine) completed training in actigraph data analysis. The team has also finalized an analysis plan for comparing baseline and follow-up PET image data. There were also two manuscripts, one published and one submitted, that the Principal Investigator and Co-Investigators have co-authored that discuss impactful techniques and information that is available in peer-reviewed journals. Our exercise coach is also completing a PD exercise specialist certification, requiring knowledge of research on exercise in PD, which is attributable to her involvement in the project.

### **How were the results disseminated to communities of interest?**

Nothing to Report. Pending completion of data collection.

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

Due to COVID-19, we halted all recruitment for those who were not already involved in the 12-week intervention. We are now phasing research back in as guidelines permit to increase sample size, as well as using novel ideas to recruit and retain participants during the lasting impacts COVID-19 is creating. Every week we aim to pre-screen between 15-20 potential patients and based on the 20% screen fail rate we are back on target. We will also start analyzing data as participants complete the study, creating preliminary results that we hope to be impactful that we can disseminate to communities of interest.

**IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

**What was the impact on the development of the principal discipline(s) of the project?**

Nothing to Report. Pending completion of data collection.

**What was the impact on other disciplines?**

Nothing to Report. Pending completion of data collection.

**What was the impact on technology transfer?**

Nothing to Report. Pending completion of data collection.

**What was the impact on society beyond science and technology?**

Nothing to Report. Pending completion of data collection.

**CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

**Changes in approach and reasons for change**

We have not significantly changed our approach to this study.

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

COVID-19 impacted study recruitment. In March of 2020, there was a mandated quarantine which caused us to pause research efforts, as well as stopped all in person exercise classes. Because of this, we lost one of our patients to follow up and had to complete another patient later, when research efforts were able to be phased back in. We were not able to recruit for 4 months, but as soon as research efforts were resumed in July, we finished our first subject, and are now adjusting to the new guidelines that have been put in place. In order to adapt to the changes that this strain has caused, we have gone about new methods of retaining participants. Because this project targets a demographic that is at risk for COVID-19, we have opted to work with our co-Investigator to tailor the exercise program, providing numerous options with smaller class sizes, stringent cleaning measures, and socially distanced practices that still create an activity-intense workout, and have relayed this information to participants who are concerned about COVID-19 guidelines. We are also continuing to ramp up our recruitment rates by pre-screening more potential subjects to make up for the time lost to COVID-19, and anticipate that with these additional safety measures to our patients that there will be a steady increase in recruitment and retention in the study that will allow us to make additional progress.

**Changes that had a significant impact on expenditures**

Nothing to Report.

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

Nothing to Report.

**Significant changes in use or care of human subjects**

Nothing to Report.

**Significant changes in use or care of vertebrate animals.**

This is a human research study, not applicable.

**Significant changes in use of biohazards and/or select agents**

None.

**PRODUCTS:**

**Publications, conference papers, and presentations**

**Journal publications.**

With this study, we have been able to publish two peer-reviewed journal articles. One has been accepted and is in press, and the other is currently going through final edits and the submission process.

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

Nothing to report.

**Other publications, conference papers, and presentations.**

Nothing to report.

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

<https://www.vumc.org/cm/54723>

<https://www.vumc.org/donahuelab/50868>

**Technologies or techniques**

Nothing to Report

**Inventions, patent applications, and/or licenses**

Dr. Daniel Claassen holds the Investigational New Drug for 11-C Pittsburg Compound B.

**Other Products**

Nothing to Report

**PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

Name:	Daniel Claassen
Project Role:	Principal Investigator, Study Neurologist
Researcher Identifier (e.g.	<a href="https://orcid.org/0000-0002-9853-4902">https://orcid.org/0000-0002-9853-4902</a>

ORCID ID):	
Nearest person month worked:	2.7 person months
Contribution to Project:	Dr. Claassen has provided oversight to the study as well as neurological exams for each patient enrolled in the study.
Funding Support:	DoD grant
Name:	Manus Donahue
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	<a href="https://orcid.org/0000-0002-4123-9275">https://orcid.org/0000-0002-4123-9275</a>
Nearest person month worked:	2.7 person months
Contribution to Project:	Dr. Manus Donahue is a Sub-Investigator on this project and has contributed his expertise in Magnetic Resonance Imaging to the study.
Funding Support:	DoD grant
Name:	Renee Rouleau
Project Role:	Study Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A.
Nearest person month worked:	6 in person months
Contribution to Project:	Ms. Rouleau is contributing effort in running the patient visits and recruiting patients for this project.
Funding Support:	DoD grant

Name:	Ciaran Considine
Project Role:	Coordinating Co-Investigator
Researcher Identifier (e.g. ORCID ID):	<a href="https://orcid.org/0000-0002-8171-2821">https://orcid.org/0000-0002-8171-2821</a>
Nearest person month worked:	2.7 person months
Contribution to Project:	Dr. Considine is providing direct support to the study and has provided rationale for assessments given to patients. He has also given his expertise on the use of Actigraphs to track activity and sleep for the duration of the study.
Funding Support:	DoD grant

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? No

**What other organizations were involved as partners?**

**Organization Name:** Vanderbilt University Medical Center

**Location of Organization:** Nashville, TN

**Partner's contribution to the project**

**Facilities:** Recruit from clinic

**Organization Name:** S.T.E.P.S. Fitness—Rock Steady Boxing & Franklin Rock Steady Boxing

**Location of Organization:** Nashville, TN & Franklin, TN

**Partner's contribution to the project**

**Facilities:** This partner's facilities are where the exercise intervention for patients takes place.

**Collaboration:** This partner's staff is working with us to supply the exercise component of this study to the subjects.

**Organization Name:** Vanderbilt University Institute of Imaging Sciences

**Location of Organization:** Nashville, TN

**Partner's contribution to the project**

**In-kind support** This collaborator allows us access to the software needed to run and download images, a main component to this project.

**Facilities** This collaborator allows us access to the use of their facilities (e.g. 3T MRI and PET Scanner) in order to complete the scanning portion of this project.

**Collaboration** Manus Donahue PhD, who is affiliated with this organization, contributes his knowledge and expertise in MR imaging, as well as the MRI technologists who assist us.

**Organization Name:** Neurametrix

**Location of Organization:** Nashville, TN

**Partner's contribution to the project**

**In-kind support** This organization has provided us with the use of their software as a tertiary component to the study.

**Collaboration** Our project staff works closely with this collaborator's staff to use software and troubleshoot any issues that arise.

**Organization Name:** Cranial Cloud

**Location of Organization:** Nashville, TN

**Partner's contribution to the project**

**In-kind support** This organization has provided us with the use of their software as a tertiary component to the study.

**Collaboration** Our project staff works closely with this collaborator's staff to use software and troubleshoot any issues that arise

**Organization Name:** Actigraph

**Location of Organization:** Nashville, TN

**Partner's contribution to the project**

**In-kind support** This partner has provided us with the use of their technology for the activity and sleep tracking component of the study

**SPECIAL REPORTING REQUIREMENTS:**

**COLLABORATIVE AWARDS:** Nothing to Report

**QUAD CHARTS:** N.A.

**APPENDICES:** N.A.