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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

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6. AUTHOR(S)
Daniel O. Claassen, MD, MS

Ciaran Considine, PhD

E-Mail: Daniel.claassen@vumc.org, Ciaran.considine@vumc.org

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

AND ADDRESS(ES)

Vanderbilt University Medical Center
1500 21st Ave S Ste 1532
Nashville, TN 37212

8. PERFORMING ORGANIZATION REPORT NUMBER
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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
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None.

14. ABSTRACT

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 suggests 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.

15. SUBJECT TERMS
Glymphatics, Parkinson's Disease, CSF flow, amyloid-beta, MRI, PET, exercise

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose, and scope of the research.*

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, which is a recently discovered novel waste clearance pathway, in patients with Parkinson's Disease (PD). 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 suggests 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.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Parkinson’s, glymphatics, CSF flow, amyloid-beta, MRI, PET, exercise

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The major goals of this project, as related to the statement of work, are as follows:

Aim 1 (50% Complete):

Quantify the association between glymphatic functioning, beta-amyloid burden, and neurobehavioral dysfunction in PD using MRI, PET, and neuropsychological examination.

- Major Task 1: Identify patients appropriate for inclusion in the study.
    - Subtask 1: Clinical neurological and neuropsychological evaluation
    - Subtask 2: Preform imaging measures (PET & MRI)
    - Subtask 3: Define clinical meaningfulness of cortical beta-amyloid levels and glymphatic functioning
- Milestone 1: Co-author manuscript on glymphatic makers in Parkinson’s patients with and without cognitive impairment.
- Major Task 2: Complete exercise intervention in 32 patients.
    - Subtask 1: Rock Steady Boxing, 12-week exercise intervention
    - Subtask 2: Clinical neuropsychological follow up evaluation
- Milestone 2: Co-author manuscript on feasibility of community-based exercise program in patients with Parkinson’s Disease

Aim 2 (50% Complete):

Quantify the glymphatic functioning and beta-amyloid burden response to 12 weeks of a community-based exercise course developed specifically for PD patients.

- Major Task 3: Complete follow up imaging measures (PET & MRI)
    - Subtask 1: Preform imaging measures (PET & MRI)
- Milestone 3: Co-author manuscript on beta-amyloid levels and glymphatic functioning response to exercise intervention

Aim 3 (25% Complete):

Evaluate the degree to which neuroimaging-based response to exercise mediates clinical improvement in neurocognitive functioning and neuropsychiatric symptomology.

- Major Task 4: Analysis of clinical and imaging data
- Milestone 4: Co-author manuscript on mediation analysis of exercise function on clinical and imaging outcomes in patients with cognitive impairment

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Specific Aim 1: Quantify the association between glymphatic functioning, beta-amyloid burden, and neurobehavioral dysfunction in PD using MRI, PET, and neuropsychological examination.

- **Major Task 1:** Identify patients appropriate for inclusion in the study.
    - Identifying patients to partake in the study has been difficult during the COVID-19 pandemic. This eventually became more of an issue when there was temporary suspension of enrollment due to various restrictions. Our enrollment efforts eventually got back on track as patients began to feel more comfortable with participating in a 12-week community-based exercise program. With this, our study team re-opened the screening period in January 2021.
- **Subtask 1:** Clinical neurological and neuropsychological evaluation
    - To address the neurobehavioral dysfunction in Parkinson's Disease participants, each subject took part in a neuropsychological battery. The list of cognitive assessments includes a memory evaluation, known as the Hopkins Verbal Learning Test, an executive function measurement which incorporates the Trail Making Test – A & B, Verbal Fluency test (FAS), and Stroop Color and Word Test (SCWT). The Montreal Cognitive Assessment (MoCA) was also given to each subject at their screening visit. A Brief Estimation of Seconds Test (BEST) was also conducted to determine accuracy for a retrospective verbal estimate, a prospective reproduction estimate, a prospective verbal estimate, and a prospective production estimate. Clinical questionnaires were also administered, which included the PROMIS Sleep Disturbance (SD) and Sleep-related Impairment (SRI) form to assess sleep disturbance symptomology and the Hospital Anxiety and Depression Scale (HADS) questionnaire.

- Physical assessments were also conducted at the baseline and follow-up visits to determine the effects that the 12-week program had on subject motor skills. These evaluations consisted of a 6-minute walking test, a mini balance evaluation systems test, and the motor assessment of the Unified Parkinson's Disease Rating Scale (UPDRS). A Simon Task computer assessment was also conducted at each visit to evaluate reaction time.

- **Subtask 2:** Preform imaging measures (PET & MRI)
  - All subject who enrolled in the study and completed the requirements, successfully underwent PET and MRI scans.
- **Subtask 3:** Define clinical meaningfulness of cortical beta-amyloid levels and glymphatic functioning
  - Clinical meaningfulness of cortical beta-amyloid levels was determined by the standardized uptake value of the injected radiotracer, C11 PiB. The meaningfulness of glymphatic functioning was partially determined by the CSF efflux in the cerebral aqueduct.
- **Milestone 1:** Co-author manuscript on glymphatic makers in Parkinson's patients with and without cognitive impairment.
  - This milestone has yet to be completed. We anticipate drafting the manuscript as participants complete the study and more data becomes available.
- **Major Task 2:** Complete exercise intervention in 32 patients.
  - At the time of the semi-annual review on 14 April 2021, we had 4 participants complete the study. With an enhanced effort to enroll more subjects following the COVID-19 suspension, to date, we have screened a total of 36 participants (27 males, 9 females, mean age 67.5 ± 7.2 years, range 55 -79 years). Of these subjects, 12 were recorded as screen failures due to contradiction of participation with regards to meeting at least one exclusion criteria parameter. Such contradictions include untreated sleep apnea, seizure disorder, potential autonomic disorder, as well as the inability to comply with the overnight dopaminergic medication washout period. 6 subjects were identified as lost to follow-up (LTFU) due to COVID-19 concerns, inability to complete study requirements, or desire to no longer participate. 9 subjects have completed all study requirements. 4 subjects are currently enrolled. 5 subjects currently meet eligibility requirements and are ready to enroll following their scheduled baseline visit. In the likelihood that all currently enrolled and ready to enroll subjects finish the study requirements, we will have 18 total participants completed by the end of the December 2021.
- **Subtask 1:** Rock Steady Boxing, 12-week exercise intervention
  - All participants who are enrolled in the study, participated in the 12-week exercise course at Rock Steady Boxing, which included a total of 24 classes.
- **Subtask 2:** Clinical neuropsychological follow up evaluation
  - All subject who enrolled in the study and completed the requirements, successfully underwent each neuropsychological measure at their follow-up visit.
- **Milestone 2:** Co-author manuscript on feasibility of community-based exercise program in patients with Parkinson's Disease
  - This milestone has yet to be completed. We anticipate drafting the manuscript as participants complete the study and more data becomes available.

Specific Aim 2: Quantify the glymphatic functioning and beta-amyloid burden response to 12 weeks of a community-based exercise course developed specifically for PD patients.

- **Major Task 3:** Complete follow up imaging measures (PET & MRI)
- **Subtask 1:** Preform imaging measures (PET & MRI)
- **Milestone 3:** Co-author manuscript on beta-amyloid levels and glymphatic functioning response to exercise intervention
  - This milestone has yet to be completed with regards to exercise intervention. We anticipate drafting the manuscript as participants complete the study and more data becomes available. However, the MRI techniques used to determine choroid plexus perfusion and diffusion along perivascular spaces can be identified in Johnson et al 2020, Johnson et al 2021, and McKnight et al 2021.

The goal of this aim is to evaluate the effects that exercise can have on improving glymphatic flow and beta-amyloid burden in Parkinson's Disease patients. The following information embodies current analysis from our initial investigation into the MRI and PET imaging.

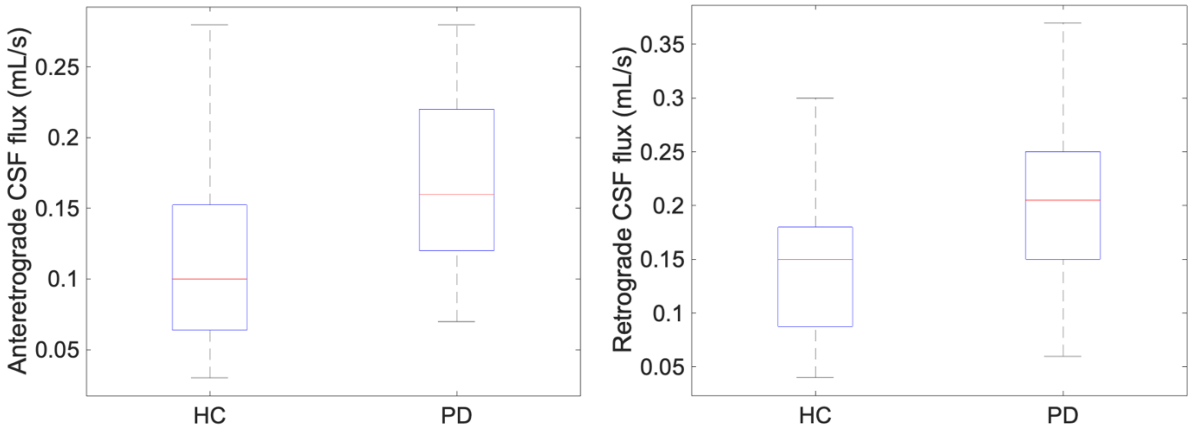

Figure 1, 2. CSF efflux: We have started to investigate changes of CSF efflux in the cerebral aqueduct in Parkinson's Disease population. A preliminary analysis indicates increase of anteretrograde and retrograde CSF flux in patients suffering from Parkinson's disease compared to an age-matched healthy control cohort (anteretrograde: mean PD=0.16, mean HC=0.11, p=0.038; retrograde: mean PD=0.19, mean HC=0.14, p=0.027). Given the current sample size, further investigations are required to validate these findings.

Parasagittal dura space: Preliminary analyses of parasagittal dura space volume are currently inconclusive in the matter of indicating group differences between Parkinson's disease and the healthy control group. Detection of differences could be hindered by the limited sample size. Therefore, further investigations are required to accept the null hypothesis.

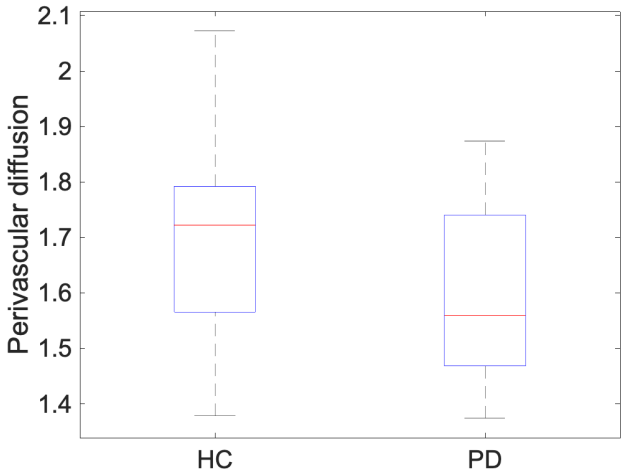

Figure 3. Perivascular diffusion: Preliminary study suggests a decrease of perivascular space diffusion in association and projection area within Parkinson's disease population compared to an age-matched healthy control cohort (mean PD=1.6, mean HC=1.7, p=0.06). Even though current analysis does not reach the threshold to be considered as statistically significant, current trends could be validated with the increase of sample size in a near future.

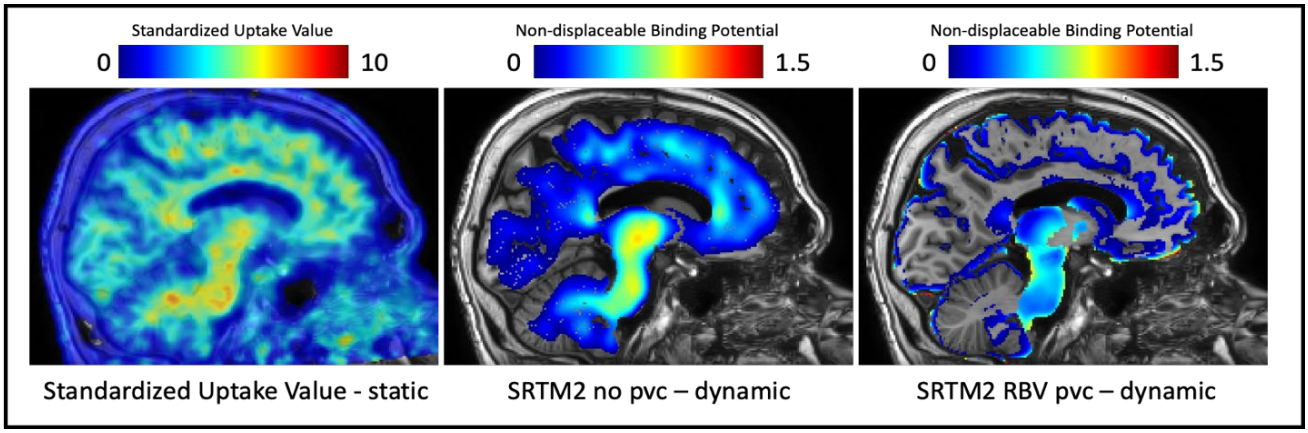

Figure 4. Representative images of static and dynamic [^{11}C]Pittsburgh Compound B scans in a single participant. (Left) The standardized uptake value, processed from the static scan, is displayed. Measurements are extracted from regions of interest and standardized to the uptake in the cerebellum. (Middle) The non-displaceable binding potential map from the SRTM2 kinetic modeling method is displayed. (Right) A region-based partial volume correction is applied to the non-displaceable binding potential map from SRTM2 to address spill-over effects from white matter uptake.

17 participants have undergone imaging with [^{11}C]Pittsburgh Compound B (PiB). We have collected both dynamic (0-70 min post-injection) and static (50-70 min post-injection) in each participant to optimize quantitative measures of beta-amyloid. We are currently processing each dynamic scan with a variety of reference region-based kinetic modeling methods including Simplified Reference Tissue Model (SRTM), Wu SRTM (SRTM2), Reference region Logan Graphical Analysis (LGA), and Multilinear Reference Tissue Models (MRTM). In addition, partial volume effect signal spill-over from white matter is being addressed with region-based partial volume corrections. We are also processing static scans with the standardized uptake value, based on the injected dosage of radiotracer and weight of participant, and normalizing to the cerebellum for comparison between subjects. Representative images of processed static and dynamic scans from a single participant are displayed in figure 4. We plan to continue collecting [^{11}C]PiB scans and optimizing the quantitative measurements of beta-amyloid for within-subject longitudinal analyses. In addition, we plan to assess the effects of Rock Steady Boxing on beta-amyloid accumulation in our Parkinson's disease participants.

Specific Aim 3: Evaluate the degree to which neuroimaging-based response to exercise mediates clinical improvement in neurocognitive functioning and neuropsychiatric symptomology.

- **Major Task 4:** Analysis of clinical and imaging data
  - The majority of our analysis of clinical imaging data has been provided under Aim 2. As we progress with enrollment efforts, we anticipate that during the next reporting period, we will have a substantial amount of analysis to share. This will be due to a larger cohort to include in our analysis, which will give us a better idea of the significance, trends, and impact that our study portrays in terms of how the neuroimaging-based response to exercise mediates clinical improvements in neurocognitive functioning and neuropsychiatric symptomology.
- **Milestone 4:** Co-author manuscript on mediation analysis of exercise function on clinical and imaging outcomes in patients with cognitive impairment
  - This milestone has yet to be completed. We anticipate drafting the manuscript as participants complete the study and more data becomes available.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This project has provided many opportunities for professional development and training. Dr. Claassen, Dr. Considine, and Dr. Donahue have provided individualized one-on-one training in the responsible conduct of research, and in specific areas of interest to each of their mentees. The list of opportunities for training and professional development are listed below in table 1.

Table 1. Training and Professional Development Opportunities

Name	**Position/Role**	**Current Training Opportunities**
Kilian Hett	Post-doctoral fellow	MRI acquisition and analysis
Jarrod Eisma	Rotating Ph.D. student	CSF production and flow through analyzing choroid plexus perfusion
Jared Phillips	Rotating Ph.D. student	Analysis of ^{11}C PiB scans gathered during baseline and follow-up visits
Sean Lee	Rotating Medical Student	Intervention effects on Parkinson's Disease
Jason Elenberger	Research Coordinator	Hired and trained to aid in recruitment, data collection, data entry, and analysis
Skylar Johnson	Undergraduate student	Evaluated choroid plexus perfusion in individuals with neurodegenerative and vascular disease. Two manuscripts published as first author.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

The following publications were reported in the semi-annual report. Since this term was dedicated to recruitment and enrollment, we do not have any new publications to report. As we continue to increase of enrollment numbers, and more data is made available, we anticipate having additional manuscripts submitted soon.

1. Johnson SE, McKnight CD, Lants SK, et al. Choroid plexus perfusion and intracranial cerebrospinal fluid changes after angiogenesis. *Journal of Cerebral Blood Flow & Metabolism*. 2020;40(8):1658-1671. doi:10.1177/0271678X19872563
2. Johnson SE, McKnight CD, Jordan LC, et al. Choroid plexus perfusion in sickle cell disease and moyamoya vasculopathy: Implications for glymphatic flow. *Journal of Cerebral Blood Flow and Metabolism*. Oct. 2021;4(10):2699-2711. doi:10.1177/0271678x211010731
3. Diffusion along perivascular spaces reveals evidence for glymphatic impairment in Parkinson disease. McKnight CD, Trujillo P, Lopez A, Petersen K, Considine C, Lin Y, Yan Y, Kang H, Donahue MJ, Claassen DO. *Parkinson's Disease and Related Disorders*. Aug. 2021;89:98-104. doi:10.1016/j.parkreldis.2021.06.004

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Since the COVID-19 pandemic halted our enrollment efforts, the previous annual and semi-annual reports were focused on literary efforts and development of publications within this study topic. Since the revamp of clinical research studies at Vanderbilt University Medical Center in early 2021, our focus within this past term has shifted to participant recruitment and enrollment. This was especially difficult, as many potential patients were not quite ready to begin participation in a research study. With that being said, we slowly began to enhance our numbers as the year continued. We are now at a point where the enrollment numbers have improved to a level where we are confident in obtaining our goal of 32 subject by the end of the allotted study period. Our enrollment goal going forward will be, January (3 enrolled), February (3 enrolled), March (3 enrolled), April (3 enrolled), May (2 enrolled). This will allow our study team to reach our accrual goal of 32 completed participants by the end of the study duration. For this reason, we will maintain our progress in terms of enrollment, but we will now begin to gather all data in order to preform our analysis. This shift to focus on data analysis will be our plan of action during the next reporting period to accomplish these goals.

4. **IMPACT:** D*escribe 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report. Pending completion of data collection.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Our research efforts, along with the utilization of novel techniques, can help to not only progress the field of Parkinson's Disease research, but other neurodegenerative diseases such as Alzheimer's and related dementias.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report. Pending completion of data collection

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Beyond science and technology, our efforts thus far, have allowed for greater outreach to the Parkinson's Disease population as well as their families and caregivers. We have had to opportunity to participate in several outreach initiatives such as attending and speaking at local support groups, foundation events, and fundraisers. Such efforts help to impact the Parkinson's Disease community far beyond the clinical setting, but rather, educate those about the importance that research participation can have for not only on themselves, but for the future of the Parkinson's Disease population.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Since the onset of COVID-19 and the eventually suspension of study related activities, recruitment has been delayed. Even with the initiation of recruitment in January 2021, potential participants were still reluctant to take part in community base exercise programs. For this reason, we have focused the efforts of the study team on obtaining our accrual goal. We are confident that we will continue to gain traction in enrolling new participants and have even seen such success in recent months.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

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

Nothing to Report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Johnson SE, McKnight CD, Lants SK, et al. Choroid plexus perfusion and intracranial cerebrospinal fluid changes after angiogenesis. *Journal of Cerebral Blood Flow & Metabolism*. 2020;40(8):1658-1671. doi:10.1177/0271678X19872563
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3. Diffusion along perivascular spaces reveals evidence for glymphatic impairment in Parkinson disease. McKnight CD, Trujillo P, Lopez A, Petersen K, Considine C, Lin Y, Yan Y, Kang H, Donahue MJ, Claassen DO. *Parkinson's Disease and Related Disorders*. Aug. 2021;89:98-104. doi:10.1016/j.parkreldis.2021.06.004

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

Website(s) or other Internet site(s)
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://www.vumc.org/cmg/54723

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

Technologies or techniques
Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

Inventions, patent applications, and/or licenses
Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Dr. Daniel Claassen holds the IND for the radioligand used for the work, ^{11}C PiB.

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

<u>Example:</u>

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	Daniel Claassen
Project Role:	Principal Investigator, Study Neurologist
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-9853-4902
Nearest person month worked:	1.35 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):	https://orcid.org/0000-0002-4123-9275
Nearest person month worked:	1.35 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:	Jason Elenberger
Project Role:	Study Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A.

Nearest person month worked:	3 in person months
Contribution to Project:	Mr. Elenberger 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):	https://orcid.org/0000-0002-8171-2821
Nearest person month worked:	1.35 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

No

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: Vanderbilt University Medical Center

Location of Organization: Nashville, TN

Partner's contribution to the project

Facilities: Recruitment of participants takes place in the Vanderbilt University Medical Center Movement Disorders Clinic. MRI and PET scans for this project take place in the Vanderbilt University Institute of Imaging Science (VUIIS).

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, 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: 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

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

Our Quad Chart has been submitted as an attachment.

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

1. Johnson SE, McKnight CD, Lants SK, et al. Choroid plexus perfusion and intracranial cerebrospinal fluid changes after angiogenesis. *Journal of Cerebral Blood Flow & Metabolism*. 2020;40(8):1658-1671. doi:10.1177/0271678X19872563

2. Johnson SE, McKnight CD, Jordan LC, et al. Choroid plexus perfusion in sickle cell disease and moyamoya vasculopathy: Implications for glymphatic flow. *Journal of Cerebral Blood Flow and Metabolism*. Oct. 2021;4(10):2699-2711. doi:10.1177/0271678x211010731

3. Diffusion along perivascular spaces reveals evidence for glymphatic impairment in Parkinson disease. McKnight CD, Trujillo P, Lopez A, Petersen K, Considine C, Lin Y, Yan Y, Kang H, Donahue MJ, Claassen DO. *Parkinson's Disease and Related Disorders*. Aug. 2021;89:98-104. doi:10.1016/j.parkreldis.2021.06.004

All appendices have also been submitted as attachments.