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Investigating Exercise-Induced Neuroplasticity and Its Mechanisms in Parkinson's Disease:
Targeting Executive Function and Brain Circuitry

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14. ABSTRACT Parkinson's disease (PD) is the second most frequent neurodegenerative disorder of old age. A common problem in PD is cognitive impairment. There are no effective treatments. Impairment in executive function (EF) is the most common subtype of cognitive impairment and leads to challenges in daily function, including decision making, multi-tasking, and quality of life. Exercise studies in the aging field and preliminary studies in our PD animal work support the role of high intensity skill practice and high motor fitness in promoting greater EF performance compared to aerobic exercise, and cardiovascular fitness (e.g. V02max). While a wide range of exercise modalities have shown to improve motor performance in PD patients, investigations of the relationship between exercise and EF in PD and mechanisms of neuroplasticity remain a significant gap in knowledge. This application will address this gap through complementary translational studies in humans and animals. The purpose of this 18-month longitudinal clinical study is to examine the association between EF related cognitive performance and fitness levels, specifically cardiovascular and motor fitness, as well as exercise intensity. We hypothesize that high intensity regular exercise as well as High level of Motor fitness will be associated with greater level of cognitive EF performance over the 18-month period, than High levels of Cardiovascular Fitness or low intensity exercise. We also hypothesize that EF related brain circuitry and connectivity will have a greater association with high level motor fitness than cardiovascular fitness and mediate the association between higher level of cognitive EF performance and motor fitness seen at 18 months.					
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1. Introduction:

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder of old age. A common problem in PD is cognitive impairment. There are no effective treatments. Impairment in executive function (EF) is the most common subtype of cognitive impairment and leads to challenges in daily function, including decision making, multi-tasking, and quality of life. Exercise studies in the aging field and preliminary studies in our PD animal work support the role of high intensity skill practice and high motor fitness in promoting greater EF performance compared to aerobic exercise, and cardiovascular fitness (e.g., V02max). While a wide range of exercise modalities have shown to improve motor performance in PD patients, investigations of the relationship between exercise and EF in PD and mechanisms of neuroplasticity remain a significant gap in knowledge. This application will address this gap through complementary translational studies in humans and animals. The focus of this clinical study application is to investigate the long-term (18 month) association between motor (MF) and cardiovascular (CF) fitness and cognitive performance, focused on EF. This study will also examine the association of MF and CF and cognitive circuitry in PD at baseline and 18 months determine whether strength of connectivity in these cognitive circuits mediate the relationship between high MF and high cognitive performance. Finally, we will also investigate the role of high-intensity exercise on EF and cognitive circuitry in PD through the use of weekly wearable heart rate device used every three months and its association with cognitive performance and strength of cognitive circuitry at baseline and 18 months. Complementary animal studies examining the molecular mechanisms, cognitive gains and enhanced cognitive circuitry (blood flow analysis) underlying motor skilled vs aerobic exercise is being conducted in parallel with Dr. Holschneider PI Award number W81XWH18-1-0666

2. **Keywords:** Cognitive Function, Circuitry, Parkinson's disease, Motor Fitness, Cardiovascular Fitness, physical activity.

3. Accomplishments

3.1 Grant Aims

1. Exercise Intensity and Cognitive Function: This objective will test the hypothesis that exercise intensity (avg METS/hr/wk over 18-months) is significantly associated with level of EF at 18 months. We will further test that the hypothesis that moderate/high intensity exercise (HIE) versus low intensity exercise (LIE) over 18-months will have significantly greater association with EF at 18 months.
2. Fitness and Cognitive Function: This objective will test the hypothesis that motor and cardiovascular fitness are differentially associated with EF at 18-months. We will also test whether high compared to low motor fitness level has a significantly stronger association with EF at 18-months. Finally, we will examine whether motor fitness mediates the association between exercise intensity and level of EF.
3. Neuroimaging will collect MRI to measure EF (cognitive/attention) network activity at baseline and 18 months. This objective test the hypothesis that changes in brain activity in networks sub-serving EF mediate the association between exercise intensity and EF at 18-months. We will also examine whether changes in brain activity in networks sub- serving EF mediate the association between motor fitness and EF.

3.2 Accomplishment under these goals:

1. At USC, 50 participants were enrolled in the study. Due to state mandates during COVID-19, the study was put on hold and then restarted in a limited capacity in August 2020 and to normal capacity in Sept 2020. We continue to follow COVID-19 safety precaution protocols at our USC clinical research sites. As of 09/15/22, a total of 42 participants have completed the study and 8 participants dropped from the study at USC. Of the 20 participants with baseline MRI at USC, 18 individuals completed a follow up MRI at USC.

2. At UCSD/VMRF 49 participants were enrolled in the study prior to the start of Covid, when all new enrollments was put on hold due to Covid restrictions on in person visits. On June 16, 2021, the VASDHS Research and Development Committee rescinded restrictions on face-to-face interactions with research participants, regardless of COVID-19 risk status, or vaccination status, and social distancing protocols such as COVID-19 symptom screening and face masks were implemented. As of 9/15/2022, a total of 36 individuals completed the study and 18 participants dropped from the study at UCSD/VMRF. Of the 31 participants with baseline MRI at UCSD/VMRF, 22 individuals completed a follow up MRI at UCSD/VMRF. 9 participants did not complete a follow up MRI at UCSD/VMRF.
3. Final total for both study sites, a total of 99 individuals were enrolled in the study and a combined total of 78 completed the study, and 26 participants dropped. There were a combined total of 51 baseline MRIs and 40 follow up MRIs, with a total of 11 individuals who were study drops and did not complete the MRI at follow-up.
4. RedCap Data Base clinical database entry has been completed at both study sites for all outcome metrics and scales.
5. We have obtained an approval from the DOD for a No Cost Extension until Sept 15, 2023 that will allow us to complete the longitudinal analysis, prepare and submit manuscripts and disseminate data.

Plans During the Next reporting period:

3.3 What do you plan to do during the next reporting period to accomplish the goals and objectives?

1. Ongoing aggregation of exercise log variables which include variety, frequency and duration of exercise over the 18-month time period.
2. All MRI imaging data has been transferred to UCSD to complete post-processing and commencement of longitudinal analysis.
3. Commencement of Longitudinal analysis.

4. Impact

This proposal will elucidate the long-term effects of exercise intensity and fitness levels on neural circuitry and cognitive function important for EF, the most common form of cognitive impairment in PD. We will conduct a longitudinal naturalistic (observational) 18-month study monitoring exercise intensity and fitness level (motor vs. cardiovascular) along with EF. This approach is novel since it examines “real world” practices using objective measures (accelerometers, fitness, neuroimaging) that translate into direct exercise prescription guidelines for patients that can be performed in the community and a means to monitor exercise activity and provide insights to guide neurorehabilitation and exercise policies for stake holders. We will also investigate exercise and fitness related changes in neural substrates important for EF and to identifying brain circuits amendable to plasticity and repair. These studies will also highlight which specific aspects of EF performance, such as switching and/or working memory, that may be associated with greater gains in fitness and intensity. Complementary Animal studies be conducting simultaneously by Dr. Holschneider (PI- Award number W81XWH18-1-0666) will provide critical synergistic and complementary insights by helping to identify specific brain networks of interest impacted by exercise as well specific cognitive gains (e.g Mental flexibility vs. working memory) as identifying exercise induced molecular mechanisms to be examined such as inflammatory and trophic factors. The overall impact of the study is to provide evidence-based medicine to support a cognitive rehabilitation program for individuals through an exercise prescription. In addition, findings from these studies will also help provide important insight regarding dimensions of cognitive performance and brain circuitry that are most targeted through cognitive neurorehabilitation exercise programs. Finally, through combining our findings with Dr. Holschneider’s complementary animal study, we will be able to begin to better understand and identify

potential peripheral targets of exercise that may underlie central CNS benefits to further enhance cognitive health in PD.

5. Changes/Problems

1. Due to COVID-19 precautions, and the fact that patients were not able to come in for follow up study visit assessments for a period of time both at USC and UCSD, we requested and obtained a second One year No Cost Extension until 9-15-2023 to complete the longitudinal analysis of our study.

6.Products: The following five papers were accomplished by DOD support as of Sep 15, 2022.

1. Donahue EK, Venkadesh S, Bui V, Tuazon AC, Wang RK, Haase D, Foreman RP, Duran JJ, Petkus A, Wing D, Higgins M, Holschneider DP, Bayram E, Litvan I, Jakowec MW, Van Horn JD, Schiehser DM, **Petzinger GM**. Physical Activity Intensity is Associated with Cognition and Functional Connectivity in Parkinson's disease, 2022. *Parkinsonism Relat Disord*. 2022 Sep 24;104:7-14. doi: 10.1016/j.parkreldis.2022.09.005. Online ahead of print. PMID: 36191358
2. Donahue EK, Bui V, Foreman RP, Duran JJ, Venkadesh S, Choupan J, Van Horn JD, Alger JR, Jakowec MW, **Petzinger GM**, O'Neill J. Magnetic resonance spectroscopy shows associations between neurometabolite levels and perivascular space volume in Parkinson's disease: a pilot and feasibility study. *NeuroReport*. 2022 May; 33(7): 291-6.
3. Venkadesh S, Shakeri H, Waugh RE, Donahue EK, Bui V, Petkus AJ, Jakowec MW, Schiehser DM, **Petzinger GM**, Van Horn JD. Spatiotemporal patterns of resting-state Blood-Oxygen-Level-Dependent signal coherence associated with cognitive impairment in Parkinson's disease. (In review)
4. Petkus AJ, Venkadesh S, Jakowec MW, Schiehser DM, Van Horn JD, Petzinger GM. Physical fitness, cognitive performance, and functional connectivity in Parkinson's disease. (In preparation) · Venkadesh S, Shakeri H, Waugh RE, Donahue EK, Bui V, Petkus AJ, Jakowec MW, Van Horn JD Schiehser DM,. **Petzinger GM**, Spatiotemporal patterns of resting-state blood-Oxygen-Level-Dependent signal coherence associated with cognitive impairment in Parkinson's disease. (In preparation)
5. Donahue EK, Foreman RP, Duran JJ, Venkadesh S, Bui V, Petkus AJ, Bayram E, Litvan I, Holschneider DP, Choupan J, Van Horn JD, O'Neil J, Schiehser DM, Jakowec MW, **Petzinger GM**. Associations between white matter perivascular spaces and cognition in Parkinson's disease. (In preparation)

7.Participants & Other Collaborating Organizations

University of Southern California

Name: Giselle Petzinger, MD

Project Role: PI

Research Identifier: N/A

Nearest person month worked: 0.67 mo

Contribution to the project: No change. Project design, development of protocol, and setting up database, and supervising collaboration with UCSD VA. Setting up of contracts of Data Sharing. Setting up imaging protocol at USC and UCSD and sharing of imaging data storage and analysis including contract agreements. Training undergraduate students on fitness metrics and wearables. Setting up meeting schedules between collaborators at UCSD-VA and USC. Responsible for all regulatory (IRB) documentation. Patient Recruitment and safety. Works on Patient scheduling. Overseeing wearable and log data collection, redcap data entry, statistical analysis, interpretation and preparation of data results. Oversees weekly meetings with group through zoom to discuss data, results, interpretation.

Name: Jennifer Hui, MD

Project Role: co-I

Research Identifier: N/A

Nearest person month worked: 0.03 mo

Contribution to the project: No change. Reviewing UPDRS Scale for study, patient recruitment, review of study protocol. Assisting with data analysis and interpretation.

Name: Andrew Petkus, Ph.D.

Project Role: co-I

Research Identifier: N/A

Nearest person month worked: 0.6 mo

Contribution to the project: No change. Development of Neuropsychiatric battery and assistance in Database design and development. Conducts neuropsychological assessments. Conducting statistical analysis and interpretation.

Name: Vy Bui, BS

Project Role: Research coordinator

Research Identifier: N/A

Nearest person month worked: 2.4 months

Contribution to the project: Establishment of Database, creation of exercise logs and organization of all scales for patient visits. Setting up patient visit and wearable calendars. Training undergraduate students on wearable education to patients. Works on patient recruitment and scheduling. Assessment of Fitness metrics and Gait and balance metrics. Assisting with follow up calls to patients for wearable devices and logs. Data entry. Coding of exercise logs.

University of Virginia:

Name: Jack Van Horn, Ph.D. (Moved from USC to University of Virginia)

Project Role: Co-Investigator

Research Identifier: N/A

Nearest person month worked: 0.36mo

Contribution to the project: Imaging data transfer from UCSD and USC. Imaging processing until RA is hired next quarter. Set up of Imaging Data base at University of Virginia. Assisting with data preparation and participating in weekly data discussion and interpretation.

Name: Siva Venkadesh

Project Role: Postdoc Research Assistant

Research Identifier: N/A

Nearest person month worked: 2.4mo

Contribution to the project: Imaging processing and Data analysis

UCSD/VA San Diego

Name: Dawn Schiehser, PhD

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 0.45 calendar months

Contribution to Project: Dr. Schiehser is the site PI of this multi-site study and oversees all aspects of the project that take place at the UCSD and UCSD/VA, including patient recruitment, cognitive behavioral assessment, fitness evaluation/monitoring, and neuro-imaging as well as supervising staff.

Name: Stephanie Lessig, MD

Project Role: Co-Investigator

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 0.04 calendar months

Contribution to Project: Dr. Lessig is a board-certified movement disordered specialized neurologist who aids with recruitment and testing patients on the UPDRS.

Name: Deyran Paredes

Project Role: Research Assistant

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 0.89 calendar months

Contribution to Project: Deryan is a research assistant who aids in patient recruitment and communication, cognitive behavioral assessment, fitness evaluation/monitoring, and neuroimaging.

Name: David Wing

Project Role: Collaborator

Research Identifier: N/A

Nearest person month worked: 0.3 months

Contribution to the project: No change. Creation of exercise logs and organization of data collection for wearable devices. Supervising protocol for wearable devices and logs. Training undergraduate students on wearable device use in study participants. Work on RedCap database with USC. Assisting with data coding.

Name: Michael Higgins

Project Role: Research Associate

Research Identifier: N/A

Nearest person month worked: 0.75 months

Contribution to the project: No change. Organization of data collection for wearable devices. Establishing database for the wearable devices and logs. Training undergraduate students on wearable device use in study participants. Setting up data transfer of wearable devices from USC to UCSD-VA for data analysis. Assisting with data coding.

4. Special Reporting Requirements N/A

5. Appendices

NONE