AWARD NUMBER: W81XWH-18-1-0665

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

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REPORT DATE: October 2020

TYPE OF REPORT: Annual

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

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2020	Annual	9/15/2019 - 9/14/2020

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH18-1-0665

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S). Giselle Petzinger

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University of Southern California
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Los Angeles, CA, 90033-9263

8. PERFORMING ORGANIZATION REPORT NUMBER

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

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

10. SPONSOR/MONITOR'S ACRONYM(S)

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

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

13. SUPPLEMENTARY NOTES

14. ABSTRACT

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. $V0_2$max). 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 circuity 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.

15. SUBJECT TERMS
Executive Function; Parkinson's disease; Motor Fitness; Cardiovascular Fitness; Exercise

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	8	19b. TELEPHONE NUMBER *(include area code)*

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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 circuity (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

4. 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.

Accomplishment under these goals:

1. Due to COVID-19 precautions, all in person study assessments we put on hold starting March 2020.

2. At USC, the study has just restarted since August 2020. Following COVID-19 safety and compliance training of all research personnel and institution of COVID-19 safety precaution protocols at our clinical research sites, USC has reinitiated in-person clinical research testing since August 2020.

3. At UCSD/VMRF, the study remains on Administrative Hold since March 2020. This requires that all in-person testing be placed on hold at UCSD until further notice. This has affected the enrollment of our final

study participant at UCSD and will continue to principally affect all 9-month mid-term patient study evaluations.

4. No new drops of study participants during Y2Q4. At USC during Y2Q4, as of 9/15/2020, the total number of subjects who were enrolled is 50; the total number of subjects who are currently enrolled and active in the study is 47 (3 drops) at USC. At UCSD/VMRF during Y2Q4, no new participants were enrolled. As of 9/15/2020, the total number of subjects who were enrolled is 49; the total number of subjects who are currently enrolled and active in the study is 43 (6 drops) at UCSD.

5. Because of COVID-19, All 9-month mid-term patient study evaluations have been affectively limited due to inability to bring patients into clinical sites for the mid-term assessments.

6. At USC, Final Study Visits commenced since in-person study assessments began on August 2020. As of 9/15/20. 11 participants out of 90 actively enrolled study participants (from USC N=47 and UCSD N = 43) have completed the DOD longitudinal study.

7. For both USC and UCSD we continued to deploy wearable devices, logs and self-report questionnaire to study participants every 3 months for all active study participants.

8. RedCap Data Base clinical database entry ongoing at both sites for all outcome metrics and scales.

9. Baseline cross-sectional analysis has commenced in collaboration with UCSD and U. Virginia.

Plans During the Next reporting period:

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

1. Due to COVID-19 precautions, the study remains on Administrative Hold at UCSD. This requires us to temporarily stop in-person testing until further notice. This will principally affect all 9-month mid-term patient study evaluations.

2. AT USC, study is currently seeing study participants in person and will continue with the final study assessments of all actively enrolled study participants at USC.
3. We will continue to deploy and collect devices and activity log data on schedule (i.e., every 3 months for 18 months).

4. Once restrictions are lifted, we will resume recruitment and enrollment to reach the total number of subjects (n = 50) required for this study as well as resume scheduling follow-up testing.

5. Once restrictions are lifted, we will resume final study visits at UCSD.

6. We will continue with baseline data cross-sectional analysis.

7. We will begin completion of data uploading for final visit assessments.

1 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 neuro-rehabilitation 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 circuity that are most targeted through cognitive neurorehab 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.

2 Changes/Problems

1. Due to COVID-19 precautions, the study remains on Administrative Hold at UCSD. This requires us to temporarily stop recruitment, enrollment, and in-person testing until further notice. This will principally affect all 9-month mid-term patient study evaluations.

2. Due to several San Diego site personnel leaving and/or not requiring salary as originally budgeted (please see Section 3) as well as a one quarter delayed start in data collection due to prolonged DoD IRB approval in Year 1, the VA San Diego/UCSD is requesting a carryforward of funds greater that the 25% of their total annual budget. Thus, I am passing on the request to you (The DoD) to carry forward their remaining funds from Year 2 to Year 3.

3. We will continue to deploy and collect devices and activity log data on schedule (i.e., every 3 months for 18 months).

4. Actual Problems or delays and actions to resolve them: Please see above. We will resume in-person data collection once administrative hold restrictions are lifted at UCSD. Due to complete shut-down of university facilities, faculty, and staff will be continuing to work on grant operations at home and will be continued to be provided salary for coverage of work effort on the grant.

3 Products

Nothing to report

1. Participants & Other Collaborating Organizations

USC Report Period 09/15/2019-09/15/2020

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: Tiana McMann
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1.46 calendar months
Contribution to Project: Tiana is a research assistant who aids in patient recruitment and communication, cognitive behavioral assessment, fitness evaluation/monitoring, and neuro-imaging.

Name: Vince Filoteo, PhD
Project Role: Co-Investigator
Research Identifier: N/A
Nearest person month worked: 0.04 mo (non-salaried as of 9/1/19).
Contribution to the project: Development of neuropsychiatric battery and assistance with statistical design. Establishment of Consensus for MCI criteria between USC and UCSD
Dr. Filoteo's UCSD appointment changed to non-salaried adjunct; as of 9/1/19, he will serve as a non-salaried consultant to the project. Helping with data analysis and MCI status assessment of study participants.

Name: Irene Litvan, MD
Project Role: Co-Investigator
Research Identifier: N/A
Nearest person month worked: 0.03 mo (non-salaried)
Contribution to the project: No change. Reviewing UPDRS Scale for study, patient recruitment, and the review of study protocol. Assisting with data analysis and interpretation of data.

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 devise 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 devise use in study participants. Setting up data transfer of wearable devices from USC to UCSD-VA for data analysis. Assisting with data coding.

2. Special Reporting Requirements N/A

3. Appendices

NONE