AWARD NUMBER: W81XWH-18-1-0665

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

PRINCIPAL INVESTIGATOR: Giselle Petzinger MD

CONTRACTING ORGANIZATION: University of Southern California Los Angeles, California 90089-0701

REPORT DATE: Oct 2019

TYPE OF REPORT: Annual

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

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2019	Annual	9/15/2018 – 9/14/2019

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
W81XWH-18-1-066
5

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S). Giselle Petzinger

E-Mail: petzinge@med.usc.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

University of Southern California
Dept. Contracts & Grants
3720 S. Flower Street, 3rd Floor
Los Angeles, California 90089-0701

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. $V0_2max$). 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		19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

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

3. Accomplishments

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 tests 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. As of 9/15/19, the total number of subjects combined from both USC and UCSD/VMRF who were enrolled is 57; The total number of subjects who are currently enrolled and active in the study is 55 (1 dropped out at USC and 1 dropped out at UCSD/VA). The total target enrollment is 100 participants.
2. As of 9/15/19 the total number of participants who completed fMRI combined from both USC and UCSD/VMRF is 33. The total target enrollment for fMRI is 40.

3. The mailing of Wearable devices to study participants is ongoing. The wearables are returned to respective clinical site and uploaded to EPARC database.
4. The RedCap Data Base is fully operational, and all data is being dual uploaded and compared for integrity at both USC and UCSD/VA clinical study sties.
5. Continual review for IRB, USAMRMC HRPO approved at USC in August 13, 2019 and submitted HRPO 8/28/2019. HRPO protocol log number E00149.1a
6. Executive Board Meeting completed on 4/24/19

Plans During the Next reporting period:

We will continue to recruit and enroll participants at USC and UCSD/VA.
We are on target to have all participants enrolled at USC by January 2020, and UCSD/VA by March 2020.
We are on target to complete all baseline imaging within the next reporting quarter (USC and UCSD/VA)
We will commence 9-month follow up visits in the next quarter of reporting.
Planning has commenced for executive Board meeting to be held Dec 7, 2018

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 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.

5 Changes/Problems

No Problems to report

6 Products

Nothing to report

7. Participants & Other Collaborating Organizations

USC Report Period 06/15/2019-09/15/2019

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.

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

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.

Name: Vy Bui, BS
Project Role: Research coordinator
Research Identifier: N/A
Nearest person month worked: 3.6 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.

Name: Jack Van Horn, Ph.D. (Replaced Meng Law, MD)
Project Role: Co-Investigator
Research Identifier: N/A
Nearest person month worked: .40 mo
Contribution to the project: Advisement on imaging protocol at USC and UCSD and data transfer between UCSD and USC. Advisement on imaging analysis

Dr. Van Horn has relocated to The University of Virginia. We have established a consortium agreement with the University of Virginia and set up a subcontract which will include Dr. Van Horn's effort and the effort of a Research Assistant.

Name: Carinna Torgerson
Project Role: Research assistant
Research Identifier: N/A
Nearest person month worked: 1.98 mo
Contribution to the project: Imaging processing and Data analysis

Carinna Torgerson's effort ended on the project due to Dr. Van Horn's departure from University of Southern California and the establishment of a subcontract with University of Virginia.

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 will oversee 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: Vincent Filoteo, PhD
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 0.06 calendar months
Contribution to Project: Dr. Filoteo will be responsible for neuropsychological testing and will work with USC to ensure standardization of the outcome measures.

Name: Stephanie Lessig, MD
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 0.05 calendar months
Contribution to Project: Dr. Lessig is a board-certified movement disordered specialized neurologist who will aid with recruitment and testing patients on the UPDRS.

Name: Fattah Nahab, MD
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 0.08 calendar months
Contribution to Project: Dr. Nahab is a board-certified movement disordered specialized neurologist who will aid with recruitment and testing patients on the UPDRS. Dr. Nahab will also be responsible for scanning participants and overseeing quality control of the brain imaging data that will be collected in this study.

8. Special Reporting Requirements N/A

9. Appendices

NONE