Department of Defense
U.S. Army Medical Research and Materiel Command
Congressionally Directed Medical Research Programs
Fiscal Year 2018 Parkinson's Research Program
Investigator-Initiated Research Award: Partnering PI Option
Peer Review Summary Statement

CDMRP Log Number: PD180091
Review Panel: Exercise - Cognitive and Psychiatric Symptoms
Discussion Period: 12/05/2018-12/07/2018

Project Duration: 36 months
Budget Requested: $1,541,585
Direct Costs: $1,150,876
Indirect Costs: $390,709

Title: Exercise and Plasticity in PD: Functional and Structural Evidence in the Cortex and the Spinal Cord

Grants.gov ID Number	GRANT12720142	GRANT12718752
Principal Investigator	Angelo Quartarone	Felice Ghilardi
Performing Organization	Universita' Degli Studi Di Messina	The Research Foundation CUNY - The City College
Contracting Organization	Universita' Degli Studi Di Messina	
Budget Requested	$860,400	$681,185
Direct Costs	$717,000	$433,876
Indirect Costs	$143,400	$247,309

OVERVIEW

The Principal Investigators (PIs) of this application propose to determine specific plasticity mechanisms underlying the general behavioral improvements after exercise in Parkinson’s disease (PD). The project’s specific aims are to (l) determine whether multidisciplinary intensive rehabilitation treatment (MIRT) in patients with PD restores motor cortex long-term potentiation (LTP)–like plasticity to normal levels and enhances beta modulation during a reaching task as in normal subjects and improves the formation and retention of motor skills and assess the changes produced in fractional anisotropy and mean diffusivity of white and grey matter as well as those in brain connectivity; (2) evaluate muscle synergies and spatiotemporal organization of the spinal motoneuronal output during gait and reaching movements to define the presence of functional changes in spinal cord mechanisms and connectivity; and (3) evaluate changes in the microstructure of sleep induced by MIRT.

	Average Score	Standard Deviation
Overall Evaluation *Rating Scale: 1.0 (highest merit) to 5.0 (lowest merit)*	1.7 **(Excellent)**	0.1
Criteria *Rating Scale: 10 (highest merit) to 1 (lowest merit)*	**Average Score**	
Research Strategy and Feasibility	7.5	
Impact	8.4	
Principal Investigator and Research Team	7.5	
Synergy	7.8	

SCORED CRITERIA

Research Strategy and Feasibility
Average Score: 7.5

Scientist Reviewer A

Strengths: The proposal draws upon the research team's pairing of exercise in PD with transcranial magnetic stimulation (TMS) and structural neuroimaging with particular focus on network and connectivity analyses. This project could generate results on the mechanisms of action of intensive exercise on cortical-spinal plasticity phenomena, skill formation, and sleep and ultimately guide better rehabilitation practices in PD. The proposal leverages the ongoing PD MIRT research at Movement Disorders Clinics at the University of Messina, which is currently paid for in total by the Italian national health care system. The PIs will test 30 patients with PD (at 3 time points) and 20 age-matched controls. The Movement Disorders Clinics at the University of Messina see over 150 de novo patients per year, and many PD patients select to undergo MIRT. The facility has 20 beds dedicated to this particular treatment for PD. The work plans to test patients at baseline and at the end of the 4 weeks' MIRT; controls subjects will be tested only at baseline. At each time point, patients will undergo 5 Hz repetitive TMS (rTMS) paired associative stimulation (PAS) to measure structural plasticity and brain connectivity, muscle synergies, and spinal maps during gait and reaching movements and sleep recordings with high-density EEG. Three months after MIRT, to ascertain whether the structural and functional changes are still present, in patients they will perform only 5 Hz rTMS PAS and MRI recordings. The preliminary data (while extremely small) demonstrate the majority of the methods; it would be helpful to have some diffusion-based connectivity network analysis methods, as these are a large portion of the work. The diffusion-based connectivity metrics are of interest although could be paired with 2 other techniques to optimize the work (arterial spin labeling for perfusion as it is mentioned in the proposal about blood flow and functional connectivity MRI) since pairing both of these with the structural diffusion work would be of particular interest to understand how exercise alters brain networks. The pairing of the MRI, EEG, and TMS metrics is novel; however, it needs to be noted how these metrics will be used together in the analysis.

Weaknesses: There are a few factors in the proposal that need consideration. Some explanation of the comparison methods for each independently and together should be included. The MIRT regimen appears to be quite involved. It is notable that patients are completing 60 sessions (4 weeks, 5 days per week, 3 times per day). There is some concern with patients undergoing this and also the other metrics involved in the study as far as patient compliance, although it appears the group has ample experience in this matter with prior work.

Scientist Reviewer B

Strengths: The scientific rationale supports the research through background and preliminary data in that the applicant has previously shown that MIRT improves motor symptoms and increases BDNF-TrkB signaling in PD and improves quality of life and sleep quality. They provide background data that PD patients have reduced plasticity (ie, reduced LTP induced by PAS TMS). The applicant proposes that the enhanced BDNF-TrkB signaling is associated with changes in cortical plasticity and thus that MIRT can rescue cortical plasticity. They plan to do 5 Hz rPAS25ms before and after MIRT, supposing that there will be less facilitation in PD before MIRT and MIRT will restore to normal, as compared to healthy control participants. They also provide background that 5 Hz rTMS improves retention of motor skills on a rotation task and preliminary data that MIRT also improves this. They provide background that PD patients have abnormal structural connectivity and that impaired longer range connections lead to increased local topographical organization and enhanced local community paradigm correlation. They propose that MIRT will ameliorate this and look for changes in geometrical markers to identify changes in latent network geometry after MIRT. They have preliminary data showing that MIRT increases beta modulation. They propose that memory deficits in PD come from deficient LTP that fail to trigger mechanisms to promote slow wave sleep, and preliminary data are shown that MIRT improves sleep quality (PD Sleep Scale). The study rationale addresses mechanisms of exercise-induced changes in plasticity and is a fascinating approach to investigation of these changes from multiple different aspects of plasticity. The applicants do address some potential problems. They do have access to the patient population.

Weaknesses: In some cases, the scientific rationale related to preliminary data is difficult to discern because figures are too small, are hard to read, and don't have adequate legends or axis names. There is concern that the study design will not be able to attain reproducible results because the sample size will be too small, and the statistical plan does not address the high number of outcomes. There are no defined primary outcomes, and there are many tests and analyses proposed for each aim. There are a total of 8 main outcomes and each is compared pre to post MIRT, and post MIRT is also compared to control outcomes and also another measure at 3 months. The investigators mention correcting for multiple comparisons but don't account for this in the power and sample size calculation. There is also insufficient detail about the statistical analyses, particularly for measures that have complex outcomes (imaging data, EMG date for over 20 muscles). There is also concern that the study design may not be able to distinguish between effects of MIRT and effects of 5Hz rPAS25ms at the second time point since there is no comparison to a no-exercise group of PD participants. They do not adequately address alternative strategies. There is concern that the exclusion criteria will make it hard to recruit participants. They exclude participants with sleep problems but don't provide detail for this. It is unclear if this will include rapid eye movement sleep behavioral disorder. Sleep problems are so prevalent in PD (often quoted as 74% to 98% of patients affected).

Impact
Average Score: 8.4

Scientist Reviewer A

Strengths: If successful, the proposal could generate a link between exercise and PD. The literature base has data to support that exercise is beneficial to PD clinical manifestation. The study addresses the focus area, "Biological mechanisms of impact from exercise on neurodegeneration in Parkinson's disease." The long-term outcomes from the work could be significant. Their proposal to use 5Hz rPAS25ms in patients with PD before and after MIRT as well as structural connectivity patterns in both global and local PD networks is novel.

Weaknesses: The data are largely correlative in nature and allude to causation. The investigators want to get to the heart of the question as to the mechanism of excessive action in ameliorating PD. It is not certain how this knowledge will adjust the field moving forward; it could be that patients are prescribed more exercise continually or a potential other therapy that contributes to these factors.

Scientist Reviewer B

Strengths: If successful, the project has potential to develop an understanding of mechanisms through which exercise enhances plasticity to improve motor symptoms, sleep, and motor learning in PD. It also has potential to help understand plasticity deficits underlying motor, learning, and sleep symptoms in PD. It addresses the focus area.

Weaknesses: The project doesn't provide additional information about clinical impact beyond what is already known.

Consumer Reviewer

Strengths: This application addresses the FY18 Parkinson's Research Program Investigator-Initiated Research Award focus area, "Biological mechanisms of impact from exercise on neurodegeneration in PD." The mechanisms by which exercise improves motor and cognitive function in PD patients are not well defined, although the benefit of exercise is well accepted. It is believed that exercise may counteract—or oppose—neurodegeneration mechanisms. Therefore, the applicant proposes using MIRT, a programed intense exercise program (three 1-hour sessions per day for 4 weeks). Using techniques that can measure structural and functional changes in the cortex and in the spinal cord, they will determine the impact of intense exercise (MIRT) compared to peer-matched no-exercise controls. In addition, a sleep study will be conducted that measures changes in sleep performance. The results would benefit PD patients by helping to define optimal therapeutic exercise interventions in earlier, perhaps even in prodromal, stages of the disease. Early detection and intervention could potentially freeze the disease state at an earlier, less negatively impactful stage, improving the quality of life of PD patients.

Weaknesses: Assuming technical success, there are no significant weaknesses.

Principal Investigator and Research Team
Average Score: 7.5

Scientist Reviewer A

The PI on this application is Angelo Quartarone, MD. Dr Quartarone is a professor of neurology at the University of Messina, the director of the Neuromodulation Labs, and research collaborator at IRCCS Bonino Pulejo. He received an MD from Universita'degli Studi, Messina, Italy, in 1990. The The Partnering PI on the application is Maria Felice Ghilardi, medical professor at City University of New York (CUNY) School of Medicine, New York. She received an MD from Universita'degli Studi, Milano, Italy, in 1983.

Strengths: The PI currently coordinates a neurophysiological and neuroimaging research group of more than 10 people. His expertise relates to TMS and on structural neuroimaging with particular focus on network and connectivity analyses. The main focus of the Partnering PI's research is motor control and learning, PD, and brain plasticity. The proposed research team is very experienced and includes pioneers of the methods outlined in the application. The investigators have published manuscripts in relevant journals on the techniques in the application. The team takes into consideration the multiple roles needed to successfully fulfill this line of research.

Weaknesses: It is not completely certain how the team will be organized. The transatlantic nature of the investigators needs discussion.

Scientist Reviewer B

Strengths: The PI and team demonstrate good potential for success in this project in that they are experienced researchers with established expertise in most of the techniques proposed in the application. They are accomplished researchers with good publication track records.

Weaknesses: There is not a statistician on the project and this is a very complex project, so that is a significant weakness. Although the applicants briefly mention a consultant with sleep expertise, the main team does not have that expertise. The PI and Partnering PI propose effort of over 15% but not salary support for the PI; greater explanation of this is needed.

Synergy
Average Score: 7.8

Scientist Reviewer A

Strengths: Both PIs have expertise in their respective fields.

Weaknesses: It is not certain why the work is not solely completed at the Italian site as it appears they largely have the complete team in place to perform the work.

Scientist Reviewer B

Strengths: The productivity of the partnership will exceed individual ability due to the individual areas of expertise of the PI and Partnering PI. The contributions are appropriate, and there is a good description of ways for communication and decision making.

Weaknesses: No weaknesses were noted.

Discussion Notes

Although the expertise of the PIs is unquestionable, some panel members desired greater clarity on why a partnership was needed given that Dr Quartarone's team appears to be able to address the majority of research needs.

UNSCORED CRITERIA

Budget

Scientist Reviewer A

The budget appears sound.

Scientist Reviewer B

The budget does not exceed the total maximum allowed and is appropriate.

Application Presentation

Scientist Reviewer A

The proposal is written clearly and presents well. There are a very few regions where discrepancies were found.

Scientist Reviewer B

The figures in the application are hard to read and are missing appropriate legends or titles in most cases. The organization of the application was hard to follow. This didn't influence the overall review but did make it take longer to review.

Environment

Scientist Reviewer A

The environment is appropriate for the proposed line of work. The institutions are well positioned to perform the line of research. The resources and organizations' support are in place to facilitate the proposal.

Scientist Reviewer B

The environment is appropriate for the research with excellent resources and agreements. Institutional support seems appropriate.