

**AWARD NUMBER: W81XWH-19-1-0790**

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

**PRINCIPAL INVESTIGATOR: Maria Felice Ghilardi**

**CONTRACTING ORGANIZATION: City College of New York, New York, NY**

**REPORT DATE: October 2022**

**TYPE OF REPORT: Annual**

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

**DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited**

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

<b>1. REPORT DATE</b> October 2022		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 30Sep2021-29Sep2022	
<b>4. TITLE AND SUBTITLE</b>  Exercise and Plasticity in PD: Functional and Structural Evidence in the Cortex and the Spinal Cord				<b>5a. CONTRACT NUMBER</b> W81XWH-19-1-0790	
				<b>5b. GRANT NUMBER</b>	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Angelo Quartarone, M. Felice Ghilardi  E-Mails: <a href="mailto:aquartar65@gmail.com">aquartar65@gmail.com</a> ; <a href="mailto:lice mg79@gmail.com">lice mg79@gmail.com</a>				<b>5d. PROJECT NUMBER</b> W81XWH-19-1-0790	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> University of Messina, Piazza Pugliatti, 98100, Messina, Italy City College of New York, 160 Convent Avenue, New York, NY, 10128				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> We will study the effects of intensive rehabilitation in PD on plasticity with a multimodal approach. We will define first, whether exercise in PD restores the potentiation of the motor cortex to normal levels with both 5 Hz-rTMS PAS and beta modulation and whether such improvements are accompanied by structural changes studied with diffusion MRI tractography and network analysis (Aim 1). With the study of muscle synergies and spatiotemporal organization of the spinal motoneuronal output during gait and reaching movements we will define the presence of functional changes in spinal cord mechanisms and connectivity and whether such changes are global or involve selective districts (Aim 2). Finally, we will study post-exercise changes in sleep pattern, as sleep is impaired in PD and plays a crucial role in the definition of plasticity-related phenomena (Aim 3). This project will generate breakthrough data on the mechanisms of exercise, novel biomarkers to monitor efficacy of treatments and thus, possibly leading to better restorative, disease-modifying and symptomatic therapies for PD.					
<b>15. SUBJECT TERMS</b> Plasticity, Parkinson's disease, sleep, aerobic exercise, skill retention, MRI, TMS, high density EEG, rehabilitation					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  Unclassified	<b>18. NUMBER OF PAGES</b>  9	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRDC
<b>a. REPORT</b>  Unclassified	<b>b. ABSTRACT</b>  Unclassified	<b>c. THIS PAGE</b>  Unclassified			<b>19b. TELEPHONE NUMBER</b> (include area code)

## TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems	6
6. Products	7
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendices	9

## 1. INTRODUCTION:

We will study the effects of intensive rehabilitation in PD on plasticity. In Aim 1, we will define whether exercise in PD restores plasticity in the motor cortex with 5 Hz-rTMS PAS, beta modulation, and structural alterations with MRI. With Aim 2 we will study muscle synergies and spatiotemporal organization of the spinal motoneuronal output during gait and reaching movements. With Aim 3, we will study post-exercise changes in sleep pattern. This project will generate information on the mechanisms of exercise, novel biomarkers to monitor efficacy of treatments.

## 2. KEYWORDS:

Plasticity, Parkinson's disease, sleep, aerobic exercise, skill retention, MRI, TMS, high density EEG, rehabilitation

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

Task 1a: Assessing the effect of MIRT on cortical plasticity tested with rPAS  
Task 1b: Assessing the effect of MIRT on structural cortical plasticity and brain connectivity tested with MRI  
Task 1c: Assessing the effect of MIRT on movement-related beta modulation  
Task 1d: Assessing the effects of MIRT on motor skills formation with reaching tasks  
Task 1e: Assessing the effects of MIRT on EEG correlates of motor skills formation  
Task 2a: Assessing the effect of MIRT on muscle synergies during gait  
Task 2b: Assessing the effect of MIRT on muscle synergies during reaching movements  
Task 3a: Assessing the effect of MIRT on sleep microstructure

### What was accomplished under these goals?

1. We have received HRPO Approval on November 17, 2021 to start our research (E00984.1a - Study Number 54/19, Proposal Number PD180091, Award Number W81XWH-19-1-0810) from Ms. Kimberly Odam, MS, CIP, Director Human Research Protection Office, ORP, US Army Medical Research and Development Command. For this reason, we were not able to proceed to the test of patients we had already selected.
2. The Messina group has so far tested 15 normal controls and 12 PD patients before and after MIRT and we are working on the transfer of such data for analysis.
3. Drs. Quartarone and Ghilardi met in June in Italy to finalize the strategy for data collection, transfer and analyses.
4. A paper has been recently accepted for publication in *Frontiers in Neuroscience*: "Movement-related Beta ERD and ERS Abnormalities in Neuropsychiatric disorders". Another paper on the Pathophysiology of dystonia is ready to be submitted.
5. Drs. Ghilardi and Quartarone organized and directed the Workshop on Synaptic plasticity focused on PD and related disorders that was held in Florence June 7-10, 2022.
6. Drs. Ghilardi and Quartarone participated as speakers and discussants to the First International Forum on Neurodegenerative diseases (Milan, October 6-7, 2022) organized by the Prada Foundation

**What opportunities for training and professional development has the project provided?**

“The 2022 Fresco International Workshop on Synaptic Plasticity and Advances in Parkinson’s Disease, Florence (Italy) June 7–10, 2022”, organized by Drs. Quartarone and Ghilardi presented data and concepts related to the DOD activity.

**How were the results disseminated to communities of interest?**

1. Four papers have been published as peer-reviewed articles. Another paper “Movement-related Beta ERD and ERS Abnormalities in Neuropsychiatric disorders” has been recently accepted for publication in Frontiers in Neuroscience. A paper on the Pathophysiology of dystonia is ready to be submitted. Another paper on gamma modulation is almost ready to be submitted for publication.
2. Drs. Ghilardi and Quartarone edited the book “Neuroplasticity in neuropsychiatric disorders” (Handbook of Neurology Series) which was published in April 2022.
3. Drs. Ghilardi and Quartarone organized and directed the Workshop on Synaptic plasticity focused on PD and related disorders that was held in Florence June 7-10, 2022. Both of them lectured in the meeting about plasticity in Parkinson.
4. Drs. Ghilardi and Quartarone participated as speakers and discussants to the International Forum on Neurodegenerative diseases (Milan, October 6-7, 2022)
5. Dr. Ghilardi presented data on exercise, rehabilitation and plasticity in PD in several Webinars, including the webinar: “Visual disorders in PD”, April 7, 2022, Fresco Parkinson Institute.

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

We have now increased the rate of recruitment and testing capability to compensate for the accumulated delay. With the current plan and capability, based on the month of October’s activity, we foresee to recruit and complete the study for two patients and two controls per month. Analyses will be performed shortly after.  
We are finalizing: a review focusing on the putative role of motor cortex in the pathophysiology of PD; a paper on the effect of practice on movement-related gamma modulation in normal subject and in patients with PD. An abstract will be presented at SFN 2022 in San Diego.

**4. IMPACT::**

**What was the impact on the development of the principal discipline(s) of the project?**

*Nothing to Report.*

**What was the impact on other disciplines?**

*Nothing to Report.*

**What was the impact on technology transfer?**

*Nothing to Report*

**What was the impact on society beyond science and technology?**

*Nothing to Report.*

**5. CHANGES/PROBLEMS:**

The direction, strategy and goals of the program have not changed. Nevertheless, the current rate of recruitment has been increased.

**Actual or anticipated problems or delays and actions or plans to resolve them**

The direction, strategy and goals of the program have not changed. We are in the process of recovering the delay accumulated due to Covid pandemic emergency. Recruitment has been significantly sped up and data analyses have started; data collection will be completed in less than a year. However, we will need extra time with a no-cost extension to finalize analyses and publication of the data.

## Changes that had a significant impact on expenditures

The impact of pandemic has changed our capability to spend money according the already approved budget. We will likely need a no-cost extension of another year and to reschedule the budget accordingly.

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

### Significant changes in use or care of human subjects

None.

### Significant changes in use or care of vertebrate animals

N/A

### Significant changes in use of biohazards and/or select agents

N/A

## 6. PRODUCTS:

- **Publications, conference papers, and presentations**

### Journal publications.

1. Tatti E, Ferraioli F, Cacciola A, Chan C, Quartarone A, Ghilardi MF. Modulation of Gamma Spectral Amplitude and Connectivity During Reaching Predicts Peak Velocity and Movement Duration. *Front Neurosci.* 16, 2022, 836703, PMID: 35281507 (published); acknowledgement of federal support (yes)
2. Quartarone A, Ghilardi MF, Boller F. Preface. Page: xi-xii, In: *Handbook of Neurology*, Vol 184, Elsevier, 2022, published; acknowledgement of federal support (yes)
3. Quartarone A, Ghilardi MF. Neuroplasticity in dystonia: Motor symptoms and beyond. Page: 207-211, In: *Handbook of Neurology*, Vol184, Elsevier, 2022, published; acknowledgement federal support (yes)
4. Milardi D, Basile GA, Faskowitz J, Bertino S, Quartarone A et al. Effects of diffusion signal modeling and segmentation approaches on subthalamic nucleus parcellation. *Neuroimage* 250, 2022, 118959, published; acknowledgement federal support (yes)
5. Peter J, Ferraioli F, Mathew D, George S, Chan C, Alalade T, Salcedo SA, Saed S, Tatti E, Quartarone A, Ghilardi MF. Movement-related Beta ERD and ERS Abnormalities in Neuropsychiatric disorders. *Front Neurosci.* (accepted); acknowledgement of federal support (yes)

### Books or other non-periodical, one-time publications.

NEUROPLASTICITY: FROM BENCH TO BEDSIDE; Volume Editors: ANGELO QUARTARONE, MARIA FELICE GHILARDI, AND FRANÇOIS BOLLER, VOLUME 184, *Handbook of Neurology*, Series Eds: MJ Aminoff, F Boller, DF Swabb; Elsevier, 2022, ISBN: 978-0-12-819410-2; book, published, 2022; acknowledgement of federal support (yes)

## Other publications, conference papers and presentations.

1. Drs. Ghilardi and Quartarone organized and directed the Workshop on Synaptic plasticity focused on PD and related disorders that was held in Florence June 7-10, 2022 (international).
2. Dr. Ghilardi lecture in the Workshop on Synaptic plasticity: "Vision and plasticity in Parkinson's Disease". (international)
3. Dr. Ghilardi speaker and discussant on Parkinson's disease to the First International Forum on Neurodegenerative diseases (Milan, October 6-7, 2022) (international)
4. Dr. Ghilardi lecture on rehabilitation and plasticity in PD in a Webinar "Visual disorders and plasticity in PD", April 7, 2022, Fresco Parkinson Institute Italia (international)
5. Dr. Ghilardi lecture on rehabilitation with art in PD in a Webinar directed to Italian patients with PD, September 27, 2022, Fresco Parkinson Institute Italia (national)

- **Website(s) or other Internet site(s)**

N/A

- **Technologies or techniques**

We are using the software for motor testing and EEG recording developed in New York.

- **Inventions, patent applications, and/or licenses**

N/A

- **Other Products**

N/A

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

Maria Felice Ghilardi, CUNY

*Project Role:* PI

*Researcher Identifier): orcid number ): 0000-0001-7351-5169*

*Nearest person month worked:* 40

*Contribution to Project:* EEG and kinematics, data analyses, paper writing

Elisa Tatti, CUNY

*Project Role:* co-investigator

*Researcher Identifier): orcid number):*

*Nearest person month worked:* 160

*Contribution to Project:* Software design and analysis of EEG and kinematics, data analyses, paper writing

Francesca Ferraioli, CUNY

*Project Role:* Researcher Assistant

*Researcher Identifier): orcid number )::*

*Nearest person month worked:* 20

*Contribution to Project:* Help in data analysis, paper writing

### Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

*Nothing to Report*

## What other organizations were involved as partners?

Angelo Quartarone, University of Messina  
*Project Role:* PI  
*Researcher Identifier): orcid number ):* 0000-0003-1485-6590  
*Nearest person month worked:* 40  
*Contribution to Project:* Coordination of the project

**Collaborators**

Demetrio Milardi, University of Messina  
*Project Role:* co-investigator  
*Researcher Identifier): orcid number ):*  
*Nearest person month worked:* 10  
*Contribution to Project:* Analysis of MRI

Alberto Cacciola, University of Messina  
*Project Role:* co-investigator  
*Researcher Identifier): orcid number ):*  
*Nearest person month worked:* 10  
*Contribution to Project:* Analysis of MRI

Angelica Quercia (starting from 09-20-2020)  
*Project Role:* co-investigator  
*Researcher Identifier): orcid number ):*  
*Nearest person month worked:* 160  
*Contribution to Project:* Analysis of neurophysiological data (TMS) and EEG

Silvia Marino (starting from 5-1-2022)  
*Project Role:* co-investigator  
*Researcher Identifier): orcid number ):*  
*Nearest person month worked:* 160  
*Contribution to Project:* Analysis of MRI data

Bonanno Letteria (starting from 5-1-2022)  
*Project Role:* co-investigator  
*Researcher Identifier): orcid number ):*  
*Nearest person month worked:* 160  
*Contribution to Project:* Analysis of MRI data

## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:**

**QUAD CHARTS:**

## 9. APPENDICES: