

**AWARD NUMBER: W81XWH-19-1-0810**

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

**PRINCIPAL INVESTIGATOR: Angelo Quartarone**

**CONTRACTING ORGANIZATION: University of Messina**

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**TYPE OF REPORT: Annual report**

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# REPORT DOCUMENTATION PAGE

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				<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-19-1-0810	
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<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					
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**1. INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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:** *Provide a brief list of keywords (limit to 20 words).*

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

**3. ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

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

*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

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?**

*For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

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. We have analyzed previously collected data on movement-related beta modulation and beta power in normal subjects. The resulting paper about the differential effects of motor learning and simple motor practice on beta modulation has been published in *Science Report*.
3. We have also published an opinion paper in *Parkinsonism and related disorders* on practice-related increases of beta modulation and mean power in PD and controls, suggesting that they likely represent the decreased availability of lactate, the major energy source for brain activity.
4. Another paper on movement-related gamma modulation showing its dependence on the planning and execution of movement characteristics has been submitted.
5. Drs. Quartarone and Ghilardi met in September in Italy to finalize the strategy for data collection, transfer and analyses.

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

*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

Nothing to report.

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

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

Two papers were published and another is under review. Drs. Ghilardi and Quartarone have edited a book on plasticity and neurological disorders that will be published at the beginning of 2022. Also Drs. Ghilardi and Quartarone have been preparing the Workshop on synaptic plasticity, an international venue where these data will be presented to experts in neuroplasticity. The date of the Workshop has been moved from October 2021 to June 2022 because of the COVID epidemics. Also Drs. Ghilardi and Quartarone with Dr. Hallett presented and discussed data relevant to exercise, rehabilitation and plasticity in PD in February 2021 in a Zoom meeting directed to experts in rehabilitation.

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

We will finalize analyses and papers on movement-related gamma and beta modulation in patients with PD. We will also write reviews on plasticity, movement and Parkinson's disease. We will participate on the initial data collection in Messina possibly in the first part of 2022 and will analyze the EEG and kinematics data when we will receive them from Messina.

- 4. IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

*Nothing to Report.*

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

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

*Nothing to Report.*

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

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

*Nothing to Report*

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

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:*

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

*Nothing to Report.*

- 5. CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

The direction, strategy and goals of the program have not changed.

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

*Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

The direction, strategy and goals of the program have not changed. However, we experienced a halt on patient recruitment and testing due to the lock down of hospital facilities in Italy due to the COVID emergency.

However, we have enrolled four normal controls and six patients that are going to be tested for baseline data collection in the next weeks.

**Changes that had a significant impact on expenditures**

*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*



The impact of pandemic has changed our capability to spend money according the already approved budget. Hopefully, we reckon to have an extension of grant duration of 1-2 year and to reschedule the budget accordingly.

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

*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

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

None.

N/A

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

N/A

**6. PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

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

*Report only the major publication(s) resulting from the work under this award.*

**Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Tatti E, Ferraioli F, Peter J, Alalade T, Nelson AB, Ricci S, Quartarone A, Ghilardi MF. Frontal increase of beta modulation during the practice of a motor task is enhanced by visuomotor learning. *Sci Rep.* 2021 Aug 31;11(1):17441, with *acknowledgement of federal support (yes).*
2. Ghilardi MF, Tatti E, Quartarone A. Beta power and movement-related beta modulation as hallmarks of energy for plasticity induction: Implications for Parkinson's disease. *Parkinsonism Relat Disord.* 2021 Jul;88:136-139; with *acknowledgement of federal support (yes).*
3. 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. Submitted; with *acknowledgement of federal support (yes).*

**Books or other non-periodical, one-time publications.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

NEUROPLASTICITY: FROM BENCH TO BEDSIDE; Volume Editors: ANGELO QUARTARONE, MARIA FELICE GHILARDI, AND FRANÇOIS BOLLER, VOLUME 184, Handbook of Neurology; in press; *acknowledgement of federal support (yes)*

**Other publications, conference papers and presentations.** *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (\*) if presentation produced a manuscript.*

N/A

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

*List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

N/A

- **Technologies or techniques**

*Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.*

Software for motor testing and EEG recording developed in New York was shared with the group in Messina

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

*Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

N/A

- **Other Products**

*Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

N/A

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

#### Example:

*Name:* Mary Smith  
*Project Role:* Graduate Student  
*Researcher Identifier (e.g. ORCID ID):* 1234567  
*Nearest person month worked:* 5

*Contribution to Project:* Ms. Smith has performed work in the area of combined error-control and constrained coding.

*Funding Support:* The Ford Foundation (Complete only if the funding support is provided from other than this award.)

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

Terranova Carmen, University of Messina  
*Project Role:* co-investigator  
*Researcher Identifier (orcid number):*  
*Nearest person month worked:* 15  
*Contribution to Project:* Analysis of neurophysiological data (TMS)

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)

Antonio Cannuli (starting from 09-14-2020)  
*Project Role:* co-investigator  
*Researcher Identifier (orcid number):*  
*Nearest person month worked:* 160  
*Contribution to Project:* Analysis of neurophysiological data (TMS)

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

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

*Nothing to Report*

**What other organizations were involved as partners?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.*

*Provide the following information for each partnership:*

*Organization Name:*

*Location of Organization: (if foreign location list country)*

*Partner’s contribution to the project (identify one or more)*

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

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, 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, paper writing

Francesca Ferraioli, CUNY

*Project Role:* Researcher Assistant

*Researcher Identifier): orcid number ):*

*Nearest person month worked:* 20

*Contribution to Project:* Help in software design, paper writing

## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

**QUAD CHARTS:** *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*