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

PRINCIPAL INVESTIGATOR: M. Felice Ghilardi

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14. ABSTRACT 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.					
15. SUBJECT TERMS Plasticity, Parkinson's disease, sleep, aerobic exercise, skill retention, MRI, TMS, high density EEG, rehabilitation					
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	6
5. Changes/Problems	8
6. Products	9
7. Participants & Other Collaborating Organizations	11
8. Special Reporting Requirements	12
9. Appendices	12

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

The general scope of the study is to determine 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. During this year we have collected further data from 6 normal controls and completed the acquisition of data from 7 patients with PD before and after MIRT.
2. Four papers have been published, including a recent paper accepted for publication in Neuroimage: “Movement-related ERS and connectivity in the gamma frequency decrease with practice”. Another paper on the Assertiveness and Health-Related Quality of Life in subject with Parkinson’s disease is ready to be submitted.
3. The results of the studies have been submitted for presentation to the 2024 Fresco International Workshop on Synaptic Plasticity and Advances in Parkinson’s Disease, that will be occurring in Sicily (Italy) from September 19–21, 2024.

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.

We have been preparing the 2024 Fresco International Workshop on Synaptic Plasticity and Advances in Parkinson’s Disease, to be held in Sicily (Italy) from September 19-21 2024 in Sicily. We will present results and concepts related to study supported by this DOD program.

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

1. Six papers have been published as peer-reviewed articles. A paper on the Quality of Life in PD is ready to be submitted.
2. Dr. Ghilardi presented some of the results of this research as invited lecturer at the international meeting: Progress in Clinical Motor Control: Movement and Rehabilitation Sciences (PCMC II) Conference in Chicago July 12- 15 2023
3. Dr. Ghilardi presented at a webinar a lecture on exercise and other complementary approaches in PD rehabilitation as part of training course for specialists in PM&R on December 13, 2022.
4. Dr. Ghilardi was invited for a speech by the JCC Manhattan for a webinar on Art, the brain and Parkinson disease on November 13, 2022 for lay public
5. Dr. Ghilardi was part of a panel at the Italian Cultural Institute in New York on November 9, 2022 discussing the effects of “Art and the brain” and its impact on PD

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

We have now completed data collection, but we will recruit additional patients to compensate. We are reckoning to start data analysis regarding the effects of MIRT on cortico-cortical connectivity as measured by resting state EEG, structural MRI and. In addition, we will analyze the effect of MIRT on movement-related beta modulation, on motor skills formation with reaching tasks and the effects of MIRT on EEG correlates of motor skills formation. Finally, we will evaluate the effect of MIRT on muscular synergies.

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. We solved the COVID-related problems about patient recruitment and retention and we were able to increase the rate of recruitment.

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. Patients' and controls' recruitment have been significantly sped up and we are close to complete data collection, very likely in the next six months. Data analyses and paper writing will shortly follow.

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.

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.

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.

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.* 2022 Nov 23;16:1045715. doi: 10.3389/fnins.2022.1045715. eCollection 2022. PMID: 36507340

Tatti E, Cacciola A. The role of brain oscillatory activity in human sensorimotor control and learning: bridging theory and practice. *Front Syst Neurosci.* 2023 Jun 20;17:1211763. doi: 10.3389/fnsys.2023.1211763. eCollection 2023. PMID: 37408694.

Tatti E, Cacciola A, Carrara F, Luciani A, Quartarone A, Ghilardi MF. Movement-related ERS and connectivity in the gamma frequency decrease with practice. *Neuroimage.* 2023 Dec 15;284:120444. doi: 10.1016/j.neuroimage.2023.120444. Epub 2023 Nov 4. PMID: 37926216

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).

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.

1. Drs. Ghilardi and Quartarone are now organizing the 7th Edition of Workshop on Synaptic plasticity focused on PD and related disorders in Sicily in 2024. (international).
2. Lecture of Dr. Quartarone lectured in the Samuel Belzberg 6th International Dystonia Symposium: "Dystonia as a disorder of neuroplasticity (international)

- **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.

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

- **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**

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, 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

Jaime Peter, CUNY

Project Role: investigator

Researcher Identifier): orcid number):

Nearest person month worked: 60

Contribution to Project: Data analyses, 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: