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

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

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6. AUTHOR(S)

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5d. PROJECT NUMBER
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Messina, Piazza Pugliatti, 98100, Messina, Italy
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

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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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. 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?

Nothing to report.

How were the results disseminated to communities of interest?

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.

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

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:

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:

Changes in approach and reasons for change

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

Actual or anticipated problems or delays 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

None

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

None.

Significant changes in use or care of human subjects

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, 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.

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.

N/A

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

N/A

- **Technologies or techniques**

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

- **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, 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

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*

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)*

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: