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Research Article

Effects of a Single Session of Repetitive Transcranial Stimulation in Parkinson Disease

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique proposed for recovery of gait and balance in patients with Parkinson's disease (PD). Our aim was to evaluate the effects of rTMS in PD patients by clinical evaluation and computerized gait analysis. Ten patients were recruited. Each patient was assessed before and after a single session of rTMS by: Berg Scale, Unified Parkinson Disease Rating Scale (UPDRS), 6 Minute Walking Test (6MWT), 10MWT, Time Up and Go (TUG) and spatial-temporal gait analysis by Pablo Gait Assessment sensor. We availed of STM 9000, stimulating with 2000 pulses of 20 Hz rTMS, delivered in 5-second trains with 25 seconds between trains, on the hand area of the motor cortex at 90% resting motor threshold (RMT) on each hemisphere, with 5 minutes pause between hemispheres. Eighty percent of the patient reported subjective benefits, corroborated by objective examination of the results. A significant improvement on the Berg scale was observed. Moreover, a tendence to a significant decrease of stiffness at the lower limbs was evident at UPDRS. Gait analysis showed not significant improvements of evaluated parameters. Although it is premature to draw conclusions, because of the small number of patients, underwent to a single session of rTMS, we confirm the possible beneficial effects and the safety of rTMS. Further studies are needed to validate our findings by clinical evaluation and gait analysis at short, medium, and long term. These may be different in relation to the age, duration and stage of the disease, prevalence of tremor or akinesia and rigidity.

Keywords

Parkinson Disease, Transcranial Magnetic Stimulation, Unified Parkinson Disease Rating Scale, Berg Balance Scale, 6- and 10-Minute Walking Test, Time Up and Go, Space-Temporal Gait Analysis

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1. Introduction

Parkinson Disease (PD) is the second degenerative disease worldwide. It affects more than 6 million people (GBD 2016 Neurology Collaborators). The incidence and prevalence of PD are increasing as the population ages [1-3]. Genetic and environmental factors, as exposure to pollutants, may account for increased risk of PD. The main clinical features are tremor, gait disturbs (bradykinesia, hypo-akinesia, rigidity), static and dynamic imbalance, dysautonomia. Moreover, non-motor signs may develop, as dysfunctions of emotional control, sleep disorders, psychiatric manifestations (obsessive-compulsive disorder, anxiety, depression) [4-7]. These may interfere with common daily life activities and relationships, even in early phase of the disease, leading to progressive neurological impairment and disability.

Neuropathological substrate of PD is related to degeneration of dopaminergic neurons in substantia nigra of mesencephalon and nigrostriatal circuits, with progressive accumulation of degradation products. Peculiar cytoplasmatic, eosinophil, alpha-synuclein positive deposits, namely Lewy bodies, are present [8, 9]. By disease progression, other dopaminergic and non-dopaminergic pathways are involved, with widespread degenerative phenomena in whole the brain. Moreover, often chronic vascular encephalopathy coexists.

Therefore, PD, vascular parkinsonism and, sometimes, neuroleptic parkinsonism, cause an irreversible progression of motor impairment, unresponsive to therapy. Indeed, while in early phase the main clinical feature is tremor, in advanced phase there is progression to akinetic-rigid syndrome.

All the aspects of PD may be treated by pharmacological and physiotherapeutical treatments. These should be individually planned, early started, and adapted to changes during the disease.

Beyond traditional therapies with anticholinergic drugs and levodopa, whose benefits and contraindications are well known, novel agents, as dopamine agonists (ropinirole, pramipexol, rotigotine), mono-amino-oxidase (rasagiline, safinamide) and catechol-methyl-transferase (entacapone, opicapone) inhibitors allowed to delay or reduce levodopa, with subsequent minor side effects.

The role of physiokinesistherapy is pivotal since the early phase of PD. It helps the patient in overcoming progressive reduction of neuropsychomotor performances, recover residual capacity in advanced stage, avoid complications related to falls [10]. It improves gait, steady state and strength and slows disease progression [11].

Although rehabilitation plans are mainly focalized on motor impairments, during the last decade they also included treatments for cognitive deterioration. All together, they are directed to maintain the maximal functional ability and improve quality of life.

Several approaches are available for treating static and dynamic motor impairments. These include both traditional methods, based on classical physiotherapeutical exercises and innovative strategies. The latter complement, support and optimize results. A growing interest is focalized on neuromodulation. The rational idea is centred on the possibility of modulating cortical activity to reorganize altered circuits, interrupting the "misfiring", and restoring functional brain connectivity, retrieving lost functions, limiting, and compensating the neuronal damage, through phenomena of neuronal plasticity, neurorestoration, neurotransmitter and blood flow modulation.

Studies on the effects of repetitive Transcranial Magnetic Stimulation (rTMS) are published (rTMS). This is a non-invasive technique, proposed for treatment of pain, headache, fatigue, bladder dysfunction, dysphagia, speech and voice impairments, anxiety, depression, cognitive dysfunction, sleep disorders, and disorders of consciousness, motor recovery in stroke and PD [12, 13]. The aim of the current observational, cross-sectional study is to deep the knowledge on the subjective and objective effects and limits of rTMS in PD patients.

2. Materials and Methods

The study was carried on May-September 2022 at the Neuron Clinic, Madrid. Ten patients were recruited. The number of patients was chosen according to incidence of PD in the city, with a degree of reliability of 95% and error range of 5%. The research was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committes. Consents were obtained from partecipants.

Inclusion criteria were age > 18 years; stage of disease according to Hoehn and Yahr scale ranging from 1 to 4. Exclusion criteria were case history of epilepsy or ongoing antiepileptic therapy, presence of electronic devices, as pacemaker, intracranial metal implants, behavioural disturbs, cognitive disorders. At recruitment, data on sex, age, duration of disease, Hoehn and Yahr stage were reported (Table 1).

Table 1. *General features of recruited PD patients.*

Age	55.9 ±6.89
Sex	M: F (5:5)
Age of onset of PD	50.2 ±8.13
Mean duration of the disease	5.7 ±3.16
Score of Hoehn and Yahr scale	2.1 ±0.53
Score of MDS-UPDRS III scale	25.5 ±11.48

Each patient was evaluated by: Unified Parkinson Disease Rating Scale (UPDRS), Berg Balance Scale, 6- and 10-Minute Walking Test (6MWT, 10MWT), Time Up and Go

(TUG). Moreover, we availed of Space-Temporal Gait Analysis by Pablo sensor. This allows to examine stride length and duration of step, stance and swing phase, foot cadence, velocity. Subjective and objective data were gathered before and one hour after rTMS session.

Patients underwent to a single session of rTMS, for one hour, by STM 9000, using 2000 impulses of 20 Hz, provided in trains of 5 seconds with 25 seconds pause between trains, on the area of hand cortical representation, at 90% of Rest Motor Threshold (RMT) for each hemisphere, with 5 minutes pause between hemispheres. RMT is the lowest intensity evocating a muscular response with an amplitude of peak-to-peak potential > 50 microvolts in 5 trials, with hand at rest. Statistical analysis was performed by Excel program, using unpaired-T test for description of differences between pre- and post-treatment parameters, Pearson Correlation Test for identification of correlations.

3. Results

Subjective opinions on rTMS are reported. Several questions were asked on general psychophysical state. Eight out of 10 (80%) of the patients reported beneficial effect on mood after rTMS and a feeling of relaxation. Two out of 10 (20%) had a sensation of fatigue after rTMS. All the patients (100%) noted a reduction of nuchal rigidity, improved cervical flexor and extensor movements, head rotation, head lateral inclination and circumduction at the maximal joint allowed excursion in the absence of pain. Moreover, they declared significant improvement of static and dynamic steady state, evaluated by Berg scale. Lastly, they experienced a sense of well-being and safety because of better stability and improved gait.

The day after, 8 out of 10 patients (80%) confirmed previous reported impressions on general psychophysical state. Two out of 10 (20%) referred a loss of beneficial effects 24 hours after rTMS, particularly for reappearance of nuchal rigidity.

After one week, 8 out of 10 (80%) patients continued to feel absence of nuchal rigidity, improvement of static and dynamic steady state, gait, especially in changing direction. Moreover, their attention ability was vivacious, and they were more involved in conversation. A female patient was enthusiastic because she was able to step into the shoes without the help of his husband, and she even succeed in picking up an object fell to the ground, without losing steady state. Another female patient reported better improved quality and duration of sleep (from 6 to 9 hours after rTMS). She was glad to remember dreams, as long time before PD. She was able to drive and even enjoyed driving an electric kick scooter with foot in tandem, maintaining the right posture without losing equilibrium. A third female patients sent us pictures of hand-made dresses for dolls she was able to make after TMS, as in the past.

TUG test was not significantly improved after rTMS (8,9 sd 2,6 sec vs 7,5 sd 1,9 sec, p ns), while no differences were observed at 6MWT and 10MWT min e max (6MWT 1,48 sd 0,3 m/sec vs 1,47 sd 0,4, m/sec, p ns; 10MWT min 1,25 sd 0,3 m/sec vs 1,28 sd 0,3 m/sec, p ns; 10MWT max 1,7 sd 0,5 m/sec vs 1,7 sd 0,7 m/sec, p ns). Scores of Berg scale were significantly higher after rTMS (52,5 sd 2,2 vs 54,8 sd 1,8, p 0,02). UPDRS was not significantly lower after rTMS (27,5 sd 11 vs 25,2 sd 11,7, p ns). A trend to significant reduction of limb rigidity was detected at UPDRS after rTMS (2,2 sd 0,9 vs 1,4 sd 1, p 0,07) (Figures 1-3).

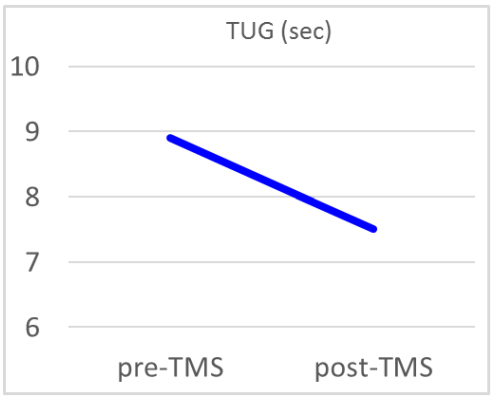

Figure 1. *Pre-TMS (left) and post-TMS (right) TUG.*

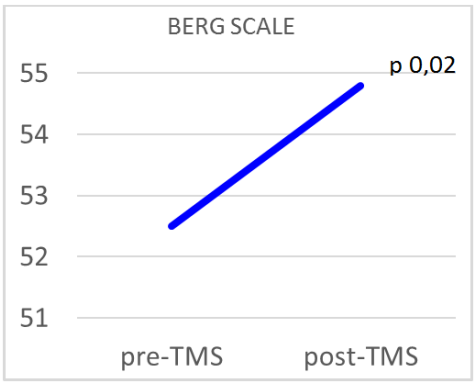

Figure 2. *Pre-TMS (left) and post-TMS (right) Berg Scale.*

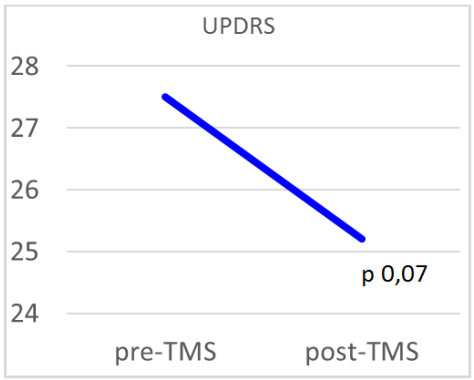

Figure 3. *Pre-TMS (left) and post-TMS (right) UPDRS.*

Data of PABLO movement analysis confirmed not significant improvement in: gait speed (4,4 sd 0,6 vs 4,7 sd 1,1 km/hour, p ns; 1,2 sd 0,2 vs 1,3 sd 0,31 m/sec, p ns), step cadence/min (115,7 sd 8,1 sd 117,8 sd 4,5, p ns), step length (128,1 sd 19,1 vs 133,4 sd 24,1 cm, p ns), maximal vertical foot elevation (left 8,9 sd 2,4 vs 9,4 sd 3,4 cm, right 8,4 sd 1,9 vs 9,4 sd 3,6 cm, p ns).

Figures 1-3: TUG, Berg Scale and UPDRS before and after TMS.

Figures 4-9: Results of PABLO movement analysis before and after TMS.

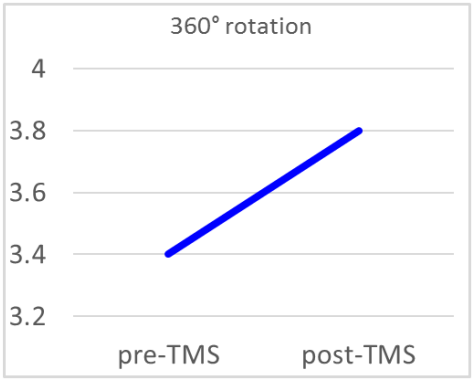

Figure 4. *Pre-TMS (left) and post-TMS (right) 360 °rotation.*

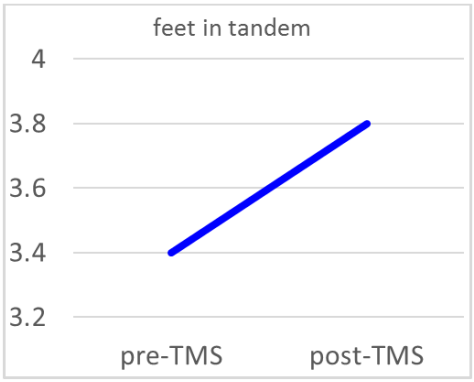

Figure 5. *Pre-TMS (left) and post-TMS (right) feet in tandem.*

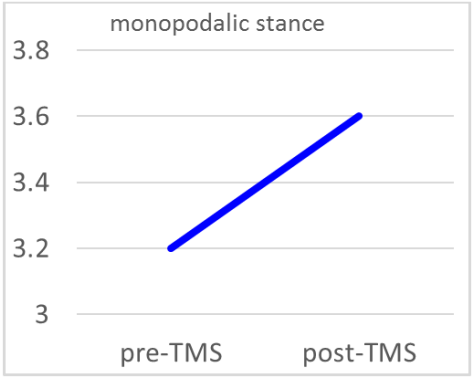

Figure 6. *Pre-TMS (left) and post-TMS (right) monopodalic stance.*

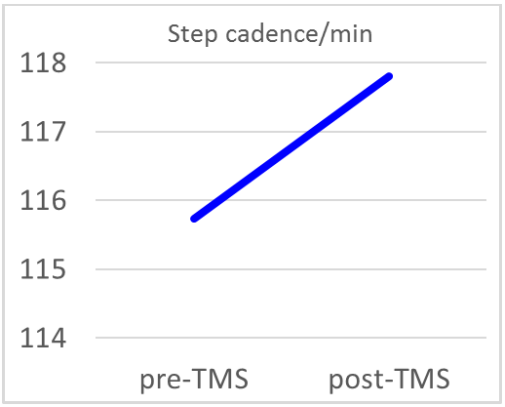

Figure 7. *Pre-TMS (left) and post-TMS (right) step cadence.*

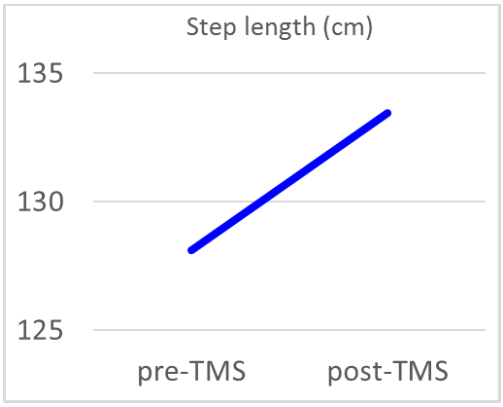

Figure 8. *Pre-TMS (left) and post-TMS (right) step length.*

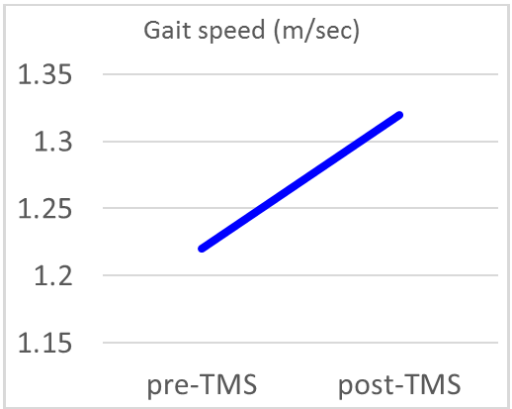

Figure 9. *Pre-TMS (left) and post-TMS (right) gait speed.*

Positive correlations were found both pre and post-treatment between Hoehn Yahr stage and TUG (pre r 0,31, post r 0,40), UPDRS and duration of disease (pre r 0,28, post r 0,38), UPDRS and Hoehn Yahr stage (pre r 0,33, post r 0,41), negative correlations between Hohen Yahr stage and 10MWT min (pre r - 0,38, post r - 0,61), Berg scale (pre r - 0,66, post r - 0,60) and between Berg scale and disease duration (pre r - 0,47, post r - 0,37) (Table 2).

Table 2. *Correlations of disease duration and Hoehm Yahr scale with UPDRS, Berg scale, TUG, 10MWT.*

	Pre-TMS	Post-TMS
Correlations disease duration		
UPDRS	r 0.28	r 0.38
Berg scale	r -0.47	r -0.37
Correations Hoehn Yahr scale		
UPDRS	r 0.33	r 0.41
Berg scale	r -0.66	r -0.60
TUG	r 0.31	r 0.40
10MWT	r -0.38	r -0.61

4. Discussion

PD is a clinical condition observed both in young and adult patients, whose rate of progression is extremely variable, according to pharmacological and physiokinetic strategies, especially when they are early prescribed, at brief and long term.

rTMS represents a possible therapeutical option. Our data showed subjective beneficial effects reported by the patients, corroborated by objective analysis of the results. Although these are significant only concerning improvement of static and dynamic steady state and tendentially significant for reduction of lower limb rigidity, the other items evaluated by health providers and PABLO sensor are promising.

Both high frequency (HF-rTMS, ≥5 Hz) and low frequency (LF-rTMS, ≤1 Hz) TMS, applied on primary motor cortex (M1), supplementary motor area, dorso-lateral prefrontal cortex, improved motor disturbs, at brief and long term. There is no consensus on results obtained by LF-rTMS compared to HF-rTMS [14]. Moreover, opposite effects of LF-rTMS and HF-rTMS may be observed: HF-rTMS and intermittent Theta Burst Stimulation (TBS) increases cortical excitability, while LF-rTMS and continuous TBS decreases cortical excitability [15-17]. Higher number of stimulations each session or distributed to several sessions may be associated with better outcomes.

A meta-analysis reported the beneficial effects of rTMS, evaluated by Freezing of Gait Questionnaire scores, 10MWT, TUG scores, Montreal Cognitive Assessment, and Frontal Assessment Battery [18]. Another meta-analysis confirmed that rTMS induced both short-term (≤3 days after last intervention session) and long-term (≥1 month following last intervention session) significant improvements in balance scales (e.g., Berg Balance Scale), TUG time, and walking speed/time/distance in PD and stroke patients. Subgroup analyses suggested that greater than 9 sessions of HF-rTMS targeting primary motor cortex with greater than 3000 pulses/week can maximize such results [19]. Moreover, beneficial effect was also observed on mood [20, 21]. A meta-analysis pointed out that motor improvements are related to of HF-rTMS on M1, while the dorsolateral prefrontal cortex (DLPFC) may be a potentially effective area in alleviating depression [22]. In hypokinetic dysarthria a single session of HF-rTMS over the left M1 mouth region significantly improved the voice intensity, speech rate, and fundamental frequency [23, 24], but did not affect the speech fluency and articulation [25]. HF-rTMS of M1+DLPFC induced the most significant improvement in UPDRS-III than other targets [21, 26]. Short-term beneficial effect of LF-rTMS in reducing levodopa induced dyskinesias was reported [26, 27]. A significant linear correlation between rTMS intensity and individual prolongation of the time to onset of dyskinesia after levodopa intake was also described [28].

In patients with PD-associated dementia, 10 sessions of bilateral M1-rTMS at the hand region significantly improved the measures of global cognition and reduced the latency of P300, an event-related potential (ERP), marker of cognitive processing speed, by the end of the treatment course. However, further 5 maintenance sessions per month for 3 months were ineffective in maintaining the above-described results [29]. HF-rTMS at M1 transiently increased neuronal oscillations in the alpha and beta frequency at Electroencephalogram [30]. In addition, fMRI studies demonstrated that HF-rTMS at M1 induced blood-oxygenation level-dependent (BOLD) changes both locally and in remote brain regions, including the supplementary motor area, dorsal premotor area, putamen, cingulate area, thalamus [31]. Experimental studies support the hypothesis of modulatory effect of TMS on both mesostriatal and mesolimbic systems, increased release of dopamine in cortico-striatal circuits, reactivating striato-thalamic-cortical pathways [32]. In a study on unilateral parkinsonian patients, increased dopamine release was detected by [11C] raclopride PET in the bilateral putamen after HF-rTMS over M1 cortex contralaterally to the clinically affected side [33]. Increased striatal dopamine release, together with improved motor symptoms, were confirmed by Kim J. Y. et al. [34]. In addition to dopamine, other neurotransmitters may account for after-effects of rTMS [35, 36].

Possible side effects of rTMS are minimal and rare (cephalalgia, algia in trigger point). Exclusion criteria are limited (epileptic seizures, presence of neurostimulators). Although published results are still conflicting, metanalysis showed a moderate efficacy rTMS according to GRADE system [37]. Then, it might be considered, at least as adjunctive tool to classical approach. The limits of our study are related to the small number of patients and the single session of rTMS.

5. Conclusions

Further studies are needed to examine in detail all the described observations and possible side effects to draw up guidelines on rTMS. Beyond subjective and objective evaluation,

computerized gait analysis is the best approach to deep knowledge on this issue. Precise objective data are extremely useful to evaluate efficacy of rTMS at brief and long term, allowing a reliable cost-benefit analysis. Response might be different according to age, duration and stage of disease, prevalence of tremor or akinesia-rigidity, concomitant chronic vascular encephalopathy. rTMS might reduce the dose of pharmacological agents, with expected minor side effects. Overall, it may help in maintaining functional autonomy and in favouring assistance by caregivers.

Abbreviations

PD	Parkinson Disease
rTMS	repetitive Transcranial Magnetic Stimulation
UPDRS	Unified Parkinson Disease Rating Scale
HY	Hoehn Yahr
TUG	Time Up and Go
MWT	Minute Walking Test

Author Contributions

Del Prete Maria Teresa: Data curation, Funding Acquisition, Investigation, Project Administration, Writing

Lerin Calvo Alfredo: Data curation, Investigation, Software

Sanchez Maria: Resources, Supervision, Validation

Gizzi Raffaele: Validation

Tecce Francesca: Validation

Moretti Antimo: Validation

Fiori Patrizia: Conceptualization, Formal Analysis, Methodology, Validation, Writing

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Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

Del Prete Maria Teresa: She is a young physiotherapist, employed at the Rehabilitation Centre S. Ciro, Cardito (Naples). She pursued a master's degree in Sport Massage in 2021. She graduated in Physiotherapy at the University of Campania, Vanvitelli (Italy), in 2023. She has been involved in Erasmus Project on Transcranial Magnetic Stimulation in Parkinson Disease, at Rey Juan Carlos University, Neuron Centre of Madrid in 2022.

Lerin Calvo Alfredo: He graduated in Physiotherapy at the Superior Centre of University Studies, "La Salle," Madrid, in 2018. He got a Master Degree in Advanced Physiotherapy and Treatment of Pain in 2019. He has been charged of the Degree of Professor of Physiotherapy and Health Sciences at the above-mentioned University since February 2022. He is also physiotherapist at the Neuron Centre, Madrid (Spain).

Sanchez Maria: She has been working at the Rehabilitation Department of the Clinica Universitaria, Rey Juan Carlos University, Madrid (Spain) for many years.

Tecce Francesca: She graduated in Physiotherapy in 2007. She got a Master's Degree in Advanced Physiotherapy in 2010, a Master's Degree in Management of Health Care in 2011. She has been working as Physiotherapist at Rehabilitation Centres from 2008 to 2013 in Avellino, 2013-2019 at Local Health Care Centre of Reggio Emilia, 2018-June 2024 at S. Ottone Frangipane Hospital, Ariano irpino (Avellino). She has been charged of the Degree of Professor of Rehabilitation Techniques since 2013 and of the role of Coordinator of Didactic Activities at the School of Physiotherapy, II University of Naples, University of Campania, Vanvitelli, Criscuoli-Frieri Hospital, S. Angelo dei Lombardi (Avellino, Italy), since June 2024. She has been Professor of Health Care Coordination at the University of L'Aquila, from 2011 to 2015.

Gizzi Raffaele: He graduated in Physiotherapy in 1983. He got Master's Degrees in Advanced Physiotherapy at the University of Florence in 2004, University of Naples Federico II in 2011, Health Care Organization at the University of Salerno in 2021. He has been charged of the role of Coordinator of Didactic Activities at the School of Physiotherapy, II University of Naples, University of Campania, Vanvitelli, from 2008 to 2014. He has been Director of Didactic Activities at the above-mentioned University, S. Angelo dei Lombardi (Avellino, Italy), from 2014 to June 2024. He has organized and attended several meetings and published on national and international journals.

Moretti Antimo: He graduated in Medicine and Surgery at the II University of Naples in 2011. He got the European Certificate in Physical and Rehabilitation Medicine 2017. He has been charged of the role of Professor of Physical and Rehabilitation Medicine since 2018, Professor of General Methodology of Rehabilitation and Kinesiology, Biomechanics of Skeletal Muscles at the Bachelor Program of Physical Therapy from 2016 to 2018, Professor of Physical and Rehabilitation Medicine at the University of Campania, Vanvitelli from 2019. He is President of the Course of Physiotherapy, Management of Theoretical-Practical Teaching activities at the above-mentioned University, Caserta (Italy), from 2023. He has organized and attended several meetings and published on national and international journals.

Fiori Patrizia: She graduated in Medicine and Surgery in 1991. She got the degree of Doctor of Philosophy in Neuroscience in 1995 and Neurology in 1999. She has been working as Physician in general and neurological centres from 2000 to June 2006, as Neurologist at S. Ottone Frangipane Hospital, Ariano irpino (Avellino) since June 2006. She has been charged of the role of Professor of Neurology at the II University of Naples, University of Campania, Vanvitelli, Criscuoli-Frieri Hospital, S. Angelo dei Lombardi (Avellino, Italy) since 2009. She has attended several congresses and published on national and international journals.

Research Field

Del Prete Maria Teresa: Rehabilitation
Larin Calvo Alfredo: Rehabilitation
Sanchez Maria: Neurology, Rehabilitation
Gizzi Raffaele: Rehabilitation
Tecce Francesca: Rehabilitation
Moretti Antimo: Rehabilitation
Fiori Patrizia: Neurology, Rehabilitation, Neuroscience