NYU School of Medicine
Continuing Medical Education

The Fresco International Workshop on Synaptic Plasticity and Advances in Parkinson's Disease

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ABSTRACTS

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NYU Langone Health

Fresco Parkinson Institute

With a major contribution from

FONDAZIONE CR FIRENZE

*****1. Effects of music reading on motor cortex excitability**

Giovannelli F.[1,2] Rossi S.[3] Borgheresi A.[2] Zaccara G.[2] Gavazzi G.[1] Viggiano M.P.[1] Cincotta M.[2]
[1]*Department NEUROFARBA, University of Florence, Firenze, Italy*
[2]*Unit of Neurology of Florence, Central Tuscany Local Health Authority, Firenze, Italy*
[3] *Department of Medicine, Neurology and Clinical Neurophysiology Section, University of Siena, Siena, Italy*

Neurophysiological studies suggest that reading sheet music facilitates sensorimotor cortex in musicians. Reading musical notes activates expectations about the type of sound to be produced and is linked to a specific action that depends on the instrument used to produce the sound. The aim of this study was twofold: to evaluate 1) whether in piano players, reading notes in the bass clef (usually played with the left hand) and in the treble clef (played with the right hand) selectively enhances right and left M1 excitability (inter-hemispheric effect); and 2) whether reading notes played with the thumb or with the little finger selectively modulate the excitability of the abductor pollicis brevis (APB) and abductor digitorum minimi (ADM) muscles (intra-hemispheric effect). Eighteen musicians (10 pianists and 8 non-pianists) participated to the study. Single-pulse TMS was applied to either M1 while subjects alternatively read the bass or the treble clef of five sheets music without any movements. As a baseline condition, TMS was delivered during the observation of a blank pentagram. When piano players read the treble clef, the excitability of the left M1 was significantly higher compared to that recorded in the right M1. No significant differences emerged for the bass clef. Moreover, MEPs were higher in the ADM muscle regardless the note in both treble and bass clef conditions. In contrast no significant MEP modulation was observed in non-pianists. These preliminary data support the view that music reading may induce some specific inter-hemispheric modulation of the motor cortex excitability.

2. The effects of music on motor learning are related to perceived emotion.

Giovanna Lagravinese[1], Gaia Bonassi[2], Elisa Pelosin[1], Martina Putzolu[1], Marco Bove[2], Laura Avanzino[2].
[1] *Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Italy;* [2] *Department of Experimental Medicine, Section of Human Physiology, University of Genova, Italy*

An important function of music is the capacity to communicate emotions. The link between emotions and motor system has been objective of recent studies. Our experiment aimed to determine whether listening to different emotional music could influence motor learning. In particular, we focused our attention on two sub-components of learning: implicit ("how" to perform the movement) and explicit learning ("what" is the right movement to achieve the goal). Twenty subjects volunteered for the study. They were asked to perform a motor sequence learning task with a digitizing tablet in three different experimental sessions. In each session they executed the task while they were listening to three different musical pieces, able to elicit sadness, happiness and finally a neutral music. In the sequence learning task eight targets were presented in a preset order and subjects were asked to learn the sequence while moving. Results showed that while listening to pleasant music onset time was shorter than when listening to neutral and fearful music. Music influenced also movement peak velocity, which resulted lower (i.e., the movement was more fluid) when listening to pleasant music compared to neutral music. Finally, when participants were asked to verbally recall the sequence they learnt, the declarative score was higher after listening to fearful music. Results seem to confirm that emotional musical pieces are able to influence both implicit and explicit component of motor learning. In particular, different emotions seem to affect the two components of learning in a different way.

3. Creativity In Parkinson's Disease

F. Ruggiero[1], C. Di Nuzzo[2], F. Mameli[1, 2,3] A. Priori [1,2,3], R. Ferrucci [1,2,3]
[1]*IRCCS Ca' Granda Foundation, Neurophysiology Unit, Milan, Italy;* [2]*"Aldo Ravelli" Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Italy;* [3]*Asst Santi Paolo E Carlo, III Neurology Clinic, Milan, Italy*

BACKGROUND: Parkinson's disease (PD) is a neurological disorder characterized by reduced flexibility, conceptualization, and visuospatial abilities. Creative problem solving typically requires divergent thinking, a thought process used to generate ideas by exploring many possible solutions, and flexibility restructuring and manipulating problem information. Although creative thinking requires a combination of these abilities, several reports described enhanced artistic creativity in PD patients treated with dopaminergic agents [1].
OBJECTIVE: We aimed to assess creativity in PD.
METHODS: We recruited 11 patients with PD (aged 49–77 years; education 5-18 years; H&Y 1-4) treated with dopamine agonists and/or levodopa and 11 healthy controls (HC) (aged 60–87 years; education 5-13 years). Creativity was assessed with The Test of Divergent Thinking (TCD). TCD, providing an overall Total Score and 5 Factor scores: Fluidity, Flexibility, Originality, Elaboration and Title. We used One-way between-subjects ANOVA to compare two groups and the Spearman test to evaluate whether there was a correlation between creativity and and L-dopa dosage.

RESULTS: We found significant differences between the groups in TCD total score [(mean±SD) PD: 64.92±21.23 vs HC: 56.64±5.48, p = 0.03] and in Originality factor (PD: 21.33±8.37 vs HC: 15.64±3.64, p=0.008). There were no significant correlations between creativity as indexed by TCD (Total Score, Originality) and L-dopa dosage (p>0.05).
CONCLUSION: Our study suggests that PD patients enhanced creativity as compared to neurologically healthy controls. PD patients seem to be more flexible and, trough creative thinking, they generated an original solution that resulting in an original and valuable artist production. We speculate that dopaminergic agents can induce a reduction of latent inhibition and enhancement of novelty–seeking behavior, resulting in widening of the associative network and enriched divergent thinking.
REFERENCE: 1. Faust-Socher A, Kenett YN, Cohen OS, Hassin-Baer S, Inzelberg R. Enhanced creative thinking under dopaminergic therapy in Parkinson disease. Ann Neurol. 2014, 75:935-42.

4. URINARY DYSFUNCTION IN PARKINSON DISEASE: SATISFACTION IS REHABILITATION

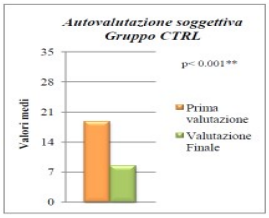
C. Beretta, MG Giantin, I. Maghini, D. Volpe
Fresco Parkinson Center "Villa Margherita" S. Stefano Rehabilitation, Vicenza, Italy

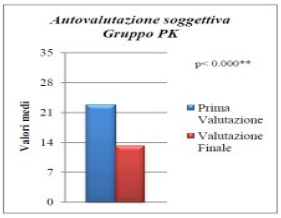
Introduction: Urinary Incontinence (UI) is one of the emerging non-motor symptoms in Parkinson Disease (PD). UI compromises the quality of life of patients and even of caregivers. PD patient have a reduced control and proprioception of pelvic floor muscuar activity. Some studies suggest that the activaction of compensatory neural pathways, that include Lateral Frontal Cortex (LFC) and Anterior Cingulate Cortex (ACC), can bypass deficitary ones. The ACC seems to have a role in integrating and elaborating afferent informations.
Research Question: Assess the efficacy of rehabilitation of urinary dysfunctions in PD based on biofeedback and visual and uditive cueing and its impact on patient and caregiver, in terms of quality of life.
Methods: Sample: 7 PD patients with UI, 7 non-neurologic patients with UI. Average age 68 years old. Outcome Measures: PuboCoccygeus muscle test, Self Assessement Questionnarie, Incontinence Impact Questionnarie IIQ-7, voiding diary, EMG activity. Treatment: 10 sessions plus 1 meeting for starting evaluation, 2 session for week, 45 minutes each session. Each session includes: consciousness raising of perineal muscular activity, behavioral education, functional elecrical stimulation, biofeedback, exercises and home training.
Results:

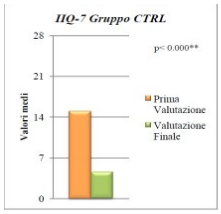
RESULTS * low statistic relevance P-value < 0.050 ; ** high statistic relevance P-value< 0.010

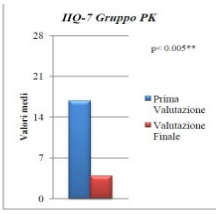
	Control patients		PD patients	
	1°V	2°V	1°V	2°V
PC muscle	5,625	8,125**	2,85	6,48**
Self-assessment	18,75	8,375**	22,71	13,14**
IIQ-7	15	4,5**	16,71	3,85**
EMG activity	4,77	7,25	3,98	6,87*

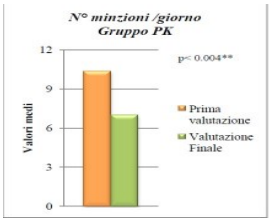
- PD patients number of daily micturitions from 10 to 7 **
- PD patients urinary leakages from 1.71 to 0.43 **

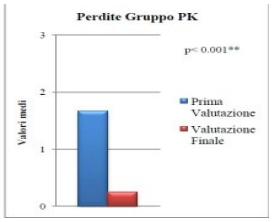


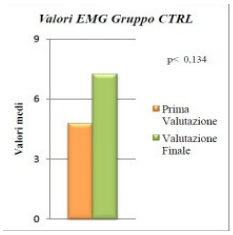


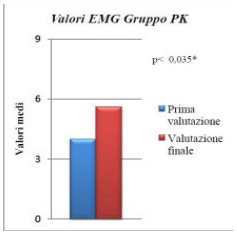












Discussion: This pilot study showed the efficacy of the treatment based on cueing, maybe due to activation of compensatory neural pathways underling a possible reintegration of perineal muscles in proprioceptive pattern, throught consciousness raising and exercise. We suggest a possibility of innovative rehabilitative

approach to urinary dysfunctions in PD patients. "Satisfaction is to improve rehab modifying patient's and caregiver's quality of life".

References: Sobhgol SS, et al. Sex Med Rev. (2018)□Herzog J, et al.(2006), Brain, Vol 129, pag 3366-75;□Winge K, et al.*(2006), Neurourology and Urodynamics, Vol 25, pag 116-122;* Winge K, et al.*(2005), European Journal of Neurology, Vol 12, pag* 842-50.

5. AMPS as a tool for evaluating the impact of occupational therapy Treatment in atypical parkinsonism

Arianna Lorenzi[1], Sara Sgarbossa[1], Ingrid Sturkenboom[2], Daniele Volpe[1]

[1]*Fresco Parkinson Center "Villa Margherita" S. Stefano Rehabilitation, Vicenza, Italy.* [2]*Radboud University Medical Center, Nijmegen, The Netherlands*

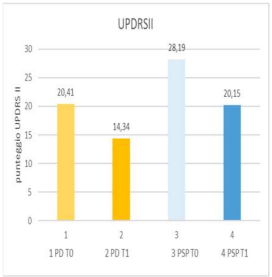
Introduction: Occupational Therapy is strongly recommended in the care of patients with Parkinson's disease (PD). General OT Guidelines indicate Assessment of Motor and Process Skills (AMPS) as a valid instrument to evaluate the quality of occupational performance in ADL. Till now, AMPS has not been used in atypical Parkinsonisms, such as progressive supranuclear palsy (PSP).

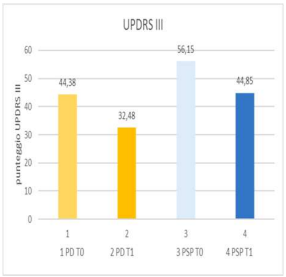
Aim: The aim of this study is to evaluate the impact of AMPS in a cohort of PSP versus a matched group of patients idiopathic PD.

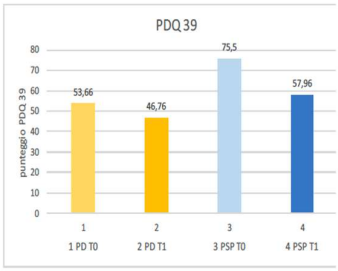
Methods: Two groups were recruited: 1. 26 persons with PSP (14 women; mean age: 67.6; mean disease duration: 4.8 (1-17); 2. 28 persons with idiopathic PD (10 women; mean age: 67.9; mean disease duration: 12.6 (3-24). Inclusion criteria were : H&Y 3-4, MMSE >23.Clinical assessment was performed with : AMPS, UPDRS II, UPDRS III, PDQ-39 before and after a multidisciplinary program that included OT intervention.

	PSP		PD	
	T0	T1	T0	T1
UPDRS II	20.41 ± 7.39	14.34 ± 6.56	28.19 ± 8.28	20.15 ± 9.38
UPDRS III	44.38 ± 17.44	32.48 ± 14.7	56.15 ± 18.87	44.85 ± 17.23
PDQ39	53.66 ± 23.34	46.76 ± 20.48	75.5 ± 29.37	57.96 ± 25.28

Results: In PSP, we found significant increases of:
– ADL motor ability in 24/26 subjects
– ADL process ability in 22/26 subjects Idiopa in PD, we found significant increases of: □
– ADL motor ability in 15/28 subjects
– ADL process ability in 13/28 subjects







Discussion:There was a significant difference between the outcomes in two groups. These results suggest that AMPS is a promising tool to measure changes in the occupational performance quality in PD but also in PSP, contributing to identify the appropriate OT strategies in an aggressive disease such as PSP. The results of this pilot study suggest a need for proposing and extending the Guidelines also for atypical parkinsonisms.

References: 1. Guidelines for Occupational Therapy in Parkinson's Disease rehabilitation, I. Sturkenboom et al., 2008 ; 2. Assessment of Motor and Process Skills: Volume I - Development, Standardization and Administration Manual, 7th Edition, Revised (2012) Anne G. Fisher. □

6. Prevalence and risk factors for impulsive compulsive behaviors in a cohort of Parkinson's disease patients

Simone Simoni[1], Nicola Tambasco[1], Paolo Eusebi[1], Pasquale Nigro[1], Elona Brahimi[1], Giulia Cappelletti[1], Federico Paolini Paoletti[1], Marta Filidei[1], Paolo Calabresi[1]

[1]*Clinica Neurologica, Azienda Ospedaliera e Universitaria di Perugia;* [2]*IRCCS Fondazione S.Lucia, Roma, Italy*

Introduction: Impulsive compulsive behaviors (ICBs) are a frequent complication in Parkinson's disease (PD), occurring in up to 20% of PD patients (Weintraubet al. (2010) Archiv Neurol, 67, 589–595). These disorders have a significant impact on quality of life, straining relationships, and worsening caregiver burden. Objective of the study was to analyze the risk factors for the development of these behaviors.

Methods: 251 PD patients receiving outpatient care at our Centre were consecutively enrolled. After clinical data were collected, each patient underwent a quick interview to determine whether or not they were suitable for ICBs diagnosis. Then QUIP, BIS, MoCA, AES and Olfactory Identification Test (IOIT) were administered to

all the patients. Reliability of the Italian version of the Questionnaire for Impulsive and Compulsive Behaviors (QUIP) was also tested.
Results: The prevalence of ICBs was 31.1%. Age of disease onset ($p < 0.001$), longer PD duration ($p< 0.001$) and Hoehn & Yahr stage ($p=0.020$) were related to QUIP positivity (Table 3). No significant correlation with non-motor symptoms were found, including apathy (AES), cognitive deficits (MoCA) or olfactory dysfunction. Regarding dopamine replacement therapy, total daily dosage of levodopa ($p = 0.017$), dopamine agonists (OR=1.8 95%CI=1.0-3.2) as well as entacapone use (OR=2.8 95% CI=1.1-7. 4) were associated with higher risk of developing ICBs. I-QUIP test-retest reliability was demonstrated.
Conclusions: Dopamine replacement therapy is associated with increased odds of having ICBs. Other significant risk factors included younger age, longer disease duration and a more severe disease presentation. No correlation with the non-motor features analyzed was found.

7. The long-term development of excessive daytime sleepiness after subthalamic deep brain stimulation in patients with Parkinson's disease

Yu Jin Jung[1], Taek Jun Lee[1], Seon Young Ryu[1], Sang Bong Lee[1], Han-Joon Kim[2], Beom.S.Jeon[2]
[1]Department of Neurology, Daejeon St.Mary's Hospital, The Catholic University of Korea, College of Medicine, Daejeon, South Korea; [2]Department of Neurology and Movement Disorder Center, Seoul National University Hospital, Seoul National University, College of Medicine, Seoul, South Korea

Subthalamic nucleus deep brain stimulation (STN DBS) has a positive effect on overall sleep quality, but its effect on wake functions are controversial. We aimed to assess the longitudinal changes of the quality of sleep and excessive daytime sleepiness (EDS) in PD patients undergoing STN DBS and identify which factors are highly associated with the presence of EDS before and after STN DBS. A total of 45 PD patients who underwent bilateral STN DBS between July 2011 and October 2015 were recruited. We evaluated subjective sleep quality assessed by Parkinson's Disease Sleep Scale (PDSS) and EDS using Epworth Sleepiness Scale (ESS) preoperatively and 6months, 1 year, and 2 years postoperatively. There is a significant improvement in PDSS, and a noticeable change occurs immediately after the surgery. After DBS, the number of patients with persistent EDS gradually decreased, but new patients with worsening of EDS were developed. At baseline, there was no significant difference between the patients with and without EDS in the demographic or clinical variables, as well as no meaningful risk factors associated with EDS. Postoperative worsening EDS was more correlated with an increase of dopamine agonist dose than the severity of PD. Bilateral STN DBS improves the subjective sleep quality, but EDS may improve or worsen. In the long term after surgery, the increase in dose of dopaminergic agonists is thought to have the greatest effect on EDS, and the disease progression might also be partially affected.

8. Computer-Based Cognitive Rehabilitation Improves Memory In Patient's With Parkinson's Disease

Chiara Di Nuzzo[1], Fabiana Ruggiero[2], Chiara Casellato[3], Cecilia Rassiga[3], Chiara Rosci[3], Francesca Mameli[2], Tommaso Bocci[1,2,3], Alberto Priori[1,3] & Roberta Ferrucci[1,2,3]
[1] *"Aldo Ravelli" Center for Neurotechnolgy and Experimental Brain Therapeutics, Dipartimento di Scienze della salute, Università degli Studi di Milano, Milan, Italy.* [2] *IRCCS Ca' Granda Foundation - Clinical Center For Neurostimulation, Neurotechnology and Movement Disorders – Milan, Italy.* [3] *III Neurology Clinic, ASST Santi Paolo e Carlo, Milan, Italy.*

INTRODUCTION: Parkinson's disease (PD) is a common neurodegenerative disorder characterized by motor and non-motor symptoms with dementia as one of the most relevant non-motor symptoms affecting patients' daily activities. Computer-based rehabilitation is a promising nonpharmacologic treatment option to enhance compromised memory functions in patients with PD.
OBJECTIVE: Our aim was to evaluate the effects of computer-based rehabilitation protocol on cognitive functions in patients with PD.
METHODS: 5 patients diagnosed as having idiopathic PD were recruited (aged 58–83 years; education 8-13 years). Patients received computerized cognitive rehabilitation program using The MediaHospital® platform 60 minutes/day, 1 time/week for 8 weeks. The platform provides a multimedia laboratories for cognitive functions training to promote the rehabilitation process using exercises specifically designed for treating patient pathological condition. A comparative analysis on all subjects was conducted before (T0) and after (T1) the treatment through a global and cognitive memory assessment (Montreal Cognitive Assessment, Rey Auditory Verbal Learning Test, Forward Digit Span, Backward Digit Span and Rey-Osterrieth figures).
RESULTS: After 8 weeks of therapy, patients presented statistically significant improvement only in Rey Auditory Verbal Learning Test- Immediate Recall [(mean±SE) T0: 21.80±3.7 vs T1: 27.80±4.5, $p= 0.04$]. No changes were found in the other tests ($p= >0.05$).
CONCLUSION: Despite the small sample size, our study revealed that a cycle of computer-based cognitive rehabilitation with the MediaHospital® improves verbal learning and memory in PD patients. Computerized

cognitive rehabilitation therapy is an easy, safe and always available program that can be used as a treatment tool beneficial not only in cognitive functions but also in other potentially disease-connected issues that may have a strong impact on patient's life.

9. Can Wii ® remap far into near space?

Giuseppe Adamo, Giuseppe Giglia, Pierangelo Sardo, Giuseppe Ferraro
Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Palermo, Italy

Background: healthy subjects show in the near space a slight attentional bias toward left (pseudoneglect) that shifts toward right when the task is performed in the far space. This bias moves back again to the left when the subject uses a tool, according to its ability to remap far into near space. On the other hand, when a laser pointer is used to this aim, no significant effects are observed as compared to no-tool condition. This phenomenon has been interpreted as due to the lack of tactile-proprioceptive feedback.
Objective: the aim of the present study was to investigate if the use of an interactive tool without tactile-proprioceptive feedback, a three axis accelerometer that works with gesture recognition (wiimote®), can remap far into near space.
Methods: fifteen right-handed healthy subjects performed a line length judgment task in the near space and in four conditions in the far space, differing for the use (or not) of three different tools (a stick, a wiimote® used as laser pointer – 'wiilaser', and a wiimote®).
Results: the visuospatial performance shifted toward left (pseudoneglect) when the task was performed in near space and in the far space with the use of stick, wiimote and, surprisingly, 'wiilaser' too.
Conclusions: wiimote is able to remap far into near space, as much as 'wiilaser'. Our hypothesis is that remapping depends on potential use and hardware features rather than on effective tool use.

10. LRRK2 genetic model of Parkinson's Disease: electrophysiological evidences for dopamine D2 receptor mediated neuroprotection.

Mancini A[1], Tozzi A[2,3], de Iure A[1], Durante V[1], Tantucci M[1], Mazzocchetti P[1], Marchi S[4], Pinton P[4], Morari M[5], Di Filippo M[1], Calabresi P [1,2].
(1) Clinica Neurologica, Dipartimento di Medicina, Università degli Studi di Perugia, Ospedale Santa Maria della Misericordia, S. Andrea delle Fratte, 06132 Perugia, Italy. (2) IRCCS, Fondazione Santa Lucia, via del Fosso di Fiorano 64, 00143, Rome, Italy. (3) Sezione di Fisiologia e Biochimica, Dipartimento di Medicina Sperimentale, Università degli Studi di Perugia, S. Andrea delle Fratte, 06132 Perugia, Italy. (4) Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy. (5) Department of Medical Sciences, University of Ferrara, Ferrara, Italy

Objectives Among genetic abnormalities identified in Parkinson's disease (PD), mutations of the leucine-rich repeat kinase2 (Lrrk2) gene are the most common, but the role of Lrrk2 has not been fully elucidated.
Materials and methods Excitatory postsynaptic currents (EPSCs) were recorded by patch-clamp experiments in MSNs from brain slices of G2019S-KI Lrrk2 mice and control mice. Striatal DA release was measured by constant potential amperometry. Neuronal vulnerability to mitochondrial dysfunction was tested during rotenone exposure. We also performed molecular and mitochondrial morphological analyses of G2019S Lrrk2-expressing SH-SY5Y neuroblastoma cells.
Results We found reduced striatal DA levels in KI mice ($p<0.001$). DA-D2 receptor agonist quinpirole (10μM) markedly reduced spontaneous EPSCs frequency by 31.3±5.2% ($p<0.001$). The application of a CB1-endocannabinoid receptor antagonist prevented this effect. Evoked EPSCs amplitude was reduced in a dose-dependent manner by quinpirole, with an increased sensitivity in KI mice. The rotenone-induced neuronal dysfunction was markedly enhanced in KI mice (59.2±4.2%,$p<.001$). This detrimental effect was reversed by the application of quinpirole through the inhibition of the cAMP/PKA pathway. The analysis performed in G2019S Lrrk2-expressing SH-SY5Y cells revealed a strong rotenone-induced oxidative stress characterized by reduced ATP synthesis and production of reactive oxygen species. Significantly, quinpirole was able to prevent all these changes.
Discussion DA-D2R activation was able to reduce striatal glutamate release and to counteract the detrimental effects of rotenone. The study suggests potential benefits for pharmacological strategies targeting DA-D2R in patients carrying the G2019S mutation, counteracting the synergistic effect of genetic and environmental factors in the pathogenesis of PD.

*****11. Microtubule Regulating Pathways in Synaptic Injury and Axonal Degeneration**

Francesca Bartolini,
Dept of Pathology, Columbia University, New York, NY, USA

Emerging studies have indicated that dynamic microtubules, typically deprived of tubulin post-translational modifications (PTMs) associated with microtubule longevity, play key roles in neuronal function. In addition, synaptic biphasic fluctuations of microtubule instability/stability and tubulin PTMs have recently been associated with memory formation and are disrupted in aging, indicating a primary role for the regulation of microtubule dynamics and tubulin PTMs in the maintenance of synaptic plasticity. In support of this model, we recently found that stabilization of dynamic microtubules and induction of tubulin PTMs by the formin mDia1 contribute to oligomeric Aβ1-42 synaptotoxicity, and inhibition of microtubule dynamics alone is sufficient to promote tau hyperphosphorylation and tau-dependent synaptotoxicity (Qu et al., J Cell Biol, 2017). To test whether these changes occur at synapses and are directly responsible for synapse loss, we have further developed microscopy assays that measure microtubule invasions into dendritic spines and microtubule contacts within single presynaptic boutons of hippocampal and cortical neurons in culture. We are currently using these assays to investigate the temporal and spatial nature of these changes in the intact synapse upon modulation of synaptic activity and upon synaptic injury. These findings are in line with a parallel study in which we are testing whether undesired fluctuations in microtubule stability/dynamics and tubulin PTMs are primary to axonal neurodegeneration induced by chemotherapeutic agents in sensory neurons using in vitro and in vivo models of disease. Altogether, our ongoing studies introduce a novel neurotoxic activity for formins through their stabilization of dynamic microtubules in neurons, and demonstrate an unforeseen role for dynamic changes in microtubule behavior in regulating tau metabolism, axonal integrity and synaptic function.

*****12. Shh signaling originating from dopamine neurons is critical for reinforcement learning and prevents formation of L-Dopa induced dyskinesia by modulating cholinergic interneurons of the striatum.**

Lauren Malave[1,2], Dustin Zuelke[1,2], Andres Stucky[1,2], Andreas H Kottmann[1,2,3]
[1]Ctr. for Discovery and Innovation, CUNY City Col., [2]CUNY The Grad. Ctr., [3]CUNY School of Medicine, Molecular, Cellular and Biomedical Sciences, New York, NY.

Mesencephalic dopamine (DA) neurons are “multilingual” signaling centers that communicate with their targets by several secreted signaling factors in addition to DA. DA neurons encode a reward prediction error which permits reinforcement learning. Whether this “teaching signal” is carried by DA alone, or together with other signaling molecules secreted by DA neurons, is not known. Finding out may have clinical importance since DA substitution therapy, the gold standard management of DA neuron cell loss in Parkinson Disease (PD), results in the progressive formation of debilitating Levo-dopamine (L-Dopa) induced dyskinesia (LID). LID is thought to reflect “aberrant learning” caused by drug-induced dopamine highs that are uncoupled from behavioral contexts. Whether the reduction in non-dopamine mediated signaling modalities of DA neurons in PD patients contributes to the formation of LID is not known.

We found that all mesencephalic DA neurons express the secreted cell signaling molecule sonic hedgehog (Shh_{DA}) throughout life, releasing it in the striatum where it acts selectively on cholinergic (CIN) and fast spiking interneurons. Shh is released by burst firing and activates the Gqi -coupled GPCR Smoothened (Smo). In CIN Shh_{DA} controls the expression of muscarinic autoreceptors, and trophic- and neuronal plasticity- factors long-term, and increases basal CIN activity while decreasing MAP kinase pathway activity acutely. Mice with selective ablation of Shh_{DA} reveal impaired reinforcement learning, normal reward devaluation, and increased motor habit formation, while displaying reduced numbers of plastic glutamatergic synapses on CIN that originate from the cortex. These mice develop LID that can be ameliorated by injection of agonists of Smo. Optically-forced prolonged stimulation of DA neurons reveals that Shh stores exhaust more quickly than DA stores, resulting in an imbalance of DA and Shh release. Mice with exhausted Shh stores display dyskinetic movements in the absence of L-Dopa, which are qualitatively reminiscent of LID and that can be attenuated by Smo agonists. Using a pharmacological epistasis approach, we show that Shh_{DA} inhibits dyskinesia by stimulating CIN, which in turn inhibit D1 type striatal projection neurons. Lastly, we observe that Smo agonists attenuate LID, while Smo antagonists facilitate it, when given as adjuvants to L-Dopa in the unilateral 6-OHDA and aphakia mouse models of LID, demonstrating that the relative difference in Shh and DA signaling strength determines LID severity. We also find that a single dose of Smo agonist can ameliorate the display of established LID without curtailing the anti-akinesia effect of L- Dopa in Parkinsonian Macaques.

Thus, Shh_{DA} counteracts the inhibition of CIN by dopamine, and is a critical component of the “teaching signal” and a determinant of LID formation and expression.

13. The Mitopark mouse suggests a causal role for HCN loss of function in the progression of Parkinson's disease.

Carmen Carbone, Alessio Masi and Guido Mannaioni,
Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, University of Florence, Italy

AIMS. Differential vulnerability between Substantia Nigra pars compacta (SNpc) and Ventral Tegmental Area (VTA) dopaminergic (DA) neurons is a hallmark of Parkinson's disease (PD). Previously, we demonstrated that MPP+, a neurotoxin able to cause selective nigrostriatal degeneration in animal models, inhibits the Hyperpolarization-activated current (Ih) in SNpc DA neurons. Consistenly, Ih is also downmodulated in the Mitopark mouse, a mitochondrial PD model, before the appearance of DA degeneration (Good et al., 2011), and low ATP (Carbone et al, 2017), likely via reduction of cAMP synthesis, suggesting the existence of a mechanistic link between Ih function and the neuron's metabolic state.
On these basis, we tested the hypothesis that Ih loss of function (LOF) is causally linked to differential DA degeneration by (1) selective blockade of Ih in TH-GFP mice and (2) a pharmacological rescue of Ih function with the Ih enhancer lamotrigine (LTG) in presymptomatic Mitopark mice.
RESULTS. Our results demonstrate that intracerebral administration of Ih blockers cause SNpc-specific neurodegeneration and parkinsonian motor phenotype. Finally, we attempted a pharmacological rescue of Ih function by administering chronic LTG in Mitopark mice, and we observed a dramatic reduction of motor decay compared to MitoPark mice treated with vehicle.
CONCLUSION. These findings support the proposition that Ih LOF is sufficient and necessary to PD-related nigrostriatal degeneration, at least in preclinical settings. Further study will be required to determine whether this mechanism may be exploited to design a neuroprotective, disease-modifying strategy for the treatment of early-stage PD patients**.**

*****14. Autophagic and mitochondrial dysfunction in iPSC-derived dopaminergic neurons of Multiple System Atrophy**

Giacomo Monzio Compagnoni, Giulio Kleiner, Maura Samarani, Massimo Aureli, Gaia Faustini, Arianna Bellucci, Dario Ronchi, Andreina Bordoni, Manuela Garbellini, Sabrina Salani, Francesco Fortunato, Emanuele Frattini, Elena Abati, Christian Bergamini, Romana Fato, Silvia Tabano, Monica Miozzo, Giulia Serratto, Maria Passafaro, Michela Deleidi, Rosamaria Silipigni, Monica Nizzardo, Nereo Bresolin, Giacomo Pietro Comi, Stefania Corti, Catarina M Quinzii, Alessio Di Fonzo,
IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Fresco Institute Milan, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

Multiple System Atrophy (MSA) is a severe neurodegenerative disease which is clinically characterized by variable degrees of parkinsonism, cerebellar ataxia, pyramidal features and dysautonomia. Intracellular accumulation of alpha-synuclein, mainly in oligodendrocytes, is the main neuropathological feature.
In order to evaluate the pathogenic mechanisms of the disease, so far almost completely unclear, we generated a cellular model based on dopaminergic neurons differentiated from induced pluripotent stem cells (iPSCs) of patients and controls.
iPSCs were generated from skin fibroblasts of 4 MSA patients (2 MSA-P and 2 MSA-C), 4 healthy controls and the healthy monozygotic twin of one of the patients.
All iPSC lines were differentiated towards mature dopaminergic neurons through an already described protocol. Neuronal markers' evaluation, lipids' analysis and electrophysiology confirmed the high efficiency and effectiveness of differentiation.
Several pathological findings were detected in patients' neurons: neurites' markers reduction at a late differentiation stage, increased basal autophagy, impaired autophagic flux, reduced activity level of some lysosomal enzymes, impaired activity of mitochondrial respiratory chain complexes II and II+III, increased amount of some subunits of respiratory chain and increased mitochondrial mass, up-regulation of some enzymes involved in Coenzyme Q10 biosynthesis. Interestingly, most of these results were confirmed both analyzing MSA and control groups and the monozygotic twins.
The present study provides new hints for the comprehension of the pathogenic mechanisms of MSA and lays the foundation for future studies aimed at identifying new therapeutic strategies for the disease.

15. Pathological features of midbrain organoids of GBA-mutated patients

Emanuele Frattini, Fulvia Milena Cribiù, Giacomo Monzio Compagnoni, Alessandra Pittaro, Giulia Ercoli, Roberta Tacchi, Massimo Aureli, Maura Samarani, Sabrina Salani, Andreina Bordoni, Arianna Bellucci, Gaia Faustini, Stefano Duga, Letizia Straniero, Mattia Tosi, Rosamaria Silipigni, Lorenza Lazzari, Mario Barilani, Stefania Corti, Nereo Bresolin, Alessio Di Fonzo.

IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Fresco Institute Milan, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

Background: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by a loss of dopaminergic neurons (DaNs) in the substantia nigra of the midbrain. Mutations in GBA gene, historically linked to Gaucher's Disease (GD), are the most frequent genetic risk factor for PD. However, the link between GBA mutations and neurodegeneration is still not clear.

Methods: Fibroblasts derived from skin biopsies of a PD patient with a heterozygous GBA mutation, a GD patient with a homozygous GBA mutation, and two healthy controls were reprogrammed into induced pluripotent stem cells (iPSCs) with transfection of OSKM factors. iPSC lines were differentiated into midbrain organoids with a protocol developed in our lab. Samples collected at various time points underwent western blot (WB), enzymatic, and immunohistochemical (IHC), and sphingolipid analyses.

Results: GBA and control iPSC lines stained positive for stem cell markers. Progressive expression of neuronal and DaN markers over time reflected the embryologic development and full maturation of midbrain structures. Schmorl's method detected positive staining for neuromelanin, suggesting a mature dopaminergic identity. GCase protein amount and enzymatic activity were decreased in GBA organoids. Sphingolipid analyses revealed an important enrichment of polisialogangliosides in organoids of all lines, and an accumulation of glucosylceramide in GBA-mutated organoids.

Discussion: Midbrain organoids may recapitulate molecular events and biochemical dysfunctions underlying GBA-related neurodegeneration. This model may represent a comprehensive human platform that could be exploited for the elucidation of mechanisms involved in PD and GD, and for the screening of potential therapeutic strategies.

16. Evolution of prodromal parkinsonian features in a cohort of GBA mutation positive individuals. A 6-year longitudinal study.

Micol Avenali* [1], M. Toffoli* [2], S. Mullin [2], A. McNeill[2], D. Hughes[3], A. Mehta[3], C. Tassorelli[1,5], F. Blandini[4], A.H.V. Schapira[2]

*These authors contributed equally to this work.

[1] Department of Neurology and Neurorehabilitation, IRCCS Mondino Foundation IRCCS, Pavia, Italy, [2]Department of Clinical Neurosciences, University College London Institute of Neurology, London, UK, [3]Lysosomal Storage Disorders Unit, Department of Haematology, Royal Free Hospital, London, UK, [4]Laboratory of Functional Neurochemistry, IRCCS Mondino Foundation, Pavia, Italy, [5]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

Objectives: GBA mutations play a pivotal role in the molecular pathogenesis of Parkinson Disease (PD) and are considered one of the most frequent risk factors for the disease. The aim of this longitudinal study is to evaluate motor and non-motor symptoms in a group of GBA positive individuals (GD and Het GBA carriers) at risk of developing PD over 6-years follow-up. Moreover, we explored whether the glucocerebrosidase (GCase) enzymatic activity level is altered in peripheral blood leukocytes of these subjects and how it is related to PD development.

Methods: We enrolled 30 GD Type1 patients, 30 Het GBA carriers and 30 mutation negative controls (HC). At baseline, we assessed motor and non-motor prodromal signs of PD in all subjects, by means of questionnaires and scales (UMSARS, MoCA, UPSIT, RBDsq, UPDRS-III and BDI). At 6 years, we repeated the assessment and collected venous blood samples to measure GCase activity.

Results: after 6 years, 1 GD patient developed a clinically defined PD syndrome. Over the 6-year follow-up, both the GD and Het GBA groups separately displayed a significant deterioration in the UMSARS, RBDsq, UPDRS-III and BDI scores compared to baseline. Among Het GBA and GD pooled together, microsmia at baseline was correlated with worse outcome at 6 years in UPSIT, MoCA, UPDRS-III and BDI. GCase enzymatic activity in Het GBA carriers was lower than HC and higher than GD.

Conclusion: in this 6-year long longitudinal study, GBA mutations positive subjects showed a worsening in motor and non-motor prodromal PD features.

17. Study of the haplotypic context as a modulator of the expressivity of GBA gene mutations in patients with Parkinson Disease and Gaucher Disease

Maria Vizziello[1], Edoardo Monfrini[1], Ilaria Trezzi[1], Giulia Franco[1], Maria Domenica Cappellini[2], Elena Cassinerio[2], Pierluigi Tocco[3], Francesca Carubbi[4], Fabio Nascimbeni[4], Enza Maria Valente[5], Simona Petrucci[6], Federica Arienti[1], Giulia Lazzeri[1], Arianna Manini[1], Giacomo Bitetto[1], Alessio Di Fonzo[1]

[1]IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy. [2]UOS Centro Malattie Rare, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico di Milano. [3]Section of Neurology, Department of Neurological and Movement Sciences, University Hospital of Verona, Verona, Italy. [4]Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università di Modena e Reggio Emilia. [5]Department of Molecular Medicine, University of Pavia, Pavia, Italy. [6]Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy.

Background. Biallelic *GBA* gene mutations are known to cause Gaucher disease (GD), the most common lysosomal storage disorder. Heterozygous *GBA* mutations are the most common genetic risk factor for Parkinson disease (PD).
Aims: To reconstruct the haplotypic context of the mutations and to identify the different phenotypes associated and the impact of distinct haplotypes on PD penetrance and expressivity.
Methods*:* We analyzed a sample of 61 individuals (34 PD, 20 GD and 7 healthy subjects) carrying the most common *GBA* mutations – N370S (*n=40*, of whom 19 heterozygous, 10 homozygous and 11 compound heterozygous) and L444P (*n=25*, of whom 21 heterozygous, 1 homozygous and 3 compound heterozygous). The genetic study was conducted through the analysis of selected polymorphic markers located in the region of interest surrounding the GBA gene.
Results*:* The L444P carriers were associated to three different haplotypes suggesting the presence of at least three independent mutational events, whereas all the N370S carriers had one single haplotype, pointing toward a single founder origin. Among L444P carriers there was a considerable difference between the three haplotypes: after age 50, 100% of subjects with haplotype 1 and 3 has been diagnosed with PD diagnosis, whereas none of haplotype 2 patients has PD. In our cohort, the haplotype 2 was also associated with a milder phenotype of GD.
Conclusions. The haplotypic reconstruction of the most common *GBA* mutations showed to be a possible useful tool to investigate the variability of penetrance and expressivity in individuals carrying the same genic variant.

18. The role of *LRP10* mutations in Parkinson's Disease and Dementia with Lewy Bodies

Manini A.[1], Monfrini E.[1], Vizziello M.[1], Arienti F.[1], Lazzeri G.[1], Franco G.[1], Di Fonzo A.[1]

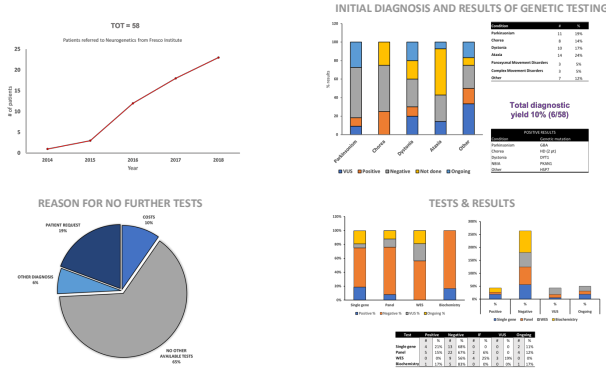
[1]IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB) belong to a continuum spectrum of neurodegenerative diseases characterized by alpha-synuclein accumulation in neurons.
Even though alpha-synucleinopathies pathogenesis remains largely uncovered, the development of novel techniques in the field of genetics has brought to the discovery of at least 23 loci and 19 disease-causing genes for parkinsonism. Recently, a new candidate gene (*LRP10*) for PD and DLB has been identified by performing a linkage analysis and positional cloning on a large Italian family with late-onset PD. After the first characterization of a *LRP10* pathogenic mutation, other eight variants have been detected in an international multicenter series of 660 probands with either a clinical or pathological diagnosis of PD or DLB.
The aim of this study was to test *LRP10* in a cohort of Italian patients, with a clinical diagnosis of either PD (n=176) or DLB (n=10). Five variants were identified, two were synonymous (c. 39C>T and c. 1923G>A); one was detected in an intronic region (c. 80-23G>A); two (c. 1685G>A and c. 415A>G) led to a missense, respectively p. R562H and p. M139V. The c 1685G>A was predicted as pathogenic, despite displays a high frequency in general population. The c. 1923G>A was rare and predicted to generate a potential splice site change. In conclusion, *LRP10* mutations seem rare in PD and DLB. Further investigations will be employed to define the precise role of *LRP10* in alpha-synucleinopathies and the pathogenic mechanisms involved, in order to identify new potential targets for therapies.

19. Genetics of Movement Disorders: The Fresco Institute's Experience

Giulietta Riboldi, Brooklyn Henderson, Heather Lau, Kara Anstett, Steven Frucht
The Marlene & Paolo Fresco Institute for Parkinson's & Movement Disorders, NYU School of Medicine, New York, NY, USA

Background: A growing number of movement disorders are are caused by genetic mutations. Genetic diagnosis are not always easy to identify and in the instance, they are properly identified, providing the patient with appropriate genetic counseling is always required. At The Marlene and Paolo Fresco Institute at NYU Langone, Fresco Institute patients whom are suspected to have a genetic condition are referred to Neurogenetics for a comprehensive assessment.



Methods: Patients referred to Neurogenetics from the Fresco Institute in the last four years were collected. Year of referral, initial diagnosis, demographics, family history, and previous genetic tests were reviewed. Genetic assessments and outcomes were compared.

Results: From 2014 to 2018, 58 patients were referred to Neurogenetics. Initial diagnoses were equally distributed among parkinsonism, dystonia, chorea and ataxia. Total diagnostic yield was 10%. Target tests were more effective to reach a diagnosis. Family history and previous genetic assessments did not affect the outcome of the genetic testing. In 10% of the cases genetic tests were not performed because of prohibitive costs. In 65% of cases it was not possible to continue the diagnostic process because no further diagnostic tests were available.

Conclusions: Genetic assessments can aid in establishing a more concise and defined diagnosis, and can allow for targeted treatments through promotion of research advancements. The number of referrals from the Fresco Institute to Neurogenetics is growing; although, the total yield of diagnosis is still low compared to the literature). In addition, available diagnostic tools are not always enough to reach a diagnosis and costs may be prohibitive. This suggests the need of research in this field for a better understanding of these conditions and possible new therapeutic approaches.

*****20. Impaired midbrain networks connectivity underlies freezing of gait in Parkinson's disease**

Droby A[1], Avanzino L[2], Putzolu M [3], Bommarito G[3], Pelosin E[3], Inglese M[1,3,4,5]
[1] Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2] Department of Experimental Medicine, Human Physiology, University of Genova, Italy,[3] Department of Neuroscience, Rehabilitation, Ophthalmology, genetics and Maternal Child Health, University of Genova, Italy, [4]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [5] Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Background: Freezing of gait (FoG) is a debilitating feature of PD and its pathophysiological mechanisms are poorly defined. It has been suggested that loss of cholinergic neurons in the midbrain contributes to gait abnormalities. Previous MRI studies in FoG patients showed a specific pattern of cortical atrophy and decreased functional connectivity (FC) within motor and cognitive networks. However, the midbrain structural and functional impairment in FoG patients has not been addressed yet. The aim of this study was to investigate the relationship between structural integrity and FC of the midbrain in PD patients with/out FoG.

Methods: 16 PD-FoG (mean age=72±3 yrs), 16 PD-nonFoG (mean age=68.2±5 yrs), and 21 sex- and age-matched healthy controls (HCs) (mean age=64±13.5 yrs) were prospectively enrolled. All subjects underwent MRI including 3D T1-MPRAGE and rs-fMRI. All reported comparisons: $P_{cFWE} < 0.05$.

Results: Compared to HCs, the overall PD group demonstrated significant structural decrease in the bilateral cuneus. In FoG vs. HCs, significant decrease was observed in the bilateral cuneus, precuneus and left lingual gyrus. In FoG vs. nFoG significant decrease was observed in midbrain, thalamus, and cerebellar vermis. Within the midbrain network, FoG patients showed significant FC decreases in the cingulum compared to nFoG, and in the right postcentral and supramarginal gyri compared to HCs. FC levels in cingulum as well as in the supramarginal gyrus were found to correlate with FoG severity (r=-0.53, r=-0.44; $p<0.05$ respectively).

Discussion: Midbrain structural damage as well as decreased FC within the mid-brain network, contribute to FoG in patients with PD.

21. Brain functional substrate of gait observation in Parkinson's disease

Giulia Bommarito[1]*, Martina Putzolu[1]*, Cecilia Cerulli[1], Luca Tagliafico[1], Carla Ogliastro[1], Giovanni Abbruzzese[1,2], Laura Avanzino[2,3], Matilde Inglese[1,2] and Elisa Pelosin[1,2].

*The authors equally contributed to this work

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genova, Italy; [2]Ospedale Policlinico San Martino, IRCCS, Genoa, Italy; [3]Department of Experimental Medicine, Section of Human Physiology and Centro Polifunzionale di Scienze Motorie, University of Genova, Italy

Background. Gait disorders are extremely frequent in Parkinson's disease (PD). Action observation training (AOT) represents a promising tool for treatment of gait impairment in PD. However, little is known about the neurophysiological substrate of observation of gait.
Aim. This study aims at evaluating the neural correlates of gait observation in PD patients.
Methods. 29 PD and 21 gender and age-matched healthy subjects were enrolled in the study. PD were then sub-classified based on the presence of Freezing of Gait (FOG) symptoms. Participants underwent a clinical evaluation, gait analysis and MRI, including functional imaging recorded during the observation of a video showing a human-gait. Spatiotemporal kinematic parameters of gait were recorded through a sensorized mat (GaitRITE®).
Results. Between group comparison showed that HS had a significantly greater activation at the level of the cingulate cortex and the precuneus compared to PD and to the FOG- subgroup. Both FOG- and HS activated more than FOG+ in the bilateral posterior medial frontal cortex, left IPL and postcentral gyrus.
Discussion. The greater activation in HS compared to patients suggests an impairment of the mirror neuron system (MNS) areas during observation of gait, in particular in FOG+ patients. In fact, IPL is involved in monitoring motor function based on visuo-spatial information and abnormal function of IPL has been associated to gait disorders in PD. However, AOT of gait could improve MNS recruitment and, hence, walking parameters in PD patients.

*****22. Freezing of gait in Parkinson's disease is a network derangement**

Nicoló G. Pozzi[1]*, Andrea Canessa[3], Chiara Palmisano[1], Joachim Brumberg[2], Claudio Pacchetti[3], Gianni Pezzoli[5], Jens Volkmann[1], Ioannis U. Isaias[1]

[1] Department of Neurology and [2] Nuclear Medicine, University Hospital and JMU Wuerzburg, Josef-Schneider-Str. 11, 97080 Wuerzburg, Germany, [3] Parkinson e Disordini del Movimento, Fondazione Istituto Neurologico Nazionale "C. Mondino", IRCCS, Pavia, Italy, [4] Fondazione Europea di Ricerca Biomedica (FERB Onlus), Cernusco s/N, Milan, Italy, [5] Centro Parkinson ASST G. Pini-CTO, Milan, Italy

Background: Freezing of gait (FOG) is a disabling symptom of Parkinson's disease (PD) that causes paroxysmal inability of effective stepping. The pathophysiological mechanisms underlying FOG remain poorly understood and response to current treatments is at best limited. We envisioned that gait freezing could be related to sudden derangements of supraspinal locomotor network dynamics.
Methods: We recorded the activity of the cortex and the subthalamic nucleus (STN), two main nodes of the locomotor network, during (effective) over-ground walking and freezing episodes in seven patients with PD and implanted for deep brain stimulation. Recordings were performed with a portable 64-channels EEG system (MOVE, BrainAmp) and with novel DBS devices that allowed on-demand measurements months after surgery (Activa PC+S®, Medtronic PLC or AlphaDBS, Newronika Srl). Neurophysiological recordings were combined with kinematic and molecular brain imaging findings (i.e. SPECT with FP-CIT).
Results: During effective walking, subjects with PD showed a sustained cortical-subthalamic low-frequency (θ-α range, 4-13Hz) coupling. This coupling was lost during gait freezing in the hemisphere with less dopaminergic innervation and re-emerged with the recovery of an effective gait pattern.
Conclusion: Locomotion requires a constant cortical-subthalamic information flow for the adaptation of the gait pattern to contextual needs. A disruption of this top-down information flow would lead to a mismatch between supraspinal and spinal locomotor processing thus causing gait freezing. These findings open the way for new therapeutic strategies (e.g. adaptive deep brain stimulation devices) that may directly target pathological brain oscillatory activity at a network level.

*****23. Predictive factors of Freezing of gait in Parkinson's disease: a prospective study.**

P. Ortelli[1], R. Maestri[2], V. Cian[1], G. Palamara[1], D. Ferrazzoli[1], G. Frazzitta[1].
[1]"Moriggia-Pelascini" Hospital, Department of Parkinson's disease- Movement Disorders and Brain Injury Rehabilitation, Gravedona ed Uniti, Italy; [2]Istituti Clinici Scientifici Maugeri Spa Società Benefit- IRCCS, Department of Biomedical Engineering, Montescano, Italy.

Background and objectives: Freezing of Gait (FoG) is a disabling symptom of PD. Its pathogenesis is multifactorial and no completely understood. We aimed to find the strongest associations among FoG occurrence and cognitive, psychological and clinical signs in PD.
Methods: 305 PD patients were enrolled and subdivided according to the presence (FoG+, n=128) or absence (FoG-, n=177) of FoG. Several clinical, cognitive and psychological data were collected: H&Y, side of motor symptoms onset (SDO), age at disease onset (ADO), disease duration (DD), LED, MMSE, FAB, WCST, TMT A-B, RAVLT, STAI-Y I-II, BDI, Apathy Scale (AS).
Results: FoG+ patients were younger at the diagnosis (p=0.04) and used higher LED (p<0.0001). In comparison with FoG-, they get worse scores in FAB (p=0.005), had higher AS (p=0.03) and are much more impaired in WCST (p=0.018), TMT A (p=0.0013), RAVLT (p=0.012). H&Y, WCST and LED were significant predictors (p=0.0007, p=0.01 and p=0.01) of FoG. Each addiction of 100 mgEq/die in LED leads to 16% increase of FoG occurrence (95%CI: 3.6, 30.5%). FoG increases about 4-fold with the H&Y worsening (95% CI: 48.9,1562 %) and of 245% with deficit in WCST (95%CI: 32.2, 800 %).
Conclusions: FoG is associated with deficits in executive functions and earlier PD onset. The main predictors of FoG occurrence are the H&Y, WCST and LED. These data suggest that FoG occurs in specific PD phenotype, where the involvement of cortical circuits is more pronounced.

24. EFFECTS OF FOCAL MECHANICAL VIBRATIONS STIMULATION ON GAIT IN PARKINSON'S DISEASE PATIENTS USING THE WEARABLE DEVICE EQUISTASI®

L. Bakdounes[1], F. Spolaor[2], N. Pegoraro[1], V. Urbani[1], I. Maghini[1], C. Beretta[1], D. Pavan[2], A. Guiotto[2], F. Fichera[2], V. Scalchi[2], P. Torresin[2], Z. Sawacha[2], D. Volpe[1].
[1]Fresco Parkinson Center "Villa Margherita" S. Stefano Rehabilitation, Vicenza, Italy, [2]Department of Information Engineering University of Padova, Italy

Introduction: Parkinson's disease (PD) is a progressive neurological condition [1]. Gait disturbance is a key component of motor disability in PD patients [2].
Aim: To investigate the effects of Equistasi®, a wearable device based on focal mechanical vibration, for the treatment of gait impairment in people affected by PD.
Methods: 10 PD patients participated in the study (BMI 25.7 ± 2.5 kg/m2, age 70.6 ± 6.4 years). Subjects walked barefoot at their preferred walking speed at BioMovLab, before and after 4 weeks of Equistasi® device treatment. The kinematics protocol reported in Volpe et al. [3] was applied. The electrical activity of 4 muscles was collected bilaterally: Rectus Femoris (RF), Tibialis Anterior (TA), Biceps Femoris (BF) and Gastrocnemius Lateralis (GL).
Results: After treatment the following changes were observed (see Fig. 1A and B): cadence and step width decreased, stride time and stride length increased, the stance phase decreased and the swing phase increased ($p < 0.03$, Paired t-test). With respect to joints kinematics, an increment in pelvis rotation, in trunk obliquity and rotation were highlighted ($p < 0.04$). Pearson's correlation showed that ankle and knee angles range of motion were increasing accordingly to GL's PoE increment. Mean and standard deviation of ankle joint are reported in Fig. 2.

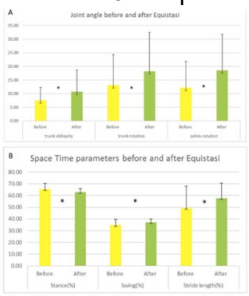


Fig. 1. A and B: Results of Paired t-test between variables before and after Equistasi® treatment, In Fig. 1A joint angles values were reported (* p < 0.05), in Fig. 1B space time parameters were reported (* p < 0.05).

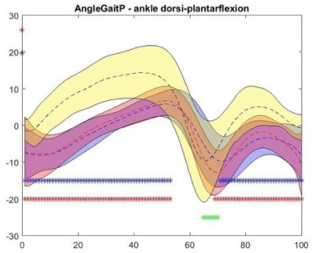


Fig. 2. In blue the ankle dorsi-plantarflexion angle (DPA) [deg] over the gait cycle (%) before Equistasi® treatment, in red the ankle dorsi-plantarflexion angle after Equistasi® treatment and in yellow the normative bands

Discussion: Beside the small number of subjects, the adoption of Equistasi® leaded to encouraging results, assessing a positive effect of the mechanical focal vibration on gait parameters in PD's patients. Fig. 1 These effects may open a new possibility on PD's management.
References: 1. Cova, et al., Parkinsonism Relat. Disord. 34 (2010) 38–42. 2. Carpinella, et al., Trans. Neural Syst. Rehabil. Eng. 15 (4) (2007) 543–551. 3. Volpe, et al., Gait Posture 52 (2016) 87–94.

25. SURFACE EMG ANALYSIS IN PARKINSON DISEASE PATIENTS BEFORE AND AFTER UNDERWATER GAIT TRAINING

F.Spolaor[2], V. Urbani[1], L. Bakdounes[1], I. Maghini[1], Beretta C[1], D. Pavan[2], A. Guiotto[2], F. Fichera[2], V. Scalchi[2], P Torresin[2], G. Frazzitta [3], Z. Sawacha [2], D.Volpe[1]

[1] Fresco Parkinson Center "Villa Margherita" S. Stefano Rehabilitation , Vicenza, Italy; [2]Department of Information Engineering University of Padova, Padova, Italy; [3]Fresco Parkinson Center Moriggia-Pelascini Hospital, Gravedona, Italy.

Introduction: Parkinson's disease (PD) is a progressive neurological condition [1] and gait impairment is an important component of motor disability in PD patients [2]. Hydrotherapy (HT) has been proposed as an innovative rehabilitative strategy for the treatment of motor symptoms and quality of life in PD patients.
Research Question: The aim of this study is to evaluate improvements in muscular activation in 10 PD patients before and after a HT program compared to healthy subjects (Control group=CG).
Methods: 10 PD patients (age: 71; BMI: 28) and 10 healthy subjects (age: 65.5; BMI: 28) were recruited. Subjects were asked to walk barefoot at they preferred walking speed in a Gait Lab. The electrical activity of 4 muscles was collected bilaterally together with the ground reaction forces. SEMG signals of the following muscles were recorded: Rectus Femoris (RF), Biceps Femoris (BF), Tibialis Anterior (TA), Gastrocnemius Lateralis (GL). The muscle activation patterns were analyzed, the peak of the envelope (POP) and the position of the peak (POP% of gait cycle) were extracted [3].

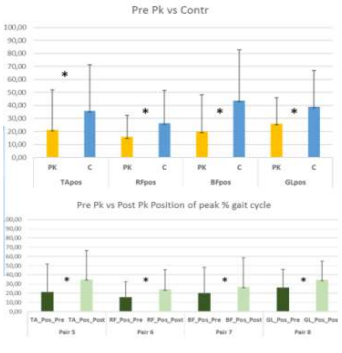


Figure 1. The results of Indipendent (up) and Paired (bottom) T-test about POP%

Results: Before HT PD patients showed earlier POP% of all muscles analyzed. After HT only BF maintained its earlier activation; all other muscles reported values similar to CG and patients showed a higher activation (POP) of all muscles acquired except for GL.
Discussion: HT has positive effect on muscles activation in PD patients in order to improve the muscle's recruitment pattern. These results may impact positively on the development of underwater rehabilitation programs in PD.
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2. Carpinella I, et al, Trans Neural Syst Rehabil Eng.15:543-51;
3. Sawacha Z, et al, Gait Posture. 35(1):101-5, 2012

26. A multimodal training attenuates cholinergic dysfunction and improves complex walking in ageing and Parkinson's disease

Laura Avanzino[1,2],Cecilia Cerulli [3], Carla Ogliastro[3], Giovanna Lagravinese[3], Gaia Bonassi[1], Anat Mirelman[4,5], Jeffrey M. Hausdorff [4,6,7], Roberta Marchese[2], Giovanni Abbruzzese[2,3], and Elisa Pelosin[2,3]

[1]Department of Experimental Medicine, Section of Human Physiology, University of Genova, [2] Ospedale Policlinico San Martino, IRCSS, Genova, Italy, [3]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genova, Italy, [4]Center for the Study of Movement, Cognition and Mobility, Department of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [5] Sackler Faculty of Medicine, and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel, [6]Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel, [7] Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center

Falls are frequent in Parkinson's disease and in ageing. Impairments in the cholinergic-mediated attentional supervision of gait may contribute to increased fall risk, especially when obstacles challenge gait. Interventions combining motor-cognitive approaches have been shown to positively act on motor performance, cognitive skills and fall episodes. Here, we hypothesized that an intervention simulating an attention–demanding walking condition could impact not only complex gait performance and falls risk but also cortical cholinergic function. Thirty-nine participants at fall risk (24 Parkinson's disease subjects and 15 older adults) were recruited in a randomized controlled trial. Participants were assigned to treadmill training or treadmill training with non-immersive virtual reality intervention and trained 3 times a week for 6 weeks. Short-latency afferent inhibition, a transcranial magnetic stimulation paradigm, was chosen to assess cortical cholinergic activity. Gait kinematics was measured during normal walking and while negotiating physical obstacles by means of a sensorized mat (GaitRite®). Transcranial magnetic stimulation and gait assessments were performed pre, post, and 6 months post intervention.
Treadmill training combined with non-immersive virtual reality attenuated cortical cholinergic dysfunction, improved obstacle negotiation performance and induced a reduction of the number of falls compared to treadmill training. Furthermore, the more the cortical cholinergic activity increased after training, the more the obstacle negotiation performance improved and fall rate decreased.
We provide evidence that an innovative rehabilitation approach targeting cognitive components of complex motor actions can induce changes in cortical cholinergic activity and possibly adaptive brain plasticity, thereby enabling functional gait improvements.

27. Cerebral blood flow and cerebrovascular reactivity correlate with severity of motor symptoms in Parkinson's disease

Laura Pelizzari[1,2], Maria Marcella Laganà[1], Federica Rossetto[1], Niels Bergsland[1,3], Giuseppe Baselli[2], Raffaello Nemni[1,4], Francesca Baglio[1]

[1]IRCCS, Fondazione Don Carlo Gnocchi, Milan, Italy; [2]Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy; [3]Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA; [4]Department of Physiopathology and Transplants, University of Milano, Italy.

Neurovascular unit (NVU) disruption has been proposed to play an important role in neurodegenerative mechanisms in Parkinson's disease (PD). However, its relationship with the development and progression of the disease is still unclear. The aim of this study was to investigate cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) in mild to moderate stages of PD.

Arterial spin labeling (ASL) MRI was acquired for twenty-eight PD patients (66.6±8.6 years, 22 males, median [IQR] H&Y=1.5 [1-1.9], median [IQR] MoCA=22.9 [20-24.9]) and thirty-two age- and sex-matched healthy controls (HC, 63.1±8.1 years, 20 males) to derive CBF maps. Thirteen PD patients and thirteen HC were also scanned at hypercapnia to compute CVR. Median CBF and CVR were extracted from cortical and subcortical regions belonging to the motor network. PD-vs-HC differences were tested for both CBF and CVR, and the correlation between them and the severity of PD motor symptoms (quantified with UPDRS III) was assessed. Multiple comparisons were corrected using the false discovery rate (FDR) method.

No significant CBF/CVR differences with HC were found. Positive significant (pFDR<0.05) CBF- UPDRS III correlation was observed in the precentral gyrus, postcentral gyrus, supplementary motor area, striatum, pallidum, thalamus, red nucleus and substantia nigra. Conversely, significant negative CVR-UPDRS III correlation was found in the striatum.

These results support the hypothesis of neurovascular involvement in the motor network at the mild to moderate stages of PD. CBF and CVR assessment provides indirect non-invasive information about NVU integrity and might be used as diagnostic and prognostic markers for PD.

28. Diffusion tensor imaging of olfactory tract in Parkinson's disease

Pasquale Nigro[1], N Tambasco[1], A Chiappiniello[2], S Simoni[1], E Brahimi[1], M Romoli[1], F Paolini Paoletti[1], M Filidei [1], P Calabresi [1]

[1] Neurology Clinic, University Hospital of Perugia; [2] Department of Medical Physics, University Hospital of Perugia

Background. Parkinson's disease (PD) can be better characterized as a multisystem disorder. It is widely accepted that motor features are preceded by a prodromal 'pre-motor' phase including a wide range of non-motor disturbances [1]. Olfactory dysfunction is recognized as one of the earliest indicators of developing PD and one of the major non-motor symptoms with a significant impact on quality of life [2]. In the present study, we investigated the olfactory-tract diffusion tensor imaging (DTI) correlates of hyposmia in patients with PD, using fiber tracking and comparing with a matched control group.

Methods. Olfactory function of each subject was assessed using the Italian Olfactory Identification Test. Motor disability was assessed in all patients using Unified Parkinson's Disease Rating Scale-III part (UPDRS III) and Hoehn and Yahr rating scale (H&Y). Imaging was performed on a 3T Philips Achieva MR scanner. The following parameters were used for groupwise comparison: fractional anisotropy (FA), mean diffusivity (MD), tract volume and length.

Results. 17 patients with PD (mean age 64.9±7.6 years, UPDRS III 24.4±11.7, H&Y stage 1.9±0.5) and 9 controls (mean age 60.7±14.2 years) were recruited. Olfactory identification function of all PD patients was decreased. DTI analysis of the olfactory tract showed significant FA signal and volume decreases of the PD group when compared with the control group (P<0.05). Significant correlations were found between the MD values and the H&Y stage (r=0.60, P<0.01).

Discussion. DTI analyses of olfactory structures may be viable as a means of establishing cohorts of subjects with probable pre-clinical PD.

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29. Mapping the topography of the human globus pallidus: the contribution of cortico-pallidal and dento-pallidal connections

Alberto Cacciola[1], Salvatore Bertino[1], Gianpaolo Antonio Basile[1], Alessandro Calamuneri[1,2], Gaetana Chillemi[1,2], Demetrio Milardi[1,2], Giuseppe Pio Anastasi[1], Angelo Quartarone[1,2]

1Department of Biomedical, Dental Sciences and Morphological and Functional Images, University of Messina, Italy; 2 IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy

According to the traditional basal ganglia model, afferents from the cerebral cortex are organized in a topographic manner in the striatum and, at the same time, each one of its territories projects to corresponding regions in the other nuclei. The topographical organization of GP has been investigated both anatomically via virus tracing studies and functionally by electrophysiology in non-human primates. Recently, we have hypothesized the existence of a direct cortico-pallidal and a dento- pallidal pathway by means of constrained spherical deconvolution based tractography.

Herein we employed high quality diffusion MRI data of 100 healthy subjects from the Human Connectome Project repository in order to assess the topographical organization of the GPi and GPe based on the direct cortical- and dentate-pallidal connectivity.

We found that the GPi is anatomically organized in three regions namely, a frontal cluster, a dentate cluster and a parietal cluster. On the other hand, all lobes, but the dentate nucleus, clustered in the GPe which was subdivided in frontal, parietal, temporal, occipital and insular clusters.

Looking at the functional distribution of the structural connectivity, the antero-dorsal aspect of GPe is occupied by fibers coming from associative cortices, the posterior dorsal region corresponds to the sensorimotor cluster and the caudal pole includes connections with other cortical areas. In the GPi, only the sensorimotor and associative territories consistently overlapped between subjects. located in the caudal two-thirds of the nucleus.

Considering that recent studies underlined the benefit from specific DBS and FUS targeting of GP, we think that our pivotal work could have clinical resonance in treating motor and non-motor symptoms in basal ganglia disorders.

30. Aberrant cerebellar network topology in prodromal and early Parkinson's Disease

Alberto Cacciola[1], Carlo Vittorio Cannistraci[2], Alessandro Muscoloni[3], Alessandro Calamuneri[1,4], Gaetana Chillemi[1,4], Demetrio Milardi[1,4], Angelo Quartarone[1,4]

[1] Department of Biomedical, Dental Sciences and Morphological and Functional Images, University of Messina, Italy, [2] Biomedical Cybernetics Group, Biotechnology Center, Center for Molecular and Cellular Bioengineering, Center for Systems Biology Dresden, Department of Physics, Technische Universität Dresden, Germany, Brain bio-inspired computing lab, IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy, [3] Biomedical Cybernetics Group, Biotechnology Center, Center for Molecular and Cellular Bioengineering, Center for Systems Biology Dresden, Department of Physics, Technische Universität Dresden, Dresden, Germany, [4] IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy

The pathogenesis of Parkinson's Disease (PD) begins in the basal ganglia and in turn spreads to numerous extranigral structures. The death of dopamine-generating cells in the substantia nigra leads to the classical motor symptoms such as bradykinesia, resting tremor, rigidity, and late postural instability. Therefore, most investigations on PD focused on the basal ganglia, whereas the cerebellum has often been overlooked. However, increasing evidence suggests that the cerebellum may have certain roles in the pathophysiology of PD. For this reason, we aimed at studying the contribution of cerebellum in PD and its prodromal stages, by looking at the cerebellar volumes profile using structural MRI data of the Parkinson's Progression Markers Initiative (PPMI) repository. Thirty-four cerebellar regions were obtained using the SUIT Atlas a free probabilistic atlas of the human cerebellum in a dedicated space designed to improve alignment of infratentorial structures in respect to conventional MNI space. Cerebellar networks were constructed using the structural correlation method on the cerebellar volumes resulting in a correlation matrix respectively for the prodromal, PD and controls groups. PD patients showed increased characteristic path length, betweenness centrality, smallworldness and modularity compared to prodromal individuals. The cerebellar networks of prodromal patients instead seem to have reduced value of characteristic path length, clustering coefficient and betweenness centrality compared to controls.

Although our knowledge about the roles of the cerebellum in PD remains limited yet, herein we showed that the cerebellum may undergo extensive changes at the network-level both in the prodromal and early phases of the disease, therefore further attention to the role of cerebellum in PD is warranted.

*****31. Is Parkinson's Disease a brain network disorder?**

Alberto Cacciola[1], Carlo Vittorio Cannistraci[2,4], Alessandro Muscoloni[3], Archit Bhatnagar[3], Alessandro Calamuneri[1,4], Gaetana Chillemi[1,4], Demetrio Milardi[1,4], Angelo Quartarone[1,4]

[1] Department of Biomedical, Dental Sciences and Morphological and Functional Images, University of Messina, Italy [2] Biomedical Cybernetics Group, Biotechnology Center, Center for Molecular and Cellular Bioengineering, Center for Systems Biology Dresden, Department of Physics, Technische Universität Dresden, Dresden, Germany, Brain bio-inspired computing lab, [3] Biomedical Cybernetics Group, Biotechnology Center, Center for Molecular and Cellular Bioengineering, Center for Systems Biology Dresden, Department of Physics, Technische Universität Dresden, Germany, [4] IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy

Neurobiological findings, together with the heterogeneous motor and non-motor symptoms experienced by patients with Parkinson's Disease (PD), suggest that PD is a multisystemic disorder involving many neural networks within the entire brain. Modern network neuroscience has led to a paradigmatic improvement in understanding the brain-network organization and has challenged the traditional framework that many neurological disorders involves exclusively focal alterations. Herein, we employed diffusion MRI data and tractography in order to map the structural connectomes of 10 de novo drug naïve PD patients and 10 age-matched healthy controls.

We found that the structural brain networks of patients with early PD present an aberrant topology reflected by changes in many network metrics, with a tendency to lose long-range connections and to reinforce a local topological organization, as a sort of possible plastic compensatory mechanism in response to the long-range dysconnectivity. A very active field of network science in recent years is network geometry that assumes that the network nodes reside in an underlying hidden metric space (latent geometry), which plays a role in shaping the observed network topology. Employing a novel class of topological-based unsupervised nonlinear dimension reduction methods to efficiently map networks in the latent network space, herein, we demonstrated that latent network geometry markers allow to uncover the altered latent geometry in the structural brain networks of PD patients. We believe that these findings will represent a convincing starting point to bridge the gap between brain networks topology and latent geometry, putting forward the idea of PD as a brain network disorder.

32. Cortical Excitability and synaptic plasticity in patients affected by brain tumors

Terranova C[1], Rizzo V[1], Brigandi' A[1], Allegra C[2], Girlanda P[1]. and Quartarone A[2,3].

[1] Department of Clinical and Experimental Medicine, University of Messina, Italy; [2] IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy; [3] Department of Biomedical, Dental Sciences and Morphological and Functional Images, University of Messina, Italy.

Objective. In this study we investigated cortical excitability, inhibitory and excitatory intracortical circuitries, by using transcranial magnetic stimulation (TMS), in both hemispheres of patients affected by brain tumors. Moreover, we looked at motor cortex synaptic plasticity in both hemispheres. We employed an electrophysiological protocol, named repetitive paired associative stimulation (rPAS).

Methods. Cortical excitability was probed with TMS in 10 right-handed patients and 10 age-matched healthy controls. We tested motor thresholds (MT), motor evoked potential (MEP) recruitment curve, cortical silent period (CSP), short and long intracortical inhibition (SICI and LICI), intracortical facilitation (ICF), short and long afferent inhibition (SAI and LAI) and inter-hemispheric inhibition (IHI). To evaluate synaptic plasticity MEPs were measured at baseline, before and for up to 30 minutes after 5Hz-rPAS in abductor pollicis brevis (APB). rPAS consisted of 600 pairs of transcranial magnetic stimuli, at a rate of 5 Hz for two minutes, coupled with electrical median nerve stimulation preceding TMS over the contralateral M1 at an interstimulus interval of 25 ms.

Results. RMT and AMT were higher in both hemispheres of patients with brain tumors than healthy controls. The slope of MEP recruitment curve was deeper in both hemispheres of patients with brain tumors. SICI, LICI, SAI and LAI are reduced in patients with brain tumors compared with aged matched healthy controls. In both hemispheres rPAS did not induce any significant changes in MEP amplitudes, compared with controls.

Conclusions. Cortical excitability, specially inhibitory intracortical circuitries, and synaptic plasticity are impaired in both hemispheres of patients affected by brain tumors.

33. Effects of acute 5Hz rTMS and 4-week intensive rehabilitation on skill retention in Parkinson's Disease: electrophysiological and behavioral evidences

Giorgia Marchesi[1], Giulia Aurora Albanese[1], Davide Ferrazzoli[2], Shaina George[3], Serena Ricci[3, 1], Maura Casadio[1], Elisa Tatti[3], A. Di Rocco[4], A. Quartarone[5], M. Felice Ghilardi[3], Giuseppe Frazzitta[2]

[1] DIBRIS University of Genova, Italy, [2]Moriggia-Pelascini Hospital, Department of Parkinson's disease- Movement Disorders and Brain Injury Rehabilitation, Gravedona ed Uniti, Italy, [3]CUNY Medical School, New York, NY, USA; [5] Northwell Care System, New York, NY, USA, [5]IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy

Parkinson's Disease (PD) is characterized by motor and non-motor symptoms, including deficits in learning and retention of new motor skills. Previous studies demonstrated that beta power modulation that accompanies

movements is decreased in PD, although in both patients and controls beta power over the sensorimotor areas shows the same pattern, decreasing before movement onset and increasing post-movement. Beta modulation increases across practice in normal subjects and less so in patients.
Here, we ascertained whether two interventions, 5 Hz repetitive Transcranial Magnetic Stimulation (rTMS, N=19) after the initial learning over the right posterior parietal cortex (P6) and 4-weeks Multidisciplinary Intensive Rehabilitation Treatment (MIRT, N=9), improve retention of motor skills and normalize beta modulation in patients.
We tested normally aging subjects (N=13) and two separate groups of patients with PD. All subjects performed a planar reaching task (MOT) and a similar task that required adaptation to 60° visuomotor rotation in 10° steps (ROT) in two subsequent days. Patients were tested before and after the two different interventions and high-density EEG was recorded.
We found that after both interventions retention of the learned rotation significantly improved reaching normal ranges. Mean beta modulation levels changed significantly only after MIRT.
We conclude the MIRT leads to global changes, in terms of sensorimotor integration and retention of motor skills, likely because intensive motor exercise has important aerobic components that may affect the brain as a whole. Conversely, rTMS produces only improvement in retention since it was applied only to the area that facilitates learning and retention. *Partial support from NPF grant.*

34. Movement-related Beta oscillations are not significantly affected by force production

E. Tatti[1]*, R. Mehraram, S. Ricci[1,2], A. B. Nelson[1], M. F. Ghilardi[1]*
[1] *CUNY School of Medicine, New York, NY, USA;* [2] *DIBRIS University of Genova, Italy*

The human sensorimotor cortex is characterized by a movement-related decrease of beta oscillatory activity (13.5-30Hz) during movement execution (event-related desynchronization, ERD) followed by a post-movement synchronization (event- related synchronization, ERS). The significance of beta modulation is not well clarified. While some evidence from the literature posits that changes in beta modulation might represent a sort of capacity for cortical plasticity, other works suggest that such changes might be related to specific feature of the movements. In this study we determined whether beta ERD, ERS and the relative modulation depth would be affected by kinematic and dynamic characteristics of the movement, in particular by the length of reaching movements. Brain oscillatory activity was recorded with 256-channels EEG system on 35 healthy young subjects while they performed a reaching task with targets located at 3 distances (4, 7 and 10 cm). Both average peak velocities and movement time increased significantly and progressively with increasing extent ($F(1.067, 36.27) = 375.55$, $p<0.0001$; $F(1.437, 48.87) = 141.5$, $p<0.0001$, respectively), suggesting that both measures were modulated in order to produce the appropriate extent. To ascertain the relative contribution of peak velocity and movement time, we performed a multiple regression on the data of each subject. The combination of peak velocity and movement time explained on average more than 90% of movement extent variance (mean±SD: 0.93±0.063; range:0.690-0.986). However, the major contributor of the variance in movement extent was variation of peak velocity (standardized coefficient Beta, mean ± SD: 0.863±0.059), while variation of movement time (0.393±0.091) played a lesser role. Thus, movement extent mostly resulted from programming a force that was appropriately scaled to the target extent, with minimal adjustments of movement duration. We then determined whether the magnitude of movement-related β ERD, ERS and modulation depth focusing on the cluster of electrodes over the left sensorimotor cortex contralaterally to the moving hand where beta modulation power was greatest. As in previous reports (Moisello et al., 2015; Nelson et al., 2017), we found that, on average, modulation depth was greater for the last 16 movements (mean±SD: 2.63±0.50) than for the first 16 (2.91±0.73, $p=0.0097$). However, we found no significant effect of target distance on the power of ERD, ERS and modulation depth ($p>0.1$). Therefore, we conclude that beta ERD, ERS and modulation depth are robust phenomena that are NOT modulated by movement length, force production or other kinematic and dynamic features. *Supported by NIH P01 NS083514*

35. Aging does not affect EEG beta modulation during reaching movements

S. Ricci[1,2], R. Mehraram[1], E. Tatti[1], A.B. Nelson[1], M. Bossini-Baroggi[2], P. Panday[1], M. Kamel[1], N. Lin[1], M.F. Ghilardi[1]
[1]*CUNY Medical School, New York, NY, USA;* [2] *DIBRIS University of Genova, Italy*

Movement planning and execution are accompanied by β EEG power modulation (15-30Hz) over the sensorimotor area contralateral to the moving limb. β power decreases during the planning phase, reaches a minimum during the movement itself and rebounds with a maximum when the movement ends. In elderly subjects, such modulation increases during one-hour practice block and returns to baseline values after 24 hours (Moisello et al, 2015; Nelson et al, 2017). Here we determine whether such practice-dependent increases similarly occur in young subjects. Thirteen young and thirteen elderly healthy subjects performed

one-hour blocks of right-arm reaching movements, while EEG activity was recorded. Performance results show that trajectory accuracy improves during practice in both conditions; even though the hand-path area, an index used to describe trajectory accuracy is significantly greater in the elderly subjects group. Also, peak velocity is significantly bigger for young compared to elderly subjects. Both groups showed practice-related increase of beta modulation and event-related synchronization (ERS), over the left sensory-motor area and the frontal region. The latter area also shows a significant event-related desynchronization (ERD) increase across time. Since no group effect had been found in ERD, ERS and β modulation; we conclude that the phenomenon does not depend on age. β modulation may reflect saturation of cortical excitability and plasticity-related phenomena and it is not linked to on-line behavioral improvement. It is thus likely that excitability of sensorimotor cortex might not change in the age range we tested. *Supported by NIH P01 NS083514*

36. The effects of extended learning on EEG and performance and the benefits of a nap

S. Ricci[1,2], E. Tatti[1], A.B. Nelson[1], J. Lin[1], B. O. Thomson[1], H. Chen[1], G. Tononi[3], C. Cirelli[3], M.F. Ghilardi[1]
[1] CUNY School of Medicine, New York, NY, USA, [2] DIBRIS University of Genova, Italy, [3] University of Madison, Madison, Wisconsin, USA

Recent work in humans and animals showed that, in the context of sleep deprivation, intense training leads to a progressive increase in performance errors that are related to the local occurrence of theta EEG activity during wake. Also, we have previously found that, without sleep deprivation, training in specific tasks for less than one hour leaves a region-specific trace in the subsequent spontaneous eyes open EEG (sEEG), in the frequency ranges involved in the task. It is not known whether the sEEG slowing, defined as local sleep, is triggered by plasticity or by temporary neuronal exhaustion due to intense activity. Here we determine if: a) Extended practice produces progressive, region-specific sEEG power increases progressively involving lower frequencies; b) Intensive learning leads to an increase in errors on a test sharing the neural bases of the task but without the learning component; c) sEEG and performance can be restored by a nap but not by quiet rest. 34 subjects underwent three 45-minutes sessions of a visuo-motor rotation reaching task. After each block, sEEG and two tests, one relying on motor performance and the other on visual working memory, were performed. We found that intensive movement adaption to new visuo-motor correspondences induced local power increases during spontaneous brain activity, which progressively involved theta range, over the specific cortical areas engaged by the task. Such EEG change was accompanied by errors when subjects performed a motor test similar to the training task. Local EEG changes, test performance and learning ability were renormalized by an afternoon nap but not an equivalent period of quiet wake. Theta power increase did not occur with the same period of extensive practice in a motor task without adaptation during the morning hours. These findings indicate that specific neural circuits can become fatigued through intense learning, just like the brain as a whole becomes tired by waking activities and needs sleep for restoration. *Supported by NIH P01 NS083514*

*****37. Electrophysiological, molecular and behavioral effects of intermittent theta-burst stimulation (iTBS) in the early model of Parkinson.**

G. Natale, F. Campanelli, G. Marino, V. Calabrese, V. Durante, E. Zianni, E. Marcello, F. Gardoni, B. Picconi, P. Calabresi, V. Ghiglieri.
University of Perugia; University of Milano; IRCSS Santa Lucia, Roma; San Raffaele, Roma, Italy

In experimental Parkinson's disease (PD), different degrees of degeneration of nigrostriatal dopaminergic neurons produce distinct alterations of dopamine-dependent corticostriatal synaptic plasticity. Repetitive Transcranial Magnetic Stimulation (rTMS) induces a selective increase of dopamine in the vicinity of highly active corticostriatal terminals, suggesting that it may alleviate symptoms and improve the response to therapy in PD patients. However, the mechanisms underlying effects of rTMS on subcortical regions are not known. Intracellular recordings in corticostriatal slices obtained from low-dose 6-hydroxydopamine-lesioned rats, modelling early symptomatic PD, show that a single session of in vivo cortical rTMS, using intermittent theta-burst stimulation protocol, was able to recover the amplitude of spontaneous glutamatergic activity, ameliorate akinesia and rescue corticostriatal long term potentiation. This rTMS-mediated plasticity was abolished through application of ifenprodil, a selective inhibitor of GluN2B subunit-containing NMDA receptors, suggesting that this effect could be associated with postsynaptic density changes. Our hypothesis is supported by molecular analysis showing a marked decrease in GluN2B in the postsynaptic compartment after rTMS, pointing to a possible recruitment of extrasynaptic GluN2B in the TMS-mediated plasticity. Accordingly, phosphorylation of ERK was also found reduced. Taken together, these data indicate that rTMS exerts evident effects in early-stage PD through a NMDA-dependent mechanism and allow to further understand the mechanisms underlying striatal adaptation in parkinsonian striatum.

*****38. Combining Reward and M1 Transcranial Direct Current Stimulation Enhances the Retention of Newly Learnt Sensorimotor Mappings**

Danny Spampinato, Zabina Satar, and John Rothwell
University College of London

It is well known that levels of motor retention (i.e. process of forming long-lasting behavioural changes) is influenced by the type of feedback given when learning a new sensorimotor mapping. For instance, providing reward while individuals learn to account for systematic perturbations does not enhance learning, but increases retention of the new motor memory. Interestingly, applying transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) during learning also results in greater retention of the newly learnt transformation. However, it remains unknown whether combining reward and tDCS results in an additive benefit of motor retention and whether these interventions rely on overlapping neural mechanisms.
Here, we investigated whether the combination of rewarding feedback and M1 tDCS while participants learned to account for 30-degree visuomotor transformation resulted in enhanced motor retention. Our study followed a 2x2 factorial design with participants (n=48) assigned to receive either *reward-stimulation*, *reward-sham stimulation*, *null feedback-stimulation*, *null feedback-sham stimulation* during visuomotor adaptation. To determine if reward and tDCS share common physiological mechanisms underpinning learning, we also assessed motor cortical excitability and inhibition (i.e. SICI) before and after all participants learned the visuomotor rotation.
We found that both the *reward-stim* group had enhanced their motor retention. Surprisingly, we also found that only the *reward-stim* had a significant increase in SICI after exposure to the perturbation, whereas no significant increases were found in M1 excitability. These findings demonstrate that the combination of reward and M1 tDCS results are additive in providing stronger retention of motor adaptation.

39. Long-term retention of motor skill after motor imagery training.

Gaia Bonassi[1], Martina Putzolu[2], Giovanna Lagravinese[2], Marco Bove[1,3], Elisa Pelosin[2,3], Laura Avanzino[1,3]
[1]Department of Experimental Medicine, Section of Human Physiology, University of Genova, Italy. [2]Department of Neuroscience (DiNOGMI), University of Genova, Italy; [3]Ospedale Policlinico San Martino, IRCCS, Genova, Italy

Complex motor tasks are learned through repetition and training, which results in lasting improvement in movement accuracy. Learning a motor skill is commonly attained via movement execution. Research has shown that also motor imagery (MI) effectively facilitates skill learning. We aimed to observe if and how a training based on motor imagery differently affected the phases of motor learning, in respect to movement execution (ME). Twenty subjects were divided into two groups performing MI or ME training. Participants wore sensor-engineered gloves and their performance was assessed over a period of 15 days with 4-days training. Each training session consisted in 10 blocks of 4 repetitions of an 8-finger touches sequence. Motor assessments were performed before, after training (5 minutes and 2 hours) and during retention (days after training). Assessment consisted in one block of 4 repetition sequences. For data analysis, we considered three different learning phases: first (within the first two training sessions), second (3rd and 4th training sessions) and retention. Related to the first two phases, MI and ME training had a similar effect on motor learning, improving movement rate, without differences between groups ($p > 0.05$). Differently, in the retention phase, whereas the ME group maintained the acquired skill, in the MI group movement rate decreased. These results showed that MI training is effective as ME in the online learning, both in the fast and the slow learning phases. Differently MI is less effective than ME in the retention phase, likely because of the lack of the sensory feedback.

40. Cerebellar direct current stimulation enhances motor adaptation in healthy subjects and in cervical dystonia patients with tremor.

Gaia Bonassi[1], Martina Putzolu[2], Giovanna Lagravinese[2], Roberta Marchese[3], Giovanni Abbruzzese[2,3], Elisa Pelosin[2,3], Laura Avanzino[1,3]
[1]Department of Experimental Medicine, Section of Human Physiology, University of Genova, Italy, [2]Department of Neuroscience (DiNOGMI), University of Genova, Italy, [3]Ospedale Policlinico San Martino, IRCCS, Genova, Italy

Cerebellum plays a major role in the ability to adapt movement to environmental changes, in order to move precisely and to learn new motor patterns. Novel evidence suggests that the cerebellum plays a role in the cerebral dysfunctional network sub-serving the expression of tremor as a phenotypic motor feature in cervical dystonia (CD). Transcranial direct current stimulation (tDCS), a form of noninvasive brain stimulation, has been shown to increase cerebellar excitability and improve learning in motor adaptation tasks. Here, we delivered cerebellar tDCS to modulate its activity during motor adaptation in healthy and in patients affected by CD and tremor**.** Ten patients with CD with tremor, and 10 healthy controls were enrolled in our two-days

paradigm, with randomized tDCS cerebellum stimulation, anodic or sham. Reaching movements on a digitized tablet were recorded. To study adaptation, we induced screen cursor rotation that created direction errors. As measure of the extent of the adaptation, we used the percentage return, the relative return of directional error during adaptation phase compared with the directional error in the baseline phase. Results showed that in both groups anodic tDCS induced an improvement in the magnitude of adaptation. Our preliminary data showed that anodic cerebellar tDCS is able to improve learning in motor adaptation task in healthy subjects and in CD patients with tremor.
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41. Reaching movements in cervical dystonia: a motor learning study.
A. Caronni[1], L.Sciumè [2], A. Montesano[1], A. Marzegan[1], A. Castagna[1]
[1]IRCCS Fondazione Don Carlo Gnocchi Onlus, Milano, Italy; [2] ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy

Introduction. Previous reports showed that patients with idiopathic cervical dystonia (ICD) make abnormal reaching movements with the clinically unaffected arm. Aim of the current study is to evaluate if random practice improves reaching movements abnormalities in ICD patients.
Methods. 14 ICD patients and 7 healthy controls took part in the study. Participants, tested in two consecutive days (D1 and D2), were asked to complete planar out and back reaching movements towards eight different targets. Within each day, participants completed 120 trials. Measures from the first 12 (baseline) and last 12 (ending) trials were averaged. Three-way ANOVAs and post-hoc tests (Bonferroni correction) were used for statistics.
Results. At D1-baseline, movement extent (ME) was smaller in patients than controls. During D1, patients increased their ME and retained this improvement at D2-baseline. No ME modification was observed in controls and, at ending, ME was comparable in patients and controls. During D1, controls (but not patients) reduced their movement time (MT) and this improvement was retained at D2-baseline. Peak velocity (PV) and peak acceleration (PA) were smaller in patients than controls, with no modification within or between sessions in both participants' groups.
Conclusions. ICD patients perform hypometric reaching movements, with reduced peak velocity and acceleration. With practice, controls and ICD patients improve their speed-accuracy trade-off, but with opposite strategies. Patients improve the accuracy of their (inaccurate) reaching movement, while controls increase movement speed. Present data suggest that ICD patients can have greater difficulties in learning to move faster, rather than learning to be accurate.

42. Transcranial Magnetic Stimulation Therapy for Focal Leg Dystonia: A Case Report
Kush Sharma, Alberto Cucca, Andrea Lee, Shashank Agarwal, Steven Frucht, Milton Biagioni
The Marlene & Paolo Fresco Institute for Parkinson's & Movement Disorders, NYU School of Medicine, New York, NY, USA

Dystonia is a debilitating disease that causes abnormal, often repetitive, movements, posture or both. The pathophysiology is unknown but related to loss of neuronal inhibition, aberrant sensorimotor integration, and/or derangements of synaptic plasticity. Current treatments include pharmacotherapy, Botulinum Toxin (Botox) injections and deep brain stimulation (DBS). The response to these treatments are often limited and carry the risk of side effects requiring alternative therapies such us non-invasive brain stimulation. We present a case report of a 65-year -old man with refractory focal 'task-specific' dystonia. The treatment plan included 10-daily sessions of 1 Hz, 2600 pulses of repetitive transcranial magnetic stimulation (rTMS) targeting the primary motor cortex. There were no clinical benefits noticed. Currently, there are no rTMS protocol treatments for dystonia. Publication of negative results will help in refining the optimal stimulation parameters, thus maximizing the effectiveness and reproducibility of future therapeutic protocols.

43. Tele-Monitored tDCS (Tele-tDCS) in Parkinson's Disease Patients with Comorbid Fatigue
Kush Sharma[1], Shashank Agarwal[2], Daniella Mania[1], Willa Molho[1], Ji Yoon Jung[1], Raphaela Sills[1], Milton C Biagioni[1]
[1] The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, NYU School of Medicine, New York, NY, USA, [2] Department of Neurology, NYU School of Medicine, New York, NY, USA

BACKGROUND: Fatigue is one of the most prevalent and largely under-assessed non-motor symptoms in PD. Current potential therapies have limited effectiveness. Presently, tDCS has shown potential to improve certain symptoms of PD. We designed an RS-tDCS protocol to allow study participation from a patient's home while maintaining clinical trial standards. We utilized a live video-conferencing platform and specially designed

equipment that 'unlocks' one session at a time. Study objective is to assess feasibility and explore the therapeutic potential of remotely supervised tDCS (RS-tDCS) paired with cognitive training (CT) for PD related fatigue.
METHODS: Preliminary analysis of eighteen PD patients, age 35-89 that participated in a double-blind, randomized, sham controlled study with RS-tDCS paired with CT. Each participant completed 10 tDCS sessions (20-minute, 2.0-mA, bi-frontal DLPFC montage, left anodal), over a span of two weeks. After completion, 10 additional open label sessions were offered. Tolerability, safety and compliance were evaluated. Preliminary clinical effects were measured with the fatigue severity scale (FSS).
RESULTS: A total of 18 participants completed 330 RS-tDCS sessions; one subject chose not to complete the 10 optional sessions and one subject was not deemed eligible for the study. Tolerability of 2.0 mA stimulation with ≤6 on visual analog scale for pain (VAS-Pain) was 100%. Systematically recorded SEs were: tingling 22.4%, itching 8.2%, burning sensation 11.5%, dizziness 0.3%, headache 3.3%, sleepiness 0.3%, and nausea 0.9%. No serious AEs were reported. Compliance was 100% as subjects completed all required visits with no attrition or interruptions. Preliminary fatigue clinical effects of 10 sessions showed a significant decrease of FSS only in real tDCS; however, there were no significant difference between groups. Further analysis of 20 real sessions showed a larger decrease in FSS (real-real; $p < 0.05$) but not in sham-real (10/10) sessions. Overall responders (>15% decrease in FSS) after 20 sessions were 75% vs 37.5%.
CONCLUSION: At-home RS-tDCS therapy paired with CT is safe and well tolerated by PD patients, with the advantages of ease of recruitment and subject compliance. Acceptability was achieved by easy setup and intuitive design of the device. At-home RS-tDCS therapy paired with CT shows potential to remediate fatigue symptoms in PD but the small sample size limits efficacy conclusions. Our paradigm may be influential in designing future studies that will facilitate clinical trials with a larger subject population and extended trial duration. Sponsor: Parkinson's Foundation Grant# 17-A0-00-007749

44. Alternative splicing as a potential biomarker for Parkinson's disease

Paola Polverino[1], Claudio Bertolotti[1], Valentina Tommasini[1], Maurizio Romano[2], Giulia Mazzon[1], Tatiana Cattaruzza[1], Lucia Antonutti[1], Emanuele Buratti[3], Mauro Catalan[1], Paolo Manganotti[1]
1 Clinical Unit of Neurology - Department of Medical Sciences – University Hospital and Health Services of Trieste - University of Trieste, 2 Department of Life Sciences, University of Trieste, 3 Molecular Pathology Group, International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy.

Introduction. In the extensive field of PD biomarkers, transcriptomic has been showing encouraging results. Only a few studies have focused on the role of aberrant alternative splicing (AS) events as PD biomarkers and their research in peripheral blood is lacking.
Objective. The aim of this pilot-study is to investigate the potential role of AS as a biomarker of dementia development in PD, by analyzing leukocyte-derived RNA.
Materials and Methods. Blood-leukocyte samples were collected from 4 early PD patients (EPD), 4 advanced PD patients with dementia (PDD), 4 patients with Alzheimer's disease (AD), and 7 age-matched healthy controls (CTR). RNA was extracted from leukocytes and analyzed by quantitative PCR (qPCR). Firstly, we assessed overall expression levels of *SNCA*, *PARK2*, and *LRRK2* genes; successively, we investigated the AS pattern on three other target genes (*ATXN2*, *HSPH1*, *LRRFIP1*), which recent studies have found to be altered in PDD.
Results. We found no significant differences in the expression levels of *SNCA, LRRK2*, and *PARK2* between PD patients and controls. Similarly, AS quantitation didn't show any significant difference in the splicing pattern of *ATXN2*, *HSPH1*, and *LRRFIP1* genes. Our data, however, suggest that *PARK2* might be poorly expressed in PDD patients compared to the other groups; also, there are some indications of abnormal exon skipping events, regarding exons 18-19 of *LRRFIP1* gene in PDD.
Conclusions. Our results provide interesting clues about gene expression and splicing alterations in PDD patients. These findings will be further investigated in the next phase of the study, through deep RNA sequencing.

45. Changes in motor-cortex excitability after different rehabilitation programs in PD patients with freezing of gait: neurocognitive rehabilitation with motor Imagery vs treadmill training

Claudio Bertolotti[1], Paola Polverino[1], Mauro Catalan[1], Pierpaolo Busan[2], Giulia Sgubin[3], Pellegrini Lorella[3], Alberto Cucca[1], Lucia Antonutti[1], Fabrizio Monti[1], Susanna Mezzarobba[3] and Manganotti Paolo[1]
1 Clinical Unit of Neurology - Department of Medical Sciences, University Hospital and Health Services of Trieste, University of Trieste, Italy; 2 Department of Life Sciences, University of Trieste, Italy; 3 Department of Life Sciences, University of Trieste, Italy; Department of Medicine, Surgery and Health Sciences, University of Trieste, Italy

Introduction. Freezing of gait (FoG) is a highly disabling symptom of Parkinson's disease (PD). Its pathogenesis isn't completely understood and pharmacological treatments generally have a poor outcome. Furthermore many rehabilitation treatments have been proposed with contrasting results.
Objective. Testing the efficacy of two different rehabilitation programs (Motor Imagery (NR-MI) versus Treadmill Training (TT) in improving FoG and studying their impact on motor cortex excitability (MCE).
Materials and methods. 20 PD patients with FoG were enrolled and randomly assigned to treatment groups. Group 1 performed 20 sessions of Neurocognitive Rehabilitation program based on NR-MI, while Group 2 underwent 20 sessions of TT. Patients were evaluated at baseline and at the end of the rehabilitation program (T1) by assessing: disease stage (H&Y and UPDRS-III), FoG (FOGQ), cognitive abilities and MCE indexes recorded by Transcranial Magnetic Stimulation (TMS).
Results. No significant differences were found at baseline. After treatment, Group 1 experienced a significant reduction of FoG, while Group 2 did not. TMS suggested a tendency toward an increase in MCE after both treatments compared to baseline indexes of motor thresholds and motor evoked potentials recruitment curves, as well as in intra-cortical inhibition. Differently, a tendency toward a prolongation of silent period duration was found in both groups, as well as a tendency toward a reduction of intra-cortical facilitation in the TT-group.
Conclusions. Although both treatments induced comparable effects on TMS, only NR-MI showed a significant improvement of FoG, suggesting different underlying mechanisms. NR-MI appears to be an interesting rehabilitation strategy in FoG treatment.