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Insights into emotions, learning and motor function in Parkinson's disease to improve the multidisciplinary approach of the treatment

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1 Chapter

Introduction

1.1 Aims of the thesis

Quantitative methods are nowadays available to assess human balance by measuring movements of the body Center of Pressure (CoP) and Center of Mass (CoM) in static (i.e. posturography) or dynamic condition (i.e. walking). The CoP displacements are commonly recorded using force platforms, as CoP is the point of application of the resultant of ground reaction forces, while the CoM is usually extrapolated from the 3D coordinates of the body anatomical landmarks related to the kinematics through biomechanical models. The availability of such methods has improved over the years the knowledge of the physiological movement and of its alterations in pathological conditions in people with neurological diseases, such as Parkinson's disease (PD). The strength of instrumented measurements lays in their ability to detect slight differences in movement patterns and motor control, not clinically detectable by a human observation, between PD patients at the early stage of the disease and healthy subjects, as well as in the possibility to capture the changes induced by rehabilitation. In addition, the usefulness of these measurements became fundamental for the management of individual patients, in particular for tailoring the therapeutic interventions on balance deficits in PD patients.

Recent narrative reviews highlighted that a multidisciplinary approach, which include pharmacological, surgical, and non-pharmacological treatments (i.e., physiotherapy, occupational-therapy, and cognitive-emotional interventions), is essential for a positive effect on PD persons, especially when Freezing of Gait (FOG) symptoms occur. In light of the above consideration, this thesis has been divided into two main lines of research, that are:

- the investigation of the effects of the emotional sphere on visual-spatial learning and gait initiation in persons with PD, with and without FOG symptoms, to advance the knowledge on PD pathophysiology and to provide useful data for a tailored therapeutic approach (Chapter 2 and 3);

- the assessment of quantitative measures of movement, related to static and dynamic balance, during gait initiation and walking in persons with PD, using both wearable systems and optoelectronic instrumentation (Chapter 4 and 5).

1.2 Neural organization of motor control involved in balance and locomotion

The neuronal networks involved in locomotion have been extensively studied in animals and humans. They are hierarchically organized through control signals from the central nervous system to the peripheral muscle effectors with a top-down scheme [1,2], including: (1) the basal ganglia and the prefrontal cortex as the higher level control systems that modulate the (2) locomotor areas located in the brainstem. These structures are in charge of producing locomotor actions when stimulated, modulating the central locomotion pattern generators (3), an organized groups of interneurons automatically generating rhythmic and alternating limb activity, and (4) finally the lower effector levels, including the musculoskeletal system and the peripheral nervous system.

The structure of the basal ganglia nuclei is very complex. In fact, although these are groups of subcortical neurons primarily responsible for motor control, they also have other roles such as motor learning, executive functions and behaviors, and emotions.

The term basal ganglia in the strictest sense refers to nuclei embedded deep in the brain hemispheres (striatum or caudate-putamen and globus pallidus), whereas related nuclei consist of structures located in the diencephalon (subthalamic nucleus), mesencephalon (substantia nigra), and pons (pedunculopontine nucleus, PPN).

The basal ganglia and related nuclei can be broadly categorized as (1) *input nuclei*, (2) *output nuclei*, and (3) *intrinsic nuclei* [3]. *Input nuclei* are those structures receiving incoming information from different sources, mainly cortical, thalamic, and nigral in origin. The caudate nucleus (CN), the putamen (Put), and the accumbens nucleus (Acb) are all considered input nuclei. The *output nuclei* are those structures that send basal ganglia information to the thalamus and consist of the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). Finally, *intrinsic nuclei* such as the external segment of the globus pallidus (GPe), the STN and the substantia nigra pars compacta (SNc) are located between the input and output nuclei in the relay of information. Cortical and thalamic efferent information enters the striatum (CN, Put, and Acb) to be processed further within the basal ganglia system. The output nuclei (GPi and SNr) project mainly to the thalamus (ventral nuclei), which, in turn, project back to the cerebral cortex (mainly frontal lobe).

The intrinsic nuclei of the mesencephalic locomotor region (MLR) in the midbrain/mesencephalon, are thought to be of particular importance in the physiological and pathophysiological gait. In fact, MLR has direct access to the spinal cord and plays an active role in the control posture and gait through the initiating and modulation of the spinal neural circuitry. Nuclei within the MLR, such as the pedunculopontine nucleus (PPN), receive inputs from the substantia nigra of the basal ganglia and neural centers within the limbic system. Studies conducted on animal models found that afferents from the basal ganglia in monkeys originate from the sensorimotor, cognitive and limbic anatomo-functional territories suggesting that the PPN is in a position to integrate motor and non-motor inputs [4]. The PPN within the MLR is composed of a diverse population of neurons containing the neurotransmitters gamma-amino-butyric acid (GABA), glutamate, and acetylcholine (ACh). Results from animal and clinical studies suggest that cholinergic neurons in the PPN play a crucial role in modulating both the rhythm of locomotion and postural muscle tone. Glutamatergic and cholinergic inputs from the MLR may be responsible for regulating the excitability of reticulospinal neurons that in turn project to spinal central pattern generators to initiate stepping.

The appropriate functioning of the basal ganglia system requires dopamine to be released at the input nuclei. Dopamine dysfunction is associated with several basal ganglia movement disorders such as Parkinson's disease.

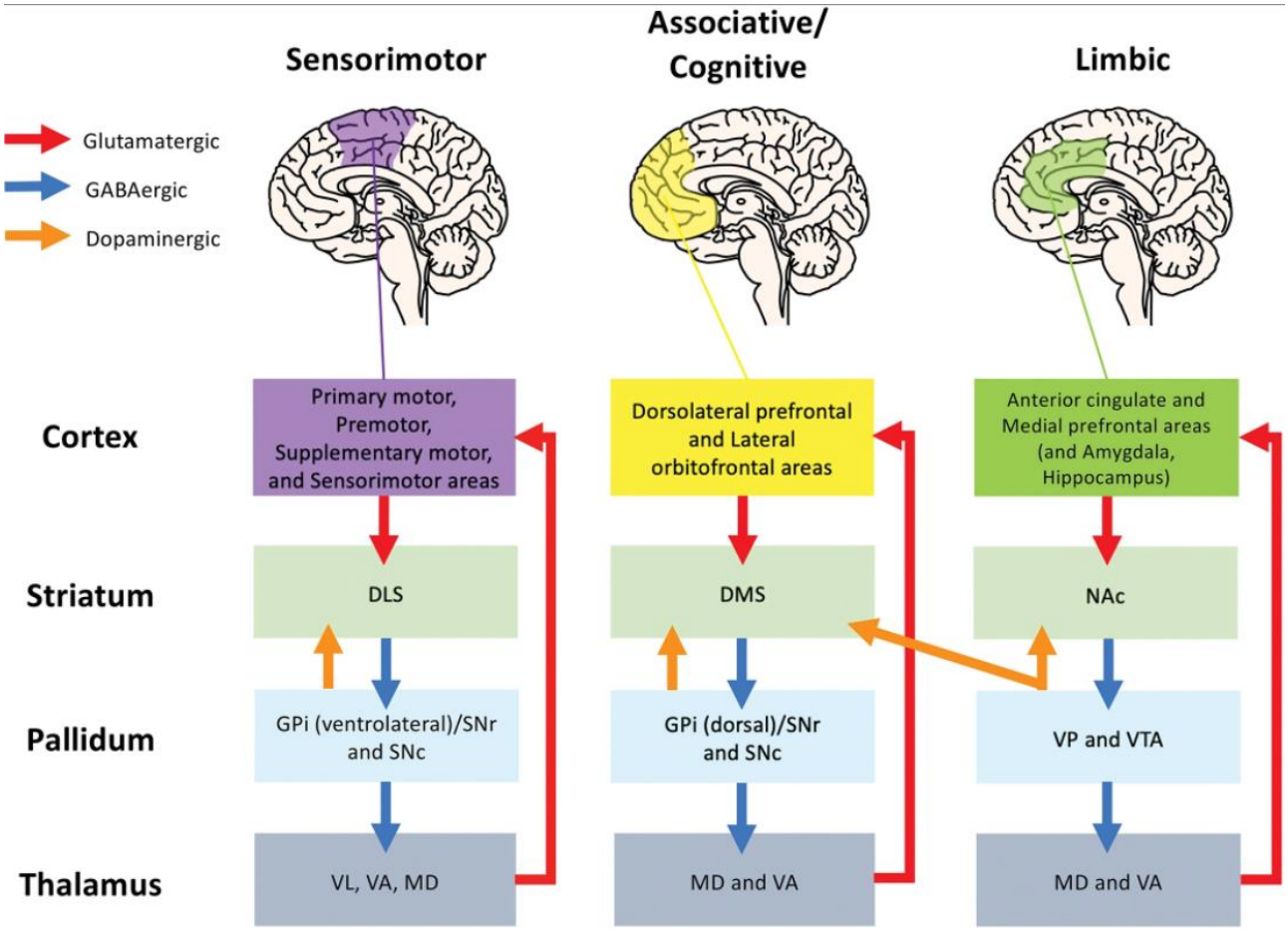

Figure 1 Basal ganglia neurocircuits. Basal ganglia neurocircuits can be broadly divided into three functional loops: the sensorimotor, associative/cognitive, and limbic neurocircuits. DLS, dorsolateral striatum; DMS, dorsomedial striatum; GPi, globus pallidus internal section; MD, medial dorsal thalamus; NAc, nucleus accumbens; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VA, ventral anterior thalamus; VL, ventrolateral thalamus; VP, ventral validum; VTA, ventral tegmental area [2].

Three different anatomically and functionally separated circuits, named motor, associative/cognitive, and limbic loops, can be identified on the basis of the function of the involved cortical area (Figure 1). Gait integrity reflects the functioning of these brain networks and their interactions (Figure 2), and the locomotor circuits are modulated by sensory feedback via sensory afferent systems (somesthetic, vestibular and visual systems).

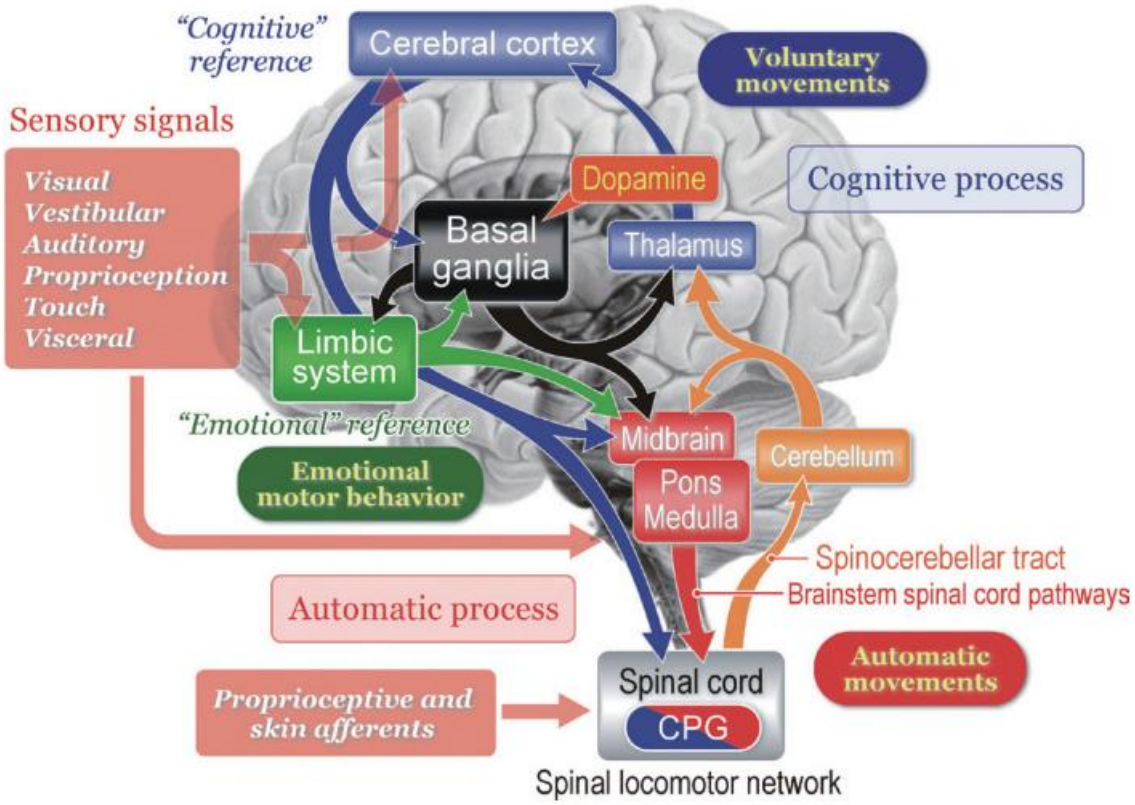

Figure 2. General schema of posture-gait control describing possible interactions between multisensory signals (e.g., visual, vestibular, auditory, somatosensory (proprioceptive), and visceral receptors) and the central nervous system. These signals may provide cognitive and emotional references to the cerebral cortex and limbic system, respectively, so that the subject may elicit either voluntary movements or emotional motor behavior depending on the context [1].

1.3 Locomotor impairment in Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative condition of the extrapyramidal system with a chronic progressive course, clinically defined by the association of tremor, rigidity, bradi-akinesia and postural instability, and neuropathologically characterized by severe degenerative changes of the substantia nigra (pars compacta) and pigmented nuclei of the brain stem, with the presence of specific cellular inclusions (Lewy bodies) in the residual neurons [5].

Since the cause of Parkinson's disease is not known, the treatment is essentially symptomatic, i.e. aimed at compensating for the dopaminergic deficit. The most effective drug therapy to date is levodopa, a natural precursor of dopamine into which it is converted by the action of dopa-

decarboxylase, which induces, in the great majority of patients, a rapid and significant improvement (of over 50%) of the disease symptoms [6]. Although dopamine restoring agents are helpful for bradykinesia, rigidity, and tremor, they have a mixed effect on gait and postural instability [7]. The effects of other pharmacological therapies on control of gait are even less well studied than levodopa. Other therapies include adjunctive therapies to levodopa, as well as medications that are used to treat cognitive deficits or other co-morbidities. Gait and balance disorders are a major problem with unmet therapeutic objectives during the course of Parkinson's disease. These symptoms are usually not severe in the early phases of PD but progress over time in a majority of the cases and represent a heavier burden later in the course of the disease [8]. The increasing impact of gait and balance disorders is mainly explained by lack of efficacy of dopamine agonists treatments on these symptoms [7,8]. Motor symptoms of PD commonly start at one side and, with the progression of the disease, they generally extend to the other one, even if the maintenance of an asymmetrical distribution of motor severity throughout the entire course of the disease is quite common [9]. Postural and locomotor alterations are continuous symptoms as they refer to stable alterations in the walking pattern, such as the inability to correctly shift the body weight between the two legs during walking, which is responsible for the steps asymmetry, the reduction in both the step length and clearance and difficulty in overcoming obstacles along the way. Subjects with Parkinson's disease manifest also difficulties in coordination between the different body areas, head, trunk and upper and lower limbs [7,10]. In addition to these continuous symptoms, there are those of episodic type that occur occasionally and intermittently, surfacing in an apparently random, inexplicable manner [11]. The episodic gait disturbances include festination, start hesitation, and freezing of gait (FOG). The latter is a debilitating phenomenon that is most commonly experienced by patients with advanced PD [12]. Early onset FOG should be suspected of other parkinsonism, such as progressive supranuclear palsy [13].

While both types of gait disturbances are a result of basal ganglia dysfunction and certain episodic symptoms are associated with other continuous symptoms (e.g. patients with freezing of gait have increased gait variability), the specific mechanisms responsible for the episodic and continuous gait disturbances are likely somewhat independent [11].

The gait and its motor tasks require varying degrees of cognitive, and therefore, cortical control in according to the specific component. The least cognitive (or most automatic) component, straight walking over a flat surface, requires only minimal attention, while the initiation of gait, involves more cortical control than straight walking as it generates goal-directed movements [14]. Gait initiation (GI) consists of a postural weight shift forward and toward the stance leg in order to unload the stepping leg. Such CoP movement is defined as the anticipatory postural adjustment (APA, Figure

3). Following the APA, the foot pushes off and moves forward to execute the first step. Relevant parameters for gait initiation include, the reaction time, the duration and amplitude of the APA, the Center of Pressure (CoP) displacement, push-off forces, and first step length [15]. Both the straight walking and APAs have been intensely studied in PD because they negatively impact the activities of daily living. Nevertheless, the alteration mechanisms behind gait difficulties and gait initiation disturbances are still unclear [16,17].

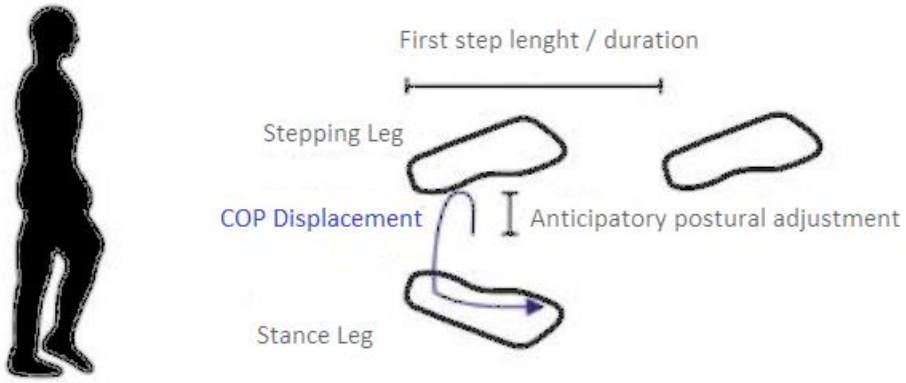

Figure 3 Gait initiation can be characterized by the anticipatory postural adjustment (APA) that precedes the onset of the first step. The Center of Pressure (CoP) first moves posteriorly and toward the stepping foot in order to accelerate the Center of Mass (CoM) forward and toward the stance foot.

Parkinson's disease is characterized also by several non-motor manifestations that encompass a range of clinical features, including neuropsychiatric problems, sleep disorders, fatigue, and pain [18–20]. Depression and dementia are also associated with the progression of the disease [21].

1.4 Emotions in Parkinson's Disease

In clinical practice gait characteristics constitute a clinical marker of well-being and level of activity in older adults, as well as in patients with neurological/psychiatric conditions [22,23]. The quantitative measures extracted from the gait pattern are part of the clinical tool for the diagnosis and monitoring of progression of neurological disorders. This approach also applies to people with PD. Gait deficits are implicated in several neurological and psychiatric disorders since probably there is a bi-directional interaction between the brain motor system (e.g. the primary motor cortex (M1), supplementary motor area (SMA)) and other cortical and subcortical structures (cerebellum, BG, PPN) related to emotions and higher cognitive function [1,24].

Gait characteristics can change according to the different emotional states of the subject. In healthy subjects, the increase of walking speed, arm swing and step length, and the reduction of postural sway and reaction time prior to the step, are associated with positive emotions, while opposite trends of these gait parameters are associated with negative emotions [24,25]. Research in neuroscience and related fields indicates that improvements in posture and gait may influence brain neurotransmitters that trigger positive emotions and moods.

The consensus of evidence in the neuroscience of the motor system supports the theory that BG forms connections with the cerebellum via the thalamus and the PPN, which are regulated by a reward cortical signal (see 1.2 paragraph). Furthermore, the cerebellum forms a feedback loop with the cortex, whose functional role is related to the improvement of precision of movements. Gait abnormalities, when they are not the result of orthopedic problems or a spinal cord injury, are linked to a physiological decline of such structures of central nervous system, and can get worse by the pathophysiological damage due to neurological conditions such as PD. In fact, people with PD have worse walking performance (e.g. slower speed, longer reaction time, reduced stride length) when performing a dual task, which means to walk and concurrently execute a cognitive task (e.g. a verbal fluency task) or a motor task (e.g. obstacle negotiation) [26]. This is an evidence that there is a link between the motor control of gait and cognition, which is strongly related to mental states and emotions.

The formation of emotions has been investigated for several decades in neuroscience as well as in psychology and psychiatry. Several theories have been developed that link specific emotions to brain structures, and hypothesize the presence of several brain network. The limbic system, which includes the frontal lobe areas, the hypothalamus, amygdala and cingulate cortex, has been strongly associated with emotions as well as behavior and motivation [27,28]. Electrical stimulation of the amygdala results in increased aggression in animal models whereas, when it is removed, the animals do not respond adequately to fearful stimulus and sexual arousal.

Among the regions that play key roles in both gait motor control and emotions are the Prefrontal Cortex (PFC) and the basal ganglia. PFC is involved in executive function, motivation and attention, and its function has been also associated with reward neural pathways and addiction [29]. The basal ganglia are strongly connected to the cortical regions such as the PFC with the function of interconnection to repetitive behaviors, reward experiences and attention.

It is widely hypothesized in the literature that emotions are probably formed via large scale cortical and subcortical brain networks and their formation cannot be charged to specific brain structures only. In general, there are strong evidences of bi-directional interactions between brain networks that underpin gait and emotions. These evidences come mainly from animal studies and PD disease

models, and they highlight brain connections of the amygdala with the basal ganglia as well as with the motor cortex. Patients with PD with the experience of FOG show increased brain connectivity between BG and the limbic system, and decreased brain connectivity between BG and cortical regions. Patients with PD with or without FOG have also shown difficulties in recognizing emotions, in interpreting facial expressions, and in detecting fear and sadness [30]. Since the growing evidences in the literature highlight that the link between emotions and gait is bi-directional, it is not surprising that GI features are influenced by emotional factors such as the emotional valence of stimulus or mood in both persons with PD and elderly. Several studies report that the manipulation of emotional states changes the GI performance in both persons with PD and healthy subjects. For example watching threatening and unpleasant images resulted in increased GI speed [31] and reaction time [32], respectively. This suggests that at least some of the high-level structures in the emotional states management are preserved in persons with PD. However, after exposure to unpleasant images, persons with PD reduced the step size with respect to those of elderly. In particular, subjects with FOG experience showed longer reaction times and shorter step sizes with respect to PD patients without FOG and elderly. Furthermore, changes in RT performance in response to unpleasant images positively correlated with the "frequency" of FOG episodes. The authors suggest that emotional load plays a role in gait disturbances of PD patients with FOG, suggesting that the limbic system may be involved in FOG pathophysiology. Furthermore, recent evidences have shown that emotional and mood disturbances are known to exacerbate FOG symptoms, these aspects deserve to be investigated [32,33].

This hypothesis is supported by the evidences that PD with FOG showed increased brain connectivity between BG and the limbic system and decreased brain connectivity between BG and cortical regions [25,34,35]. In addition, although longitudinal evidence for predictors of FOG remains conflicting, at the current state of knowledge, among the non-motor domains (cognition, sensory-perceptual, affective), those of an affective nature (i.e. anxiety and depression) seem to be the only ones able to predict the future development of FOG [33]. Based on this evidence, part of this thesis focused on the study of the effects of affective stimuli on motor performance in subjects who experienced FOG (see Chapter 2).

1.5 Visual-Spatial Learning in Parkinson's Disease

Executive function is a set of mental skills that include working memory, flexible thinking, and self-control. We use these skills every day to learn, work, and manage activities of daily life. Deficit with

executive function can impair the ability to focus, follow directions, and handle emotions. In fact, executive function is responsible for many skills, including:

- Paying attention
- Organizing, planning, and prioritizing
- Starting tasks and staying focused on them for completion
- Understanding different points of view
- Regulating emotions
- Self-monitoring (keeping track of what you're doing)

There are three main areas of executive function, namely:

- Working memory
- Cognitive flexibility (also called flexible thinking)
- Inhibitory control (which includes self-control)

Working memory (WM) is a latent cognitive structure that serves for storing and manipulating a limited amount of information over a short time period. How information is maintained in WM remains a debated issue. The most accredited model assumes that working memory recruits both domain-general and domain-specific neural networks.

The domain-specific approach to working memory assumes specialized working memory systems dedicated to maintaining different types of information (e.g. orthographic, phonological, semantic, visuospatial) which serve for supporting processing in that domain. The degree to which visuospatial working memory (VSWM) is separable from working memory in general is an open question [36]. In fact, as reported above, on one hand the construct is often researched as a unitary, domain-specific system, and on the other, there is evidence that VSWM shares a common processing component with verbal memory [36].

Probably, VSWM shares a domain-general component with verbal memory tasks and has a domain-specific component that is independent of verbal memory, suggesting its multiply determined nature. Visual-spatial learning refers to a person's ability to perceive, analyze, and understand visual information in the world around them. This skill requires coordinated activity with surroundings elements, to use representations of the environment in order to comprehend and conceptualize visual representations and spatial relationships [37]. On this ability, in addition to VSWM, also attention plays a significant role in the storage of visuospatial information and not just in the various processes of the central execution. Attention and VSWM share very similar characteristics, indicating a common shared underlying mechanism [38]. However, their relationship is currently still debated.

Beside the motor deficits, also the decline in cognitive function has been recognized as a feature of PD and, in particular, one of the prominent cognitive symptom of PD involves the deficits on tasks of spatial ability [39]. The studies that have highlighted visual-spatial deficits in PD are often complex, showing sensitivity to other cognitive processes as well. To date there is not a clear understanding of the brain mechanisms that underlie visual-spatial deficits in PD. One of the theory of cognitive dysfunction in PD suggests that these cognitive deficits are in some way related to the disruption of frontal-basal ganglia neural circuits, which are important in executive functions [40]. Furthermore, it has been suggested that factors such as age, sex, education, duration of illness, level of disability, medications, and the presence of dementia should be taken into consideration as cofounding factors. In fact, the frontal-basal ganglionic dysfunction does not appear to account entirely for the visual-spatial cognitive deficits seen in PD. Subtle differences in performance on executive function measures appear to dissociate individuals with frontal lobe damage from individuals with PD. Recent studies indicate that PD is indeed associated with deficits in visual-spatial ability. These findings also indicate that the relationship between visual-spatial ability and frontal-executive function in PD is likely complex, and that the visual-spatial deficits in PD may be sensitive to the emotions of the PD individual [41]. Recently Chan et al found that the exposure to negative emotional stimuli influences the PD subjects' ability to navigate during an object placing task with respect to the target location aimed to reach [41]. The cognitive dysfunction, such as the visual-spatial deficit in PD, are commonly thought to be due, either primarily or secondarily, to frontal-executive deficits resulting from frontal-striatal dysfunction. Since cognitive information is proposed to travel through the basal ganglia via a series of parallel circuits, also including the limbic one which is thought to be involved in emotional and motivational processes, we focused a part of this study to investigate the potential role of emotion on visual-spatial ability in PD (see Chapter 3).

1.6 Rehabilitation in Parkinson's Disease

Non-pharmacological interventions are essential in the management of gait impairments in Parkinson's disease, as locomotor deficits only partially improve in response to dopaminergic medication and deep brain stimulation. These interventions are usually delivered using a multidisciplinary approach [42]:

Physiotherapy

• compensation strategies (including internal and external cueing)

• functional gait training (either overground or treadmill-based)

• exercise
• multi-task training

Occupational therapy

• reducing constraints in the physical environment
• daytime planning to reduce stressful moments

Coaching by a psychologist

• cognitive behavioral therapy to reduce fear of falling, possibly improving executive functioning

In recent years, evidence on rehabilitation for gait impairments in PD has been growing, particularly for physiotherapy. Exercise has received much attention in the past decade as a way to delay the onset of balance impairment and mobility disability, as well as to slow down the degenerative course. Dynamic postural control is defined as the ability to control the center of mass during continuously changing conditions, including the transfer of body weight between the legs (weight-shifting) during walking. This body-weight shifting ability is reduced in PD and locomotor training is often focused on the recovery of the proper body weight shift to improve the patients' gait pattern.

The clinical scales used to measure the patient performances are subjective, and prone to ceiling effects, in contrast to objective instrumental measures of balance and gait [43–45]. Those limits of the clinical scales makes it difficult to determine whether a specific type of exercise is more effective with respect to another one [46].

The gait analysis is becoming a routine examination in clinical practice and following a growing diffusion of wearable instruments it is now possible to carry out a gait assessment outside the clinical settings, e.g. at home. For this reason, it is important to understand if there are quantitative and objective measures, focused on the analysis of body-weight shift and APAs recovery, which can potentially detect changes following the treatment.

The abnormalities of the body-weight transfer are a common problem among patients with PD, however some patients experience also the symptom of FOG, that is considered one of the most disabling gait symptom. It is a major cause of falls and injuries that in turn contributes to immobility, loss of independence, and reduced quality of life. Despite its relationship with disease severity, FOG symptoms do not correlate with the cardinal features of PD, such as tremor, bradykinesia, or rigidity, but correlate with falls, postural instability and executive dysfunction (e.g. set-shifting and conflict resolution).

Although FOG has been extensively studied, it is still considered a "mysterious phenomenon", because its pathophysiology is not yet clear, and FOG empirical treatments are of poor efficacy. Consequently, it is considered an important clinical problem.

The typical physiotherapy approach for treating the symptom of FOG consists in trying to train the patient to manage 'dangerous' situations that can lead to the triggering of the symptom, such as dual tasks and environmental factors (e.g. turning, passing through narrow doorways, etc). Although physiotherapy showed to be effective in improving FOG in the short term when compared with no intervention, the positive effect is reduced significantly just after 4 weeks from the end of the treatment [47]. Probably, to achieve more effective results, interventions should be more intensive and prolonged (e.g. continuing in home-based settings) in order to foster motor learning and promote long-lasting effect. However, the evidence so far suggest that the purely motor treatment alone is not sufficient for improving FOG symptoms, and a multidisciplinary approach, including other aspects of control besides the motor one, is the most promising way to understand and therefore treat FOG.
For the above reasons, we have focused part of this thesis on identifying instrumental outcome measures to characterize motor performances both in static and dynamic conditions in PD patients with and without FOG (see Chapter 4 and Chapter 5), with the final aim to provide useful tools for improving symptom monitoring and developing rehabilitation protocols.

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2 Chapter

Evoked Emotions and Freezing of Gait

2.1 Chapter Summary

Background: Freezing of gait (FOG) in subjects with Parkinson's disease (PD) can be triggered by three domains: motor (e.g., turning), cognitive (e.g., dual task) or limbic (e.g., fear). However, persons with PD and FOG did not show alteration of the anticipatory postural adjustments during gait initiation after the exposure to images with emotional valence.
Objectives: To investigate whether step initiation characteristics are influenced by ecological auditory stimuli with emotional valence in patients with FOG compared to non-freezers subjects.
Methods: A total of 45 participants, divided into 3 groups (15 PD with and 15 PD without FOG, and 15 healthy subjects), stood on a force platform and were asked to take a step forward in response to neutral, pleasant, or unpleasant ecological auditory stimuli. Anticipatory postural adjustments characteristics were investigated both in imbalance and unloading phases whereas spatio-temporal parameters, including the center of pressure (CoP) displacements, were computed for step initiation.
Results: PD with FOG showed a reduction of the CoP displacements after the listening to unpleasant stimuli. Conversely, pleasant stimuli seemed to facilitate the CoP displacements in these subjects. No influence of affective stimuli on CoP displacements was found in the other two groups. Multiple regression analysis revealed that the behavioral pattern in PD with FOG, modulated by stimuli with affective valence, was mainly associated with a depression state.
Conclusions: The findings of this study showed that emotional network has an important role in the pathophysiology of the freezing, generating probably an interference with attentional reserves that trigger the FOG.

This work is being submitted to a peer reviewed scientific journal.
Title: Emotional auditory stimuli influence step initiation in Parkinson disease with freezing of gait.
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2.2 Introduction

Safe gait represents one of the foremost determinants for quality of life and independence for persons with Parkinson Disease (PD). Along with the typical pathological symptoms (bradykinesia, rigidity, and reduced amplitude and automaticity of movement), there are many factors that affect the gait performance in PD. Among them, Freezing of Gait (FOG), defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [1], is one of the most disabling symptoms that severely affect gait, increase risks of falls, impact on independence of daily life, imposing an immense burden on patients' and caregivers' quality of life [1].

Although FOG is a paroxysmal phenomenon triggered by several environmental factors (e.g., doorway, crosswalk), it is well recognized [2] that other stressors or emotional circumstances (e.g., fearful or anxious scenarios) can exacerbate FOG symptoms [3–6]. A possible involvement of the limbic/affective basal ganglia circuit in FOG pathophysiology has been also confirmed by recent imaging studies showing an increased striato-limbic connectivity [7–9], an abnormal attentional fronto-parietal network control over the amygdala [7] and a weakened interaction within the motor network and between the cognitive control network and the striatum [8].

Lagravinese and collaborators, recently investigated how emotional visual stimuli influence the step initiation in PD participants [5]. Results revealed that unpleasant images modulated the spatio-temporal parameters of step initiation in subjects with experience of FOG: longer reaction times and shorter step sizes were found in PD subjects with FOG with respect to PD without FOG. However, the expected changes in the Anticipatory postural adjustments (APAs) were not found. APAs displacements [10] in PD subjects with FOG were comparable with those of healthy subjects and people without FOG, regardless of the emotional valence of stimuli [5,11]. This finding is unexpected since it has been demonstrated that people with PD who have a history of FOG show smaller Medio-Lateral APAs (weight shifting) during gait initiation compared to PD-FOG [12].

The "cross-talk" model proposes that a transient overload of the basal ganglia to process competing, yet concurrent inputs (cognitive, sensorimotor, and emotional inputs), may be responsible for FOG. More precisely, it is assumed that limbic demands overload during the motor tasks could contribute to transiently increase the inhibitory output of the basal ganglia [13,14], resulting in the reduction of the activity of the brainstem centers (e.g. PPN pedunculopontine nucleus) that coordinate gait [15]. Following the "cross-talk" model, we would have expected hypometric APAs, that worsened when gait initiation is triggered by emotional stimuli. Possible explanations for the no significant difference between PD with FOG and PD without FOG and HC may be related either to the method of measurement of APA or to the nature of the emotional stimuli.

Indeed, the lack of evidence of the emotions influence on the APA displacements could be linked to the type of stimulus used in the in experiments. Indeed, the role of emotion on the control of human movement has been mainly investigated through visual stimuli, despite affective nonverbal vocalizations have also been shown to activate the human amygdala, regardless of attentive state [16–18], suggesting that humans might be more sensitive to emotionally salient background auditory stimuli.

The purpose of this study was to elucidate whether emotional inputs would impact on step initiation, and in particular the feedforward control in PD with FOG. We hypothesized that APA, in response to emotional auditory stimuli, would be altered/affected more in PD subjects with FOG when compared with non-freezers and healthy controls.

2.3 Material and methods

2.3.1 Participants

Thirty patients with PD, were recruited at IRCCS Fondazione Don Carlo Gnocchi in Milan. Inclusion criteria were: age> 18 years, diagnosis of idiopathic PD (according to the United Kingdom Parkinson's Disease Society Brain Bank criteria), Hoehn & Yahr between 2 and 3, Mini Mental State Examination≥ 24 and able to walk unassisted. Exclusion criteria were: deep brain stimulation implant, history of neurologic disorders (except PD), and visual, orthopedic, or vestibular impairments that could hamper task performance, subjects who need hearing aids.

Severity of motor symptoms was evaluated with the MDS–Unified Parkinson Disease Rating Scale (MDS-UPDRS) part III. Executive functions were assessed by means of the Frontal Assessment Battery. The affective status was evaluated using the Beck Depression Inventory II and the Beck Anxiety Inventory (BAI). Mobility was assessed using the Short Physical Performance Battery, and the modified Dynamic Gait Index (mDGI) was used to evaluate participants' balance. A total of 15 patients were confirmed to experience FOG (PD-FOG) according to the Characterizing Freezing of Gait Questionnaire (C-FOG) [19]. All PD participants were under treatment with dopaminergic therapy, and the experiment took place during the "ON" medication state.

Fifteen healthy subjects (HC, healthy control), without any history of neurological disorders, or severe musculoskeletal impairments, provided normative data for the measurement of the APAs and step initiation characteristics.

All participants gave their written informed consent to the study that was approved by the ethical committee of IRCCS Don Carlo Gnocchi Foundation, Milan, Italy (session October 16, 2019).

2.3.2 Experimental paradigm

Participants stood still with their feet in a self-selected stance width, with both feet on one force platform and were asked to initiate gait in response to auditory stimuli. The instruction was always to start the step as soon as the stimulus was heard through Bluetooth headphones and to stop as soon as possible with both feet on the ground. The experimental protocol always began with the baseline condition, and subsequently the auditory-emotional stimuli were delivered in a random sequence (see below for details).

The optoelectronic system with ten cameras (BTS, Smart DX) was used to record the coordinates of 9 retro-reflective markers: 4 for each foot (heel, first toe, 5th metatarsal head and lateral malleolus) and one for the pelvis. Two force plates (BTS, P-6000) provided ground reaction forces (GRFs). Before starting the experiment, each participant was given the opportunity to walk around the testing environment to become familiar with the instrumentation.

A custom-made Software, developed in the Visual Studio (Microsoft, USA) environment, controlled the trial onset and offset, the auditory stimulus presentation and the synchronization with the optoelectronic system including the GRFs. For each stimulus sent to the headphones, a synchronous trigger signal was sent to SMART Capture software (BTS).

2.3.3 Emotional stimuli

Auditory stimuli were used to induce emotional states during experimental trials. Fifteen digitized sounds were chosen from the International Affective Digitized Sounds (IADS-2) [20]. We selected 5 ecological auditory stimuli for three affective categories, according to the Self-Assessment Manikin (SAM) rating scale of pleasure [21]. The SAM value for unpleasant stimuli (i.e., attack, ambulance siren, car wreck, scream, buzzer) was between 1 and 3, for neutral stimuli between 4 and 6 (i.e., newspaper, writing, toilet, brush teeth, rain), and for the pleasant ones >6 (e.g., laughing, brook, beer applause, happy crowd) [20].

The order of presentation of the emotional stimuli was random. Five catch trials were also included, where a neutral voice saying ‘Go’ was used as stimulus with cognitive load (baseline condition).

2.3.4 Step initiation metrics

The temporal instants of the APA onset (i.e. the toe-off of the trailing limb (TO_{tr}) and of the leading limb (TO_{ld}), the heel-off and the heel-strike of the leading limb (HO_{ld}, HS_{ld})) were automatically

extracted by means of ad hoc Matlab (MathWorks, USA) algorithms according to Crenna et al [22]. These instants were necessary to identify the imbalance phase, during which CoP shifts backward and toward the leading limb (swing foot), and the unloading phase, during which the CoP moves laterally toward the trailing limb (stance foot).

Once the temporal instants were determined, the following set of parameters were measured:

- Reaction Time (RT): latency between the movement trigger (stimulus release) and the initiation of the motor response (APA onset).
- Duration of imbalance phase (T_{IMB}): difference between the instant of Heel-Off leading foot (HO_{ld}; the foot which performs the first step) and the instant of APA onset [22].
- Duration of unloading phase (T_{UNL}): difference between the instant of Toe-Off of the leading foot (TOld) and the instant of HOld [22].
- Duration of step (T_{STEP}): difference between the instant of the Heel-strike of the leading foot (HS_{ld}) and the instant of HOld [22].
- Step Length (L_{STEP}): displacement of the lateral malleolar marker trace from HO_{ld} to HS_{ld}.
- CoP movement during imbalance phase (CoP_{IMB}): displacements of the CoP trace in both the medio-lateral (CoP_{IMB_ML}) and anterior–posterior (CoP_{IMB_AP}) directions normalized to the distance between lateral malleolar and fifth metatarsal marker [22].
- CoP Displacement during unloading phase (CoP_{UNL}): displacements of the CoP trace in both the medio-lateral (CoP_{UNL_ML}) and anterior–posterior (CoP_{UNL_AP}) directions normalized to the inter-malleolar distance during standing [22].

The AP displacements were considered positive if CoP moved forward and negative if backward. ML displacements were positive if CoP moved toward the swing foot and negative when toward the stance foot.

2.3.5 Statistical analysis

Patients were grouped according to the presence of the FOG, PD (without FOG) and PD-FOG (with FOG). The normality of data distribution and homogeneity of variances were assessed by Shapiro–Wilk and Levene test, respectively. Groups (HC, PD and PD-FOG) were compared using the chi-squared ($\chi 2$) test for sex distribution and ANOVA for age and anthropometric data. The differences in the clinical scales between PD and PD-FOG were tested using unpaired t-test. Instrumental parameters were analyzed with a 3 x 4 repeated measures ANOVA (between-factor Group: PD-FOG, PD, HC, within-factor stimulus Valence: Baseline (B), Neutral (N), Pleasant(P), Unpleasant(U)) with

age as covariate. Post-hoc analysis (Bonferroni test) was used to verify statistically significant differences among groups or/and valences. P values <0.05 were considered statistically significant. Based on the marked difference in motor response after pleasant (i.e. unblocking) and unpleasant (i.e. blocking) stimuli in PD-FOG and the absence of such behavior in PD, we have implemented a multivariate linear regression model to investigate if any - of the cognitive and motor measures could be associated which such behavior. The difference CoP_unpleasant - CoP_pleasant was the dependent variable, while FAB, MDGI, and BDI were the independent variables. The inclusion of three independent variables was in accordance with the rule of thumb suggesting at least 10 subjects for each independent variable [23]. The normality and homogeneity of variances of the regression model residuals were verified by Shapiro–Wilks test and White's test, respectively. Multicollinearity was not an issue since the Pearson's correlation coefficients (r) between each pair of independent variables were always below 0.5 and the variance inflation factors (VIFs) were always in the range between 1 and 10.

2.4 Results

Demographic and clinical data are reported in Table 1. PD-FOG group was older than the other groups PD ($p = 0.012$) and HC ($p < 0.001$).

	PD-FOG Median (1st–3rd)		PD Median (1st–3rd)	
Number of participants	15		15	
Age (years)	73.0	(71.0-82.0)	70.0	(66.0-75.0)*
Number of falls	2.0	(0.0-6.0)	0.0	(0.0-1.0)
Education (years)	8.0	(8.0-17.0)	12.5	(8.0-15.0)
Disease duration (years)	12.7	(5.8-19.4)	7.4	(4.5-9.7)*
H&Y stage	3.0	(3.0-3.0)	2.5	(1.5-2.5)*
UPDRS motor	52.0	(38.0-61.0)	42.5	(22.0-47.0)
C-FOG	50.0	(37.0-64.0)	-	-
MDGI	42.5	(39.0-51.0)	57.0	(50.0-60.0)*
SPPB	7.0	(6.0-9.0)	10.0	(9.0-11.0)*
MOCA	23.0	(21.0-25.0)	25.5	(22.0-29.0)

FAB	15.0	(14.0-16.0)	17.5	(14.0-18.0)
BDI (II)	15.0	(12.0-18.0)	10.0	(8.0-16.0)
BAI	29.0	(8.0-38.0)	12.5	(10.0-21.0)

Table 1 Demographic and clinical characterists.

Asterisk indicates significant difference between PD and PD-FOG (* P<.05)

PD, Parkinson's disease; FOG, freezing of gait; H&Y stage, Hoehn and Yahr stage; UPDRS, Unified Parkin-son Disease Rating Scale; C-FOG Characterizing FOG questionnaire; MDGI modified Dynamic Gait Index; SPPB, Short Physical Performance Battery; MOCA Montreal Cognitive Assessmen; FAB, Frontal Assessment Battery; BDI (II) Beck Depression Inventory; BAI, Beck Anxiety Inventory.

2.4.1 CoP displacements

For CoP_{AP} and CoP_{ML} displacements during the imbalance phase statistical analysis revealed a significant effect of GROUP (AP: $F(2,41)=3.9$ $P=0.03$; ML: $F(2,41)=8.6$, $P<0.001$, Table 2). Post-hoc analysis revealed that the posterior shift in the CoP_{AP} was reduced in PD-FOG compared to HS ($P<0.001$, Table 2), while the CoP_{ML} displacement significantly decreased both in PD and PD-FOG compared to HC (Table 2). Moreover, a significance GROUP x VALENCE interaction was found for both CoP_{AP} and CoP_{ML} displacements (CoP_{AP} $F(6,123)=4.56$ $P<0.01$ Figure 1 C1-4; CoP_{ML} $F(6,123)=7.07$ $P<0.01$ Figure 1 D1-4).

For CoP_{AP}, post-hoc analysis showed that the posterior shift in PD-FOG was reduced with respect to HC in response to the unpleasant stimuli ($P<0.01$, Figure 1 C1). In addition, in PD-FOG the posterior shift was smaller after listening to unpleasant stimuli with respect to the neutral and pleasant stimuli ($P<0.0001$, Figure 1 C4).

Regarding CoP_{ML} (Figure 1 D1-4), post-hoc analysis revealed that PD-FOG had smaller displacement with respect to HC in response to unpleasant stimuli ($P<0.01$, Figure 1 D1). PD-FOG showed larger CoP_{ML} displacements in response to pleasant stimuli ($P<0.0001$) and smaller after unpleasant stimuli ($P<0.001$) with respect to the other two conditions, the baseline and the one after neutral stimuli (Figure 1 D4). Finally, in PD-FOG a significant difference between the response after pleasant and unpleasant stimuli ($P<0.0001$, Figure 1 D4) was also detected.

Regarding the unloading phase, results for CoP_{AP} displacement showed a significant effect of GROUP ($F(2,41)$, $P=0.03$, Table 2). Post-hoc analysis revealed a significant difference between PD

and HC during the shift toward the trailing leg (Table 2). No further differences either for valence or CoP_{ML} data were found (Table 2, Figure E1-4 and F1-4).

Table 2 Values of the Center of pressure displacements (Mean and 95% CI) during Anticipatory

	CoP_{IMB_AP}		**CoP_{IMB_ML}**		**CoP_{UNL_AP}**		**CoP_{UNL_ML}**	
P Group	0.03		<0.001		0.03		0.09	
HC	-0.24	(-0.28/-0.19)	0.30	(0.25/0.35)	-0.04	(-0.08/0.01)	-0.49	(-0.54/-0.43)
PD	-0.17	(-0.21/-0.13)	0.18	(0.13/0.22)*	0.05	(0.00/0.09)*	-0.41	(-0.46/-0.35)
PD-FOG	-0.11	(-0.15/-0.07)*	0.19	(0.15/0.24)*	-0.02	(-0.07/0.03)	-0.41	(-0.46/-0.35)
P Stimuli	0.07		0.30		0.56		0.90	
B	-0.15	(-0.18/-0.13)	0.21	(0.18/0.25)	0.02	(-0.01/0.04)	-0.43	(-0.45/-0.41)
N	-0.19	(-0.22/-0.15)	0.24	(0.20/0.27)	-0.01	(-0.04/0.02)	-0.43	(-0.46/-0.40)
P	-0.20	(-0.23/-0.17)	0.25	(0.21/0.28)	0.00	(-0.03/0.03)	-0.44	(-0.48/-0.40)
U	-0.15	(-0.18/-0.12)	0.20	(0.17/0.23)	-0.01	(-0.05/0.02)	-0.43	(-0,51/-0.36)
P Group x Stimuli	<0.001		<0.001		0.91		0.09	

Postural Adjustments reported for the between-factor Group (PD, PD-FOG and HC) and the within factor Stimuli (B, N, P, U).

Asterisk indicates significant difference between PD or PD-FOG and HC (* P <.05)

CI, Confidence Interval; COP, Center of Pressure; IMB Imbalance phase; UNL, Unloading phase; AP, antero posterior; ML medio lateral; PD, Parkinson's disease; FOG, freezing of gait; PD, Parkinson's disease; FOG, freezing of gait; HC, Healthy Control; B, Baseline, N, Neutral; P pleasant; U Unpleasant.

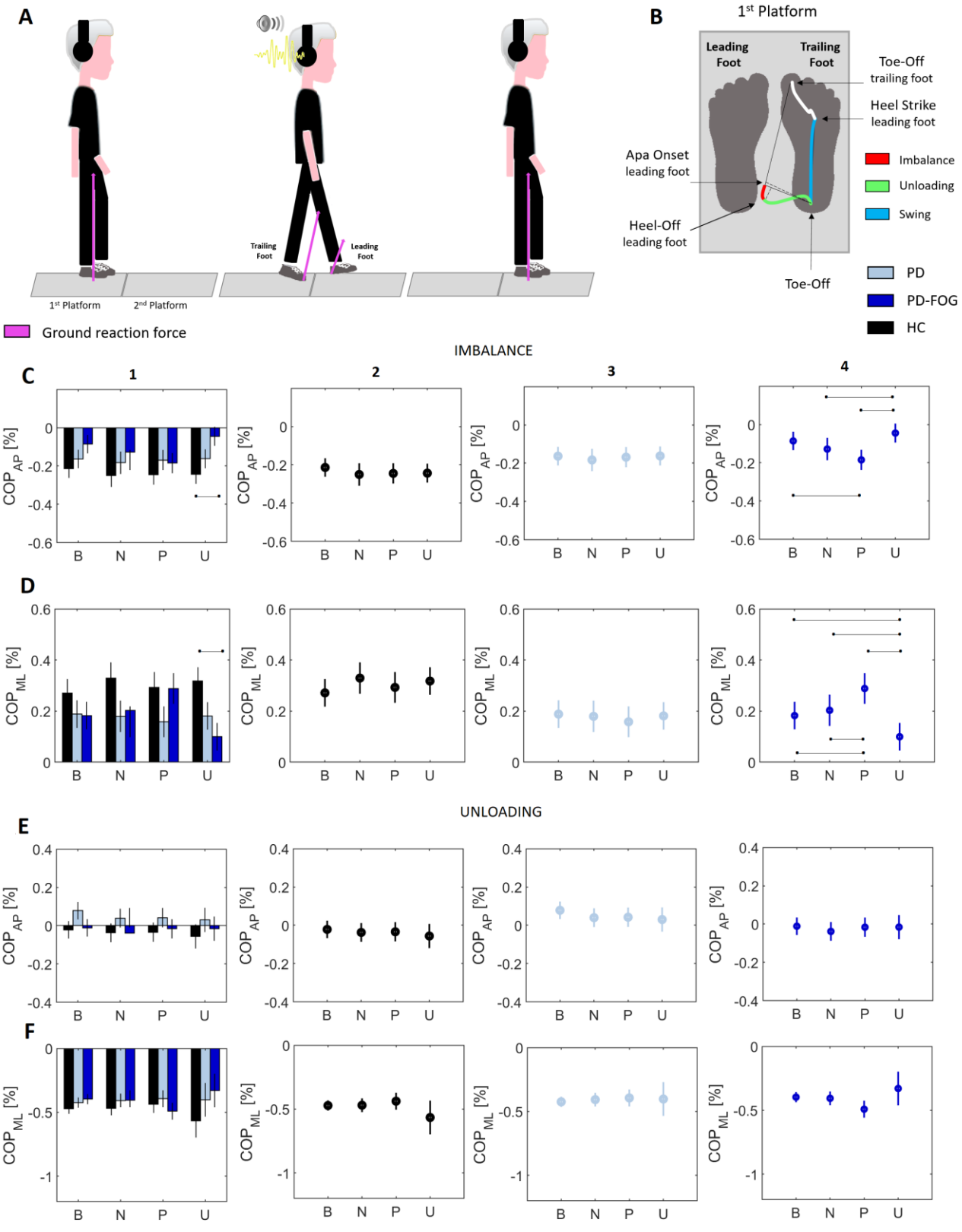

Figure 1 A) A schematic representation of the experimental paradigm. B) The physiological CoP displacement in the medio-lateral and antero-posterior directions during the step initiation process. The graphs in the first column report the CoP displacements during the imbalance (C-D) and unloading phase (E-F) attained by persons with Parkinson's Disease without (PD) and with freezing

of gait (PD-FOG) and healthy subjects (HC) in response to the baseline (B), neutral (N), pleasant (P) and unpleasant (U) stimuli. The remaining graphs in the other columns detail the CoP within each group.

Circles/vertical bars and whiskers represent, respectively, the mean score and 95% confidence interval. * P < 0.05 post hoc test

2.4.2 Timing and kinematic parameters

The RTs values were comparable among groups ($F(2,41)=1.29$, $P=0.29$, Table 3) and emotional stimuli ($F(3,123)=0.50$, $P=0.68$, Table 3), and no significant interaction ($F(6,123)=1.25$, $P=0.28$, Table 3) was found.

The T_{STEP} showed a significant main effect of GROUP ($F(2,41)=4.78$ $P=0.01$, Table 3), and post-hoc test revealed that both PD and PD-FOG took longer to complete the first step than HC (PD: $P<0.01$; PD-FOG: $P=0.01$ Table 3). Also, the TIMB and TUNL showed a significant main effect of GROUP ($F(2,41)=6.64$ $P=0.02$ and $F(2,41)=3.92$ $P=0.03$, Table 3). Post-hoc analysis revealed that PD had both longer phases ($P=0.01$), while PD-FOG only the unloading phase ($P<0.01$).

Step length and velocity were comparable among groups and emotional valences ($P>0.05$, Table 3).

Table 3 Spatio-temporal parameters of Step Initiation (Mean and 95% CI) reported for the between-factor Group (PD, PD-FOG and HC) and the within factor Stimuli (B, N, P, U).

	RT	[s]	T_{IMB}	[s]	T_{UNL}	[s]	T_{STEP}	[s]	L_{STEP}	[%]	Velocity	[m/s]
p Group	0.29		0.02		0.03		0.01		0.83		0.16	
HC	0.38	(0.31/0.44)	0.27	(0.24/0.30)	0.29	(0.19/0.39)	0.72	(0.59/0.84)	2.72	(2.39/3.05)	0.65	(0.55/0.74)
PD	0.45	(0.39/0.51)	0.33	(0.30/0.36)*	0.50	(0.40/0.60)*	1.02	(0.90/1.15)*	2.70	(2.37/3.04)	0.50	(0.41/0.59)
PD-FOG	0.41	(0.35/0.48)	0.32	(0.29/0.35)	0.52	(0.43/0.62)*	0.99	(0.87/1.12)*	2.43	(2.09/2.76)	0.47	(0.37/0.56)
p Stimuli	0.68		0.37		0.61		0.51		0.85		0.53	
B	0.45	(0.42/0.48)	0.33	(0.31/0.35)	0.42	(0.38/0.46)	0.89	(0.84/0.94)	2.59	(2.44/2.73)	0.52	(0.48/0.56)
N	0.41	(0.35/0.47)	0.30	(0.27/0.32)	0.44	0.35/0.52)	0.90	(0.80/0.99)	2.66	(2.43/2.88)	0.56	(0.49/0.62)
P	0.41	(0.36/0.45)	0.31	(0.29/0.33)	0.45	(0.38/0.52)	0,94	(0.85/1.03)	2.61	(2,39/2.83)	0.53	(0.47/0.59)
U	0.38	(0.34/0.43)	0.28	(0.26/0.30)	0.44	(0.36/0.52)	0,91	(0.82/1.01)	2.61	(2.39/2.83)	0.54	(0.48/0.61)
p Group x Stimuli	0.29		0.68		0.83		0.94		0.84		0.95	

Asterisk indicates significant difference between PD or PD-FOG and HC (* P <.05)

RT, Reaction Time; TIMB, duration of imbalance phase; TUNL duration of unloading phase; TSTEP duration of step; LSTEP length of the step normalized to the body height; CI, Confidence Interval;

PD, Parkinson's disease; FOG, freezing of gait; PD, Parkinson's disease; FOG, freezing of gait; HC, Healthy Control; B, Baseline, N, Neutral; P pleasant; U Unpleasant.

2.4.3 Multiple linear regression

Results of the regression analysis of the difference of CoP displacement after unpleasant and pleasant stimuli ($DIFF\_COP_{U-P}$ parameter, outcome measure), and of walking ability (MDGI), cognitive executive functions (FAB) and depression (BDI) (predictive variables) are reported in Table 4.

Table 4 Results of the multivariate linear regression analysis with the difference between the COP displacement after unpleasant and pleasant simuli (COPunpleasant - COPpleasant) as dependent variable in the PD subjects with and without FOG.

Dependent Variable	**F**	**P**	**Independent viariable**	**Coefficient b**	**Standard error b**	**Standardized coefficient β**	**P**
Imbalance Phase							
$DIFF\_COP_{AP(U-P)}$	2.9	0.05	MDGI	-0.001	0.002	-0.094	0.62
			FAB	0.002	0.007	0.054	0.76
			BDI (II)	0.008	0.003	0.458	0.02
$DIFF\_COP_{ML(U-P)}$	4.5	0.01	MDGI	0.004	0.002	0.303	0.10
			FAB	0.008	0.008	0.149	0.37
			BDI (II)	-0.007	0.004	-0.331	0.07
Unloading Phase							
$DIFF\_COP_{AP(U-P)}$	0.8	0.52	MDGI	-0.001	0.001	-0.105	0.62
			FAB	0.002	0.004	0.093	0.63
			BDI (II)	0.002	0.002	0.230	0.27
$DIFF\_COP_{ML(U-P)}$	3.7	0.02	MDGI	-0.003	0.002	-0.331	0.08
			FAB	-0.003	0.006	-0.073	0.66
			BDI (II)	0.005	0.003	0.300	0.11

PD, Parkinson's disease; FOG, freezing of gait;

FAB, Frontal Assessment Battery; MDGI modified Dynamic Gait Index; BDI (II) Beck Depression Inventory; AP, antero posterior; ML, medio lateral; U, unpleasant; P, pleasant.

The model was statistically significant in the difference parameter during the imbalance phase in both directions AP and ML, and only in the ML direction during unloading phase (Table 2).

Depression was found as the main factor accounting for the difference found in the imbalance phase: higher BDI-II score (β=0.45) was significantly associated (P=0.02) with a greater value of DIFF_COPU-P parameter in the AP direction, while in the ML direction the association was not significant (P=0.08, β=-0.33). No clinical variable was found to be a significant contributor for the outcome measure in the unloading phase.

2.5 Discussion

This study aimed to examine the effect of ecological emotional auditory stimuli on step initiation in persons with PD who experience FOG. We compared behavioral data from a cohort of PD participants with or without the FOG symptom and a control group of healthy subjects. To mimic the most realistic circumstances during which emotional stimuli may influence gait patterns, unpleasant and pleasant stimuli were used.

The main finding of our study was that in PD patients with FOG auditory emotional stimuli influence automatic movement parameters (i.e, APAs), whereas they do not affect step characteristics (e.g., step length). Precisely, two novel findings emerged from this study: first, the exposure to emotional stimuli modulates step initiation in PD patients with FOG, while no modulation was found in PD without FOG and healthy participants, and second, the negative-oriented auditory stimuli (i.e., unpleasant stimuli) reduced the CoP displacements in PD patients with FOG, while positive-oriented ones (i.e., pleasant stimuli) enhance the APA displacement.

The CoP displacements during the imbalance phase showed that both the anterior-posterior and medio-lateral components were influenced by emotional stimuli only in PD with FOG (Figure 1 C4 and D4). In particular, in response to unpleasant stimuli CoP displacements (AP and ML components) were significantly reduced compared to that of the healthy control (Figure 1 C1 and D1). Conversely, in response to the other stimuli CoP displacement values were comparable to those of the control group. In particular, the amplitude of CoP displacements after pleasant stimuli was the closest value to the physiological one of the control group, suggesting a process of facilitation of the motor response induced by pleasant stimuli, as already hypothesized by previous studies [24].

Finally, our finding showed a reduced medio-lateral CoP displacement also in PD participants without FOG (Table 2). However, no differences among the valence of emotional stimuli were detected.

As regard the unloading phase, our finding revealed no significant emotional modulation on the body-weight shift from the leading leg to the trailing one. The body weight shift action is mainly regulated by the proprioceptive feedback based on the detection of kinematic features such as joint position and muscle activation timing and strength. PD without FOG had a greater sensorimotor damage (e.g. delayed activation of ankle, thigh and trunk muscles) at ankle or hip level compared to individuals without FOG [25]. This could be the cause of the different biomechanical strategy adopted by PD without FOG consisting in the CoP placed forward (closer to the toes) at the beginning of unloading phase, conversely compared to PD with FOG and healthy persons (Table 2 and Figure 1 E1).

From the visual inspection of Figure 1, the inter-subject variability of the CoP_{ML} displacement (F2, F3, F4) appears as a function of stimuli affective context, with higher values of the coefficient of variation in response to unpleasant stimuli (18.7% B, 24.3% N, 29.5% P, 60.9% U). This could be related to the startle blink reflex which is mediated by the brainstem circuits, that generally regulated the unloading phase [26,27]. After the listening to unpleasant stimuli, the startle response is usually larger and electromyographic activity is increased compared to other affective stimuli [28], consequently these factors may have contributed significantly to the higher inter-subject variability.

The experimental protocol of this study was designed based on the central theory approach [29], based on the effects of emotions on movement through an automatic (unintentional) motivational mechanism of avoidance-approach. According to this theory, we should have found that the APAs features (e.g., reaction time, CoP displacement amplitude) were modulated by the emotional valence of the stimuli in all groups, as found in our previous work using visual stimuli [5]. However, the effect did not emerge in all of the analyzed parameters (Table 2 and Table3), but only in PD with FOG who showed a marked reduction of the CoP backward shift movement (i.e., imbalance) in response to unpleasant stimuli. This result could be attributable to the type of stimuli used (i.e., easily categorizable real life sounds), which allowed the HC and PD without FOG to properly react/respond to emotional stimuli while starting walking. On the other hand, the subjects with FOG, were influenced by the specific emotions evoked by the sounds. As recently suggested [2,30], this behavior could be related to the altered neural networks involved in the FOG both of the limbic system and cognition processes. Indeed, the forward step in response to unpleasant stimuli is considered an incongruent task with a high cognitive load. We hypothesize that the incongruent mode has exacerbated the neural circuits involved in the FOG, requiring goal-directed movements. It turns out that in conditions of greater cognitive deficit the postural response is more altered, and PD with FOG exhibit more pronounced cognitive dysfunction than PD without FOG [31,32].

In addition, the negative valence of unpleasant stimuli could have increased the level of the postural threat experienced [33] and therefore activated in these patients defensive strategies inducing an automatic immobility reaction, as already found in animals and humans when facing a threat [34].
Also in our previous work, the incongruent task was the most demanding one for persons with FOG as it revealed a block of motor response in terms of longer reaction time and shorter step length [5]. This evidence suggests to use this paradigm for studying of the pathophysiology of FOG. The different behavior of the CoP displacements according to the affective valence in subjects with FOG here presented was not found using visual stimuli. This discrepancy could be attributed to the different methodology used. Lagravinese et al [5] did not separate the APA movements in the two phases, imbalance and unloading. However, these phases cannot be considered only as a single phase because it has been shown that they are controlled by different central nervous system structures. The imbalance processes are controlled mainly by cortical and subcortical structures (i.e. supplementary motor area, premotor cortex, basal ganglia) and the unloading ones are generally regulated by lower-level control processes (i.e. brainstem and spinal processes) [26,27]. Furthermore, the study protocol designed by Lagravinese et at was based on movements less automatic and more cognitively controlled, where participants were also asked to take a step backward in response to a pleasant image and a step forward in response to an unpleasant one. This may have influenced the result of the study: an influence of the emotional stimuli on gait parameters reflecting gait program (step length, reaction time) and no influence on APA, more automatically controlled.
Also the greater inter-subject variability of the CoP displacement after unpleasant stimuli during the unloading phase could be explained by the incongruent mode. The body weight shift is an automatic movement that does not require the involvement of cognitive processes, however the forced step forward against an avoidance impulse may have required access to greater cognitive load, and consequently the greater inter-subject variability may reflect the individual response of each subject.
Although affective and cognitive disturbance and freezing of gait are closely related, little research has examined the neural correlates of anxiety or depression in Parkinson's disease. Interesting results of the regression model highlighted that the differential behavior of the CoP backward shift during the imbalance phase (reduced and increased in response to unpleasant and pleasant stimuli, respectively) was associated with emotional-mood sphere, whereas an influence of the motor domain on the body weight shifting phase (i.e. unloading) seems to be, although not significantly. No influence was found for the cognitive domain, quantified by the FAB, likely because the APA are movements controlled in feedforward mode and mostly unconscious. The associations found are consistent with the current knowledge of the neural networks that control the APA phases and of the non-motor symptoms that can contribute in the developing of the FOG [26,27,35]. In fact, among the

non-motor contributors to FOG (i.e. cognition sensory-perceptual and affective), studies published so far only confirm the role of the affective domains, such as anxiety and depression, as longitudinal predictors for the future development of FOG in PD patients [35]. Therefore, in light of the association found between pleasant/unpleasant valence-based CoP shift and depression, the affective valence-based APA measures could be a biomarker of FOG, which could be used for monitoring the FOG development and for detecting changes induced by rehabilitation.

The pathogenesis of FOG is not yet understood and treatments are still not effective [36,37]. For these reasons, FOG represents a critical issue of PD with a severe impact on activities daily living and quality of life.

Different circumstances can trigger this symptom while walking, which include both the motor acts (turning), performing cognitive (i.e., dual-tasking) and overcoming environmental challenges (i.e. negotiating doorways) or contexts that generate greater anxiety [38]. Therefore, a multi-domain training, cognitive, cognitive-behavioral and sensorimotor is desirable. A recent review highlighted that to reduce FOG episodes tailored training are needed [38]. Our results support this approach suggesting that cognitive and behavioral cognitive interventions could be a valuable tool for reducing FOG, e.g. positive stimulus-based training could promote larger backward CoP movements facilitating the step initiation and reducing the risk of falls.

In conclusion, our findings support evidence for an involvement of emotional factors in the pathophysiology of freezing of gait. Importantly, the findings of this study showed how emotional features in PD patients with FOG are correlated to the affective valence-based different behavior during the APA, probably going to pathologically interfere with attentional reserves.

2.6 Study limitation

Some issues related to the experimental protocol deserve to be discussed. First, our patients were tested in the ON state and with auditory stimuli. This allowed to test how emotional processing influences gait initiation in a condition that is more ecological but does not favor FOG and facilitate gait initiation itself. However, we think it will be worthwhile to directly address the role of emotional modulation on gait initiation parameters using daily life stimuli that PD patients encounter. Future studies on a larger sample should be performed to corroborate present findings.

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3 Chapter

Visual Spatial Learning and evoked Emotions in Parkinson’s Disease

3.1 Chapter summary

Emotional states have been shown to influence cognitive processes including visual-spatial learning. Parkinson's Disease (PD), besides manifesting with the cardinal motor symptoms, presents cognitive and affective disturbances. Here we aimed at investigating whether manipulation of the emotional state by means of music was able to influence the performance of a visual-spatial learning task in a group of PD participants.

Ten PD patients and 11 healthy elderly (ELD) were asked to perform a visual-spatial learning task while listening two musical pieces evoking a neutral emotion or fear. Targets were presented on a screen in a preset order over four blocks and subjects were asked to learn the sequence order by attending to the display. At the end of each block, participants were asked to verbally recall the sequence and a score was assigned (Verbal Score, VS).

Analysis of variance-type statistic test on the VS disclosed a significant effect of Music and sequence Blocks ($p = 0.01$ and $p < 0.001$, respectively) and a significant interaction between Group and sequence Blocks. Sequence learning occurred across the training period in both groups, but PD patients were slower than ELD and at the end of the training period learning performance was worse in PD with respect to ELD. In PD patients, like in ELD, fear-inducing music has a detrimental effect on visual-spatial learning performances, which are slower and decreased.

These findings confirm an impairment in visual-spatial learning in PD and indicates that the emotional state influences this learning ability similarly to healthy controls.

This work has already been published, the references are reported below.

Title: The effect of music-induced emotion on visual-spatial learning in people with Parkinson's disease: A pilot study.

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Keywords: Cognitive learning; Emotion; Parkinson's disease.

3.2 Introduction

The listening to music elicits emotions, and the improvement of the cognitive performance after the listening to music evoking positive emotions is widely known in literature. Since then, using several valid experimental protocols, a wide range of studies investigated the effect of music eliciting emotions and arousal on concurrent mental processing in healthy subjects and in patients with neurological diseases [1].

Visual-spatial learning requires coordinated activity with surroundings: individuals are required to use representations of the environment to comprehend and conceptualize visual representations and spatial relationships in learning. Emotions have been shown to influence this form of learning. Chan and colleagues [2] found that parahippocampal activity enhanced bilaterally when participants were engaged in an active object location memory task within a virtual house with rooms in which they had previously encountered negatively arousing events. Palmiero and colleagues [3], by using music to induce emotional states, showed that the persons after listening to positive music produce better scores at a visual-spatial learning task.

Parkinson's Disease (PD), beside manifesting with the cardinal motor symptoms, presents cognitive dysfunctions, including impairment in visual-spatial abilities, and affective disturbances. Interestingly, Marinelli and colleagues [4] showed that impaired performance at visual-spatial sequence learning in PD correlates with motor performance in a reaching task: patients with higher reaction times are the ones with a more impairment of visual-spatial sequence learning, suggesting that movement preparation shares resources with learning of visual-spatial sequences. Recently, we demonstrated that motor performance in PD is influenced by emotional processing: when patients with freezing of gait were asked to perform a step forward in response to unpleasant images inducing fear, the motor performance deteriorated, with increased reaction times [5]. A low performance at tasks implying the use of executive functions to perform movements under emotional contextual clues may imply a dysfunction of basal ganglia and of subcortical-cortical interaction. However, it is difficult to precisely localize which neural structure is pivotal in this dysfunction, given the behavioural nature of the tasks and the fact that PD is a network-based disorder.

Starting from all the above-mentioned observations, the aim of the present study was to investigate whether the manipulation of the emotional state by means of music was able to influence the performance of a visual-spatial learning task in a group of PD participants. In particular, we investigated the effect of fear-inducing music on visual-spatial learning since fear together with anxiety, is one of the most negative emotions experienced by PD patients [6] (e.g. fear of the

future/falling/cognitive decline). However, while the negative effects of the anxiety on cognitive functions and quality of life are widely investigated [7], the impact of fear on cognitive performance is not yet well known. To this aim participants were asked to perform a visual-spatial learning task while listening two musical pieces evoking a neutral emotional state or fear.

3.3 Methods

3.3.1 Participants

A total of 21 participants (10 PD patients and 11 healthy elderly (ELD) gave their written informed consent to participate in this study. The study was approved by the regional ethics committee (n. 141/12). For PD subjects the inclusion criteria were: diagnosis of idiopathic PD (according to the United Kingdom Parkinson's Disease Society Brain Bank criteria) and Hoehn and Yahr stage ≤ 3. General exclusions criteria were: Mini Mental State Examination score <24, history of neurologic disorders (except PD), and visual, orthopaedic, or vestibular impairments that could hamper task performance. Executive and memory functions and affective status were evaluated by means of Tower of London test (TOL), Rey Auditory Verbal Learning Test (RAVLT), Beck Depression Inventory 2 (BDI-2), Apathy Evaluation Scale (AES). Fatigue and daytime sleepiness were evaluated with Fatigue Severity Scale (FSS) and the Pittsburgh Sleep Quality Index (PSQ-I) respectively. Only in PD participants, disease severity was evaluated with section III of the MDS–Unified Parkinson Disease Rating Scale.

3.3.2 Study design

In a repeated measures design (two separate sessions, one week apart), all participants were invited to learn two different alphanumeric sequences while listening two musical pieces evoking neutral or fearful emotions. The sequence and the music piece were randomly combined before starting the first session. During the visual-spatial learning task, subjects were sitting in front of the screen and were instructed to memorize an alphanumeric sequence displayed trough a set of 8 white circles placed on a circumference with a radius 10 cm at an interval of 45° from each other (Fig. 1A). Each target turned black for 700 ms, one at the time, according to a predetermined sequence with a time interval of 800 ms. Each session consisted of 5 blocks of trials: one familiarization block with 5 repetitions of 8 targets lighting up in a random order (40 trials) and four sequence blocks (S1, S2, S3, S4) with

4 repetitions of the predetermined sequence (128 trials). At the end of each session, participants were asked to verbally recall the alphanumeric sequence and a declarative score was assigned (Verbal Score, VS, expressed as %) ranging from 0 (unawareness-of-the-sequence) to 100 (complete-correct-sequence) [8]. We selected this task, without motor component, because engages visual-spatial attention and working memory [8,9] and it has been associated with EEG activity of the frontal and posterior parietal areas mostly in the right hemisphere [9]. This pattern likely reflects encoding of new information, access to memory storage and memory traces activation.
Regarding music, we chose two pieces able to evoke negative (fearful) and neutral emotions [10]. Participants listened to musical tracks with headphones while performing the learning sequence task only.

3.3.3 Statistical Analysis

Group difference was assessed by Mann-Whitney-U Test for demographic and clinical characteristics and by Chi-square for gender. To test differences in VS across Group (PD vs ELD), Music (neutral vs fearful) and sequence Blocks a rank-based analysis of variance-type statistic (ATS) was. We used the F1-LD-F2 model, where Blocks and Music were the within-subject factors (repeated factors) and Group the between-subjects factor. In case of statistically significant differences (threshold of $p < 0.05$), Bonferroni-Holm post-hoc test for contrast analysis was applied.
In PD participants, the associations between VS and clinical variable (MDS-III), cognitive functions (TOL, RAVTL) and neurobehavioral features (BDI-2, AES, FSS and PSQ-I) were evaluated using Spearman correlation coefficients and the analysis was corrected for multiple comparisons using Bonferroni correction ($0.05/2 = 0.025$ for cognitive variables; $0.05/4 = 0.0125$ for neurobehavioral variables). Marinelli et al. [4] have explored the visual-spatial learning between PD and ELD, reporting significant unpaired differences in the verbal score not normalized (mean(SD), PD 4.4(0.9) vs HS 7.1(0.7)). Hence given $\alpha = 1\%$ and $1\text{-}\beta = 95\%$, the minimum sample size per group is 5. Statistical analysis was performed using the nparLD package in R statistical software.

3.4 Results

Descriptive statistics for demographic and clinical data are reported in Table 1. Age, Sex and Education were comparable between groups ($p > 0.05$).

Table 1. Demographic and clinical characteristics

	PD	**ELD**	**P value**
Number of participants	10	11	
Age [year] median (IQR)	72.0 (69.0-75.0)	67.0(62.5-71.0)	0.09
Sex Female (F) Male (M)	5F 5M	5M 6F	0.83
Education [year] median (IQR)	12.0(6.0-13.0)	11.0(8.0-13.0)	0.51
Disease duration [years] median (IQR)	11.0(6.0-13.0)	-	-
UPDRS motor score	23.5(22-25)	-	-
H&Y stage median (IQR)	2(2-2)	-	-
ToL score median (IQR)	27.0(21.0-29.0)	32.0(29.5-33.8)	0.01
ToM score median (IQR)	11.0(6.0-13.0)	11.0(9.3-12.0)	0.78
RAVLT G score median (IQR)	29.0(26.5-34.0)	33.0(32.3-35.0)	0.02
RAVLT E score median (IQR)	31.1(28.8-34.5)	35.0(33.0-35.9)	0.05
BDI (II) score median (IQR)	7.5(3.0-11.0)	4.0(2.3-6.8)	0.17
AES score median (IQR)	16.0(13.0-20.0)	9.0(7.3-14.0)	0.08
BAT score median (IQR)	3.5(1.0-9.0)	4.0(1.0-5.0)	0.78
FSS score median (IQR)	12.5(11.0-16.0)	2.0(1.3-3.0)	0.00
ESS score median (IQR)	7.0(5.0-9.0)	4.0(2.3-7.3)	0.12
PSQI score median (IQR)	15.0(9.0-17.0)	8.0(3.3-9.0)	0.00

3.4.1 Visual-spatial Sequence learning

Verbal score improved significantly across the training period (main effect Block $p < 0.001$). Statistical analysis also revealed a significant Block × Group interaction ($p = 0.03$, Fig. 1 B and C) and post-hoc analysis showed that VS improved significantly after two Blocks in ELD, whereas significant changes were detected in the last block in PD (ELD: S1vsS3, S1vsS4 $p < 0.01$, Fig. 1C; PD S1vsS4 $p < 0.01$, Fig. 1D). Also, post-hoc analysis revealed that VS was significantly higher in the ELD compared to PD at the end of the task (S4, ELD vs PD $p = 0.001$, Fig. 1B). A main effect of Music ($p = 0.01$, Fig. 1E) and a Block × Music interaction ($p = 0.001$, Fig. 1F and G) were also found. Post-hoc analysis showed that VS improved since the third block (S1vsS3 and S1vsS4 $p < 0.001$, Fig. 1F) when participants listened to neutral music, whereas significant changes were seen only at the last block when participant listening to fearful music (S1vsS4 $p < 0.001$, Fig. 1G). Post-hoc analysis also showed a significant difference in VS between music pieces from the third block (NvsF, S3 $p = 0.01$ S4 $p < 0.001$). No significant Group X Music × Block interaction ($p = 0.99$, Fig. 1H and I) was detected.

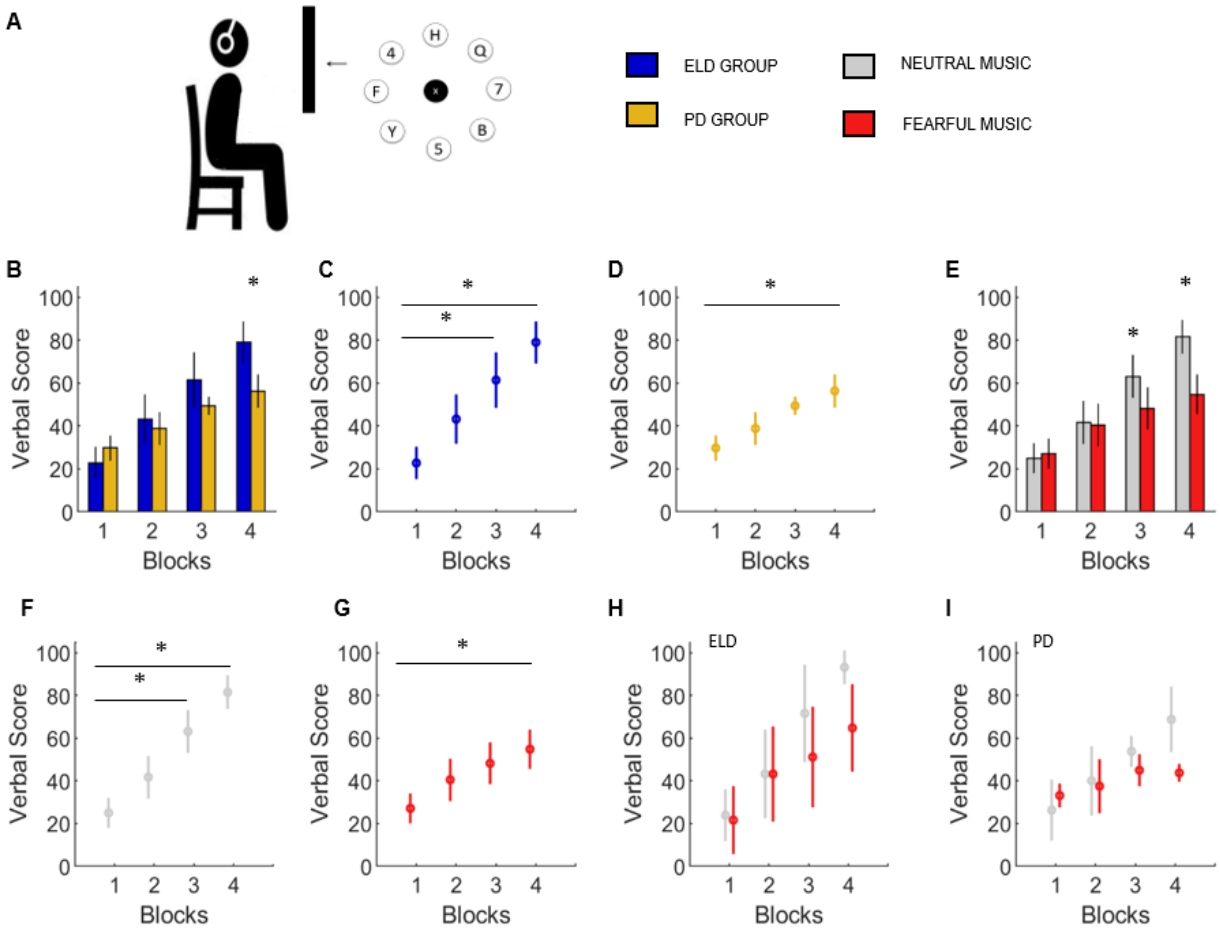

Figure 1. A schematic representation of the experimental paradigm, where the subjects were seated in front of a screen and had to memorize the alphanumeric sequence shown, is reported in the panel A. The remaining panels report the Verbal Score attained by persons with Parkinson's Disease (PD) and Elderly (ELD) according to the interaction effect between-factor Group and the sequence Blocks (B, C, D), the interaction effect within-factor Music and the sequence blocks (E,F,G), and the interaction effect Group, Music and sequence Blocks (H,I). Circles/vertical bars and whiskers represent, respectively, the mean score and 95% confidence interval. * $P < 0.01$ post hoc test between PD vs ELD or Neutral vs Fearful Music at each sequence block (A,D). * $P < 0.01$ post hoc test between sequence blocks for each Group (ELD or PD, B and C) or Music (N or F, E and F).

3.4.2 Correlation Analysis

Significant positive correlations were found between VS obtained after listening to neutral music and cognitive functions (RAVLT: $r = 0.600$ $p = 0.004$; TOL: $r = 0.564$ $p = 0.007$). Notably, these correlations disappeared when the VS obtained after listening to fear music was used for the analysis.

3.5 Discussion

In this study we tested declarative scores of visual-spatial sequence learning in healthy elderly and in PD patients. In particular, we explored whether it was possible to influence visual-spatial memory ability by using fearful music to manipulate emotional states.

The first result obtained is that the verbal score (VS), our primary outcome measure to test visual-spatial learning, improved significantly in both groups regardless of the type of emotional music. Improvements in declarative scores were seen at each block up to the end of the experimental session suggesting that both elderly and PD patients benefit from training, which is known to be a key element of motor learning process [4]. However, subjects with PD improved significantly only at the last block and at the end of the task, VS was lower compared to ELD. Indeed elderly learned about 80% of the sequence while PD patients about 60%. . The reduced learning in PD could reasonably be ascribed to cognitive disturbances associated with the disease. Indeed, in our sample of patients, differences on executive functions (i.e., ToL) and memory abilities (i.e., RAVLT) emerged in the assessment phase, where patients performed significantly worse than elderly.

Regarding the specific effect of music, we observed that listening to fearful music worsened visual-spatial learning performance in both groups. Thus, music-induced fear decreased the ability to store

an alphanumeric sequence. Our results also showed no differences between PD patients and elderly regarding the effect of fearful music on visual-spatial learning. Although it is known that PD symptoms include also emotional aspects [5] and results on the ability to recognize music-induced emotions are still controversial [1], our finding are in accordance with previous data [1] showing that recognition of emotions from musical excerpts is still preserved.

The frontoparietal network is greatly involved in visual-spatial learning: it might be responsible for the active representation of attended and goal-relevant stimuli and thus for promoting adequate domain-dependent information processing [11]. Particularly, the dorsolateral prefrontal cortex (DLPFC) is likely engaged in maintaining working memory representations. Recent views suggest that neural regions traditionally being considered more involved in cognition, as the DLPFC, are not restricted to "cognition" processes; rather, their activity is modulated by "emotional" processes, indicating the interaction between cognition and emotion as a seamless function [12]. The DLPFC, although representing an abstract and higher-order goal representation, due to its lack of direct connectivity with sensory cortex and regions that represent affective value, is likely to receive affective information via the anterior cingulate in order to represent fear in the environment, influencing cognitive functions in relation to emotional states [13].

Interestingly, correlation analyses showed that, only when visual-spatial learning task was performed while listening the musical piece evoking neutral mood, the ability in the task correlated with cognition (verbal memory and executive functions) and not with neurobehavioral variables. However, this result may also be linked to the small sample size and has to be confirmed in a larger sample. Correlations between VS and cognitive scores disappeared when listening to the fearful music. One possible explanation is that the induced fear state exerts its effect on cognitive circuits underpinning visual-spatial ability making less prominent the contribution of individual cognitive and affective characteristics.

The study results show that in PD patients, like in ELD, fear-inducing music has a detrimental effect on visual-spatial learning. This finding indicates that the emotional state influences learning skills, suggesting the importance of carefully considering non-motor aspects of PD (anxiety/depression) when planning a rehabilitation program.

3.6 Limitations and future directions

This is a pilot study and a larger number of participants is needed to confirm our results. The visuo-spatial task adopted here, although been used in previous studies also for testing visuo-spatial abilities

in PD [8,9] is not a clearly validated measure for testing this ability and this should be acknowledged as a limitation of the present study. Furthermore, we didn't measure the valence and arousal perceived by participants, useful to estimate the intensity of the emotional experience. Future studies should be planned to deeply investigate the effect of fear on cognitive performance, such as memory, in PD subjects. Finally, it could be interesting to also explore the effect of pleasure-evoking music on visual-spatial abilities, to gather more information useful for a tailored cognitive rehabilitation aimed at improving this performance.

3.7 References

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4 Chapter

Dynamic balance in persons with neurological disorders

4.1 Chapter Summary

Maintaining a stable gait requires a dynamic balance control, that can be altered in persons with Multiple Sclerosis (MS), Stroke (ST), and Parkinson's disease (PD). The understanding of the strategy for Center of Mass (CoM) positioning adopted by patients during walking is important to be able to program treatments aimed at improving gait control and preventing falls.

Forty-four persons with a mild-to-moderate neurological disorder (20 with MS, 14 with ST, 10 with PD) underwent clinical examination and gait analysis. Ten Healthy Subjects (HS) walking at matched speed provided the normative data.

Dynamic balance was assessed using the margin of stability (MoS). It was calculated as the distance between the extrapolated Center of Pressure and the extrapolated CoM at mid-stance. The MoS values for lower limbs were calculated in patients and compared with speed-matched values of HS.

Persons with neurological disorder showed increased MoS in the medio-lateral direction with respect to HS. Within-group comparison analysis showed a symmetry between lower limbs in HS (Mean (95%CI) [mm], Dominant vs non-dominant limb, 43.3(31.9-54.6) vs 42.9(28.8-56.9)) and PD (Less affected vs more affected limb, 71.1(59.8-82.5) vs 72.5(58.5-86.6)), while a significant asymmetry was found in MS (54.4(46.4-62.4) vs 81.1(71.2-91.1)) and ST (52.1(42.6-61.7) vs 74.7(62.8-86.6)) participants. The history of falls was comparable among PD, MS, and ST groups, and the MoS in the frontal plane showed a strong correlation with these records.

Objective assessment of MoS revealed pathology-specific strategies showing different impacts in MS, ST, and PD on the ability to control CoM information to manage the balance between limbs during gait. MoS evaluation will provide useful information to address a tailored rehabilitation program and to monitor disease progression.

This work has already been published, the references are reported below.

Title: Strategies for maintaining dynamic balance in persons with neurological disorders during overground walking.

Authors: Lencioni Tiziana, Anastasi Denise. Carpinella Ilaria, Castagna Anna, Crippa Alessandro, Gervasoni Elisa, Marzegan Alberto, Rabuffetti Marco, Pelosin Elisa, Cattaneo Davide. Ferrarin Maurizio.
Peer-reviewed journal: Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 235, 9, 1079-1087. DOI 10.1177/09544119211023624. PMID: 34112028.
Keywords: Gait analysis, dynamic balance, center of mass, center of pressure, neurological diseases.
Abbreviations
CoM: center of mass.
XCoM: extrapolated center of mass.
CoP: center of pressure.
XCoP: extrapolated center of pressure.
BoS: base of support.
MoS: margin of stability.
MS: Multiple Sclerosis.
ST: Stroke.
PD: Parkinson's Disease.
EDSS Expanded Disability Status Scale.
H&Y: Hoehn and Yahr stage.
mRS: modified Rankin Scale.
TUG: Time Up and Go.
DGI: Dynamic Gait Index.
ML: Medio Lateral.
AP: Antero Posterior

4.2 Introduction

Walking is the result of the interaction of cognitive and sensorimotor components, controlled by the cortex, brain stem, and spinal cord [1, 2]. The corrective reflexes are modulated through the integration of central and peripheral inputs throughout the entire gait cycle [3]. Although Multiple Sclerosis (MS), Stroke (ST), and Parkinson's disease (PD), some among the most common neurological disorders, have different causes and are characterized by different neurological impairments, they result in a similar impairment of mobility and cognition, and/or in common

symptoms such as fatigue, depression, pain, and reduced quality of life and participation [4, 5]. Persons suffering from such diseases also show a common gait pattern characterized by a reduced gait speed and step length, and by an altered range of motion of leg joints when compared to those of healthy persons [7–13].

Among the disease symptoms, balance impairments are highly disabling since balance control is a challenging task for daily life activities and consequently the assessment and training of stability is important to prevent the risk of falls [18].

In both healthy and pathological persons the maintaining a stable gait requires the control of balance, which is achieved by integrating sensory feedback to estimate the position and the velocity of the Center of Mass (CoM). On the basis of this information dynamic balance is reached and maintained through appropriate step placements which require the right relationship between the CoM and the Base of Support (BoS) [6, 22, 23]. BoS includes all possible positions of the Centre of Pressure (CoP, i.e. ground reaction force application point) and therefore consists of the union of feet-ground contact areas and the area between those two areas (in monopodalic phases it is simply the foot-ground contact area). During gait, CoM must stay outside BoS in the sagittal plane for most of the time, to allow the forward displacement of the body. This makes balance control more difficult in dynamic conditions. On the other hand, the control of CoM positioning in the frontal plane is different since CoM must remain inside the lateral border of the supporting foot during the monopodalic phases of gait to prevent lateral instability, which can easily lead to fall [24]. Instrumental indexes have recently been adopted to describe dynamic balance during gait, these new metrics include the position and velocity of CoM relative to the feet [23–25].

Among these measures, the "Margin of Stability" (MoS) describes locomotion stability during the single-limb support phase [24], a challenging condition considering that all body weight is supported by one leg only. MoS index is based on the inverted pendulum model, which is widely used for modeling human gait [26], and can be considered as a measure of stability/instability during walking. The MoS provides indications on the relationship between the limit of stability (e.g. the lateral border of the feet or the CoP) and the CoM. Negative values of MoS indicate an unstable walking pattern (CoM outside BoS), with the consequent risk of falling, while positive values are associated with a more stable pattern (CoM within BoS) [27] (see Methods for details). Gait stability has been already investigated in persons with Multiple Sclerosis (MS) [19, 28, 29], Stroke (ST) [10, 21], and Parkinson's disease (PD) [20], which are among the most prevalent neurological conditions, all presenting an increased frequency of falls [6, 18]. These studies have considered patients walking under perturbed conditions and/or during treadmill gait, which is known to be quite different compared to overground walking [30, 31]. In the literature, the increase of gait stability parameters

is interpreted as a strategy adopted by persons with neurological diseases to improve their walking pattern. In detail, persons with MS and ST increase their MoS through wider steps [10, 28], while persons with Parkinson's manage stability by walking slower [20]. It must be noted that a recent review of post-stroke gait stability highlighted how the widening of the steps does not improve stability in persons with stroke and pointed out the need to study the stability of both limbs [32].

However, the adoption of a cautious gait strategy to improve stability through slower walking, with shorter step length, and wider step widths, seems not sufficient since falls still occur. Therefore, there is a need to further investigate gait stability and identify appropriate measures to design new rehabilitative interventions aimed at reducing fall risk.

The gait analysis (GA) is becoming a routine examination in clinical practice [33, 34], and the MoS index could be easily integrated into the GA reports providing clinicians with quantitative information that better characterizes the dynamic balance. Recently the prospective observation of persons with PD, MS, and ST confirmed the high tendency of these three diseases to give rise to falls and highlighted that persons with poor dynamic balance are at the highest risk of falling [18]. Regardless of the disease, these patients usually undergo common rehabilitation protocols for balance improvement (e.g. aerobic/resistance training) [4]. The clinical measures, used to assess balance and to evaluate the response to rehabilitation in persons with neurological diseases, do not describe the biomechanical mechanisms underlying the changes in balance ability. In this context GA measures (e.g. MoS index) of gait stability are promising indices to describe balance abilities during overground walking and could help clinicians in tailoring the therapeutic intervention and measuring the rehabilitation effects.

Based on the above-mentioned issues, this work aimed to characterize the gait stability, as measured by MoS index, during straight-line overground walking in persons with MS, ST, and PD compared to healthy controls.

4.3 Methods

4.3.1 Participants

This is a cross-sectional study conducted at Fondazione Don Carlo Gnocchi. Eligible patients were persons with PD, MS, or ST requiring rehabilitation for balance and gait disturbances consecutively enrolled from April 2017 to April 2019. Inclusion criteria were age ≥18 years and ability to stand independently in an upright posture and to walk autonomously without assistive devices. Exclusion

criteria were Mini-Mental State Examination score <24, and being in the acute phase of the disease. Persons with PD were assessed in their ON-medication state (2 hours after taking their usual antiparkinsonian drugs).
An age-matched group of 10 healthy subjects (HS), without any neuromuscular and balance deficits that could interfere with their gait and with normal joint range of motion and muscle, strength was included to provide normative data.

All participants gave written informed consent to the protocol approved by the ethical committee of Fondazione Don Carlo Gnocchi (2017-3-29, Milan, Italy).

4.3.2 Clinical Assessment

Disease severity was defined according to disease-specific scales: Expanded Disability Status Scale (EDSS) for MS [35], modified Rankin Scale (mRS) for ST [36], and Hoehn and Yahr stage (H&Y) for PD [37]. The self-reported number of falls in the 6 months before data collection was recorded. Dynamic Gait Index (DGI, ranging from 0 (severe impairment) to 24 (normal)) [38] and Timed Up and Go test (TUG, greater timings indicating greater impairment) [39] were administered to patients to measure dynamic balance skills and mobility impairment, respectively.

4.3.3 Data collection

The LAMB marker set was adopted [40]. Markers' coordinates were collected using a 9-camera SMART-D motion capture system sampling at 200 Hz; while a force plate, with 960 Hz sampling frequency, provided the CoP coordinates of the ground reaction force (GRF).
Persons with MS, ST, and PD were asked to perform at least five gait trials at their natural speed, and HS performed additional trials at slower velocities.
Since there are speed-dependent effects on the MoS parameter [41, 42], only trials of HS with speed [43] smaller than 90% of the maximum speed value of patients, were selected for the dynamic stability analysis to form speed-matched normative data.
For each subject included in the protocol, only trials with GRF data were analyzed and the average values of the selected parameters were calculated separately for each limb.

4.3.4 Data Processing

The 3D trajectory of the body's CoM was calculated as the weighted sum of the 16 segments' CoMs (Chest, abdomen, pelvis, arms, forearms, hands, thighs, shank, foot, and head) [44]. Dynamic stability was investigated at the midstance of the gait cycle. The study at this time instant is considered sufficient for the characterization of most locomotor impairments [45]. Midstance was identified as 50% of the time interval from foot strike to foot off [46], respectively defined as the first/last time frame including non-null GRF data in each gait trial [47].

For both HS and patients, gait stability was evaluated on both sides. Then they were grouped into dominant/non-dominant side in HS and less affected/more affected side for patients. The dominant side of HS was individuated by asking the subject to kick a ball, while the more affected side of patients was selected according to item 13 of the Berg Balance Scale (Standing unsupported one foot in front) [48].

Following the indications by Terry et al [25], MoS was calculated in medio-lateral (ML) and antero-posterior (AP) directions as the distance between the extrapolated CoP (XCoP) and the extrapolated CoM (XCoM) (Eq. 1). XCoP and XCoM are defined by Eq. 2 and 3, respectively.

$$\mathrm{MoS}_{\mathrm{ML(AP)}} = \mathrm{XCoP}_{\mathrm{ML(AP)}} - \mathrm{XCoM}_{\mathrm{ML(AP)}} \quad (1)$$

$$\mathrm{XCoM}_{\mathrm{ML(AP)}} = \mathrm{CoM}_{\mathrm{ML(AP)}} + \frac{\mathrm{V\_CoM}_{\mathrm{ML(AP)}}}{\omega_0} \quad (2)$$

$$\mathrm{XCoP}_{\mathrm{ML(AP)}} = \mathrm{CoP}_{\mathrm{ML(AP)}} + \frac{\mathrm{V\_CoP}_{\mathrm{ML(AP)}}}{\omega_0} \quad (3)$$

where $\mathrm{V\_CoM}_{\mathrm{ML(AP)}}$ and $\mathrm{V\_CoP}_{\mathrm{ML(AP)}}$ are, respectively, the CoM and CoP velocity in medio-lateral (ML) and antero-posterior (AP) directions, $\omega_0 = \sqrt{\frac{g}{L}}$ is the inverted pendulum's eigenfrequency, L the maximal height of the estimated CoM and g the gravity acceleration.

As references for MoS calculation, the right foot was chosen and the unit vector was defined from medial-to-lateral (posterior-to-anterior) on the frontal (sagittal) plane. Therefore, a positive MoS means that the CoM is within the area delimited by the XCoP (Figure 1A) while a negative MoS means that the CoM has exceeded such limit (Figure 1B). An increased MoS means that the CoM is further inside the area bounded by XCoP, and a decreased MoS means that the CoM is closer to the XCoP limit.

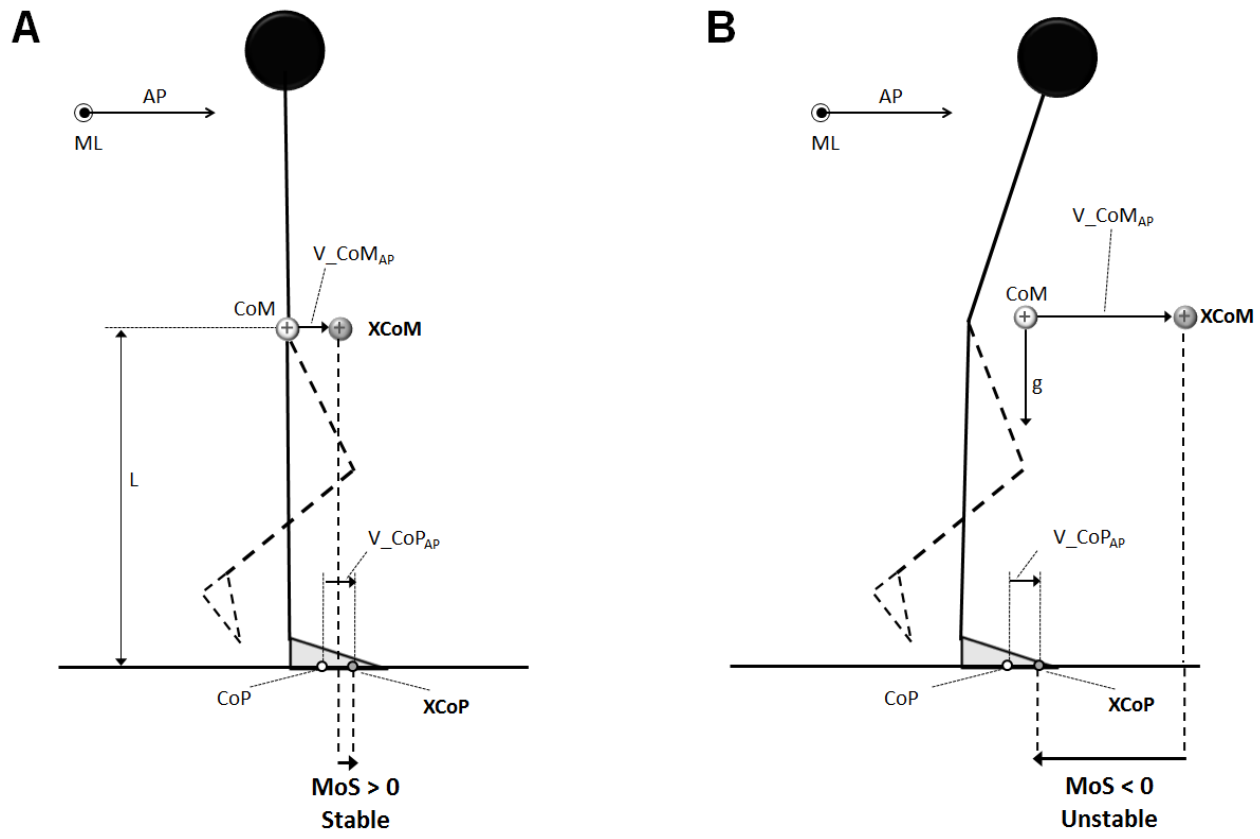

Figure 1. Schematic illustration of Margin of Stability in the sagittal plane in two conditions: a) the 4 projection of the Center of Mass is inside the area delimited by XCoP, resulting in positive value of 5 MoS and b) CoM projection is outside such limit, resulting in negative value.

4.3.5 Statistical Analysis

A Chi-square test was conducted to test the potential difference in the gender frequency among groups (PD/MS/ST/HS). All anthropometric measures (age/height/weight) and instrumental parameters were investigated through parametric tests, after verification of data normality (Shapiro-Wilk test) and homogeneity of variances (Levene's test).

Since the number of falls, TUG and DGI tests were not normally distributed, non-parametric tests were used.

Potential differences among groups in anthropometric measures and clinical test outcomes were also investigated by one-way ANOVA test and Kruskal-Wallis test, respectively.

An ANOVA for repeated measures using Group as the between-group factor (PD/MS/ST/HS) and lower limb (LL) as repeated measure factor (More/Less Affected and Non-Dominant/Dominant) was used to analyze the difference on spatio-temporal gait parameters and dynamic stability data.

Correlation analysis was performed between the number of falls and the dynamic stability index using the Spearman correlation test. To interpret the magnitude of the correlation coefficients ρ, the following guidelines were followed: for absolute values between 0 and 0.19 a very slight relationship, between 0.20 and 0.39 a slight one, between 0.40 and 0.59 moderate relationship, between 0.60 and 0.79 a strong one, and between 0.80 and 1 very strong [49].

For each analysis, the significance level was set to 0.05. Fisher's post-hoc test was applied for multiple comparison analysis.

In a preliminary study on the physiological asymmetry/symmetry between legs, Lencioni et al [50] found significant paired differences in the MoS values in the frontal plane (mean (SD), left 59.6±14.1 mm, right 97.1±16.6 mm). Hence, given α=1% and 1-β=95%, the minimum sample size (per group) is nine subjects. Based on pooled data from previously published studies on MS, ST and PD [19, 20, 51], this sample size is adequate to detect a difference in the medio lateral stability between persons with neurological diseases and healthy persons (Cohen's d = 1.24, Power = 0.81, p = 0.05).

4.3.6 Results

The study sample included forty-four adult persons with neurological disorders (20 MS, 14 ST, and 10 PD) and 10 HS.

The MS cohort included participants with primary progressive (n=1), secondary progressive (n=3), and relapsing-remitting (n=16) clinical course.

Regarding disease severity, the median (interquartile range, IQR) value of H&Y, EDSS, and mRS was 2.5 (2.0-3.0) 5.3 (5.0-6.0), and 2.5 (2.0-3.0) points for PD, MS, and ST respectively. All people with ST showed hemiparesis (8 on the left and 6 on the right lower limb) and all were in the chronic stage (months post-stroke: median (IQR) 40.0 (14.0-66.0)).

No differences ($p>0.05$) in gender, age, and anthropometric data were found among groups (Table 1). The history of falls in the previous 6 months was comparable in people with MS, PD, and ST (Table 1). TUG times were not significantly different among PD, MS, and ST, whilst DGI scores of people with MS were significantly lower than those of PD (Table 1). No significant effects ($P>0.05$) of Group,Lower Limb, and Group x Lower Limb factors were found on spatio temporal gait parameters after the speed-matching procedure (Table 2).

ANOVA disclosed a significant effect of the Lower Limb factor ($P<0.001$) on the antero-posterior MoS (Figure 2B), with the projection of the XCoM being more forward displaced (relatively to the XCoP) when the stance limb was the more affected one (non-dominant for HS).

Table 1. Demographics and spatio temporal gait parameters (mean and 95%CI) of people with Multiple Sclerosis (MS), Stroke (ST), Parkinson (PD) and Healthy Subjects (HS)

Parameters	**MS**	**ST**	**PD**	**HS**
N	20 (13F 7M)	14 (9F 5M)	10 (7F 3M)	10 (6F 4M)
Falls in previuos 6mo	3.5 (1.7-5.3)	3.3 (1.5 5.0)	3.6 (1.7-5.5)	-
Demographic and antropometric data				
Age [yrs]	54.6 (48.9-60.3)	53.5 (46.7-60.3)	67.1 (59.1-75.1)	58.1 (50.1-66.1)
BW [kg]	67.2 (61.4-73.0)	66.9 (59.9-73.8)	65.5 (57.3-73.7)	67.7 (59.5-75.8)
BH [cm]	164.7 (160.5-169.0)	163.7 (158.6-168.8)	160.9 (154.9-166.9)	169.2 (163.1-175.2)
Spatio temporal gait parameters				
Gait Speed/BH [%BH s^{-1}]	47.3 (39.7-54.8)	42.4 (33.4-51.4)	49.5 (38.8-60.2)	44.2 (33.5-54.9)
Stride Length/ BH [%]	58.3 (52.5-64.1)	55.2 (48.3-62.2)	59.4 (51.2-67.6)	66.8 (58.6-75.0)
Cadence [steps min^{-1}]	85.7 (78.8-92.7)	91.3 (83.0-99.6)	96.1 (86.3-105.9)	78.9 (69.1-88.7)
StepWidth/BH [%]	8.7 (7.6-9.8)	9.7 (8.4-11.0)	8.5 (6.9-10.0)	7.4 (5.9-9.0)

F: Female; M: Male; BW: Body Weight; BH: Body Height; mo: months

History of falls in the previous 6 months was comparable in people with MS, PD and ST (Table 1).

Moreover, ANOVA disclosed a significant effect of both Group (P=0.002, Figure 2D) and Lower Limb factors (P<0.001, Figure 2E) on the medio-lateral MoS, with a larger MoS in all patient groups than in HS and a larger MoS for the more affected/non-dominant side compared to the other side. In addition, a significant interaction effect (P<0.001, Figure 2F) between Group and Lower Limb emerged on medio-lateral MoS. PD showed higher values for both sides compared to those of the HS, whilst MS and ST showed larger values with respect to those of HS only for the most affected side (Figure 2F). Within-group comparisons showed that persons with MS and ST presented with medio-lateral MoS values significantly larger for the more affected side than for the less affected one (Figure 2F).

No significant correlations were found between the number of falls and MoS in the antero posterior direction. Conversely, in the medio lateral direction, falls and MoS showed slight and strong correlations for the less affected and the more affected side, respectively (P=0.04 ρ=0.30; P<0.001 ρ=0.74).

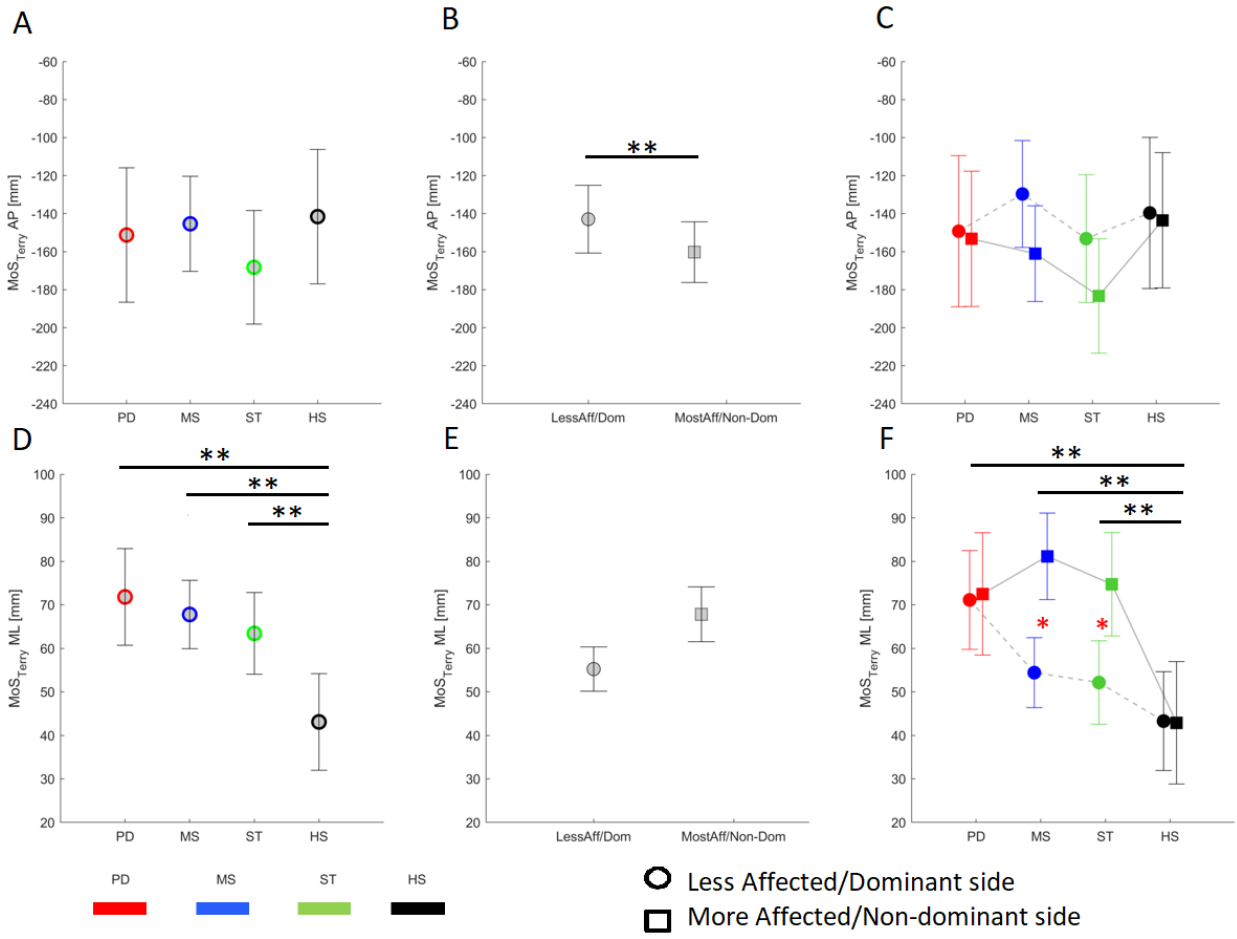

Figure 2. ANOVA results (mean(95%CI)) of the main factor Group and Leg on MoS in the sagittal (A and B) and frontal (D and E) plane. The results of the interaction effects (Group X Lower Limb) is reported in C (sagittal plane) and F (frontal plane).

* $P < 0.05$ Bonferroni-Holm post-hoc test.

** $P < 0.01$ Bonferroni-Holm post-hoc test.

$0.05 < P < 0.10$ Bonferroni-Holm post-hoc test.

MoS: Margin of Stability; PD: Parkinson's Disease; MS: Multiple Sclerosis; ST: Stroke; HS:healthy subjects; LessAff/Dom: Less Affected/Dominant Side; MoreAff/Non-Dom: More Affected/ Non Dominant Side.

4.4 Discussion

In the present study, we analyzed the dynamic balance of gait on a small cohort of people affected by three among the most prevalent neurological disorders leading to similar clinical conditions regarding balance and gait patterns. We also compared their dynamic balance to that characterizing healthy subjects walking at matched velocities. In particular, we focused on the Margin of Stability, an index increasingly used to quantify dynamic balance during walking, using, for the first time, the position and velocity of the Center of Pressure, as these parameters are continuous variables that can be measured objectively and could be used, in future, as a responsive measure to detect pathological alterations as well as changes induced by rehabilitation.

We found no differences in MoS values in the sagittal plane among persons with PD, MS, ST, and HS. All values were negative, indicating that XCoM was in front of the XCoP limit. This is a necessary condition to move the CoM forward during midstance and indeed all enrolled subjects were able to walk and thus move forward.

4.4.1 Gait stability between Limbs

The analysis of MoS values obtained for dominant and non-dominant LL in HS did not highlight a significant difference between limbs, suggesting the presence of a gait stability symmetry. This result supports the hypothesis that motor control is based on the neurophysiological symmetry of limbs and

is in line with findings already published on a sample of healthy subjects wider than the one considered in the present study [50].

The comparison of MoS data among persons with neurological disorders showed that only people with PD presented a symmetry in gait stability, although both limbs showed larger MoS values compared to HS. In contrast, persons with MS and with ST showed a strong asymmetry between the medio-lateral and antero-posterior directions (Figure 2C and 2F). These results reflect the clinical differences among the groups, PD is the least lateralized disease among the three pathologies and leads to a loss of postural reactions compared to ST and MS. In addition, the H&Y values of the enrolled patients were between 2 and 3, indicating a bilateral limbs involvement due to the disease.

4.4.2 Gait stability in the frontal and sagittal planes

The most significant results of this study are related to the MoS in the frontal plane, in line with previous literature showing that medio-lateral measures are more sensitive to detect walking instability [52]. Regarding the MoS related to the less affected side, persons with MS and with ST showed comparable values to those of HS and only people with PD had greater values than HS. For what concerns the most affected side, the whole sample of patients (PD, MS, and ST) showed increased MoS values compared to those of HS. Increased MoS values indicate that the CoM is kept far from the lateral stability limit, fixed by the position and velocity of the CoP. This motor behavior can be interpreted as a protective strategy implemented by patients due to sensory deficits and muscle weakness, useful to control potential external perturbations [20, 53, 54]. In particular, persons with MS exhibited the highest values of MoS in their more affected side. This could be directly related to the damage in the spinal cord that alters both the afferent and efferent pathways in MS. This does not occur in the other two neurological disorders (PD and ST), where the damage is located in the brain [55, 56]. Regarding this last consideration, it should be noted that persons with MS enrolled in this study showed a severe disability condition. Interestingly, the worst performance in the control of dynamic balance in persons with MS is confirmed by the clinical evaluation performed through the DGI, which resulted to be the lowest among the three pathologies.

In the sagittal plane, the MoS absolute value of the more affected/non-dominant side was found higher than that of the other side (Figure 2B). This means that XCoM is projected far ahead of XCoP limit and this could be a compromise to ensure greater stability in the frontal plane because of their strong asymmetry (Figure 2E).

Interestingly, the results of the present study are not dependent on confounding factors that could influence the results, (i.e. age/gait speed/cadence/step width/step length. This suggests that the differences found among PD, MS, ST, and HS are really due to different pathophysiological factors involved in these different disorders. The TUG and the spatial temporal gait parameters (e.g. speed) do not discriminate disease-specific behavioral patterns. This could be attributable to the clinical stage of the whole sample, since all enrolled persons were in the moderate stage of the disease. Despite this, differences are detected by the MoS index.

4.4.3 Gait stability and falls

The high risk of falling is a common factor among persons with PD, MS, and ST, although the neurological causes that contribute to the fall can be different. This is related to the complexity of gait, where information coming from different systems (e.g. visual/vestibular/sensory-motor) is elaborated and integrated (by the central and peripheral nervous system) to guarantee posture stability and body advancement during the gait. In this highly integrated control, it is sufficient that a single system is deficient to compromise the dynamic balance and increase the falling risk. Indeed, the history of falls was comparable among PD, MS, and ST groups, and interestingly it was associated with MoS in the medio lateral direction. The emerged strong positive correlation indicates that a greater number of falls is associated with an increased value of MoS. These suggest that patients who had a high number of falls adopt a more marked cautious gait strategy, probably because of their poor balance confidence[18, 28]. This finding further supports the evidence of this index as a biomarker for monitoring the worsening of balance during walking.

4.4.4 Study limitation

The sample size of the study was calculated on the basis of available data of the instrumental parameter MoS. Consequently, the size of the ST and PD groups could be underestimated for the clinical variables. Furthermore, the participants with neurological disorders were mainly in the moderate stage of the disease, therefore a comparison among different stages (e.g. low/moderate/severe) would require further studies.

4.5 Conclusion

The objective assessment of dynamic balance through MoS in the frontal plane revealed disease-specific strategies of MS, ST, and PD on the ability to control the CoM position between limbs. MoS was able to reveal the strong asymmetry in people with ST and MS. For this reason, it is important to assess the dynamic balance unilaterally, for each limb separately. MoS evaluation will provide useful information 1) to address a tailored rehabilitation to improve gait control and prevent falls for patients affected by different neurological disorders and 2) to monitor the course of the disease and the efficacy of treatments.

4.6 References

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5 Chapter

APA detection from IMU sensor for home-based rehabilitation

Title: Events detection of anticipatory postural adjustments through a wearable accelerometer sensor is comparable to that measured by the force platform in subjects with Parkinson's disease.

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5.1 Chapter Summary

Out-of-the-lab instrumented gait testing focuses on steady-state gait and usually does not include gait initiation (GI) measures. GI involves Anticipatory Postural Adjustments (APAs), which propel the center of mass (COM) forward and laterally before the first step. These movements are impaired in persons with Parkinson's disease (PD) contributing to their pathological gait. The use of a simple GI testing system, outside the lab, would allow improving gait rehabilitation of PD pa-tients. Here, we evaluated the metrological quality of using a single inertial measurement unit for APA detection as compared with the use of a gold-standard system, i.e. the force platforms. Twenty-five PD and eight elderly subjects (ELD) were asked to initiate gait in response to auditory stimuli while wearing an IMU on the trunk. Temporal parameters (APA-Onset, Time-to-Toe-Off, Time-to-Heel-Strike, APA-Duration, Swing-Duration) extracted from the accelerometric data and force platforms were significantly correlated (mean(SD), r: 0.99(0.01), slope: 0.97(0.02)) showing a good level of agreement (LOA [s]: 0.04(0.01), CV [%]: 2.9(1.7)). PD showed longer APA-Duration compared to ELD ([s] 0.81(0.17) vs 0.59(0.09) $P<0.01$). APA parameters showed moderate correlation with the MDS-UPDRS Rigidity, Characterizing-FOG questionnaire and FAB-2 planning. The single IMU-based reconstruction algorithm was effective in measuring APAs timings in PD. The current work sets the stage for future developments of tele-rehabilitation and home-based exercises.

5.2 Introduction

Gait initiation (GI) is a complex transient task performed between the quiet standing posture and steady state walking, requiring a shift from a static stable state to a, relatively less stable, dynamic state of movement [1]. For this reason, it is a challenging task which demands balance and postural control due to a decreasing base of support from a two leg stance to an alternating single leg stance. Prior to step initiation, anticipatory postural adjustments (APAs) act to accelerate the center of body mass forward and laterally over the stance leg by moving the CoP posteriorly and toward the swing leg [2]. To capture the complex physiological changes that occur during the transition from a quiet standing to the first step, following a stimulus to move (e.g. "go"), GI has been divided into three phases [3]. The first phase, related to the motor planning, be-gins with the "go" stimulus and ends when the APA begins. The second phase, related to the postural adjustments, extends from the beginning to the end of APA, and aims to shift the body weight towards the stance leg for stabilizing the body to prevent falls when gait begins. The third phase, related to the gait execution, extends from the end of APA to the completion of the first step.

APAs have been extensively studied in persons with Parkinson's disease (PD), because of their balance deficits, gait impairments and frequent falls [4]. PD is characterized by motor signs resulting from a degenerative loss of dopaminergic neurons in the substantia nigra as well as in multiple motor and non-motor regions of basal ganglia [5]. The basal ganglia are understood to be essential in planning and initiating movement, and APAs are consequently abnormal in PD [2,6]. Several studies have shown that subjects with PD have a reduced magnitude of muscle activity and abnormal muscles co-contractions during the postural adjustments with subsequent alteration in postural balance [2,7,8]. This results in prolonged timing of the GI, decreased propulsive forces and reduced CoP displacements, compromising the shift of the body mass over the stance limb. Impaired APAs are associated with gait start hesitation or gait freezing that leads to falls, injuries, and fear of falling with a substantial worsen-ing of several activities of daily living [9]. For this reason, the identification of a be-havioral measurement that can describe balance disturbances in PD is highly needed, especially in a home-based unconfined context. This would allow monitoring the occurrences of dangerous situations and defining a personalized training program to improve APAs. This last aspect is particularly important in light of the results of a re-cent study that found a preserved flexibility of dynamic postural control in individuals with PD [10]. Indeed, home-based training, applying IMU-based systems, have been recently developed to improve gait performance, gait-related activity and

health-related quality of life in people with PD and results are encouraging [11–13]. However, in these studies gait training was focused on the execution phase only, without considering the planning phase and postural adjustment of the APA, which are fundamental for a correct gait execution. Moreover, it is worth considering that recently IMUs have been used for evaluating GI and the APA with a fair success [14,15]. Nevertheless, for the automatic detection of the APA onset, the toe-off and the heel-strike, the proposed protocols require either a minimum of three IMUs [16] (placed on the trunk and on the shanks) or the integration of data coming from footswitches [17] or pressure insoles [18]. The need for multiple sensors located on the body restricts the usability of these protocols in patients with neurological disease [19] both in home-based and clinical settings [20–24]. Furthermore, these approaches are limited because they require the subject to stand in a pre-specified manner, and often require a relatively extensive calibration phase.

To address this gap, Gazit et al [3] developed an algorithm for the detection of GI events from a single wearable sensor. The published algorithm allows evaluating the above reported three phases of GI and identifying which mobility impairments they are related to: planning, postural adjustments, or execution. The use of this algorithm in the clinical practice could help the development of personalized physiotherapy training for gait impairments. APAs-focused training has already been shown to be effective in the elderly, improving their postural control, functional balance, mobility and quality of life [25]. Indeed, elderly enhanced their anticipatory postural action and achieved a greater body stability resulting in better performances also in untrained tasks. In the light of these results, it is desirable to introduce APAs-focused exercises in PD patients given their impairment in APAs.

In consideration of the limitation of using the multiple wearable sensors approaches reported above, the twofold aim of this work was to evaluate: 1) if the accelera-tion-based algorithm described in [3], that needs a single sensor, has a metrological quality comparable to that of the gold standard for APA detection (i.e. force platforms) in PD and 2) its concurrent validity with PD disease-specific clinical scale. The potential validity of a simple GI testing system, made up of a single sensor placed on the lower back, would allow home-based monitoring and could contribute to improve APA rehabilitation treatments in PD patients.

5.3 Materials and Methods

5.3.1 Participants

Twenty-five subjects with mild-to-moderate idiopathic PD (13 without and 12 with previous experiences of FOG) [26] and 8 healthy controls (ELD) participated to the study, after giving their informed consent. Subjects with PD that met the following inclusion criteria were recruited at the IRCCS Fondazione Don Carlo Gnocchi in Milan: age > 18 years, diagnosis of idiopathic PD (according to the United Kingdom Parkinson's Disease Society Brain Bank criteria), Hoehn & Yahr between 2 and 3, Mini Mental State Examination ≥ 24 and able to walk unassisted. Exclusion criteria were: deep brain stimulation implant, history of neurologic disorders (except PD), visual, orthopedic, or vestibular impairments that could hamper task performance, and need of hearing aids. Subjects with PD were tested in their practical ON-medication state (approximately 1 hour after taking their antiparkinsonian medications).

Considering the main aim of the present study (i.e. validation of APA measures from a single accelerometer sensor), the sample size calculation was estimated using previous published data related to the Bland–Altman mean difference (GRF vs IMUs) of the APA duration parameters. Bonora et al [15] found a bias of -0.02 s with a SD of 0.13 s- Hence, estimating a maximum allowed difference comparable to the published LOA, a minimum sample size of 23 is recommended for the Bland-Altman method with $\alpha = 0.05$ and power $(1-\beta) = 0.9$ [27].

5.3.2 Clinical Assessment

Disease severity was evaluated with the section III of the MDS–Unified Parkinson Disease Rating Scale [28]. The patients' more affected side was determined on the basis of MDS-UPDRS III items in which a score for each side is available (i.e. items from 20 to 26): the right and left symptom scores were calculated and the more affected side was individuated as the one with the higher score. Subsequently, the scores for tremor, rigidity of extremities, and leg agility were calculated for the most impaired side [29].

The clinical assessment included the administration of the following clinical scales: the short physical performance battery (SPPB range from 0, severe impairment, to 12, normal [30]), the Four Step Square Test (FSST, lower values - better performance [31]), and the Modified Dynamic Gait Index for the dynamic balance (MDGI, range from 0, severe impairment, to 64, normal [32]) for balance and motor skills; the Frontal Assessment Battery and its three subscales for the executive functions (FAB range from 0, severe impairment, to 18, normal, FAB-1 linguistically mediated EF, FAB-2 planning, and FAB-3 inhibition [33]), and finally the Characterizing Freezing of Gait Questionnaire for the freezing of gait episodes experience (C-FOG, 0 indicate no FOG [34]).

5.3.3 Procedures

Participants stood on the first force platform with their feet in parallel at hip width and were asked to initiate a gait in response to auditory stimuli provided through a headphones set and to stop as soon as possible with both feet on the second force platform. The protocol included five trials and the auditory stimulus was a neu-tral voice saying ‘go’. No indication was given on the starting foot.

The wearable measurement system used consists of a single IMU with a 16-bits resolution, analog-to-digital converter and a full scale of ±16 g (Cometa, Italy, https://www.cometasystems.com/), equipped with a MEMS sensor (https://invensense.tdk.com/products/motion-tracking/9-axis/mpu-9250/). The device has a low weight (5.3 g) and small-size (32 mm × 24 mm × 7 mm), is waterproof and is equipped with a wireless interface for real-time data streaming, as well as 1 GB of on-board memory which allows to store locally up to 6 hours of continuous measure-ments. For the study purposes, only data of the triaxial accelerometer were analyzed at a sampling rate of 140 Hz with a 16-bits resolution. The sensor was fixed with an elastic band on the trunk at L5 level. The acceleration signal was processed using a 4th-order, band pass Butterwoth filter between 0.2 and 4.5 Hz.

Ground reaction forces and center of pressure (CoP) displacement were measured with the force platforms, considered as gold standard, at 1000 Hz (BTS, Italy). Retroreflective markers were placed on malleolar anatomical landmarks (BTS, Italy). CoP displacements recorded from the force platforms were filtered with a fourth order, zero-lag, low-pass Butterworth filter with a cut-off frequency of 10 Hz.

A custom-made Software, developed in Visual Studio dot net (Microsoft, USA) environment, recorded the accelerometric data and controlled the trial onset and off-set, the auditory stimulus presentation and the synchronization with the optoelectronic system including the GRFs. For each stimulus sent to the headphones, a synchronous trigger signal was sent to SMART Capture software (BTS).

APAs timings quantification were calculated from 3 automatically-detected time points: 1) APA onset, 2) toe-off, and 3) heel-strike both from the CoP data [2] and the trunk acceleration [3].

Briefly, the identification of the time points from the force platforms and optoe-lectronic signals was calculated as follows [2]: 1) the instant of APA onset was identi-fied as the first frame in which both antero-posterior and medio-lateral components of the CoP velocity were negative, 2) the toe-off of the swing limb (TOswl, Figure 1A)was identified as the frame in which the position of CoP attained the maximum distance from the line identified by the position of CoP at APA onset and at the toe-off of the stance leg (i.e. the last frame on the GRF signal) and 3) the heel-strike of the swing limb

(HSswl) were calculated as the frame in which the malleolar marker antero-posterior velocity reached the zero value.

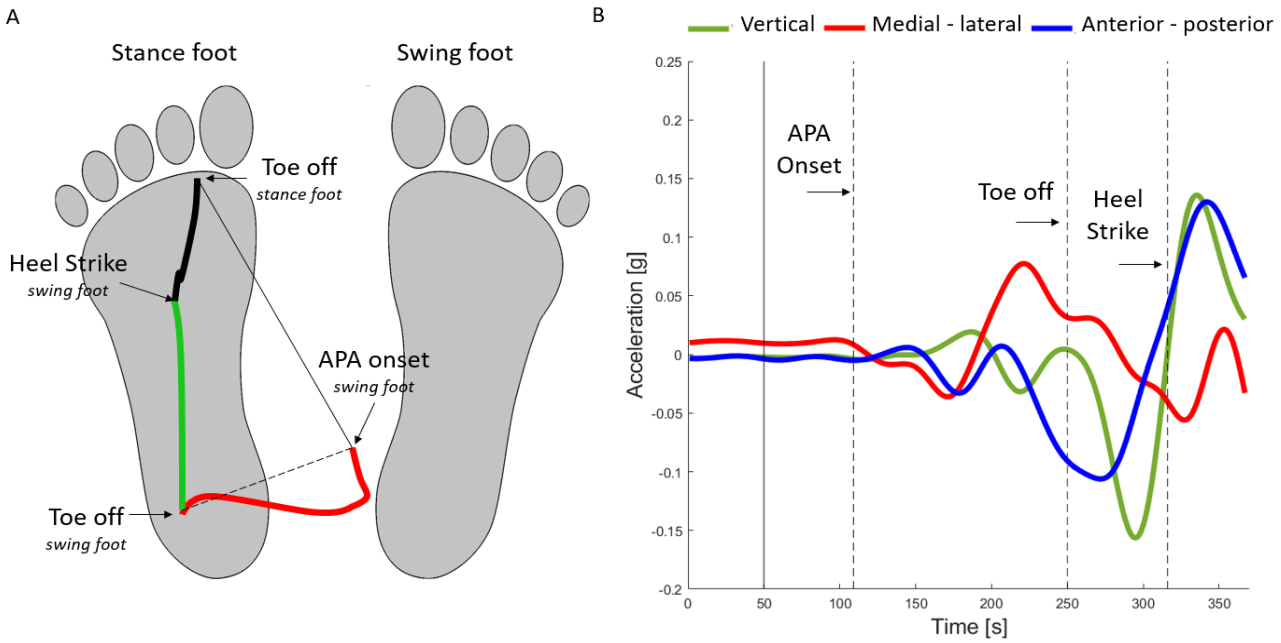

Figure 1 A) CoP displacement and B) Acceleration signal during the gait initia-tion prior to the step in a healthy subject. In the panel A, the CoP trace from APA on-set to APA end (i.e. toe off) is reported in red and during the swing phase in green. In the panel B the first vertical line represents the auditory cue release and the next 3 ver-tical lines are the points derived by the algorithm, APA onset, swing leg toe-off and heel strike.

The same temporal instants were then extracted from the accelerometer data of the wearable inertial system (Figure 1B) as detailed in [3] and briefly reported below. The APA onset calculation was performed separately for each of the three axis of the accelerometer signal through the two steps approach reported in the following. The overall APA onset instant was determined as the earliest detected APA time-point of the three axis. For each axis the APA calculation consisted in the following steps: Step 1) , the instant (APAchange) were identified, within a temporal window from 0.5 s prior to the stimulus until 1.2 s after it, as the time frame at which the sum of the re-sidual error was minimal, indicating a significant change of the signal mean and slope. Step 2) From the APAchange the algorithm search backwards the first local minimum, which was identified as the instant of APAonset. The TOswl was identified from the ver-tical accelerometer data in the temporal window from 800 ms after the stimulus until 2 s after it, though the following four steps. In the step 1 the algorithm identified the signal positive peaks with amplitude over the threshold set to 1% of the values be-tween 10th and 90th percentile of the signal (vector Peakva). In the step 2, the peak with

maximum amplitude over the threshold set at 1/4 from percentile 95th of the values (Peakva_max) was selected among the Peakva Then, during the step 3, in the temporal window from 1.5 s until 0.5 before the frame of Peakva_max, the instant of the first step (I_PeakFS) was calculated as the signal peak (PeakFS) closest to the temporal window closure. Finally (step 4), the TOswl was defined as the zero-crossing point in the vertical acceleration just before the I_PeakFS. The HSswl is detected in the vertical acceleration axis prior to I_PeakFS as the point where the signal crossed the 20% value of the PeakFS. A schematic summary of the main steps of the algorithm for the APA instants identification is reported in Table 1.

Table 1. Schematic summary of the main steps of the algorithm for the APA instants identification.

Parameter	**Axis**	**Temporal Window [s]**	**Description**
		Identification of anticipatory postural adjustments onset	
APA_{change}	AP, ML , V	$[0.5 - t_s : t_s + 1.2]$	Time point where significant change of mean signal occurs
APA_{onset}	AP, ML, V	$[t(APA_{change})-t_s: t(APA_{change})]$	From $t_{APAchange}$ search backwards for the time point of the first local minimum
		Identification of toe-off of the swing limb	
$Peak_{va\_max}$	V	$[0.8 + t_s : t_s + 2]$	Time point of the signal positive peak over a predefined threshold
I_Peak_{FS}	V	$[t (Peak_{va\_max}) -1.5 : t (Peak_{va\_max}) - 0.5]$	Time point of the first step calculated at the peak closest to the temporal window closure
TO_{swl}	V	$[t (Peak_{va\_max}) -1.5 : t (I\_Peak_{FS})]$	The zero-crossing time point just before the I_Peak_{FS}
		Identification of heel strike of the swing limb	
HS_{swl}	V	$[t(TO_{swl}) : t(I\_Peak_{FS})]$	Time point where the signal crossed the 20% value of the vertical accelation signal at I_Peak_{FS}

ts: time of stimulus; APAonset: anticipatory postural adjustments onset; TOswl: toe-off of the swing limb; HSswl: heel strike of the swing limb; AP anterior-posterior axis; ML: medio-lateral axis; vertical axis.

Based on the timing of APAonset, TOswl and HSswl, the following GI measures were computed for the trials of the participants (Figure 2A) [1]:

- Time-to-APA, time from the "go" to the beginning of the APA (i.e. APA Onset).
- Time-to-toe-off, time from the "go" to the APA end, calculated as the toe-off event of the swing leg.
- Time-to-heel-strike, the time from the "go" to the heel-strike of the swing leg.
- APA duration, the time from the beginning (i.e. APA onset) to the end (i.e. Toe-off) of the APA waveform.
- Swing phase duration, the time from the toe-off to the heel-strike of the swing leg.

5.3.4 Statistical analyses

The data processing and the statistical analysis were performed using Matlab (MathWorks, USA) and SPSS (IBM, USA). For each subject, variables were averaged over the five trials. The agreement in measures between the force platforms and IMU was investigated through the Bland-Altman analyses and the intra-class coefficient correlation (ICC). For the former analysis, bias or systematic error, coefficient of varia-tion (CV) and lower and upper limits of agreement (LOAs) were calculated. For the latter, an alpha model, two-way mixed and absolute agreement were adopted [35]. The ICC was interpreted by the Fleiss' classification using the following thresholds: below 0.40 indicated poor reliability; between 0.40 and 0.75, fair to good reliability; and above 0.75, excellent reliability. Mean absolute errors (MAEs) between instants recognized from force platforms and IMU were averaged among all subjects. Age, anthropometric data and APA parameters were compared between PD and ELD using parametric tests (unpaired t test) since the normality of the data distribution was satisfied (Shapiro-Wilk's method). Between-group (PD/ELD or FOG-/FOG+) effect sizes of the APA parameters were examined by calculating the Cohen's d value and was classified according to its absolute value as small (0.20-0.49), moderate (0.50-0.79) or large (>= 0.80) [36].

Linear correlations were used to assess the association between GI metrics, whereas the concurrent validity of the GI metrics with clinical scales was assessed us-ing Spearman's correlation coefficient, as the latter were not normally distributed. To interpret the magnitude of the correlation coefficients, the following guidelines from [37] were followed: for absolute values between 0 and 0.19 a very slight relationship, between 0.20 and 0.39 a slight one, between 0.40 and 0.59 moderate relationship, be-tween 0.60 and 0.79 a strong one, and between 0.80 and 1 very strong.

The method sensitivity was assessed by comparison of the GI metrics through unpaired t-test between PD and ELD, and between PD without and with freezing of gait (FOG- and FOG+). The experience of FOG was determined by the positive response to the item 1 of the Characterizing Freezing of Gait Questionnaire (C-FOG).

The P-value for statistical significance was set at 0.05.

5.4 Results

5.4.1 Participants' Demographics and clinical assessment

The PD and ELD groups did not differ in age, weight and height (PD 17 Males, mean (SD), age [yrs]: 73.9 (6.2), body mass [kg]: 68.4 (10.8), body height [cm]: 169.0 (6.0)); ELD 5 Males, mean (SD), age [yrs]: 68.9 (7.5), body mass [kg]: 70.6 (13.0), body height [cm]: 169.1 (6.8), P = 0.07; P = 0.63, P = 0.97). The clinical features of the PD group are summarized in Table 2.

Table 2. Clinical characteristics of the sample of persons with Parkinson's Disease en-rolled in this study.

	Median	**(1st-3rd quartile)**
Number of falls	0 (2.0-2.0)	
H&Y	3.0 (2.5-3.0)	
MDS-UPDRS III	42.5 (35.5-54.0)	
MDGI *	50.0 (42.0-55.0)	
SPPB	9.0 (2.0-4.0)	
FSST	13.5 (11.2-20.2)	
C-FOG	25.0 (0.0-47.0)	
FAB	16.0 (14.0-18.0)	
BAI	17.0 (8.0-31.0)	
BDI-II	13.0 (10.0-16.0)	

* H&Y stage, Hoehn and Yahr stage; MDS-UPDRS, Unified Parkinson Disease Rating Scale Part III; MDGI, modified Dynamic Gait Index; SPPB short physical performance battery; FSST Four Step

Square Test; C-FOG, Characterizing Freezing of Gait; FAB Frontal Assessment Battery; BAI, Beck Anxiety Inventory; BDI-II Beck Depression Inventory.

5.4.2 Validation of body-fixed sensor gait initiation metrics

A good agreement of the IMUs compared to the reference system was observed for the APA timing measures through both the Bland-Altman method and linear cor-relation (Figure 2 B-F). There was no bias in the measurement methods since the bias was very close to 0 in all variables. In line with the results of Bland–Altman analysis, also the ICC analysis showed a satisfying agreement between the measurements made using the two systems. In fact, all the parameters revealed an excellent agreement (Table 3).

Table 3. Intraclass correlation coefficients (ICC) of gait initiation (GI) metrics extracted from the inertial measurement unit and the force platforms.

GI Metrics	**ICC**	**Lower Bound**	**Upper Bound**	**Cronbach's Alpha**
Time-to-APA	0.99	0.98	0.99	0.91
Time-to-toe-off	0.99	0.98	0.99	0.99
Time-to-heel-strike	0.99	0.99	1.00	1.00
APA duration	0.99	0.97	0.99	0.99
Swing duration	0.98	0.97	0.99	0.98

5.4.3 MAEs values

No significant differences were found between PD and ELD subjects considering MAEs for APA onset (mean ± SD [s], PD 0.00 ± 0.02, ELD 0.01 ± 0.01, P = 0.50), toe-off ([s], PD -0.01 ± 0.02, ELD -0.01 ± 0.02, P = 0.92) and heel-strike ([s], PD -0.01 ± 0.01, ELD -0.01 ± 0.01, P = 0.39) instants. Also for the MAEs values of the parameters APA and Swing durations no significant differences were found ([s] PD -0.02 ± 0.03 ELD -0.02 ± 0.03, P = 0.68; PD 0.00 ± 0.02 ELD 0.01 0.02, P = 0.66, respectively).

5.4.4 Correlations between gait initiation metrics

Significant positive correlations were found by examining the association among the GI metrics in persons with PD, as depicted in Figure 3. Time-to-APA and APA duration were correlated with Time-to-toe-off and Time-to-heel-strike, through strong and very strong associations respectively. Also a strong correlation between Time-to-toe-off and Time-to-heel-strike was found, whereas the swing phase parameter was slightly correlated with Time-to-heel-strike.

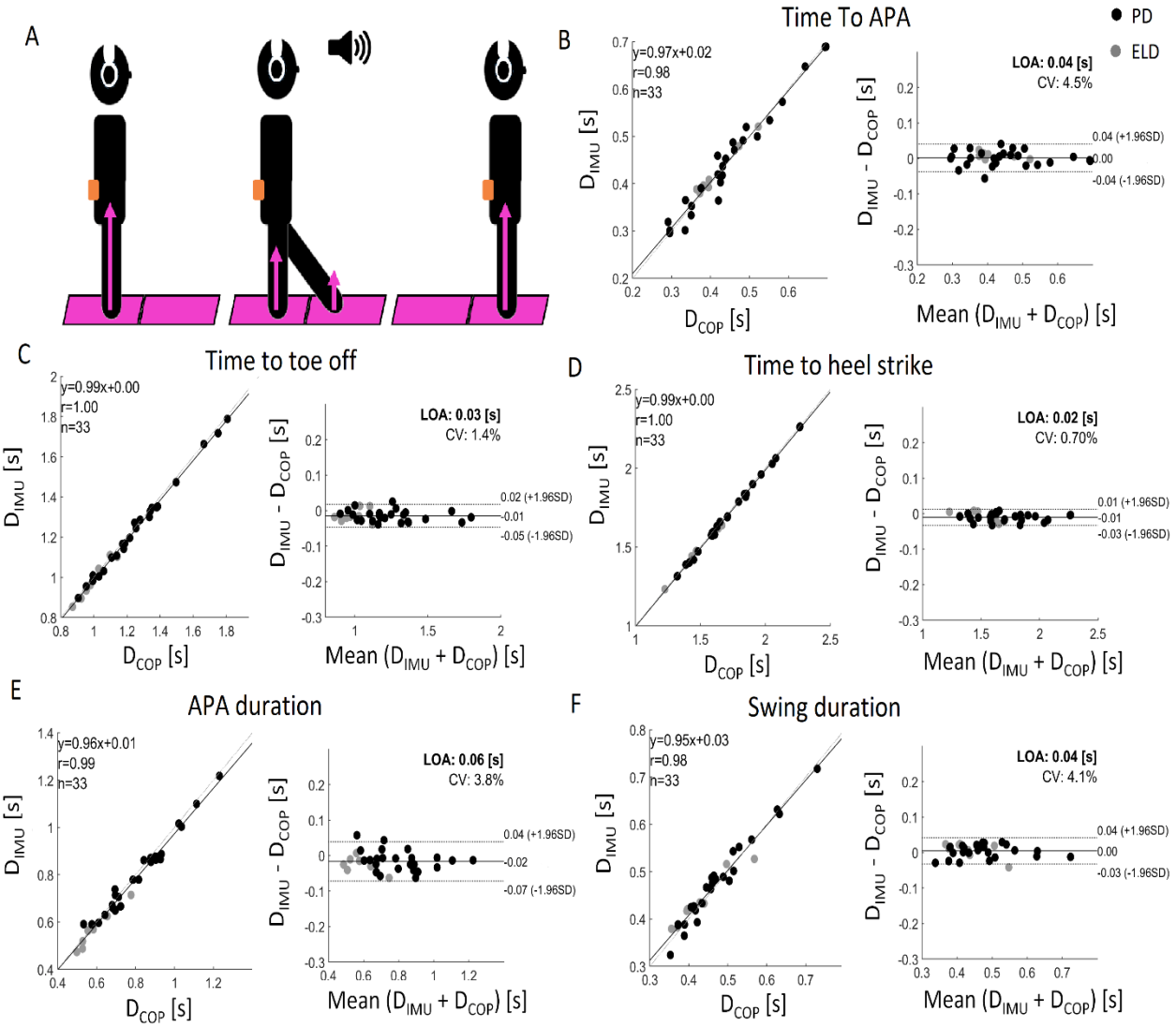

Figure 2. A schematic representation of the experimental paradigm, where the subjects stood on the first platform and took a step forward on the second platform when the stimulus arrived in the headphone (A). Bland-Altman plots of Time-to-APA (B), Time-to-toe-off (C), and Time-to-heel-

strike (D), APA duration (E) and Swing phase duration (F). PD persons with Parkinson's Disease; ELD elderly.

5.4.5 Correlation between gait iniation metrics and clinical scales

Figure 3 reports the correlation analysis between clinical outcomes and APAs parameters. GI metrics showed statistically significant correlations with the clinical outcomes. In particular, APAs parameters showed moderate-to-strong correlations with the assessement of episodic symptom FOG in persons with PD (Figure 3). Three parameters, Time-to-toe-off, Time-to-heel-strike and APA duration, correlated negatively with the MDS-UPDRS item 3.11 (i.e FOG Figure 3 A) and the C-FOG questionarie (Figure 3 B). All the GI metrics, except for the swing phase duration, showed moderate positive correlations with the dynamic stability (FSST, Figure 3 B). In addition, the time-to-APA correlated negatively with the score of the lower extremity function (i.e. SPPB and its item 3, Figure 3 B) and the executive functions (FAB and its sub-item planning, Figure 3 B). Time-to-toe-off, Time-to-heel-strike and APA duration correlated positively with the assessment of the body rigidity (i.e. MDS-UPDRS Rigidity, Figure 3 A).

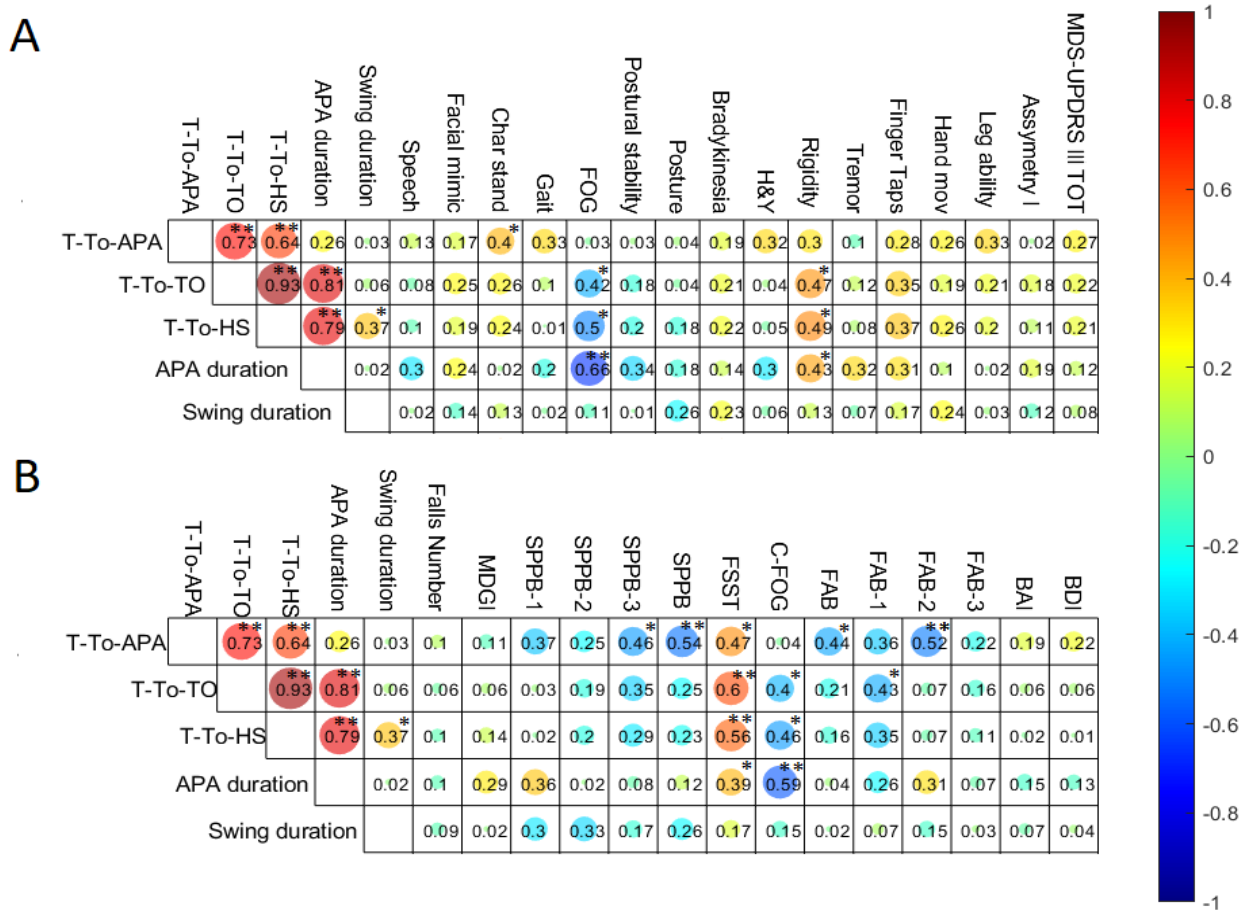

Figure 3. Correlations between gait initiation metrics and clinical outcomes for MDS-UPDRS III and its sub-items (A) and the other clinical scales (B). Absolute values are reported in the boxes, whereas the circle color indicates the positive (red) or negative (blue) degree.

Significant correlation indices are indicated with * $p < 0.05$ and ** $p < 0.01$. H&Y stage, Hoehn and Yahr stage; MDS-UPDRS III, Unified Parkinson Disease Rating Scale Part III; MDGI, modified Dynamic Gait Index; SPPB short physical performance battery; FSST Four Step Square Test; C-FOG, Character-izing Freezing of Gait; FAB Frontal Assessment Battery; BAI, Beck Anxiety Inventory; BDI-II Beck Depression Inventory.

5.4.6 Differences in APAs timing parameters between PD and ELD

PD showed a significantly longer time phase of APA with respect to that of ELD. Furthermore, toe-off and heel strike events were significantly delayed from stimulus release in PDs compared with healthy subjects (Table 4). On the other hand, the Time-to-APA and the swing phase duration metrics were comparable between the two groups, PD and ELD.
When comparing FOG- and FOG+, it emerged that FOG+ showed a reduction of APA duration with respect to FOG- (Table 4).

Table 4. Gait initiation metrics for both groups, PD and ELD.

Parameters	**PD**	**FOG-**	**FOG+**	**ELD**	**Cohen' d**	
					PD/ELD	FOG+/FOG-
Time-To-APA [s]	0.45(0.12)	0.44(0.10)	0.46(0.13)	0.42(0.05)	0.30	0.18
Time-To-Toe-Off [s]	1.26(0.24)	1.31(0.20)	1.21(0.26)	1.00(0.09)*	1.07	0.45
Time-To-Heel-Strike [s]	1.73(0.26)	1.80(0.23)	1.66(0.27)	1.44(0.15)*	1.10	0.55
APA duration [s]	0.81(0.17)	0.88(0.12)	0.75(0.19)+	0.59(0.03)*	1.20	0.78
Swing phase duration [s]	0.47(0.09)	0.49(0.12)	0.46(0.06)	0.43(0.07)	0.48	0.38

* P<0.05 PD vs ELD; + P<0.05 FOG- vs FOG+

5.5 Discussion

In this study, we investigated the validity, accuracy and sensitivity of a single IMU-based method for cued GI assessment in persons with PD.

Our findings confirmed the validity of the algorithm for the population under investi-gation. Results demonstrated low errors and good agreement between the single IMU-based system and the force platforms acquisition system for the estimation of the APAs timings. The APAs movements are needed to prepare the body for the upcoming disturbance, they are the first line of defense that the central nervous system (CNS) uses to maintain and restore balance when the equilibrium state is perturbed or changed [38]. Human vertical posture is inherently unstable due to the high location of the center of mass (COM), small base of support area, and multiple joints between the feet and the body's COM position [39,40]. When a standing person performs a quick movement, as the gait initiation, the mechanical coupling of body segments leads to postural perturbations that may endanger fragile balance [41]. By activating the trunk and leg muscles, prior to a forthcoming predictable body perturbation (i.e. APAs), CNS minimizes the risk of losing equilibrium. It is well established that these postural ad-justments are altered in subjects with PD [6]. However, so far, home-based exercises using IMUs-based system, are focused on steady-state gait, therefore not including the GI phase. Our findings encourage the implementation of exercises for APA training with out-of-lab system in persons with PD, as events such as the APA onset, the toe off and the heel strike of the swing leg are detectable accurately and effectively from a single IMU positioned on the lower back. This sets the stage for future developments to improve the home-based training in PD. In fact, the significant correlations between parameters from IMU and force platforms support the possibility to adopt a single IMU to assess APAs outside a laboratory setting.

Concerning the sensitivity, GI metrics extracted from a single IMU were able to discriminate between PD and elderly on the basis of APAs alterations. More precisely, persons with PD showed prolonged APAs compared to those of elders during GI (Table 4, APA Duration parameter). This finding was consistent with the ones published by previous studies [2,42,43] that have used the gold standard system to investigate the differences in the APAs timings between persons with PD and elderly subjects. Halliday et al [42] found preserved temporal and spatial patterns of GI in elderly and PD subjects but also increased APA phases durations in PD patients compared to those of the elderly, which in turn were longer than those of the young subjects. This trend suggests a progressive slowing of GI patterns from the young to the elderly, up to the PD subjects. Also Crenna et al [2] and Burleigh-Jacobs et al found [43] that the APA duration was prolonged in PD subjects and that could be improved using external stimuli. The same prolonged duration has been detected also by the method here pre-sented, supporting the validity of a single IMU-based system to investigate alterations in the APAs pattern.

Furthermore, the algorithm has also detected differences within PD group, be-tween FOG- and FOG+. The alterations of APAs in PD are the result of the pathological characteristics of the disease

that compromises not only the movement execution but also movement preparation involving postural features related to the dopaminergic deficit [44]. In fact, interesting correlations between APA duration and clinical features emerged. The timing alteration of APAs was related to worst dynamic stability and greater limbs rigidity, assessed by FSST and MDS-UPDRS Rigidity subscore re-spectively. Limbs rigidity and dynamic stability were strongly connected, as body rigidity decrease the ability to control the center of mass with the feet in place, requiring frequent steps to maintain balance [45]. Consequently, it is not surprising that these characteristics were significantly correlated with the APAs duration. Instead, the strong negative correlation between APAs timing alteration and the FOG symptom was unexpected. Longer durations of the APA phase (i.e. worst performance) was as-sociated to a lower severity of FOG. This association reflects the differences emerged between FOG+ and FOG-, with FOG+ showing a reduction of APAs duration compared to FOG-, indicating a better performance of FOG+. This result was opposite to what was expected, since FOG symptom is associated with less automatic gait and more impaired postural transitions compared to persons with PD who do not have FoG [46]. This result could be ascribed to the use of the auditory stimulus (i.e., "go") prior to the step, as the evidence regarding the external cueing effects in patients with PD with FOG suggest that cue-trigger use improves gait parameters [47,48], especially for the preparation of GI [49,50]. Indeed, it has been shown that auditory cues appear to make use of a prompt motor entrainment to an external beat, activating the frontoparietal control and motor cerebellar networks to override internal rhythm deficits of the basal ganglia [51]. Therefore, we could hypothesize that FOG+ participants had greater benefits from the auditory cues with respect to FOG- participants. It is interesting noticing that the APA parameters strongly correlated with the two sub-scores of the MDS-UPDRS III associated to limb rigidity and FOG, but not with its overall score. This could be related to the fact that the final score of the MDS-UPDRS III is obtained by the sum of motor items that are not only specific to balance stability and gait, but also related to several other symptoms (e.g. speech, facial mimic, finger taps), which are probably not relevant for the APA performances.

The APA Onset, quantified by the parameter Time-to-APA, was comparable between person with PD and healthy subjects. This was probably due to the stimulus used. In fact, sensory cues, such as the auditory ones, can facilitate GI in PD patients, speeding up the APA reaction onset [52]. APA onset moderately correlated with the SPPB, FAB and its sub-part specific for planning. Greater latencies in the onset of APAs were associated with less dynamic stability and greater impairment of executive functions, confirming that the preparation of GI is associated with both the motor and cognitive domains. It should be noted that, among GI metrics, APA onset parameter was the measure that most reflected motor-planning processes, being associated with the FAB-2 planning score that assess the residual functions of the frontal lobe structures mainly delegated to the movement control.

This correlation further highlighted that the parameters extracted from the IMUs are related to pathophysiological mechanisms.

All of the above correlations between the GI metrics and the clinical evaluations of persons with PD demonstrated that the concurrent validity of the single IMU-base algorithm was good.

The present study has some limitations. First, the algorithm provides only temporal measures of gait initiation and not information regarding the CoP displacement or the APA magnitude. Hence, the algorithm should be improved by integrating these additional measures. Second, we tested the accelerometer-based method for the quantifica-tion of the APA only during gait initiation. Future studies should test the APA detection algorithm on the performance of other daily tasks. Finally, the PD participants were classified between 1 and 3 according to the H&Y scale (mild to moderate PD). Thus, the ability of the algorithm to detect differences in more homogeneous groups should be further investigated.

5.6 Conclusions

The acceleration -based algorithm tested in this study is a promising tool for assessing GI of persons with Parkinson's Disease. Results of the validity procedure conducted in this study demonstrated a strong agreement between a single IMU-based measurement system and the platforms acquisition system to estimate the APAs timings. In addition, the GI metrics were associated with clinical features of persons with PD, being able to discriminate between persons with PD who experienced freezing of gait and those that did not. APA impairment is a common feature among subjects with different neuro-logical diseases and therefore, future studies to validate the method on subjects affected by other neurological disorders, such as Multiple Sclerosis, are encouraged. In fact, a recent study highlighted that in the early stage of multiple sclerosis, although the APA of GI are strongly affected, there are no significant alterations of the executive phase [53], suggesting that APA is probably a reliable biomarker for early detection of motor deficits. Our results support the development of monitoring and telerehabilitation protocols through the use of a simple GI testing system. In fact, to obtain long-term effects of gait rehabilitation, it is necessary to train the APAs, which are needed to walk as physiologically as possible. Here we have shown that it is possible to detect the fundamental GI events (i.e. APA onset, toe-off and heel strike of the swing leg) starting from a single wearable sensor in PD. This sets the basis for the development of home-based training including exercises on the preparation phase, never realized so far. The GI testing system here presented could be a valuable tool for home-based re-habilitation programs yielding to a high patient adherence and a low risk of adverse events. Future studies should indeed investigate the patient satisfaction with the usability of

the system, as well as the potential improvement of walking performances and quality of life aspects related to the use of the single sensor system for GI detection in persons with neurological diseases.

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6 Conclusions and future developments

This thesis have the objective of adding a piece of knowledge about the neurophysiological basis of usual and complex gait in healthy subjects and in people with PD by means of movement analysis methodologies.

Overall, our results highlighted some relevant findings regarding: (i) the protective strategy adopted by subjects with PD to manage their dynamic balance deficit; (ii) the development of home-based rehabilitation protocol based on a single wearable sensor to improve the anticipatory postural adjustments in subjects with PD; (iii) the effects of music evoked-emotions on visual-spatial learning in elderly and in subjects with PD; (iv) the correlates of emotions aroused by the common real-life sounds with the FOG symptom experienced in subjects PD.

Although physiotherapy is considered an essential intervention to improve independence and quality of life of PD patients, the development of innovative, multi-domains, and personalized treatment, to support patients along the course of the disease is still needed. Nowadays, the availability of cost-effective technologies, able to detect movements in ecological settings (e.g. home, outdoor activities), allow researchers to deeply investigate motor and cognitive disturbances induced by PD.

Humans are emotional beings. We have the ability to accept and give love, feel anger and fear, experience shame, guilt, and humiliation, transform with joy, pride, and elation, and so much more. Our ability to be emotional sets us apart from other living beings in the world. And it’s our emotional responses to stimuli in our world that can either bring out the best or the worst from us.

The results reported in this project (Section 2 and 3) suggest that emotions play an important role in motor and cognitive ability in healthy subjects and in subjects with PD. In the more advanced stages of the disease more severe symptoms appear such as FOG, which is a very disabling episodic symptom. For this reason, a part of this thesis has been focused on trying to understand what the triggering factors of FOG may be. Based on the study of APAs, which are fundamental movements for dynamic balance and for the integrity of walking, it emerged that the unpleasant emotions can be among the triggering factors of the FOG symptom in subjects with PD. We compared behavioral data from a cohort of PD participants with or without the FOG symptom during gait initiation, to investigate which among the most realistic circumstances involving emotional factors may influence gait patterns. The main finding of our study was that the influence of auditory emotional stimuli on automatic movement during gait initiation is different in subjects with and without FOG. In particular, the negative-oriented auditory stimuli (i.e., unpleasant stimuli) reduced the APA generation in PD

patients with FOG, while positive-oriented ones (i.e., pleasant stimuli) facilitate the APA displacement. In addition, we found that this emotion-evoked behavior was mainly associated with non-motor domain factors, such as depression, confirming the role of non-motor symptoms in the developing of the FOG.

The results of cross sectional studies conducted in this project (Section 4 and Section 5) highlighted the possible lines of development on rehabilitation protocols to improve the dynamic balance in subjects with PD and increase their effects with testing protocols applicable in a home-based setting. The training as constant as possible could prolong the maintenance of the beneficial effects after the end of therapy. The availability of easy-to-administer tests for the evaluation of balance control and motor skills makes a realistic scenario the one in which similar solutions will be soon adopted in the tele-monitoring of community-dwelling healthy elderly and neurological patients, offering the possibility of an early diagnosis and fast intervention. The possibility to learn new motor strategies in a familiar domestic environment could be of high value for the patient, since it could enable the possibility to directly improve activities that are really conducted in that setting on a daily basis, thus assisting the final users in preserving their lifestyle, autonomy and health.

Our results support previous finding, suggesting that emotional management (also known as emotion-focused therapy), which assumes that lacking emotional awareness or avoiding unpleasant emotions can cause harm, might be an adjunctive therapeutic intervention to improve gait and balance performance in PD patients and in particular in those who experience FOG. Future studies should investigate whether adding emotion-focused training to physiotherapy might reduce the effects of FOG in individuals with Parkinson's disease.

7 Chapter PhD activities

7.1 Publications related to the PhD thesis

Strategies for maintaining dynamic balance in persons with neurological disorders during overground walking.
T. Lencioni, D. Anastasi, I. Carpinella, A. Castagna, A. Crippa, E. Gervasoni, A. Marzegan, M. Rabuffetti, E. Pelosin, D. Cattaneo, M. Ferrarin.
Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2021, 235: 1079-1087.

Events Detection of Anticipatory Postural Adjustments through a Wearable Accelerometer Sensor Is Comparable to That Measured by the Force Platform in Subjects with Parkinson's Disease.
T. Lencioni, M. Meloni, T. Bowman, A. Marzegan, A. Caronni, I. Carpinella, A. Castagna, V. Gower, M. Ferrarin, E. Pelosin.
Sensors 2022, 22: 2668.

The effect of music-induced emotion on visual-spatial learning in people with Parkinson's disease: A pilot study
T. Lencioni, C. Ponte, C. Cosentino, S. Mezzaroba, I Carpinella, M. Ferrarin, L. Avanzino, G. Lagravinese, E. Pelosin
Parkinsonism & Related Disorders 2022, 94: 120-123.

7.2 Other publications during PhD period

Smoothness of movement in idiopathic cervical dystonia
A. Caronni, P. Arcuri, I. Carpinella, A. Marzegan, **T. Lencioni**, M. Ramella, A. Crippa, D. Anastasi, M. Rabuffetti, M. Ferrarin, A. Castagna.
Scientific Reports, 2022, 12: 5090

The Falls Efficacy Scale International is a valid measure to assess the concern about falling and its changes induced by treatments
A. Caronni A, M. Picardi, V. Redaelli, P. Antoniotti, G. Pintavalle, E. Aristidou, G. Gilardone, I. Carpinella, **T. Lencioni**, P. Arcuri, M. Corbo

Clinical Rehabilitation, 2022, 36: 558–570

A randomized controlled trial on the effects induced by robot-assisted and usual-care rehabilitation on upper limb muscle synergies in post-stroke subjects
Scientific Reports, 2021, 11:5323

Sequentially applied myoelectrically controlled FES in a task-oriented approach and robotic therapy for the recovery of upper limb in post-stroke patients: A randomized controlled pilot study
G. Perini, R. Bertoni, R. Thorsen, I. Carpinella, **T. Lencioni**, M. Ferrarin, J. Jonsdottir.
Technology and Health Care, 2021, 29: 419–429

Improved Gait of Persons With Multiple Sclerosis After Rehabilitation: Effects on Lower Limb Muscle Synergies, Push-Off, and Toe-Clearance
J. Jonsdottir, **T. Lencioni**, E. Gervasoni, A. Crippa, D. Anastasi, I. Carpinella, M. Rovaris, D. Cattaneo, M. Ferrarin.
Frontiers in Neurology, 2020, 11: 668

Measures of dynamic balance during level walking in healthy adult subjects: Relationship with age, anthropometry and spatio-temporal gait parameters
T. Lencioni, I. Carpinella, M. Rabuffetti, D. Cattaneo, M. Ferrarin
Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2020, 234: 131–140.

Effects of robot therapy on upper body kinematics and arm function in persons post stroke: a pilot randomized controlled trial
I. Carpinella, **T. Lencioni**, T. Bowman, R. Bertoni, A. Turolla, M. Ferrarin, J. Jonsdottir
Journal of NeuroEngineering and Rehabilitation, 2020, 17: 10.

The LAMB gait analysis protocol: Definition and experimental assessment of operator-related variability
M. Rabuffetti, A. Marzegan, A. Crippa, I. Carpinella, **T. Lencioni**, A. Castagna, M. Ferrarin,
Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2019, 233: 342–353

Human kinematic, kinetic and EMG data during different walking and stair ascending and descending tasks
T. Lencioni, I. Carpinella, M. Rabuffetti, A. Marzegan, M. Ferrarin.
Scientific Data, 2019, 6: 309

Clinical validity of novel postural stabilization experimental indices based on hyperbolic transformation
M. Rabuffetti, **T. Lencioni**, D. Cattaneo, P. Quadri, M. Ferrarin.
Gait and Posture, 2019, 67: 147–150

7.3 Conference abstracts

LIMPE-DISMOV (Accademia per lo Studio della Malattia di Parkinson e i Disordini del Movimento) 2021. Poster.
1) Effetto di una musica emozionante sull'apprendimento visuospaziale in pazienti con malattia di Parkinson
G. Lagravinese, **T. Lencioni**, M. Putzolu, C. Ponte, C. Cosentino, L. Avanzino, G. Bonassi, S. Mezzarobba.
2) Aggiustamenti posturali anticipatori e malattia di Parkinson: effetti degli stimoli uditivi con carica emotiva
A.V. Milner, M. Meloni, F.L. Saibene, A. Castagna, G. Fusaroli, M. Ferrarin, E. Pelosin, E. Pelosin, **T. Lencioni**.

SIAMOC (Società Italiana di Analisi del Movimento in Clinica) 2021 Oral Presentation.
The analysis of gait initiation using a wearable sensor detects specific-disease feature in subjects with Parkinson's Disease
T. Lencioni, M. Meloni, T. Bowman, A. Marzegan, G. Fusaroli, A. Caronni, I. Carpinella, M. Ferrarin and E. Pelosin.

LIMPE-DISMOV 2020. Poster.
Emotional state modulates gait initiation in individuals with Parkinson's disease differently from healthy subjects.
T. Lencioni, T. Bowman, A. Marzegan, A. Castagna, C. Cosentino, L. Avanzino, M. Meloni, M. Ferrarin, E. Pelosin.

SIN (Società Italiana di Neurologia) 2020. Oral Presentation.
Emotional state modulates gait termination differently in PD patients with or without freezing of gait
T. Lencioni, M. Meloni, T. Bowman, A. Marzegan, A. Castagna, C. Cosentino, M. Putzolu, M. Ferrarin, E. Pelosin.

SIAMOC 2019. Poster
'AEGON' Project: Auditory-emotional stimuli and gait in Parkinson's disease
T. Lencioni, C. Cosentino, T. Bowman, I. Carpinella, A. Marzegan, A. Caronni, A.Castagna, D. Cattaneo, M. Meloni, M. Ferrarin, E. Pelosin
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