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BIOFEEDBACK BASED PHYSICAL REHABILITATION IN PARKINSON'S DISEASE AIMED AT SELF-ENHANCEMENT

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Alla mia famiglia

"It is the mind which is really alive and sees things, yet it hardly sees anything without preliminary instruction."

JEAN-MARTIN CHARCOT
(1825 - 1893)

Abstract

Parkinson's disease (PD) is a progressive neuromotor disorder that results in a progressive deterioration of balance and motor abilities with a consequent increase of the risk of falls and a reduction of quality of life.

Physical therapy revealed to be fit for the symptomatic treatment of the disease and the adoption of biofeedback signals showed to be effective in prolonging the benefits of the therapy.

Thus, this doctoral project has been designed to assess the benefits that wearable technologies for biofeedback generation could have in physical therapy. To further improve the developed biofeedback-based system, the assessment of new methods for the objective evaluation of balance control was included into the study.

The dissertation is divided into three different set of studies, respectively aimed at: 1) presenting new wearable systems specifically designed for biofeedback-based rehabilitation; 2) assessing proprioceptive impairments in PD subjects through the adoption of a robotic platform to destabilize the base of support; 3) discussing new methods for the evaluation of balance preceding the execution of voluntary movements.

The efficacy of the main proposed solution was assessed in a 6-months RCT study by comparison of subjects with PD trained with the biofeedback system and patients that received usual care. Both clinical and instrumental outcomes supported the higher efficacy of the biofeedback-based approach. The developed instrumented tests showed good sensitivity in discriminating patients and in detecting changes induced by physical therapy.

The results reported in this thesis lead to the conclusion that the adoption of biofeedback based physical rehabilitation systems is promising in the treatment of Parkinson's disease. The availability of a set of fast, easy-to-manage tests for the evaluation of balance and motor control might be useful in the design of home-delivered, user-tailored exercises for both healthy elderly and neurological subjects.

Keywords

Parkinson's disease
Physical therapy
Augmented feedback rehabilitation
Wearable sensors
Balance control
Anticipatory postural adjustments

List of Publications

International Peer-Reviewed Journals

1. **G. Bonora**, M. Mancini, I. Carpinella, L. Chiari, F. B. Horak, M. Ferrarin. *Gait initiation in subjects with Parkinson's disease in the OFF state: evidence from the analysis of the anticipatory postural adjustments.* Submitted to Clinical Biomechanics.

2. **G. Bonora**, I. Carpinella, D. Cattaneo, L. Chiari, M.Ferrarin. *A new instrumented method for the evaluation of gait initiation and step climbing based on inertial sensors: a pilot application in Parkinson's disease.* Journal of Neuroengineering and Rehabilitation 2015 May 5; 12:45.

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1. **G. Bonora**, I. Carpinella, D. Cattaneo, L. Chiari, M. Ferrarin. *Evaluation of the initiation of level walking and stair ascending in Parkinson's disease: An instrumented method based on inertial sensors.* Gait & Posture 2015; 42,S88.

2. I. Carpinella, D. Cattaneo, **G. Bonora**, M. Ferrarin. *Instrumented finger-to-nose test for the quantitative assessment of intention tremor in multiple sclerosis: A Hilbert-Huang-based approach.* Gait & Posture. 2015; 42:S34.

3. **G. Bonora**, I. Carpinella, E. Casati, D. Cattaneo, L. Chiari, M. Ferrarin. *Development of a new intrumented system for evaluating the "stair negotiation" based on inertial sensors.* Gait & Posture 2014; 40:S4-S5.

National Conference Proceedings

1. **G. Bonora**, I. Carpinella, M. Rabuffetti, T. Bowman, D. Cattaneo, F. Patané, P. Cappa, M. Ferrarin. *Postural stabilization following dynamic perturbations of the supporting base: feasibility and preliminary results on healthy subjects and patients with Parkinsons disease.* Proceedings of the XVI National Congress of SIAMOC, Padova, Italy, October 2015.

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Chapter 1

Introduction

1.1 Objectives of the thesis

Parkinson's disease (PD) is a progressive neuromotor disorder that mainly affects people aged 60 years or older and represents the second most common neurological disease worldwide after Alzheimer's dementia (Olanow et al. 2009). The illness is caused by a progressive loss of dopaminergic neurons in correspondence of the basal ganglia that results, in particular, in a progressive impairment of the natural neural pathways associated with voluntary motor activities.

Typical symptoms of PD are akinesia, bradykinesia, rigidity, tremor, difficulties in balance and walking. Motor symptoms make their appearance when a loss of at least 70% of the substantia nigra within the basal ganglia is reached (Bernheimer et al. 1973). Non-motor deficits (e.g. sleep disorders, depression, dementia) may appear in later stages. As a consequence of the disease progression, patients may experience difficulties in performing activities of daily living and a general reduction of the quality of life. Motor symptoms, in particular, may lead to an increase of the fear of falling and risk of falls, with a correspondent loss of self-confidence and autonomy. The real causes undergoing the dopaminergic depletion have still to be clarified, thus, people with Parkinson's disease are still waiting for an effective cure. Although no available therapies alter the underlying neurodegenerative process, symptomatic pharmacological treatment can improve patient's quality of life. In addition, surgical interventions are available for symptoms relief in advanced stages. Because of the long-term medication-induced side effects and of the level of risk inherent in any brain surgery, the interest for alternative therapies that may enforce the primary pharmacological treatment is rising. In previous studies, physical therapy revealed to be effective in slowing down the symptomatic progression and in increasing quality of life (Oguh et al. 2014). Usual therapy comprehends both quasi-static and dynamic exercises mainly focused on balance control and it is administered by professional physiotherapist in equipped physical rehabilitation settings.

Previous studies showed that beneficial effects can be brought by motor learning, especially if biofeedback signals are used (Abbruzzese et al. 2009): the presence of an appropriate well-timed stimulus (e.g. acoustic, visual or vibrotactile signal) may help the patient in focusing on the crucial aspect of a complex motor task, thus transforming an automatic motor response in a conscious gesture. This motor adjustment in the execution of the task makes the motor response explicit, thus involving brain regions typically linked to voluntary movements with a consequent reduced intervention of the damaged area. Furthermore, Marchese et al. (Marchese, Diverio, et al. 2000), after testing a 6-week physical therapy protocol, consisting of postural control stimulation, exercises for articular mobility and oscillations in different positions, reported a higher short term efficacy when an external cue signal was adopted for the execution of the exercises.

At the state of the art, exercises that integrate biofeedback signals or virtual reality are now often included in game consoles as an off-the-shelf cost-effective and commonly accepted gaming product. However, these solutions are often intended for mere entertainment or general well-being and active ageing practices while only few evidences emerged about the possible beneficial effects provided by the integration of such technologies in the usual treatment of neuromotor disorders.

These considerations support the idea of a possible useful adoption of biofeedback solutions in physical therapy practice for subjects with PD. The BIOPHASE (*"Biofeedback based Physical rehabilitation in Parkinson's disease Aimed at Self-Enhancement"*) doctoral project has been designed to develop an innovative rehabilitation system for making the training experience more engaging and, consequently, improving the beneficial effects of the physical therapy.

Main objective of this thesis is the evaluation of the effect that the adoption of wearable technologies and biofeedback could have in the physical rehabilitation of Parkinson's disease. Indeed, even though some results about cue and biofeedback driven exercises are already present in literature, the potentiality of biofeedback in a complete multifactorial training has still to be assessed. Moreover, the usage of wearable sensing devices suggests the possibility of a prosecution of the training in a domestic environment. Hence, the development of tests based on the same technology for the tele-monitoring of the training efficacy is of great interest. Thus, this thesis has been divided into different development steps, that are:

- To develop a wearable system for the generation of real-time biofeedback signals to be used during rehabilitation sessions conducted in a typical institutional setting (i.e. rehabilitation gym) under the direct supervision of a trained therapist. The developed system has been finally tested on Parkinson's disease affected people during a 6-week training intervention. For this aim, we determined: i) the users' final satisfaction in the adoption of the wearable system; ii) the efficacy of the treatment; and iii) the beneficial effects induced by the biofeedback adoption in comparison with traditional physical rehabilitation practice.

- To realize a single waist-mounted wearable prototype for biofeedback based gait rehabilitation. In particular, an effort to minimize the system computational cost for preserving battery life was conducted. A new algorithm for real-time step recognition has been specifically designed for the adoption in embedded systems. The developed solution has been tested off-line on data previously recorded from PD patients. For this aim, the following parameters were extracted: i) mean absolute errors between the foot contact instants calculated by the new algorithm and the de facto gold standard, and ii) the sensitivity of the step recognition method.

- To investigate proprioceptive deficits in Parkinson's disease. A new method for testing the ability to promptly react to modifications of the base of support was developed and applied in a pilot study on PD patients and healthy subjects of different ages. The reaction time to randomized controlled perturbations and the performance in going back to the horizontal configuration of the platform have been analyzed.

- To develop instrumented methods for the evaluation of the anticipatory postural adjustments (APAs) preceding specific voluntary movements. A new solution has been developed for the evaluation of APAs preceding gait initiation and step climbing. The method has been validated in a motion analysis laboratory on PD patients in their practical medication-ON state and healthy subjects of different ages and later applied in a pilot study on PD patients in a typical rehabilitation gym. In a second study, the proposed solution was adopted for assessing gait initiation on patients in their practical medication-OFF state. Finally, an instrumented one-leg stand test based on wearable inertial sensors was designed to assess balance deficits in different neurological disorders. Spatio-temporal parameters were extracted to investigate both the anticipatory and the practical balance phases.

1.2 Parkinson's disease

Parkinson's disease is the second most common degenerative disorder of the nervous system after Alzheimer's dementia, counting more than 5 million cases worldwide (Olanow et al. 2009). The disease usually begins in the fifth or sixth decade and the frequency increases with advancing age. The prevalence rates of PD increase with age, as these neurodegenerative conditions gradually become symptomatic with aging (Nussbaum et al. 2003), rising from 425 in every 100.000 people between 65 and 74 years old to 1903 in every 100.000 people with more than 80 years (Pringsheim et al. 2014). No apparent plateau was noticed in the prevalence rising trend (Wright Willis et al. 2010). Epidemiologic studies conducted on the US population showed that the age-standardized prevalence and incidence were greater in men than in women for all races, with a mean prevalence sex ratio of 155 males per 100 females and mean incidence sex ratio of 146 males per 100 women (Wright Willis et al. 2010). Furthermore, Whites were reported having a substantially higher prevalence and incidence in PD than Asians and Blacks (Wright Willis et al. 2010).

The disorder was acknowledged and described for the first time by James Parkinson in 1817 in his most famous work titled: *"An essay on the shaking palsy"* (Parkinson 2002). In his pamphlet the British scientist introduce the disorder as "Shaking Palsy" (*"Paralysis Agitans"*), capturing the clinical picture:

> *"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with propensity to bend the trunk forwards, and to pass from walking to a running pace: the senses and intellect being injured."*

Over fifty years later, Jean-Martin Charcot, considered the French father of the modern neurology, referred for the first time to the illness as Parkinson's disease" and offered a more complete description of the disorder, recognizing bradykinesia as one of its cardinal features (Charcot 1872):

> *"Long before rigidity actually develops, patients have significant difficulty performing ordinary activities: this problem relates to another cause. In some of the various patients I showed you, you can easily recognize how difficult it is for them to do things even though rigidity or tremor is not the limiting feature. [...] In spite of tremor, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action there is a considerable time lapse."*

However, the most complete pathological analysis of PD and its origin from brain stem lesions was given only in 1953 by Greenfield and Bosanquet (Greenfield et al.

1953). In 1967, Hohen and Yahr contribute to the research in Parkinson's disease offering a deeper view in the morbidity and clinical progression of the disease. In their important article (Hoehn et al. 1967), they introduced a clinical scale for the evaluation of the disease stage based on the observation of motor symptoms, that is still one of the most adopted staging system for PD worldwide.

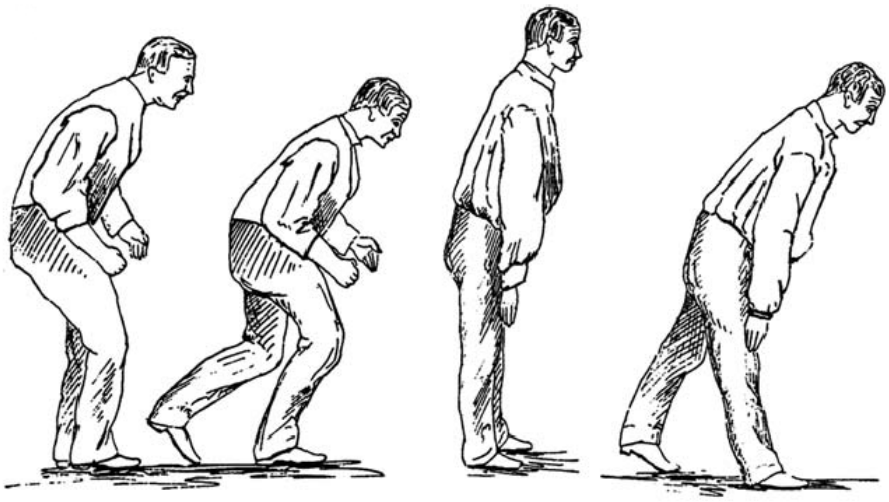

Figure 1.1: Drawing from one of the Charcot's original lesson in which he compared a typical Parkinson's disease posture (left) with Parkinsonian variants.

As brilliantly noticed in the above mentioned contributions and reported in several other articles, the primary manifestations of PD are typical symptoms affecting neuromotor system, including tremor at rest, slowness of movements (bradykinesia), akinesia, movement start hesitation, balance difficulties, postural and gait instability. Affected people generally present also rigidity in the extremities and the neck, with a possible reduction of the swing of the upper and lower limbs. In particular, the reduction of the arm oscillation during gait represents one of the earlier clinical signs for the initial diagnosis (Redgrave et al. 2010). The walking pattern is typical and it is characterized by short steps, stooped position, and difficulties in turning. 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 (Djaldetti et al. 2006). 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 (Ou et al. 2016; Antonini et al. 2015; Bloem and Stocchi 2012). Depression and dementia are also associated with the progression of the disease (Zweig et al. 2016; Martinez-Martin et al. 2015). In addition, it is reported that almost the totality of patients suffers of delayed gastric emptying (Pellegrini et al. 2015) and accounts for early satiety, bloating, nausea, vomiting and weight loss (Goetze et al. 2006).

Taken altogether, physical and mental disabilities related to Parkinson's disease can have significant impact on different dimensions of quality of life and activities of daily living (ADL) (Irwin et al. 2012). For example, tremor and rigidity influence manual dexterity and reduce ability to perform daily activities, while gait disorders and postural instability increase the risk of falls with critical consequences for functional ability and quality of life (Bloem, Hausdorff, et al. 2004; Grimbergen et al. 2004). It was demonstrated that typical walking difficulties, turning hesitations, and limited capability to climb stairs are strictly related to Fear of Falling in Parkinson's population (Nilsson et al. 2012). Furthermore, due to the above mentioned motor deficits, people affected by Parkinson's disease have an increased risk of falling when compared to healthy subjects of comparable age (Allen et al. 2013).

Considering other factors that may impact the patients' quality of life, the progressive loss of dopamine, as well as pharmacological interaction in dopaminergic treatments, can induce psychiatric disorders (F. Schneider et al. 2008). A percentage between 70% and 85% of patients with PD suffers from anxiety, depression, hallucinations, delusions, or behavioural disorders. Depressive disorders affect almost 40% of the patients, while anxiety disorders in PD present a prevalence between 25 and 45 percent (Dissanayaka et al. 2010; Rutten et al. 2015). Between neurovegetative disorders, it is reported in literature that insomnia symptoms, including difficulty of initiating sleep, disruptive sleep, and non-restorative sleep, are quite common in patients, with a higher prevalence of diagnoses respect to general population (Ylikoski et al. 2015). Nocturnal disturbances detected by the extended version of the PD sleep scale (PDSS-2) showed to be associated with higher Hoehn and Yahr stages and Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, impaired quality of life, daytime sleepiness, and depressive symptoms (Suzuki et al. 2015).

Due to the aging progress of the world population, it is estimated that in 2020 more than 40 million people in the world will suffer for Parkinson's disease (Morris 2000) and that the prevalence of PD in world's most populous nation will at least double by 2030 (Dorsey et al. 2007). As a consequence of these projections and of the great variety of debilitating symptoms, PD will have a progressively increasing impact also under the socio-economical perspective. It was previously reported that PD motor symptoms frequently lead to loss of independence, falls with a consequent increase of the fear of falling, injuries, and inactivity. The consequent social isolation and increasing risk of osteoporosis or cardiovascular disease (Bloem, Vugt, et al. 2001; Garrett et al. 2004) might cause an increasing of the costs (Pressley et al. 2003) and a contemporary decreasing of quality of life (Schrag et al. 2000). Taking into account the disability adjusted life years lost (DALY) - that is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death - Parkinson's disease is ranked at the 8^{th} place in the European ranking for DALY estimates for neuropsychiatric disorders for men, and at the 11^{th} place in the global rank. When only neurological disorders are considered, without listing the psychiatric ones, PD is ranked 3^{rd} both for men and women (after stroke and dementia) resulting as one of the most debilitating neurological diseases (Wittchen et al. 2011). Under an economical point of view, the total costs (direct health care costs, direct non-medical costs, and indirect costs) per patient is estimated in € 11153 per year, with a total annual cost in Europe of almost 14 billion euros (Olesen et al. 2012). Similar economical estimates are reported in studies conducted in the United States where the annual economic impact of PD has been estimated to exceed $ 14.4 billion (Kowal et al. 2013).

1.3 Neuromotor control circuitry

Proper execution of voluntary movements results from the correct processing of sensorimotor information by a complex neural network, which includes the cerebral cortex, the motor thalamus, and the basal ganglia nuclei. These structures operate together forming a complex structure of parallel and largely closed neural circuits (DeLong and Wichmann 2015). Of the three neural structures the major role in the motor control procedures is carried out by the basal ganglia circuit that is functionally interposed between the cortex and the thalamus (Blandini 2001). The term basal ganglia refers to a large and functionally diverse set of nuclear structures that lie deep within the cerebral hemispheres; this complex structure includes the caudate, putamen and the globus pallidus (GP).

Due to the close association with the motor functions of the basal ganglia, two additional neural structures, the substantia nigra and the subthalamic nucleus (STN) are generally associated with the basal ganglia nuclei. Under an anatomical point of view, the substantia nigra is divided in two parts, substantia nigra pars compacta (SNc) and pars reticulata (SNr), and located in the base of the midbrain, while the subthalamic nucleus is in the ventral thalamus. As above mentioned, the basal ganglia nuclei with, in addition, the substantia nigra and the subthalamic nucleus form a subcortical loop that connects different areas of the cortex. Within the complex structure of the basal ganglia nuclei, it is possible to distinguish an input and an output zone. The input signals originated from the cerebral cortex enter the basal ganglia region through the corpus striatum, which includes the caudate and the putamen, and after being elaborated are sent to the thalamus via the medial globus pallidus and the substantia nigra pars reticulata. Finally, the elaborated

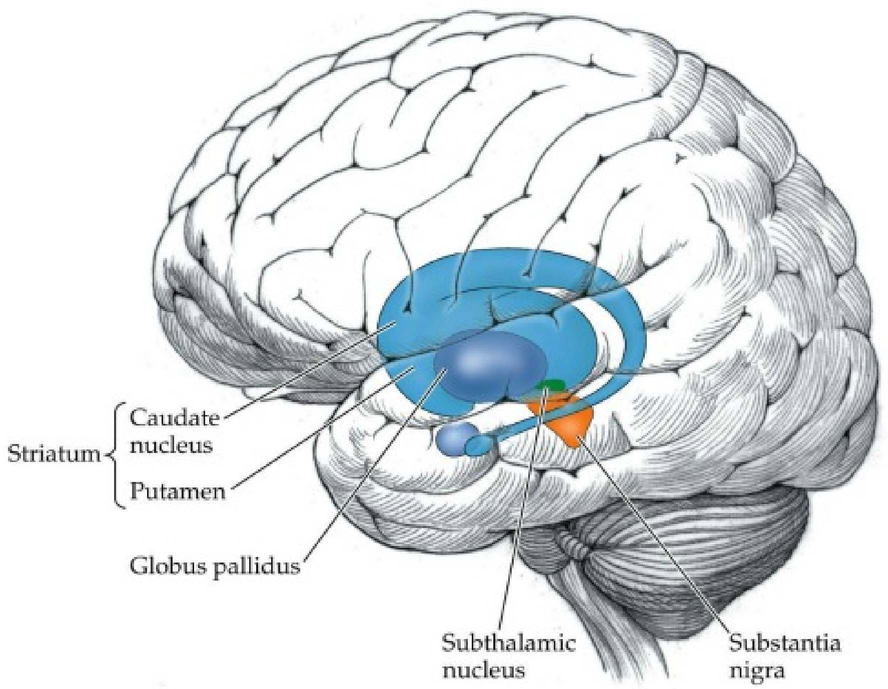

Figure 1.2: Anatomical localization of thalamus and basal ganglia viewed from the left.

signals reach their individual sites of origin in the frontal lobe passing through the thalamus.

Three different anatomically and functionally separated circuits, named motor, associative, and limbic loops, can be identified on the basis of the function of the involved cortical area: (Alexander, DeLong, et al. 1986; Alexander and Crutcher 1990; Kelly et al. 2004; Middleton et al. 2000).

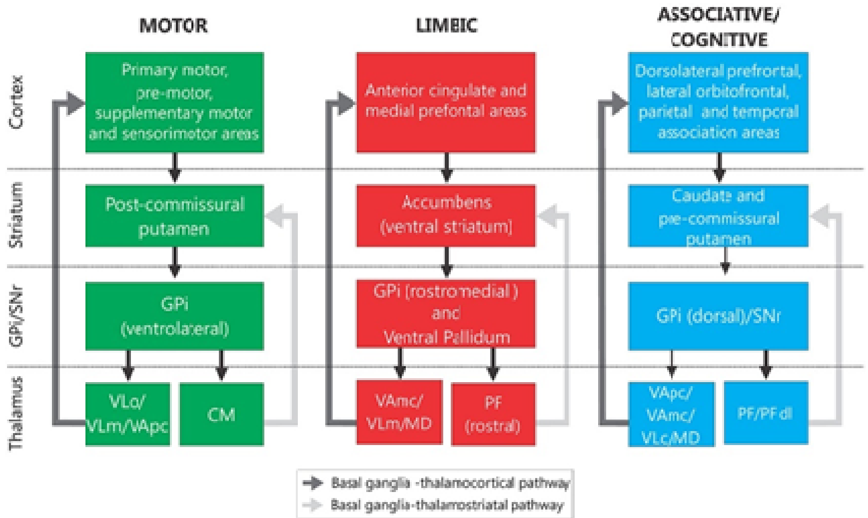

Figure 1.3: Segregated basal ganglia-thlamocortical and basal ganglia-thalamostriatal functional loops.

Focusing on the motor loop, in accordance with a very popular model (Albin et al. 1989; Alexander and Crutcher 1990), the transmission of the signals from the input to the output areas of the basal ganglia is performed via a monosynaptic "direct" striatal projection, and an textit"indirect" pathway, which includes projections to the external segment of the globus pallidus (GPe), and from GPe to the internal pallidal segment (GPi), both directly and through the intercalated STN. The correct activation of neural circuitry for motor control at the level of the basal ganglia is regulated by a very fine tuning of several neurotransmitters: dopamine, gamma-aminobutyric acid (GABA), enkephalin, glutamate, acetylcholine, and substance P (Alexander and Crutcher 1990). The direct and indirect pathways differ for the kind of interaction with those neurotransmitters. Moreover, the two pathway have different effects in the basal ganglia output; activation of direct pathway neurons would lead to inhibition, while activation of the indirect pathway would lead to disinhibition of GPi/SNr neurons. Because basal ganglia output is inhibitory, the activation of neurons of the direct pathway would lead to disinhibition of the thalamocortical activity, while the activation of the indirect pathway, on the contrary, would produce an increase of the inhibition of the thalamocortical projections (Delong et al. 2009).

Some criticism and limitations in the direct-indirect pathways model have still to be assessed. In particular, it has to be noticed that recent anatomic studies have shown that the separation between the two pathways could be weaker than initially hypothesized (Parent et al. 2000). In addition, the impact of different conduction velocities along the two pathways on the timing of the inhibition-disinhibition mechanism have to be further investigated. This problem was already addressed in the specific movement-related *"focusing"* function invoking the existence of an additional *"hyperdirect"* cortico-subthalamic pathway that might permit to the cortical inputs to reach the basal ganglia via a faster non-striatal route (Nambu 2008; DeLong and Wichmann 2015). Even if the exact contribution of the direct-indirect model of the ganglia-thalamocortical circuitry in the regulation of sequencing movements and in the generation of internally generated or habitual movements is still partially unclear (Delong et al. 2009),the proposed model, the basic circuit model of the intrinsic connections between the basal ganglia, and the importance of dopamine in regulating the transmission at specific synapses in the striatum are commonly accepted and represent the current basis for the research and the development of new therapeutic approaches (Delong et al. 2009).

1.4 Pathophysiology of Parkinson's disease

It is already well established that the first symptoms to make their appearance in the developing of Parkinson's disease mainly affect the neuromotor system and that the progression of those manifestations is one of the major factors at the basis of the exhibited difficulties in performing the activities of daily living.

Under a pathophysiological point of view, the motor deficits associated with PD are mainly due to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) that is functionally strongly interconnected with the basal ganglia structures.

It has been demonstrated that the degeneration of dopaminergic neurons in the SNc and in their projections to the striatum is a slowly evolving process that may take decades to develop (Galvan et al. 2008). The earlier degeneration of SNc projections to the putamen respect to those linking the associative or limbic portions of the striatum justifies the fact that motor symptoms generally make their appearance before the non-motor ones. It has been reported that motor symptoms manifestate when the degenerative process impacts at least 70% of the nigrostriatal neurons (Bernheimer et al. 1973), and this fact may be one of the possible cause of the typical late diagnosis of PD, often with patients 55 years or older.

Dopamine depletion in the basal ganglia also triggers prominent secondary morphological changes, that may greatly alter the corticostriatal transmission (Ingham et al. 1989; Villalba et al. 2006), with modifications in the density and sensitivity of dopamine receptors, in particular D2-type receptors (Aubert et al. 2005; Bezard et al. 2001).

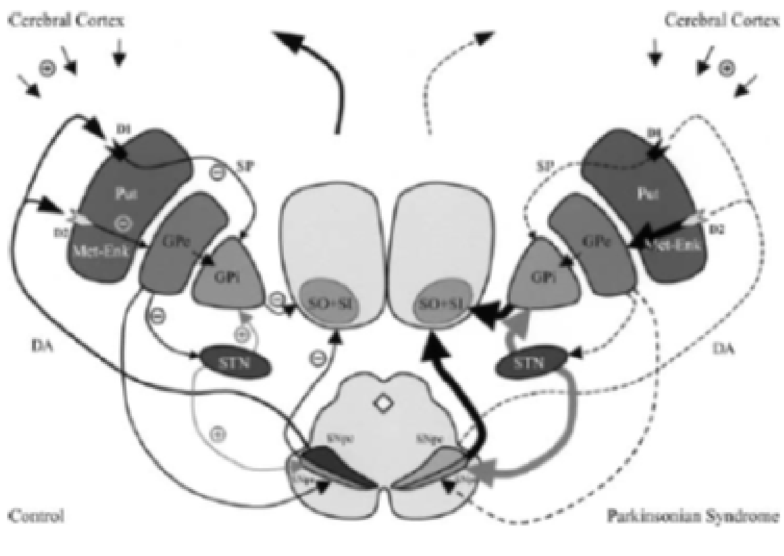

Figure 1.4: Cortico-basal ganglia-cortical circuitry in control brain (left) and in one affected by Parkinson's disease (right). Imbalance in both direct and indirect pathways is seen by the size of the arrows (as proposed in (Herrero et al. 2002)).

As a consequence of dopamine loss, and of the subsequent primary and secondary morphological changes, it is possible to detect abnormal changes in the neuronal activity of several brain regions, including basal ganglia, thalamus, and cortex.

Changes in the basal ganglia activity concern, in particular: altered firing rates, burst discharges, oscillations, abnormal synchrony, and changes in sensory response patterns and task-related activity.

Altered firing rates can be explained by the rate model of the pathophysiology of parkinsonism (Albin et al. 1989; DeLong 1990) as the result of disturbances of the balance of activity in the direct and indirect pathways. In particular, the loss of D2-receptor activation and the contemporary decrease of striatal D1-receptors may lead to an increase in the activity of GPi and SNr neurons with a consequent inhibition of neurons in the thalamus and brainstem (Albin et al. 1989; DeLong 1990).

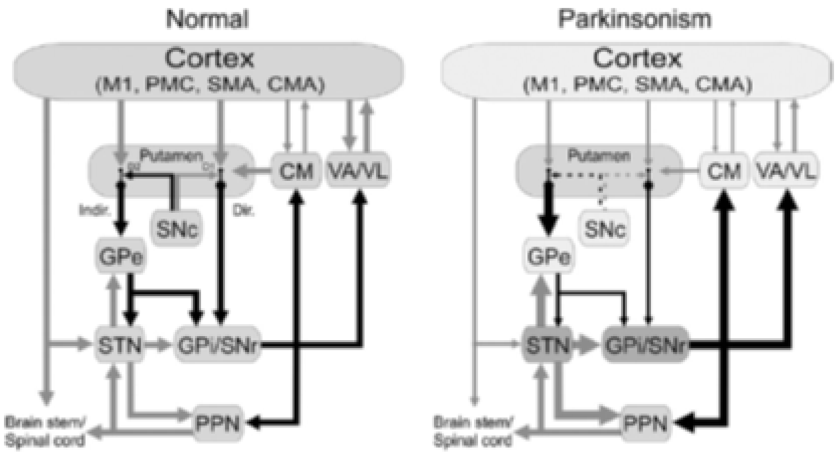

Figure 1.5: Rate model of parkinsonism-related changes in overall activity in the basal ganglia-thalamocortical motor circuit. Black arrows indicate inhibitory connections and the gray ones indicate excitatory connections. The thickness of each arrow corresponds to the correspondent presumed activity.

Bursting activity of the STN, along with changes in discharge rates and metabolic markers (Breit et al. 2007; Ni et al. 2001b; Vila et al. 2000) and the incidence of burst firing in the basal ganglia was reported to be high in PD (Hutchinson et al. 1994; Magnin et al. 2000). It is likely that bursting is related to dopamine loss in the striatum, but also the depletion reported in other basal ganglia regions, such as the STN, may be important (Ni et al. 2001a). The interplay between GPe and STN may contribute powerfully to the developments of burst discharges in both nuclei (Ni et al. 2001a; Plenz et al. 1999). Although it is likely that the emergence of excessive burst discharges alters information processing in the basal ganglia-thalamocortical circuitry, doubts remain as to whether bursting per se has pro-parkinsonian effects (Galvan et al. 2008). The emergence of abnormal oscillatory activity, both at the single-cell level and in larger ensembles of neural elements, is another distinct abnormality in the electrical activity of the basal ganglia neurons. It has been hypothesized that oscillatory activity would be induced by the periodical occurrence of burst activity in the basal ganglia neurons (Nambu et al. 2015). The typical oscillation range is in the tremor frequency ($4-9\,\mathrm{Hz}$) and beta frequency ($10-30\,\mathrm{Hz}$) bands. Oscillatory activity is also observed in the high, gamma frequency ($> 60\,\mathrm{Hz}$) (Nambu et al. 2015). The global effect of this pathological basal ganglia behaviour is supposed to have a prominent role in the showing off of movement disorders; in particular, while the oscillatory activity in the tremor band is suggested to be anti-kinetic, thus they represent one of the possible causes of akinesia and bradykinesia, the activity in gamma frequency band is believed to be pro-kinetic. Studies conducted on DBS implanted patients, showed that those oscillations likely reflect oscillatory synaptic or neuronal activities generated by large groups of neurons separated by considerable distances (Galvan et al. 2008). The mechanism undergoing the abnormal oscillator behaviour is not clear, even if it was speculated that changes in striatal activity may be the logical origin of the phenomenon (Galvan et al. 2008). It is more likely that changes in extrastraital basal ganglia, specifically the interplay between GPe and STN that may generate a sort of STN-GPe pacemaker, may be important in the development of oscillations (Galvan et al. 2008).

Abnormal high level of synchrony between neighbouring basal ganglia cells is another typical consequence of dopamine depletion that can be easily counteracted by the consumption of dopaminergic agents (Heimer et al. 2002; Levy et al. 2002).

Finally, while under normal conditions appropriate modulation of basal ganglia activity is controlled by the influence of proprioceptive inputs, the noticed reduction in the specificity of responses to those inputs (Rothblat et al. 1995; J. Schneider et al. 1996) and the increase in the proportion of neurons with excitatory responses (Boraud et al. 2000) may be due to abnormal basal ganglia processing, or may reflect abnormal cortical inputs to the basal ganglia. Through disruption of cortico-subcortical feedback mechanism that control the extent and speed of movement, they may contribute to abnormal scaling of movements and bradykinesia in PD (Wichmann et al. 1993).

Studies conducted using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) showed a reduction of the cortical activity in PD patients both at rest and during the performance of motor or cognitive tasks that could contribute in the appearance of PD motor symptoms. Cortical activation resulted strongly compromised in the supplementary motor area (SMA) and in the anterior cingulate cortex (Brooks 1997; Haslinger et al. 2001; Jahanshahi et al. 1995; Jankins et al. 1992; Playford et al. 1992; Samuel, Ceballos-Baumann, et al. 1997; Thobois et al. 2000; Turner et al. 2003). Considering that the activation of the SMA is critical in regulating the increase in neural activity required before a movement can be executed (Brotchie et al. 1991; Cunnington et al. 1995), and that it also ensures the correct timing of the movement termination, an incorrect functioning of the SMA might be involved in the reduction of movements' size and speed (bradykinesia) and, in the worst cases to the total inability to initiate movements (akinesia).

1.5 Balance impairments during quiet standing and voluntary movement initiation

Postural instability is one of the most disabling features of PD that can lead to a general deterioration of the balance control system (Rinalduzzi et al. 2015), thus representing a major cause in worsening the patients' physical and psychosocial disability. Postural instability is a common feature in PD (Smania et al. 2010) with patients in quiet stance typically presenting an alteration of the physiological postural sways consisting of higher velocity and frequency compared to healthy controls (Schoneburg et al. 2013) and exposes patients to unexpected falls (Marchese, Bove, et al. 2003). Starting from stage 2 of the Hohen & Yahr clinical scale (Hoehn et al. 1967), increased muscle tone in flexor muscles and an impaired proprioception, modifying the sense of position, contributing to the increasingly narrow stance and stooped posture (Burleigh et al. 1995; Schoneburg et al. 2013). This particular posture leads to a displacement of the body centre of mass (COM) over the base of support (Schoneburg et al. 2013) representing a dangerous behaviour for balance preservation.

Classically, examination of static posture is conducted through clinical inspection, while for the evaluation of postural responses under dynamic conditions several tests have been proposed. One of the most accepted and clinically adopted exam for testing dynamic posture is the so called *"pull test"* (fig. 1.6) in which the examiner stands behind the patients and pulls him backward suddenly by the shoulders. As a natural response to the perturbation, patients could take recovery steps to recover balance without falling; zero to one recovery step is considered a natural healthy behaviour, while two or more steps are associated with an alteration of the capability of maintaining postural stability and this fact clinically translates in loss of balance control (Rinalduzzi et al. 2015).

The term balance control extends the concepts at the basis of the definition of postural instability referring to a multisystem function intended for keeping the body upright while standing quietly as well as preparing to perform a voluntary movement. Balance control is needed to maintain the body appropriately oriented

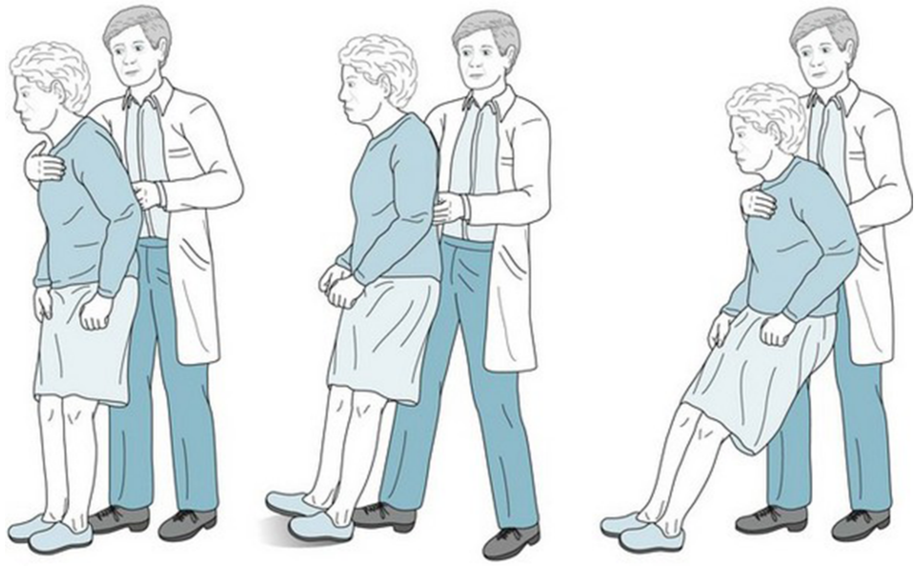

Figure 1.6: The "pull test" consists of the physician gently but rapidly pulling the patient's shoulders. Unaffected individuals will compensate by taking one or two steps backward. Patients suffering of Parkinson's disease, whose generally have impaired postural reflexes, will take many steps backward (i.e. have retropulsion), because they are unable to stop through weight-shifting compensatory maneuvers. In advanced stages of the disease, as the one pictured on the right, patient are unable to alter their posture and will tilt backward falling into the physician's arms.

while performing voluntary activity, during external perturbation, and when the support surface or environment change (Rinalduzzi et al. 2015).

The deterioration of balance control caused by PD contributes to the rise of the fall risk and fear of falling, and to the restriction of gait patterns and decreased mobility with a consequent loss of functional independence and possible social isolation (Rinalduzzi et al. 2015). The possibility to stand in an upright position is granted by the capability of maintaining the projection of the COM within the base of support. The sensorimotor control of posture that is the main requirement for postural stability is regulated by a complex integration of multisensory inputs that results in a final adjustment process (Rinalduzzi et al. 2015).

Responding to external stimuli requires three major concatenated procedures: i) activation of the sensory systems; ii) integration at the level of the central nervous system; and iii) formulation of a motor response aimed at maintaining the body centre of mass within the base of support of the subject (Bronstein et al. 2004).

Theoretically, it has been proposed that, in patients affected by PD, postural instability may be the result of faulty processing in three main distinct processes. Probably, the first pathological alteration involves the sensory organization in which one or more of the orientation afferences (i.e. visual, vestibular, and somatosensory inputs) are involved and integrated at the level of the basal ganglia. Secondly, the motor adjustment process aimed at providing a properly scaled neuromuscular

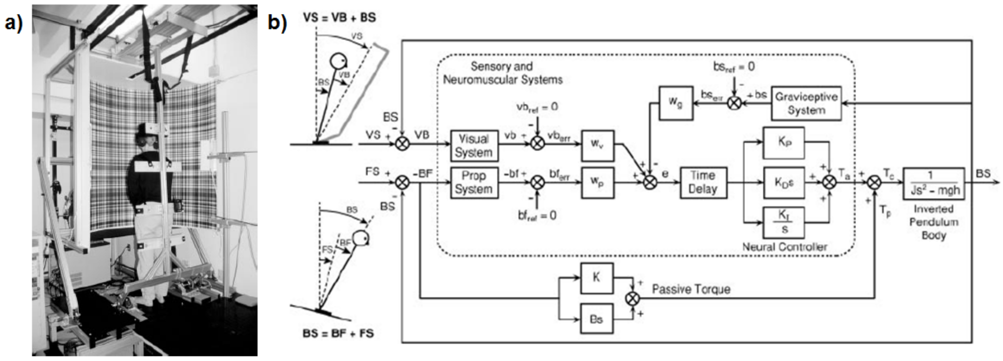

Figure 1.7: Sensory integration for balance control. a) Balance test device. The subject stands on a support surface and views a high contrast visual surround. Both the support surface and visual surround can rotate in the antero-posterior direction about the ankle joint axis. Single-link inverted pendulum dynamics are ensured by use of a backboard assembly. b) "Independent channel" model of sensory integration in postural control showing a weighted addition of contributions from visual, proprioceptive, and graviceptive (vestibular) system (Peterka 2002).

response may fail. Finally, another problem in the weakening of balance control may be represented by the background muscle tones, that is known to be hypertonic in PD patients (Rinalduzzi et al. 2015).

Considering balance control under dynamic conditions, one of the most relevant aspects in PD is represented by compromised anticipatory postural adjustments (APAs).During gait initiation, for example, healthy subjects always follow a highly stereotypical preparation pattern. Foot-off of the swing leg is preceded by co-activation of the tibialis anterior that generates a displacement of the center of pressure (COP), that is the point of application of the resulting ground forces, backward and towards the swing leg. Next, a lateral COP movement towards the stance leg and then forward is observed. The heel-off of the swing leg occurs at the start of the second phase of the COP movement (Delval et al. 2006), with the lateral shift towards the stance leg, while the toe-off instant of the swing leg is recognizable when COP starts moving forward (Crenna et al. 2006). Therefore, heel-off of the stance leg has been suggested to mark the division between the two highly coordinated motor programs (Brunt et al. 1991). All these preparatory movements constitute the APAs and are required for the unloading of the swing leg permitting the following progression of the body (Breniere et al. 1986). Failure of gait initiation is a complex problem in advanced PD patients and is sometimes refractory to treatment with medications. Gait initiation difficulties are a typical functional sign of akinesia, defined as a failure or slowness of willed movement (Hallett 1990), and as difficulty initiating or maintaining movement (referred to as "freezing of gait" (FOG) or "motor block") (Halliday et al. 1998). The timing and size of bilateral excitation of tibialis anterior during gait initiation are often abnormal, and when initiating gait, PD patients spend a greater amount of time with low or no tibialis anterior excitation (Gantchev et al. 1996). As a consequence, the mediolateral and the anteroposterior ground reaction forces and COP displacement that characterize APAs in PD patients are longer and weaker, with prolonged delays between the beginning of APAs and step onset (Burleigh-Jacobs et al. 1997; Dibble et al. 2004; Halliday et al. 1998; Hass et al. 2005; Krystkowiak et al. 2006; Vaugoyeau et al. 2003). Postural adjustments are often absent causing either hesitation or very slow progression (Burleigh-Jacobs et al. 1997). Multiple APAs can also occur and correspond to a subtype of FOG referred to as “knee trembling” (Jacobs et al. 2009). These abnormalities can occur very early in the course of PD. Low-magnitude APAs (measured from peak COP displacement and accelerations) have already been observed in untreated early-to moderate-stage patients in whom start hesitation may not be clinically detectable (Mancini et al. 2009).

In a model proposed by Massion (Massion 1992), the APA is generated by a circuit that includes the supplementary motor area (SMA) and basal ganglia, whereas goal-directed movement (e.g. the swing of step) is generated by a circuit that includes the dorsolateral premotor cortex and primary motor cortex. These parallel circuits are then integrated within the brainstem’s postural and locomotor centers (Massion 1992; Schepens et al. 2004; Takakusaki 2008). In general, APAs and stepping determine the intervention of separate groups of spinal projecting neurons in the pontomedulary reticular formation, although some neurons are activated for both the APA and the step (Schepens et al. 2004). Chastan et al. (Chastan et al. 2009) evaluated the effect of deep brain stimulation of the subthalamic nucleus (STN) and of the substanzia nigra pars reticulate (SNr) in seven patients. Bilateral SNr stimulation relieved axial Parkinsonian motor symptoms (gait and balance disorders) and braking capacity of the COM fell but did not have a significant effect on distal parkinsonian motor symptoms (segmental akinesia, rigidity and tremor) and first step parameters. Conversely, STN stimulation relieved both distal and axial parkinsonian motor symptoms and the control of APAs and the first step. These results reinforce the idea that APAs and stepping are controlled by two distinct systems within the basal ganglia circuitry (representing locomotion and balance, respectively).

1.6 Treatment of Parkinson’s disease

Three possible approaches have demonstrated their efficacy in the treatment of Parkinson’s disease over time: pharmacotherapy, stereotactic neurosurgery, and physical rehabilitation.

1.6.1 Pharmacotherapy

The discovery of dopaminergic deficits in patients with PD led to two alternative and complementary approaches in the pharmacological treatment of the disease. The most common intervention is focused on the restoration of dopaminergic activity using levodopa, a precursor of dopamine, and dopamine receptor agonists. On the other hand, an attempt to recover the balance between cholinergic and dopaminergic inputs on the basal ganglia by employing anticholinergic drugs can be attempted (Kakkar et al. 2015).

Four decades after its first introduction, levodopa remains the single most effective agent in the treatment of PD. Principal adverse effects of levodopa therapy are nausea, motor complications including *wearing off"* phenomenon, dyskinesia and on-off effects, confusion, hallucinations, orthostatic hypotension and sleep disturbances (Schapira 2005). Between all the possible medication-induced side effects, dyskinesia has a major impact on patients' affecting activities of daily living, quality of life with a consequent worsening of the global disability of PD patients (Colosimo 2012). To reduce the induced peripheral side effects, such as nausea, vomiting, and postural hypothension, the drug is usually administered with carbidopa, a peripheral decarboxylase inhibitor which blocks peripheral conversion of levodopa to dopamine. The contemporary administration of levodopa and carbidopa can also allow a reduction of the levodopa dose. To delay the need for levodopa therapy, dopamine receptor agonists are often employed. By offering receptor selectivity, these medications have theoretical advantages over levodopa in terms of not requiring enzymatic activation, having longer duration of actions and causing fewer adverse effect (Alonso Cánovas et al. 2014). This therapeautic approach can also be adopted in more advanced PD stages for allowing a reduction in levodopa doses with a consequent relief of the drug induced symptoms. As for levodopa, also dopamine receptor agonist can present adverse effects, including hallucinations, confusion, nausea, postural hypotension, somnolence, and an increased incidence in impulse control disorders (e.g. pathological gambling, shopping, eating, and hypersexuality) (Constantinescu 2008). Anticholinergic agents principally reduce tremor and their adoption is indicated in the treatment of early PD or as an adjunct to dopamine replacement therapy. They were first adopted in the treatment of PD before the introduction of levodopa (Brocks 1999). Their adverse effects, consisting of constipation, urinary retention, worsening of angle closure glaucoma and cognitive impairment, represent a strong limitation to their adoption in elderly patients (Schapira 2005). Finally, the treatment of levodopa-induced motor fluctuations and dyskinesia can be often conducted through the adoption of amantadine, a firstly-introduced antiviral agent for treating influenza that was serendipitously found to mitigate PD symptoms

(Schwab et al. 1969). The drug efficacy is modest, however it improves PD symptoms in mildly affected patients with early disease and reduces motor fluctuations in patients with advanced disease (Hubsher et al. 2012). Although many trials have assessed the efficacy of amantadine versus placebo for the treatment of PD motor impairments, its real effectiveness has still to be firmly proved (Warren et al. 2004). Side effects include livedo reticularis, dizziness, anorexia and blurred vision, and appear to be mild and transient (Warren et al. 2004). Confusion and hallucinations can be problematic in the elderly PD patients (Postma et al. 1975).

As reported, at the state of the art, all the available medications adopted in the treatment of PD present mild to severe side effects that can have a strong impact on the patients' quality of life with the prolonging of the therapeutic intervention. Chronic levodopa therapy can also produce a kind of ceiling effect that is associated with motor fluctuation, such as wearing-off, early morning dystonia, delayed ON or no-ON response and eventually ON-OFF phenomena (Marsden 1994).

Even though a fine tuning of the pharmacological treatment can be useful in the management of drug-induced adverse effects, it is possible that, in advanced stages of the disease, the motor fluctuations and dyskinesia become medically intractable. In those cases, a non-pharmacological alternative treatment has to be considered.

1.6.2 Stereotactic surgery

Treatment of levodopa-induced dyskinesia is one of the most common indications for stereotactic surgery in Parkinson's disease. In the light of previous results, surgery has been considered as the only treatment available for Parkinson's disease that can predictably improve both the parkinsonian motor syndrome and the medication-induced disorders (Guridi et al. 2008). At the state of the art, surgery, in particular deep brain stimulation (DBS), is a commonly performed procedure that revealed to be effective in the treatment of parkinsonian symptoms (Encarnacion et al. 2008).

The renaissance of stereotactic surgery for patients with PD was determined by the emerged evidence of weakness of L-dopa based long-term pharmacologic treatment (J. D. Speelman et al. 1998), and in particular with the challenging continuous attempt to balance the relief of PD motor signs against motor fluctuation and induced dyskinesia once that the high doses of levodopa determined the insurgence of collateral effects (Lang et al. 1998). The mechanism involved in the relief of the symptoms is still not completely understood. The basal ganglia circuit model above described, for example, cannot explain the lack of association between lesions in the moto thalamus and worsening of akinesia (Marsden and Obeso 1994), or the improvement in dyskinesia that has been observed after pallidotomy (Guridi et al. 2008). Different methodologies can be chosen for reducing drug-induced dyskinesia and motor disorders. At the state of the art, the most common surgical interventions are: pallidotomy and DBS, in particular addressing subthalamic nucleus (STN) or globus pallidus internus (GPi) (Follett 2004).

Between the possible interventions, pallidotomy has to be considered as the more invasive technique due to the irreversibility of the procedure. Starting from the second half of the 90s, many studies reported unilateral pallidotomy in patients with PD provided successful control of contralateral dyskinesia (Munhoz et al. 2014); several papers reported the positive effect that the intervention had on relieving dyskinesia, while no effect on dopaminergic dosages was noticed (Lozano et al. 1998; Fine et al. 2000; Samuel, Caputo, et al. 1998; Vitek et al. 2003). The patients' age presented a clear relationship with clinical outcome, independently of disease duration, with younger patients showing more improvement (Vitek et al. 2003). Bilateral pallidotomies, staged and simultaneous, produce similar improvements to unilateral procedures, with the possible advantage of improvements in axial dyskinesia, dystonia and different aspects of gait (e.g. walking speed, freezing of gait) (Pincus 2000; Siegel et al. 2000), but presenting the unacceptable limitation of cognitive and bulbar (mainly speech) adverse effect (Intemann et al. 2001).

Considering alternatives to pallidotomy, since its first application in late 1980s, DBS has developed and become a distinguished symptomatic treatment for Parkinson's disease, having progressively reached a prominent role in stereotactic surgical treatment of medication-induced motor symptoms for PD patients. Due to the proven efficacy of DBS, ablative procedure as pallidotomy are currently considered only as an alternative when DBS is not available due to technical, travel patient preference, and economic reasons (Hariz et al. 2001; Hashimoto et al. 2003). DBS presents three main advantages when compared with pallidotomy. Firstly, the entire surgical procedure is absolutely not intended for producing lesions to the cerebral tissue. Secondly, the DBS stimulator can be programmed taking into account several variables, including electrode position, amplitude, frequency, and pulse width, to induce better therapeutic effects while minimizing adverse effects. Finally, on the contrary of pallidotomy whose effects are irreversible, the parameters controlling the DBS stimulator can be changed several times after the implantation to respond to the disease progression obtaining optimal tuning over time. The most adopted DBS system uses a four-contact stimulating electrodes connected via a subcutaneous wire to a pacemaker-like unit called an implantable pulse generator (IPG) that is generally placed on the chest wall underneath the collarbone (Herrington et al. 2016). For relieving of drug-induced symptoms in PD, DBS electrodes are generally placed in correspondence of two specific targets: the globus pallidus internus (GPi) and the subthalamic nucleaus (STN), even if other regions have been targeted (e.g. ventral intermedius nucleus, VIM) (Terzic et al. 2012; Moldovan et al. 2015). Target point localization is attained by preoperative imaging. Intraoperative neurophysiology imaging (MRI) is used for target identification, then target coordinates are calculated relative to the stereotactic frame placed on the patient's head (Dormont et al. 2010). Fusion of MRI and computed tomography (Liu et al. 2001) can provide a working alternative. Electrodes are typically implanted bilaterally although clinical needs sometime dictate unilateral stimulation.

Once the device has been implanted and programmed, it is possible to carefully increase the amplitude of the stimulus with a simultaneous reduction of dopaminergic medication during several programming sessions to achieve an optimal, patient-tailored reduction of the dopamine- induced side effects. However, the increase of amplitude is limited by the appearance of stimulation-related symptoms.

It is possible to programme the IPG to obtain an optimal balance between the reduction of motor symptoms and the necessity to limit side effects of stimulation. For L-dopa-induced symptoms relieving, IPG is commonly programmed to generate a monopolar stimulation, with frequency set at 130 Hz and impulse duration in the range $60-90\,\mu s$ (Volkmann, Moro, et al. 2006). For most applications, DBS resulted to be most effective at high frequency (> 130 Hz); in particular, for PD patients, DBS at $5-10$ Hz worsened bradykinesia, in the range $30-100$ Hz resulted ineffective, while efficacy was generally obtained only with frequency between 130 and 200 Hz (Moro et al. 2002; Timmermann et al. 2004). First generation devices delivered electrical stimulation in a voltage-controlled mode whereas later technologies predominantly adopt the constant-current mode. Recently, more advanced devices can use both the two possibilities. It has been reported that constant-current devices make possible to maintain the stimulation field stable in size, reducing the vulnerability to changing tissue impedances (Lempka et al. 2010; Okun et al. 2012). DBS of the STN and GPi has demonstrated to be an effective option to improve motor symptoms and manage long-term motor complications resulting from levodopa treatment. Furthermore, patient's mobility, activities of daily living, emotional well-being and health related quality of life, which are impaired motor symptoms and complications, can be enhanced by DBS (Volkmann, Allert, et al. 2001; Deuschl et al. 2006).

1.6.3 Physical rehabilitation

The treatment of PD symptoms has been traditionally centred on drug therapy, with levodopa viewed as the *"gold standard"* treatment (Rascol et al. 2002). However, even with optimal medical management, patients with PD experience deterioration in body function, daily activities, and participation (Nijkrake et al. 2007). For this reason, support has been increasing for the inclusion of rehabilitation therapies as an adjuvant to pharmacological and neurosurgical treatment (Gage et al. 2004; Nijkrake et al. 2007), and a call for the move towards multidisciplinary management of this multidimensional condition (Rubenis 2007).

As previously reported, even if the pharmacological treatment presents the highest beneficial impact in the treatment of Parkinson's disease, one of its major limitation is represented by the insurgence of drug-induced motor disorders. Even if stereotactic surgery, in particular DBS techniques, offers interesting symptomatic benefits, the procedure has to be considered highly invasive and, as usual for critical surgery, can lead to several complications and infections. Therefore, other non-pharmacological treatment strategies have been investigated. Between the non-pharmacological therapies, physical rehabilitation is the most commonly used procedure in adjunct to medication intervention to treat PD movement disorders (Smania et al. 2010). As a confirmation of the increasing interest in this therapeutic approach, the number of publications addressing exercise for PD has more than triple in the past decade (Kolk et al. 2013).

To avoid possible misunderstandings caused by an overlap in the definition of terms that are often used interchangeably, a distinction has to be done between the terms physical therapy, physical activity and exercise. The World Health Organization defines physical activity as *"any bodily movement produced by skeletal muscles that requires energy expenditure"* (e.g. walking, cycling, or participating in sports) (*Physical activity* 2016). The American College of Sports Medicine (ACSM) has accepted that definition and considers exercise as *"a subcategory of physical activity involving planned, structured, and repetitive body movements that are performed to improve or maintain one or more components of physical activity"* (Chodzko-Zajko et al. 2009).

Finally, the term physical therapy refers to an intervention that uses exercise and other elements that are not traditionally considered exercise, such as cognitive strategies, as a modality to facilitate more effective movement (Kolk et al. 2013).

Consequently, the physical therapist is a member of a multidisciplinary team (Robertson 2003; Rubenis 2007), whose purpose is to maximise functional ability and minimise secondary complications through movement rehabilitation within a context of education and support for the whole person (Plant et al. 2000; Deane et al. 2001).

Physiotherapy for PD focuses on transfers, posture, upper limb function, balance (and falls), gait, and physical capacity and activity by using cueing and cognitive movement strategies, and exercise to optimise the patient's independence, safety, and well-being, thereby enhancing quality of life (S. Keus et al. 2004; S. H. J. Keus et al. 2007).

The first aim of this kind of intervention in PD is not to influence the disease process itself, but to improve daily functioning by teaching and training patients in the use of compensatory movement strategies (S. H. J. Keus et al. 2007). Physical therapy may be useful for the maintenance and improvement of mobility, posture, and balance (Fox et al. 2011). It was previously reported that different modalities of treatment based on walking, running, strength training, functional exercises, and whole body vibration significantly reduced the risk of falls and improved motor performance (Ashburn et al. 2007; Caglar et al. 2005), balance and gait (Ebersbach et al. 2008), and executive functions (Tanaka et al. 2009). Furthermore, straight training based on improved muscle strength and contributed in enhancement of mobility and disease progression (Cruickshank et al. 2015).

Several studies suggested the possibility that physical therapy could induce changes to the brain functioning due to a residual cerebral motor plasticity of the involved neural circuits. A translational pilot study reported that intensive aerobic exercise in early PD patients resulted in better postural control and increased postsynaptic D2 receptor binding potential on PET imaging (Fisher et al. 2013). Functional MRI revealed that a single bout of forced exercise produce the same change in activation pattern that are seen between medication states (Alberts et al. 2011).Moderate-intensity interval training performed 3 times per week for about an hour involving cycling at high pedaling rated resulted in an increase of the basal level of BDNF serum, the brain-derived neurotrophic factor protein expressed in several brain areas and is involved in multiple neural process, such as: synapse development and plasticity, neuronal connectivity and development of immature neurons and survival of adult ones. The same training determined a releafing of the inflammatory status in PDand a general improvement of the patients' conditions as shown by a reduction in the UPDRS total score (Zoladz et al. 2014).

Even if the exercise-induced neuroplastic and neurochemical changes are less straightforward in humans that evidence reported in animal literature, the obtained results raise the possibility that high-intensity aerobic exercise could result in enhanced central motor processing (Kolk et al. 2013).

Physical therapy has the potential to also beneficially affect also some of the non-motor symptoms associated with PD (A. D. Speelman et al. 2011). Aerobic exercise has been associated with: i) improvement in executive function, ii) decrease age-related cognitive decline in the healthy elderly (Colcombe, Kramer, Erickson, et al. 2004; Colcombe, Kramer, McAuley, et al. 2004), iii) improved self-reported quality of sleep and quality of life in older people with insomnia (Reid et al. 2010), and with iv) a reduction of depressive symptoms in older adults (Bridle et al. 2012). Considering only literature specifically focused on PD, it was reported that exercise have beneficial effects on cognition (Cruise et al. 2011; Tanaka et al. 2009) and sleep (Rodrigues de Paula et al. 2006). Moreover, benefits can be observed also in secondary complications such as cardiovascular diseases and osteoporosis (A. D. Speelman et al. 2011).

Physical therapy is often prescribed next to medical treatment, but, at the state of the art, there are no widely accepted guidelines in PD with practical recommendation about optimal series and intensity of exercise graded according to scientific evidence (S. H. J. Keus et al. 2007). However, the guidelines provided by the ACSM for older adults (and patients older than 50 years with chronic disorders) seems to be a valid support (Nelson et al. 2007). The Practice Recommendation Development Group of the Movement Disorders Society (MDS) in a recently published recommendation for physical therapy in PD identified six different areas of intervention: 1) Transfers (e.g. turning in bed or rising from a chair), 2) Posture (including neck and back problems), 3) Reaching and grasping, 4) Balance and falls (including fear of falling), 5) Gait, 6) Physical capacity and (in)activity (S. H. J. Keus et al. 2007). Concerning the improvement of gait, it has been suggested that physical therapy has to target three key elements: strategy training, management of musculoskeletal and cardiorespiratory systems, and promotion of physical activity (Morris et al. 2010).

Different types of physical activity revealed to be useful in the treatment of PD. The practice of martial arts, such as Tai chi (Hackney and Earhart 2008; Li et al. 2012), and dance (Earhart 2009; Hackney and Earhart 2010; Hackney, Kantorovich, et al. 2007; Duncan et al. 2012; Foster et al. 2013; Shanahan et al. 2015) demonstrated its efficacy in the relief of symptoms. Some exercise-related risks have to be considered before prescribing a physical rehabilitation for PD patients. In particular, accounting aerobic and intensive tasks, possible complications related to the age, the disease stage, and the general higher fragility of this population, it is already known that an increase in physical activity often result in a higher incidence of leisure time and sports-related injuries (Haskell et al. 2007). Considering specific motor deficits in PD, patients can present inability to perform exercise in a safe way; for example, in the case of extreme freezing, treadmill aerobic exercise could result unsafe to practice, whereas the use of a stationary bike could provide a safer alternative (Snijders et al. 2011). Furthermore, the use of stationary equipment can be generally considered safer and provide the possibility of exercise at home (Kolk et al. 2013). To reduce the incidence of all the above mentioned risk factors, all PD patients should be encouraged to exercise at their optimal medicated state, as dopaminergic medication allows better, safer, and longer performance of aerobic exercise (LeWitt et al. 1994). Taking into account the desirable beneficial effects and possible risks, exercise and rehabilitation that use a wide variety of movements and address many different constraints on mobility are strongly suggested at all stages of the disease (Kolk et al. 2013).

1.6.4 Biofeedback based approaches in the treatment of Parkinson's disease

Physical therapy has been proven to be beneficial for people suffering of PD by improving motor performance (Ashburn et al. 2007; Caglar et al. 2005), posture and balance (Fox et al. 2011; Ebersbach et al. 2008), gait and mobility (Fox et al. 2011; Ebersbach et al. 2008; Cruickshank et al. 2015), executive functions (Tanaka et al. 2009), and by reducing fall risk (Ashburn et al. 2007; Caglar et al. 2005). However, a prerequisite for having patients fully involved and adhere to a training protocol is that the exercises are meaningful, engaging, and challenging (Heuvel et al. 2013). Recently, the availability of cost-effective wearable devices based on inertial sensor for human body motion monitoring is offering the possibility to create applications aimed at making the users more conscious about how they act for maintaining balance or executing specific motor task.

Given the evidence that externally guided movements are mediated by neural pathways that differ from those involved in the internally guided ones (Debaere et al. 2003; Elsinger et al. 2006; Glickstein et al. 1991) and considering the extensive evidence regarding the benefits of using external stimuli in patients with PD (Rubinstein et al. 2002; Lim et al. 2005; Nieuwboer et al. 2007; Rochester et al. 2010) the provision of explicit biofeedback signals generated on the basis of patient's own movements may be an important element in rehabilitation interventions in patients with PD.

The use of biofeedback has been offered in the past as a training instrument that enables an individual to learn how to change physiological activity or behaviour for the purposes of improving performance (Mirelman et al. 2011). Biofeedback training of balance and posture has shown to be effective for posture control in adolescents with scoliosis (Wong et al. 2001) and, when applied to elderly patients with peripheral neuropathy, it has helped in lowering fall rate (Wu 1997). In patients with bilateral vestibular loss (Dozza, Chiari, and Horak 2005), biofeedback training was also found useful in enhancing postural stability even under challenging standing conditions (e.g. tandem walking), beyond the effect of practice alone (Dozza, Chiari, and Horak 2005; Dozza, Chiari, Chan, et al. 2005; Horak et al. 2009). Several studies were conducted assessing the feasibility and the efficacy of biofeedback in persons suffering from stroke, resulting in ameliorations of the typical spatiotemporal asymmetry (Afzal et al. 2015; Lewek et al. 2012), higher gait speed (Lewek et al. 2012), and reduced balance sway (Priplata et al. 2006).

Biofeedback devices has been previously adopted on subjects with PD for rehabilitation of balance and gait (Nanhoe-Mahabier et al. 2012; Lee et al. 2015; Casamassima et al. 2014; Novak et al. 2006). However, at the knowledge of the author, no previous studies focused on the possibility of using biofeedback based solutions to help patients performing the different motor tasks required in a multi-factorial training approach.

Novel technological developments in the field of wearable devices allow for making patients more conscious of their movements and motor performances through the adoption of real-time biofeedback signals. At the same time, the availability of commercial off-the-shelves gaming accessories (e.g. Nintendo BalanceFit, Microsoft Kinect) for integrating a patient's own movements in virtual environments characterized by real-time 3D rendering, avatars, and score-keeping offers the opportunity to design new solutions for intriguing videogames that may include, for example, different set of exercises for balance improvement. Moreover, both the possibilities for a future translation of patient-tailored rehabilitation program to the domestic environment.

1.7 Outline of the thesis

In the first chapter, the current one, the objectives of the thesis are presented. Parkinson's disease, its pathophysiology and the major induced impairments are presented. Finally, the different possible therapeutic approaches are discussed.

Chapter 2 is focused on the development of sensor-based solutions for physical rehabilitation. In the first section of the chapter, a new multi-sensor system for biofeedback based physical rehabilitation in Parkinson's disease is presented. The system has been designed and tested at the Biomedical Technology Department of the Don Carlo Gnocchi Foundation Onlus (Milan, Italy). The results obtained in its pilot application in a randomized controlled trial (RCT) study conducted in collaboration with the Department of Neurorehabilitation of the IRCCS (the Italian Scientific Institutes for Health Research and Health Care) S. Maria Nascente Hospital of the Don Carlo Gnocchi Foundation. In the second section of the paragraph, a prototype of a single-sensor embedded system for gait rehabilitation is presented. In particular, a novel algorithm for step detection has been developed. The algorithm's characteristics and performances are discussed considering possible requirements for its future adoption in biofeedback based solutions for gait rehabilitation. The development of the first developed prototype was conducted in collaboration with the Dipartimento di Elettronica, Informazione e Bioingegneria of the Politecnico di Milano (Milan, Italy).

Chapter 3 presents the results from the application of a rotating robotic platform (RotoBIT3D) for the assessment of proprioceptive deficits in subjects with Parkinson's disease. The robot has been developed in collaboration with the Department of Mechanical and Aerospace Engineering of the Sapienza University of Rome (Rome, Italy).

In Chapter 4, new methods for the evaluation of balance during the preparation and subsequent execution of voluntary movements are presented. The chapter is divided into three sections. In the first one, a new algorithm for the evaluation of anticipatory postural adjustments prior to gait initiation and stair climbing is presented. Validity and sensitivity of the method were assessed on subjects with PD under their usual pharmacological therapy (ON-medication state) and healthy control subjects. The second section is centered on the extension of the previously presented method to subjects with PD in the OFF-medication state. In the third and last section, a new instrumented method for the evaluation of the one-leg stand test is presented. The last two studies were conducted in association with the Balance Disorders Laboraty of the Oregon Health and Science University (Portland, Oregon, USA).

Finally, the last chapter, Conclusions, summarizes the contribution of this thesis and presents the perspectives of future studies. All the chapters of the thesis present a similar structure. Each chapter starts with an introduction to bring the subjects of the chapter into focus, and it is followed by detailed methods, results, and conclusions. In addition, at the end of each chapter, in the bibliography section, the cited articles, books, and resources used throughout the chapter are listed.

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Chapter 2

Developed solutions for physical rehabilitation

2.1 Multi-sensor system for biofeedback based rehabilitation

2.1.1 Introduction

Despite the fact that the striatum, that is largely involved in the consolidation and automatization of learned material, is highly affected in PD, a number of studies showed that the acquisition of both simple and complex motor skills is still possible (Nieuwboer, Rochester, et al. 2009). In a model proposed by Fitts and Posner (Fitts et al. 1967), the motor learning process is divided into three different stages of learning: i) cognitive stage, ii) associative stage, and iii) autonomous stage. In the first one, the patient is able to figure out which movements have to be done to successfully complete a given motor task and how to perform the required actions by receiving instructions and feedback from the instructor. During the second stage the patient can benefit of specific association between environmental cues and the movements required to achieve the goal. Finally, in the latter one, automaticity in performing the specific movement is achieved, commonly allowing the patient to perform another task at the same time. This process could be facilitated by the application of external sensory information provided through rhythmical cues or biofeedback signals. The adoption of cues demonstrated to be effective for improving motor performance (Nieuwboer, K. Baker, et al. 2009; Kadivar et al. 2011; I. Lim et al. 2005; Rochester, K. Baker, et al. 2010; Ferrarin, Brambilla, et al. 2004; Ferrarin, Rabuffetti, et al. 2008). One possible explanation for the reported efficacy is represented by the possibility to bypass the basal ganglia through the activation of premotor cortex by better focusing the cortical-basal ganglia-thalamo-cortical motor loop (Nieuwboer, Rochester, et al. 2009). Furthermore, the biofeedback signals can be considered as a form of cueing to direct better performance by enhancing the acquisition of new strategies of movement through sensory integration (Mirelman, Maidan, et al. 2013). While performing a movement an intrinsic feedback is provided by integration of different own sensory-perceptual information that is available as a result of movement being performed. This kind of feedback is always present during motor learning (Sigrist et al. 2013), even though it can be impaired by pathophysiological conditions. The related data are fundamental for the creation and the continuous update of the personal internal representation of the body and, consequently, for programming voluntary movements (van Vliet et al. 2006). The amount and quality of information can be improved through external stimuli. Extrinsic or augmented feedback is defined as information that cannot be elaborated without an external source represented either by a therapist or trainer or by an external device or display (e.g. screens or projectors for visual modality, headphones and speakers for audio modality, and robot or vibrator for the haptic one) (Schmidt et al. 2008; Utley et al. 2008; Sigrist et al. 2013). These solutions have been previously used to reinforce the intrinsic feedback in normal motor learning (Wierinck et al. 2005), sport training (Wulf et al. 2002), and motor recovery in neurological patients (van Vliet et al. 2006). Extrinsic feedback has been categorized into two categories: *"knowledge of results"* (KOR) and *"knowledge of performance"* (KOP) (Proteau et al. 1992; Magill 2003). Knowledge of results is defined as the terminal feedback provided to the performer after the completion of a requested task about the outcome of the execution or about achieving the prefixed goal (Adams 1968; Adams 1971; Magill 2003; van Vliet et al. 2006) (e.g. an acoustic signal generated when an avatar reaches the target in a virtual-reality scenario). Instead, knowledge of performance is information about the movement characteristics that led to the performance outcome (Magill 2003) (e.g. the therapist suggestions or audiovisual signals indicating how to move different body segments for reaching the final goal). Hence, knowledge of results can influence the motor learning process over repeated trials, by improving the open-loop (feedforward) control, while knowledge of performance can beneficially impact the closed-loop (feedback) control. Thus, considering the contemporary application of both the components of the extrinsic feedback to a repeated task, during the first trial only knowledge of performance can influence the execution, while starting from the second one also the knowledge of result has to be considered, as proposed in fig. 2.1.

Considering people affected by Parkinson's disease, as reported by Mirelman et al. (Mirelman, Maidan, et al. 2013), virtual reality techniques have been mainly adopted in the treatment of freezing of gait disturbances and to assess the ability to maintain a steady walking path. However, the majority of the studies already published in literature presents small samples of treated patients and lacks of a control group made up of patients treated with usual care physical training. Due to the difficulties to evaluate and map proprioceptive information onto voluntary and reflexive motor commands that are typical of this disorder (Konczak et al. 2009), it is opinion of the author that the physical rehabilitation of people affected by Parkinson's disease could be improved through the adoption of task-specific, patient-tailored biofeedback signals.

Thus, aim of this study is to try to overcome the reported limitations by: i) developing a new system for biofeedback based rehabilitation that can be patient-tailored on the specific motor ability of the different users and adopted in a multifactorial physical treatment, ii) applying the developed system in a pilot RTC clinical trial to assess the beneficial effects of the augmented sensory approach by comparison with usual care treatment and to verify the possibility of improvement retention over time.

2.1.2 Methods

Participants

Forty-two subjects affected by Parkinson's disease participated to the study. Patients was randomly divided into two groups: i) a treated group (TG, n = 22) to whom the new rehabilitation protocol based on the biofeedback rehabilitation system was administered, and ii) a control group (CG, n = 20) that was trained with usual care methodologies without biofeedback. Five patients of the treated group dropped out of the study before the POST evaluation, while five controls dropped out before the follow-up evaluation. Thus, thirty-two subjects completed the clinical trial (TG: n = 17, CG: n = 15). Demographic and clinical data of the two groups are presented in Table 2.1.

Inclusion criteria were: diagnosis of idiopathic Parkinson's disease, Hoehn and Yahr (H&Y) stage (Hoehn et al. 1967) between 2 and 4, Mini Mental State Examination (MMSE) score (Folstein et al. 1975) higher than 24, ability to stand unsupported in unipodal stance for more than 10 s and to walk for 6 meters without any aid, stable drug treatment over time.

Subjects were excluded if they had an implanted DBS device or any other health related problem including cardiopulmonary, orthopedic, and neurological disorder, or if they presented Mini-Mental score lower than 24, participation in rehabilitative training in the preceding last 2 months.

The first 17 subjects to receive the biofeedback based training (mean age ± SD: 73.0 ± 7.1, 3 females) were asked to answer to a self-administered satisfaction questionnaire.

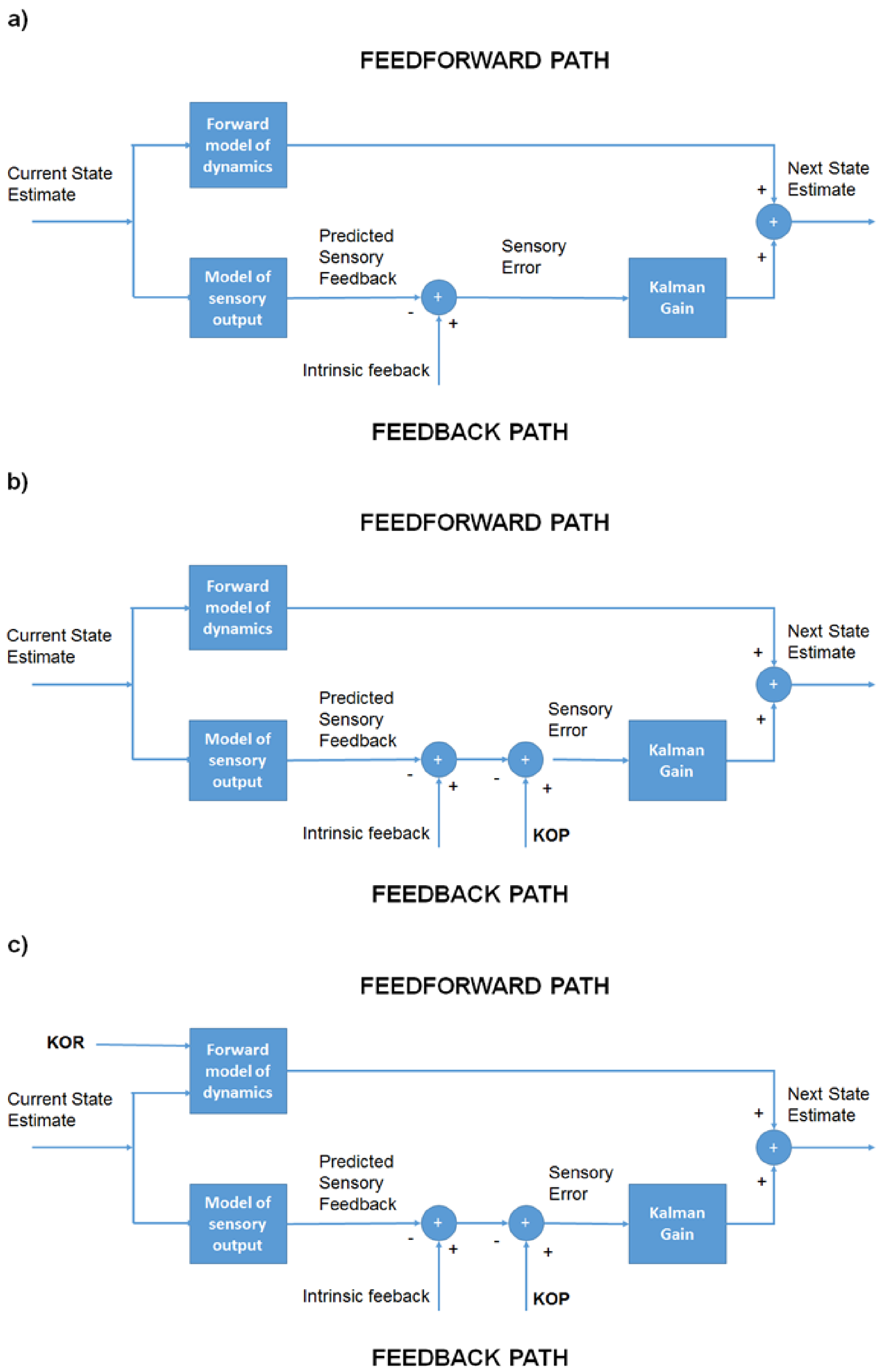

Figure 2.1: Descriptive model of the integration of intrinsic and extrinsic feedback: a) the original model for sensorimotor integration when no external signals are applied, as proposed in (Wolpert et al. 1996); b) descriptive model of the first task repetition where knowledge of performance (KOP) determines a reduction of the sensory error in the feedback path; c) descriptive model of the subsequent task repetitions where both KOP and knowledge of result (KOR) are applied.

All the participants signed informed consent forms approved by the Ethical Committee of Don Carlo Gnocchi Foundation.

Table 2.1: Demographic and clinical data (median [range]) of the Trained Group (TG) and Control Group (CG) at baseline.

TEST	CG	TG	p-value
Gender [M/F]	8/7	14/3	
Age [year]	75 [57-89]	74 [63-87]	0.639
PD duration [year]	8 [2-22]	8 [2-17]	0.467
H & Y stage	3 [2-4]	3 [2-4]	0.218
UPDRS [pts]	22 [10-36]	18 [4-31]	0.150
BBS [pts]	47 [19-56]	48 [17-55]	0.540
10MWT [s]	12 [8-20]	10 [7-24]	0.140
GABS [pts]	11 [1-23]	8 [1-19]	0.122
TUG [s]	18 [8-33]	15 [7-33]	0.150
ABC [pts]	48 [13-81]	61 [23-98]	0.122
FOGQ [pts]	14 [3-18]	12 [2-21]	0.245
PDQ-39 [pts]	56 [12-98]	43 [14-98]	0.160

The GAMEPAD rehabilitation system

A new rehabilitation system was developed to provide virtual reality scenarios and biofeedback signals for the execution of the designed physical training. The system, formally named GAMEPAD (Gaming Experience in Parkinson's Disease), integrated six wearable inertial measurement units or IMUs (TMA, Tecnobody, Italy) placed on the trunk, anteriorly on the sternum and posteriorly in correspondence of L4-S2 vertebra, and laterally on shanks and thighs (fig. 2.2). The devices were fixed over clothing through anti-slippery elastic bands. Each IMUs integrated one 3D accelerometer, gyroscope and magnetometer to collect data at a sampling frequency of 50 Hz; a sensor-optimized Extended Kalman Filter (EKF) was internally applied to determine the orientation of the IMU in the space. Raw signals of the accelerometer, gyroscope and magnetometer and the quaternion reassuming the spatial orientation were acquired by a remote laptop from each IMU via Bluetooth connections for subsequent soft real-time analysis. As reported in figure 2.2a, the IMUs placed on the thigh and shank of the left leg were wired connected together, as well as the correspondent sensors placed on the right limb. The wireless transmission of data from these two pairs of sensors was performed through a single Bluetooth connection for each pair. This configuration was chosen by the manufacturer to reduce the number of remote links, lowering the risk of malfunctioning due to possible criticality in wireless connection. Hence, the acquisition of data from all the IMUs required only four wireless connections: one for the single IMUs on the trunk, another one for the

IMU on the waist, and a connection for each pair of sensors on the lower extremities.

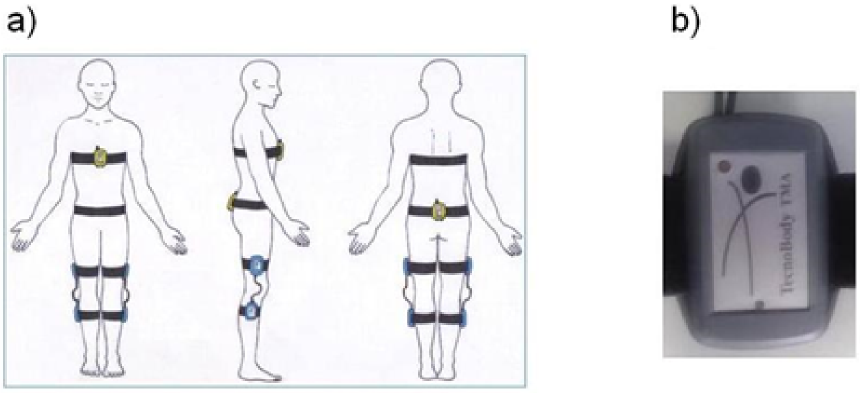

Figure 2.2: a) Sensor placement over the patient's body. b) Adopted sensor (TMA, Tecnobody, Italy)

A lightweight software for data acquisition and synchronization was developed ad hoc. The solution was written in C# language using the native library of the Microsoft .NET platform and the Microsoft Windows 7 graphic libraries and Bluetooth drivers. The first time that the sensors were connected to the remote laptop, the software interface guided the operator through a brief configuration procedure required to associate each device to the correspondent body segment and activate the Bluetooth transmission (fig. 2.3).

Data were send to the biofeedback generation application through an internal UDP (User Datagram Protocol) connection. Due to the fact that UDP is a non-reliable protocol, the acquisition and synchronization software was designed to avoid possible interruption in the biofeedback generation procedure due to missing data; data were acquired simultaneously from all the sensors at a sampling frequency of 50 Hz and, in case of incorrect reception from one sensor, the correspondent values collected in the previous sampling step were considered.

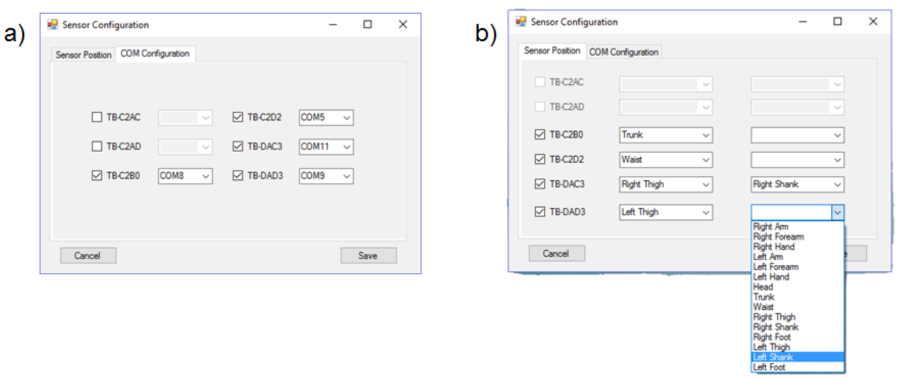

Figure 2.3: User interface of the data acquisition and synchronization software: a) Association between wearable sensors and virtual serial ports (COM); b) Definition of the wearable sensors' location.

This solution was tested in the Laboratory of Electronic at the Biomedical Technology Department of the Don Carlo Gnocchi Foundation to evaluate the robustness of the system and to estimate the amount of missing samples that have to be replaced during in the acquisition. In fact, the presence of the replacing procedure ensures the continuous functioning of the biofeedback generation system, however a high percentage of replaced data could negatively impact the precision of the system, possibly decreasing the efficacy of the rehabilitation treatment.

Considering that the maximum duration of each rehabilitation exercise was set in 60 s, the same duration was adopted for the test trials. The IMUs were tested singularly starting from the battery full-charge condition, corresponding to the status at the beginning of the exercise session, till the total charge depletion. Then, all the six possible multi-sensors configuration used during the execution of the developed exercises were assessed in the battery full-charge state. Five trials were conducted for each condition, recording 15000 samples for each sensor.

Biofeedback generation procedure

Data collected from the GAMEPAD system were analyzed on-line with an ad hoc software developed using Simulink (Mathworks Inc., USA). Three main variables were controlled: the body center of mass (COM) displacement, and the trunk inclinations in the antero-posterior (AP) and medio-lateral (ML) directions separately.

The adoption of quaternions to describe the spatial orientation of each device avoid the problem of gimbal lock at the sensor level. Hence, the orientation of the single sensor can be described as follow:

$$q = \begin{pmatrix} q_0 \\ q_1 \\ q_2 \\ q_3 \end{pmatrix} = \begin{pmatrix} e_x \sin\frac{\theta}{2} \\ e_y \sin\frac{\theta}{2} \\ e_z \sin\frac{\theta}{2} \\ \cos\frac{\theta}{2} \end{pmatrix}$$

where $e = [e_x\, e_y\, e_z]^T$ represents the principal axes, q_3 is the scalar term of the quaternion, and θ is the principal angle. After receiving the data through wireless connection, it was possible to convert quaternion data into Euler angles without experiencing troubles with gimbal lock by imposing restriction due to the knowledge of the sensors' location on the patient's body and of the specific motor tasks that has to be performed. Easy mathematical steps lead to the following conversion formulas:

$$\begin{aligned} \psi &= \arctan\left(\tfrac{2(q_0 q_1 + q_3 q_2)}{q_3^2 - q_2^2 - q_1^2 + q_0^2}\right) \\ \omega &= \arcsin\left(-2\left(q_0 q_2 - q_1 q_3\right)\right) \\ \phi &= \arctan\left(\tfrac{2(q_1 q_2 + q_0 q_3)}{q_3^2 + q_2^2 - q_1^2 + q_0^2}\right) \end{aligned}$$

where ψ, ω, and ϕ are, respectively, the yaw, pitch, and roll angles. The algorithm needed to execute the conversion was then implemented in the Simulink code of the GAMEPAD system.

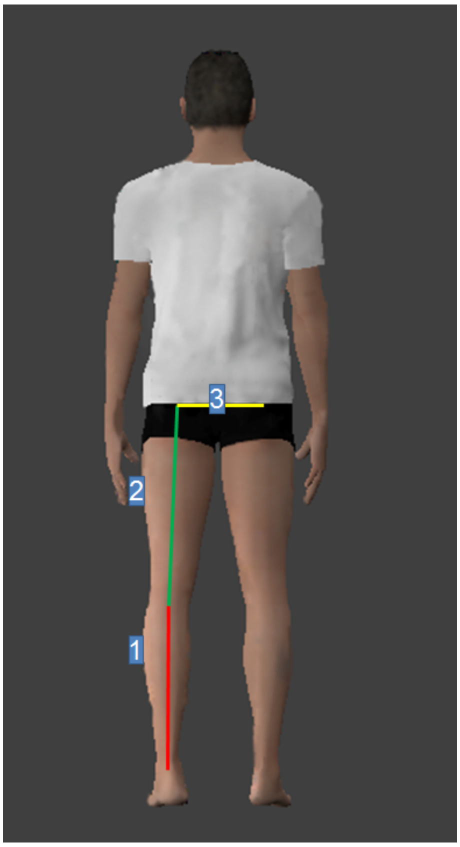

Figure 2.4: Example of multilink kinematic chain (left pivotal feet). Considering the three sensors as rigidly connected to the correspondent anatomical link, it is possible to estimate the position of the COM by the knowledge of the sensor-link orientation in the subsequent order: shank (1 - red), thigh (2 - green), and waist (3 - yellow).

The COM position was estimated by tracking the waist mounted IMU. Thus, the sensor position was calculated adopting a multi-link model of the waist and bottom limbs (fig. 2.4). The knowledge of the patient's height and weight permitted to calculate the length of each link using parameters reported in anthropometric tables.

Starting from the pivotal feet, that was selected by the physical therapist at the beginning of each task, it was then possible to reconstruct the links' orientation on the basis of the collected quaternions, thus determining the relative position of shank, hip and waist (COM) sensors. The orientation of the trunk both in the AP and ML directions was extracted from the quaternions collected from the sensor worn over the sternum.

It has to been noticed that measures collected through the body-worn sensors, expecially those placed on the bottom limbs, could be affected by errors due to soft-tissue artifacts and malpositioning. However, even though caution has to be taken, other rehabilitation systems based on wearable inertial sensors, Kalman filter-based orientation detection, and similar positioning of the sensors have shown good accuracy in the calculation of joint angles proving to be suitable for possible adoption in biofeedback-based rehabilitation practice (Leardini et al. 2014). Moreover, several studies reported that IMUs well estimate the trunk flexion (Leardini et al. 2014; Picerno et al. 2008; Plamondon et al. 2007).

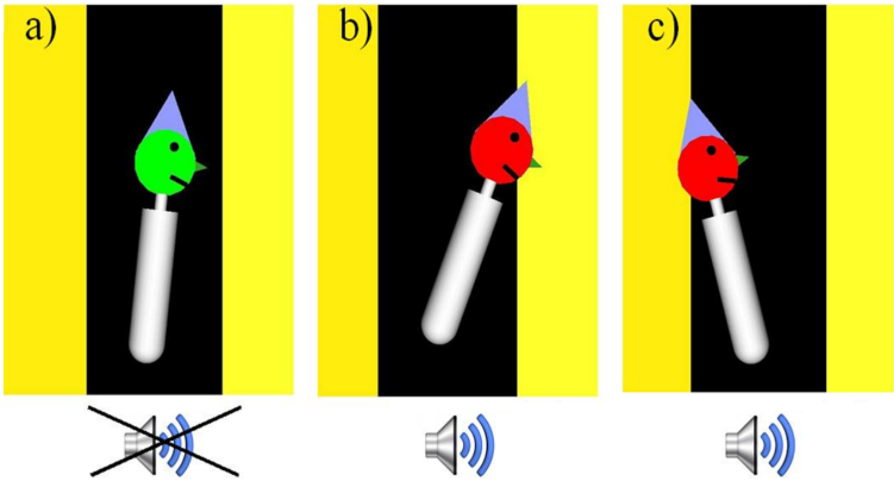

Figure 2.5: Example of administration of acoustic and visual biofeedback during antero-posterior sway of the trunk. a) Correct execution with no feedback, b-c) Wrong execution with the trunk inclination exceeds the patient-tailored threshold: acoustic (beeping) and visual (red face) feedback is provided.

Visual and acoustic biofeedback signals were used for real time correction of the motor task execution. As shown in fig. 2.5, visual feedback was administered through simple virtual reality scenarios. The simplified polygonal design and the adoption of easy detectable complementary colors were chosen to take into account possible age-related or disease-induced cognitive and visual deficits. A final summary feedback, that consisted in an overall score reflecting the obtained performance, was given at the end of each task. The difficulty of the proposed items, and consequently the thresholds used for biofeedback generation, were totally patient-tailored: thresholds were set considering the performance that the patient obtained in a brief test preceding the beginning of each item. Then, the physical therapist had the possibility to change the parameters assigned automatically on the basis of the observation of the patients.

Description of the rehabilitation program

In accordance with the specific literature about the rehabilitation of Parkinson's disease a new task-oriented rehabilitation protocol based on biofeedback signals was designed in collaboration with the clinicians of the Department of Neurorehabilitation, Don Carlo Gnocchi Foundation (Milan, Italy).

Three different kinds of exercises were instrumented:

- Static exercises: they were characterized by a fixed placement of the feet during the entire task execution. Main goal of this group of exercises was the training of balance control in quiet stance and while leaning toward a given direction. Controlled variables for the generation of the biofeedback were the COM displacement and the trunk inclination in the antero-posterior and medio-lateral directions.

- Quasi- dynamic exercises: they were characterized by the assignment to move one foot during the execution of the task with the consequence of modifying the base of support, thus allowing bigger excursion of the COM. To complete this set of items, the patients were asked to switch from an initial straight posture to a different balance configuration (e.g. tandem position, foot on a chair step) and to control in the meantime the COM displacement and the inclination of the trunk. Thus, this set of exercises could be considered propaedeutic for the rehabilitation of dynamic skills, specifically targeting the ability to change postural strategies while performing transitional movements.

- Dynamic exercises: these exercises were characterized by the fact that during their execution the base of support changed continuously allowing the patient to move around in the rehabilitation gym (e.g. walking). During the execution, only trunk inclination in the AP and ML directions was controlled.

For the first two sets of exercises both visual and acoustic feedbacks were used, while for the latter one only the acoustic feedback was adopted due to limitation in the portability of the system.

The final summary feedback report was presented at the end of each task, regardless of the category, and represented an occasion for both the patient and the physical therapist to discuss which motor strategies had to be developed, changed or adapted to improve the specific motor task that was targeted in the exercises.

Data analysis

All the patients, regardless of the group participated to 20 rehabilitation sessions of the duration of 45 minutes each, administered 3 times per week. The treated group (TG) was trained with the newly developed GAMEPAD system for biofeedback rehabilitation, while the control group received *"usual care"* treatments. To evaluate beneficial effects of the two different therapies 5 clinical outcome variables were assessed:

1. Gait and Balance Scale (GABS) (Thomas et al. 2004)

2. Activities-specific Balance Confidence scale (ABC) (Powell et al. 1995)
3. Berg Balance Scale (BBS) (Berg et al. 1992)
4. Timed Up and Go test (TUG) (Podsiadlo et al. 1991)
5. 10-meter walk test (10MWT) (Bond et al. 2000)

Berg Balance Scale (BBS) and 10-meter Walk Test (10MWT) scores were chosen as primary outcomes of the study to investigate the beneficial effects of the therapy.

A stabilometric platform (Prokin PK252, Tecnobody, Italy) was used to assess balance control. Data were collected at the sampling frequency of 20 Hz. Subjects were tested for 30 s during upright standing under four different sensory conditions: i) eyes open, ii) eyes closed, iii) eyes open with foam a foam pad under feet, and iv) eyes closed with a foam pad under feet. All the data were averaged among the four sensory conditions before proceeding with the subsequent analyses. The evaluation was conducted considering 2 parameters that describes the center of pressure (COP) trajectory in the antero-posterior (AP) and medio-lateral (ML) directions (fig. 2.6):

- ML (AP) COP Sway [mm]: the amplitude of the COP oscillation in the ML (AP) direction, measured as the standard deviation of the COP trajectory in that direction.
- ML (AP) F95% [Hz]: the oscillatory frequency extracted as the frequency comprising 95% of the signal in the ML (AP) direction.

The two selected instrumental outcomes are widely adopted for the assessment of human balance (Rocchi, Chiari, Cappello, and Horak 2002; Rocchi, Chiari, and Horak 2002; Chiari, Rocchi, et al. 2002) and offer the possibility to investigate balance control both in the time and in the frequency domain. A previous study based on principal component analysis highlighted that, between all the commonly investigated COP measures, COP sway can be considered as one of the most meaningfull features for investigating postural control mechanisms both in ON- and OFF-medication (Rocchi, Chiari, Cappello, and Horak 2002). The selected outcomes are reported to be independent from the medication state (Rocchi, Chiari, and Horak 2002), thus reducing confounding effects due to the different time elapsed between the levodopa administration and postural sway test. Moreover, COP sway were found to be unaffected by gender effect and almost independent on the subjects' height and weight.

The procedure was conducted in accordance with a previous work of our group (Cattaneo et al. 2015). The considered parameters were previously investigated in several studies revealing to be influenced by differences related to somatosensory

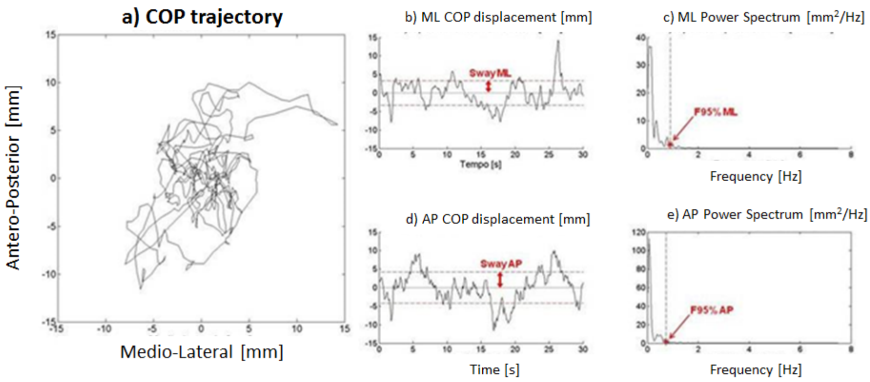

Figure 2.6: Force plate extracted features. a) COP trajectory. b-d) COP trajectory in the medio-later (ML, top) and antero-posterior (AP, bottom) direction. c-e) Power spectrum of the COP signal in the ML (top) and AP (bottom) directions.

conditions, age, and neurological disease deficits (Abrahamová et al. 2008; Rocchi, Chiari, and Cappello 2004; Prieto et al. 1996).

Patients were evaluated three times:

1. PRE: immediately before the beginning of the training program.
2. POST: immediately after completing the training program.
3. Follow Up (FU): 1 month after the POST evaluation.

At the end of the rehabilitation program, members of the TG were asked to fill in a previously validated self-compiled questionnaire, the Telehealthcare Satisfaction Questionnaire-Wearable Technology (TSQ-WT) (Chiari, van Lummel, et al. 2009), to assess the final users' satisfaction level after experiencing the new developed training based on biofeedback signals and wearable sensors. Patients could answer to the proposed questions marking their selection within five different possible levels: very negative, negative, neutral, positive, and very positive. In particular, collected answers about perceived utility, usability, and comfort of the GAMEPAD system were investigated.

Statistical analysis

Statistical analyses of the clinical scores were conducted with non-parametric tests. For each group, Friedman test was used to verify the beneficial effects of the administered treatment by comparison with data extracted during PRE, POST, and FU evaluations. If the test detected a significant difference, post-hoc analysis was conducted using Wilcox test with Bonferroni-Holm correction. Comparisons between the two different groups were conducted at PRE, POST, and FU by adoption of the Mann-Whitney U test.

Data extracted by instrumented test was analyzed with a Two-Way Mixed Design ANOVA considered as factors the time (PRE, POST, and FU) and the group (TG and CG). Due to the fact that data resulted not to be normally distributed, a logarithmic transformation was applied before proceeding with ANOVA. If significant differences were detected the following four comparisons were conducted: PRE vs POST, PRE vs FU, CG vs TG at PRE and POST.

2.1.3 Results

Performance of the GAMEPAD rehabilitation system

Sensors were singularly tested by continuous acquisition of data, starting from the battery-full state till the power-down, without reporting any malfunctioning. The mean battery life duration was estimated in 48′32″.

Considering the single- and multi-sensor configuration adopted in the exercises, six possibilities were tested. The correspondent results are reported in Table 2.2.

Table 2.2: Tested configuration of sensors and errors (absolute and percentual) over 15000 samples collected for each set of sensors.

Sensor Configuration	Number of Sensors	Number of Errors	Errors%
Trunk	1	0	0
Waist + Left Limb	3	0	0
Waist + Right Limb	3	1	0.01
Trunk + Waist + Left Limb	4	0	0
Trunk + Waist + Raight Limb	4	2	0.02
Trunk + Waist + Left Limb + Right Limb	6	1	0.01

Efficacy of the treatment - Clinical scale assessment

Assessing the effect that the biofeedback based therapeutic intervention had on the treated group (TG) the primary outcomes show a significant improvement of the clinical scores in the POST evaluation respect to the PRE test. In particular, the beneficial effect of the training can be noticed in the increasing of the BBS score (PRE, median [non-outlier range]: 48 [41-55]; POST: 52 [37-55]; $p = 0.003$) and in the reduction of the time needed to complete the 10MWT (PRE: 10.1 [6.9-17.8] s; POST: 9.1 [6.6-11.1] s; $p = 0.01$). Those differences were present also at the FU both for the BBS score (PRE: 48 [41-55]; FU: 52 [45-55]; $p = 0.021$) and 10MWT (PRE: 10.1 [6.9-17.8] s; FU: 10.8 [7.5-17.6] s; $p = 0.015$).

Analysis of the scores of the control group (CG) at the PRE, POST, and FU, did not evidence any significant modification neither in the BBS score (BBS; PRE: 47 [6-56]; POST: 49 [34-55]; FU: 47 [32-55]; $p = 0.472$) nor in the 10MWT (PRE: 12.3 [7.9-20.5] s; POST: 10.6 [7.3-16.4] s; FU: 10.8 [7.5-17.6] s; $p = 0.455$).

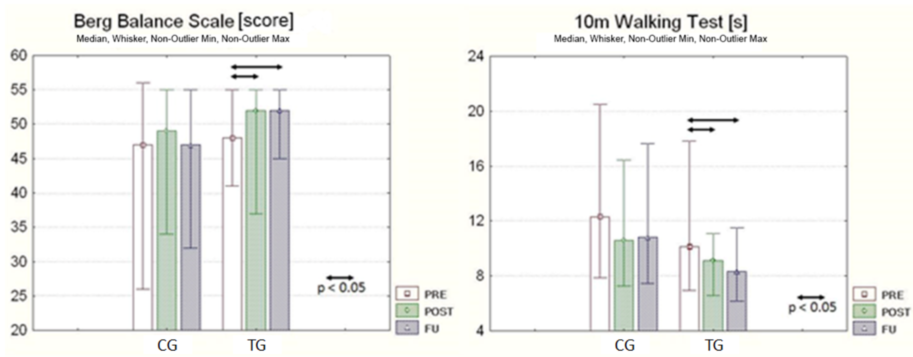

Figure 2.7: Berg Balance Scale (BBS) and 10-meter Walk Test (10MWT) scores for the Trained Group (TG) and the Control Group (CG) obtained at PRE, POST, and FU. Significant differences (p-value < 0.05) are marked with black arrows.

No differences were noticed in the other clinical scale adopted as secondary outcomes with exception of the GABS score that reported a significant better (lower) score for the trained group (TG) at the POST evaluation, as reported in Table 2.3.

When comparing TG and CG performances (fig. 2.7), TG presented better scores than CG in the BBS at POST (CG: 49 [34-55]; TG: 52 [37-55]; p = 0.091) even though the statistical significance was not completely fulfilled. Instead, the significance was reached at the FU (CG: 47 [32-55]; TG: 52 [45-55]; p = 0.039).

Analyses of the 10MWT did not present significant differences between the two groups at the POST (TG: 9.1 [6.6-11.1] s; CG: 10.6 [7.3-16.4] s; p = 0.109), while the difference at the FU was almost significant (TG: 8.3 [6.2-11.5] s; CG: 10.8 [7.5-17.6] s; p = 0.065).

*Table 2.3: Secondary clinical outcome scores (median [range]) for the Treated Group (TG) and the Control Group (CG) measured at PRE and POST. p-values extracted through the adoption of Friendman Test (Ft) are reported. Statistical significance detected using Wilcox test with Bonferroni-Holm correction is marked with *.*

TEST	GROUP	PRE	POST	FU	p(Ft)
GABS [pts]	CG	11 [1 - 23]	9 [2 - 23]	9 [1 - 20]	0.060
	TG	8 [1 - 19]	4 [0 - 18] *	6 [0 - 16]	0.011
TUG [s]	CG	18 [8 33]	13 [9 60]	14 [9 60]	0.280
	TG	15 [7 33]	12 [8 28]	12 [8 36]	0.731
ABC [pts]	CG	48 [13 81]	56 [9 83]	53 [9 75]	0.863
	TG	61 [23 - 98]	72 [29 - 98]	62 [10 94]	0.668
FOGQ [pts]	CG	14 [3 18]	14 [6 17]	12 [1 17]	0.623
	TG	12 [2 21]	11 [3 22]	11 [1 19]	0.591
PDQ-39 [pts]	CG	56 [12 98]	54 [17 - 98]	52 [13 91]	0.379
	TG	43 [14 98]	47 [3 94]	39 [8 117]	0.939

Efficacy of the treatment - Instrumetal assessment

Taking into account as factor the Time (PRE, POST, FU), the analysis of variance conducted on the amplitude of the registered oscillations (Sway) reported no significant differences neither in the antero-posterior (AP: $F_{(2,64)} = 0.004$, p = 0.996) nor in the medio-later (ML: $F_{(2,64)} = 1.36$, p = 0.263) directions (fig. 2.8a, c). When the investigation was conducted considering the factors Time and Group, a significant difference between the two groups was found in the ML Sway ($F_{(2,64)} = 5.17$, p =0.008). In particular,, at the POST a significant reduction of the ML Sway was noticed for TG and not for CG (fig. 2.8b). Those differences were not maintained at the FU. A similar behavior was noticed also in the AP Sway (fig. 2.8d) , but no significant differences were found ($F_{(2,64)} = 1.28$, p = 0.285).

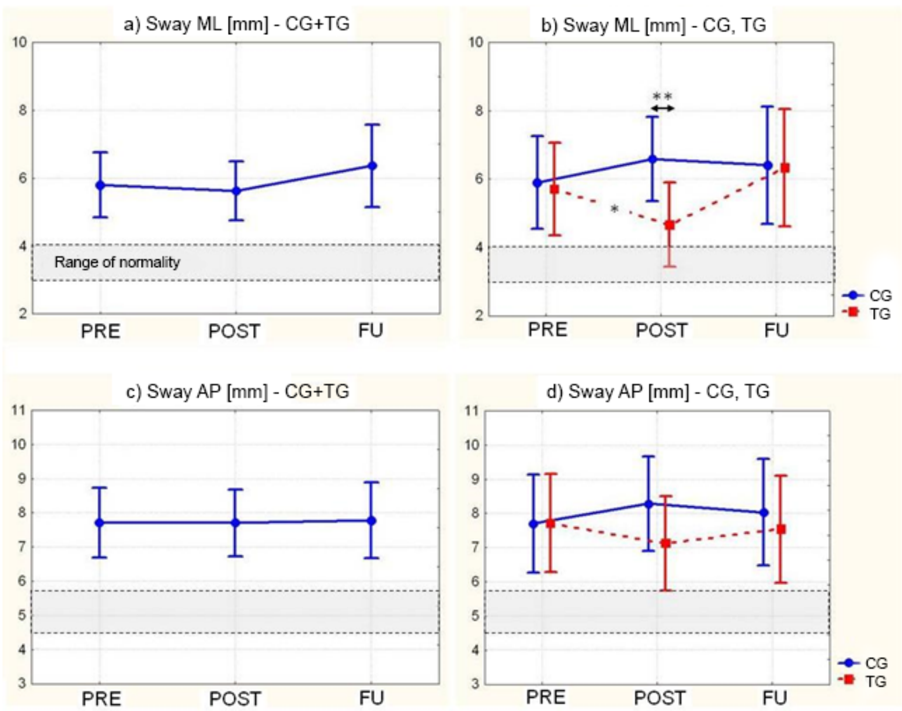

Figure 2.8: COP sway (mean 95% CI) in the ML and AP directions. a-c) measured obtained from the entire population (CG+TG); b-d) Comparison between measures obtained for CG (blue) and TG (red). Significant differences are reported (p < 0.05, ** p < 0.01). Normality bands obtained from healthy subjects of comparable age (n = 16, age, mean ± SD: 71.3 ± 6.8 years).*

Considering the oscillatory frequency, ANOVA test conducted on all the participants (TG + CG) highlighted a significant difference in the ML direction ($F_{(2,64)} = 12.92$, $p < 0.001$), while in AP a difference approaching statistical significance was observed ($F_{(2,64)} = 3.07$, p = 0.053). At the POST, a significant increase of F95% was noticed in all the directions (fig. 2.9a, c). These improvements were partially maintained at the FU. Similar results were obtained with both the treatments, as demonstrated by the lack of reported significant differences in the ML ($F_{(2,64)}$ =

1.66, p = 0.199) and AP directions ($F_{(2,64)} = 0.34$, p = 0.715) when considering in the ANOVA analysis both factors Time and Group (fig. 2.9b, d).

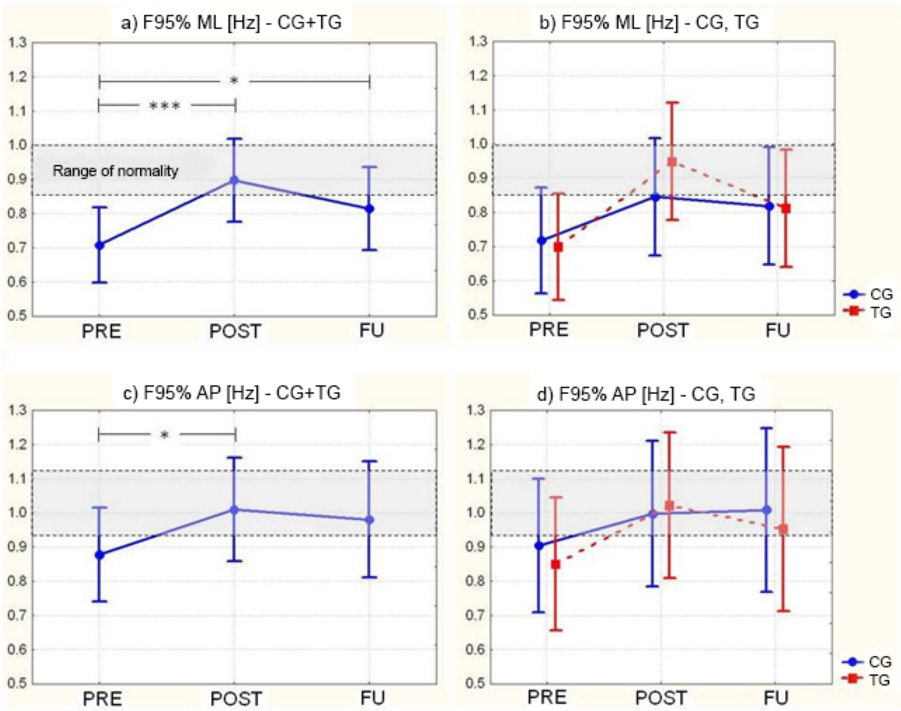

Figure 2.9: Oscillatory frequency of the COP (mean, 95% CI) in the medio-lateral (F95% ML) and antero-posterior (F95% AP) directions. a-c) measured obtained from the entire population (CG+TG); b-d) Comparison between measures obtained for CG (blue) and TG (red). Significant differences are reported ($p < 0.05$, *** $p < 0.01$). Normality bands obtained from healthy subjects of comparable age (n = 16, age, mean ± SD: 71.3 ± 6.8 years).*

Users's satisfaction questionnaire results

Data collected through the Telehealthcare Satisfaction Questionnaire Wearable Technology (TSQ-WT) were analyzed. Extracted results about utility, usability, and comfort are reported in fig. 2.10. The complete list of items for the three assessed topics and the correspondent collected answers are reported in Table 2.4.

Considering the answers collected on the perceived utility, more than half the interviewed patients reported a very positive opinion (49%), and the second most common choice was positive (41%). Only 6% of the considered sample reported a negative opinion, and no very negative answers were reported.

Concerning usability related aspects, 70% of the sample reported a general positive opinion (very positive: 39%; positive: 31%), while 12% of the collected opinions were negative and 3% very negative.

When considering the collected answers about comfort, the majority of the sample appreciated the system (very positive: 46%; positive: 29%), while 5% of the

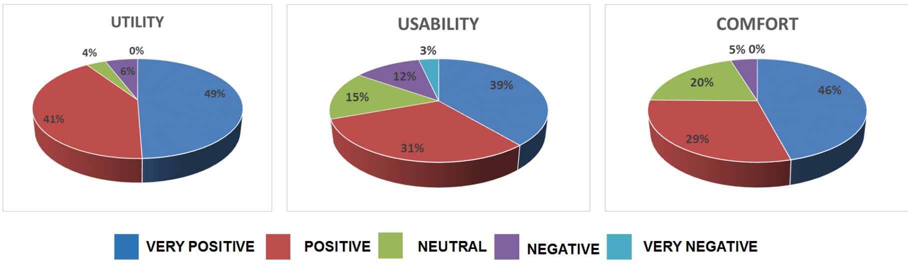

Figure 2.10: Telehealthcare Satisfactionary Questionnaire Wearable Technology. Treated group collected answer conceiving utility (left), usability (center), and comfort (right) of the adopted GAMEPAD system.

interviewees expressed a negative opinion. No participants reported a very negative score.

Looking at the single item scores, reported in Table 2.4, the most controversial result was represented by the first item of the usability part with 6 positive and 11 negative opinions. The comfort part presented the highest level of uncertainty with 17 neutral scores reported (corresponding to 20% of the total scores), followed by the usability part (13 neutral scores, 15%). Almost a half of the neutral scores reported in the comfort part of the questionnaire were given in the third item (*"I would not wish another look and design of the device (parts of the device)"*), followed by the fifth item (*"The body-worn parts of the device are difficult to adjust (fix, fasten)"*). All the other neutral answers can be considered equally distributed over the remaining items. A single interviewee reported to be mostly in disagreement with all the utility-items, with the exception of the second one scored as *"mostly agree"*, with usability-item 5, reporting a neutral score in items 2 to 4, and with comfort-items 1 and 5.

Table 2.4: Telehealthcare Satisfaction Questionnaire Wearable Technology (TSQ-WT) collected answers.

		Strongly Disagree	Mostly Disagree	Neither Agree nor Disagree	Mostly Agree	Strongly Agree
UTILITY	1 I can benefit from this technology	0	1	0	9	7
	2 The effort of using this technology/method is worthwhile for me	0	0	1	7	9
	3 I am confident I'm getting the most out of this technology/method	0	2	1	4	10
	4 This Technology/method is helping me to achieve my goals	0	1	1	10	5
	5 I would this technology/method to other people in my situation	0	1	0	5	11
	Total	0	5	3	35	42
USABILITY	1 The use of this technology/method does not require effort	3	8	0	4	2
	2 The technology/method is reliable according to my estimation and experience so far	0	0	3	6	8
	3 This technology/method is easy to use	0	0	3	5	9
	4 I feel safe when using this technology/method	0	0	3	8	6
	5 I feel good while using this technology/method	0	2	4	3	8
	Total	3	10	13	26	33
COMFORT	1 Wearing this device (parts of the device) is comfortable	0	2	1	5	9
	2 I am pleased with the size of the device (parts of the device)	0	0	2	6	9
	3 I would not wish another look and design of the device (parts of the device)	0	0	8	1	8
	4 I am pleased with the weight of the device (parts of the device)	0	0	1	8	4
	5 The body-worn parts of the device are difficult to adjust (fix, fasten)	0	2	5	5	5
	Total	0	4	17	25	35

2.1.4 Discussion

The tests conducted on the developed GAMEPAD rehabilitation system before its application in the experimental study confirmed the usability of this technical solution in the rehabilitation practice. The adoption of commercial wearable sensors product reduced the time required for the development without presenting any substantial side effect. The duration of the battery life of the wearable devices resulted to be suitable with the rehabilitation training, even if a full-charging operation had to be performed between two consecutive training sessions. Considering problems in data acquisition and synchronization, the minimal number of detected wrong events, confirmed that the reliability control included in the software was suitable to prevent crashes during the execution of the exercises without influencing the correctness of the collected data. This result is of major importance for both the biofeedback generation and the final data analysis.

The preliminary results, obtained from the conducted RCT study, suggested a higher efficacy of the physical rehabilitation protocol based on biofeedback signals in comparison with usual care training. In particular, only the patients that received the novel treatment presented significant improvements in both the Berg Balance Scale score (BBS: +4) and the 10-meter walk test (10MWT: -1 s). These benefits were maintained at the follow up evaluation conducted one month after the training ended. Better performances of the patients that received the treatment with biofeedback respect to the control group were also detected by direct comparison of the two populations at the end of the rehabilitation intervention and at follow up, even though the statistical significance was not reached. Instrumental measures extracted from the stabilometric platform supported the higher efficacy of the biofeedbackbased therapy showing a significant reduction of the postural oscillations, that is commonly considered to be an index of better balance control (Abrahamová et al. 2008; Rocchi, Chiari, and Cappello 2004; Prieto et al. 1996), in particular in the medio-lateral directions.

One of the main risks associated with the adoption of augmented external information in the rehabilitation practice is represented by the possibility that the presence of biofeedback could lead to a kind of specificity of learning, with a consequent deterioration of performance once the sensory information is withdrawn (Proteau et al. 1992; Verschueren et al. 1997; Nieuwboer, Rochester, et al. 2009). This risk seems not to influence the intervention methodology adopted in this study as shown by all the evaluations performed at POST and FU on different tasks respect to those adopted in the training and with no external sensory aid. Previous studies were external stimuli were adopted reported controversial results about the long-term efficacy of the treatment (Nieuwboer, Rochester, et al. 2009; Morris et al.

1996; Rochester, Nieuwboer, et al. 2007). Interestingly, the ameliorations obtained with the adoption of the GAMEPAD system were maintained 1 month after the end of the treatment.

The preliminary data reported in the Telehealthcare Satisfaction Questionnaire supported a possible interest of subjects affected by Parkinson's disease in the use of wearable devices for rehabilitation. The opinion of the final user on the GAMEPAD multi-sensor rehabilitation system was positive. In particular, the majority of the interviewees reported very good opinions when asked about the perceived utility of the device. The most controversial result was obtained for the first item of the usability part. This was the only item to receive very negative scores (n = 3) and to report the worst evaluation with a total of 11 negative scores (3 *"very negative"* and 8 *"negative"*). However, it has to been noticed that the questionnaire was administered translated into Italian and this fact could lead to a possible misunderstanding of the meaning of the proposed question. The word *"effort"* has been translated as *"impegno"* and could be interpreted with either a negative (i.e. *"Obligation assumed in regard to other people to do something or to perform a service"* (Treccani 2016)) or positive (i.e. *"Attentive and diligent care, use of all the good will and strength in doing anything"* (Treccani 2016)) meaning. Hence, the obtained answer could be strongly affected by the personal interpretation and this fact might partially explain the distribution of the given answers. This hypothesis is supported by the very small number of negative opinions given in all the other items of the usability part. Without considering the first item 78% of the collected answers was positive or very positive, 3% negative, while no very negative scores were reported. Considering the comfort sub-questionnaire, negative scores were reported in item 1 (*"Wearing this device (parts of the device) is comfortable"*) and 5 (*"The body-worn parts of the device are difficult to adjust (fix, fasten)"*). It is our opinion that the adoption of anti-slippery elastic bands with Velcro could represent a sub-optimal solution. In fact, elastic bands could be uncomfortable if they are too too thight, and Velcro could strongly adhere to different fabrics making the fixing of the sensors not immediate. These two possible limitations need future assessment with the adoption of alternative fixing solutions. Finally, the item number 3 (*"I would not wish another look and design of the device (parts of the device)"*) was scored with the highest number of neutral opinions. This fact could be explained by the lack of a basis for comparison due to the novelty of this kind of technological rehabilitation systems. A future miniaturization of the adopted wearable devices might possibly lead to a reduction of the discomfort manifestated by some of the interviewee. However, considering that subjects affected by PD are typicall elderly and that both the disorder- and the age-related problems could impair fine movements (Pradhan et al. 2015; Uitt et al. 2005), the manageability of the system will have to be safeguarded, thus limiting the reduction of the sensor's external case.

Limitations

The main limitation of the present study is represented by the small sample size that could have affected the statistics reducing our comprehension of the obtained results. Another constraint was induced by the small sample size of the interviewees on the final satisfactory questionnaire. This last problem would be partially overtaken when all the data collected from the entire treated group will be available.

2.1.5 Conclusions

Considering that BBS reflects ability in static and quasi-static balance control and that 10-meter Walk Test assesses ability in dynamic balance control and walking, it can be speculated that the adoption of biofeedback, administered both as real-time correction signals and as a final summary score, could have a widespread beneficial effect on several different aspects of the multifactorial rehabilitation of Parkinson's disease. Finally, it is opinion of the author that the adoption of robust biofeedback system based on small, cost-effective, wearable inertial sensors in the treatment of Parkinson's disease might offer an intriguing possibility to counteract, at least partially, the progression of the symptoms by administering patient-tailored exercises directly at home.

2.2 A low complexity algorithm for real-time step recognition designed for wearable embedded systems: a pilot evaluation on previously recorded data from people affected by Parkinson's disease.

2.2.1 Introduction

Gait analysis is a valuable instrument for obtaining objective quantitative information on motor deficits and it is widely adopted by clinicians to assess, plan, and treat patients affected by neurological disorders. Kinetic and kinematic data are commonly recorded through stereophotogrammetric optoelectronic systems and force platforms, that can be considered as gold standard. Otherwise, the adoption of these instruments results to be quite expensive and time-consuming and requires dedicated motion analysis laboratory and trained personnel (Henriksen et al. 2004). As a consequence of the fact that typical gait analysis needs to be conducted in a laboratory setting, this kind of solutions cannot consistently account for subject's daily functioning (R. Baker 2006).

In the last two decades the availability of cheap miniaturized inertial measurement unit (IMU) sensors made possible to investigate their adoption for posturographic exams and gait analysis with reliability similar to commercial movement analysis systems (Whitney et al. 2011). Since their introduction, IMUs have been widely used to realize cost-effective and easy-to-use wearable motion-sensing systems. So far, wearable inertial solutions have been applied in studies focused on balance control (Mancini, Carlson-Kuhta, et al. 2012; Mancini, Salarian, et al. 2012), anticipatory postural adjustments (APAs) (Rocchi, Mancini, et al. 2006; Mancini, Zampieri, et al. 2009; Bonora et al. 2015), gait analysis (A. Zijlstra et al. 2003; Salarian et al. 2004; Dijkstra et al. 2008; Gonzalez et al. 2010; Yang et al. 2011; Rampp et al. 2014; Ferrari et al. 2015), tremor estimation and filtering (Mellone et al. 2011; Carpinella et al. 2014). Due to their high level of portability, wearable motion-sensing systems were also used to monitor falls in the elderly and frail people (Bagalá et al. 2012; Kwolek et al. 2014; Ozdemir et al. 2014) and to study daily activities (Weiss, Herman, et al. 2011; Weiss, Brozgol, et al. 2013; Fokkenrood et al. 2014; Gupta et al. 2014; Lauret et al. 2014; Verwey et al. 2014; Vooijs et al. 2014). More recently, these devices were also adopted in biofeedback based rehabilitation tools (Chiari, Dozza, et al. 2005; Nicolai et al. 2010; Mirelman, Herman, et al. 2011).

The importance of physical exercise to prevent or, at least, to slow down the deterioration of postural control and motor performances, and to prevent falls in older adults is well known and documented (Cameron et al. 2012; Gillespie et al. 2012), as well as in subjects affected by neuromotor disorders (Park et al. 2016; Sparrow et al. 2016). In particular, for patients affected by Parkinson's disease (PD), the most common disorder which leads to gait disturbance and falls between neurological patients (Stolze et al. 2005), exercise interventions proved to be useful for improving balance and gait, and for reducing the fall risk (V. A. Goodwin, Richards, Taylor, et al. 2008; V. A. Goodwin, Richards, Henley, et al. 2011; V. a. Goodwin et al. 2014; Oguh et al. 2014). It has been estimated that the amelioration induced by effective rehabilitation strategies can lead to a reduction of fall risk, increasing, at the same time, the level of autonomy and quality of life of PD patients, thus resulting in a significant socio-economic impact (Fletcher et al. 2012).

However, due to the chronic progressive course of the disease, physical therapy can only induce temporary motor improvements with the consequence that training sessions have to be repeated over time as often as possible. In particular, exercises conducted with the aid of augmented sensory information have been reported to be particularly enhancing in the treatment of neurological disorders, but their efficacy in the rention of the beneficial effects over a long-time period is still controversial (Nieuwboer, Rochester, et al. 2009; Morris et al. 1996; Rochester, Nieuwboer, et al. 2007). In order to reduce the number of training sessions to be conducted in typical rehabilitation gyms and to preserve the patients' autonomy and quality of life, the possibility to administer exercises directly at home is progressively generating more interest. In the last few years several studies investigated the opportunity of developing tele-monitoring and tele-medicine solutions to propose home-based training. Commercial products such as Nintendo Wii Fit (Jorgensen et al. 2013; Rendon et al. 2012; Klompstra et al. 2014; Pau et al. 2015; Llorens et al. 2015) and Microsoft Kinetic (D. Lim et al. 2015; Clark et al. 2015; Colagiorgio et al. 2014; Morrison et al. 2014) have already been adopted. Nevertheless, in the majority of the studies presented in literature, only exercises for upper limb and balance control were mainly assessed. More recently wearable solutions for gait rehabilitation have been proposed (Casamassima et al. 2014; Hegde et al. 2015), however the adoption of biofeedback for gait rehabilitation has still to be adequately investigated. It is our opinion that the adoption of a single wearable embedded device characterized by good performance in real-time step recognition, mechanical robustness, ease-of-use, and long-lasting battery life might represent an intriguing solution to help healthy elderly and neurological affected people in improving their walking skills. Therefore, the purpose of the present study is to develop a novel algorithm for real-time step recognition that could be easily integrated in a cost-effective embedded sensor.

2.2.2 Methods

Participants

Ten healthy young adults (age, mean $\pm$ SD: 33.4 $\pm$ 7.9 yo, range 23 - 43 years, 5 females), ten healthy older adults (age 65.6 $\pm$ 6.1 yo, range 60 - 77 years, 5 females) and ten patients affected by Parkinson's disease (71.2 $\pm$ 7.5 yo, range 62 - 83 years, 4 females) voluntarily participated to the study.

Healthy subjects were excluded if they presented any neurological disorders, if they used orthotic devices or had artificial joints, or if they were under medication that could affect balance or locomotor functions.

Subjects with PD were recruited within a group of patients enrolled in a neuromotor rehabilitation program administered at Don Carlo Gnocchi Foundation rehabilitation institute. Inclusion criteria were: diagnosis of idiopathic Parkinson's disease, Hoehn & Yahr (H & Y) stage (Hoehn et al. 1967) between 2 and 4, Mini Mental State Examination (MMSE) score (Folstein et al. 1975) higher than 24, ability to stand unsupported for more than 10 s, ability to walk for at least 3m without any walking aid. Patients were clinically rated by a trained examiner on the H & Y scale and on the motor section III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al. 1987) immediately before the beginning of the experimental section.

All the participants provided informed consent forms approved by the local Ethical Committee.

Experimental design

Each subject was asked to perform a 3m-walk test at self-selected speed. At the beginning of the task, participants stood in an upright comfortable position with arms laying on the sides for at least 10 s, waiting for a start vocal command from the examiner. Each task was performed 3 times.

Participants wore comfortable clothes and shoes with no heels: no given distances between the feet were imposed.

Patients were tested while being under their routine therapy in a typical rehabilitation setting before the beginning of their conventional physiotherapy session, while healthy subjects were examined in a typical motion analysis laboratory.

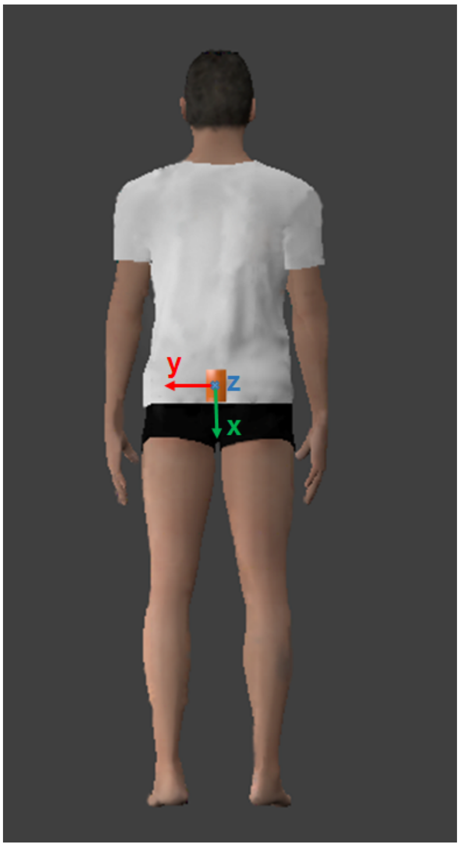

Figure 2.11: Wearable inertial sensor placement

All the participants wore an inertial sensor (TMA, Tecnobody, Dalmine, Italy) embedding a 3D accelerometer (range ± 5 g), and a 3D gyroscope (range ± 2000 °/s). The sensor was placed over the clothes on the posterior trunk, in correspondence to L2-L4 vertebra, with the sensing axes (x, y, and z) oriented along the body vertical, medio-lateral, and antero-posterior directions, respectively (fig. 2.11).

Linear acceleration and angular velocity data were sampled at 50 Hz and transmitted to a remote PC via a Bluetooth wireless connection where they were recorded. For the purpose of the present study only linear acceleration data were considered for the subsequent signal analysis.

Data processing

The shape of the antero-posterior acceleration signal collected from a sensor placed posteriorly on the trunk at the lumbar level can be predicted adopting a single-link inverted pendulum model (W. Zijlstra et al. 1997). During physiological straight walking, in midstance the body is supported by one single leg and starts to move from force absorption at impact to force propulsion forward. The resulting practical fall of the inverted pendulum determines an increase of the forward acceleration. After the contralateral foot contact, during the transition from single to double support, the forward fall of the body changes into an upward movement, inducing a consequent deceleration of the forward movement. Consequently, the foot contact can be recognized approximately in correspondence of the zero-crossing of the antero-posterior acceleration signal (A. Zijlstra et al. 2003). In a refinement of the method proposed in the same paper, the authors suggested to take as the instant of foot contact the peak forward acceleration preceding the change of sign.

Hence, the design of the novel algorithm has been intended for a correct real-time detection of the above mentioned peak of acceleration using only simple and computationally cost-effective filtering techniques.

Of the three signals acquired by the 3D accelerometer only the one recorded along the body sagittal axis was considered. The signal was automatically smoothed in real-time with two parallel moving average filters characterized by lengths of 8 and 16 samples respectively.

To implement the moving average filter in a way suitable for the adoption in low-cost embedded systems a ring buffer structure was adopted and a smart procedure for the extraction of the mean that reduced the arithmetical operations was proposed (fig. 2.12). In particular, adopting the classic definition of arithmetic mean (fig. 2.12b) implies a dependency of the filtering function from the length of the ring buffer. Indeed, N additions, with N equal to the length of the buffer, and one division are required. On the contrary, the smart method adopted in the final solution (fig. 2.12c) is independent from the buffer length and needs one subtraction, one division, a)

```c
typedef struct {
   float *data;
   int index;
   int length;
   float mean;
   float previous_mean;
} FILTER;
```

b)

```c
void filter_update (FILTER *filter, float value)
{
   int counter = 0;
   float accumulator = 0;
   filter->previous_mean = filter->mean;
   filter->data[filter->index] = value;
   for (counter = 0; counter < filter->length; counter++)
      accumulator = accumulator + filter->data[filter->index];
   filter->mean = accumulator / filter->length;
   filter->index++;

   if (filter->index == filter->length)
      filter->index = 0;
}
```

c)

```c
void filter_update (FILTER *filter, float value)
{
   filter->previous_mean = filter->mean;
   filter->mean = filter->mean – filter->data[filter->index];
   filter->data[filter->index] = value / filter->length;
   filter->mean = filter->mean + filter->data[filter->index];
   filter->index++;

   if (filter->index == filter->length)
      filter->index = 0;
}
```

Figure 2.12: C code implementation for the moving average filter: a) Definition of the filter structure; b) function for the extraction of the filter output through the adoption of a classic arithmetic mean approach; c) proposed method for the extraction of the filter output.

and one addition at each cycle. Fixed point mathematic was also adopted to fastener the computational procedures. When the values were reported as fixed point the chosen length of the filters permitted to operate the only required division - by a simple logical shift.

The subsequent recognition process is based on a finite-state machine (FSM) with five states (i.e. INIT, CALIBRATION, WAIT, SEARCH, REFRACTARY), as reported in fig. 2.13. The algorithm execution starts in the INIT state needed for filling up the filters' buffers. When the operation on the longer buffer is finished the state machine changes to CALIBRATION. Here, the subject wearing the device has to freely perform a first 3m training walk. On the basis of the recorded data, a threshold was computed as 20% of the maximum value of the raw signal and maintained in memory for all the subsequent analyses. The FSM goes on to the WAIT state and remains there until the raw signal becomes higher than the previously set threshold. Hence, the FSM state changes to SEARCH, where the foot contact instant is detected as the first instant in which both the filtered signals decrease (double check decision).

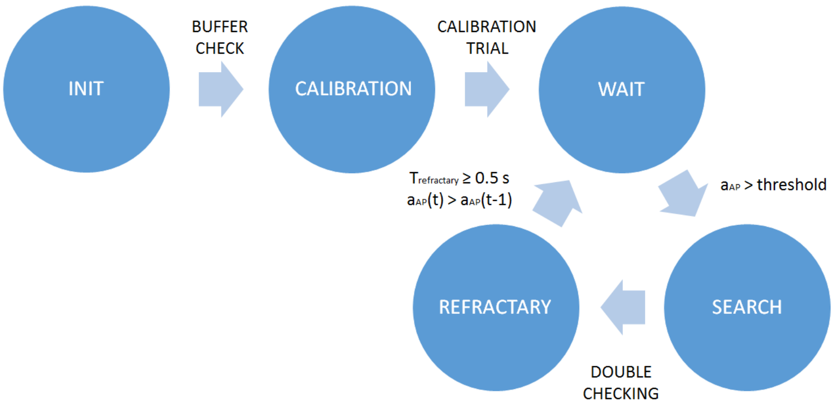

Figure 2.13: State diagram of the recognition finite state machine (FSM).

Each step recognition is followed by a refractory period (REFRACTARY state), lasting at least 0.5 s, in which no foot contact detection is conducted. When the refractory period of 0.5 s is ended and both the filtered signals present an increasing trend the FSM goes to the WAIT state starting a new cycle.

The algorithm performances were tested on two different evaluation board: a ST NUCLEO STM32F030 (ST Microelectronics, Italy), and an Arduino Uno R3.

The STM32F030 represents the entry-level MCUs from ST Microelectronics. The board is intended for a fast development of mainstream solution, particularly oriented to the 8-/16-bit world. Our model (STM32F030R8) included an ARM Cortex-M0 operating at 48 MHz, 32 Kbyte of SRAM, and 64 Kbytes of flash memory. The board was programmed using the ARM Mbed SDK and the compiler available freely online.

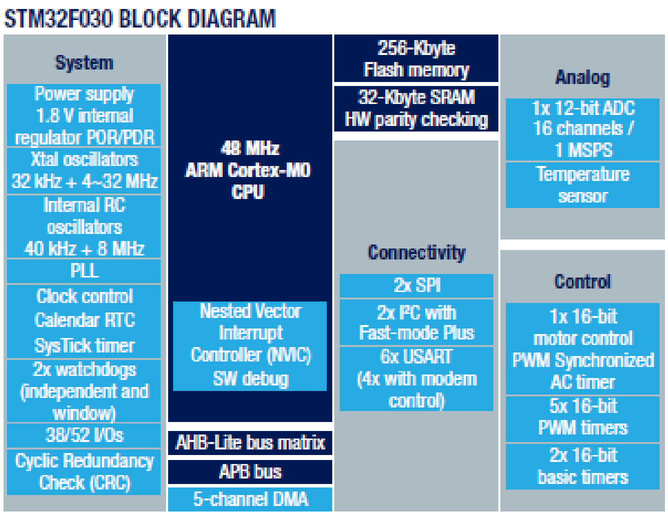

Figure 2.14: Block diagram of the STM32F030 boards family.

The Arduino UNO Rev3 is a microcontroller board based on the 8-bit ATmega328P core by Atmel. It works at a clock frequency of 16 MHz, with 2 Kbyte of SRAM, and 32 Kbyte of flash memory. This board represents one of the most popular low-price, open source (Creative Commons CC-SA-BY License) boards for hobbyists worldwide. Indeed, it has been estimated that in mid-2011 over 300,000 official Arduinos had been commercially produced, and that in 2013 700,000 official boards were in final users' hands (Wikipedia 2016). The Arduino board was programmed using the Atmel Studio 6.0 software (Atmel Corporation, USA).

Algorithm performances were measured by extracting the time needed to update the filters and for performing the step recognition procedure (i.e. update of the filters and double check). Considering the filter update function, the classic arithmetic mean and the smart procedure reported in fig. 2.12b with both the floating point and fixed point variables representation were considered.

A brief test to verify the technical applicability of the developed method in an embedded system was conducted on 4 healthy people. The algorithm was uploaded in a wearable prototype, formally named DGstep, designed in collaboration with the Dipartimento di Elettronica, In formatica, e Biongegneria, Politecnico di Milano, Milan, Italy. The device includes a microprocessor and 3D accelerometer, gyroscope and magnetometer (i-NEMO, ST Microelectronics). Raw acceleration signals and the detected foot contact instants were send to a remote laptop through zig-bee connection. Visual inspection was conducted on the on-line plotted signal reporting also the recognized step instants while subjects were performing 3m-walk test and free walking (fig. 2.15).

Figure 2.15: DGStep Diagnostic tool. Foot contact events detected in real-time are marked with red dots. Step frequency extracted from the last 10 steps (Last Frequency) and the average value since the beginning of the trial (with the correspondent standard deviation) are reported in the boxes on the left. Time is reported in [s]*, accelerations in* [mm/s^2]*, step frequency in* [Hz]*.*

The method proposed by Zijlstra et al. (A. Zijlstra et al. 2003) (reference method or R-method) was considered as gold standard due to the optimal performances demonstrated when applied to different populations including subjects with PD, as reported in a previous study (Trojaniello et al. 2015). This method was applied off-line on data previously collected from 3 different populations (i.e. healthy young and older adults, and subjects with PD) to identify the exact foot contact (FC_{ex}) instants to be used in subsequent comparison. The algorithm developed in this study (novel method or N-method) was tested in a real-time simulation conducted on the same dataset. To verify the benefits introduced by the signal double-check decision, data extraction was performed two more times by applying a single check decision based on only one of the two filters each time (foot contact is detected when the single filtered signal considered presents a value lower than the ones computed in the previous computational step) (fig. 2.13). Finally, a real-time simulation was performed also with the zero-crossing procedure presented by Zijlstra et al. (A. Zijlstra et al. 2003) (zero-crossing method or Z-method). For each method, the delays in the recognition of foot contact instants, measured as the time difference between the detected instants and the ones extracted with the gold standard were calculated.

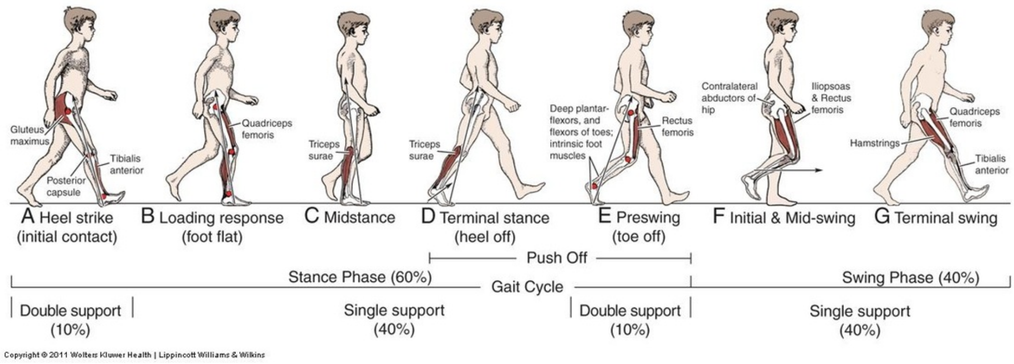

Figure 2.16: Different phases of the gait cycle.

The mean step duration for the three goups of participants was extracted through the application of the gold standard as the time between two consecutive foot contact detections (one per leg). Considering that the step time corresponds to a half of the gait cycle duration, the foot contact identification was considered correct if the contact was recognized during the double support phase, corresponding to approximately 10% of the gait cycle or 20% of the step time measured by the gold stard (fig. 2.16). The number of correct foot contact identifications (true positive, FC_{tp}) and of additional incorrect detections (false positive, FC_{fp}) were extracted.

Sensitivity of the different methods and the percentage of false recognition over the total number of FC detected by the considered method were finally compute as:

$$Err\% = FC_{fp} / \left(FC_{tp} + FC_{fp}\right) * 100$$

Statistical analysis

For each subject, the extracted delays in the recognition of the foot contact instants were averaged over the three trials. Kruskal-Wallis rank sum test was used to verify if the mean step duration was significantly different between the 3 groups of paticipants and to assess differences in the application of all the methods to the 3 different populations. Wilcoxon test was adopted to compare performances obtained by applying N- and Z-method to each population.

The level of significance was set at 0.05 for all the tests.

All the analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

2.2.3 Results

Algorithm performance

The evaluation of the time needed to update the moving average filter was conducted considering three different implementations of the filter:

- Based on the definition of arithmetic mean (fig. 2.12b)
- Based on the proposed smart approach (fig. 2.12c)
- Based on the proposed smart approach using fixed point numerical representation.

Results obtained for the 8- and 16-samples filters using both the ST Nucleo STM32F030 and the Arduino boards are reported in Table 2.5.

The required time reported for the entire step recognition procedure, that in the FSM SEARCH state corresponds to the update of the two filters and a subsequent double check to verify that both the filtered signal start to decrease (fig. 2.13), can result inferior to the sum of the time needed for the two filtering procedures. This result, even though being counterintuitive, can be explained considering the code optimization conducted by the compiler on the specific hardware.

Table 2.5: Algorithm performance for filtering and for the full step recognition procedure. Data are reported in [s]. Percentage value respect to the sampling time (0.02 s) are reported in parentheses.

Board Model	Clock Frequency	Computational Method	8-samples Filter	16-samples Filter	Step Recognition
ST Nucleo	48 MHz	Arithmetic Mean	27 (0.14)	42 (0.21)	70 (0.35)
		Smart (Floating Point)	16 (0.08)	16 (0.08)	33 (0.17)
		Smart (FixedPoint)	5 (0.03)	5 (0.03)	9 (0.05)
Arduino UNO	16 MHz	Arithmetic Mean	90 (0.45)	137 (0.69)	235 (1.18)
		Smart (Floating Point)	53 (0.27)	53 (0.27)	115 (0.58)
		Smart (FixedPoint)	5 (0.03)	5 (0.03)	24 (0.12)

Step recognition

Applying the R-Method to the collected data, a total of 377 foot contacts were detected and used for subsequent comparative analyses.

No singnificant differences were found considering the step duration between the 3 considere groups (young, mean $\pm$ SD: $0.73 \pm 0.09\,s$, old: $0.75 \pm 0.07\,s$, PD: $0.68 \pm 0.11\,s$, p-value $= 0.2$). Hence, the maximum accepted delay for considering the step detection as correct was set as 20% of the mean step duration calculated over the 3 groups ($\Delta t_{MAX} = 0.14\,s$).

The number of correct (FC_{tp}) and incorrect (FC_{fp}) detections obtained on the different groups are reported in Table 2.6. Sensitivity of the different methods and the percentage of incorrect detection (Err%) are also shown.

Table 2.6: Real-Time step recognition performance. The number of foot contact events detected through the gold standard (FC_{ex}), and the number of true positive (FC_{tp}) and false positive (FC_{fp}) detection are report for the double check decision and for the two single check decision (8-samples and 16-samples) are reported. The sensitivity (in percentage, Se%) and the percentual error (Err%) are also shown.

		Single Check (8-samples)				Single Check (16-samples)				N-method (Double Check)			
	FC_{ex}	FC_{tp}	FC_{fp}	Se %	Err %	FC_{tp}	FC_{fp}	Se%	Err%	FC_{tp}	FC_{fp}	Se%	Err %
YOUNG	107	74	31	69.2	29.5	95	14	88.8	12.8	97	5	90.7	4.9
OLD	114	86	27	75.4	23.9	102	10	89.5	8.9	109	0	95.6	0
PD	156	129	21	82.7	14.0	140	10	89.7	6.7	151	0	96.8	0

As reported, the sensitivity was higher than 90% for all the groups, and over 95% for healthy elderly and PD patients. Sensibility of the N-method resulted to be significantly higher than the values obtained by using the single check decision approach.

Table 2.7 summarizes the delays in the initial foot contact recognition computed applying the novel proposed solution and the zero-crossing algorithm.

Considering the delay values extracted with novel algorithm, it is possible to notice that the worst performance, thus the longer delay, was obtained on the group of the PD patients, while the best one was reported for the healthy elderly. However, no differences resulted significant when statistical analysis was performed. Using the Z-method, instead, the best result was obtained for the PD group, while no difference was shown between the two groups of healthy subjects. Comparing the delays obtained with N- and Z-method the first ones resulted to be significantly shorter, thus better, for all the different populations.

Table 2.7: Delays in the foot contact recognition (mean ± SD [s]) respect to the instant detected through the gold standard.

	Single Check (8-samples)	Single Check (16-samples)	N-method (Double Check)	Z-method
YOUNG	0.067 ± 0.058	0.052 ± 0.024	0.052 ± 0.025	0.320 ± 0.048
OLD	0.053 ± 0.018	0.048 ± 0.016	0.047 ± 0.015	0.298 ± 0.067
PD	0.061 ± 0.021	0.066 ± 0.021	0.063 ± 0.019	0.305 ± 0.050

2.2.4 Discussion

The developed procedure for step recognition demonstrated to be suitable for application in low-cost embedded systems. All the test conducted on the development boards reported durations inferior to 1% of the sampling time with the exception of the adoption of the algorithm based on the definition of arithmetic mean on the Arduino board. As expected, the board based on the 32-bit core architecture resulted to be more performing respect to the 8-bit core system. However, with the adoption of fixed point numeric representation also the Arduino 8-bit board required only 0.12% of the available time to complete the step recognition procedure.

These results underlined the possibility to utilize the majority of the time between two consecutive data acquisitions by performing more complex analysis for biofeedback generation, suggesting the usability of this solution for future development on embedded systems.

The application of the developed method in real-time simulation on data previously recorded has shown interesting performances both for the entity of the delay in foot contact recognition and for the reported sensitivity. The detection of no false positive events supports the possibility of a future adoption on the algorithm for the real-time augmented feedback correction of gait disturbances without introducing disturbing not synchronized signals.

The introduction of a delay is unavoidable when the algorithm for foot contact recognition is applied in real-time analysis, hence it is important to guarantee that the delay is as short as possible or, at least, short enough to be acceptable for a clinical adoption. Considering previous studies already published in literature, the detected instant, due to the introduced delay, could not correspond to the initial foot contact, but more possibly with the beginning of the forefoot loading (Gonzalez et al. 2010; Menz et al. 2003).

Other solutions for real-time step detection have been proposed before, however the proposed methods used numerous sensors or complex computational operation that could slow down the system or inhibiting the contemporary functioning of algorithm designed for signal analysis and biofeedback generation (Gonzalez et al. 2010). On the contrary, it was our intention to develop a new methodology that, by using only very simple smoothing filtering solution, could be integrated in future biofeedback based solution for gait rehabilitation.

Limitations

Major limitation of this study is represented by the fact that the developed algorithm has been tested only in real-time simulation on previously recorded data. However, the simplicity of the method would permit the integration of the correspondent code in an embedded system (e.g. Arduino) with the consequent possibility to conduct a complete on-line validation of the method. Even though the developed real-time step recognition algorithm might offer the possibility to develop cost effective, easy-to-administered, embedded systems for gait rehabilitation, the possibility to identify the different phases of the gait cycle could offer addiotional important information for the design of more effective exercises. Hence, future studies are needed to investigate the applicability of the proposed smoothing solution to the identification of the gait phases.

2.2.5 Conclusions

The present study demonstrated the applicability of the developed low complexity algorithm for real-time step recognition in low-cost embedded devices. The good performances reported in the detection of foot contact instans during healthy and pathological straight waliking, and the low computational requirements suggest the the possibility to adopt the proposed solution in future wearable systems for gait rhabilitation.

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Chapter 3

Postural stabilization following dynamic perturbations of the base of support

3.1 Postural stabilization following dynamic perturbations of the base of support: feasibility and preliminary results on healthy subjects and patients with Parkinsons disease

3.1.1 Introduction

Balance control represents a highly demanding task that is required in almost all the activities that people perform in their daily living. In particular, all the situations that need a transition to or from different postures, such as initiation or termination of gait, sit-to-stand and vice versa and balance recovery after an external perturbation depend upon the modulation and switch between specific motor programs (Krebs et al. 2001). However, the ability to preserve balance under different environmental conditions could be affected by ageing, neurological disorders, and several sensorimotor factors. It is already well known that aging is characterized by a progressive functional loss with a gradual deterioration of the integrity of many physiological systems that participate in the control of postural stability (Horak, Shurpert, et al. 1989; Overstall 1980; Woollacott et al. 1988). In particular, age-related modifications can be observed in changes to the properties of the neuromuscular system (Hamerman 1990), reduced neural conduction velocity (Mortimer et al. 1982), and increased reaction time to external stimuli (Harridge et al. 1996). Age-related changes in the neuromuscular control and decreased resolution of the sensory inputs result in augmented noise and physiological delays of the sensory signals when compared to young healthy subjects (Blaszczyk, Hansen, et al. 1993; Blaszczyk, Lowe, et al. 1994). Body-orienting reflexes, muscle strength and tone, and height of stepping also decline with ageing (Rubenstein 2006). As a consequence of the deterioration of the physical systems involved in the balance control process, falls are a common and often devastating problem among older people. In a previous study (Rubenstein 2006), it was reported that about 40% of the population of the United States aged 65 or more fall at least once per year. Even if the majority of the falls result in no serious injury, about 5% of the events in people between 65 and 75 years and 10% in people over 75 years induces fractures or requires hospitalization. Of those admitted to hospital after a fall, only about a half will be alive a year later. In the same paper the author reported that gait and balance disorders or weakness are the second cause of falls in the elderly, accounting for 17% of the total, while accidental and environment-related causes represent the first one, accounting for 31% of the total.

Due to the general deterioration of motor performances, the capability to react efficiently to an external perturbation, as well as to avoid a fall after an unexpected trip or slip are often compromised.

Previous studies have shown that compensatory postural adjustments needed for the recovery of stability consist of multijoint coordination underlying the contribution of a variety of body segments (Hsu et al. 2013) and that the sensorimotor system uses the movement of all the major body segments to stabilize the centre of mass (COM) in healthy young adults (Scholz et al. 2007). Nevertheless, the strategies adopted for maintaining balance change with ageing with a progressive reduction of the ability to correct in time to prevent a fall (Rubenstein 2006). Greater balance perturbations may result in stepping or grabbing onto a stable object as the only potential strategy to recover equilibrium, since the ankle or hip strategies might not be successful anymore (Blaszczyk and Michalski 2006).

Balance control, as well as general motor performances, can be worsened by typical age-related disorders (Batchelor et al. 2012; Callaly et al. 2015; Minet et al. 2015; Bonora et al. 2015). Parkinsons disease (PD), in particular, is known to cause postural instability (Oates et al. 2013), to interfere with the integration of feedforward and feedback-based movements (Abbruzzese et al. 2003; Horak, Dimitrova, et al. 2005), and to affect the ability to quickly change motor programs and to appropriately scale the size of postural responses depending on the magnitude of the perturbation (Bronstein et al. 1990; Horak, Frank, et al. 1996; Horak, Nutt, et al. 1992). This disorder represents one of the most debilitating pathologies in the elderly and affecting more than 5 million cases worldwide (Olanow et al. 2009). The incidence of the pathology raises with age with no evidence of a plateau (Wright Willis et al. 2010). Typical symptoms are akinesia, bradykinesia, rigidity, tremor at rest, difficulties in balance and gait. Patients generally present also reduced anticipatory postural adjustments (Bonora et al. 2015) and sensorimotor deficits (Abbruzzese et al. 2003; Snider et al. 1976; Schneider et al. 1987; Jobst et al. 1997; Zia et al. 2000). People with PD generally experience a higher number of falls (Pickering et al. 2007), and it is thought that this increased fall risk could be related to inadequate postural responses (Bloem et al. 2001; Horak, Frank, et al. 1996; Horak, Dimitrova, et al. 2005). Dynamic balance control in presence of external perturbations represents a challenging task requiring continuous central integration of somatosensory, vestibular, and visual inputs, and an accurate sensorimotor coordination, which are partially reduced in older people respect to young adults (Seidler et al. 2010) and highly impaired in subjects with Parkinsons disease (PD) (Vaugoyeau et al. 2011). In particular, considering somatosensory impairments, clinical investigation in subjects with PD have found a decrease in two-point discrimination, static joint position sense, and movement perception (Schneider et al. 1987; Jobst et al. 1997; Zia et al. 2000). Moreover, the ability to generate a step quickly and accurately after a loss of balance as the last effort for avoiding fall is disrupted in PD, and neither levodopa medication (L. A. King et al. 2008; L. a. King et al. 2010) nor deep brain stimulation (St George et al. 2015) seems to offer any benefit.

For all these reasons, it is important to measure the effects of somatosensory deficits on balance control and the residual ability to react efficiently to an external perturbation. Aims of this work are: i) to verify the feasibility of a new instrumented test for evaluating the reaction to an external perturbation induced by changes of position in the support base on three different populations of healthy young and older adults, and patients affected by Parkinsons disease, and ii) to evaluate its specificity in distinguishing the three groups on the basis of the extracted spatio-temporal parameters.

3.1.2 Methods

Participants

Six PD patients (mean age $\pm$ SD: 72.3 ± 5.4 yo, 6 M), four older healthy subjects, aged 60 years or older (mean age: 63.3 ± 2.2 yo, 1 M), and eight young healthy adults (mean age: 37.5 ± 9.6 yo, 7 M) participated voluntarily to the study. Healthy volunteers, regardless to their age, were excluded if they presented any neurological disorder, if they used orthotic devices or had artificial joints, or if they were under medication that could affect balance.

Considering subjects with PD, inclusion criteria were: diagnosis of idiopathic Parkinsons disease, Hoehn and Yahr (H&Y) score (Hoehn et al. 1967) between 2 and

4, Mini Mental State Examination (MMSE) score (Folstein et al. 1975) higher than 24, ability to stand unsupported for more than 20 s. Patients were clinically tested on both the H&Y scale and the Unified Parkinsons Disease Rating Scale (UPDRS) (Fahn et al. 1987) by a trained clinician immediately before the beginning of the experimental session. subjects with PD participated to the test session while they were on their routine pharmacological therapy. All the participants signed informed consent forms approved by the local Ethical Committee.

Experimental equipment

A new prototype of a 3D rotating platform (RotobBit3D, fig. 3.1a) has been developed in collaboration with the Department of Mechanical and Aerospace Engineering of the Sapienza University of Rome (Rome, Italy). A similar system was already developed for routine use with pediatric patients (weight range $[200 - 600]\,\mathrm{N}$) and occasional use with adult subjects ($[600 - 900]\,\mathrm{N}$) (Cappa et al. 2010) and it is actually used for research purpose at the Bambino Ges Childrens Hospital (Rome, Italy). The original design resulted to be a tradeoff between two opposite constraints: a high payload does not permit sufficient sensitivity with children, while a low payload does not allow for testing adults (Patané et al. 2012). The new design has been intended mainly for the assement of balance control mechanism in neurological and healthy elderly patiens. A bigger range of motion of the rotating platform had been reached by scaling the mechanical components. A larger base of support has been provided to allow adult subjects standing with feet wide apart and to prevent falling while possibly performing a recovery step.

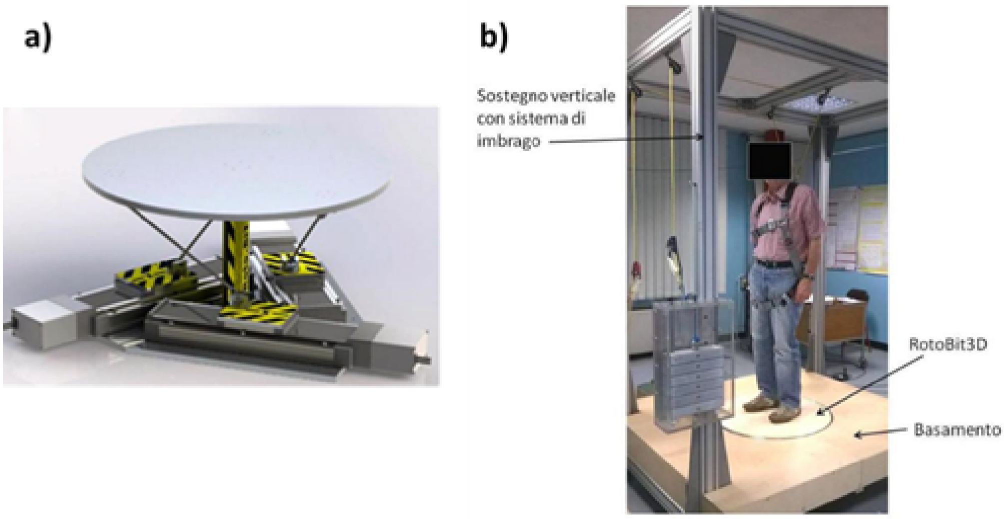

Figure 3.1: ROTOBIT3D robotic platform. a) 3D rendering of the robotic platform characterized by 3 degrees of freedom, b) Experimental setup adopted during the study. The robotic platform is hide under the wooden basement. It is possible to notice the suspension arness system used to minimize the risk of falling during the task execution.

In addition, as shown in fig. 3.1b, a vertical harness suspension system was provided to prevent volunteers from falling without significantly limiting their movements. Similar safety solutions have been already adopted in studies where a significant perturbation of the base of support was administered (Mansfield et al. 2007; Mansfield et al. 2010).

The RotoBit3D system is a parallel robot that can rotate a circular plate around a fixed point, that coincides with the geometrical center of the plate, along the roll, pitch, and yaw axes.

The platform can be operated in two different ways: position control and impedance control.

By selecting the position control mode, rigid rotations of the base of support are imposed by moving 3 linear axis actuators. The movement is transmitted to the plate through three passive arms connected with spherical joints to the bottom face of the plate, resulting for the subject to be tested in a final controlled, rigid rotation of the base of support. The imposed trajectory is calculated by a high performance FPGA servo-controller. The solution of the inverse kinematics of each motor is:

$$l = - \left| u_m \left(P_b - P_m \right) \right| \pm \sqrt{a^2 - \left| P_b - P_m \right|^2 + \left(u_m \cdot \left(P_b - P_m \right) \right)^2}$$

where:

l: displacement of the linear motor;

P_b: position of the upper ball joint center;

P_m: position of the lower ball joint center at the initial position of the robot;

a: floating arm length;

u_m: unity vector of the linear motor.

The direct kinematics can be determined by adopting the Newton-Raphson method, as proposed by Cappa et al. (Cappa et al. 2010).

Selecting the second operational modality, that is the impedence control mode, the RotoBit operates as a 3D spring acting in parallel with a 3D damper. Then, the platform movement is governed by the equation:

$$C\dot{\gamma} + K \left(\gamma_0 - \gamma \right) = \mu$$

where:

C: damping coefficient;

γ: actual inclination angle described by the roll, pitch and yaw angles ($\gamma = (\gamma_1, \gamma_2, \gamma_3)$);

γ_0: initial inclination angle;

μ: torque array.

A client-side PC running Windows 7 (Microsoft Corporation, USA) is connected to the main controller through a wired TCP/IP connection. A specific application has been developed in Labview 2014 for programming the main controller by imposing specific sinusoidal movements around the 3 Cardano angles, when operated in position control, or by varying rigidity coefficient, equilibrium angle, and time constant ($\tau_i = C_{ii}/K_{ii}$), while the robot is working in the impedance control mode.

Even though the mechanical components have been scaled and the industrial servo-drives have been changed to satisfy the new requisites, the control hardware has been substantially maintained from the previous project. Thus, the update rate of the system is 100 Hz and the hardware delays can be estimated in 2ms fot the postion control mode, and 7 ms for the imedence control. The control software installed in the main controller has been realized using Labview 2014 (National Instruments, USA) running under the non-RTOS (real-time operating system) Windows XP SP3 (Microsoft Corporation, USA). The update rate of the system and the delays introduced by the hardware architecture can be considered sufficient for dynamic posturography studies (Cappa et al. 2010).

Experimental protocol

Participants stood on Rotobit3D robotic platform, looking straight ahead, with their arms at their sides, wearing comfortable flat shoes. To all the participants was asked to stare at a small spherical target for the duration of the experiment. The target was positioned at a distance of 1 m in front of the subject in correspondence of the subjects eye level at rest. To take into account the dependency that performance in maneuvering the platform has from participants weight, the feet position was selected case by case varying the distance between heels to guarantee that the same theoretical maximum torque would be applied to the platform. As reference point, the maximum value, corresponding to the complete weight shifting over a single leg, was fixed in 78.5 Nm.

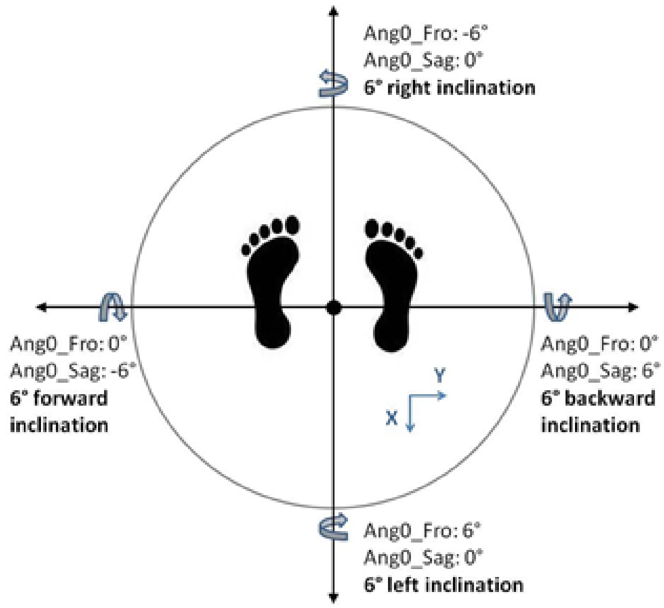

Figure 3.2: Scheme of the perturbations of the base of support in the four different possible directions.

The distances between heels ranged between 20 cm and 28.2 cm, depending on the weight of the subject. Thus, the feet placement would have a slight effect on the ground reaction force that corresponds to the acceleration of the whole body center of mass (Kim et al. 2014). At the meantime, the limits of stability in the medio-lateral directions, that are known to be critical for subjects with PD in narrow stance (Horak, Dimitrova, et al. 2005), resulted not to be influenced. Participants were asked not to move their feet during the test, unless they felt the urgency to perform a recovery step to prevent a fall. In such a case, the entire test was repeated. The platform was operated in impedance control mode.

A set of 4 perturbations, obtained by varying the platform equilibrium angle with a $\pm 6\,^\circ$ rectangular ramp waveform toward right, left, forward, and backward (fig. 3.2), was repeated 3 times in a random order. Subjects were instructed to react as fast as possible to the external perturbation trying to bring the platform back to the horizontal position by shifting their body weight, therefore applying an opposite torque to the plate, and keeping it still for 20 s. Between two consecutive perturbations the base of support automatically went back to the horizontal position for 10 s. A specific Labview application was developed to control the RotoBit3D system during the test (fig.3.3). To minimize the risk of fall during the execution of the task, if the inclination angle of the plate exceeded a threshold set as $\pm 6\,^\circ$ the rigidity coefficient was progressively increased to its maximum allowed value, and the platform was firmly blocked if the angular value of $\pm 10\,^\circ$ was reached.

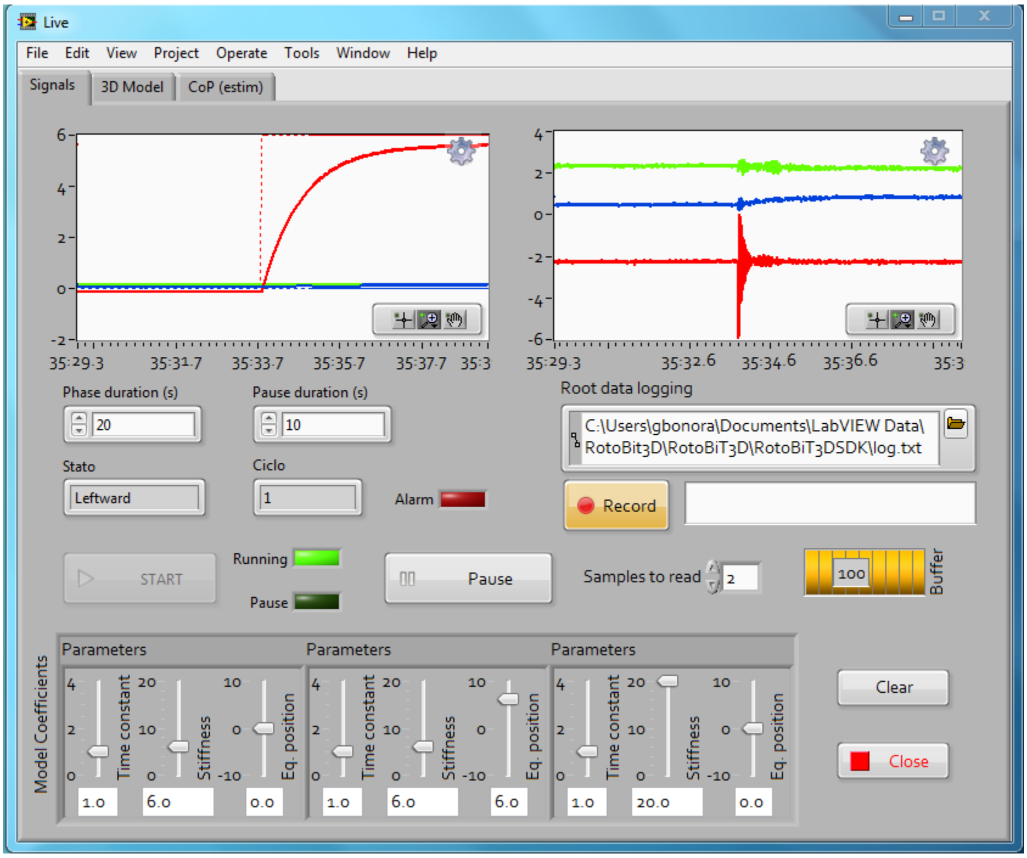

Figure 3.3: User interface of the Labview software (client side) developed for administering the perturbation test.

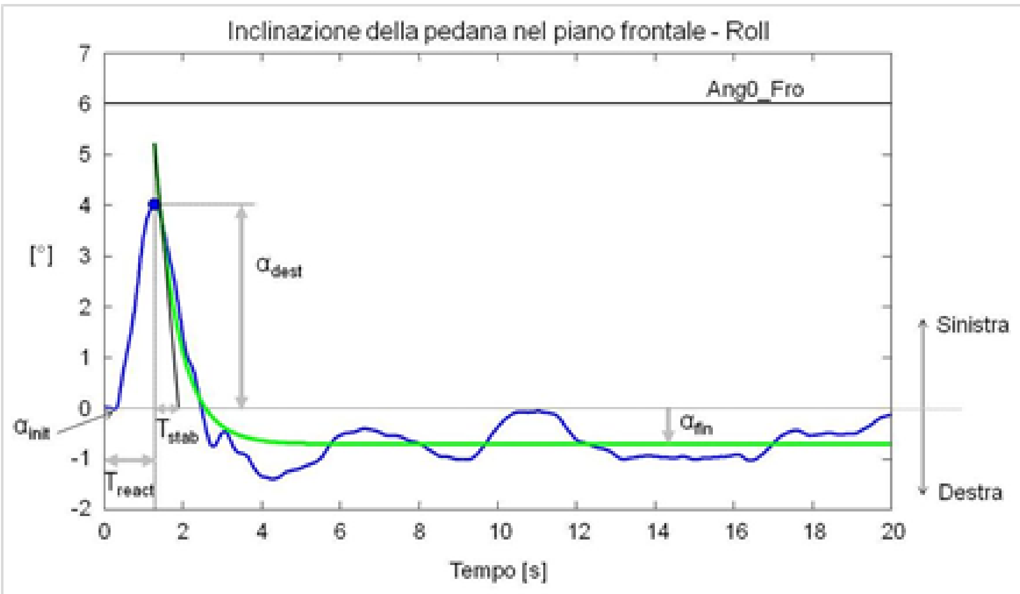

Figure 3.4: Representation of the inclination angle assumed by the base of support during a (leftward) perturbation. The adopted fitting curve is reported in green. The extracted spatio-temporal parameters (α_{init}, α_{dest}, α_{fin}, T_{react}, T_{stab}) are shown.

Data processing

Taking into account the given instructions, the assigned task can be considered as made up of two different phases. In the initial destabilization phase, participants try to preserve balance while experiencing the modification of the base of support in a passive manner. In the subsequent reaction phase, they begin to actively counteract the perturbing factor by moving back the platform to its horizontal configuration. Thus, the duration of the destabilization phase reflects the ability of the subjects to promptly react to an external perturbation and to switch to a different postural condition. The onset of the reaction phase can be identified with the instant in which participants make the support base inverts its movement by shifting the body weight in the opposite direction respect to the received perturbation, thus determining a change of sign in the platform angular velocity. The reaction phase is then characterized by a progressive reduction of the absolute inclination angle until the perceived horizontal configuration of the plate is reached. The detection of the initial reaction time (T_{react}) is therefore mandatory for the subsequent analysis.

The angular inclination measured by the robot was smoothed with a fourth order, zero-lag, low-pass Butterworth filter to ignore small oscillations reflecting postural adjustments needed for dynamic balance control. The angular velocity of the force plate was then extracted by derivation of the filtered signal. Considering the angular inclination to be positive in the direction of the perturbation, only the different segments of the angular velocity where the signal was negative were considered to detect the initial reaction movement. For each segment, the area under the curve was estimated by integration; then, T_{react} was chosen as the zero-crossing instant at the beginning of the region with the maximum area.

After T_{react} was reached, the inclination angle commonly presented a fast decreasing profile that became progressively flat while reaching the perceived horizontal configuration. An exponential fitting model was then adopted:

$$\alpha = k \cdot e^{-t/T_{stab}} + \alpha_{fin} \tag{3.1}$$

Temporal parameter T_{stab}, the inverse of the decay rate derived from the tangent at T_{react}, is proportial to the time needed to reach the final horizontal balance configuration. fin represents the final asynthotic stabilization angle. Finally, the parameter $\alpha_{dest} = k + \alpha_{fin}$ is the maximum angle of destabilization measured at T_{react}.

The complete analysis was performed in accordance with the method previously presented in (Rabuffetti et al. 2011).

Statistical analysis

For each subject, the median over the three repetition performed in the four different direction was calculated. For each extracted parameter the value extracted in each direction and the averaged measures calculated over the full set of perturbations were investigated. Comparison between parameters extracted from the 3 different groups were conducted taking into account the direction of the received perturbations, as well as the values averaged over the 4 directions. Kruskal-Wallis rank sum test was used for assessing between-group differences. Dunn test with Holm-Bonferroni correction was performed for post-hoc analysis. The level of significance was set at 0.05. All the analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria).

3.1.3 Results

All the participants were able to complete the test. Averaged extracted parameters are reported in Table 3.1. No significant differences were found between the initial angle (α_{init}) measured at the beginning of each trial while the platform was already in the imbalance control modality but no perturbation was applied.

Statistically significant differences in 3 of the 5 extracted parameters were detected between PD patients and young adults (p-value: $\alpha_{dest} = 0.002$, $\alpha_{fin} < 0.005$, and $T_{react} = 0.001$). Subjects with PD differed from healthy elderly in the maximum destabilization angle and in the measured reaction time, even though statistical significance was reached only for the spatial parameter (p-value < 0.02 and p-value $=$ 0.05, respectively). No significant differences were found between young and older healthy subjects; despite the fact that the latter ones showed higher error in the estimation of the horizontal position (α_{fin}, p-value $= 0.09$).

Table 3.1: Spatio-temporal parameters (median [range]) extracted for the three different group: healthy young (YOUNG), and older (OLD) subjects and PD patients.

Parameter	YOUNG subjects	OLD subjects	PD subjects
$\alpha_{init}[°]$	0.52 [0.27-1.33]	0.76 [0.63-0.81]	0.41 [0.25-1.40]
$\alpha_{dest}[°]$	4.68 [3.15-5.64]	4.76 [3.31-5.92]	6.77 [6.64-8.29]
$\alpha_{fin}[°]$	0.84 [0.46-2.06]	1.42 [1.18-1.66]	2.21 [1.20-6.32]
$T_{react}[s]$	1.71 [1.45-2.22]	1.86 [1.71-2.18]	6.77 [6.64-8.29]
$T_{stab}[s]$	1.26 [0.76-2.68]	1.12 [1.07-1.53]	2.96 [1.01-10.86]

A comparison between the different parameters extracted for each direction of perturbation was then conducted. Table 3.2 reports the values measured for the 3 groups when a perturbation in the body frontal plane was applied.

Table 3.2: Etracted spatio-temporal parameters (median [range]) extracted when a perturbation in the medio-lateral direction was applied.

Parameter	Direction	YOUNG subjects	OLD subjects	PD subjects
$\alpha_{init}[°]$	leftward	0.36 [0.20-1.47]	0.48 [0.38-0.54]	0.52 [0.20-2.11]
	rightward	0.26 [0.01-0.83]	0.56 [0.41-0.92]	0.47 [0.24-0.68]
$\alpha_{dest}[°]$	leftward	5.31 [3.78-7.24]	4.54 [3.22-5.88]	7.84 [5.41-8.42]
	rightward	4.29 [2.19-5.65]	4.54 [3.40-6.16]	7.16 [3.07-8.64]
$\alpha_{fin}[°]$	leftward	0.90 [0.09-2.17]	0.64 [0.29-1.6]	1.44 [0.8-4.71]
	rightward	0.68 [0.14-1.50]	0.98 [0.55-1.81]	2.06 [0.37-8.12]
$T_{react}[s]$	leftward	1.65 [1.46-2.12]	1.91 [1.45-2.08]	3.2 [2.08-6.92]
	rightward	1.47 [1.32-1.94]	1.84 [1.49-3.45]	2.81 [1.90-20.00]
$T_{stab}[s]$	leftward	1.02 [0.58-1.68]	1.00 [0.59-1.49]	2.86 [1.01-10.86]
	rightward	1.15 [0.64-2.72]	1.12 [0.74-1.47]	3.29 [0.79-20.00]

Considering perturbations in the medio-lateral direction, significant differences were found between PD patients and healthy elderly in both the dest (OLD: $4.54°[3.22° - 5.88°]$, PD: $7.84° [5.41° - 8.42°]$, p-value < 0.03) and T_{react} (OLD: $1.91 [1.45 - 2.08]s$, PD: $3.2 [2.08 - 6.92]s$, p-value < 0.03) when a perturbation toward the left limb was applied, while no differences were detected when the perturbation was applied in the contralateral direction. Similar results were obtained by comparison between young and older adults (p-value < 0.03 for both dest and Treact). Young adults and subjects with PD differed for the same parameters in the leftward direction (p-value: $\alpha_{dest} < 0.02$, $T_{react} < 0.003$), and only for the reaction time in the rightward one (p-value < 0.003).

Table 3.3: Spatio-temporal parameters (median [range]) extracted when a perturbation in the antero-posterior direction was applied.

Parameter	Direction	YOUNG subjects	OLD subjects	PD subjects
$\alpha_{init}[°]$	forward	0.74 [0.52-1.42]	0.94 [0.34-1.42]	0.45 [0.12-2.16]
	backward	0.60 [0.08-2.47]	1.06 [0.90-1.52]	0.26 [0.17-0.98]
$\alpha_{dest}[°]$	forward	3.04 [1.33-6.74]	2.46 [1.53-3.43]	6.77 [1.77-8.04]
	backward	5.34 [3.41-7.71]	7.00 [5.23-8.23]	7.49 [5.07-8.29]
$\alpha_{fin}[°]$	forward	0.70 [0.10-2.66]	1.05 [0.13-1.96]	3.26 [0.57-5.89]
	backward	2.14 [0.45-4.48]	2.96 [2.51-5.05]	4.29 [0.88-8.00]
$T_{react}[s]$	forward	1.66 [1.38-4.77]	1.95 [1.64-2.24]	6.35 [3.49-7.94]
	backward	1.69 [1.59-2.67]	1.90 [1.60-3.06]	5.55 [2.68-20.00]
$T_{stab}[s]$	forward	2.35 [0.65-3.01]	1.14 [0.86-1.60]	1.64 [0.83-7.41]
	backward	1.04 [0.47-4.90]	1.62 [1.00-3.15]	3.38 [0.61-20.00]

When perturbations in the antero-posterior direction were applied (Table 3.3), no differences at all were found in the maximal angle of destabilization. Subjects with PD presented higher reaction time values than both healthy elderly (OLD: $1.90[1.60 - 3.06]s$, PD: $5.55\ [2.68 - 20.00]s$, p-value < 0.03) and young adults (YOUNG: $1.69\ [1.59 - 2.67]s$, PD: $5.55\ [2.68 - 20.00]s$, p-value < 0.003) in case of backward perturbations. A similar behavior was noticed when forward perturbations were applied, but the statistical significance was reached only in the comparison with young adults (p-value: PD vs young < 0.003, PD vs old $= 0.06$) A significant difference between young and subjects with PD was also detected in the estimation of the horizontal configuration (p-value < 0.02).

3.1.4 Discussion

The reported preliminary analysis suggests that the designed test is feasible for evaluating the reaction to support base modifications in either healthy adults of different ages and subjects with PD.

The application of perturbations of the base of support in four different directions chosen randomly permitted to investigate the initial reactive postural adjustments, which are defined as automatic movements performed to recover balance in response to an external perturbation of the COM (Schoneburg et al. 2013). Then, the assignment to maintain balance and move back the platform to the perceived horizontal position maintaining the feet in their initial location permitted to investigate the quality of sensory integration, mainly between proprioceptive inputs from feet and ankles and vestibular information, and the ability to safely control the COM shifting. The collected results seem to be consistent with postural proprioceptive impairments observed in previous works on PD patients (Vaugoyeau et al. 2011) and with typical motor symptoms, such akinesia and bradykinesia. Subjects with PD showed overall deficits in the initial recovery strategies, presenting higher values for both the maximum perturbation angle and the reaction time than healthy elderly and, as expected, young adults. Considering the performances obtained depending on the direction of the perturbation, when a lateral (left) perturbation was applied patients presented higher values in both the spatio-temporal parameters respect to healthy elderly. When the platform was tilted along an antero-posterior trajectory only the temporal parameter (T_{react}, even if not significantly. This results could reflect a deficit in the perception of the base of support modification and/or a hesitation of subjects with PD in moving back the platform o the horizontal position. During backward and forward tilting, the restoration of the horizontal position of the plate (without moving the feet) can be obtained by shifting the body weight in the opposite direction through the adoption of knees and hips strategy, and the difference registered in the reaction time could reflect typical bradykinesia and hesitation in starting the movements. Instead, considering biomechanical limitations, the reaction to a lateral perturbation involves mainly the extension and rotation of waist and trunk and movements of the arms (Schoneburg et al. 2013) that are typically reduced in Parkinsons disease (M. Schenkman et al. 2000; M. L. Schenkman et al. 2001; Dimitrova et al. 2004; Wright et al. 2007; Burleigh et al. 1995). Thus, these typical deficits could explain the weaker reaction of subjects with PD in the medio-lateral direction and the presence of both temporal and spatial differences. These results are in accordance with previous publications reporting directional specific postural instability in PD (Horak, Dimitrova, et al. 2005; Dimitrova et al. 2004).

Considering the following postural modifications conducted to bring back the platform to the horizontal configuration, no significant difference was found in the stabilization time (T_{stab}) between PD and healthy elderly, while a minor difference was detected in the error of estimation of the final horizontal configuration when a forward perturbation was applied (p-value = 0.09). The reduced performance could be ascribed to typical difficulties presented by PD patients in moving the COM backward.

Finally, by comparison of young and older healthy subjects, the conducted test has not detected any strong evidence concerning different ability levels neither in recovery balance after a perturbation of the base of support or in the subsequent restoration of the horizontal positioning.

The response of the human balance control system to a modification of the base of support has already been widely investigated imposing translatory or rotational stimuli (Buchanan et al. 1999; Corna et al. 1999; Schieppati et al. 2002; Gurfinkel et al. 1976; Walsh 1973; Han et al. 2014; Schmid et al. 2011; Jacobs et al. 2007; Horak, Dimitrova, et al. 2005; Dimitrova et al. 2004).

The RotoBIT3D robotic platform itself has been previously used in research studies to assess balance control in healthy (Cappa et al. 2010; Amori et al. 2015) and neurological subjects (Cappa et al. 2010). However, at the knowledge of the author, in all the previous studies the external perturbations were represented by rigid movement of the basement.

The adoption of a robotic platform programmed to provide a perturbation of the support base while operating in impedance mode represent a novelty respect to previous studies about postural responses to external perturbations. In particular, the usage of the platform in impedance mode maintains the base of support unstable during the entire test, thus reducing the contribution of ankles and knees proprioceptive information in the sensorimotor integration needed to preserve balance. The prolonged instability of the base of support inhibits the adoption of the ankles recovery strategy for preventing falls. These results could not be easily obtained without using a robotic platform, thus the adoption of this kind of setting might represent a novel approach in the investigation of the contribution of visual and vestibular inputs on balance control.

However, it is opinion of the author that the main opportunity for future studies might consist in the possibility to implement new therapeutic exercises for improving the balance ability by precise control of weight shifting under different perturbing conditions. For this purpose, the integration of appropriate biofeedback signals in future rehabilitation exercises might result beneficial by facilitating the final users in the comprehension of complex recovery strategies offering, in this way, the possibility to improve motor learning. Furthermore, the contribution of visual and vestibular inputs on balance control during the test have yet to be evaluated. The integration of task performed under different sensory information (i.e. eyes closed) might be of interest for assessing precisely the role played by sensorimotor integration deficit in PD postural impairments.

Limitations

The most critical limitation to the study is represented by the small number of subjects included in the study that could have influenced the accuracy of statistical analyses and the correct understanding of the obtained results. Furthermore, a minor limitation to be considered is represented by the different ages of healthy and subjects with PD. Even though the applicability of the method, that is the main goal of this pilot study, is not affected by this aspect, further investigations are required to verify the capability of the test to correctly differentiate subjects with PD from aged matched healthy controls.

3.1.5 Conclusions

The result of the present study showed that the proposed test based on a robotic 3DOF rotating platform is applicable to investigate the postural responses to different perturbation of the base of support and the ability to counteract the destabilizing phenomenon in people affected by Parkinsons disease as well in healthy adults of different ages. Participants affected by Parkinsons disease showed difficulties to recover balance when a perturbation of the base of support was administered in either the antero-posterior or the medio-lateral direction. Even though caution must be taken due to the small sample size and age-related issues, this study suggests that the adoption of a robotic platform could offer an intriguing opportunity to achieve a better comprehension of neuromotor automatic responses aimed at preventing falls. The possibility to develop new therapeutic exercises for balance rehabilitation deserves further investigations.

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Chapter 4

Instrumented methods for the evaluation of balance and of the preparatory strategies preceding voluntary movements

4.1 A new instrumented method for the evaluation of gait initiation and step climbing based on inertial sensors: a pilot application in Parkinson's disease

4.1.1 Introduction

The ability to move safely during level walking and stair negotiation is a relevant aspect to guarantee success in performing many activities of daily living (ADLs), such as maneuver over a curb or access to public environments and public transport (Reuben et al. 1990).

Stair negotiation (i.e. ascending and descending stairs) is a demanding and hazardous task for frail people, in particular for older adults and subjects affected by neuromotor disorders, such as Parkinson's disease (PD). Compared to level walking, stair climbing necessitates of greater range of motion (Nadeau et al. 2003; Protopapadaki et al. 2007; Reeves et al. 2008; Reeves et al. 2009) and moments at the ankle, knee and hip joints (Nadeau et al. 2003; Protopapadaki et al. 2007; Costigan et al. 2002; McFadyen et al. 1988), and these requirements can force older adults to use almost their maximal motor capabilities (Hortobágyi et al. 2003) with a consequent increase of the risk of falling. It is reported that falling on stairs is the second more common type of falls in the elderly, and that approximately 75% of all injurious falls on stairs occurs in people aged 65 years or older (Ojha et al. 2009). Moreover, it was demonstrated that subjects affected by PD have an increased risk of falling compared to healthy controls (Allen et al. 2013), and that Fear Of Falling (FOF) in the PD population is strongly dependent on walking difficulties, turning hesitation and limited ability to climb stairs (Nilsson et al. 2012). Previous studies showed that these functional limitations are highly associated to alterations in dynamic balance control and to poorly coordinated anticipatory postural adjustments (APAs) prior to voluntary limb movements (Horak 2006).

APAs represent the transient phase between quiet standing and a dynamic condition chosen voluntarily such as walking, stepping up or down a stair, and over an obstacle (Degani et al. 2007). They involve complex interactions between neural and biomechanical factors that serve to maintain postural stability by compensating for destabilizing forces associated with moving a limb (Horak 2006). In the case of gait initiation, APAs act to accelerate the center of body mass (COM) forward and laterally over the stance foot by moving the center of pressure (COP) posteriorly and toward the stepping leg. Considering COP displacements, APAs can be divided into two different phases (Crenna et al. 2006): firstly, the Imbalance Phase characterized by initial displacement of the COP backward and toward the stepping (leading) foot, and then the Unloading Phase in which the COP shifts laterally toward the stance (trailing) foot.

It was demonstrated that APAs are essential to create appropriate initial dynamic conditions (Palluel et al. 2008), that they are affected by modifications of motor behavior due to aging (Palluel et al. 2008; Halliday et al. 1998) and neurological disorders such as Huntington's chorea (Delval et al. 2007) and Parkinson's disease (Crenna et al. 2006; Halliday et al. 1998; Carpinella et al. 2007; Mancini, Zampieri, et al. 2009; Rocchi, Carlson-Kuhta, et al. 2012; Mazzone et al. 2014), and that they are dependent on the specific task, i.e. stepping forward or upward (Degani et al. 2007; Gélat and Brenière 2000; Gélat, Pellec, et al. 2006; Sims et al. 2000). Given the great importance of APAs in the control of dynamic balance, previous studies have suggested to include their analysis to evaluate disease progression in patients with neurological disorders (Delval et al. 2007), as well as to detect their early clinical signs (Carpinella et al. 2007; Mancini, Zampieri, et al. 2009).

APAs related to gait initiation are usually recorded using force plates, electromyography, and motion-analysis systems (Crenna et al. 2006; Carpinella et al. 2007). Although all these systems have been proven effective, their cost and complexity limit their application to clinical practice.

Instrumented methods based on low-cost and easy-to-manage inertial sensors were developed in recent years to investigate human balance and postural sway during quiet stance (Mancini, Salarian, et al. 2012; Marchetti et al. 2013) and to perform instrumented tests for the evaluation of balance deficits and risk of falling (Weiss et al. 2013; Palmerini et al. 2013). Concerning APAs, inertial solutions were previously developed only for level walking (Mancini, Zampieri, et al. 2009; Rocchi, Mancini, et al. 2006; Martinez-Mendez et al. 2011), but not for stair negotiation. Furthermore, in the majority of these studies the analysis was focused only on the imbalance phase, not investigating the subsequent unloading phase that is indeed essential for a correct transition from bi- to mono-pedal stance.

On the basis of the above considerations, in the present study, an easy-to-administer instrumented method based on wearable inertial sensors was developed and applied to healthy subjects and persons affected by PD to analyze the initiation of level walking and step climbing in a typical physical rehabilitation setting: in particular, considering the importance of the unloading process in balance control during the transition from quasi-static to dynamic conditions, a novel algorithm was developed to recognize the initial and final frames of the unloading phase, allowing its subsequent analysis. Aims of this work were to test the validity and sensitivity of the proposed method by: i) validating it against force plate recordings, and, ii) evaluating its ability to differentiate APAs of subjects with PD from APAs of healthy controls.

4.1.2 Methods

Participants

Twenty healthy subjects (age, mean ± SD: 49.6 ± 17.9 yo, range 23 77 years, 10 females) and eleven patients affected by PD (age 72.5 ± 6.8 yo, range 62 83 years, 4 females) voluntarily participated in the study.

Healthy subjects were excluded if they presented any neurological disorders, if they used orthotic devices or had artificial joints, or if they were under medication that could affect balance or locomotor functions.

Subjects with PD were recruited within a group of patients involved in a neuromotor rehabilitation program administered at our rehabilitation institute. They were included in the study if they fulfilled the following inclusion criteria: diagnosis of idiopathic Parkinson's disease, Hoehn and Yahr (H&Y) stage (Hoehn et al. 1967) between 2 and 4, Mini Mental State Examination (MMSE) score (Folstein et al. 1975) higher than 24, ability to stand unsupported more than 10 s, ability to walk for at least 3 m without any walking aid, ability to step up onto a 18 cm high step. Patients were clinically rated by a trained examiner on the H&Y scale and on the Motor Section III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al. 1987) immediately before the beginning of the experimental sessions. Demo-

Table 4.1: Subjects' characteristics at the time of the study (H&Y: 1 $\div$ 5; 5 maximum disability. UPDRS III: 0 $\div$ 56; 56 maximum motor impairment).

Subject	Gender (M/F)	Age (years)	Disease Duration (years)	H&Y stage	UPDRS III score
P1	M	71	17	2	27
P2	F	83	7	2.5	15
P3	F	62	8	2	9
P4	M	79	9	3	23
P5	M	72	5	3	22
P6	M	65	6	2	9
P7	M	72	7	2.5	12
P8	M	66	12	2.5	18
P9	F	72	5	2.5	22
P10	F	82	7	2.5	20
P11	M	74	6	2	17
Mean	7M/4F	72.5	8.1	2.4	17.6
SD		6.8	3.6	0.4	5.9

graphic and clinical characteristics of subjects with PD are reported in Table 4.1. Patients were tested while they were on their routine therapy.

All the 20 healthy subjects and a subgroup of 5 PD patients (age 73.4 $\pm$ 6.1 yo, range 65 82 years, 2 females) got involved in a validation group (VG) for investigating the validity of the proposed method.

The eleven oldest subjects of the twenty healthy volunteers (age 66.6 $\pm$ 6.1 yo, range 60 77 years, 5 females), that presented comparable ages respect to subjects with PD (p-value = 0.09), were selected as healthy controls (HC) for the comparative analyses.

All the participants signed informed consent forms approved by the local Ethical Committee.

Experimental Equipment

All the subjects with PD and healthy controls wore 2 inertial sensors (TMA, Tecnobody, Dalmine, Italy) embedding a 3D accelerometer (range $\pm 5\,g$), and a 3D gyroscope (range $\pm 2000\,^{\circ}/s$). Linear acceleration and angular velocity data were sampled at 50 Hz and transmitted to a remote PC through a Bluetooth wireless connection for subsequent offline analysis.

As shown in fig.4.1, one sensor was placed on the posterior trunk, in correspondence to L2-L4 vertebra, with the sensing axes (x, y and z) oriented along the body vertical, medio-lateral (ML) and antero-posterior (AP) directions, respectively. The second sensor was placed proximally on the lateral aspect of the shank of the first

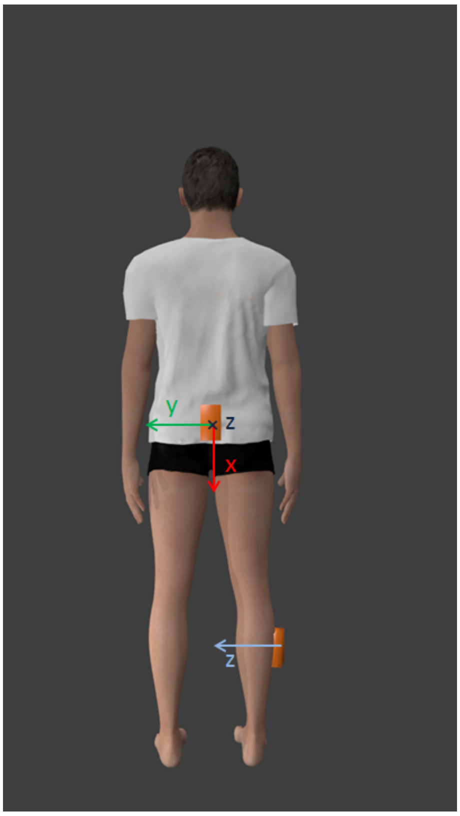

Figure 4.1: Wearable sensors placement

stepping leg with the z-axis oriented along the limb medio-lateral direction. Sensors were fixed over clothing through anti-slip elastic bands.

Ground reaction forces and COP displacement of VG subjects tested in the motion analysis laboratory were measured by means of two dynamometric platforms (Kistler Gmbh, Winterthur, Switzerland) with a sampling frequency of 800 Hz, considered as gold standard for APAs analysis (fig. 4.2a).

Experimental Protocol

Subjects were asked to perform two different transitional tasks: 1) quiet standing to level walking (gait initiation); and 2) quiet standing to single step climbing (step climbing). Three consecutive repetitions for each task were recorded in the above mentioned order.

At the beginning of each trial, subjects stood upright for 10 s in a comfortable position with the arms laying on their sides, wearing flat shoes with no heels: no given distances between the feet were imposed, in accordance with protocols developed in previous studies about anticipatory postural strategies preceding stepping upward (Gélat and Brenière 2000; Gélat, Pellec, et al. 2006; Sims et al. 2000) and over an obstacle (Degani et al. 2007). As soon as they received a vocal command from the experimenter, participants started the task execution. In the first task, subjects had to walk along a straight trajectory for about 3 m, while in the second one, they were asked to step up onto the first level of a two-step staircase. Each step measured 18 cm in height, 38 cm in width, and 34 cm in depth. The step dimensions were chosen to be among the most frequently encountered in public places and new residential buildings.

Both gait initiation and step climbing were executed by all the participants, both healthy and subjects with PD, starting with their right leg, as reported to be the dominant one, at self-selected speed.

Six of the eleven PD patients were tested in a typical rehabilitation setting before the beginning of their conventional physiotherapy session while all the members of the validating group, composed of the 20 healthy subjects and the five PD patients who accepted to be tested outside the rehabilitation gym, executed the tasks in a motion analysis laboratory equipped with two dynamometric platforms embedded in the floor (see previous section). In the laboratory, VG subjects were required to

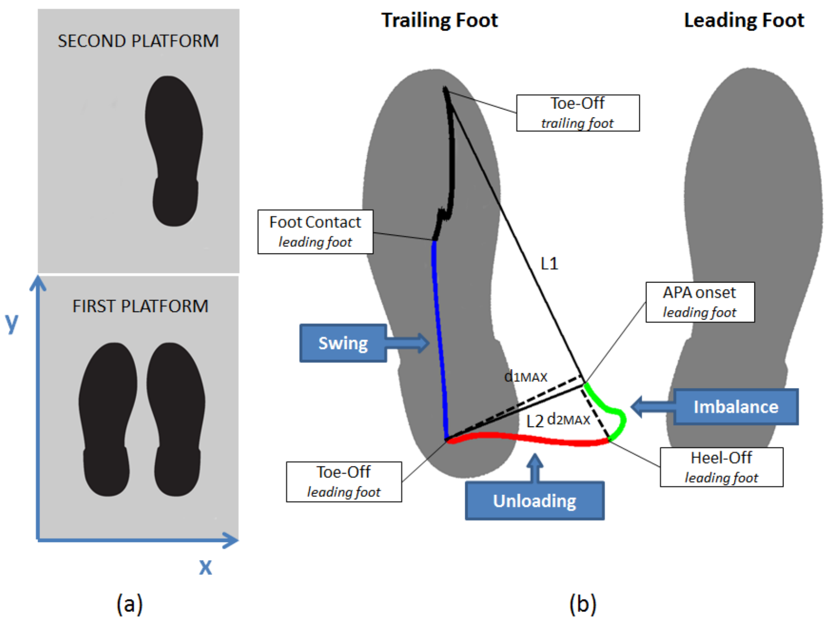

Figure 4.2: Laboratory setup for the analysis of COP displacement during APAs. a) Placement of the two force plates b) COP displacement in the medio-lateral (x) and antero-posterior (y) directions during the gait initiation process in a healthy subject. APA onset, Heel-Off, Toe-Off, and Foot Contact instants of the leading foot and the Toe-Off instant of the trailing one are reported. Imbalance (from APA onset to heel-off of the leading foot), unloading (from heel-off to toe-off of the leading foot), and swing (from toe-off to foot contact of the leading foot) phases are indicated. L1 line passing through the points representing the COP position at APA onset and at the toe-off of the trailing foot instants, and L2 line passing through the points representing the COP position at APA onset and at the toe-off of the leading foot instants are drawn. d1MAX represents the maximal distance from L1 attained by the COP (corresponding to toe-off of the leading foot), while d2MAX represents the maximal distance from L2 attained by the COP (corresponding to heel-off of the leading foot).

start the gait initiation task with both feet on the first force plate and then to step forward on the second platform, while in the step climbing task, they were asked to stand upright with both feet on the first force plate and then stepping up onto the lower step of the staircase placed in front of them on the second dynamometric platform.

Data Processing

After data recording, signals from force plates and inertial sensors were processed to analyze the anticipatory postural adjustments preceding gait initiation and step climbing.

COP displacements recorded from the dynamometric platform were filtered with a fourth order, zero-lag, low-pass Butterworth filter with a cut-off frequency of 10 Hz (Mancini, Zampieri, et al. 2009). COP trajectory and vertical ground reaction force were then used to subdivide each task into the initial quasi-static APA phase, made up of the imbalance and unloading phases, and the subsequent dynamic phase corresponding to the swing of the first leading foot. For this purpose, 4 instants were automatically identified by a dedicated algorithm and visually checked through an interactive software: 1) APA onset, 2) heel-off, 3) toe-off, and 4) foot contact of the leading foot (see fig. 4.2b). In particular, APA onset was detected with a threshold-based algorithm applied to the COP medio-lateral displacement with the threshold set as twice the standard deviation (SD) of the signal during the quiet standing period preceding task initiation, as proposed in (Mancini, Zampieri, et al. 2009). Heel-off and toe-off of the leading foot were detected as proposed in (Crenna et al. 2006): referring to fig. 4.2b, the toe-off of the trailing limb was detected as the last frame of the first force platform signal; then the toe-off of the leading foot was recognized as the instant in which the position of the COP attained the maximal distance (d1MAX) from the line passing through the two points representing the APA onset and the toe-off of the trailing limb (L1). Finally, the heel-off of the leading foot was computed as the frame in which the COP position attained the maximal distance (d2MAX) from the line passing through the two points representing the APA onset and the toe-off of the same foot (L2). The foot contact of the leading limb was recognized as the instant when the vertical ground reaction force of the second platform exceeded a threshold of 6.5% of body weight, as suggested in (Zijlstra and Hof 2003). The same detection method was adopted for both the gait initiation and the step climbing tasks.

Temporal instants were then extracted from the wearable inertial system data. The acceleration signals recorded at trunk level were transformed to horizontal-vertical coordinate system (Moe-Nilssen 1998) and filtered using a fourth order, zero-phase, low-pass Butterworth filter with a cut-off frequency of 3.5 Hz, as proposed by

Mancini et al. (Mancini, Zampieri, et al. 2009). The same filter was also applied to angular velocity data recorded by the sensor placed on the shank. The APA onset was detected with a threshold-based algorithm applied to the ML acceleration of the trunk sensor (Mancini, Zampieri, et al. 2009) with the threshold set as the SD of the signal during the quiet standing period preceding task initiation, multiplied by a factor A. The shank angular velocity around the ML axis was used to identify heel-off and toe-off instants, as shown in fig. 4.3a. In particular, the first peak of the signal (Ω_{pk1}) was detected, then the heel-off was estimated as the first instant, following the APA onset, at which the angular velocity became higher than Ω_{pk1} value multiplied by a factor H. Toe-off was identified as the first instant, following the peak, at which the signal became lower than Ω_{pk1} multiplied by a factor T (fig. 4.3b). Considering the data collected from the VG group tested in the motion lab with both dynamometric platform and inertial sensors, different sets of temporal instants were computed by varying the multiplicative parameters A, H and T. In particular, factor A was varied between values 1 and 5 with unitary incremental steps, while H and T were varied between 0 and 1 with incremental steps equal to 0.01 and 0.05 respectively. For each set of instants and for each subject, the mean absolute errors (MAEs) between instants calculated from force plates data and frames extracted from inertial sensors signals were computed and averaged among all subjects. The final values of A, H and T were then chosen as those which minimized the averaged errors. Finally, the foot contact instant was estimated as the median point between the second peak of the angular velocity (Ω_{pk2}) and the preceding zero-crossing event (fig. 4.3c); the point was chosen as the one that minimize MAEs.

After the events detection algorithm was applied, the following spatio-temporal parameters were computed from both COP displacement and trunk accelerations: Temporal parameters:

- Imbalance phase duration: from APA onset to the heel-off of the leading foot.
- Unloading phase duration: from the heel-off tot he toe-off of the leading foot.
- APA duration: from APA onset to the toe-off of the leading foot, as the sum of imbalance phase and unloading phase durations.
- Swing phase duration: from the toe-off to the foot contact of the leading foot.
- Step duration: from APA onset tot he foot contact of the leading foot.

Spatial parameters:

- Imbalance phase amplitude in ML (AP) direction: i) calculated from force plate data as the difference between COP ML (AP) position at heel-off and

COP ML (AP) position at APA onset; ii) estimated from inertial sensors signals as the difference between trunk ML (AP) acceleration measured at heel-off and trunk ML (AP) acceleration measured at APA onset.

- Unloading phase amplitude in ML (AP) direction: i) calculated, from force plate data, as the difference between COP ML (AP) position at toe-off and COP ML (AP) position at heel-off; ii) estimated, from inertial sensors signals, as the difference between trunk ML (AP) acceleration measured at toe-off and trunk ML (AP) acceleration measured at heel-off.

Spatial parameters were computed only for the APA phase, due to the quasi-stationary condition required by Moe-Nilssen (Moe-Nilssen 1998). Recognizing that, during APAs, COM and COP typically act as they were reciprocally linked (i.e. in the imbalance phase, COM moves forward and laterally over the stance foot, while COP moves posteriorly toward the stepping foot) and considering the results already reported in literature (Mancini, Zampieri, et al. 2009), we hypostasized that i) lower trunk accelerations are significantly correlated with COP displacements during APAs and that ii) lower trunk acceleration data can therefore be used to estimate force platform variables.

Statistical analysis

For each subject, variables were averaged over the three trials of each test. Parametric statistical tests were used for the analysis, as data normality and homoscedasticity were confirmed by Shapiro-Wilk's W test and Bartlett's test, respectively.

Mean absolute errors (MAEs) between temporal instants extracted from force plate data and inertial sensors were compared among young adults, older healthy subjects, and PD patients by using ANOVA test.

The concurrent validity of the proposed method for evaluating APAs was investigated through a linear regression analysis between the parameters extracted from the force plate and the correspondent ones computed from inertial sensors, as proposed in previous studies (Mancini, Zampieri, et al. 2009; Mancini, Salarian, et al. 2012). Pearson's correlation coefficient r and the related p-value were therefore calculated considering data recorded from the VG subjects tested in the motion lab.

For each parameter, a Student's t-test was adopted to detect differences between PD patients and the subset of comparable aged control subjects (HC). Finally, comparisons of the above mentioned temporal and spatial parameters were performed between the two tasks (gait initiation and step climbing) by using paired t-test.

The level of significance was set at 0.05 for all the conducted analyses.

All the analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria).

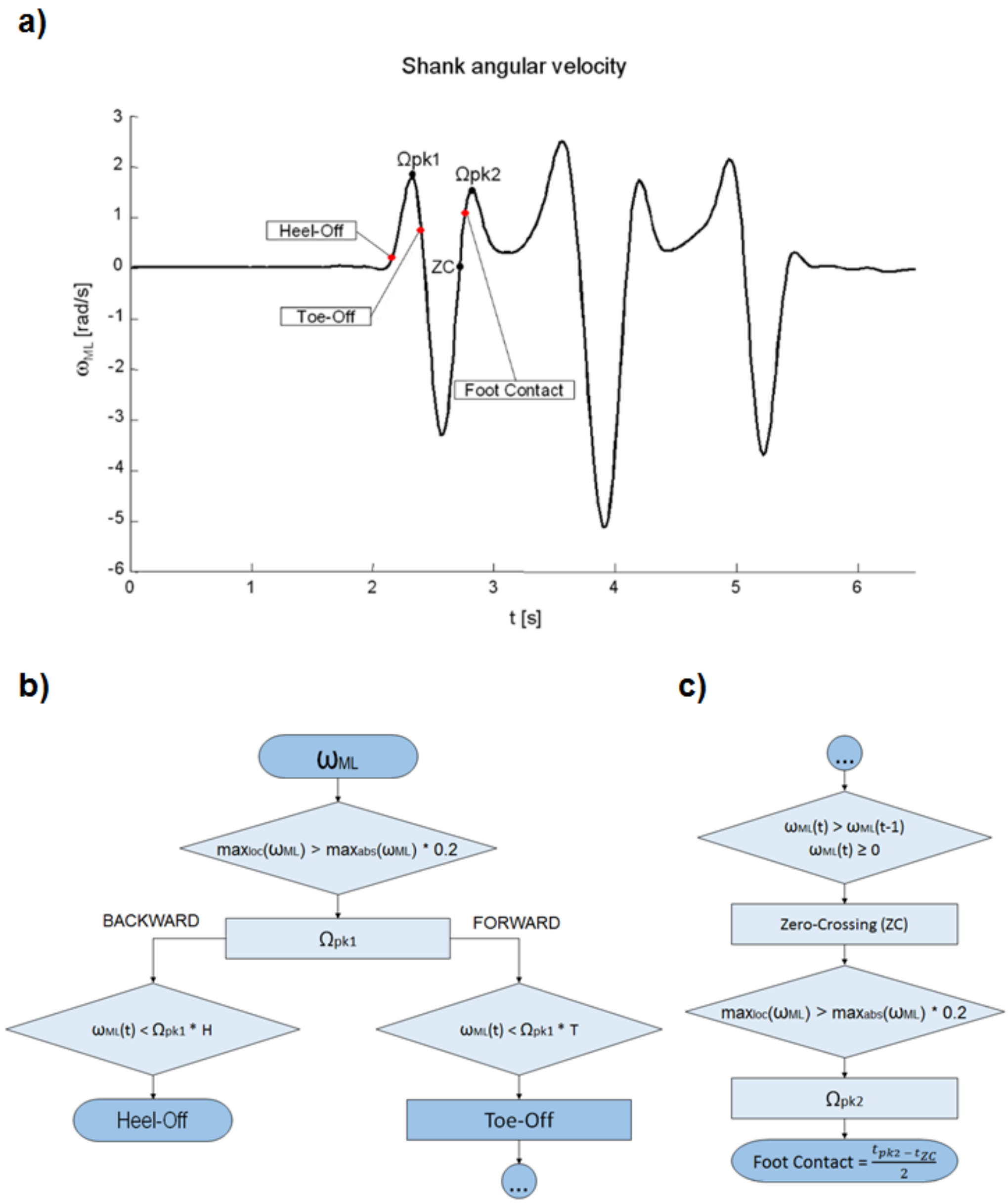

Figure 4.3: Detection of the heel-off, toe-off, and foot contact instants. a) Angular velocity of the shank respect to its medio-lateral axis: the first (Ω_{pk1}) and second (Ω_{pk2}) peaks of the signal and the zero-crossing instant (ZC) needed to recognize the foot contact are reported as black dots. The heel-off, toe-off, and foot contact instants of the leading limb, as detected by the proposed detection algorithm are reported as red marks. b) Algorithm for the detection of heel-off and to-off instants. Once the first peak on the shank angular velocity (Ω_{pk1}) is detected, a threshold-based backward search is performed to identify the heel-off instant. Similarly, toe-off is detected through a threshold-based forward search. c) Algorithm for the detection of the foot contact instant. After recognizing of the toe-off the algorithm identifies the first zero-crossing event (ZC) in which the signal becomes positive. The subsequent signal peak (Ω_{pk2}) is identified and the foot contact instant is calculated as median point between ZC and Ω_{pk2}.

4.1.3 Results

Validity of the method

Validity of the proposed method was assessed considering data related to the VG subjects tested with both inertial sensors and force plates.

Table 4.2: Mean absolute error of event detection (mean ± SD [s]) and, in brackets, percentage error referred to the step duration (from APA onset to foot contact). Multiplicative coefficients (A, H and T) set in the threshold-based algorithm for the event detection are reported.

	Gait Initiation		Step Climbing	
APA onset	A = 2	$0.05 \pm 0.03(5.0\%)$	A = 2	$0.09 \pm 0.05(6.3\%)$
Heel-Off	H = 0.07	$0.07 \pm 0.03(5.8\%)$	H = 0.08	$0.08 \pm 0.05(5.6\%)$
Heel-Off	T = 0.25	$0.05 \pm 0.03(4.1\%)$	T = 1	$0.06 \pm 0.03(4.2\%)$
Heel-Off	-	$0.06 \pm 0.08(5.0\%)$	-	$0.07 \pm 0.04(4.9\%)$

Table 4.2 shows the values of the multiplicative factors (A, H, and T) used by the threshold-based algorithm for the event detection procedure, the correspondent mean absolute errors (MAEs) between instants computed from inertial sensor signals and frames identified from force plate data, and the percentage errors referred to the step duration. It is possible to notice that the highest error (6.3%) is associated with the detection of the APA onset in the step climbing task: no statistically significant differences in MAEs were noticed between the two tasks ($p = 0.79$) and between younger adults (< 60 yo), elderly subjects (> 60 yo), and PD patients ($p = 0.73$).

As reported in Table 4.3, a significant linear correlation was found between COP medio-lateral displacements and the correspondent trunk accelerations in both tasks, while no correlation was found for the antero-posterior features. A significant linear correlation between the two methods was also noticed considering the duration of the whole test and its phases.

*Table 4.3: Pearson's correlation coefficients (r) between phase durations Δt measured by force platform and wearable sensors and between COP displacement and trunk acceleration in the antero-posterior (AP) and medio-lateral (ML) directions. Significant correlations ($p - value < 0.05$) are shown with *.*

	Gait Initiation			Step Climbing		
	AP	ML	Δt	AP	ML	Δt
Imbalance	0.20	0.81*	0.78*	0.36	0.81*	0.77*
Unloading	0.15	0.65*	0.48*	0.19	0.81*	0.62*
Unloading	0.16	0.69*	0.70*	0.14	0.65*	0.83*
Swing	-	-	0.73*	-	-	0.77*
Step	-	-	0.82*	-	-	0.83*

Differences between subjects with PD and comparable aged controls (sensitivity)

To assess the sensitivity of the proposed method, comparison between PD patients and healthy controls (HC) was performed considering only temporal and medio-lateral spatial parameters extracted from the inertial sensors, as we proved their validity in the former analysis.

Collected results are shown in Table 4.4, while Figure 4.4 shows examples of the trunk acceleration signal recorded from a representative control and a PD subject in the level walk and step climbing tasks. Regarding the imbalance phase, trunk ML acceleration was significantly smaller in subjects with PD with respect to HC both in level walking and step climbing. Furthermore, as shown in Fig. 4.4a-b, control subjects showed a significant increase of the medio-lateral acceleration during step climbing with respect to level walking (Level walking: $0.19 \pm 0.08\,m/s^2$; Stair climbing: $0.26 \pm 0.13\,m/s^2$; p = 0.01). No such a difference was found in the PD group (Level walking: $0.08 \pm 0.12\,m/s^2$; Step climbing: $0.09 \pm 0.15\,m/s^2$; p = 0.78) (see Fig. 4.4c-d). Regarding the unloading phase, a significant reduction of the ML acceleration in subjects with PD was found in the step climbing task but not in the level walking.

As for temporal parameters, a statistically significant difference between the two groups was found only in swing phase duration that was lower in subjects with PD with respect to HC. In addition, the correlations between the investigated parameters and the UPDRS III scores resulted to be not significant; this result is in accordance with (Mancini, Zampieri, et al. 2009).

*Table 4.4: Trunk acceleration in the medio-lateral direction (ML; mean ± SD [m/s^2]) and durations (Δt; mean ± SD [s]) of the different phases and the complete test in the two different transitional tasks. Significant differences ($p-value < 0.05$) are marked with *.*

		Gait Initiation			Step Climbing		
		HC	PD	p-value	HC	PD	p-value
Imbalance	ML	0.19 ± 0.08	0.08 ± 0.12	0.02*	0.26 ± 0.13	0.09 ± 0.15	< 0.01*
	Δt	0.40 ± 0.17	0.30 ± 0.20	0.70	0.47 ± 0.18	0.38 ± 0.14	0.20
Unloading	ML	-0.65 ± 0.37	-0.42 ± 0.32	0.14	-0.76 ± 0.49	-0.56 ± 0.42	0.03*
	Δt	0.30 ± 0.06	0.37 ± 0.15	0.17	0.30 ± 0.06	0.32 ± 0.17	0.56
APA	ML	-0.53 ± 0.24	-0.57 ± 0.37	0.45	-0.57 ± 0.37	-0.52 ± 0.46	0.41
	Δt	0.70 ± 0.15	0.85 ± 0.66	0.63	0.77 ± 0.20	0.84 ± 0.57	0.31
Swing	Δt	0.49 ± 0.07	0.42 ± 0.07	0.03*	0.65 ± 0.10	0.62 ± 0.13	0.30
Step	Δt	1.23 ± 0.11	1.28 ± 0.37	0.70	1.33 ± 0.10	1.36 ± 0.25	0.75

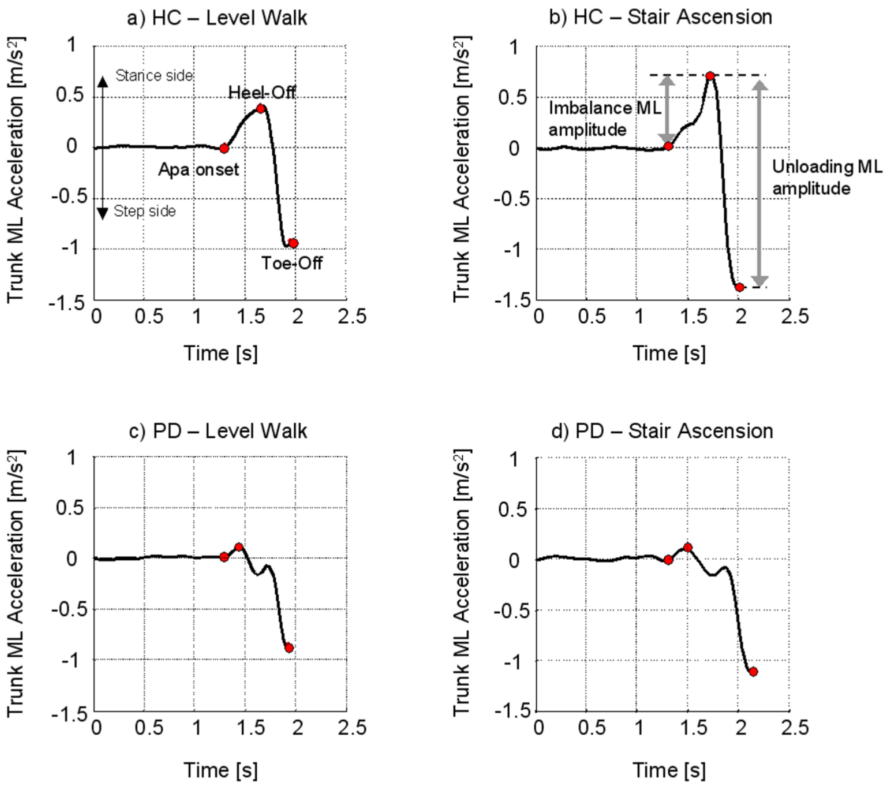

Figure 4.4: Trunk acceleration during APAs in two representative subjects: control subject (upward) and PD subject (downward). APA onset, heel-off and toe-off are reported as red marks.

4.1.4 Discussion

In the present study an instrumented method based on wearable inertial sensors was developed and applied on healthy subjects and on persons affected by PD to analyze the initiation of gait and step climbing. To our knowledge this is the first study aimed at comparing the APAs prior to level walking and step climbing through wearable inertial sensors, and it represents the first attempt to investigate differences between the two tasks in a group of subjects with PD under their usual medication state. Specific aims of this work were: i) validating it against force plate recordings, and, ii) evaluating its ability to differentiate APAs of subjects with PD from APAs of healthy controls. These two different aspects will be discussed separately.

Methodological apsects and validity of the procedure

The first objective of this work was to develop a method that offers the possibility to study APAs prior to level walking and stair climbing directly in a typical physical rehabilitation setting, without the necessity of expensive equipment such as force platforms. For this reason, it was chosen to use low-cost, easy-to-use wearable inertial sensors, as previously proposed by other authors for the investigation of the gait initiation process (Mancini, Zampieri, et al. 2009; Martinez-Mendez et al.

2011); in these studies a single inertial measurement unit was used and the analysis was limited to lower trunk acceleration during imbalance phase, in which COP shifts backward an toward the stepping foot. To our knowledge, no studies exist about the use of inertial sensors to analyze the subsequent unloading phase (from the heel-off to the toe-off instant of the leading leg) which implies COP shift toward the trailing foot. Considering that correct unloading is essential for the maintenance of dynamic balance during the transition from bi- to mono-pedal stance, in the present work we decided to include this specific aspect into the analysis. For this reason, a second sensor was applied on the lower limb to allow an easier detection of heel-off and toe-off frames from shank angular velocity.

The proposed procedure was validated for healthy subjects with different ages (from 23 to 77 years) and a subgroup of 5 subjects with PD by means of a comparison with force plates data, considered as a gold standard. Analysis of the temporal frames extracted with the two systems (i.e. APA onset, heel-off, toe-off and the subsequent foot contact of the leading foot) revealed mean absolute errors (MAEs) ranging from 0.05 s to 0.09 s. At our knowledge, no previous studies evaluated errors in the estimation through wearable inertial sensors of specific movements of the leading limb; in absence of term of comparisons, we considered the reported MAEs acceptable for the aim of the present study. No statistically significant differences in MAEs were recognized after comparisons between level walking and stair climbing, and between young adults (age $<$ 60 yo), healthy elderly subjects (age 60 yo), and PD patients. This result suggests that the method is applicable with comparable accuracy to adults with different age and subjects affected by PD in both tasks.

Importantly, linear regression analysis related to both level walking and stair climbing revealed a significant positive correlation between temporal parameters (i.e. duration of the step and of each phase of the test) extracted from inertial sensor and the same variables computed from force plate data. Regarding spatial parameters, the amplitude of APAs measured from COP displacement and estimated from acceleration signals in medio-lateral direction were significantly correlated, in accordance with (Mancini, Zampieri, et al. 2009; Martinez-Mendez et al. 2011). No such a correlation was found considering the antero-posterior direction. This difference between AP and ML directions could be ascribed to the following consideration. While medio-lateral movements characterizing APAs can be considered mono-segmental (i.e. the entire body moves laterally around the feet to prepare the subsequent step, using mainly the ankle joint), antero-posterior movements can be considered multi-segmental, involving not only the ankle but also the hip joints, especially in elderly subjects (Manchester et al. 1989). For this reason, the link between COP AP displacement and trunk AP acceleration might result more complex than that observed in the ML direction, thus explaining the lack of correlation found in the present results.

In summary, the present results suggested the validity of the proposed method for evaluating temporal aspects and medio-lateral features of the APAs preceding both gait initiation and step climbing.

Method's application on subjects with PD

The method was applied on a group of subjects with PD and the results were compared to those related to healthy controls (HC) of comparable age. Only temporal parameters and spatial variables related to ML direction were considered, because we formerly proved their validity on the selected validation group. As a consequence of the good correlation with the force platform and of the applied transformation to horizontal-vertical coordinate system (Moe-Nilssen 1998), the trunk acceleration pattern registered by the waist-worn sensor can be considered reciprocally linked to the COP displacement pattern during APAs, as previously proposed by other authors (Mancini, Zampieri, et al. 2009; Rocchi, Mancini, et al. 2006; Martinez-Mendez et al. 2011).

In the case of level walking, a significant reduction of trunk medio-lateral acceleration was observed in subjects with PD during the imbalance phase, confirming that APAs related to gait initiation are hypometric in PD (Halliday et al. 1998; Mancini, Zampieri, et al. 2009; Rocchi, Carlson-Kuhta, et al. 2012). On the contrary, ML amplitude of the unloading phase was similar in both groups, confirming the results obtained by Mazzone et al (Mazzone et al. 2014) on force plate data.

The feed-forward postural preparation during the imbalance phase has the primary consequence of determining the COM disequilibrium needed for lowering the load of the stepping leg and allowing its forward and upward progression; a reduction of that perturbation could be therefore seen as an attempt to minimize postural instability (Carpinella et al. 2007; Mancini, Zampieri, et al. 2009; Schieppati et al. 1991; Vaugoyeau, Viallet, et al. 2003). Analysis of temporal aspects of gait initiation did not reveal any difference between the two groups both in imbalance and unloading phase. This result is in contrast to that found by Crenna et al (Crenna et al. 2006) and Halliday et al (Halliday et al. 1998) who demonstrated a significant prolongation of both phases in PD patients. This discrepancy may be explained by differences in the medication state of the participants, as subjects included in the cited studies were in OFF-medication state while in contrast in the present work the subjects with PD were tested while they were under their routine therapy.

In addition to the reduction of the ML trunk acceleration, our results revealed a significantly shorter duration of the first step swing phase for the PD group. Even though step length was not considered in the present study, previous works demonstrated a significant reduction of this parameter during gait initiation (Halliday et al. 1998; Gélat, Pellec, et al. 2006; Rocchi, Mancini, et al. 2006). On the basis of this consideration, it can be speculated that the reduction in step duration found in the present study could be related to a shortening of the stride length and to an increase in cadence that are typical of PD patients (M. E. Morris et al. 1994).

Furthermore, a significant reduction in medio-lateral amplitude of the unloading phase was also present, suggesting that APAs prior to step climbing are more compromised with respect to those preceding gait. Previous electromyographic studies demonstrated that the preparation to stepping up is characterized by a greater activity of hip abductor muscle and an earlier onset of gluteus medius (Sims et al. 2000); hence, the greater request at the expense of the hip muscles, that is indeed weaker in subjects with PD (Cano-de-la-Cuerda et al. 2010), could partly explain the significant reduction in medio-lateral acceleration that was noticed both in the unloading and in the imbalance phase prior to step climbing.

Interestingly, a further difference between PD and HC groups emerged from the comparison between level walking and stair ascending APAs; in particular, in healthy subjects, the medio-lateral amplitude of unloading phase prior to stepping upward was significantly larger with respect to that preceding stepping forward, as found in previous studies (Degani et al. 2007; Sims et al. 2000). This finding could be ascribed to the fact that stepping up is more challenging for ML balance control than level walking, as it presents the additional constraint of not stumbling with the leading foot on the step, and this can be the reason for larger medio-lateral unloading, which ensures that center of mass is safely within the contact area of the supporting foot (Degani et al. 2007). No such a difference was found in subjects with PD who showed similar medio-lateral amplitude of unloading phase in both tasks. This result is particularly interesting taking into account the already published findings on healthy subjects; in those studies, the ability to scale the anticipatory postural strategies on the basis of task requirements (Gélat, Pellec, et al. 2006; Couillandre, Breniere, et al. 2000; Couillandre, Maton, et al. 2002), and the differences in APAs preceding stepping over an obstacle or up a stair (Degani et al. 2007; Gélat and Brenière 2000; Gélat, Pellec, et al. 2006; Sims et al. 2000) have been well documented. These in turn can be considered as a mechanism adopted by the central nervous system to safeguard balance during different transitional tasks. On the contrary, the absence of scaling found in the PD group could imply a difficulty to adapt feed-forward anticipatory strategies to different stepping task, that seems to be consistent with deficits in neural control, proprioception (Dietz et al. 2000; Vaugoyeau, Viel, et al. 2007) and muscle weakness, mainly of the hip joint (Cano-de-la-Cuerda et al. 2010). Such reduced adaptability may have a role in step climbing limitations that are typical of PD patients, with a consequent increase of anxiety and risk of falling (Nilsson et al. 2012).

Limitations of the study

There are some limitations that need to be addressed regarding the present study. A first limitation is represented by the small number of subjects included in this study; the proposed method should be applied on a greater number of patients in order to confirm these preliminary results. Secondly, the validity of the proposed procedure was performed on healthy subjects and 5 PD patients. In fact, only 5 of all the tested subjects with PD gave their consent to perform the test outside the rehabilitation gym in the motion laboratory equipped with force plates. Moreover, considering that the aim of the present work was to verify the applicability of the method directly in a physical rehabilitation setting, we considered the described validation procedure suitable for a first pilot study. Anyway, future studies are warranted to validate the method on a greater sample of PD patients and, possibly, on subjects affected by other different neurological disorders such as Multiple Sclerosis, and to test the reliability of the proposed variables. A third limitation of the study is represented by the fact that no given distances between the feet were imposed in both the tasks. Spontaneous feet placement on the floor with no constraints was allowed in accordance with previous studies on the adaptation of anticipatory postural strategies for stepping upward (Gélat and Brenière 2000; Gélat, Pellec, et al. 2006; Sims et al. 2000) and over an obstacle (Degani et al. 2007), and it was intended to guarantee the maximal level of comfort, self-confidence, and safety prior to attempt the requested complex transitional tasks without walking aid. Finally, a further investigation to define the minimum significant detectable changes is desirable for a future application of the method to evaluate the course of the disease and possible rehabilitation effects.

4.1.5 Conclusions

In summary, the results of the present study showed that the proposed method based on inertial sensors i) is applicable in clinical settings to evaluate APAs preceding both gait initiation and step climbing, and ii) is able to discriminate APAs of subjects with PD under their usual medication state from those of healthy controls of comparable age. In particular, subjects with PD showed altered APAs in both gait initiation and step climbing, with the latter task showing more pronounced alterations. Moreover, difficulties in modifying feed-forward anticipatory strategies on the basis of the specific transitional task was demonstrated in PD group. Validity of the method was verified through the comparison with force plate data.

Even though caution must be taken due to the small sample size, these preliminary findings suggest that the proposed procedure could be a fast, easy-to-manage and cost effective solution for a quantitative characterization of APAs in PD patients in those clinical settings where force platforms are usually not available.

4.2 Gait initiation in subjects with Parkinson's disease in the OFF state: evidence from the analysis of the anticipatory postural adjustments.

4.2.1 Introduction

The anticipatory postural adjustments (APAs), that are the transient phase between quiet standing and a dynamic, voluntary movement (Degani et al. 2007), are known to be reduced in subjects with Parkinson's disease (PD) (Bonora et al. 2015; Mancini, Chiari, et al. 2015; Mancini, Zampieri, et al. 2009; Crenna et al. 2006), with consequences on balance control and fall risk (Horak 2006). The motor symptoms of PD are mainly due to a progressive deterioration of the dopaminergic neurons in the basal ganglia (LeWitt 2015). Hence, the typical pharmacological therapy improves motor symptoms by replacing dopamine with L-dopa or dopaminergic agonists (Hosckivcová et al. 2015; Mancini, Rocchi, et al. 2008). Dopaminergic treatment has been shown to be effective in improving APAs (Curtze et al. 2015; Rocchi, Chiari, et al. 2006), therefore, measuring APAs in the ON state might not be representative of motor impairments. We recently presented a new, instrumented method for evaluating APAs preceding gait initiation and stair climbing in subjects with PD in their ON-medication state and healthy control subjects by using wearable inertial sensors (Bonora et al. 2015), as previously discussed in Chapter 4.1. In particular, our new method differs from previous approaches based on inertial sensors for the possibility to characterize both the imbalance and unloading phases preceding the limb movement (Crenna et al. 2006; Mancini, Chiari, et al. 2015). Unlike force plates and EMGs, a wireless, body-worn sensor approach to measuring APAs enables measurement of postural preparation for movement in clinical settings.

The aim of this study is to validate our recently developed algorithm on patients with PD in the OFF-medication state. The accuracy and sensitivity of the method will be assessed.

4.2.2 Methods

Participants

Ten subjects with mild-to-moderate idiopathic PD (age 67.2 ± 5.0, UPDRS III: 27.5 ± 9.0, Hoehn & Yahr: 2.5 ± 0.5, disease duration: 8.5 ± 3, 2 female) and 12 healthy controls (68.0 ± 5.0, 3 female) participated voluntarily to the study, after giving informed consent according to the Oregon Health & Science University Institutional Review Board. The subjects with PD and control group showed no significant difference in age and BMI. Subjects were excluded if they presented with any neurological disorder other than PD or conditions that could affect balance. The PD diagnosis was made by a movement disorders expert. Subjects with PD were tested in their practical medication-OFF state, following a washout period of at least 12 hours.

Procedures

Participants stood with feet externally rotated on separate, side-by-side custom force plates and heel-to-heel distance fixed in 10 cm (Mancini, Chiari, et al. 2015; Maki et al. 1990). They performed 3 gait initiation trials starting to walk with their most affected leg at their comfortable pace. Initial foot position was made consistent from trial to trial by tracing feet outlines on the force plate.

Data were collected from 3 IMUs (Opal, APDM Inc.) fixed with elastic bands on the trunk at L5 level, and laterally on the shanks (fig. 4.5) The sampling frequency was set at 128 Hz. IMUs signals were resampled at 50 Hz to match our previous study. Ground reaction forces and center of pressure (COP) displacement were measured by means of the force plates, considered as gold standard for APAs analysis, at a sampling frequency of 480 Hz.

COP displacement on each force plate was filtered with a zero-lag, low-pass Butterworth filter with a cut-off frequency of 10 Hz (Mancini, Zampieri, et al. 2009). APA quantification, consisting of the imbalance and unloading phases (Fig. 4.2), were calculated from 3 time-points automatically identified on COP displacement by a dedicated algorithm: 1) APA onset, 2) heel-off, and 3) toe-off (Bonora et al. 2015; Crenna et al. 2006). The acceleration signals, recorded from the trunk IMU were transformed to horizontal-vertical coordinate system (Moe-Nilssen 1998), and angular velocities from the shank IMUs were filtered using a fourth order, zero-lag, low-pass Butterworth filter with a cut-off frequency of 3.5 Hz (Mancini, Zampieri, et al. 2009). The initial mid-swing phase of each leg was detected as the first peak of the shank angular velocity around the medio-lateral (ML) axis exceeding a threshold set as 0.2 times the signal absolute maximum, and the leading limb was associated with the first peak detection. The APA onset, heel-off, and toe-off instants were then

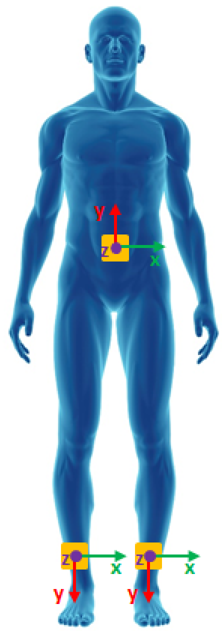

Figure 4.5: Wearable sensors location

extracted as proposed previously (Bonora et al. 2015) and hereafter summarized: i) APA onset was detected from the ML trunk acceleration with a threshold-based algorithm and threshold set as twice the SD of the signal during the initial quiet standing, ii) heel-off was detected as the instant in which the ML angular velocity of the stepping limb became higher than 7% of the signal's first peak value, and iii) toe-off was recognized as the subsequent instant when the signal became lower than 25% of the peak value.

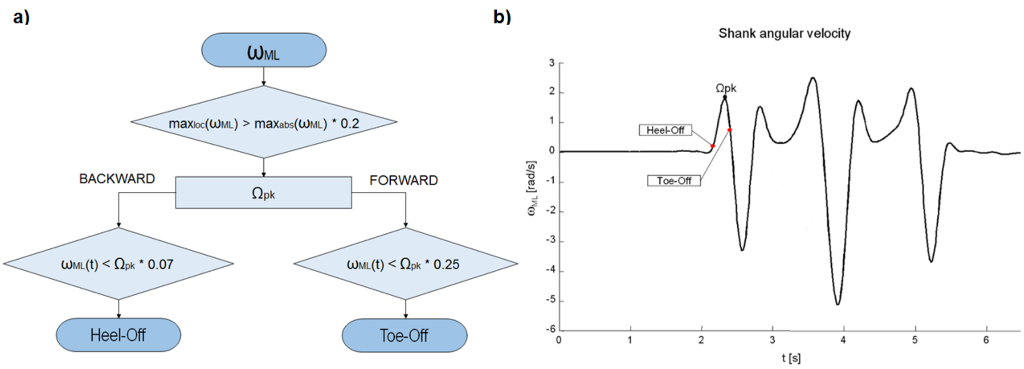

Figure 4.6: Detection of the heel-off and toe-off instants. a) Flowchart of the developed algorithm. Once the first peak on the shank angular velocity (Ω_{pk}) is detected, a threshold-based backward search is performed to identify the heel-off instant. Similarly, toe-off is detected through a threshold-based forward search.

Mean absolute errors (MAEs) between instants recognized from force plate and IMUs were computed and averaged among all subjects. The following spatio-temporal parameters were then extracted (Bonora et al. 2015):

- Imbalance phase duration: from APA onset to the heel-off;
- Unloading phase duration: from the heel-off to the toe-off;
- APA duration: as the sum of the imbalance and unloading phases durations;
- Imbalance phase amplitude: i) as the difference between COP ML (AP) positions at heel-off and APA onset respectively, and ii) as the difference between trunk ML (AP) acceleration measured at heel-off and APA onset respectively;
- Unloading phase amplitude: i) as the difference between COP ML (AP) positions at toe-off and heel-off respectively, and ii) as the difference between trunk ML (AP) acceleration measured at toe-off and heel-off respectively;
- APA amplitude: as the sum of the imbalance phase and unloading phase amplitudes in the ML (AP) direction measured from the force plate and the IMUs respectively.

Statistical analysis

For each subject, variables were averaged over the three trials. Data normality and homeschedasticity were assessed through the application of the Shapiro-Wilk normality test and the Bartlet test respectively. Hence, parametric statistical tests were adopted for all the analyses. The relationship between the parameters extracted from the force plate and the correspondent ones computed from IMUs was investigated through Pearson's product moment correlation. For each parameter, Student's t-test was used to evaluate differences between subjects with PD and healthy controls. Finally, comparison of the durations of the two phases was assessed by using a paired t-test.

All the analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria), with level of significance set at 0.05.

4.2.3 Results

Validity of the method

MAE values between instants detected from IMUs and from force plate (Table 4.5) are comparable with results of our former work.

Table 4.5: Mean absolute error (MAE) of event detection (mean ± SD [s]) between wearable sensors and force plate. Measured MAEs of all the participants (All), of the healthy controls (CT), and PD subjects are shown. Signicance of the difference between group are reported.

	All	CT	PD	p-value
APA onset	0.06 ± 0.02	0.06 ± 0.02	0.06 ± 0.03	0.33
Heel-Off	0.08 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.27
Toe-Off	0.07 ± 0.04	0.07 ± 0.04	0.07 ± 0.04	0.68

The associations between temporal and spatial parameters measured from the force plates and the IMUs are shown in Table 4.6. Interestingly, while the temporal measures showed significant associations ($p < 0.05$), only the ML spatial measures were significantly correlated, but not the AP.

*Table 4.6: Linear correlation between inertial sensors and force plates measures. Correlation between COP displacement and trunk acceleration in the antero-posterior (AP) and medio-lateral (ML) directions, and between phase durations (Δt) measured by force plate and wearable sensors. Pearson's correlation coefficients (r) and the correspondent p-values are reported. Significant correlation (p-value < 0.05) are marked with *.*

	AP		ML		Δt	
Imbalance	0.29	(0.21)	0.60	(0.004 *)	0.82	($< 0.001*$)
Unloading	0.05	(0.83)	0.60	(0.003 *)	0.63	($0.002*$)
APA	0.23	(0.30)	0.42	(0.050)	0.72	($< 0.001*$)

Method sensitivity

The method sensitivity was assessed by comparison of the significantly correlated spatio-temporal parameters (Table 4.7, Trunk results). Specifically, subjects with PD showed lower ML aplitudes than controls in all the phases.

*Table 4.7: Comparison of parameters extracted in PD patients and healthy controls (HC) from force plate and wearable sensors respectively. COP displacement (ML; mean ± SD [mm]), trunk acceleration (ML; mean ± SD [m/s^2]) and durations (Δt; mean ± SD [s]) of the different phases and the entire test. Significant differences (p-value < 0.05) are marked with *.*

		COP			Trunk		
		HC	PD	p-value	HC	PD	p-value
Imbalance	ML	40.04 ± 11.91	22.72 ± 8.44	$< 0.001*$	0.38 ± 0.14	0.15 ± 0.02	$< 0.001*$
	Δt	0.33 ± 0.14	0.28 ± 0.10	0.31	0.33 ± 0.10	0.29 ± 0.07	0.28
Unloading	ML	149.82 ± 23.28	115.96 ± 21.48	$0.003*$	1.06 ± 0.32	0.67 ± 0.20	$0.003*$
	Δt	0.32 ± 0.05	0.48 ± 0.14	$0.005*$	0.34 ± 0.11	0.48 ± 0.17	$0.04*$
APA	ML	109.57 ± 16.78	93.57 ± 21.13	0.07	0.68 ± 0.26	0.53 ± 0.23	0.18
	Δt	0.69 ± 0.20	0.76 ± 0.22	0.46	0.70 ± 0.17	0.73 ± 0.17	0.72

For the temporal parameters, a significant difference was found in the duration of the unloading phase with longer duration for PD than control subjects. All the results obtained from IMUs data were confirmed by force plate analysis (Table 4.7, COP results). The unloading phase was significantly longer than imbalance for subjects with PD (COP: $p\text{-value} < 0.001$, Trunk: $p\text{-value} = 0.003$), not for controls (COP: $p\text{-value} = 0.69$, Trunk: $p\text{-value} = 0.72$).

4.2.4 Discussion

This study suggests the validity of our previously developed method for gait initiation assessment using IMUs to subjects with PD in the OFF-medication state.

The measured MAEs were comparable with the measures calculated in our previous work. Interestingly, these results were obtained using the method introduced in the former study without requiring any further calibration process. In our opinion, this further supports the robustness of our method.

The significant correlation found between parameters extracted from IMUs and force plates supports the possibility to adopt IMUs for the assessment of APAs outside a typical motion analysis laboratory.

Compared to healthy controls, subjects with PD in their OFF-medication state showed a significantly smaller medio-lateral trunk acceleration in all the phases, but not in the entire APA. In addition, subjects with PD took significantly more time to perform the unloading phase compared to healthy control subjects. Both the small spatial parameters and the long duration of the unloading phase were newfindings compared to our study and could be explained by having the subjects in OFF-medication state. A significant difference in the duration of the two phases was limited to the PD group. Similar results with patients in medication-OFF state have been observed in previously laboratory studies (Crenna et al. 2006; Rocchi, Mancini, et al. 2006; Rosin et al. 1997; Burleigh-Jacobs et al. 1997; N. Gantchev et al. 1996).

Limitations

This study has several limitations. Comparison of the APA metrics between our former and present study may be limited by differences in foot position. In this study, a consistent foot position was imposed during all the trials and participants started walking with their most affected leg. In contrast, in our former experiment participants stood in a self-selected comfortable position and started walking with their preferred leg. Considering that initial stance conditions are proven to influence APAs (Rocchi, Mancini, et al. 2006) and that the process of choosing the initial swing leg does not affect APA during gait initiation in healthy subjects (Hiraoka et al. 2014), further investigations are required to verify how these factors may have impacted our results. Moreover, the test-retest reliability of our algorithms need testing.

4.2.5 Conclusions

These results demonstrated the validity of our previously developed APA algorithms when applied to healthy subjects and subjects with PD, either in medication-ON or OFF states, suggesting its possible adoption as a fast, easy-to-administer alternative for the assessment of gait initiation when force plates are not available.

4.3 A new instrumented method for the evaluation of the one-leg stand test based on wearable sensors

4.3.1 Introduction

Falls represent a very dangerous events for elderly and frail people. These perilous accidents are associated with increased morbidity, mortality, and consequent high health care costs (*SMARTRISK. The Economic Burden of Injury in Canada* 2009).

It was reported that 40% of the population of the United States aged 65 or more fall at least once per year, and that about 5% of people between 65 and 75 years and 10% of people over 75 years that experienced a fall event reported fractures or hospitalization (Rubenstein 2006). The mortality rate within a year from the accident in case of hospitalization was estimated in almost 50% of the cases (Rubenstein 2006).

Between the numerous factors that influence the fall risk, balance impairments have been recognized as one of the most important (Delbaere et al. 2010; Rubenstein 2006; Sattin 1992; Tinetti and Kumar 2010; Fabre et al. 2010).

Defined as the capability to maintain the body's center of mass (COM) projection inside the base of support (O'Hoski et al. 2013), balance control represents a complex motor task that requires the rapid, automatic, anticipatory, and reactive integration of information from many different physiological systems (A. Shumway-Cook and Woollacott 2007; Horak 2006). However, many of the components required in preserving balance, such as muscular strength, sensorimotor integration, neural conduction velocity, and reaction time to external stimuli, could result impaired in older people (Rubenstein 2006; Sattin 1992; Fabre et al. 2010; Mortimer et al.

1982; Harridge et al. 1996). Furthermore, age-related neurological disorders may contribute in the stability deterioration.

Parkinson's Disease (PD), the second most common neurodegenerative disease (Löfgren et al. 2014) affecting more than 5 million people worldwide (Olanow et al. 2009), is known to cause postural instability (Oates et al. 2013), to interfere with the integration of feedforward and feedback-based movements (Abbruzzese et al. 2003; Horak, Dimitrova, et al. 2005), and to affect the ability to quickly change motor programs. With the disease progression, balance impairment becomes one of the most disabling symptoms interfering with physical independence (Kim et al. 2013) and quality of life (Jankovic et al. 1990; Schrag et al. 2000; Muslimovic et al. 2008).

Physical therapy has been proven to be effective in improving balance control (Lee et al. 2013; Conradsson et al. 2015; Gusi et al. 2012; Zijlstra, Mancini, et al. 2010; Hoffman et al. 1995; Howe et al. 2011). In the past years, many intervention programs have been studied including exercises for muscle strength, flexibility and endurance (Gillespie et al. 2009). Recently, the availability of increasingly affordable and accessible technologies for movement monitoring and computer-human interaction, has given the possibility of developing and successfully testing rehabilitation systems based on biofeedback signals and exergaming (Zijlstra, Mancini, et al. 2010; Dozza et al. 2007; Schapira 2005; Tanaka et al. 2001; Esculier et al. 2012; Sienko et al. 2013; Wall et al. 2009; Kosse et al. 2011; Bisson et al. 2007; Heiden et al. 2010; Diest et al. 2013). However, the assessment of balance performance is mandatory for the initiation of an effective therapy (Schlenstedt et al. 2015).

Several functional balance tests are commonly used in the clinical practice to assess balance impairments. In particular, Berg Balance Scale (BBS) (Berg et al. 1992), Tinetti Mobility Score (TMS) (Tinetti 1986), and Timed Up and Go test (TUG) (Podsiadlo et al. 1991), and One-Leg stand (OLS) test (Vellas et al. 1997) showed the ability to discriminate between fallers and non-fallers and demonstrated to be good predictors of falls (Muir et al. 2008; A. Shumway-Cook, Brauer, et al. 2000; a. Shumway-Cook et al. 1997; Lin et al. 2004; Chiu et al. 2003). Nevertheless, none of the previously mentioned tests was specifically designed to investigate the underlying impaired mechanisms in postural control.

On the contrary, the Balance Evaluation System Test (BESTest) is a clinical tool that targets six subsystems of postural control (Tab. 1) in order to identify the different components contributing to dysfunctional balance (Horak, Wrisley, et al. 2009). BESTest has been used in a variety of populations (Horak, Wrisley, et al. 2009; Leddy et al. 2011; Kurz et al. 2011; Jones et al. 2009), showing strong psychometric properties in people with Parkinson's disease (Leddy et al. 2011), and it was identified as the only standardized balance measure that evaluates all the components of balance in a consistent way with commonly accepted conceptual models (Sibley, Beauchamp, et al. 2015). One of the major limitations of the test, that reduces its application in clinical practice (Sibley, Straus, et al. 2011), is the required administration time, which has been reported to range between 20 and 60 minutes (Horak, Wrisley, et al. 2009; Franchignoni et al. 2010; Padgett et al. 2012).

To overcome this limitation, an abbreviated version of the test, called mini-BESTest was developed (Franchignoni et al. 2010). The mini-BESTest presents a reduction of the total number of the items from 36 to 14, appointing only 4 of the 6 section of the original BESTest. In this way, the administration time of the test has been restrained in less than half the time of the complete original one (Franchignoni et al. 2010). The mini-BESTest have been shown to correlate well with total BESTest scores (Leddy et al. 2011), balance confidence scores (L. King et al. 2013), and BBS scores in people with PD (McNeely et al. 2012; L. A. King, Priest, et al. 2012). The test has presented also high interrater and test-retest reliability (Leddy et al. 2011). However, as the totality of the clinical rating scales commonly used in the medical practice, these tests could be greatly affected by clinicians' bias (Mancini, Salarian, et al. 2012).

On the basis of the evidence emerged in previous studies (Salarian et al. 2010; Zampieri et al. 2010; Mancini, Salarian, et al. 2012; Mancini, Salarian, et al. 2012; Horak and Mancini 2013), it is our opinion that the adoption of small, body-worn, inertial measurements units (IMUs) for measuring each item of either BES or mini-BESTest in a quick and objective way may enhance the test sensitivity permitting a deeper comprehension of the condition of the numerous physiological systems involved in balance control. Considering the different items that are present both in the BES- and in the mini-BESTest, it is opinion of the author that the one leg stand test may be one of the task that may offer new interesting information once instrumented. In fact, the one-leg stand test has been proven to be effective in the evaluation of balance disorders (Vellas et al. 1997) and fall risk (Jacobs et al. 2006; Smithson et al. 1998; M. Morris et al. 2000), and that shows a good correlation with the Unified Parkinson's Disease Rating Score Part 3 (UPDRS-III) gait and posture sub score (Adkin et al. 2003). The availability of a fast and easy-to-administer measuring tool may also give the possibility to perform balance tests in a typical rehabilitation or domestic environment permitting daily monitoring of the disease progression or of the efficacy of the therapy. Hence, objectives of this study are: i) to validate the developed instrumented method by comparison with force plate recordings, ii) to evaluate the ability to differentiate between subjects affected by different neuromotor disease and complications on the basis of the extracted features, and iii) to assess the possibility of an adoption of the instrumented test to investigate the effects of administered treatments.

4.3.2 Methods

The study consists of three experiments.

In Experiment 1, patients with Parkinson's disease and healthy control subjects of similar age were tested to validate the developed instrumented method for the evaluation of the One-Leg Stand test. Validity of the method was investigated through a linear regression analysis between the parameters extracted from the wearable inertial sensors and from a force plate assumed as gold standard.

In Experiment 2, the method's sensitivity in discriminating between different disorders was evaluated. For this purpose, several parameters were extracted through the IMUs from four different groups of subjects: i) PD presenting freezing of gait (FOG), ii) PD without FOG, iii) patients affected by frontal gait disorder, and finally iv) control subjects of similar age.

In Experiment 3, the sensibility of the method to treatment -induced changes were assessed by comparing parameters measured before and after a 4-weeks physical intervention based on the Agility Book Camp (ABC) program (L. A. King and Horak 2009). The intervention consisted of a total of 16 training sessions (4 sessions per week for 4 weeks). In each session the participants performed a set of exercise accounting for 6 different types of sports skill activities focused on improving basic postural systems. The entire cycle included tasks inspired to: 1) pre-Pilates, 2) kayaking to improve biomechanical constraints on joint flexibility, muscle strength, and postural alignment, 3) tai-chi to improve kinesthesia and increase functional limits of stability, 4) boxing to improve anticipatory postural adjustments prior to stepping in multiple directions, 5) lunges to improve the speed and size of automatic stepping for postural correction, and 6) agility course to improve stability and coordination during gait challenged by quick changes in direction, avoiding or overcoming obstacles and simultaneously performing a secondary cognitive or motor task. In the last experiment only patients with PD (FOG and no-FOG) were involved.

Participants

In all the experiments, subjects were excluded if they presented any neurological disorder other than PD or if they had any other condition that could affect balance.

People with PD were clinically rated on the Motor Section III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn et al. 1987) and on the Hoehn & Yahr (H&Y) scale (Hoehn et al. 1967) immediately before the beginning of each experimental session by a movement disorder expert. Classification of the patients as FOG or NO-FOG was conducted on the basis of the New Freezing Of Gait Questionnaire (NFOG-Q) scores (Nieuwboer et al. 2009). All the tests were conducted in a laboratory setting.

Subjects with PD were tested in their practical medication-OFF state after a washout of antiparkinsonian medication of at least 12 hours. All the participants provided informed consent according to the Oregon Health & Science University Institutional Review Board.

Experiment 1: validity analysis

Eight patients with mild-to-moderate idiopathic PD (age, mean ± SD: 72.9 ± 9.1, UPDRS III: 42.0 ± 13.0, Hoehn & Yahr: 2.1 ± 0.4, 8 males) and 2 healthy control subjects of similar age (74.1 ± 4.2, 2 male) were recruited for the validity study.

Experiment 2: sensitivity

Twenty-two patients with idiopathic PD presenting FOG (age: 67.5 ± 9.1, UPDRS III: 60.5 ± 11.7, H&Y: 3.0 ± 1.1, 8 males), thirty-five patients with idiopathic PD and no FOG (age: 68.2 ± 7.9, UPDRS III: 34.3 ± 9.3, H&Y: 2.2 ± 0.4, 24 males), 10 people affected by frontal gait disorder (age: 74.6 ± 5.2, UPDRS III: 32.2 ± 16.1, H&Y: 3.0 ± 0.7, 8 males,), and 10 healthy control subjects of similar age (75.5 ± 6.6, 5 males) participated to the study on the sensitivity of the method.

Experiment 3: sensitivity to changes

Twenty-four patients with idiopathic PD (age: 68.4 ± 8.0, UPDRS III: 42.5 ± 16.0, H&Y: 2.3 ± 0.6, 16 males) took part in the study to assess the method's sensitivity to changes.

Experimental protocol

Three IMUs (Opals, APDM Inc., Portland, Oregon, USA), respectively positioned on the posterior trunk at the level of L4-L5 and on the left and right shank, in correspondence of the frontal face of the tibias, were used for measuring 3D acceleration and angular velocity of the correspondent body segments (fig. 4.5). IMUs were placed on the skin and fixed with self-adhering elastic bandages. Data were recorded at a sampling frequency of 128 Hz and later downsampled at a frequency of 50 Hz in accordance with (Mancini, Chiari, et al. 2015; Mancini, Zampieri, et al. 2009).

Participants stood barefoot in an upright posture with feet externally rotated and heel-to-heel distance fixed at 10 cm (Maki et al. 1990; Mancini, Chiari, et al. 2015). Their hands were maintained on their belt for the entire duration of the test. They were asked to perform the one-leg stand task two times for each leg maintaining the unipodal balance as long as possible. At the beginning of each repetition, the examiner gave a vocal instruction specifying which leg had to be lifted up. Each

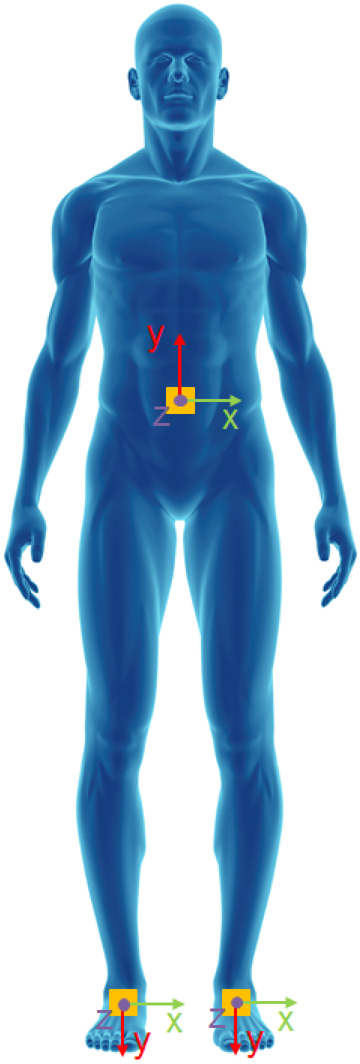

Figure 4.7: Wearable sensors placement.

trial ended after maintaining single-limb balance for 20 s or when the lifted foot touched the ground again.

In Experiment 1, a force plate (AMTI Inc, USA) was considered as gold standard and used for the acquisition of ground reaction forces and of the center of pressure (COP) position. Data from force plate were acquired at a sampling frequency of 240 Hz and subsequently low-pass filtered at 10 Hz, as proposed in previous studies (Bonora et al. 2015; Mancini, Zampieri, et al. 2009). Data from IMUs and force plate were synchronized through an electric triggering signal.

Data processing

After data recording, signals from inertial sensors and, limiting to Experiment 1, from the force plate were processed to analyze the task execution. Two different phases of the test were considered: i) the anticipatory postural adjustments (APAs)

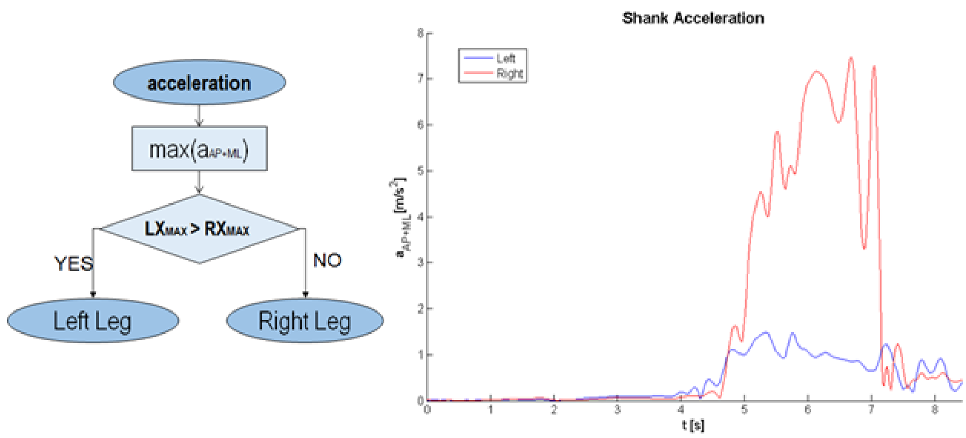

Figure 4.8: Flowchart of the procedure for the detection of the lifted limb from the shank acceleration.

phase immediately preceding the lift of the selected limb, and ii) the balance phase that starts when the rising of the limb ends and finishes at the beginning of the final descending movement of the shank.

The acceleration signals recorded at trunk level were transformed to horizontal-vertical coordinate system (Moe-Nilssen 1998), then, the transformed acceleration signals from the trunk and the acceleration and angular velocity signals collected from the shank-mounted IMUs were filtered using a fourth order, zero-phase, low-pass Butterworth filter with a cut-off frequency of 3.5 Hz, as previously proposed in (Mancini, Zampieri, et al. 2009; Bonora et al. 2015; Mancini, Chiari, et al. 2015).

The antero-posterior (AP) and medio-lateral (ML) accelerations at the shank level were used to automatically detect which limb had been lifted up, with the higher maximum value of the sum of the two accelerations, measured during all the task, corresponding to the risen one (fig. 4.8). Once the lifted limb was detected, the first instant in which the shank angular velocity of that limb became higher than a threshold set as 40% of the maximum of the signal was detected (T_{lift}) (fig. 4.9a). The threshold value adopted is significantly higher than the one proposed in a previous paper for detecting the heel-off instant (Bonora et al. 2015) as this choice guarantees that anticipatory postural adjustments (APAs) needed to unload the limb that has to be lifted already ended before T_{lift} was reached. Hence, analyzing the anticipatory phase, it was possible to detect the peak acceleration toward the stance foot of the lateral trunk acceleration (Peak ML-Acc) (Mancini, Zampieri, et al. 2009) with a backward search starting from T_{lift} (fig. 4.9b). The APA onset was identified as the first instant, from the beginning of the task, in which the trunk ML acceleration exceeded a threshold set as 5% of the Peak ML-Acc value (fig. 4.9b). To detect the initial and final instants of the balance phase, the shank angular velocity of the lifted limb around the ML axis was analyzed. The beginning

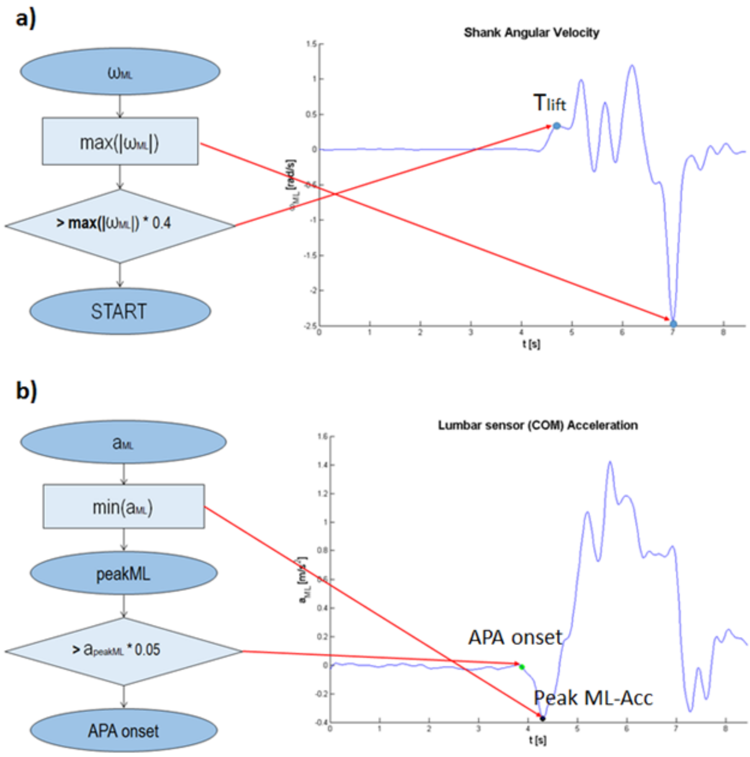

Figure 4.9: Algorithms for the analysis of APAs. a) Flowchart describing the procedure for the detection of the beginning of the rising movement of the lifted limb (T_{lift}). b) Flowchart describing the procedure for the identification of the APA onset and of the Peak ML-ACC instants.

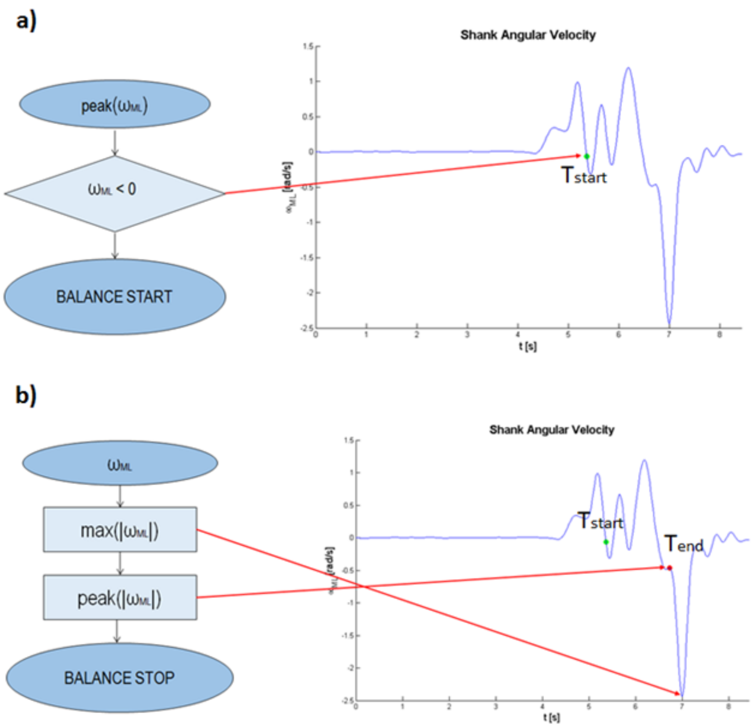

Figure 4.10: Algorithm for the detection of the unipodal balance condition. a) Flowchart of the procedure for the recognition of the beginning of the unipodal balance (T_{start}). b) Flowchart of the procedure for the recognition of the end of the unipodal balance (T_{end}).

of the phase (T_{start}) was detected as the first zero-crossing event following T_{lift} (fig. 4.10a). To detect the end of the phase, firstly the last negative peak of the ML angular velocity was detected, then the final instant of the balance phase (T_{end}) was computed as the zero-crossing instant preceding that peak (fig. 4.10b).

Limited to Experiment 1, COP displacements recorded from the force plate were filtered with the same 3.5 Hz cut-off, fourth order, zero-lag, low-pass Butterworth filter previously used on collected IMUs data (Mancini, Zampieri, et al. 2009; Mancini, Chiari, et al. 2015; Bonora et al. 2015). The APA magnitude was measured by the peak of the COP excursion in the lateral direction toward the lifting foot (Peak ML-COP), extracted as previously proposed in (Rocchi, Chiari, et al. 2006; Mancini, Zampieri, et al. 2009; Mancini, Chiari, et al. 2015).

Similarly to the method adopted for the IMUs signals, APA onset was detected as the first instant starting from the beginning of the recording in which the ML-COP displacement exceed a threshold set as 5% of the Peak ML-COP value. To compute the balance phase duration, subjects were considered to be in a stable unipodal balance condition as long as the COP moved laterally toward the stance leg and remained over a threshold set at 75% of the maximum ML COP excursion in the considered direction. Thus, the beginning of the balance phase was computed as the first instant at which the COP displacement became higher than the threshold and the end of the phase was extracted as the following instant in which the signal became lower than the threshold.

After the events detection algorithm was successfully applied, spatio-temporal parameters were extracted from the IMUs and, when available, from the force plate data:

- Peak ML-Acc amplitude $[m/s^2]$: calculated as the difference between the trunk ML acceleration at Peak ML-Acc and at APA onset;
- Peak ML-COP amplitude $[m/s^2]$: calculated as the difference between the ML COP displacement at Peak ML-COP and at APA onset;
- Balance Duration [s]: from the beginning (tstart) to the end (tstop) of the balance phase;
- Time-to-Peak [s]: from APA onset to Peak ML-Acc;
- Time-to-Balance [s]: from APA onset to the beginning of the balance phase (T_{start});
- Peak-to-Balance [s]: from Peak ML-Acc to the beginning of the balance phase (T_{start}).

Considering a desirable future adoption of the method for instrumenting the *"stand on one leg"* items in the BES- (Horak, Wrisley, et al. 2009) and mini-BESTest (Franchignoni et al. 2010) (the 11th and 3rd tasks respectively), an assessment approach similar to the one proposed by the authors of the two tests was chosen. In particular, in the guidelines of both the tests it was reported that for a correct scoring only the best performance of the two trials performed for each leg has to be considered. Then, while in the full BESTest for extracting the section sub-score and test total-score, the performances obtained on both sides are scored, in the faster mini-BESTest only the result obtained on the side that presents the lowest numerical value (the *"worst"* one) is considered. Analogously, in designing this instrumented method for the evaluation of the one- leg stand test only the best result for each side was considered for further analysis, while the other trials were discarded. For the detection of the best performance, the balance duration parameter was initially evaluated, in accordance with BEST- and mini-BESTest. In case of equal values between the two sides, the amplitude of the Peak ML-Acc was taken into account. Considering that larger displacements of the COP, that reflects the body mass behavior, facilitate the unloading of the leg that has to be lifted (Mancini, Zampieri, et al. 2009; Bonora et al. 2015; Mancini, Chiari, et al. 2015), in both the comparison the performance that presented higher values was considered to be the best one.

To allow a wider investigation on the method specificity, in Experiment 2 multiple comparisons between groups were conducted considering: i) parameters extracted from the side with the best performance, ii) parameters extracted from the side with the worst performance, and iii) mean values of the parameters extracted from both sides.

In Experiment 3, the presence of significant differences in performing the test was assessed by comparison of the parameters recorded while standing on the left leg and on the right one. For each subject, the side that showed at the baseline the highest balance duration or, in case of parity, the highest value of the Peak-Acc was considered to be the *"best"* side, and, consequentially, the other side was labeled as the *"worst"* one. To evaluate the sensitivity of the method to changes induced by the physical rehabilitation program, pre-post analysis was conduct for all the extracted parameters on both the best and worst sides separately. Finally, the presence of significant differences between parameters extracted from the two sides was assessed also after the ABC rehabilitation training.

UPDRS part III and the mini-BESTtest (total and anticipatory) scores were selected as clinical outcomes for evaluating the efficacy of the treatment.

Statistical analysis

In Experiment 1, for each subject, variables were averaged over all the four task repetitions (two for each leg). The concurrent validity of the proposed method for evaluating the one-leg stand test was investigated through a linear regression analysis between the Peak ML and Peak-COP amplitudes and the balance duration extracted from the force plate and the correspondent value from inertial sensors, as proposed in (Mancini, Zampieri, et al. 2009; Mancini, Salarian, et al. 2012; Bonora et al. 2015). Correspondent Pearson's correlation coefficient (r) and the related p-value were then calculated.

In experiment 2, Kruskal-Wallis rank sum test was adopted to detect differences between groups. Post-hoc analysis was perfomed using Nemenyi test with Tukey-Distribution approximation for independent samples.

In Experiment 3, Wilcoxon test was used for conducting a pre-post analysis of the extracted features for the best and the worst sides separately and to investigate differences in performing the one-lag stand on the two different sides, both before and after the training intervention. Finally, WilcoxonTest was also adopted to investigate differences in the selected clinical outcomes.

The level of significance was set at 0.05 for all the conducted analyses in the three experiments. All the analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

4.3.3 Results

Experiment 1: validity analysis

Aim of the experiment was to assess the validity of the proposed method through comparison of the spatio-temporal parameters extracted from the force plate, assumed as gold standard, and the wearable sensors.

Considering temporal parameters, as reported in fig. 4.11a significant linear correlation between the measures extracted from inertial sensors and from force plate was found for the duration of the balance phase ($r = 0.88$, p-value < 0.001) and for the duration of Time-to-Balance ($r = 0.7$, p-value $= 0.025$).

On the contrary, no significant correlation was found between the Peak ML-COP and the Peak ML-Acc values.

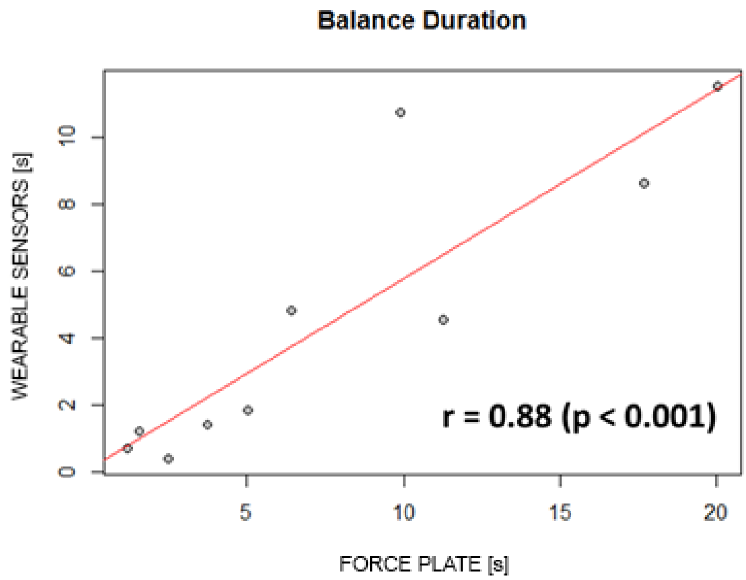

Figure 4.11: Linear correlation between balance duration measured from the force plate and the wearable sensors. Pearson's correlation coefficient (r) and the correspondent p-value are reported.

Experiment 2: sensitivity

In this experiment spatio-temporal parameters of the 4 groups of participants (i.e PD FOG, PD NO-FOG, patient with frontal gait disorder, and healthy controls) were compared to investigate the sensitivity of the method. Comparison between the parameters extracted while performing the test on the individual best side, the worst one, and the mean value between the two conditions were conducted. All extracted spatio-temporal parameters were assessed, reporting significant differences only for balance duration. Considering balance duration, significant differences between groups were detected in all three standing conditions, as reported in fig. 4.12.

In particular, the test was able to differentiate PD FOG subjects from PD NO-FOG and healthy controls. The group of patients affected by frontal gait disorder were distinguished from PD NO-FOG patients and healthy controls. However, the method was unable to detect differences between PD NO-FOG and healthy controls and between people affected by frontal gait disorder and PD FOG patients. Despite the fact that the same differences were detected under the three different conditions, data recorded while performing the test on the worst side presented a higher number of outliers (fig. 4.12 on the right).

Experiment 3: sensitivity to changes

Objective of this experiment was to evaluate the sensitivity to changes due to the rehabilitation training program. Spatio-temporal parameters were measured before (PRE) and after (POST) the physical therapy for both the best and the worst side. No differences were noticed between parameters other than balance duration for both conditions.

Balance duration presented a significant difference when considering the worst side (PRE: 6.3 8.1, POST: 9.3 10.0, p-value: 0.011*) and not in the best side (PRE: 12.0 10.0, POST: 11.3 9.6, p-value: 0.29). Interestingly, as reported in fig. 4.11, a significant difference was found between balance duration measured on the best and on the worst side at PRE (best: 12.0 10.0, post: 6.3 8.1, p-value: < 0.01), while no difference was noticed at POST evaluation (best: 11.3 9.6, post: 9.3 10.0, p-value: < 0.72).

UPDRS part III and the mini-BESTtest (total and anticipatory) data are shown in Table 4.8. As reported, no differences were found in the PRE vs POST analysis of the three clinical scores.

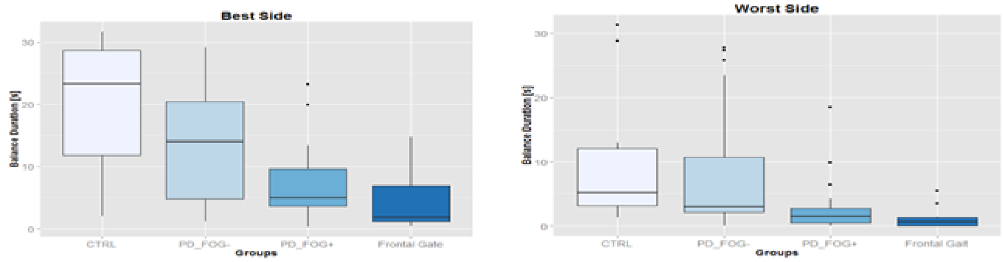

Figure 4.12: Measured balance for healthy controls (CTRL), PD subjects without FOG (PD_FOG-), PD subjects with FOG(PD_FOG+), and persons with frontal gait disorder. Both the results obtained while standing on the best side (on the left) and on the worst one (on the right) are reported.

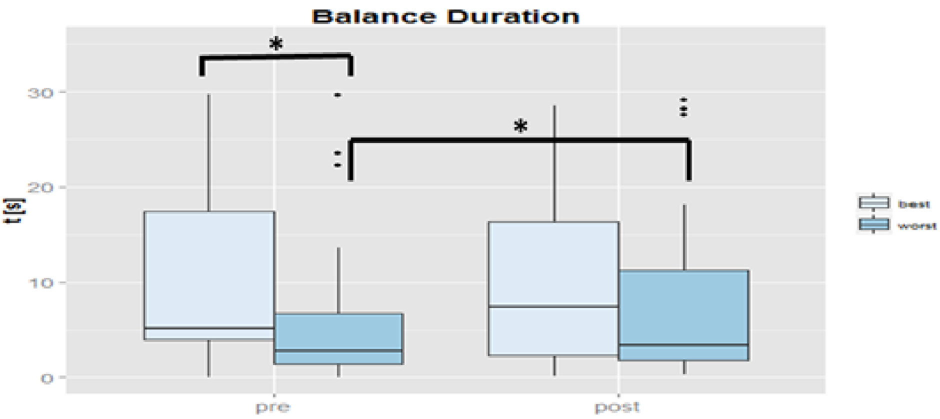

Figure 4.13: Comparison between balance duration measured while standing on the best and on the worst side at PRE (left) and POST (right). Significant differences are marked with a star (p < 0.05).*

Table 4.8: Clinical outcomes (mean [range]) measured before (PRE) and after (POST) the treatments.

	PRE	POST	p-value
UPDRS III	43.3 [22 - 63]	41.7 [26 - 65]	0.71
Mini-BESTest (Total score)	18.3 [5 - 27]	19.1 [7 - 28]	0.78
Mini-BESTest (Anticipatory sub score)	3.6 [0 - 6]	3.9 [2 - 6]	0.31

4.3.4 Discussion

In the present study an instrumented method based on wearable inertial sensors was developed and tested on healthy people, patients affected by PD, with and without freezing of gait (FOG), and persons affected by frontal gait disorder. To our knowledge this is the first study in which wearable sensors were used for assessing both the APAs preceding the standing on one leg and the subsequent unipodal balance phase. Actually only other two studies developed an instrumented version of the one-leg stand test for assessing balance deficits and risk of fall. In one study the test was instrumented by using sensorized insoles for the estimation of COP parameters (Ayena et al. 2015), while in the other one a trunk mounted smartphone was used to estimate COM displacements for the measurement of spatial parameters that covered all the task execution without considering APAs and balance phase separately (Guimaraes et al. 2013). Moreover, this work is the first effort to adopt an instrumented version of the one-leg stand test on people affected by several disorders and, in particular, on subjects with frontal gait disorder.

Validity of the method

Considering the validation analysis conducted in Experiment 1, between the extracted spatio-temporal parameters only the balance duration and the Time-to-Balance parameters presented a significant correlation between measures extracted from inertial sensors and from force plate. The only measured spatial parameter, the Peak ML-Acc, does not present a significant correlation with the correspondent Peak ML-COP displacement extracted from the force plate. This result seems to be in conflict with previous observation of APAs preceding gait initiation (Mancini, Zampieri, et al. 2009; Mancini, Chiari, et al. 2015; Bonora et al. 2015) and stair climbing (Bonora et al. 2015). However, it has to be noticed that in the reported studies the APAs were intended for preparing the body to a subsequent forward (gait initiation) or upward and forward (step climbing) movement of the entire body, and consequently of the COM, determining the activation of a highly stereotypical preparation pattern (Crenna et al. 2006; Mancini, Zampieri, et al. 2009; Bonora et al. 2015). In the case of the one- leg stand the APAs are not intended for preparing the body to project the COM outside of the base of support. Hence, it can be speculated that a lower stereotypical preparation pattern is activated. At the same time, the one-leg stand condition presents a greatly reduced base of support respect to the usual bipodal stance and surely represents a less stable condition. This fact may modify balance control strategies resulting mainly in an adaptation of the motor program according to the postural requirements rather than in changes the postural strategies (G. N. Gantchev et al. 1996). Both scenarios suggest the possibility of more subject-tailored anticipatory strategies, thus resulting in the loss of significant correlation between COM and COP spatial measures. Our result seems to be partially supported by an earlier study (Guimaraes et al. 2013) in which, when a chest mounted smartphone was used for measuring COM acceleration during the central more-stable unipodal standing on a group of healthy older adults, only moderate correlation in the displacements and no correlation in velocity-based variables were noticed.

Application of the method on subjects with different neurological disorders

The developed method was applied on four different populations: i) PD subjects with FOG, ii) PD subjects with NO-FOG, iii) people affected by frontal gait disorder, and iv) healthy controls of similar age.

Considering duration of the balance phase, significant differences were found between PD patients with and without FOG, and between PD patients with FOG and healthy controls. Differences were also shown in the comparison between persons affected by frontal gait disorder and PD NO-FOG patients and healthy controls respectively.

Due to the fact that reduced balance time are generally associated with poor balance abilities and higher fall risk (Jacobs et al. 2006; Vellas et al. 1997; Smithson et al. 1998; M. Morris et al. 2000; Adkin et al. 2003), the detected differences in balance duration seem to correctly reflect different levels of postural control debilitation. No difference was detected between PD NO-FOG persons and healthy subjects and this result seems to be in accordance with a previous work (Ayena et al. 2015) in which comparable values of the unipodal balance duration were measured between these two populations.

Sensitivity to changes induced by physical rehabilitation

The instrumented one-leg stand test has been applied on subjects with PD that participated in a physical rehabilitation intervention based on the Agility Boot Camp program (ABC) conducted at the Oregon Health and Science university (OHSU, Portland, Oregon, USA) to investigate possible objective outcomes of the physical intervention.

Comparing the parameters extracted while standing on the two different legs at the baseline it was possible to notice a significant difference in the balance duration, with longer unipodal balance duration recorded on their best leg.

On the contrary, after participating at the 4-weeks ABC training program, this difference was not detected, with patients standing on the worst side almost as long as on the best one. This fact can be justified by the significant improvement obtained on the worst side, rather than by a decrease in the performance of the best side, and this fact seems to support the efficacy of the chosen training program.

Considering clinical scores (UPDRS III, Mini BESTtest), no differences were found in the PRE vs POST analysis. Thus, it is conceivable a higher sensitivity of the instrumented method in comparison with typical clinical scales.

Limitations

Numerous limitations are still present in the study. The first limitation is represented by the small number of subjects involved in the validation study (Experiment 1) that could represent one of the possible causes at the basis of the lack of correlation between spatial parameters extracted from the wearable sensors and those from the force plate, assumed to be the gold standard. Moreover, the spare number of healthy controls enrolled in Experiment 2 could have affected the analysis conducted on the sensitivity of the method. However, it is reasonable to suppose that both limitations will be overcome with the progress of the study conducted in the Balance Disorders

Lababoratory of the Oregon Health & Science University. Considering the validation study, the second limitation that requires further consideration is represented by the methodology adopted to conduct the validation process. The most correct approach for determining the exact duration of the test and of all its phases would probably be represented by the adoption of an optoelectronic stereophotogrammetric system to exactly detect the hell-off, toe-off, and the following foot contact instant. Another possible approach would consist in the adoption of two force plates to determine the toe-off and foot contact instants with a higher accuracy. However, the unavailability of these instruments at the time of the study made it impossible to choose one of those solutions. Hence, the adoption of the proposed methodology seemed to be reasonable for a first validation attempt.

4.3.5 Conclusions

In the present study, a new instrumented method for the evaluation of the one-leg stand test was presented. Even though caution is needed due to the inadequate number of subjects involved in the validation procedure, it is opinion of the author that the reported results are promising.

In particular, the sensitivity in discriminitating subjects on the basis of their medical conditions and the sensibility in detecting possible benefits associated with the administered therapies could represent important features for a future application of the method in a clinical setting.

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Chapter 5

Conclusions

Parkinson's disease is a progressive neurological disorder that could heavily impact the quality of life of affected people, in particular inducing motor disability, dysfunctional balance control, an increased risk of fall and fear of falling. Bradykinesia, thus the typical slowness in performing motor tasks, is also one of the most disabling symptoms of the disorder. Moreover, possible non-motor disturbances could emerge during the progression of the disease causing a further deterioration of the patients' condition.

Pharmacological therapy, mainly based on levodopa, demonstrated its efficacy since its introduction, however the possibility of high-dosage drug-induced side-effects, especially in the later stages of the illness progression, obligates to consider the administration of different kind of intervention. Stereotactic surgery, and in particular deep brain stimulation (DBS), has proven to be useful in the treatment of Parkinson's disease symptoms, but the risks related to any complex neurological surgical intervention make DBS to be a reasonable symptomatic therapy only for people in the most advanced stages of the illness.

Physical therapy can represent an interesting alternative to be applied in combination with the pharmacological one, and in later stages also for people with DBS implants.

Despite the fact that physical rehabilitation represents an interesting and effective symptomatic intervention that has been reported to be able to slow down the progression of Parkinson's related symptoms, no specific guidelines based on clinical results have been already accepted worldwide. Recently, the availability of cost-effective technologies for the detection of information related to body movements allows researchers to investigate the effect that external feedback could have on the residual motor learning abilities of the patients.

The results of a pilot RCT study that we have conducted (Section 2.1) highlighted the possible usefulness of adopting patient-tailored biofeedback signals in the treatment of Parkinson's disease. In particular, the obtained results support the efficacy of the new treatment in comparison with usual care intervention and seem indicate prolonging maintenance of the beneficial effects for at least 1 month after the end of therapy. However, due to the typical chronic progressive course of the illness, several interventions are required during the entire life of the patients, starting from the moment of the first diagnosis. This fact, in combination with the increasing incidence of Parkinson's disease in the older population, suggests that the availability of cost-effective, easy-to-manage, robust devices for at home physical rehabilitation might permit to a large group of patients to maintain an optimal level of exercise between institutionally administered rehabilitation intervention. For this reason, we investigated also the possibility to adopt a computationally low-cost algorithm for step recognition that could be successfully implemented in simple embedded wearable rehabilitation devices (see Section 2.2).

It is reported in literature, that a core aspect to develop effective rehabilitation intervention is represented by a good comprehension of the effect of the disease on the neural circuitry. For this reason, we started to investigate, in subjects with PD, sensory deficits in the reaction to an external perturbation. Most importantly, the study presented in Chapter 3, aspires to be the first step toward a rehabilitation treatment of sensory integration processes that are known to be impaired as a consequence of this neurological disease.

In the last chapter of this thesis, we presented novel methods based on wearable inertial sensors to assess balance control and motor deficits. In particular, our interest has been focused on the detection and subsequent evaluation of the anticipatory postural adjustments (APAs) that are automatic postural modifications needed to preserve balance while the body is preparing to perform a voluntary motor task. Once again, our attention was directed on the evaluation of adjustments that precede tasks that are common during the daily activities, such as walking and step climbing. A common and easy-to-administer test for the assessment of balance control, the one-leg stand test, has been also instrumented and tested on healthy subjects and people affected by Parkinson's disease and frontal gait disorder and presenting different level of disability. The availability of easy-to-administer tests for the evaluation of balance control and motor skills makes it possible to suppose that 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.

A promising area of interest might be the development of a tele-rehabilitation infrastructure to allow both healthy elderly and neurological subjects to participate in exercises and training programs directly at home. The possibility to learn new motor strategies in a familiar domestic environment could be of interest 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.