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Rehabilitation Engineering in Parkinson's disease

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Finally thanks to my brother to take care of me and help just in case I need it….As my brother said once, and I can not say better, my life is like flying with my suitcase... and with all the stuff that I carry with me... I know my suitcase is always too heavy but I need it.. I need it to fly in all the places where I am.. all the scatter places in the world where I am. He also said that I know only few places so far, and this is the reason that has to makes me happy when I'm leaving, when I'm coming back from my places, there will be tons of places and will fly to each of them.
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…….Anything is one of a million paths. Therefore you must always keep in mind that a path is only a path; if you feel you should not follow it, you must not stay with it under any conditions. Any path is only a path and there is no affront, to oneself or to others, in dropping it if that is what your heart tells you to do. But your decision to keep on the path or to leave it must be free of fear or ambition. I warn you: look at every path closely and deliberately. Try it as many times as you think necessary. This question is one that only a very old man asks. Does this path have a heart? All paths are the same: they lead nowhere. They are paths going through the bush, or into the bush. Does this path have a heart? If it does, the path is good; if it doesn't, it is of no use…..

From: "Teaching according to Don Juan", C. Castaneda

Keywords
Parkinson's disease (PD)
Postural Control
Step Initiation
Accelerometry
Early detection of PD
Augmented Biofeedback Rehabilitation

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Thesis abstract

Impairment of postural control is a common consequence of Parkinson's disease (PD) that becomes more and more critical with the progression of the disease, in spite of the available medications. Postural instability is one of the most disabling features of PD and induces difficulties with postural transitions, initiation of movements, gait disorders, inability to live independently at home, and is the major cause of falls. Falls are frequent (with over 38% falling each year) and may induce adverse consequences like soft tissue injuries, hip fractures, and immobility due to fear of falling. As the disease progresses, both postural instability and fear of falling worsen, which leads patients with PD to become increasingly immobilized.

The main aims of this dissertation are to: 1) detect and assess, in a quantitative way, impairments of postural control in PD subjects, investigate the central mechanisms that control such motor performance, and how these mechanism are affected by levodopa; 2) develop and validate a protocol, using wearable inertial sensors, to measure postural sway and postural transitions prior to step initiation; 3) find quantitative measures sensitive to impairments of postural control in early stages of PD and quantitative biomarkers of disease progression; and 4) test the feasibility and effects of a recently-developed audio-biofeedback system in maintaining balance in subjects with PD.

In the first set of studies, we showed how PD reduces functional limits of stability as well as the magnitude and velocity of postural preparation during voluntary, forward and backward leaning while standing. Levodopa improves the limits of stability but not the postural strategies used to achieve the leaning. Further, we found a strong relationship between backward voluntary limits of stability and size of automatic postural response to backward perturbations in control subjects and in PD subjects ON medication. Such relation might suggest that the

central nervous system presets postural response parameters based on perceived maximum limits and this presetting is absent in PD patients OFF medication but restored with levodopa replacement.

Furthermore, we investigated how the size of preparatory postural adjustments (APAs) prior to step initiation depend on initial stance width. We found that patients with PD did not scale up the size of their APA with stance width as much as control subjects so they had much more difficulty initiating a step from a wide stance than from a narrow stance. This results supports the hypothesis that subjects with PD maintain a narrow stance as a compensation for their inability to sufficiently increase the size of their lateral APA to allow speedy step initiation in wide stance.

In the second set of studies, we demonstrated that it is possible to use wearable accelerometers to quantify postural performance during quiet stance and step initiation balance tasks in healthy subjects. We used a model to predict center of pressure displacements associated with accelerations at the upper and lower back and thigh. This approach allows the measurement of balance control without the use of a force platform outside the laboratory environment.

We used wearable accelerometers on a population of early, untreated PD patients, and found that postural control in stance and postural preparation prior to a step are impaired early in the disease when the typical balance and gait intiation symptoms are not yet clearly manifested. These novel results suggest that technological measures of postural control can be more sensitive than clinical measures. Furthermore, we assessed spontaneous sway and step initiation longitudinally across 1 year in patients with early, untreated PD. We found that changes in trunk sway, and especially movement smoothness, measured as Jerk, could be used as an objective measure of PD and its progression.

In the third set of studies, we studied the feasibility of adapting an existing audio-biofeedback device to improve balance control in patients with PD. Preliminary results showed that PD subjects found the system easy-to-use and helpful, and they were able to correctly follow the audio information when available. Audiobiofeedback improved the properties of trunk sway during quiet stance.

Our results have many implications for i) the understanding the central mechanisms that control postural motor performance, and how these mechanisms are affected by levodopa; ii) the design of innovative protocols for measuring and remote monitoring of motor performance in the elderly or subjects with PD; and iii) the development of technologies for improving balance, mobility, and consequently quality of life in patients with balance disorders, such as PD patients with augmented biofeedback paradigms.

Chapter 1

Introduction

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Objectives of this thesis

The objectives of this thesis are:

- To *detect and assess*, in a quantitative way, postural impairments in subjects with PD. Also, to *investigate* the central mechanisms that control postural motor performance, and how these mechanisms are affected by levodopa.

Because the motor impairments in subjects with PD are strongly *time-varying* and *context-dependent*, traditional approaches to quantify postural impairments bsed on sample observations taken in a sophisticated movement analysis laboratory setting may have a limited validity. New, state-of-the-art technologies provide valuable tools for developing more sophisticated and dedicated *portable systems* for *anywhere-anytime monitoring* of PD subjects' postural motor behavior.

For this reason, other objectives of this thesis are:

- To develop and validate a new protocol, using wearable inertial sensors to measure postural sway and postural transitions.
  For this aim, we determined: i) the optimal number and ii) the combination of sensors (accelerometers, gyros and compasses), and iii) their placement on the body and validated this approach to estimating center of pressure from accelerometers with young, healthy subjects.

- To investigate postural sway and postural transitions in untreated, early-to-moderate PD subjects, in order to find: i) quantitative measures sensitive to motor impairments in the early stages of the pathology, and ii) quantitative biomarkers of disease progression.

- To develop a protocol for testing the feasibility and effects of wearable, audio-biofeedback system in maintaining balance in subjects with PD.

Parkinson's disease

Parkinson disease (PD) is common among older people, affecting more than 1 in every 100 people over the age of 75 years and 1 in every 1,000 people over the age of 65 years. [1] On a worldwide basis, it is thought that approximately 10 million older people have PD. [2] With a large proportion of the population aging, by the year 2020 more than 40 million people in the world will have this progressive neurological condition [1].

Patients with PD report that balance disorders are the most important cause of reduced quality of life (PD Alliance.org). Balance disorders are the hallmark of PD and can severely compromise an individual's ability to perform important motor skills such as walking, turning around, and transferring in and out of bed.

A better understanding of balance disorders associated with PD can not only help improve their treatment and improve quality of life, but also improve our understanding of how the central nervous system controls balance and movement. This understanding should be based on accurate measurements of balance and mobility, but this is often lacking. The most common method for assessing balance and movement disorders associated with PD consists of questionnaires and clinical rating scales known to suffer from subjective bias, poor reliability and insensitivity. New technologies, novel protocols, and sensitive, feasible approaches are needed for assessing and treating postural instability in PD.

The Background of this thesis will review the : i) pathophysiology of PD, ii) basis for postural instability in PD and its current laboratory assessment, iii) current treatments for PD, and iv) how to move from qualitative-clinical assessment to quantitative-ambulatory assessment of postural instability of PD.

Pathophysiology of the Movement Disorders in PD

In recent years, there has been a rapid growth in knowledge about the pathogenesis of the movement disorders that occur in people with PD [3]

The *most frequently observed movement disorders* are described in Table 1.

Bradykinesia	Reduced movement speed and amplitude; at the extreme, it is known as "hypokinesia," which refers to "poverty" of movement
Akinesia	Difficulty initiating movements
Episodes of freezing	Motor blocks/sudden inability to move during the execution of a movement sequence
Impaired balance and postural control	Difficulty maintaining upright stance with narrow base of support in response to a perturbation to the center of mass or with eyes closed; difficulty maintaining stability in sitting or when transferring from one position to another; can manifest as frequent falling
Dyskinesia	Overactivity of muscles; can manifest as dystonia; wriggling/writhing movements; chorea or rarely athetosis
Tremor	Usually resting tremor; more rarely postural or action tremor
Rigidity	Hypertonicity and hyperreflexia in agonist and antagonist muscle groups in a given limb
Adaptive responses	Reduced activity, muscle weakness, reduced muscle length, contractures, deformity, reduced aerobic capacity

***Table 1**: Common movement disorders in people with Parkinson's disease*

Of these movement disorders, slowness in the performance of movement sequences (*bradykinesia*) is the most common and affects around 80% of people with PD [1]. Slowness may be so marked as to result in poverty of movement, which is known as "hypokinesia." People with hypokinesia typically have an expressionless, mask-like face and walk with reduced trunk rotation, short steps, and diminished arm swing, which is more pronounced on one side than the other. Although PD-related movement disorders characteristically occur bilaterally, movement disorders such as bradykinesia are asymmetrical in their severity. There is growing evidence that bradykinesia in people with PD results from disruption of the neurotransmitters used in the neural projections from the internal segment of the globus pallidus of the basal ganglia (BG) to the motor cortical regions known as the supplementary motor area (SMA) and the primary motor cortex [4]. The SMA is critical in regulating the increase in neural activity that needs to occur before a movement is executed [5;6]. It also ensures that a movement is terminated at the appropriate time [5;6]. If the preparation for forthcoming movement is disrupted, then movements can be reduced in size and speed (bradykinesia). At the extreme, if there is no activity in the

SMA and primary motor cortex, movement fails to occur. Absence of movement associated with an inability to initiate movement is known as "akinesia." [7]

Sudden cessation of movement (*motor blocks*) partway through an action sequence is known as "freezing" (Table 1). Clinical evidence suggests that akinesia and freezing episodes are *context dependent* [7]. For example, the person may "freeze" when attempting to walk through a narrow doorway or when making a transition from walking on carpet to wooden floorboards, even though the or she can walk quickly without motor blocks across an empty parking lot [1]

The neurotransmitter imbalance in the motor cortex-BG-motor cortex feedback loop arises due to a relentless and progressive death of neurons in the substantia nigra pars compacta (SN) of the brain stem [4]. These brainstem neurons normally secrete the neurotransmitter dopamine that apparently plays a role in allowing people to execute well-learned skilled movements quickly and smoothly. Why cell death occurs in this region of the brain stem is not known, although exposure to environmental toxins coupled with a genetic predisposition to PD is one hypothesis [8]. What is known is that the balance of dopamine, gamma-aminobutyric acid (GABA), enkephalin, glutamate, acetylcholine, and substance P in the BG is normally very finely tuned [4]. In people with bradykinesia, there is a decrease in the excitation of the dopaminergic projections from the SN to the striatum and the internal globus pallidus coupled with a reduction in the inhibitory activity of dopaminergic projections from the SN to the striatum and the external globus pallidus [4]. The net result is excessive inhibitory output from the globus pallidus to the thalamus that leads to reduced movement.

Bradykinesia, akinesia, and freezing are not the only movement disorders in PD. As early as 1967, Martin [9] recognized that *balance disorders* were also an inherent feature of the disease. The reason why balance is disrupted is unclear, although it appears to be associated with neurotransmitter disturbances in the output projections from the internal globus pallidus to the midbrain and brain-stem regions involved in maintaining upright stance and extensor muscle activity [1]. Since many balance disorders associated

with PD are not improved with levodopa medication, nondopaminergic pathways involving the brainstem and cortex are thought to be involved.

Another hallmark of idiopathic PD is rigidity [10]. *Rigidity* can be detected by slow passive movement of the affected body part while the person focuses his or her attention on a secondary task (such as reciting the days of the week backward to avoid compensating for his or her movement disorder).

Resting tremor (4–6 Hz) is also characteristic of idiopathic PD and is often the first symptom reported [1]. It may be due to an altered firing rate of thalamic neurons, although the exact mechanism by which this occurs is not known. Less commonly, action tremor (6–8 Hz) can be observed during the execution of movements, or postural tremor can be observed when the person bears weight through the limb or encounters resistance to movement of the limbs, trunk, head, or neck. Physical therapists rarely need to treat individuals with resting tremor because it disappears during movement and therefore does not interfere with the ability to perform everyday tasks such as walking, writing, or grasping objects.

Postural instability

Postural instability is one of the most disabling features of PD. It is due to a dysfunction of postural reflexes, which is generally a manifestation of the late stages of the disease, and usually occurs after the onset of non-motor symptom[11].

In spite of their forward inclination in upright posture, PD patients tend to fall backwards very easily, with only a slight push, resulting in retropulsion[12]. Both axial rigidity and poor trunk coordination contribute to the poor stability of PD patients in response to backward body sway. Horak et al.[13] studied PD patients in their off-state and showed different dynamic stability margins for different directions of body sway. The smallest stability margin occurred for backward body sway in both narrow and wide stance, suggesting that PD patients are more vulnerable to falls in the backward

direction. The reduced stability margin in PD patients was due to a slower rise and a smaller peak of their centre of pressure, when compared to control subjects. Therefore, widening the sustentation base is unlikely to help PD patients to prevent backward falls.

Beyond abnormal postural reflexes, several other factors may contribute to postural instability in PD patients as well as other parkinsonian symptoms: orthostatic hypotension, age-related sensory changes, and their ability to integrate visual, vestibular, and proprioceptive inputs.

This postural instability induces difficulties with transfers, gait disorders, inability to live independently at home, and is the major cause of falls [14]. Falls are frequent, with a 38% risk of falling found among 100 PD patients by Koller et al.[15], among these, 13% felt down more than once a week. Moreover, falls may induce adverse consequences like soft-tissue injuries, hip fractures, and fear of falling. As the disease progresses, both PI and fear of falling worsen, which leads PD patients to become increasingly immobilized.

Evaluation of postural instability in Parkinson's disease

Static posturography

Static posturography consists in recording the displacements of the center of pression (COP), using a force platform, during quiet stance. In these conditions, the CoP sways reflect patient instability. Reported results of static posturography in PD were often contradictory [16]. Several studies reported that the body sway of PD patients is closed to normal under quiet stance, at least at the earlier stages of the disease [17;18], whereas one recent study reported impairment early in the disease [19]. In addition, Horak et al.[20] reported a decrease in postural sway in PD patients, while Mitchell et al.[21] showed an increase of the postural sway in the mediolateral direction. For these authors, the mediolateral posturographic measures were also associated with a history of falls and a poor balance performance. Błaszczyk

et al.[22] reported an increase of spontaneous sway indices and suggested that this method should be supplemented by additional measures of stability range such as the functional reach or maximal voluntary leaning.

The use of static posturography in PD is limited because of the heterogeneity of the results and because this method assesses only a single component of posture. Overall, these data suggest that the technics of postural analysis we have at our disposal are not suitable for clinical evaluation of postural troubles[16].

Dynamic posturography

The control of balance involves multiple components of postural control, including reactions triggered by external perturbations, antigravity muscle tone, and centrally-initiated postural adjustments preceding or accompanying voluntary movements[16]. Although balance under dynamic conditions has been rarely investigated in PD patients, some specific impairment of postural reflexes have been underlined. Analyses of postural reflexes in response to an unpredictable perturbation of the support (usually an unexpected toe-up tilt) showed that PD patients exhibit abnormal and "inflexible" postural reflexes, as reflected by an increase in amplitude and duration of the EMG response latency [23;24]. Using perturbations of the supporting surface in the lateral and sagittal planes, Horak et al.[13] showed that PD patients have directionally specific postural instability. Same dissociation between antero-posterior and lateral control of posture were also demonstrated in studies assessing postural control of PD patients during slow oscillation of the support[25] and during locomotor tasks[26].

Impairment of anticipatory postural adjustments (APA)

Voluntary movement is usually accompanied or preceded by an adjustment of posture aimed at preventing the disequilibrium generated by the movement [27]. Lee et al. [28] analyzed APA in a lateral leg-raising task in PD patients. They showed that in the more severely affected parkinsonian patients, the amplitude of the initial displacement of CoP was markedly

reduced, the interval between the earliest force changes and the onset of leg elevation was prolonged, and the relative timing of the kinematics adjustments during this interval was disrupted. The authors concluded that abnormalities in programming APA might contribute to postural instability in Parkinson's disease.

Considerable attention has also been focused on gait initiation impairments in PD [29-31]. The main abnormality consisted in an increased duration of the postural phase and a decrease in propulsive forces during postural and movement phases.

Treatment

Pharmacotherapy

Currently the principle treatments include medications that mimic dopamine, compounds used to create dopamine in the brain (such as levodopa) and drugs that inhibit the breakdown of dopamine. Among the others, levodopa is the most important and commonly used.
However, a major disabling symptom of chronic levodopa therapy is dyskinesia [32]. Dyskinesia generally occurs at the maximal benefit from a single levodopa dose (peak-dose dyskinesia) that can involve any body part with choreic or dystonic movements. As dyskinesia is a side effect of the levodopa therapy, it is often referred to as levodopa-induced dyskinesia [33]. The actual emergence of dyskinesia during the day depends on timing and quantity of each individual does of levodopa and also to a lesser extent, depends on stress, food and many other factors [33]. Other chronic levodopa therapy related motor manifestations that may develop are motor fluctuations such as wearing-off, early-morning dystonia, delayed ON or no-ON response and eventually ON-OFF phenomena [3].
Two important and commonly used terms regarding the parkinsonian state of the patients are *ON* and *OFF* states. During the ON state, the medication (in particular levodopa) is active and motor performance of the patient is improved. OFF state is the period that starts when the effects of the medications wear off and PD symptoms reemerge. Many of PD patients

start to fluctuate between the ON and OFF states. Moreover, during the ON state patients may suffer from dyskinesia. The clinicians constantly need to adjust the dose and the time between each intake of the medications to maximize the period of ON state and minimize the periods of OFF and dyskinesia. Over the time the response to a fixed dose of the levodopa therapy decreases and as a result, the dose or the time between each intake needs to be adjusted. Clearly, to optimally adjust the treatments, knowing the exact periods of ON and OFF state during the day is invaluable to the clinicians.

Stereotactic neurosurgery

Over the last decade high-frequenct deep brain stimulation (DBS) has emerged as an efficient therapy for patients with advanced PD [34-38]. An important advantage of DBS, in contrast to drug therapy, is that a constant level of stimulation can be maintained throughout the day. Modern neurosurgical interventions might provide some therapeutic benefit, which appears most pronounced for bilateral stimulation of the subthalamic nucleus (STN) [39;40] or internal globus pallidus (GPi) [41].For postural instability, this beneficial effect is particularly evident when patients are tested without concurrent dopaminergic medication [42].

Quantitative studies showed that STN- and GPi-DBS improve advanced PD patients' stability in quiet stance [43-45] and increase the step length and the speed of steady-state gait [46-49]. STN-DBS is assumed to present a higher risk of dyskinetic side-effects than does GPi-DBS [50]; thus, patients suffering predominantly from L-dopa-induced dyskinesia are commonly directed to GPi-DBS [51].

A recent analysis of patient outcomes [52;53] highlighted how PD patients who had undergone STN-DBS and those who had undergone GPi-DBS experienced comparable improvements both in motor function and in performance of activities of daily living following surgery. In a multicenter study with a 4-year followup, PD patients who had undergone STN-DBS and those who had undergone GPi-DBS exhibited significant improvement in many cardinal features of PD, such as tremor, rigidity, bradykinesia, and tremor [54]. The GPe has been recently proposed as a DBS target for PD. Vitek

et al. [55] have shown that patients undergoing GPe-DBS improved more in terms of bradykinesia, akinesia, and rigidity than did patients undergoing GPi-DBS. GPe-DBS induced more dyskinetic events than did GPi-DBS. In addition, recently low-frequency stimulation of the pedunculopontine nucleus region has been shown to improve Parkinsonian gait and balance disorders similarly to high-frequency STN stimulation [56], and high frequency stimulation of the substantia nigra pars reticulate has been tested for balance control during gait initiation process [57].

However, DBS does not represent a cure for Parkinson's. Though the surgery can help improve patients' movement, DBS does nothing for non-motor symptoms of the disease, such as depression, anxiety, balance problems, cognitive decline and memory loss. In some cases, the procedure can make these issues worse; in others, it can cause problems where there were none. In all cases, patients need sustained medical care after surgery, as their disease continues to progress.

To date, more than 35,000 patients around the world have had DBS electrodes implanted in their brains. Though it's no longer considered experimental, DBS is, for now, still used as a second- or third-line treatment, reserved for patients with relatively advanced cases of the disease and those for whom medication alone is inadequate or can't be adjusted precisely enough to keep their tremors and writhing under control.

Physiotherapy

There is increasing attention for the possible beneficial effects of physical exercise in Parkinson's disease [58;59]. Overall, physical functioning, balance, gait speed, strength and health-related quality of life improve for people with Parkinson's disease after a physical exercise intervention. Exercise therapy may also lead to a reduction in FOG [60]. Management guidelines of the American Academy for Neurology concluded that exercise may be helpful in improving motor function in people with Parkinson's disease [61].

However, there is insufficient evidence to support (or refute) that physical exercise is beneficial for reducing falls or depression [59]. The lack of clear effect on falls was also shown in an RCT, which showed that a combination of exercise and movement strategies (i.e. prevention of falls and movement initiation) only tended to decrease the incidence of falls compared with controls receiving usual care [62]. However, it was encouraging that recurrent near-falls were decreased in the intervention group, and either with longer follow-up, a more intensive intervention or prolonged treatment this may eventually translate into fewer actual falls and injuries, possibly even among prior nonfallers.

A novel approach in delivering exercise is using *motor imagery*, engaged previously to promote recovery of stroke patients [63]. An innovative study [64] compared a control group that was treated with physical exercise alone with an experimental group that was treated with a combination of actual physical exercise and imagery of the very same exercises. The combined treatment group showed the greatest improvement, but much work is needed to fully underpin the merits of motor imagery for rehabilitation in PD.

Clinical assessment of motor impairments

Currently, motor assessment in PD is mainly based on historical information, home diaries and neurological examination during visits to the clinic. These methods clearly suffer from many drawbacks: data from these sources can be highly subjective, they rely on the patient's memory and perception of his own symptoms and they depend on the physician's experience in the field. Moreover, most of the patients may not be aware of mild tremor or dyskinesia. They may not necessarily understand medical terminology. They may unconsciously exaggerate or attenuate symptoms' severity. Finally, short-term memory can be affected by PD [65;66].

In an attempt to solve these problems and to find more objective assessments, several rating scales have been designed and used [67]. Among

them, the Unified Parkinson's Disease Rating Scale (UPDRS) is the most widely used [68]. This rating scale tries to quantify selected symptoms and signs of parkinsonism in a 5-points scoring system (with 0 for no sign and 4 for a marked severity of the sign). In addition, several researchers have developed methods to assess gait, FOG, postural instability and balance confidence [69-73].

Unfortunately, the UPDRS like any other semi-objective rating scale has limitations like intra and inter-observer inconsistencies, can be time consuming and can be biased by subjectivity issues related to historical information.
So, the ideal assessment method should provide objective, quantitative measurements that could be easily translated into simple and useful information. For this purpose an instrumental method is undoubtedly more appropriate.

From the laboratory settings towards ambulatory assessment of PD motor symptoms

In the last decade, quantitative assessment of gait and posture in a movement analysis laboratory has become a widely used clinical tool, and an increasing number of physical therapists and doctors are choosing suitable treatments for their patients based on the information from kinematic and kinetic data [74-76].
A complete movement analysis system uses optical motion analysis system, force platforms, and electromyography in order to obtain the 3D realistic representation of the movement of the musculo-skeletal systems. Normally, the following quantities are measured. Instantaneous positions of markers located on the skin surface are obtained using stereophotogrammetry (motion capture) either based on conventional photography or optoelectronic sensors [77;78]. External forces are measured using dynamometers, such as force plates [77;79]. Electrical activity of muscles is recorded through electromyography [77;80]. Metabolic energy is assessed using indirect calorimetry. Anthropometric quantities are acquired either using a scale, a tape measure and callipers, or more sophisticated methods

such as 3D scanners. Such systems are very accurate and represent a gold standard in studying movement analysis, however they are expensive, require a large space and cannot be used outside a laboratory environment. For these reasons, in the last few years, many sensors have been developed for industrial, robotics, aerospace and biomedical measurements using the continuously advancing circuit technology [81;82]. Recent developments in microelectronics have led to design and production of a new generation of small, cheap and robust sensors that can be used to measure kinematic parameters of the movements of the body segments. These developments have breathed a new life in design of ambulatory systems for long-term monitoring of body movements [75;83].

Accelerometers and gyroscopes have been used to detect and quantify tremor [84-86], bradykinesia and hypokinesia [86-89] in PD patients. Ambulatory gait analysis systems has been design based on accelerometers [90-92] and gyroscopes [93-95] for healthy subjects, elderly and pathological cases. These sensors have been used as activity monitor [96] or to classify different body postures [97;98]. Also recently kinematic sensors has been used in detection and quantification of dyskinesia [99-101], and ON-OFF state in subjects with PD [102].

Today, especially regarding assessment of PD, none of the abovementioned techniques are perfect or sufficiently investigated and overall there is little experience with them. Long-term quantification has rarely been achieved. These methods are yet young and none of them has been used in large scale nor has reached consensus as a gold standard in the scientific and clinical community. Moreover, body worn inertial sensors that have been optimized for gait measurement are not currently tuned appropriately to sensitively measure the much smaller body motions associated with quiet stance.

Outline of the thesis

The thesis is organized into eleven chapters, as showed in Table 2

The first (current) chapter introduces the objectives of the thesis, provides a short review of the literature, and an outline of the thesis.

***Table 2**: Thesis outline*

	Title	Instrumentation	Subjects
Chapter 2	Effects of Parkinson's Disease and Levodopa on Functional Limits of Stability	Force plate + Motion Analysis	Advanced PD, OFF-ON Levodopa + healthy aged-matched subjects
Chapter 3	Is the size of postural response related to voluntary limits of stability in Parkinson's disease?	Force plate + Motion Analysis	Advanced PD, OFF-ON Levodopa + healthy aged-matched subjects
Chapter 4	Step initiation in Parkinson's disease: influence of initial stance conditions	Force plate + Motion Analysis	Advanced PD, OFF-ON Levodopa + healthy aged-matched subjects
Chapter 5	Accelerometry-based prediction of center of pressure during quiet standing	Accelerometers + force plate	young healthy subjects
Chapter 6	Dependence of anticipatory postural adjustments for step initiation on task movement features: a study based on dynamometric and accelerometric data	Accelerometers + force plate	young healthy subjects
Chapter 7	Multisegmental analysis of postural sway in untreated Parkinson's disease an accelerometer-based approach	Accelerometers + force plate	untreated early-to-moderate PD
Chapter 8	Anticipatory postural adjustments prior to step initiation are hypometric in untreated Parkinson's disease: an accelerometer-based approach	Accelerometers + force plate	untreated early-to-moderate PD
Chapter 9	Longitudinal monitoring of posture in patients with early-to-moderate Parkinson's disease	Accelerometers + force plate	untreated early-to-moderate PD
Chapter 10	Biofeedback for training balance and mobility in older people: a systematic review		older people
	Effect of Audio-Biofeedback in maintaining balance in Parkinson's disease: preliminary results	Accelerometer + palmtop	moderate PD ON Levodopa + healthy aged-matched subjects

The second, third, and fourth chapter focus on the quantitative assessments of some of the most disabling postural impairments that negatively affect the quality of life in PD subjects. In particular, we investigated how Parkinson's disease and Levodopa affect: i) self-perceived limits of stability, ii) postural responses to external perturbations, and iii) anticipatory preparation to voluntary movements.

The fifth and sixth chapters describe the validation of tools based on the use of accelerometric sensors in order to quantify and assess postural sway and postural transition in young, healthy subjects.

The seventh, eighth, and ninety chapters present the results obtained applying the methodology previously validated in a group of untreated, early-to-moderate PD.

The tenth chapter provides a review of the literature on the use of biofeedback for training balance and mobility in elderly and PD subjects. Here are also presented preliminary results on the use of an audio-biofeedback system in maintaining balance in PD subjects.

The last chapter, Conclusions, summarizes the contributions of this thesis and presents the perspectives of future studies.

All chapters of the thesis follow a similar structure. Each chapter starts with an introduction to bring the subject 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 referenced articles, books, and resources used throughout the chapter are listed.

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Chapter 2

Effects of Parkinson's Disease and Levodopa on Functional Limits of Stability

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Abstract

Background.
The voluntary, maximum inclined posture reflects the self-perceived limits of stability. Parkinson's disease is associated with small, bradykinetic postural weight shifts while standing but it is unclear whether this is due to reduced limits of stability and/or to the selection of abnormal strategies for leaning. The aim of this study was to investigate the effects of Parkinson's disease and levodopa medication on voluntary limits of stability and strategies used to reach these limits.

Methods.
Fourteen subjects with Parkinson's disease (OFF and ON levodopa) and 10 age-matched controls participated in the study. Functional limits of stability were quantified as the maximum center of pressure excursion during voluntary forward and backward leaning. Postural strategies to achieve functional limits of stability were assessed by i) body segments alignment, ii) the difference between center of pressure and center of mass in preparation for a lean, iii) the timing and the velocity of the preparation phase.

Results.
Functional limits of stability were significantly smaller in subjects with Parkinson's disease compared to control subjects. Subjects with Parkinson's disease maintained their stooped posture while leaning, initiated leaning with a smaller difference between center of pressure and center of mass and had a slower leaning velocity compared to control subjects. Levodopa enlarged the limits of stability in subjects with Parkinson's disease because of an increase in maximum forward, but not backward lean, but did not significantly improve postural alignment, preparation for a leaning movement, or velocity of leaning.

Conclusions.
Parkinson's disease reduces functional limits of stability as well as the magnitude and velocity of postural preparation during voluntary, forward

and backward leaning while standing. Levodopa improves the limits of stability but not the postural strategies used to achieve the leaning.

Introduction

Postural stability is the ability to maintain equilibrium under both static and dynamic conditions, such as during quiet stance [1-3], in response to postural perturbations [4-6], or during the postural preparation for movements [7;8]. One way to quantify postural stability involves measuring the limits of stability. The limits of stability can be defined, under dynamic conditions, as the maximum displacement of the center of body mass during a feet-in-place response to external postural perturbations that can be controlled without a fall or a step (Horak et al., 2005). To investigate limits of stability in the absence of external perturbations, the maximum, voluntary, inclined posture can be used [9;10]. Statically holding the center of body mass near the forward or backward limits of foot support simulates functional positions that occur in motor tasks such as in the transition from stance to gait and from sit to stand [11]. Limits of stability, quantified by the maximum, voluntary inclined posture may be considered "functional" limits of stability, since they are influenced by subjective perception, internal postural control abilities, and environmental factors, and not only by body biomechanics or segment properties [12]. One way to measure functional limits of stability involves quantification of the maximum center of pressure (COP) displacement with respect to the base of support [13].

Postural instability is a frequent problem in subjects with Parkinson's disease (PD) [14-16] and has a great impact on their quality of life, often resulting in falls, subsequent injury, and increased fear of falling. Previous studies reported reduced antero-posterior COP excursions in PD subjects in their ON dopaminergic medication state compared with age-matched control subjects while voluntarily leaning [9;17]. Another study [10] did not detect any differences in COP position at maximum leans between healthy and PD subjects. However, the previous studies investigated postural stability while statically maintaining the maximum inclined posture, and did not consider the anticipatory and executive phases used to reach the maximal inclinations or the influence of levodopa on the limits of stability (i.e., OFF vs. ON state).

The purpose of the present study was to investigate how PD subjects manage their forward and backward functional limits of stability, and how this is affected by levodopa. Since COP displacements reflect not only

displacement of the body center of mass (COM) [18], but also anticipatory postural control [1;7], we used i) the relationship between COP and COM, ii) leaning velocity and duration, and iii) body segments alignment, to investigate the postural strategies used to achieve the forward and backward stability limits.

Methods

Participants

Fourteen patients with idiopathic PD (mean age 65.6 years, SD 8.7), see Table 1, and 10 age-matched control subjects (mean age 64.9 years, SD 8) free of any neurological or musculoskeletal disorders, participated in this study. All subjects gave informed consent in accordance with the OHSU Institutional Review Board.

All subjects with PD were sensitive to levodopa as noted by the Motor Subscale (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS), [19], reported in Table 1. PD subjects were tested in their practical OFF state after at least 12 hours of medication wash-out, and again on the same day in their ON state, at least one hour after taking their usual dose of medication. All subjects with PD had gait difficulties, impaired balance, and moderate to severe PD (from III to IV on the Hoehn and Yahr scale). These subjects were approved for deep brain stimulation surgery, attesting to homogeneity of the PD group, consistent with surgery inclusion criteria [20]. A summary of PD subjects' characteristics is reported in Table 1.

SubjID	*Age[yrs]*	*Disease duration [yrs]*	**UPDRS**[(1)]		**Rigidity**[(2)]		**Posture**[(3)]	
			OFF	ON	OFF	ON	OFF	ON
1	*67*	*9*	*59*	*34*	*15*	*8*	*5*	*1*
2	*73*	*24*	*64*	*55*	*14*	*8*	*5*	*6*
3	*76*	*14*	*63*	*42*	*12*	*10*	*3*	*3*
4	*74*	*17*	*57*	*23*	*11*	*6*	*5*	*2*
5	*75*	*13*	*32.5*	*21*	*10*	*5*	*4*	*4*
6	*56*	*15*	*29.5*	*19*	*3.5*	*2*	*3*	*3*
7	*73*	*10*	*70*	*53*	*17*	*13*	*6*	*5*
8	*57*	*3*	*26*	*13*	*10*	*7*	*3*	*0*
9	*55*	*13*	*43*	*13*	*6*	*0*	*4*	*1*
10	*55*	*10*	*39.5*	*23*	*6*	*6*	*3.5*	*2.5*
11	*52*	*5*	*42*	*16*	*10*	*0*	*2*	*2*
12	*67*	*13*	*43*	*13*	*7*	*0*	*1*	*0*
13	*67*	*15*	*59*	*34.5*	*14*	*9*	*3*	*1*
14	*71*	*14*	*48*	*39*	*5*	*4*	*3*	*2*
Mean	***65.6***	***12.5***	***48.3***	***28.5***	***10.0***	***5.6***	***3.6***	***2.3***
Std	***8.7***	***5.1***	***13.9***	***14.5***	***4.1***	***4.0***	***1.3***	***1.8***
			P=*0.001*		***P=****0.007*		***P=****0.03*	

[(1)] UPDRS Motor Subscale, /108; [(2)] Item #22 of UPDRS, /20; [(3)] Item #28 & 30 of UPDRS, /8

Table 1: *Characteristics of subjects with Parkinson's disease*

Procedure

At the beginning of a trial, the subjects stood with each foot on a separate, side by side, force plate with feet parallel at their comfortable stance width. Initial stance position was consistent from trial-to-trial by tracing foot outlines on the force plates and by coaching subjects to maintain their initial COP position prior to each trial based on oscilloscope COP traces. Subjects were asked to maintain an upright standing position with arms crossed on the chest, eyes open and gaze straight ahead at an art poster 3-meters ahead of them. To allow for subsequent parameters normalization,

foot length was measured, from the heel to the tip of the hallux, with an electronic calliper.
Starting from an upright, natural position, subjects performed three tasks sequentially: 1) maximum forward lean (1 repetition acquired for 15 s), 2) maximum backward lean (1 repetition acquired for 15 s), and 3) quiet stance (3 repetitions of 60 s each). Subjects were asked to lean as far as they could at their comfortable speed, without lifting their toes or heels or flexing their hips, and to hold their maximum position for at least 5 seconds.

Measurements

Force platform data

Four vertical forces were recorded from each strain-gauge, custom-made force plate at 480 Hz, low-pass filtered at 8 Hz, and down-sampled at 20 Hz. The excursion of the total body COP (i.e., the application point of the total ground-reaction force) was computed from the vertical forces [21], both in the antero-posterior (AP) and medio-lateral (ML) direction.

Body kinematics

A Motion Analysis System (Santa Rosa, CA) with 6 video cameras and sampling frequency of 60 Hz recorded the kinematics of body segments. Reflective markers were placed on both feet and on the right side of the body on the following bony landmarks: fifth metatarsal head, lateral malleolus, lateral femoral condyle, greater trochanter, anterior superior iliac spine, clavicular acromion, elbow, temple of head, and mastoid process. Body segment kinematics, and appropriate anthropometric tables [3], were used to estimate the position of the total body COM in the sagittal plane. In addition, we reconstructed the shank, thigh, and trunk segment angles with respect to vertical to characterize postural alignment.

Data analysis and extracted parameters

The leaning tasks consisted of a motion phase followed by a maximal leaning phase. The 3 quiet stance trials were considered to characterize the natural standing of subjects, through the estimation of the average COP position.

Functional Limits of Stability

The steady-state positions of AP COP during backward and forward maximal lean were used to quantify the functional limits of stability (fLOS). Their extension was estimated as

$$fLOS = maxFW - maxBW,$$

where maxFW and maxBW represented the average AP COP over the first 5 seconds of stabilized, forward and backward leaning, respectively (see Figure 1A). fLOS, maxFW, and maxBW were normalized to foot length, and are, in the following, expressed as a percent of foot length. The 5 s window of stabilized, maximal leaning was manually identified analyzing AP COP time-series.

The steady-state positions of ML COP were also computed during maximal leans, to check for potential, lateral asymmetries.

To express the COP coordinates in an anatomically-based reference frame, the position of the AP COP was referenced to the lateral malleolus marker, and the position of the ML COP was referenced to the mid-point between right and left malleolus markers.

Postural strategies

Postural strategies were characterized by means of average segmental kinematics. Average inclination of the trunk, thigh, and shank segments with respect to vertical were used to describe the body segments alignment (postural attitude) during the 3 tasks (see Figure 1B for details).

Motion phase of the leaning tasks

The onset of the motion phase was detected by a threshold-based algorithm, with threshold set as twice the standard deviation (SD) of AP COP during the initial, standing position of each trial (Figure 1). The motion phase was considered completed when AP COP ended its rapid migration to

a new steady-state position, coincident with the start of the leaning phases (see Figure 1C). The size of the anticipatory postural adjustments to initiate the motion phase of the lean was quantified by the peak of the COP-COM time series (see Figure 1C) [22]. The motion phase of leaning was characterized by its duration (motion duration, Figure 1C), and by the ratio between the AP COP path and the motion duration (motion velocity).

Statistical analyses

Group means and SD of the means are summarized in the text. For each parameter, a separate one-way ANOVA was used to detect differences between the control versus PD OFF and between the control versus PD ON groups. A repeated measures ANOVA was used to compare PD subjects OFF and ON. Correlations between functional limits of stability parameters and the UPDRS Motor Subscale and the UPDRS items characterizing rigidity and posture (Items 22 and 28 & 30, respectively) were investigated using Pearson's correlation analysis. For the entire set of statistical analyses the level of significance was set at $p<0.05$. All the analyses were performed with NCSS Software, Kaysville, Utah.

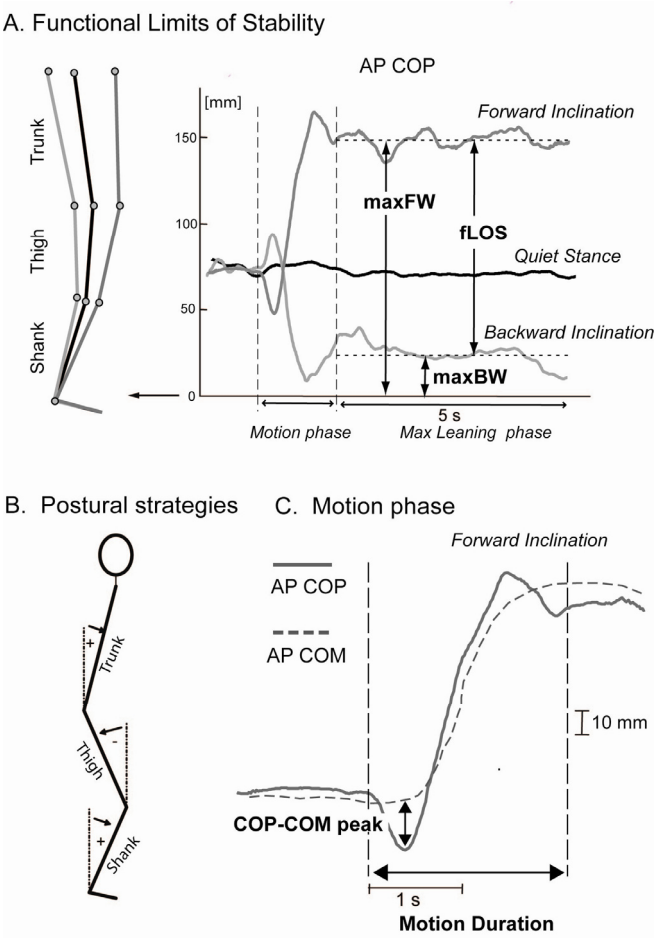

***Figure 1**: Signals collected from a representative control subject and main parameters considered in the data analysis. (A) Functional limits of stability and parameters that quantify the maximal leaning phase. (B) Parameters that characterize the motion phase (example for forward leaning).*

Results

Functional limits of stability

The mean position of AP COP in quiet stance and during maximal backward leaning was not significantly different between control and PD subjects, both in the OFF and ON states, as shown in Figure 2A. Similarly, the mean position of ML COP during the 3 tasks was not different between control and PD subjects, or between PD subjects in the OFF and ON states.

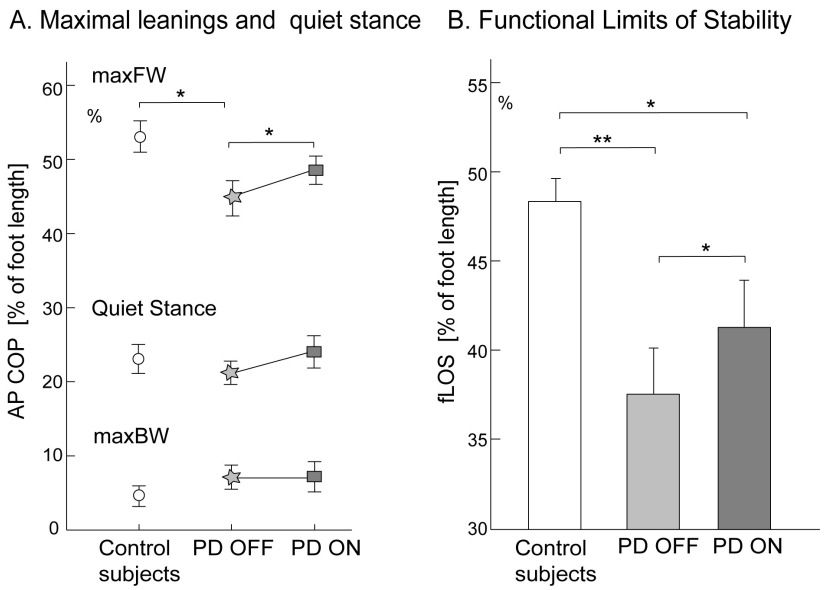

Figure 2: *Functional limits of stability in control and parkinsonian subjects. (A) Position of antero-posterior center of pressure (mean and SD) during the maximal leaning tasks and in quiet stance. (B) Functional limits of stability (mean and SD) quantified as the difference between maximal forward and maximal backward lean position. * p<0.05, ** p<0.01*

Maximal forward leaning was significantly smaller in PD subjects in the OFF state compared to control subjects ($p<0.05$), and was increased by levodopa, although remained smaller than normal (Fig. 2A). MaxFW reached a mean of 53.1% (SD 2.1) of foot length ahead of the lateral

malleoli in control subjects versus 44.7% (SD 2.4) in PD OFF and 48.5% (SD 1.9) in PD ON.

The magnitude of the functional limits of stability, as measured by fLOS (Figure 2B), and expressed as percent of foot length, was significantly smaller in PD OFF, compared to control subjects (37.6% (SD 2.6) and 48.5% (SD 1.2), respectively, with $p < 0.01$). Levodopa significantly increased fLOS in PD subjects, (41.4% (SD 2.6)), however, fLOS remained significantly smaller than normal values ($p<0.05$). All 14 PD subjects increased their fLOS with levodopa except one subject, who was the least responsive to levodopa (see the Motor UPDRS Motor subscale and rigidity score in Table 1, Subject #14). All correlations between fLOS and UPDRS Motor subscale were not significant (ranging from -0.56 to -0.42 with $0.09 < p < 0.17$) even after we removed two outliers (Subjects #2 and #7 in Table 1) who had been unable to maintain backward lean for 5 seconds.

Postural Strategy

During quiet stance, the kinematic analysis of body segment alignment with respect to vertical confirmed the typical stooped posture in PD subjects. Fig. 3, upper panel, shows the group average, sagittal body alignment as stick diagrams for the 3 subject groups. PD subjects showed significantly larger forward inclination of the trunk ($p<0.05$), larger backward inclination of the thigh ($p<0.01$), and larger forward inclination of the shank ($p<0.05$) compared to control subjects, reflecting their increased hip, knee, and ankle joint flexion. Levodopa decreased forward trunk inclination to some extent, although not significantly, but did not change thigh or shank inclinations, which remained significantly different from control subjects' values ($p<0.01$ and $p<0.05$, respectively).

During forward lean, all subjects significantly increased their forward trunk inclination compared to quiet stance ($p<0.05$; Fig. 3B upper panel). However, unlike control subjects, PD subjects, both OFF and ON, maintained similar leg alignment as during quiet stance, with a smaller forward thigh inclination and a smaller forward shank inclination than control subjects ($p<0.05$). In addition, PD subjects maintained the knees flexed during backward leaning, as highlighted by corresponding shank and thigh inclination values and by stick diagrams.

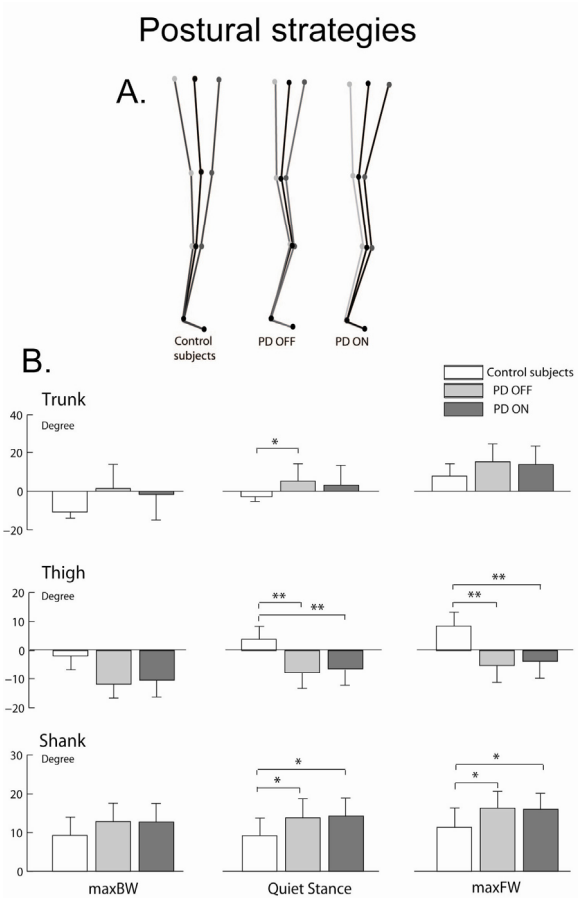

Figure 3: *Postural strategies during maximal leaning tasks and quiet stance in control and parkinsonian subjects, represented by: (A) average stick diagrams. (B) trunk, thigh, and shank inclinations (mean and SD). *p<0.05, **p<0.01*

Motion phase of the leaning tasks

The AP COP-COM time-series is shown in Figure 4A during the backward and forward leaning tasks for a representative control subject.

The COP-COM peak was significantly smaller in PD compared to control subjects ($p<0.05$), both for the forward and backward leaning. Figure 4B summarizes the group means and SD of the COP-COM peak. Levodopa did not significantly change the COP-COM peak.

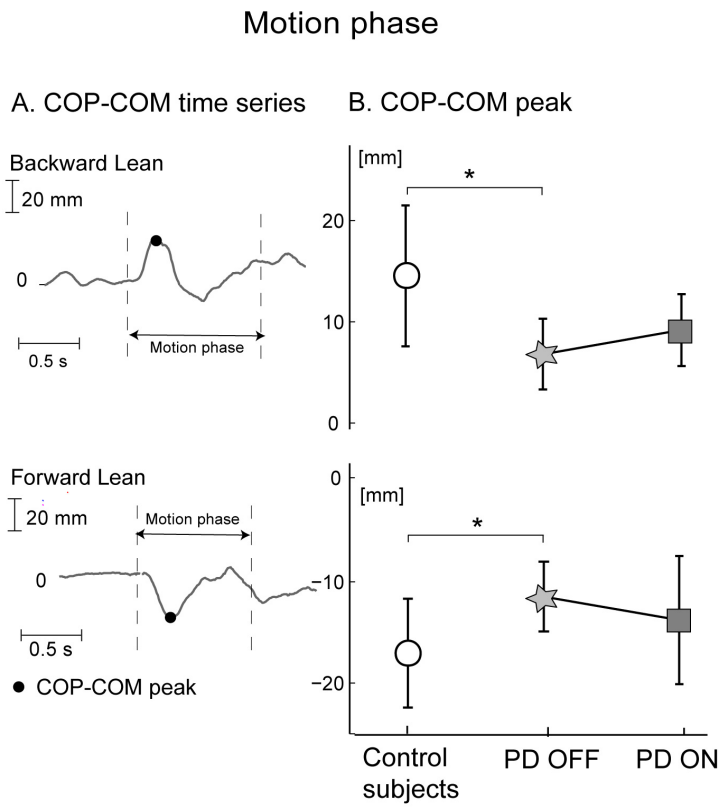

Figure 4: *Peak of COP-COM time series during backward and forward leaning. (A) Example of COP-COM time-series for a representative control subject. (B) COP-COM peaks for control and parkinsonian subjects (mean and SD). *p<0.05*

During backward leaning, PD subjects showed significantly longer and slower movements compared to control subjects (Fig. 5). In contrast, during forward leaning, movement duration and velocity were similar for control and PD subjects (Fig. 5). Levodopa did not change significantly movement duration and velocity.

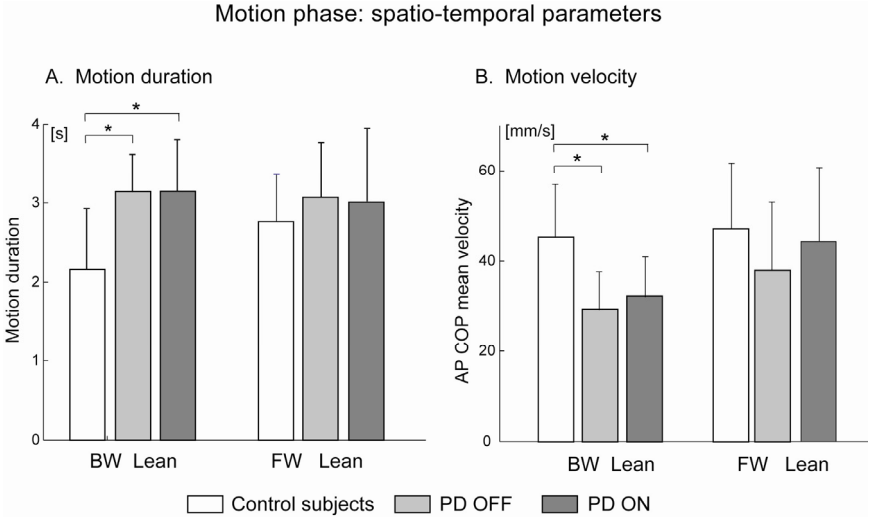

Figure 5: *Spatio-temporal characterization of the motion phase (mean and SD) in control and parkinsonian subjects. (A) Motion duration. (B) Motion velocity quantified by the AP COP mean velocity.*

Discussion

The present study showed that subjects with PD have smaller functional limits of stability in the sagittal plane compared to age-matched control subjects. The small stability limits in PD subjects was primarily due to a reduction of maximum forward body leaning. The small maximum forward lean in PD subjects may be related to their impaired postural preparation for gait initiation [8;23;24], that similarly requires a preparatory forward lean. In contrast to the forward direction, stability limits in the backward direction were not significantly different between control and PD subjects. This result could be due to an age-effect or "floor"-effect on maximum backward inclination common to both PD and control subjects due to biomechanical constraints for backward leaning [9].

We did not find any left-right asymmetry during the leaning tasks. However, future studies aimed at a better characterization of postural stability should more extensively evaluate COP position in both the AP and ML directions, during longer leans. Indeed, previous studies found differences in medio-lateral sway between PD and control subjects during body sagittal inclinations [10;25] .

Unlike a previous study [9], we did not see a significant difference in average COP position during quiet stance between PD and control subjects. Such differences might be explained by different inclusion criteria for PD subjects (our subjects where candidates for DBS surgery) and by the specific instructions for subjects to gaze forward and to maintain consistent initial COP position prior to each trial.

Postural kinematic strategies [26] in the steady-state upright and leaning positions confirmed the typical, stooped posture of PD subjects [5]. PD subjects also maintained their stooped posture during the voluntary leaning tasks [27]. The stooped posture probably contributed to the reduced forward limits of stability, because the flexed ankle, knee and hip joints resulted in longer ankle plantarflexor muscles and larger antigravity forces required to maintain equilibrium. This unchanged body posture is consistent with previous studies showing that PD subjects have difficulty in changing postural strategies with changes in initial conditions [5;8;23;28]. Although our subjects were instructed to move without flexion/extension of

knee or hip, both control and PD subjects were not able to use a pure, inverted pendulum-like behavior but flexed the hips for forward leans and flexed the knees for backward leans.

Although these PD subjects were highly sensitive to levodopa, as shown by changes in their UPDRS Motor subscale, and levodopa increased their limits of stability, the medication did not change postural strategies used to reach such limits. It is possible that reduced rigidity allowed larger stability limits with levodopa, although the parameter fLOS did not correlate with UPDRS measures of rigidity. Indeed, previous studies demonstrated that PD subjects in the ON levodopa state reduced, compared to the OFF state, the background EMG, consistently with reduced rigidity, and then they can move the COM farther and faster in response to external perturbations and during quiet stance [29]. Possibly reduction of leg, not axial, rigidity may be related to increased functional stability limits in the ON state, consistently with a previous study that showed no reduction of axial rigidity with levodopa [30].

Postural preparation for the voluntary leaning movement, characterized by the peak of the COP-COM time series, was impaired in subjects with PD, particularly in the OFF state, consistently with other tasks requiring anticipatory postural adjustments [8;23;31]. The COP-COM variable has been shown to detect stability during preparation for a voluntary rise from a chair [7]. Our results showed reduced COP-COM peak in preparation for a lean as well as reduced functional stability limits in PD subjects, suggesting that PD affect both preparation and achievement of limits of stability. Subjects with PD reached their functional stability limits slowly compared to control subjects, during backward, but not during forward, leaning. The slowness of backward leaning may reflect weakness in the ankle extensors or a perceived difficulty of the backward leaning motor task. In fact, slowness of movement may reveal cautiousness or fear of falling and a higher perceived difficulty of the backward leaning task [32]. In this case, rehabilitation programs focused on increasing postural limits of stability and/or reducing fear of falling may be useful for PD.

The present study highlights the importance of a quantitative approach for postural evaluation in PD. In fact, the lack of correlation between the UPDRS Motor subscale and limits of stability parameters is consistent with poor specificity of the UPDRS Motor subscale for the postural requirements

associated with a voluntary lean. Forward voluntary leaning may be a good clinical measure of postural ability in PD by reflecting composite effects of segment orientation, perceived postural stability, fear of falling, whole body kinaesthesia and leg rigidity

Our results showed that levodopa improves the static, functional limits of stability, but did not ameliorate postural preparation for a leaning movement or postural kinematic strategies for leaning. These findings suggest separate central mechanisms and different constraints on perceived postural limits of stability, multisegmental postural alignment, and postural preparation for whole body movement.

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Chapter 3

Is the size of postural response related to voluntary limits of stability in Parkinson's disease?

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Abstract

The relationship between voluntary limits of stability and automatic postural responses may reveal how perceived limits of stability affect balance when reacting to perturbations. Both voluntary and automatically-triggered postural limits of stability are compromised by Parkinson's disease (PD), but the relationship between them is unknown. Nine subjects with PD were tested ON and OFF medication and compared to nine healthy control subjects. Subjects were asked to: 1) voluntarily lean and hold maximally from the ankle joint in the backward direction and 2) maintain balance in response to a forward surface translation of 12 cm at 9 cm/s, which induced backward postural sway. Voluntary and automatic limits of stability were defined by the peak center of pressure and center of mass in the backward direction, normalized to foot length. The strong relationship between backward voluntary limits of stability and size of the automatic postural responses suggests that the central nervous system might presets postural response parameters based on voluntary maximum limits. Such relation is disrupted in PD.

Introduction

Postural equilibrium is the condition in which all the forces acting on the body are balanced such that the center of body mass (COM) is controlled relative to the base of support, either in a particular position or during movements [1]. Control of balance, or equilibrium, can be reactive, that is, in response to external forces displacing the COM, or proactive, as occurs in voluntary leaning to functional Limits of Stability. The role of the nervous system is to detect and predict instability and produce the appropriate muscle forces that move the center of foot pressure (COP) so that the COM is well controlled and balance is maintained [1]. The COP is the location of the net reactive forces at the surface.

Voluntary limits of stability can be quantified asking a standing subject to lean as far as possible without taking a step [2;3], and maybe considered 'functional' limits of stability since they are influenced by subjective perception, internal postural control abilities, and environmental factors, and not only by body biomechanics [4].

The ability to maintain equilibrium under reactive conditions depends how automatic postural response (APR), triggered by proprioceptive receptors, are scaled to how fast and far the COP is displaced over the base of support [5].

No response to an external postural perturbation is totally reactive. Platform perturbation studies [6-9] indicate that although automatic postural responses to external displacements of the body COM are shaped by the sensory characteristics of the perturbation, responses are also shaped by CNS mechanisms related to expectations, attention, experience, environmental context, and intention, as well as by preprogrammed muscle activation patterns (synergies) [1]. Because automatic postural responses are initiated at 100 milliseconds [1], the CNS does not have sensory information available about the amplitude and duration of displacements. For this reason, some automatic response parameters may be pre-selected based on voluntary (or perceived) limits of stability and stored subcortically for quick execution of a synergistic response with minimal online modification.

The relationship between voluntary limits of stability and automatic postural responses is unknown. We hypothesized that the excursion of the COP during the voluntary task would be correlated with the automatic postural response observed during the surface translation, such that as perceived voluntary limits increase, the larger the system will allow the COP to travel during the automatic postural response. Further, we expected a disruption of this correlation in Parkinson's disease (PD) subjects, since previous study [8] showed that automatic postural response are impaired in such subjects particularly in backward direction. Other studies found that limits of stability are reduced in PD with respect to control subjects [2;3], however such reduction in [2] was mainly due to a reduction of forward than backward lean. If a correlation exists, this might suggest the neural representation of voluntary limits of stability maybe used to set the parameters for the automatic postural responses.

Methods

Subjects and experimental protocol

Nine healthy, elderly control and 9 patients with idiopathic PD were a subset of subjects included in a previous study regarding voluntary limits of stability [2]. All subjects with PD had gait difficulties, impaired balance, and moderate to severe PD (from III to IV on the Hoehn and Yahr scale). These subjects were approved for deep brain stimulation surgery, attesting to homogeneity of the PD group, consistent with surgery inclusion criteria [10]. All subjects gave informed consent in accordance with the OHSU Institutional Review Board.

All PD subjects were sensitive to levodopa as noted by the Motor Subscale (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS), [11], (43±3.8 OFF, 28±4.8 ON). PD subjects were tested in their practical OFF state after at least 12 hours of medication wash-out, and again on the same day in their ON state, at least one hour after taking their usual dose of medication.

At the beginning of a trial, the subjects stood with each foot on a separate, side by side, force plate with feet parallel at their comfortable stance width. Initial stance position was consistent from trial-to-trial by tracing foot outlines on the force plates and by coaching subjects to

maintain their initial COP position prior to each trial based on oscilloscope COP traces.

Starting from an upright, natural position, and looking straight ahead at an art poster 3-meters ahead from them, subjects were asked to: (1) voluntarily lean backward without lifting their toes or heels or flexing their hips, and to hold their maximum position for at least 5 seconds; and (2) maintain balance in response to a forward surface translation of 12 cm at 9 cm/s, which induced backward postural sway.

Data collection and analysis

Apparatus and methods of the two different tasks have been described in detail elsewhere and will be summarized here [2;8]. Four vertical forces were recorded from each strain-gauge, custom-made force plate at 480 Hz, low-pass filtered at 8 Hz, and down-sampled at 20 Hz. The excursion of the total body COP was computed from the vertical forces [12], both in the antero-posterior (AP) and medio-lateral (ML) direction.

A Motion Analysis System (Santa Rosa, CA) with 6 video cameras and sampling frequency of 60 Hz recorded the kinematics of body segments. Reflective markers were placed as in [2;8] to estimate the position of the total body COM in the sagittal plane. In addition, we reconstructed the shank, thigh, and trunk segment angles with respect to vertical to characterize postural alignment.

Since the main movements of the two tasks were in the antero-posterior direction we focused the analyses in this direction.

The extracted parameters were: i) voluntary Peak COP: the average value of backward COP during the 5 seconds of holding the maximum backward lean [2]; ii) voluntary Peak COM: the average value of backward COM during the 5 seconds of holding the maximum backward lean; iii) automatic Peak COP: maximum backward COP during the forward platform translation; iv) automatic Peak COM: maximum backward COM at the instant of automatic Peak COP; v) automatic Peak of the COP-COM time series during the forward platform translation (). Figure 1 shows examples of COP and COM signals collected from a representative control (Fig. 1A) and PD subjects (Fig. 1B) in the antero-posterior direction, together with the extracted parameters. To express the COP and COM coordinates in an anatomically-based reference frame, the position of the COP and COM was

referenced to the heel marker. The parameters were then normalized to the foot length.

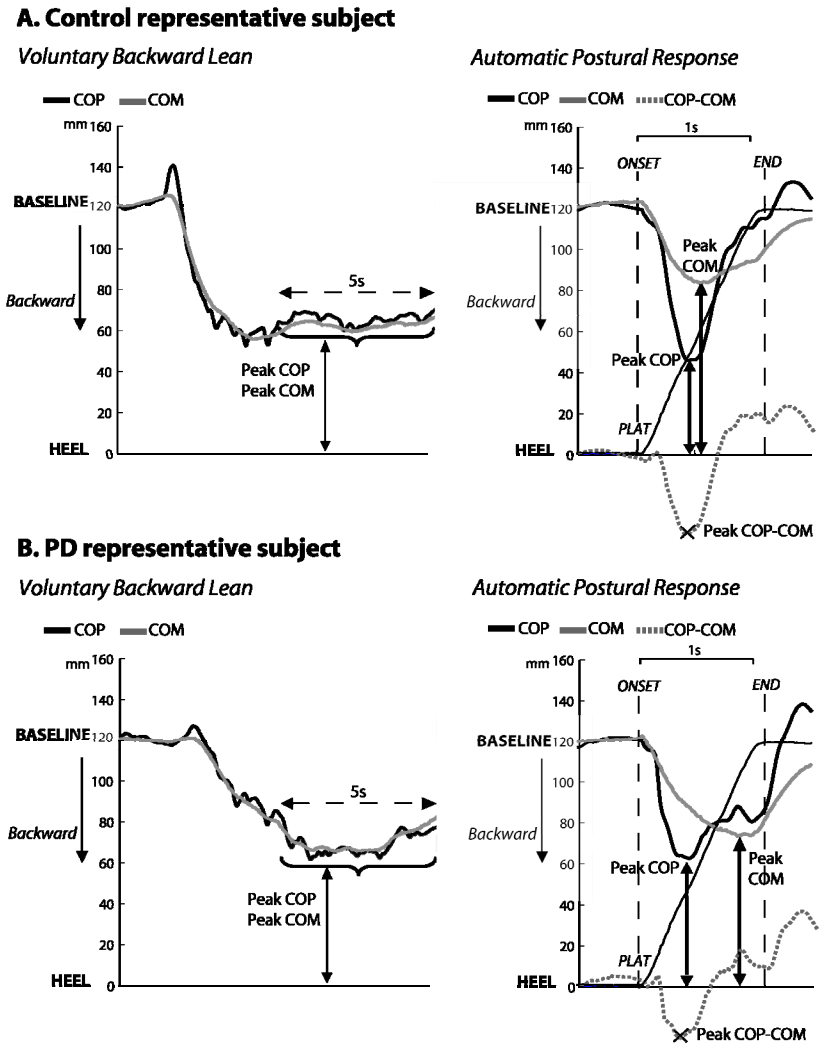


Figure 1

Postural strategies, during the two tasks, were characterized by segmental kinematics. Inclination of the trunk, thigh, and shank segments with respect to vertical were used to describe the body segments alignment in the

steady-state before the beginning of the two tasks, and at the automatic and voluntary limits of stability.

Statistical analyses

For each parameter, a separate one-way ANOVA was used to detect differences between the control versus PD OFF and between the control versus PD ON groups. A repeated measures ANOVA was used to compare PD subjects OFF and ON. Correlations between voluntary and automatic Peak COP and COM were investigated using Pearson's correlation analysis. For the entire set of statistical analyses the level of significance was set at $p<0.05$. All the analyses were performed with NCSS Software, Kaysville, Utah.

Results

The automatic Peak COP was larger than the voluntary Peak COP in all groups, control, PD OFF and PD ON ($p<0.05$). However there were no significant differences between groups on either of these measures (see Figure 2A).This means that we did not found differences in the voluntary and automatic Peak COP between control and PD subjects. The automatic Peak COM was smaller ($p<0.05$) than the voluntary Peak COM only in control subjects, while was similar among PD OFF and ON medication (see Figure 2B).

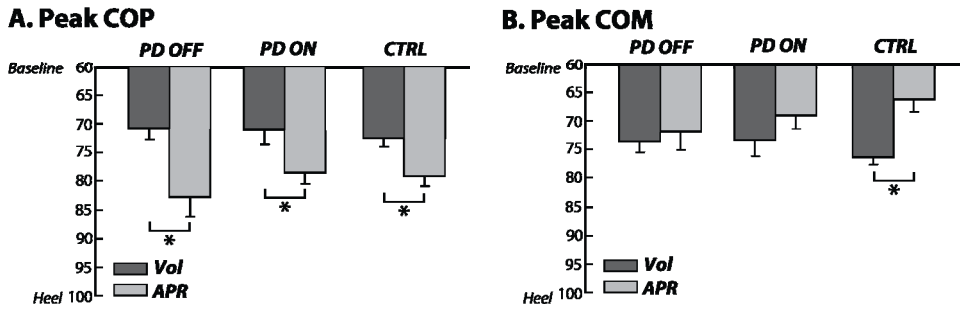
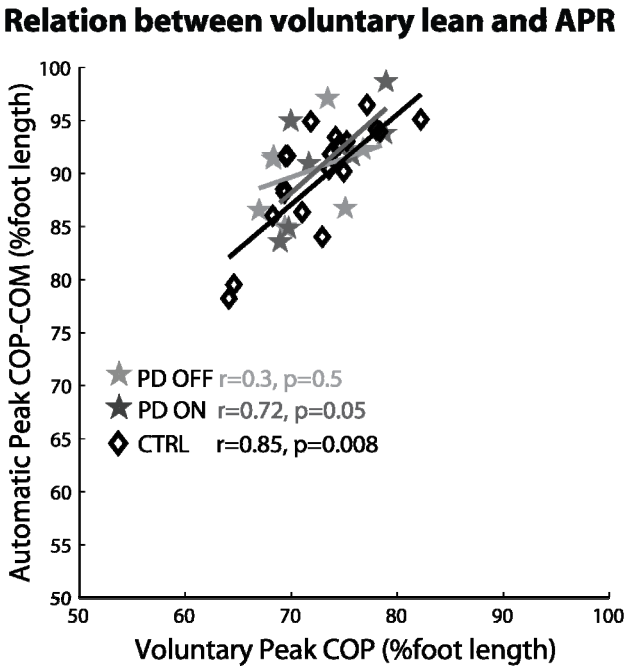


Figure 2

There was a positive correlation between backward voluntary Peak COP and backward automatic Peak COP-COM for healthy controls (r=0.85, p=0.002), and PD ON (r=0.72, p=0.05). In contrast to these results, PD OFF medication didn't show significant correlation. The further a subject leaned backward, greater stability the subject has during the automatic postural responses to the forward platform translation.



Figuere 3

During the stance phase before leaning, in both tasks, the kinematic analysis of body segment alignment with respect to vertical confirmed the typical stooped posture in PD subjects. PD subjects showed significantly larger forward inclination of the trunk ($p<0.05$), larger backward inclination of the thigh ($p<0.01$), and larger forward inclination of the shank ($p<0.05$) compared to control subjects, reflecting their increased hip, knee, and ankle joint flexion, as showed in [2]. Levodopa did not significantly change their typical posture. In each group, PD and controls, the voluntary backward

lean was performed by extending trunk and thigh from the baseline. The same strategy was adopted for reach the backward Peak COP during the automatic postural response, in both groups. However, control subjects showed less trunk extension during the automatic postural response with respect to the voluntary backward lean ($p<0.001$).

Discussion

The results of this study were in part consistent with our hypothesis. The automatic postural responses due to platform forward translation (quantified by the automatic Peak COP) were significantly bigger than the voluntary limits of stability (quantified by the voluntary Peak COP) in all groups, PD OFF, ON and control. This means that subjects can lean more, without falling, than they perceived and that is measured by the backward voluntary limits of stability. However, we didn't find differences between group, neither for automatic Peak COP, nor for voluntary Peak COP. Such similarity could be due to an age-effect or 'floor'-effect on backward leaning common to both PD and control subjects due to biomechanical constraints for leaning backward [2;3]. In keeping with our results, our previous work [2] showed that backward voluntary limits of stability were similar in PD compared to control subjects, while forward were not.

The kinematic analysis of body segment alignment in upright position confirmed the typical stooped posture of PD subjects [13] reflecting their increased hip, knee, and ankle joint flexion. A similar strategy was used to achieve voluntary and automatic limits of stability consisting in extending trunk and thigh segment. However, only control subjects showed a significant smaller trunk extension to achieve automatic Peak COP respect voluntary Peak COP. PD subjects maintained their stooped posture during both tasks, consistent with previous study that showed their difficulty in changing postural strategies with changes in initial condition [6;14;15].

We found a strong relationship between backward voluntary limits of stability and size of the automatic postural response that suggests that the central nervous system might presets postural response parameters based on perceived maximum limits. We also found a disruption of such relation

in PD subjects, meaning that dopaminergic denervation might impair scaling of postural response based on voluntary limits of stability.
It is believed that the characteristics of APRs are shaped by a combination of somatosensory, vestibular, and visual inputs [16]. Also, APRs are rapid muscular responses that restore balance after unexpected disturbances. Since Stapley et al., found that somatosensory informations are critical for the timing of automatic postural response, another hypothesis for the disrupted relation in PD could be due to a delay in sensory integration. In fact, the timing of the APR is critical to maintaining balance, and it is likely that there is only a limited time period in which the response must occur to maintain control of the COM [17]. The role of the APR after a perturbation is to decelerate the COM and return it to a position that ensures the maintenance of balance.

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Chapter 4

Step initiation in Parkinson's disease: influence of initial stance conditions

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Abstract

In this study, we investigated how the size of preparatory postural adjustments prior to step initiation, and step length and velocity depend on initial stance width in healthy elderly subjects and in patients with Parkinson's disease (PD) both in the ON and OFF levodopa state. Twenty-one subjects with idiopathic PD and 24 age-matched healthy control subjects took two steps starting with feet on a two-plate force platform, from either narrow or wide stance width. We measured how the magnitude of anticipatory postural adjustments (APA) and step characteristics scaled with stance width. Results showed that preparation for step initiation from wide stance was associated with a larger lateral and backward CoP displacement than from narrow stance. Velocity and length of the first step were also sensitive to initial stance conditions, probably in relation with the differences in the corresponding APA. On the contrary, the duration of APA was not significantly affected by initial stance width, but it was longer in PD compared to healthy subjects, and speeded up by levodopa.

Although subjects with PD did scale up the size of their APA with stance width, they had much more difficulty initiating a step from a wide stance than from a narrow stance, as shown by the greater differences from control subjects in the magnitude of the APA. Our results support the hypothesis that PD subjects maintain a narrow stance as a compensation for their inability to sufficiently increase the size of their lateral APA to allow speedy step initiation in wide stance.

Introduction

Step initiation is a complex motor task that entails the transition from a quiet standing posture in double-limb support, to dynamic equilibrium that allows forward body progression. Step initiation involves a preparatory phase and a stepping phase, both of which are thought to be controlled by parallel pathways from secondary and primary motor cortex areas, respectively [1]. The preparatory phase involves anticipatory postural adjustments (APA) in which the center of pressure (CoP) shifts backward and toward the swing limb, to move the body center of mass (CoM) forward and over the stance limb, in preparation for single-limb support [1-3]. The stepping phase begins when the weight has been transferred to the stance limb and in particular velocity of the step was found to correlate with the magnitude of APA ([4;5]).

Problems with step initiation, clinically identified as 'start hesitation', are common in Parkinson's disease (PD) and disturbances in the APA are considered the major pathophysiological mechanism that underlies hindered gait initiation in PD subjects [2;3]. Start hesitation in PD is associated with diminished and prolonged preparatory CoP displacements as well as reduced step length and velocity, compared to age-matched control subjects [2;3;6;7]. Both the preparatory and stepping phases of step initiation are improved by levodopa medication [2]. Previous studies suggested that the APA may be impaired in PD because of the many connections of the basal ganglia with the supplementary motor area and the premotor area of the cortex, both of which are implicated in movement preparation [1;8] or with the penduncular pontine nucleus in the brainstem, which is implicated in locomotion initiation [9]. Gait initiation problems in subjects with PD may also originate from changes in the basal ganglia that result in slowing of the sequential execution of the preparatory and stepping subcomponents of the task [7].

Like all motor programs, the motor program for step initiation needs to change when characteristics of the motor task change: e.g. APA prior to step initiation adapts to initial asymmetric weight loading [5], to initial stance on a narrow beam [10]. Previous studies have shown that PD impairs adaptation of the APA prior to rising to toes [11] and of reactive postural

responses when the conditions of support change [12-14]. However, the effects of initial stance width on adaptation of the APA and step characteristics, such as the effects of PD on this adaptation, are unknown.

Because of the importance of unloading the initial swing limb prior to a step, we supposed that the size of the preparatory postural adjustments prior to step initiation would depend on initial stance width. Since PD is associated with a narrow stance width, we hypothesize that narrow stance width may be a compensation for the inability to generate large enough APA in a wider stance.

The aims of the present study were: 1) to understand how healthy elderly and PD subjects adapt their postural preparation for a step when initial stance changes from narrow to wide and 2) to investigate the effect of levodopa on step preparation and adaptation.

Methods

Twenty-one subjects with idiopathic PD (16 males, 5 females, age 61.7 ± 7.8 years), and 24 age-matched healthy control subjects (18 males, 6 females, age 62.4 ± 7.4 years), free of any neurological or musculoskeletal disorders, participated in this study, after giving informed consent in accordance with OHSU Institutional Review Board regulations for human subject studies. Three of the PD subjects could not be tested in the OFF state, as their symptoms were too severe to complete the wide stance trials. There was no difference in height between the two groups (mean ± SD, PD = 1.77 ± 0.1 m; control = 1.75 ± 0.1 m). The PD subjects were first tested in the practical OFF state, with a medication washout of at least 12 hours and again on levodopa medication, at least one hour after taking their usual dosage (ON state). The Motor Section (III) of the UPDRS was administered immediately before each test condition [15]. Control subjects completed two sets of trials to match the two states of the PD subjects. The repetition allowed us to check for the possible presence of any trend of fatigue or learning effect due to the repetition of trials.

At the start of each trial, the subjects stood with each foot on separate side-by-side force plates. They were instructed to voluntarily take 2 steps, starting with the right foot, at their normal, comfortable pace.

Three trials of step initiation were acquired, starting with feet parallel, 5 cm apart (narrow stance) and then 26 cm apart (wide stance). Initial stance position and symmetrical weight loading were made consistent from trial to trial by tracing foot outlines and by monitoring anterior-posterior and medio-lateral.

We acquired force-platform and kinematic data (Figure 1). Four vertical forces under each force plate were used to calculate the position of the total body CoP (i.e., the application point of the total ground-reaction force). The lateral CoP excursion toward the initial swing limb and the symmetrical changes of the vertical forces recorded from the two force plates were used to detect the APA [2]. The APA magnitude was measured both by the peak of the antero-posterior CoP excursion in the backward direction and by the peak of lateral CoP excursion towards the swing foot. The APA timing was measured by the foot-off latency, computed from the onset of the first measurable change in lateral CoP to the time of foot-off (e.g., the instant the initial swing limb left the force plate). Data from the force-platform were acquired at 480 Hz and low-pass filtered at 50 Hz. Length and velocity of the first step were measured with reflective markers placed on the right lateral malleolus detected by infrared cameras (Motion Analysis, Inc., Santa Rosa, CA). Kinematic data were acquired at 60 Hz. Length and velocity of the first step were expressed as percentage of subject's height.

In Figure 1 an example of data collected and the relative timing for a control subject are represented, together with the main dependent variables considered to characterize the preparation and execution phases.

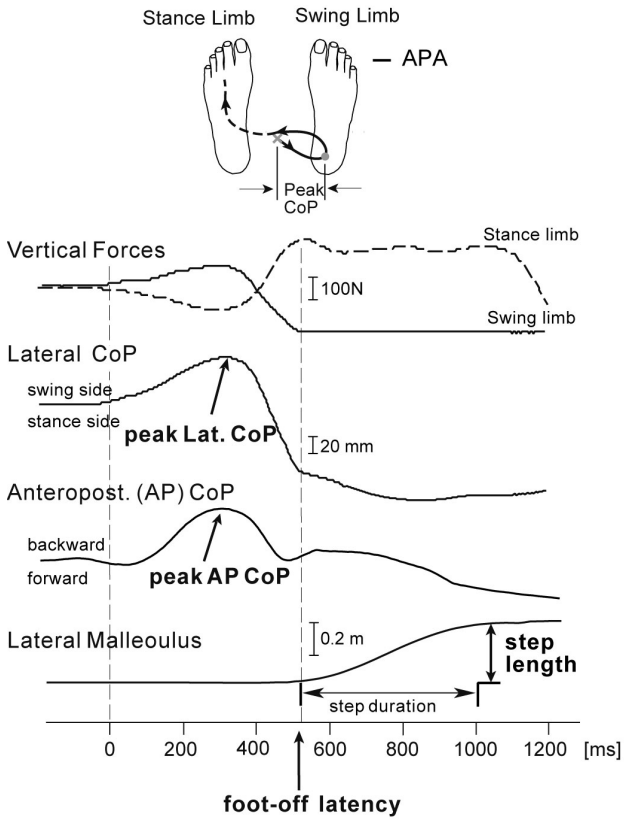

Figure 1*: Data collected in each trial and their relative timing from a representative control subject during step initiation. The schematic feet at the top show the trajectory of the CoP during the APA. The onset of the APA (first lateral displacement of the CoP) is defined as 0 ms and the variables peak CoP displacement, foot-off latency and step length, are shown in bold. Step velocity was measured as step length divided by step duration.*

The relation between clinical scores and adaptation of the APA to stance width was investigated by linear regression analysis [16] between the UPDRS and the change in peak of lateral CoP from narrow to wide stance, both in ON and OFF state. The effect of levodopa was investigated by correlating the change, from OFF to ON, in the UPDRS and in the peak lateral CoP, both in narrow and wide stance.

Differences in adaptation between groups of subjects were detected with a 2-factors (stance and group) ANOVA (repeated measures). Sensitivity to stance width (adaptation) of the APA and of the step properties within group of subjects, were detected with a 1-factor (stance)

ANOVA (repeated measures). All the analyses were performed by NCSS Software, Kaysville, Utah [16].

Results

The PD subjects included in the study were responsive to levodopa, as proven by the improvement of UPDRS Motor Scores with levodopa (mean ± SD: 47±13.6 in the OFF state, 22.4±11.2 in the ON state). The Hoehn and Yahr scores were 3.3 ± 0.8 when OFF and 2.6 ± 0.7 when ON. No difference was found between the two test sessions in the control group – showing that no fatigue or learning effects occurred by the repetition of trials. Hence, in the figures and when listed, control data from the two test sessions were grouped together.

The APA magnitude, as measured by the peak lateral CoP toward the swing side, was sensitive to initial stance width, as shown in Figure 2A by examples in narrow and wide stance in representative control and PD subjects. Adaptation from narrow to wide stance width involved increasing peak lateral CoP (Figure 2B), from (mean ± SEM in mm) 28.5±1.1 to 80.7±2.6 in control subjects ($p<0.0001$), from 14.8±1.8 to 37.2±4.2 in PD OFF ($p<0.001$), and from 23±2.5 to 60.3±6.2 in PD ON ($p<0.0001$). Such values corresponded to a percentage increase of peak of lateral CoP in wide compared to narrow stance (mean±SEM) of 199±12% in control subjects, 181±34% in PD OFF, 197±45% in PD ON . PD subjects' peak of lateral CoP was significantly smaller than control subjects' ($p<0.0001$ in the OFF state, $p<0.05$ in ON state). Levodopa increased peak lateral CoP from the OFF state ($p<0.05$), toward the normal range in narrow, but not in wide stance.

Regression analysis showed a significant correlation between the UPDRS and peak lateral CoP during the APA ($r^2=0.4$ in narrow, $r^2=0.5$ in wide stance, $p<0.01$). In contrast, regression analyses did not reveal any correlation between the UPDRS and adaptation of lateral APA from narrow to wide stance, either in the OFF or ON state.

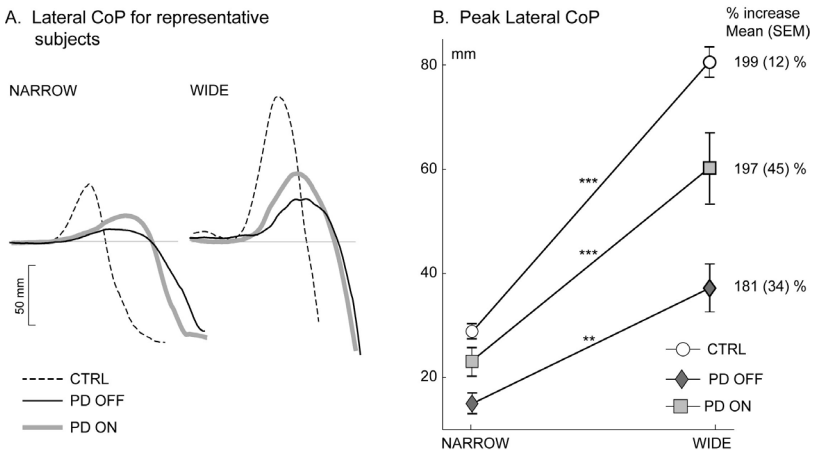

***Figure 2**: Scaling of APA from narrow to wide stance. A. Lateral CoP excursion during APA in narrow and wide stances for a representative control and PD subject, OFF and ON levodopa. B. Mean values ± SEM of peak of lateral CoP during narrow and wide stance, and corresponding percentage increase ,of control and PD subjects. *** p<0.0001; ** p<0.001.*

Preparation for step initiation was also associated with larger backward CoP displacement from wide than from narrow stance, both in control and PD subjects, as detailed in Table 1, along with statistics. When OFF, the PD subjects always exhibited a smaller CoP backward peak than did control subjects, while levodopa caused an increase of peak of backward CoP, which approached control values in narrow but not in wide stance.

***Table 1.** Peak of backward CoP displacement during APA (mean values ± sem, [mm])*

	Narrow Stance	Wide Stance
Control subjects	32.4±2.8	39 ±2.9
PD subjects OFF	15.7±2.6	18.5±2.7
PD subjects ON	27.8±3.1	31±2.6

* p<0.05, **p<0.01, *** p<0.001

Unlike APA magnitude foot-off latency was not significantly affected by stance width. The postural preparation was longer in PD than control subjects, and longer in PD subjects when OFF than when ON, as shown by the examples in Figure 2A, and by the larger values of foot-off latency (Table 2 summarizes statistics). Levodopa speeded up the step preparation from the OFF state ($p< 0.05$), although foot-off latency in the PD ON group remained significantly longer than in control subjects.

Table 2. *Foot-off Latency from APA onset (mean values ± sem, [s])*

	Narrow Stance	Wide Stance
Control subjects	0.55±0.02	0.54±0.01
PD subjects OFF	0.83± 0.09	0.87± 0.1
PD subjects ON	0.69± 0.07	0.68± 0.04

* $p<0.05$, * *$p<0.01$, *** $p<0.001$

Kinematic characteristics of the first step (Figure 3) were also sensitive to initial stance width, although less sensitive than the APA. Step length (in % height, mean ± SEM) was 30.1±1% and 32.4±1% ($p<0.001$) when control subjects stepped from the narrow and wide stance, respectively. Corresponding step velocity (in % height/s) in control subjects was 43.2±1% (narrow stance) and 48.1±1% (wide stance) ($p<0.001$). Step characteristics of subjects with PD also slightly, but consistently, increased from narrow to wide stance. For PD OFF, step length (Figure 3A) increased from 18±2% to 19.5±2 and for PD ON, step length increased from 22.9±2% to 23.8±1% from narrow to wide stance ($p<0.05$). Step velocity (Figure 3B) also increased significantly from narrow to wide stance for PD subjects both when OFF (from 26.6±3% to 31.9±3%; $p<0.05$) and when ON (from 38.7±3% to 41.4±2.6%; $p<0.05$). Independent of stance width, subjects with Parkinson's disease (OFF state) showed smaller step length ($p<0.0001$) and velocity ($p<0.001$) compared to control subjects. Levodopa significantly increased the step length and velocity from the OFF state ($p<0.05$), but,

differences between control subjects and PD ON in wide stance remained significant ($p<0.001$ for step length and $p<0.05$ for step velocity).

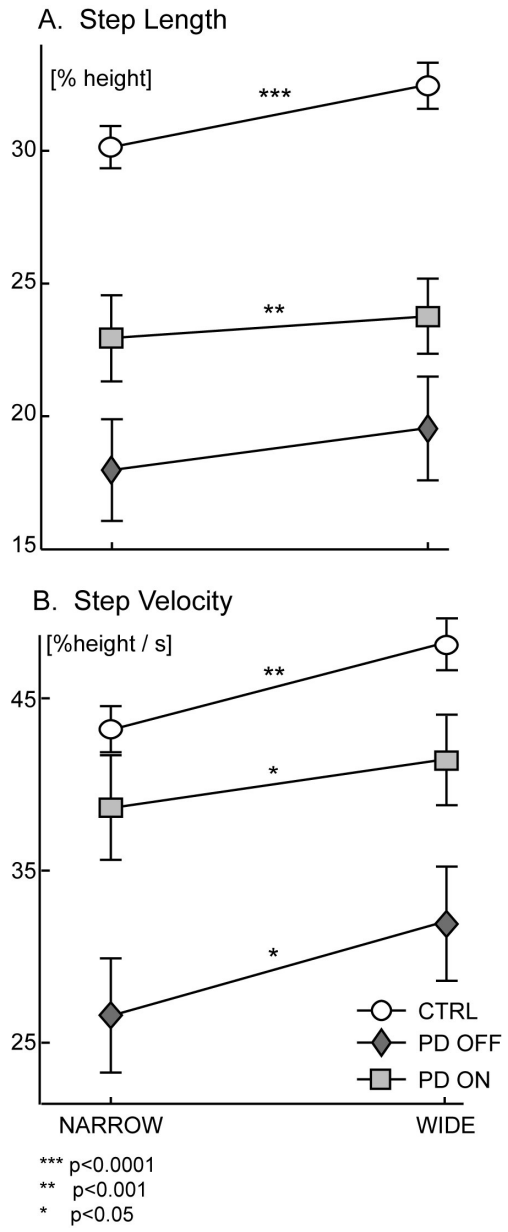

Figure 3: *Kinematics of the first step in narrow and wide stance for control and PD subjects. A. Step length (mean values ± SEM) B. Step velocity (mean values ± SEM). *** p<0.0001; ** p<0.001; * p<0.05.*

Discussion

This study showed that preparation for step initiation from wide stance was associated with a larger lateral and backward CoP displacement than from narrow stance. The characteristics of the first step (velocity and length) were also sensitive to initial stance conditions, probably because of differences in the corresponding APA. In fact previous studies found a linear correlation between lateral CoP displacement and velocity of locomotion [7]. A larger APA was required in wide stance to move the weight off of the initial swing leg, and a larger APA resulted in a longer and quicker step, even when subjects were instructed to step at their natural, comfortable rate for both stance widths in this study. The changes in step characteristics when the APA changed to accommodate an increased biomechanical demand, suggests a close relationship between the program for postural preparation and for stepping.

Basal ganglia deficits resulting from dopamine loss associated with moderate to severe PD did not prevent subjects from scaling their APA for initial stance width, although the magnitude of their APA was less than in age-matched control subjects. PD subjects had much more difficulty initiating a step from a wide stance than from a narrow stance, as shown by the greater differences from control subjects in the magnitude of the APA and by the fact that three PD subjects in the OFF state could not initiate a step at all from wide stance although they could from narrow stance. It is not clear whether PD subjects' increased difficulty in initiating a step from wide stance was due to difficulty in increasing the activation level of muscles for the lateral weight shift due to bradykinesia or was due to difficulty scaling or adapting the APA motor program. Consistent with previous studies, the pattern of step preparation in PD subjects were similar to control subjects, but their movements were characterized by slowness and weakness [2;7;17]. These results could suggest inability to generate appropriate force to execute the movements. Nonetheless, the PD subjects had the ability to produce larger APA when switching to a wider stance, suggesting that they do not lack the ability to produce force, but they seem

to underestimate force in relation to initial stance conditions. Consistently, previous studies have shown that PD subjects undershoot targets and poorly scale the magnitude of voluntary arm movements [18;19] and automatic postural responses [13].

It has been suggested that the basal ganglia may play a specific role in selecting and adapting motor programs based on initial conditions using proprioceptive input, or in formulating an internal model of body kinesthesia [20]. For example, PD subjects show poor modulation of postural response magnitude when the support conditions change from a flat surface to a beam, from free stance to a handle support, or from standing to sitting [21], similar to the loss of APA modulation with stance width in our study. The significant relation between disease severity (as quantified by the UPDRS) and magnitude of step preparation but the lack of relation with adaptation from narrow to wide stance suggests that bradykinesia, but not motor adaptation is measured by the UPDRS.

Start hesitation, or freezing at the start of locomotion, is notoriously difficult to quantify because it is very context dependent. None of the subjects in our study actually showed freezing, as lack of a step during the study, although many showed freezing when walking up to the platform and through the laboratory door when in the OFF state. This lack of freezing may be because of the visual cues on the floor, increased attention during the study, or due to the experimenter's instruction to "step whenever you are ready", even if great attention was paid to avoid explicit cue or trigger to step in order to evaluate self-initiated and self-paced steps. The several hundred-millisecond delays in step initiation from onset of APA, combined with smaller than normal postural weight shifts in our PD subjects, could be the basis for start hesitation, and eventually, freezing.

We suppose that the likelihood of a PD subject's freezing when attempting step initiation would increase with stance width, since the differences in step preparation between PD subjects and controls were much larger when PD subjects stood in wide stance (actually only about shoulder width apart in our study). In fact, one of the characteristics of PD gait is their narrow width, despite their significant balance deficits [22]. Our results support the hypothesis that PD subjects maintain a narrow stance as a compensation for their inability to sufficiently increase the size of their lateral APA to allow speedy step initiation in wide stance.

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Chapter 5

Accelerometry-based center of pressure estimation during quiet stance

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The content of this chapter is currently in preparation to be submitted to IEEE Trans Neural Syst Rehab Eng
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Introduction

Natural sway and corrective surface reactive forces are important signs of postural function during standing and are usually quantified with force plates. Force plates are well established precision instruments being used for a long time in human movement analysis. Force plates are typically embedded in the ground and require a laboratory setting to be properly operated. For this reason, force plates do not represent a viable solution for measuring body sway and postural stabilization in everyday life conditions, as in the home environment or in the workplace.

On the other side, accelerometers are lightweight, portable sensors, which allow natural movement of the subject and do not confine data collection to a laboratory environment. Additionally, they are simple to use, inexpensive, and allow long-term measurements. Adequate attention must be paid, on the other side, to eliminate possible sources of measurement error such as gravity, a function of the spatial orientation of the accelerometer [1].

The use of accelerometry in balance evaluation is supported by theoretical arguments and results of prior studies (e.g. see [2;3]). Despite the attractive opportunity of replacing force plates with accelerometers, as yet only few studies have used accelerometers to investigate balance control during standing [1;4-6] or have extensively compared force plate and accelerometer measures [1;5;6;7;8].

Kamen et al. [1] in order to differentiate healthy older adults against those with a tendency toward frequent falls used two uniaxial accelerometers taped to the back (at S2 level) and forehead of the subject and measured in the anterior–posterior (A/P) direction. They calculate root mean square and frequency spectrum of the gathered signals as performance parameters. Unfortunately this sensor configuration is affected by the acceleration of gravity, a function of the angle of the accelerometer with respect to the vertical. Moe-Nilssen [5;6] used a triaxial accelerometer placed on the back. The average tilt of the sensor is used to subtract the static gravity error and then the data are transformed to a horizontal–vertical orthogonal co-ordinate system by a trigonometric algorithm. Root mean square is used on

the data from each of the three axes as a performance parameter. This system has demonstrated a good test-retest reliability [5].

Mayagoitia et al. [8] used a tri-axial accelerometer mounted on the back of young, healthy subjects to compare the trunk sway in different test conditions as well as to compare trunk sway with force plate measurements. Five performance parameters are considered. More recently, our group [7] investigated the association between the center of pressure (COP) displacement and linear trunk acceleration measured at the fifth lumbar vertebra. We performed a correlation analysis in the time-domain and a coherence analysis in the frequency-domain between the two signals in three sensory conditions, but also a correlation analysis between the same 5 performance parameters computed from COP and acceleration signals. Not surprisingly, COP displacement and trunk acceleration were found largely mutually dependent as expected for an inverted pendulum model of postural sway. The coherence between COP displacement and trunk acceleration along the AP and ML axes was high (>0.8) for frequencies below 1 Hz, peaking at 0.5 Hz, in agreement with the low-pass nature of the biomechanical filter that relates trunk (and body) motion and the location of the COP [9].

All these results suggest that an accelerometry-based system may be evaluated as a portable, miniaturized force platform. However, it should be remarked that all listed works used a single sensor on the body that is a valid measure of sway only if people moved as an inverted pendulum without relative motion of body segments. That's not the case of various conditions where a multisegmental sway comes to light even in quiet standing, e.g. as a result of different sensory strategies.

So far, all these methods lack of a biomechanical 'validation' that explains with the support of a model the intimate relationship between trunk acceleration and COP trajectory measured with a force plate. In this direction we have to find the most appropriate model (single segment versus double segment) that better describes the relationship between the COP and acceleration. Moreover, we have to investigate how many sensors we need to better describe such relation and where we should mount them on the body.

For these reasons the main aims of the study are to explain with a biomechanical model the relationship between COP and acceleration

measured at different body levels, and to find the combination, in number and position, of accelerations that give the best fitting.

METHODS

Biomechanical models

The relationship between the body center of pressure (COP) and the sway angles, following a low frequency approximation, were determined by a Newton-Euler formulation of dynamic equations written in the case of a single-segment (SS) and a double-segment (DS), inverted pendulum model of the body in the sagittal plane. Then the sway angles were related to the accelerometers output in order to obtain a simple equation to estimate the antero-posterior COP from the measured antero-posterior accelerations.

A. Double-segment inverted pendulum

In case we use one sensor on the lower body and one on the upper body (LB and UB respectively), writing the forces/moments equilibrium equations of the free body diagram in figure 1, we obtain:

UB segment

$$\begin{cases} H_{UB} = m_{UB}\left(l_{LB}\ddot{\alpha}_{LB} + l_{UB}\ddot{\alpha}_{UB}\right) \\ V_{UB} = m_{UB}g \\ J_{UB}\ddot{\alpha}_{UB} = T_{UB} - H_{UB}h_{UB}\cos\alpha_{UB} + V_{UB}h_{UB}\sin\alpha_{UB} \end{cases} \quad (1)$$

LB segment

$$\begin{cases} H_{LB} = H_{UB} + m_{LB}\left(h_{LB}\ddot{\alpha}_{LB}\right) \\ V_{LB} = V_{UB} + m_{LB}g \\ J_{LB}\ddot{\alpha}_{LB} = T_{LB} - H_{LB}h_{LB}\cos\alpha_{LB} + V_{LB}h_{LB}\sin\alpha_{LB} - T_{UB} - H_{UB}\left(l_{LB} - h_{LB}\right)\cos\alpha_{LB} + V_{UB}\left(l_{LB} - h_{LB}\right)\sin\alpha_{LB} \end{cases} \quad (2)$$

Foot

$$\begin{cases} F_H = H_{LB} F_V \\ F_V = V_{LB} + m_{foot} g \\ F_V COP = -T_{LB} - F_H h_{mall} \end{cases} \quad (3)$$

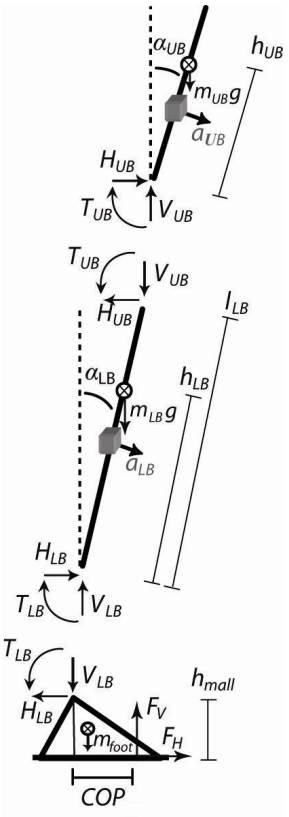


***Figure 1*:** Double-segment inverted pendulum. The COP is referred to the ankle articular center (or center of ankle joint)

Replacing the terms in the moments equilibrium equation of the foot (Eq. 3), and in case of low frequency approximation we obtain the following equation that connect the COP to the sway angles:

$$COP = \frac{\left[m_{LB}\, h_{LB} + l_{LB}\, m_{UB}\right] \mathrm{g} \sin \alpha_{LB} + m_{UB}\, h_{UB}\, \mathrm{g} \sin \alpha_{UB}}{Mg} \quad (4)$$

where:
COP is the center of pressure displacement in the AP direction
M is the whole-body mass
m_{LB} is the lower body mass without feet
m_{UB} is the upper body mass
h_{LB} is the distance of the lower body center of mass from the ankle
h_{UB} is the distance of the upper body center of mass from the hip
l_{LB} is the length of the lower body
α_{LB} is the sway angle of the lower body with respect the vertical axis
α_{UB} is the sway angle of the upper body with respect the vertical axis

The accelerations along the antero-posterior direction, measured by the two sensors, considering the low frequency approximation, are:

$$a_{LB} = g \sin \alpha_{LB} \quad (5)$$

$$a_{UB} = g \sin \alpha_{UB} \quad (6)$$

where *g* is the acceleration due to gravity.

Replacing Eqs. (5,6) in Eq. (4):

$$COP = C_{LB} a_{LB} + C_{UB} a_{UB} \quad (7)$$

where:

$$C_{LB} = \frac{m_{LB}\, h_{LB} + l_{LB}\, m_{UB}}{Mg};$$

$$C_{UB} = \frac{m_{UB} h_{UB}}{Mg};$$

B. Single-segment inverted pendulum

In case we consider a single-segment inverted pendulum Eq. (4) is reduced to the contribution of only one sway angle, consequently we consider one measured acceleration (Eq.(5)). In this way, always considering the low frequency approximation, Eq. (7) becomes:

$$COP = C_{LB+UB} a_{LB} \quad (8)$$

where:

$$C_{LB+UB} = m_{LB+UB} h_{LB+UB};$$

m_{LB+UB} is the body mass without feet

h_{LB+UB} is the height of the body center of mass from the ankle

Experimental sessions

Six young and healthy subjects (age 25.3±4, weight 77±15kg, height 1.76±0.07m) participated voluntarily in the study. All subjects did not report any history of neuromuscular or central nervous system disorders. They stayed on a force platform with eyes open in a comfortable position with arm crossed for two different tasks: 1) quiet standing (QS), in which subjects were asked to stand as still as possible, and 2) trunk sway (TS), in which subjects were asked to slowly lean back and forth their trunk. Subjects repeated each task 3 times, with the QS trials before the TS trials. Each trial was recorded for 2 minutes.

Data acquisition and analysis

Ground reaction forces and COP displacement were measured by a BERTEC 4060-08 force platform. Accelerometric measurements were taken by means of 4 multi-sensor inertial measurement units. Each unit (XSENS MTX-49A33G15, ±1.7g acceleration range), measured 3D acceleration, 3D angular velocity, and 3D earth-magnetic field, but in this study we only used the accelerometric measurements. Subjects wore the 4 units by means of Velcro belts in the following locations: 1 laterally on the right thigh and 3 on the posterior trunk, at the level of C7, T10, and L5. All units were mounted with the sensing axes approximately oriented along the antero-posterior (AP) and medio-lateral (ML) directions of the anatomical reference frame.
Signals from the two systems were online synchronized and sampled at 50 Hz and after filtered with a cut-off frequency determined by studying the frequency spectrum, in particular 0.4 Hz for QS and 0.6 Hz for TS. The filter was zero-phase, low-pass Butterworth filter.
All the analysis, as stated before in the biomechanical models part, were done in the antero-posterior direction, but they could be easily extended to the medio-lateral direction.

Correlation between COP and accelerations analysis
First, we performed a time-domain correlation analysis between the COP and acceleration signals at the 4 different measurement sites, in QS and TS trials (representative signals are showed in figure 2).

Accelerometry-based estimate of COP analysis
We reconstructed the COP from the single- and double-segment inverted pendulum models (SS and DS) previously illustrated; then we calculated the root mean square error (RMSE) between the COP measured by the force plate and the estimated with the two models. Moreover, we compared the coefficients of the models (C_{LB+UB} for the SS; C_{LB} and C_{UB} for the DS) with the one obtained starting from four different anthropometric tables [10-12].

Performance parameters analysis

Five performance parameters were calculated from the COP (both measured and estimated with the DS model): root mean square distance (RMS), mean velocity (MV), frequency containing 50% of the power (F50), and frequency dispersion (FD) [13]. We subsequently performed a correlation analysis between the parameters extracted from the COP measured and estimated. The correlation analyses were investigated by linear regression analysis, the level of significance was set at $p<0.05$. All the analyses were performed with Matlab©.

Results

Correlation between COP and accelerations

COP and acceleration signals were largely related, as shown in figure 2. In particular, COP and accelerations at all levels were in phase in QS task (Fig.2A), while COP and thigh acceleration were in phase and COP and trunk accelerations were in anti-phase in TS task, accordingly to a mixed strategy (Fig.2B).

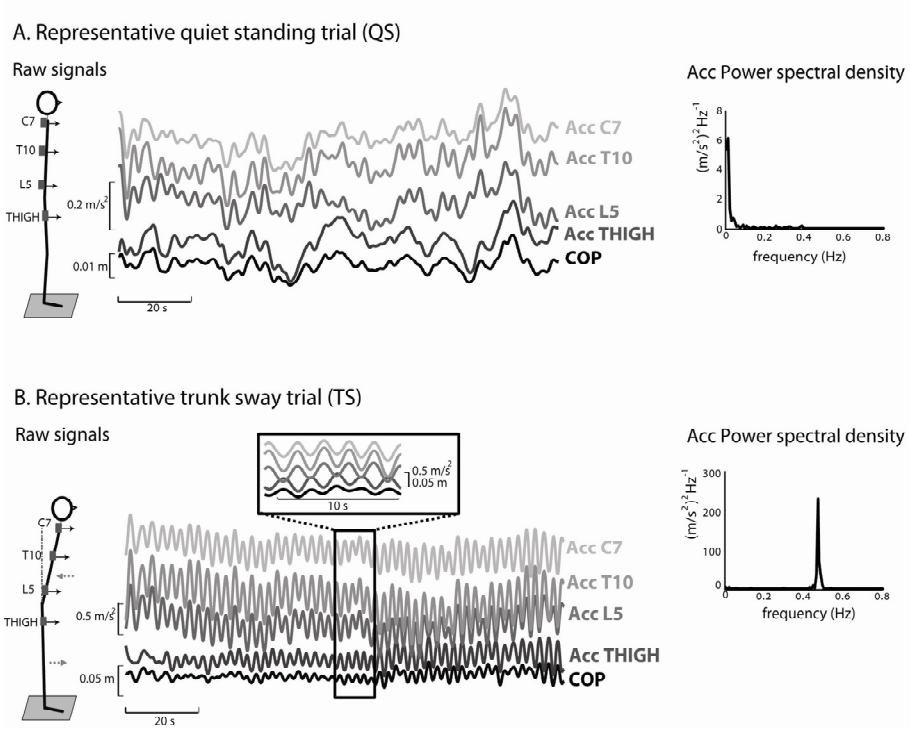


Figure 2: Signals collected from a representative subjects. (A) Raw signals and acceleration power spectral density during a quiet standing trial. (B) Raw signals and acceleration power spectral density during a trunk sway trial. Abbreviations: COP is the antero-posterior center of pressure. Acc is the antero-posterior acceleration.

The combination COP-thigh accelerations showed the highest correlation for both trials (0.7 <r <1), Figure 3. This could be explained considering Eq. (8), in particular the first term is greater than the second since C_{LB}>>C_{UB}. The correlation between COP and trunk accelerations showed similar values for the three different levels (L5, T10, and C7) (0.45<r<0.65). This means that the three sensor placements on the trunk are equivalent. The multiple correlation coefficients between COP and couples of accelerations, (thigh and L5 levels, thigh and T10 levels, thigh and C7 levels) showed similar values among the three couples of accelerations; all values were higher than the values of correlation between COP and single acceleration for both QS and TS trials. Lastly, the multiple correlation coefficients between COP and all the accelerations was higher than the values for both single or coupled accelerations.

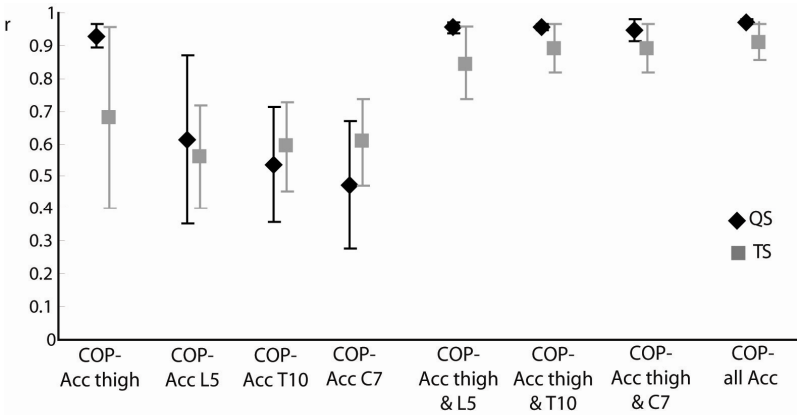


Figure 3: Correlation coefficients (mean±std) between COP and accelerations at different levels, in quiet standing and trunk sway trials.

Accelerometry-based estimate of COP

The RMSE between the COP measured by the platform and the COP estimated with the SS model was 1.12mm (±0.15) with a COP range excursion of 18.9mm(±3.40) among the subjects in QS trials, but was of 7.04mm (±0.96) with a COP range excursion of 58.54mm(±9.53) in TS trials. The RMSE computed between

the COP measured by the platform and the COP estimated with the DS model was lower, in particular was 0.92mm (±0.13) in QS trials, and 4.51mm (±0.65) in TS trials. In table 1 are presented the RMSE across all subjects (mean±std).

	QS trials			**TS trials**		
	RMSE SS	**RMSE DS**	**RANGE**	**RMSE SS**	**RMSE DS**	**RANGE**
Subject 1	0.98(±0.02)	0.95(±0.05)	20.46(±2.01)	3.20(±0.53)	1.90(±0.12)	51.33(±9.34)
Subject 2	1.24(±0.25)	0.87(±0.23)	16.94(±2.03)	5.10(±1.06)	4.93(±1.19)	52.63(±5.12)
Subject 3	0.97(±0.16)	0.88(±0.21)	18.23(±4.35)	9.47(±2.82)	5.44(±0.86)	59.57(±22.36)
Subject 4	0.71(±0.24)	0.59(±0.18)	13.55(±6.86)	5.15(±0.07)	4.70(±0.57)	68.75(±5.16)
Subject 5	1.21(±0.24)	1.09(±0.01)	24.97(±2.31)	7.50(±1.19)	5.06(±0.20)	53.46(±11.51)
Subject 6	1.61(±0.02)	1.17(±0.13)	19.25(±2.84)	11.85(±0.07)	5.01(±0.98)	65.53(±3.72)
Mean	***1.12***	***0.92***	***18.9***	***7.04***	***4.51***	***58.54***
Std	*0.15*	*0.13*	*3.4*	*0.96*	*0.65*	*9.53*

Table 1: Root mean square error (RMSE) (mean±std) between COP measured and COP estimated with the single-segment (SS) inverted pendulum and the double-segment (DS) inverted pendulum across subjects. Values are in mm.

Figure 4 shows the COP measured and estimated with the DS model during a QS (Fig.4A) and TS (Fig.4B) trials in a representative subjects.

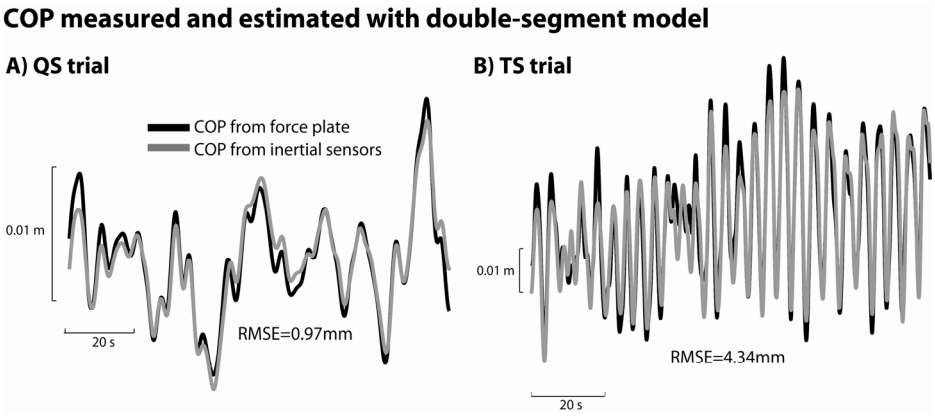
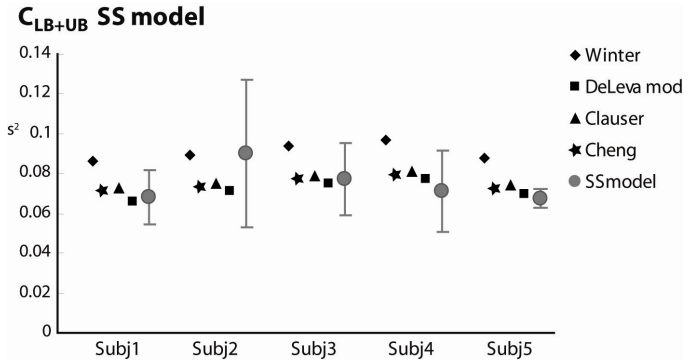


Figure 4: Example of COP measured and estimated with double-segment inverted pendulum model during a QS (A) and TS (B) trials in a representative subject.

Moreover, the model coefficients, C_{LB+UB} for the SS (Figure 5A), C_{LB} and C_{UB} (Figure 5B) for the DS, were similar to the equivalent obtained by four different anthropometric tables in the five subjects.

A)



B)

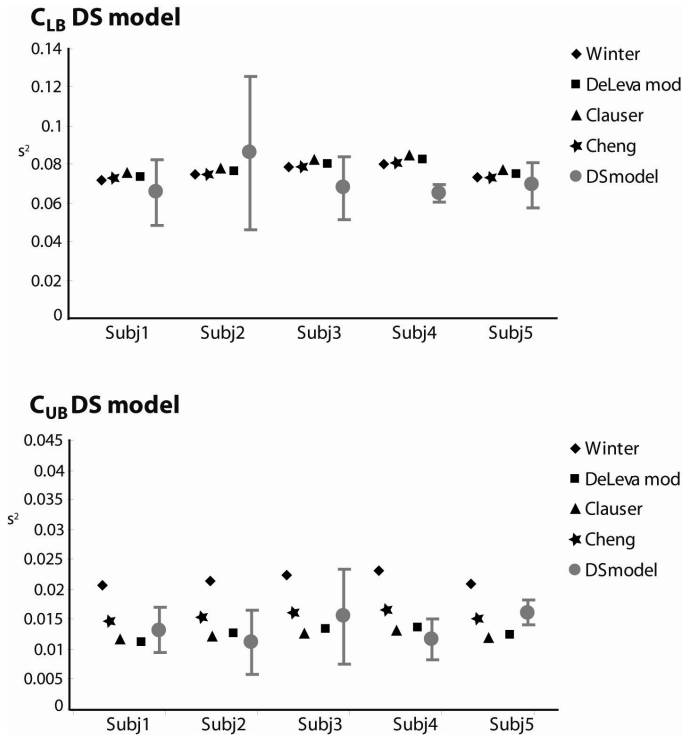


Figure 5: Comparison of the model coefficients, C_{LB+UB} for the SS (A), C_{LB} and C_{UB} (B) for the DS, and the equivalent obtained by four different anthropometric tables among subjects.

Performance parameters extracted from measured and estimated COP

Figure 6 shows the correlation between the parameters extracted from COP measured and estimated with the DS model. We observed a very good correlation for all the extracted parameters, in particular the correlation coefficients (r) were: r=0.98 for RMS, r=0.90 for MV, r=0.98 for F50, and r=0.91 for FD

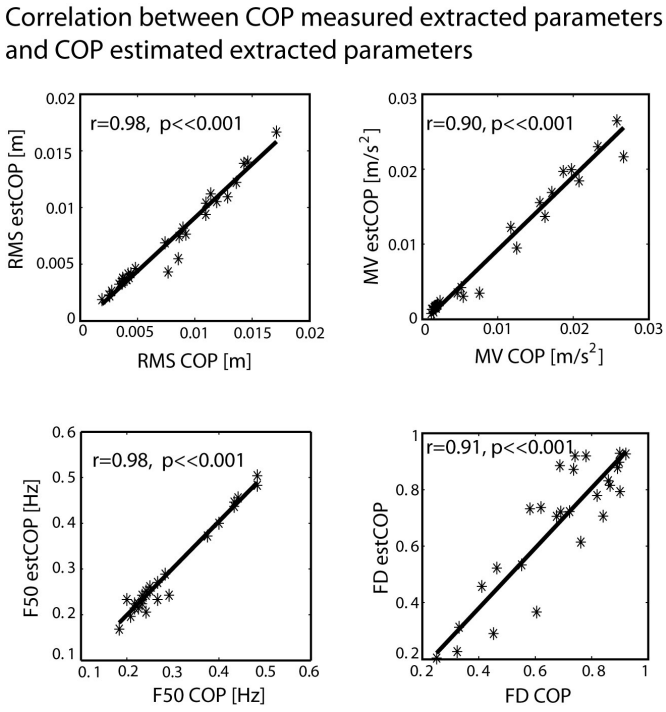


Figure 6: Correlation between the parameters extracted from measured and estimated (with the double-segment inverted pendulum model) COP.

Discussion

The main aim of this study was to explain with a biomechanical model the relationship between COP and acceleration measured at different body levels, and to find the combination, in number and position, of accelerations that give the best fitting.

Results of the present study indicated that, depending on the purpose, we can use one or two accelerometers to reproduce the same amount of information carried by a force platform in measuring postural sway. In particular, using one accelerometer, the best placement will be on the thigh, confirmed by the highest value of correlation found between COP and acceleration at this level. However in this condition we depend on the assumption of single-segment inverted pendulum, and results show that we can obtain better reconstruction of the COP with the double-segment inverted pendulum model, especially in TS trials. Therefore, in order to better reconstruct the information given by the force plate it is advisable to use two accelerometers, one placed on the lower body and one on the upper body. The placement would be for the lower body on the thigh, while for the upper body we found that the three placements, L5, T10, and C7 are equivalent, as is supported by the similar values of correlation found between the COP and trunk accelerations in both QS and TS trials; then we decided to use the acceleration at T10 level as acceleration of the upper body-(UB) for the DS inverted pendulum. The lower values of correlation found for acceleration along the trunk are explicable with the different values of the model coefficients, in fact the coefficient that weights the LB acceleration is bigger than the one that the UB. Also we compared the model coefficients, C_{LB+UB} for the SS, C_{LB} and C_{UB} for the DS, with the equivalent obtained by four different anthropometric tables [refs and equations]. The model coefficients were similar to the ones calculated starting by anthropometry, but underestimated for most subjects. This could be due mostly because of our main assumption of low frequency, in fact in this way we neglect the inertial term of the Euler-Newton equations; but also to a degree of inaccuracy of the anthropometric tables.

The extracted parameters from the COP estimated with the DS model showed a strong correlation ($0.90<r<0.98$) with the parameters extracted from the COP measured. Such high correlations are important as parameters extracted from the COP carry different information and are able to distinguish other conditions [14] or discriminate between healthy and person with balance disorders [15].

Other authors reported acceleration-based measures of quiet standing [6;8]. In particular they found that parameters extracted from acceleration at trunk level were able to discriminate between young and elderly subjects,

or to discriminate between different conditions in healthy subjects. The proposed method can also add a biomechanical explanation, relating body accelerations to angle sway and COP, of why with accelerometers we can obtain analogous information carried by a force plate. In fact, we demonstrated that we're able to estimate the COP starting from accelerations and anthropometric measures with good accuracy.

However, there are some limitations in the model due the fact that the followed approach works at lower frequencies, for this reason the model is appropriate only for cases in which the inertial terms are negligible, like in quiet standing. Future prospects should provide a real-time estimation of COP and try to develop a model in case of more dynamic motor tasks.

Acceleration signals from different body-segment represent a good tool to quantify spontaneous, multisegmental body sway. This allow to measure balance without the use of force platform and also outside the laboratory environment. Such ambulant measures may be helpful in remote monitoring in elderly or person with balance disorders and also in monitoring progress during balance training at home. In addition, the angle estimation given by the two accelerometers allow the exploration of the motor strategies used by the subjects to accomplish the task. This is not possible with the force-plate and could be useful when testing subjects with motor disturbances or neurological disease.

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Chapter 6

Dependence of anticipatory postural adjustments for step initiation on task movement features: a study based on dynamometric and accelerometric data

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Abstract

The present study investigates the dependence of anticipatory postural adjustments (APA) for step initiation on velocity and length of the first step, by means of both dynamometric data, acquired by a force platform, and accelerometric data, achieved by means of sensor nodes positioned on the lower legs and on the trunk. Results focus on antero-posterior center of pressure (CoP) displacement and antero-posterior accelerations. Peak of backward CoP excursion during APA, considered as magnitude of APA, was found to depend mostly on step velocity, and, in less amount, to step length. Accelerometers detected a reliable accelerometric pattern during APA, and stance leg backward acceleration before stepping presents a peak with a behavior very similar to peak of CoP in terms of dependence on velocity and step. The results allow deduction on the role of APA to control step initiation, and suggest possible promising applications of portable and low-cost accelerometric sensors, to monitor motor performance in several fields as rehabilitation, clinics and closed loop applications.

Introduction

Voluntary movements are associated with postural phenomena that precede the onset of the movements and that are referred to as anticipatory postural adjustments (APA). Such postural preparations occur in the opposite direction of the task voluntary movement, usually following a diagonal pattern [1;2]. APA have been largely considered on the basis of global biomechanics variables, such as resultant forces, centre of mass (CoM) kinematics, centre of pressure displacement [3-5], or considering muscle activations with surface EMG [6], and, in less amount, considering single segments involvement in the APA [2].

The present study focuses on APA for step initiation. Such preparatory phase implies the center of pressure (CoP, i.e. the application point of the resultant groundreaction force) to move backward and laterally toward the swing limb to move the body CoM forward and over the stance limb, in preparation for single-limb support [1;4;7]. The movement phase begins when the swing limb start to move, i.e. at heel-off of the stepping foot [5]. Postural preparations change according to the characteristics of the corresponding task movement. For example, APA prior to step initiation were found to be sensitive to a reduction of postural basis or to constraint imposed to CoM displacement. Previous studies suggested that APA duration might be related to forward displacement of the CoM, or to CoM velocity at the end of the first step for gait initiation [3;8]. However which is the primary role of APA in function of characteristic of the task movement has not been widely exploited. In particular, it is not well known which kinematic variable APA control mostly, in terms of velocity or length of the step. This information may be relevant in rehabilitation programs, in clinics to monitor possible step and gait impairments because of a specific disease (such as Parkinson's disease) or because of chronic deterioration of the movement system as in the elderly [4;9]. Since APA were found to be impaired in several disease and to need to be appropriately scaled in function of both the task movement and the initial support conditions [3;10;11], they result as key variables that might be monitored to evaluate ability of movement preparation in different diseases or after rehabilitative or pharmacological therapies.

The recent advances in miniaturized sensors, such as accelerometers, allowed the use of such sensors for a variety of biomedical applications, as human movement analysis, because of their characteristic

of low-cost, portability and the useful kinematic information they provide [12]. In addition, accelerometers allow measurements that are not directly attainable by classical movement analysis systems, as dynamometric platform and optical movement analysis systems for kinematic acquisition, since they can directly provide acceleration of a single body segment.
In the present study we investigated the possible detection of APA by accelerometric sensors, the dependence of APA, measured by CoP displacement (global biomechanics), on step features, and the possible relation between APA accelerometric variables and APA CoP variables in terms of dependence on step features.

Methods

Participants and Protocol

Five male volunteers (age 25±2.8 years, height 1.72±0.07 m) participated in the study. All subjects were right-handed and did not report any history of neuromuscular or central nervous system disorders. At the beginning of each experimental trial, subjects stood barefoot and motionless on a dynamometric platform, with arms at their side. Heels location was fixed on the platform, to ensure accurate execution of the entire experiment. The subjects were asked to voluntarily take two steps starting with the right foot. Length of the first step was imposed in each trial by a target line on the ground, which subjects had to hit with the heel. Three different step lengths were considered (Figure 1): 1) Short step (SS), defined by a 35 cm heel-heel distance; 2) Normal step (NS), defined by a 65 cm heel-heel distance 3) Long step (LS), defined by a 95 cm heel-heel distance. Subjects performed 3 trials for each step length at their natural velocity, without receiving any specific instruction, and 3 trials for each step length at their maximal velocity.

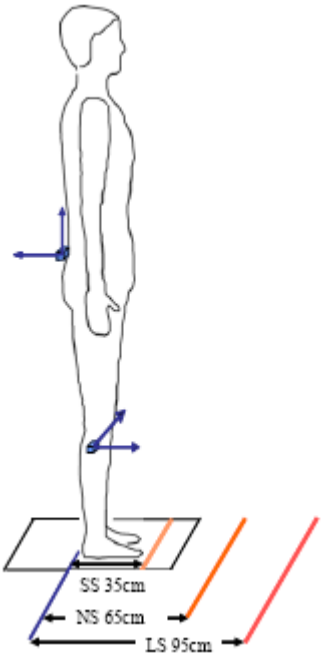

***Figure 1**: Experimental set up: target step length and accelerometers positioning (leg accelerometers were positioned symmetrically)*

Data acquisition

The ground reaction forces and CoP displacement were obtained by a BERTEC 4060-08 dynamometric platform. Accelerometric data were obtained by means of 3 sensor nodes, each of them based on a dual-axes accelerometer (ADXL202, sensitivity 312 mV/g). The sensor nodes were mounted on the subjects, by means of Velcro belts, as follows (Figure 1): - one node on the posterior trunk, about at the level of the total body CoM with the sensing axes oriented approximately along the body antero-posterior and vertical directions; - two nodes on the lower limbs, laterally just below the knee of the right and left leg respectively, with the sensing axes oriented approximately along the body antero-posterior and medio-lateral directions. The experimental set-up also included kinematic data that were acquired by means of a 6-infrared cameras motion analysis system (BTS SMART), and 18 reflective markers placed on anatomical landmarks [13]. However, in the present study, only the kinematic of the stepping foot was considered, to identify the initiation of the stepping

phase, by means of the markers placed on the malleolus and metatarsus. All signals were acquired at 60 Hz.

Anticipatory postural adjustments variables

The onset of the anticipatory phase for stepping was identified by the first measurable change on CoP excursion, toward the backward direction and, laterally, toward the swing limb [4]. The end of the APA was identified by the time of heel-off, detected by the reflective marker on the malleolus of the stepping foot. The APA magnitude was measured by the peak of antero-posterior CoP (CoP-AP) excursion in the backward direction during APA. The antero-posterior accelerations measured by the sensor nodes were primarily considered in the present study, to investigate the presence of a reliable acceleration pattern during APA. In Figure 2 timing and excursion of principal acquired signals are shown, for a representative subject during a natural velocity SS. Anteroposterior acceleration of the stance leg (Acc-AP) was then mainly considered for analysis and results. Dependence of APA measures on velocity and length of the step was evaluated by means of a 2 factors repeated measures ANOVA, followed by Tukey-Kramer multicomparison tests [14].

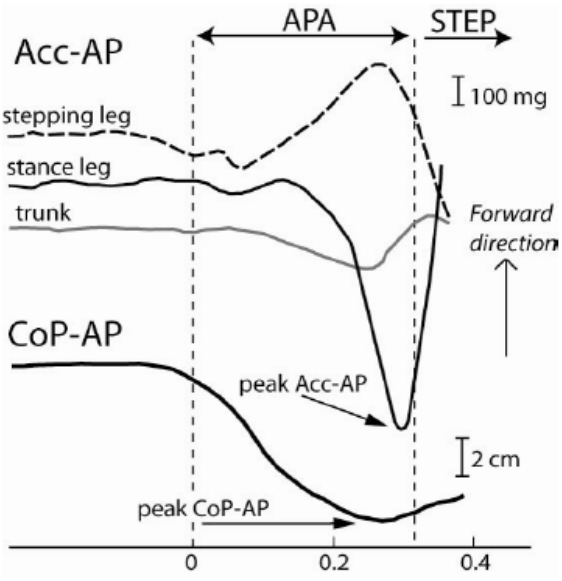

Figure 2: *Accelerometric and CoP signals during APA for a representative trial*

Results

Accelerometric data

Figure 2 already suggested the presence of a consistent pattern in accelerometric data during APA, that was particularly reliable for stance leg Acc-AP. Such pattern was characterized by a backward acceleration peak that followed peak of CoP-AP and preceded heel-off. In each trial, the postural preparation was associated with a peak of backward acceleration of the stance leg and such measure was then considered as the index of APA performance as detected by accelerometric data. As represented in Figure 2, antero-posterior acceleration of the stepping leg was generally in phase with that of the stance leg, for the first phase of APA, and in opposition of phase during the second phase. This behaviour was present for the majority of cases, but with several exceptions mainly concentrated on one of the subjects. The trunk accelerometer, that approximated CoM acceleration, detected a backward, followed by a forward acceleration pattern during APA. Similarly to stepping leg acceleration signals, such pattern, even if present in the majority of cases, was not largely consistent for the entire population and experimental conditions.

Dependence of APA on step features

Magnitude of APA as measured by peak of CoP-AP was found to be sensitive both to step length ($p<0.05$) and to step velocity ($p<0.01$). No factors (velocity and length) interaction was detected. In particular (multi-comparison tests), at natural velocity, APA magnitude for SS was significantly smaller than for LS. On the contrary, at maximal velocity, there were no APA magnitude differences due to length of the task step. Strong dependence of peak CoP-AP on velocity was present for each step length, where APA magnitude for maximal velocity steps was significantly larger than for natural velocity steps. Mean values and SD of peak of CoP-AP for each experimental condition are represented in Figure 3A.

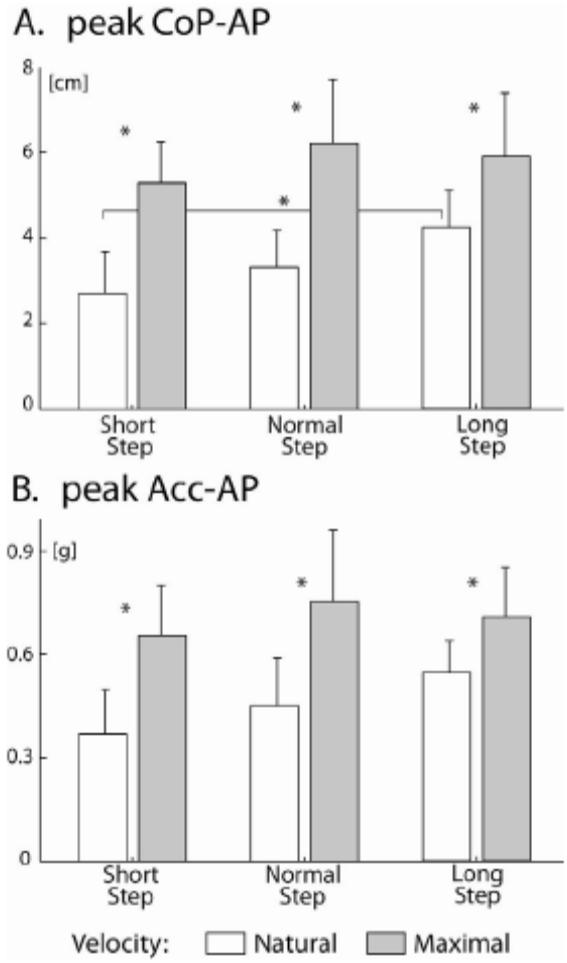

Figure 3: *Mean values and SD of peak during APA in the 3 step length and 2 step velocity conditions. A. peak of CoP-AP; B. peak of Acc-AP*

Interestingly, a very similar behaviour was present in peak of Acc-AP of the stance leg. Such variables was also sensitive to step length ($p<0.05$) and velocity ($p<0.01$). Multi-comparison tests on Acc-AP did not detect any differences for step length pairwises, mostly because of variability higher for accelerometric than CoP data. However differences between peak of Acc-AP were always significant when comparing natural and maximal velocity, with peak Acc-AP higher at maximal than natural velocity for each step length condition. Mean values and SD of peak of stance leg Acc-AP are represented in Figure 3B. We did not find any differences due to length or

velocity of the step in the APA timing, both in terms of APA duration, peak of CoP-AP or peak of Acc-AP timings.

Discussion

In the present study we primarily considered signals in the antero-posterior direction since characteristics of the step were in this direction. Indeed such variables resulted the most significant and sensitive to step velocity and length.

Results, even if preliminary, suggest that anteroposterior magnitude of APA is functional to step velocity more than to step length, even if, at natural velocity, magnitude of APA is sensitive to step length, in particular to differences between short and long step. Accelerometric signal detects reliably characteristics of APA for step initiation, in particular the backward peak of Acc-AP may be considered as an index of APA functions, since it occurs at the end of APA, and it has the same behaviour of peak of CoP-AP as regard dependence on velocity and step length. Peak of backward Acc-AP just prior step initiation might be due to an action necessary to balance the following propulsive push of the stepping foot, or, on the contrary it might be necessary to cause the following propulsive motion of the stepping foot. Supplementary developments of the study will be necessary to further exploit the topic, considering also body segments kinematics during APA. The reliable pattern of peak of Acc-AP suggests possible promising applications. In fact, peak of Acc-AP is a sort of trigger of movement execution and a signal very easy to be acquired, hence it might be used to monitor step onset, appropriateness of APA, with relevance in rehabilitation programs, clinics and research on motor control, for example programming exercises or experiments to perturb the step just before it happens, or in designing closed loop applications for step and gait initiation. Further investigations will be also necessary to evaluate inter-correlation of accelerometric pattern of the single segments under investigation. In addition, to complete the use of inertial sensors in monitoring step and gait, it will be interesting to study the accelerometric segmental patterns during gait and to identify optimal signal processing to separate dynamic from static accelerations and provide information about position and movement accelerations.

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Chapter 7

Multisegmental analysis of postural sway in untreated Parkinson's disease: an accelerometer-based approach

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Abstract

While several studies have shown that subjects with advanced Parkinson's disease (PD) exhibit abnormalities in sway parameters during quiet standing, few studies have investigated postural changes in patients with early PD who show not clinical signs of balance or gait disorders. In our study, we determined whether it is possible to measure abnormalities of postural sway in untreated, early-to-moderate PD using body worn accelerometers.

We examined 12 PD and 12 healthy, age-matched control subjects. The PD subjects were newly diagnosed and were not yet taking any Parkinson's medications. Postural sway was measured from three linear accelerometers on the posterior trunk (C7 and L5), and the right lateral thigh, as well as from a forceplate. Two-minutes trials of quiet standing were performed under three conditions: eyes open (EO), eyes closed (EC), and eyes closed with cognitive task (ECC). The following sway parameters were computed on center of pressure (COP) and acceleration signals in the transverse plane: root mean square value, mean velocity, 95% power frequency, frequency dispersion. In addition, from the measured acceleration signals we calculated a smoothness of sway index, and a postural strategy index.

The most sensitive measure of postural sway distinguishing the early PD from the age-matched control group was the smoothness of lower body sway in the EO condition as measured from the jerk. Root mean square and the frequency dispersion of postural sway also differentiated early PD subjects from control subjects in the EO condition using either the COP (forceplate) or the lower body acceleration measurements. The accelerometers based parameters showed more groups differences at the lower trunk and thigh levels than at the cervical level.

Thus, even the simple, EO condition, without the need of vision deprivation or concurrent cognitive task, disclosed changes in body sway in the early stage of PD. Our results confirm that postural control is affected in early PD, and that wearable inertial sensors can be useful for monitoring patients' progression in the home or community environment.

Introduction

Postural instability is an inevitable feature of PD, clinically apparent in the later advanced stages of the disease [1]. Balance difficulties in PD include reduced magnitude of postural responses [2], reduced anticipatory postural adjustments [3-5], and reduced limits of stability [6;7]. Due to an inability to adequately balance the body's center of mass over its base of support, subjects with PD are more prone to loss of equilibrium and falls than subjects with any other neurological disease [8].

The so far most popular and practical approach to quantify balance is to characterize spontaneous body sway in quiet standing by means of a stabilometric approach. Postural sway during quiet standing reflects the interplay between gravity destabilizing the body and actions by the postural control system to prevent a loss of balance. Due to its complexity, the postural control system is challenging to measure with simple methods, although simple methods are needed, especially in clinical practice. Since a direct, multisegmental analysis of postural sway during stance may require complex kinematic trackers such as motion analysis systems, postural sway is most often described indirectly by the fluctuations of the center of pressure (COP) on the ground, measured with a forceplate. The COP reflects control by the central nervous system of torques exerted on the surface to maintain equilibrium using integrated sensory information derived from visual, vestibular and somatosensory systems.

Previous studies have shown that subjects with advanced Parkinson's Disease (PD) exhibit abnormalities in spontaneous body sway during quiet stance [5;7;9-11]. Inconsistent results have been reported concerning postural instability during stance tasks in PD; for example, increased, decreased or no change in postural sway has been reported for PD patients when tested on medication compared to normal subjects [12]. Furthermore, medications and surgical treatments for PD have been shown to produce significant changes in spontaneous body sway, but often do not restore spontaneous sway to normal [5;13-15].

To the best of our knowledge, the control of postural stability in quiet stance early in the disease, before any treatment has started, was never investigated before. Recent studies of COP sway using a forceplate during quiet stance in patients with early PD (ON medication) found: increased

postural sway area, velocity, and path length with eyes open and/or closed [11;16;17]. However, all in all of these studies most of the PD subjects had already started dopaminergic treatment, which has been shown to modify posture [5;10;13].

Since patients in early stages of PD do not show clinical signs of balance or gait problems, quantitative detection of balance abnormalities in untreated PD could provide an early marker of PD deficits. Furthermore, since a recent study suggested that dopamine denervation from PET scans is correlated with postural instability, a tool that could assess this subclinical posture change could provide a valid, useful instrument for tracking clinical progression of PD.

Ground-reaction force and COP measured with a forceplate are related to postural sway, more precisely, to the motion of the body center of mass (COM), and consequently provide important insights into the process of controlling balance. Still, they are not direct measures of sway, nor they allow a multisegmental evaluation of postural strategies. Recent technological developments have led to the production of inexpensive, portable systems, based on miniaturized, inertial sensors (accelerometers, gyroscopes), that can estimate postural sway during quiet stance similar to a forceplate [12;18-20] but that can also allow for a direct, multisegmental analysis of actual body sway and postural coordination.

In the present study, we hypothesized that: i) subjects with early, untreated PD, if analyzed with appropriate tools, may disclose to some extent postural abnormalities, prodromic of more severe alterations observed with disease progression; ii) a set of accelerometers mounted on axial segments can be such an appropriate tool to sensitively quantify spontaneous body sway and postural coordination.

Methods

Participants

Our study involved 12 subjects with idiopathic PD (7 male and 5 female) and 12 age-matched healthy control subjects. Only subjects who

were early-to-middle stage in PD disease course and had never been treated with dopaminergic or other anti-parkinsonian medication were invited to participate. Subjects were excluded if they presented any neurological disorders other than PD or if they had any other condition that could affect their balance. Patients were clinically rated by a trained examiner on the Motor Section (III) of the Unified Parkinson's Disease Rating Scale [21] and the Hoehn and Yahr Scale [22] immediately before the experimental sessions (Table 1). All subjects scored 0 (normal) in the postural pull test and in the PIGD (Items 27, 28, 29, and 30) of the Motor UPDRS. All participants provided informed consent according to the Oregon Health & Sciences University Institutional Review Board.

Subj	*AGE (years)*	*Disease onset (months)*	*H&Y*	*UPDRS III Total Motor Score*
P1	*63*	*26*	*3*	*46*
P2	*77*	*13*	*2.5*	*45*
P3	*70*	*15*	*2.5*	*35*
P4	*50*	*10*	*2*	*35*
P5	*53*	*26*	*2*	*33*
P6	*64*	*11*	*2*	*32*
P7	*61*	*13*	*2*	*27*
P8	*61*	*8*	*2*	*21*
P9	*58*	*48*	*1.5*	*21*
P10	*58*	*22*	*1*	*17*
P11	*49*	*5*	*1*	*7*
Mean	**60.3**	**17.9**	**1.9**	**29**
SEM	0.76	1.11	0.05	1.08

Table 1: Characteristics (individual means and group means ±S.E.M) of subjects with untreated Parkinson's disease, sorted to severity of UPDRS Motor Score. Abbreviations: H&Y=Hoehn and Yahr Scale.

Procedure

All participants were instructed to maintain an upright standing position on a forceplate (AMTI OR6-6, Watertown, MA), with arms crossed

and heel-to-heel distance fixed at 10 cm. Feet were allowed to be externally rotated at a comfortable amount for each subject [23]. Initial stance position was consistent from trial-to-trial by tracing foot outlines on the forceplate and by coaching subjects to maintain their initial COP position prior to each trial based on oscilloscope COP traces.

Subjects wore 3 MTX Xsens sensors (49A33G15, XSens, Enschede, NL) with 3-D accelerometers (±1.7g range), and 3-D gyroscopes, (±300º/s range) mounted on: i) the spinous process of C7, ii) the posterior trunk at the level of L5, near the body center of mass, iii) the lateral aspect of the right thigh. The sensing axes were oriented along the anatomical antero-posterior (AP), medio-lateral (ML), and vertical directions.

A total of nine, 2-minute trials were performed consisting of three blocked repetitions for three different conditions: i) eyes open (EO) with gaze straight ahead at an art poster, ii) eyes closed (EC), and iii) eyes closed with a concurrent cognitive task (ECC). The cognitive task consisted of counting out loud, backwards in multiples of seven.

The COP displacement was calculated from the ground reaction forces recorded by the forceplate at a 100-Hz sampling frequency and after applying a 10-Hz cut-off, zero phase, low-pass Butterworth filter. Acceleration signals were collected with a 50-Hz sampling frequency, transformed to a horizontal-vertical coordinate system [24] and filtered with a 3.5 Hz cut-off, zero-phase, low-pass Butterworth filter. This filter was applied in order to eliminate a possible contribution of tremor at rest, a well-known PD symptom, which is identified in the range from 4-to-7 Hz.

Data analysis and extracted parameters

To quantify postural stability, parameters were calculated from the COP as well as from acceleration signals.

COP postural sway parameters

Four main parameters were computed from the 2D, planar COP displacement: 1) root mean square distance (RMS), which quantifies the amount of COP variability around the mean COP trajectory; 2) the mean velocity (MV) of COP displacement; 3) the frequency that encloses the 95% of the power of the signal (F95%); 4) the frequency dispersion (FD), a

unitless measure of variability of the frequency content of the power spectral density (0 for a pure sinusoid, it increases with spectral bandwidth to 1). This set of parameters was chosen based on their relative independence, according to [25].

Acceleration postural sway parameters

Similarly to the COP, four main parameters were calculated from the 2D, planar acceleration measured at each level: 1) root mean square acceleration (RMS); 2) mean velocity (MV), computed by the integration of the AP and ML components of acceleration; 3) the frequency that encloses the 95% of the power of the signal (F95%); 4) the frequency dispersion (FD).

In addition, the jerk, an indicator of the smoothness of postural sway, was computed as follows, according to [26]:

$$JERK = \frac{1}{2}\int_0^t \left(\frac{dAccAP}{dt}\right)^2 + \left(\frac{dAccML}{dt}\right)^2 dt$$

where AccAP and AccML are respectively the acceleration components in AP and ML direction, respectively.

Postural strategy

In order to identify the extent to which subjects use an ankle versus a hip postural kinematic strategy in the sagittal plane, we used an approach similar to the one used by Colobert et al. [27], and previously proposed by Kuo et al. [28]. In particular, we analyzed the covariance matrix between the upper and lower body accelerations, defined as:

$$Q_{L5-C7} = \mathrm{cov}(x) = \frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})\cdot(x_i - \bar{x})^T$$

$$Q_{THIGH-L5} = \mathrm{cov}(y) = \frac{1}{n-1}\sum_{i=1}^{n}(y_i - \bar{y})\cdot(y_i - \bar{y})^T$$

where x_i is the ith measurement of a vector containing accelerations sensed at L5 and C7 level,

$$x = [AccL5; AccC7]^T,$$

and y_i is the ith measurement of a vector containing accelerations sensed at THIGH and L5 level,

$$y = \left[AccTHIGH; AccL5\right]^T .$$

The resulting matrices, $Q_{L5\text{-}C7}$ and $Q_{THIGH\text{-}L5}$, are positive definite matrices. Also, the covariance matrix may be described by three graphical measures, tracing an ellipse in the plane. The ellipse has major and minor semi-axis length given by the square root of the eigenvalues λ of Q, and the orientation of the ellipse is defined by the eigenvectors of Q.
Postural strategy coordination is interpreted based on the eigenvalue descriptors [27;28]. Colobert et al., in [27] proposed a strategy index, θ, given by the ratio of the largest and the smallest eigenvalues of the covariance matrix. To adapt such an approach to our data, in which we have a set of 3 accelerations, we defined the ratio:

$$\theta_{TOT} = \frac{\theta_{L5-C7}}{\theta_{THIGH-L5}} \quad ,$$

where , $\theta_{L5-C7} = \frac{\lambda_1(\mathrm{Q_{L5\text{-}C7}})}{\lambda_2(\mathrm{Q_{L5\text{-}C7}})}$ and . $\theta_{THIGH-L5} = \frac{\lambda_1(\mathrm{Q_{THIGH\text{-}L5}})}{\lambda_2(\mathrm{Q_{THIGH\text{-}L5}})}$

With this definition, an ankle strategy is revealed by values of $\theta_{TOT:}$ closer to 1, and a hip strategy is revealed by $\theta_{TOT}>1$.

Statistical analyses

To assess changes across the 3 conditions (EO, EC, and ECC), and group we performed a Linear Mixed models analysis with Bonferroni correction. Receiver operating characteristics (ROC) analysis compared the discriminative value of each COP and Acc parameter. The relation between postural parameters and UPDRS Motor Scores was investigated by linear regression analysis. All the analyses were performed with NCSS Software, Kaysville, Utah.

Results

General characteristics of postural sway

Postural sway measured with linear accelerometers on the body showed differences between the untreated PD and control groups, similar to the traditional measures of postural sway from forceplate COP displacements. For example, the COP trajectories of a representative control and untreated PD subject during quiet stance EO are illustrated in Fig. 1A and the corresponding accelerations of the lower trunk in the horizontal plane are illustrated in Fig. 1B. The area of COP and of the acceleration signal estimated from RMS, were both larger in subjects with untreated PD compared to the control subjects. Similarly, both sway-related signals (COP and acceleration) showed faster components (reflected in MV) in the untreated PD compared to the control subjects (Fig. 1B).

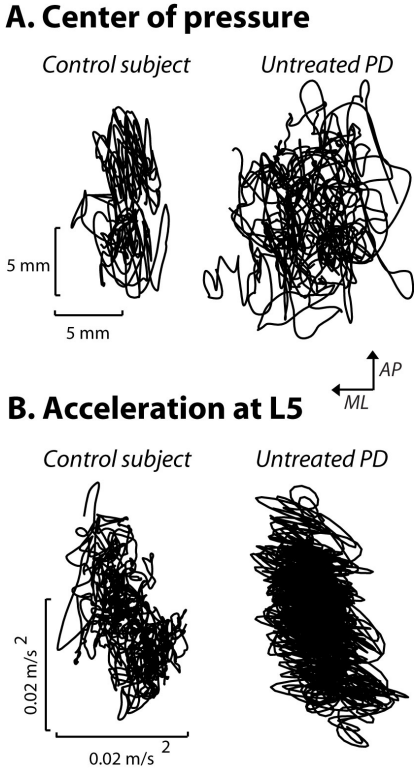

Figure 1: (A) Center of pressure (COP) and (B) lower trunk (5th lumbar vertebra level = L5) acceleration trajectories in the horizontal plane of representative control and untreated PD subjects.

COP analysis

Differences between groups

Untreated PD subjects showed (Table 2, upper panel): i) a larger RMS, a larger FD, and a reduced F95% than the control group in the EO condition; ii) a reduced F95% than the control group in the EC condition; and iii) a reduced F95% and a larger FD than the control group in the ECC condition.

Differences among conditions

The untreated PD group, but not the control group's sway, had a higher FD in the EC and ECC conditions compared to EO condition. In contrast, the control group, but not the untreated PD group's sway, had a larger MV in the ECC condition than in EO condition.,

The most discriminative COP parameter to distinguish untreated PD from control subjects was F95% in the EO condition, which showed an area under the curve (AUC) of 0.95 (Fig. 2A).

COP parameters

	RMS [mm]			MV [mm/s]			F95% [Hz]			FD		
	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC
Control subjects	4.9 (0.4)	5.5 (0.5)	6.5 (0.5)	7.7 (0.7)	10.2 (1.2)	12.3 (1.3)	1.50 (0.07)	1.64 (0.06)	1.56 (0.09)	0.768 (0.008)	0.753 (0.008)	0.751 (0.009)
Untreated PD	7.3 (0.5)	7.2 (0.4)	7.3 (0.4)	6.8 (0.5)	9.1 (0.8)	10 (0.9)	0.98 (0.06)	1.16 (0.06)	1.26 (0.08)	0.827 (0.008)	0.784 (0.009)	0.787 (0.012)

ACC thigh parameters

	RMS [m/s²]			MV [m/s]			F95% [Hz]			FD		
	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC
Control subjects	0.067 (0.005)	0.071 (0.005)	0.084 (0.006)	1.18 (0.16)	1.34 (0.14)	1.08 (0.1)	2.32 (0.05)	2.32 (0.07)	2.48 (0.08)	0.767 (0.009)	0.764 (0.008)	0.723 (0.014)
Untreated PD	0.094 (0.004)	0.093 (0.007)	0.107 (0.012)	1.69 (0.12)	1.67(0.4)	1.81 (0.21)	2.10 (0.11)	2.19 (0.11)	2.37 (0.14)	0.823 (0.01)	0.804 (0.011)	0.776 (0.014)

ACC L5 parameters

	RMS [m/s²]			MV [m/s]			F95% [Hz]			FD		
	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC
Control subjects	0.074 (0.006)	0.084 (0.007)	0.117 (0.01)	1.18 (0.12)	1.33 (0.14)	2.04 (0.23)	1.5 (0.08)	1.56 (0.06)	1.72 (0.09)	0.762 (0.009)	0.771 (0.01)	0.766 (0.009)
Untreated PD	0.106 (0.012)	0.094 (0.007)	0.106 (0.01)	1.83 (0.25)	1.69 (0.2)	1.7 (0.22)	1.15 (0.08)	1.25 (0.09)	1.53 (0.12)	0.821 (0.008)	0.798 (0.01)	0.798 (0.009)

ACC C7 parameters

	RMS [m/s²]			MV [m/s]			F95% [Hz]			FD		
	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC	EO	EC	ECC
Control subjects	0.119 (0.007)	0.150 (0.019)	0.197 (0.024)	2.41(0.17)	3.44 (0.48)	3.53 (0.48)	1.67 (0.06)	1.67 (0.08)	1.96 (0.1)	0.778 (0.007)	0.767 (0.013)	0.757 (0.011)
Untreated PD	0.185 (0.02)	0.158 (0.015)	0.154 (0.008)	3.72 (0.41)	3.37 (0.53)	2.96 (0.35)	1.65 (0.11)	1.76 (0.07)	1.93 (0.07)	0.807 (0.012)	0.782 (0.011)	0.769 (0.012)

Table 2: Mean (±S.E.M) of COP and thigh, L5, and C7 horizontal acceleration parameters in 3 conditions (eyes open=EO, eyes closed=EC, eyes closed with cognitive task=ECC). Statistical differences between conditions, groups, and interactions are shown, after Bonferroni correction. (* p<0.05, ** p<0.001)

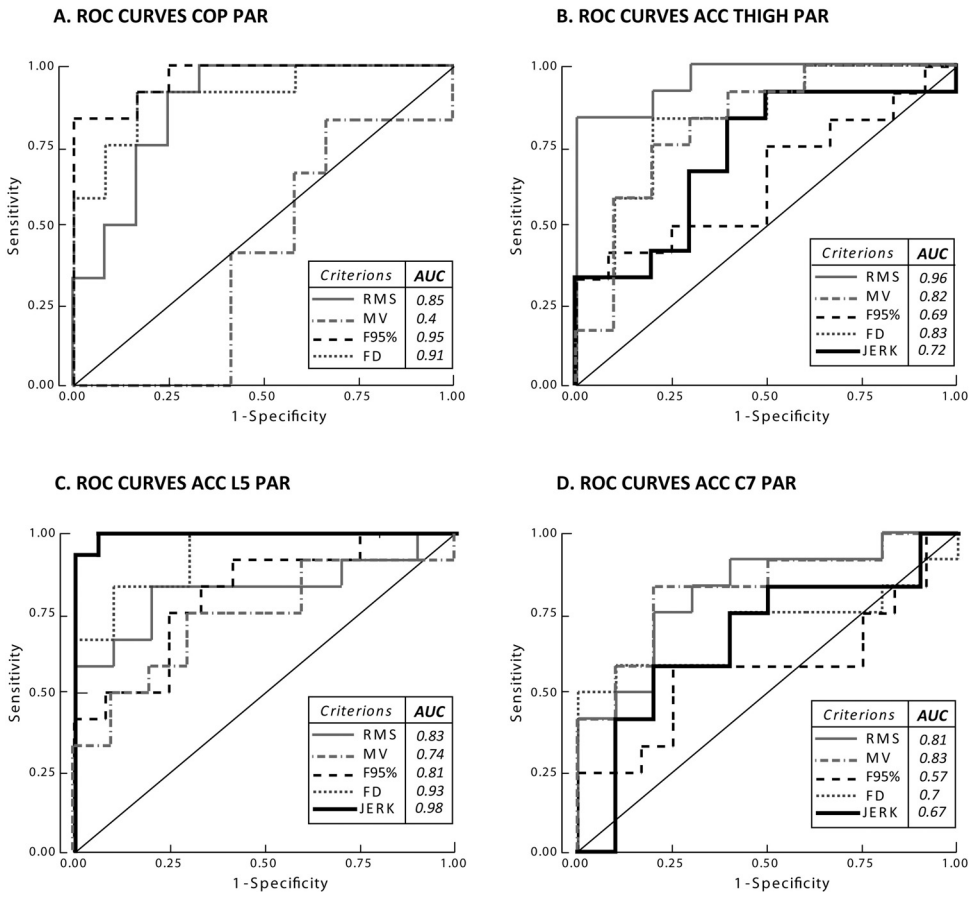

Figure 2: ROC curve for: A) COP parameters, B) thigh acceleration parameters, C) lower trunk acceleration parameters, and D) cervical acceleration parameters. AUC= area under the curve for each parameter.

Acceleration analysis

Differences between groups

Both the PD and control groups's sway had lower FD of the thigh acceleration in ECC condition than in EO condition (Table 2). The control group, but not the untreated PD group's sway, had a larger RMS and MV of the lower trunk acceleration in ECC condition than in the EO condition. The control group also showed a larger RMS of the cervical acceleration in the ECC condition than in EO condition.

Differences among conditions

In the EO condition, untreated PD subjects showed (Table 2): i) larger RMS and FD of the thigh acceleration, ii) larger RMS, larger FD, and lower F95% of the lower back acceleration, iii) larger RMS and MV of the cervical acceleration with respect to control subjects. In addition, in the ECC condition, PD subjects' sway had higher MV and FD than control subjects. Differences in postural sway from accelerometers were not significantly different between groups in the EC condition.

Sway jerk

Postural sway smoothness was altered in the untreated PD, compared to the control group. The PD subjects showed significantly larger JERK than control subjects at the thigh and L5 level in the EO condition ($p<0.05$, Fig. 3B), while JERK at cervical level was similar between the two groups. In contrast, control subjects presented a higher JERK than PD subjects at the cervical level in the ECC condition ($p<0.05$, Fig. 3C).

Both groups presented larger JERK at the thigh level in the ECC condition than in the EO condition ($p<0.05$, Fig. 3A). The control, but not the PD group, showed higher JERK at lower trunk and cervical levels in the ECC condition compared to the EC or EO conditions (Fig. 3B and 3C).

ROC analysis revealed an area under the curve (AUC) of 0.98 for JERK of the lower back acceleration in the EO condition, which was the highest discriminative value of all parameters. The second highest value of AUC was 0.96 for RMS of the thigh acceleration. The acceleration parameter ROC areas are compared in Fig. 2B, C, and D.

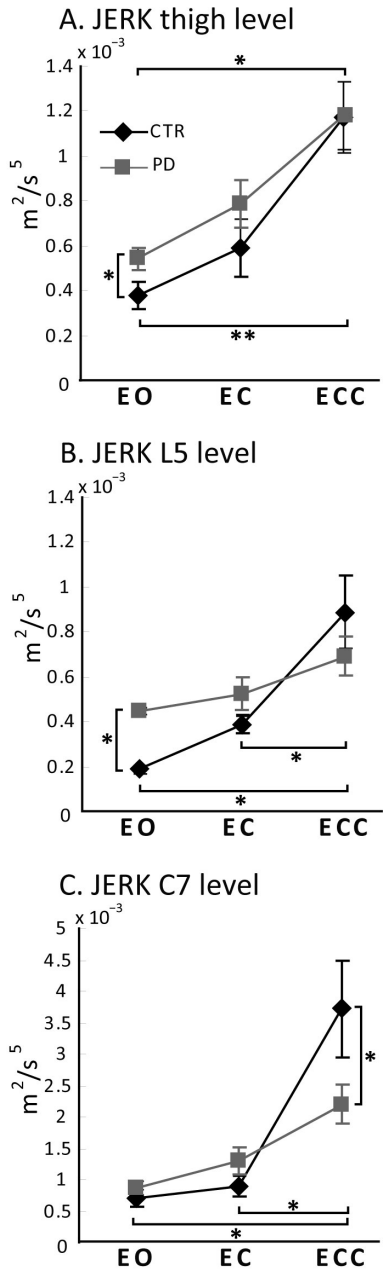

***Figure 3**:* Comparison of group mean JERK in PD and control subjects. The mean values (±S.E.M) of JERK of the thigh (A), lower trunk (B), and cervical (C) accelerations are presented. Significant differences, after Bonferroni correction, are showed with * $p<0.05$.

Postural strategy

The strategy index, for both untreated PD and control subjects, was near 1, suggesting that both groups used mainly an ankle strategy during quiet stance (Fig. 4), regardless the sensory condition or the presence of the dual task.

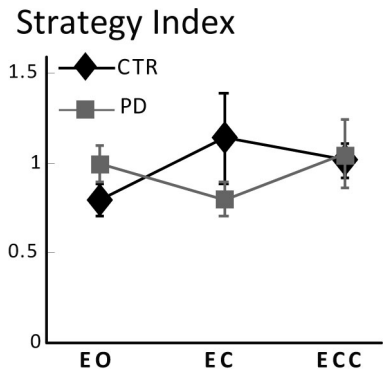

Figure 4: Mean (±SEM) of the Strategy index in untreated PD and control across EO, EC, and ECC condition.

Correlations between sway and severity of PD

All correlations between COP or acceleration parameters and UPDRS Motor Section total score or subscores, in the EO condition, were not significant. However, the sum of the UPDRS rigidity items was significantly correlated with the strategy index, r=-0.63, p=0.03. Higher rigidity was related to a lower strategy index, which indicated ankle strategy preponderance. The RMS and F95% of the lower trunk acceleration were also significantly correlated with disease duration in PD subjects (r=0.68, p=0.02 for RMS, r=0.72, p=0.01 for F95%).

Discussion

The key findings of this study are: 1) postural control is affected in subjects with untreated, early PD; 2) postural sway is more compromised at the lower body than at the upper body in PD; and 3) even the simple condition of eyes open, without visual deprivation or a concurrent cognitive task, discloses changes in body sway associated with early stages of untreated PD. The most sensitive measure of abnormal postural sway in early, untreated PD was smoothness of sway (JERK) of the lower trunk, suggesting that an accelerometer on the pelvis or waistband is the most effective method for monitoring abnormal postural control associated with PD.

The results of this study show, for the first time, that postural control is impaired, even in subjects with untreated PD, when it is not clinically apparent. Previous studies examining postural sway during quiet stance in subjects with PD have inconsistent results. Some studies [5;10;12] showed that postural sway is abnormal in PD, whereas others [29] have not found differences between PD and control subjects. The majority of studies focused on the advanced stages of the disease, when medication and dyskinesia influence postural sway. Partially consistent with our results, recent studies [11;16;17] , focusing on earlier stages of the disease, also showed subclinical signs of postural instability. However, all of the previous studies included subjects who had already started dopaminergic treatment, and were tested in the ON state[11;17] or, in one study [16], tested OFF and ON medication. Sway in subjects with PD who are in the ON state has been shown to be larger and faster than when in the OFF state, perhaps because levodopa reduces rigidity without improving control of posture, or because dyskinesia increases body motion [5].

The accelerometer-based parameters showed more differences between groups at the lower trunk and thigh levels than at the cervical level. Smoothness of sway was compromised in untreated PD at the thigh and lower trunk level, but not at the cervical level in the EO condition. In fact, JERK of the lower trunk was the best discriminative parameter to differentiate sway between untreated PD and control subjects. In addition, F95% of the lower trunk acceleration, and not at cervical or thigh level, was

significantly lower and FD was significantly higher, in untreated PD compared to control subjects.

The larger differences in postural control in the lower, than the upper body is consistent with larger deficits in integrating proprioceptive information than vestibular information in PD [30]. Motor deficits in PD are at least partly caused by proprioceptive disturbances. Afferent information itself is presumably normal, but proprioceptive signals are abnormally processed within the basal ganglia because of defective higher-level integration [31]. The larger postural sway amplitude found in PD might be related to impaired bottom-up control via somatosensory inputs, while the similarities between groups at the cervical level might be related to intact top-down control via vestibular and visual inputs [30;32]. Since somatosensory information is the most critical sensory information for control of equilibrium during standing [14;32], increased postural sway in PD might reflect noisy somatosensory feedback from foot pressure, muscle proprioceptors and joint receptors in the postural control loop resulting in inaccurate information about body position in space and an abnormal internal map of stability limits [5;31]. The frequent corrections of postural sway in untreated PD is responsible for the higher MV and higher JERK compared to control subjects, and may reflect compensation by vestibular and visual postural feedback loops. Increased JERK could contribute to, or reflect, increased axial rigidity [33].

The EO condition was best for differentiating untreated PD from age-matched controls. Surprisingly, PD subjects did not show increased dependence upon vision to control postural sway compared to control subjects. Studies of arm reaching show that subjects with PD are very inaccurate in pointing or stepping tasks without view of the limb [34]. However, in quiet stance, subjects with PD did not increase their sway more than control subjects.

Surprisingly, subjects with early PD also did not show less automatic control of postural sway compared to control subjects. It has been suggested that the basal ganglia is important for automatizing motor control so less cortical, conscious control of movement is necessary for habitual tasks like standing and walking. Studies of walking speed show that subjects with PD slow more than controls when adding a secondary cognitive task [35]. In contrast, our study, adding a cognitive task to quiet

stance with EC increased RMS sway at the cervical and lumbar trunk of control subjects, but not subjects with untreated PD. Thus, the increased sway area, velocity and JERK associated with early PD is not likely due to lack of automatic control of posture with dependence on longer, cortical feedback loops.

The strategy index revealed that both untreated PD and control subjects used primarily an ankle strategy to maintain standing balance in each of the EO, EC, and ECC conditions. Thus, use of one accelerometer on the pelvis or low back should be sufficient to measure postural sway in subjects with PD. We suspect that tasks requiring use of a hip strategy, such as standing across a narrow beam or on a compliant surface would separate controls from PD subjects, who may not be able to control a hip strategy because of their high hip postural tone [33]. Our previous studies showed that hip postural tone is 3-5 x larger in patients with PD than in age-matched control subjects [33]. In our study, the strategy index in untreated PD was significantly correlated with the UPDRS rigidity, with higher rigidity correspond to more use of an ankle strategy in the EO condition. The lack of hip motion with larger ankle during postural sway in rigid subjects is also consistent with high hip postural loop gain and low ankle loop gain in PD (Seyoung et al, in press).

We demonstrate how accelerometers on the pelvis can detect impairments in postural control even better than a forceplate. The ROC curves to differentiate the PD and control groups were largest for JERK of lower trunk acceleration, and next highest for RMS of the thigh acceleration and next highest for FD of lower trunk acceleration. Accelerometers attached to a patient's belt are a practical, inexpensive alternative to forceplate measures of postural sway because they are an unobtrusive and accurate measure of postural control that can be used in a clinic or community setting.

Future developments

Accelerometers provide sensitive measures of postural alterations in early PD and added new insight into multisegmental posture control, compared to traditional forceplate posturography. In addition, JERK of lower trunk postural sway may be the most sensitive measure of early PD. Longitudinal studies of postural sway are needed to determine if lower trunk JERK is also

a sensitive measure of disease progression, useful in clinical trials of neuroprotective interventions.

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Chapter 8

Anticipatory postural adjustments prior to step initiation are hypometric in untreated Parkinson's disease: an accelerometer-based approach

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Abstract

Background and purpose.
Anticipatory postural adjustments (APAs), prior to step initiation, are bradykinetic in advanced Parkinson's disease (PD) and may be one of the factors associated with 'start hesitation'. However, little is known about APAs in the early stage of PD. In this study, we determined whether body-worn accelerometers could be used to characterize step initiation deficits in subjects with early-to-moderate, untreated PD.
Methods.
Eleven PD and 12 healthy control subjects were asked to take two steps. Postural adjustments were compared from center of pressure (COP) and from acceleration of the trunk at the center of mass level (L5).
Results.
Our findings show that APAs measured from the peak COP displacement towards the swing leg and the peak trunk acceleration towards the stance leg were smaller in untreated PD compared to control subjects. The magnitude of APAs measured from peak COP displacements and accelerations were correlated.
Conclusion.
These results suggest that quantitative analysis of step initiation from one accelerometer on the trunk could provide useful information for the characterization of patients in early stages of PD, when clinical evidence of start hesitation may not be detectable. Ambulatory monitoring of step initiation is also promising for monitoring patient progression in the home environment, and eventually providing feedback for preventing freezing of gait episodes.

Introduction

When attempting to voluntarily initiate the first step to begin walking, many patients with PD exhibit start hesitation and freezing, especially in advanced stages of the disease [1;2]. Patients with advanced PD generally show bradykinetic step initiation, measured as increased movement preparation time, reduced lateral shift of the body mass over the stance limb and decreased propulsive forces [3-5]. These abnormalities of step initiation are sensitive to levodopa replacement [5;6], external cues [5], initial stance width [6], and to bilateral deep brain stimulation of the Subthalamic nucleus [7-9].

However, it has been debated whether step initiation is impaired in early stages of PD, before the start of dopaminergic medication [10]. The only study of step initiation in early to moderate PD reported smaller than normal initial backward displacement of the center of pressure under the feet compared to control subjects, but many of these subjects were taking medications that may affect step initiation [11]. Since patients in early stages of PD do not show clinical signs of balance or gait problems, quantitative detection of deficits of step initiation could provide early markers for later developing problems. For these reasons, the evaluation of step initiation in untreated PD represents a novel, valid, and objective measure to test the effects of potential neuroprotective drugs.

Step initiation requires a tight proprioceptive coordination between motor commands for postural adjustments and for stepping [12-14]. Immediately prior to step initiation, anticipatory postural adjustments (APAs) act to accelerate the center of body mass forward and laterally over the stance foot by moving the center of pressure (COP) posteriorly and toward the stepping leg [15]. APAs are thought to be initiated via motor circuits including the supplementary motor area (SMA), that are independent from the more volitional lifting of the foot during step initiation [14]. APAs prior to step initiation are usually described using force plates and EMG activation patterns [16-18]. The backward COP displacement results from a deactivation of bilateral gastrocnemius and soleus muscles, and activation of tibialis anterior; the lateral COP displacement is a consequence of preloading of the stepping foot by the hip abductors [15;19].

However, the cost and complexity of measuring APAs using traditional motion analysis, force plate, and EMG systems limit their application to clinical practice. Recently, small, inexpensive, wearable inertial sensors such as accelerometers have been used to quantify gait and postural sway [20-22]. Our group has recently demonstrated how to detect APAs, represented by anticipatory trunk accelerations, prior to step initiation in young healthy subjects [23].

The purpose of this study was to determine if APAs prior to step initiation were bradykinetic in early, untreated PD and if trunk acceleration measures could be used to differentiate the magnitude of APAs in untreated PD from age-matched controls.

Methods

Participants

Eleven patients with idiopathic PD and 12 age-matched healthy control subjects participated in this study. The diagnosis of idiopathic PD was made by a movement disorders expert by clinical exam, history and any pertinent laboratory results. Only patients who were early-to-middle stage in disease course and had never been treated with dopaminergic or anti-parkinsonian medication were invited to participate. Subjects were excluded if they presented any neurological disorders other than PD, orthopedic disorders or other impairments that could potentially interfere with gait, or if they used orthotic devices or had artificial joints.

Patients were clinically rated by a trained examiner on the Motor Section (III) of the Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr Scale immediately before the experimental sessions. Table 1 summarizes subject characteristics, ordered by severity of PD. All participants provided informed consent according to the Oregon Health & Sciences University Institutional Review Board.

Table 1: *Characteristics of subjects with Parkinson's disease, individual and means (±S.E.M) values. Abbreviations: H&Y=Hoehn and Yahr Scale, PIGD=Postural Instability and Gait Disorder subscore, Peak ML-COP= peak lateral center of pressure excursion toward the swing foot during APA.*

Subj	*AGE (years)*	*Disease onset (months)*	*H&Y*	*UPDRS III Total Motor Score*	*Bradykinesia (Items 23:27) subscore*	*PIGD (Items 27:30) subscore*	*Peak ML-COP (mm)*
P1	*63*	*26*	*3*	*46*	*21*	*5*	*19.03*
P2	*77*	*13*	*2.5*	*45*	*19*	*2*	*25.17*
P3	*70*	*15*	*2.5*	*35*	*15*	*4*	*39.9*
P4	*50*	*10*	*2*	*35*	*19*	*1*	*25.28*
P5	*53*	*26*	*2*	*33*	*17*	*0*	*36.6*
P6	*64*	*11*	*2*	*32*	*13*	*1*	*8.65*
P7	*61*	*13*	*2*	*27*	*17*	*0*	*21.38*
P8	*61*	*8*	*2*	*21*	*9*	*1*	*24.25*
P9	*58*	*48*	*1.5*	*21*	*10*	*0*	*28.83*
P10	*58*	*22*	*1*	*17*	*10*	*0*	*17.1*
P11	*49*	*5*	*1*	*7*	*2*	*0*	*28.12*
Mean	**60.3**	**17.9**	**1.9**	**29**	**13.82**	**1.27**	**24.94**
SEM	0.76	1.11	0.05	1.08	0.51	0.16	0.79

Experimental Setup

At the beginning of each trial, the subjects stood on a force plate (AMTI OR6-6, Watertown, MA) with feet externally rotated at their comfortable stance but with heel-to-heel distance fixed at 10 cm for all subjects. Initial stance position was consistent from trial-to-trial by tracing foot outlines on the force plate and by coaching subjects to maintain their initial COP position prior to each trial based on oscilloscope COP traces. Subjects wore 3 MTX Xsens sensors (49A33G15, XSens, Enschede, NL) with 3-D accelerometers (±1.7g range), and 3-D gyroscopes, (±300º/s range) mounted on: i) the posterior trunk at the level of L5, near the body center of mass, ii) lateral aspect of the right thigh, limb that took the first step, and iii) the spinous process of C7. Accelerations sensed at C7 level were not reliable measures of APAs because of inadvertent head and trunk motion, and will not be considered further. The sensing axes were oriented along the body antero-posterior, medio-lateral, and vertical directions. Figure 1A shows the experimental setup. Subjects were instructed to self-initiate two steps, starting with the right foot, at their normal, comfortable pace as if they were going to start walking. Three trials of step initiation were acquired.

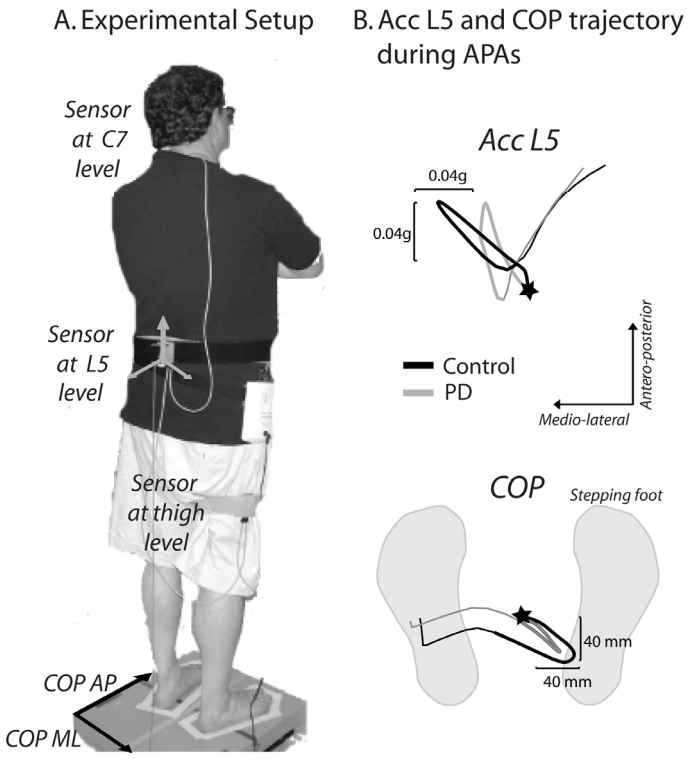

Figure 1*: Experimental set-up and representative trunk acceleration and center of pressure (COP) trajectory during APA. A. Experimental setup: sensors placement on subject. B. The trajectory of trunk acceleration sensed at L5 level and COP from force plate during APAs in two representative subjects: control subject (black) and PD subject (grey). The stars represent the onset of APAs. The total APA phase in represented by the bold signal.*

APAs were evaluated from COP displacements recorded from the force plate with a 100-Hz sampling frequency after applying a 10-Hz cut-off, zero phase, low-pass Butterworth filter to the ground reaction forces. APAs were also evaluated from L5 acceleration data collected with a 50-Hz sampling frequency, transformed to horizontal-vertical coordinate system [24] and filtered with a 3.5 Hz cut-off, zero-phase, low-pass Butterworth filter.

Data analysis and extracted features

A specific set of step initiation features was automatically extracted by ad hoc algorithms and then visually inspected to check for possible errors in the event classification. Figure 2 shows examples of COP (A and C) and acceleration (B and D) signals collected from a representative control and PD subject both in medio-lateral (ML) and antero-posterior (AP) directions, together with the extracted features.

The following APA characteristics were compared from the COP displacements and trunk accelerations: 1) APA duration (from the onset to the end of APAs), 2) APA ML amplitude, that is (i) Peak ML-COP, peak lateral COP excursion toward the swing foot from baseline and (ii) Peak ML-Acc, peak acceleration toward the stance foot of the lateral trunk acceleration; and 3) APA AP amplitude, that is (i) Peak AP-COP, peak of backward COP excursion and (ii) Peak AP-Acc, forward trunk acceleration from the baseline. Relative time-to-peak, from the onset of APAs to the instant of each peak APA, was also measured.

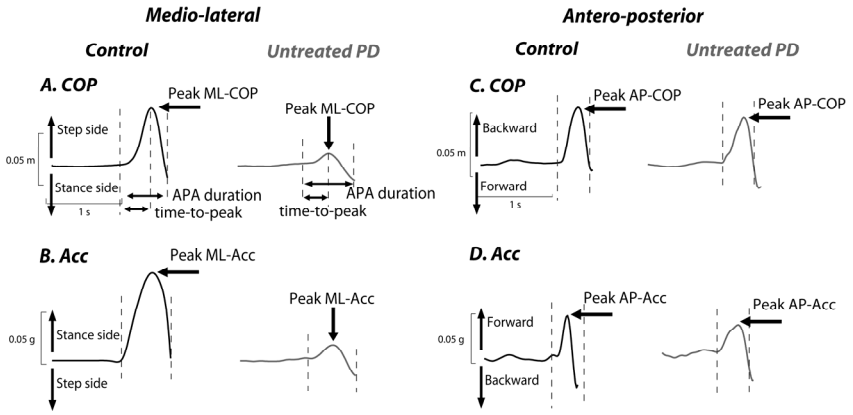

***Figure 2**: COP and trunk acceleration at L5 during APAs in two representative subjects: control subject (black) and PD subject (grey). Left panel: medio-lateral direction, A. COP signals and B. trunk acceleration signals. Right panel: antero-posterior direction, C. COP signals and D. trunk acceleration signals. Parameters computed from the signals are shown. The onset and end of the APA are represented by the dashed lines.*

The onset of APAs (first measurable change in COP from baseline) was detected by an automated threshold-based algorithm, with threshold set as twice the standard deviation of signal during the initial, pre-step initiation, period of each trial. The APAs were considered completed (end of APAs) when both the AP and ML COP went back to their baseline values.

To determine the relationship between the APAs and the velocity and length of the first step, the gyroscope sensing AP thigh angular velocity was used to determine: i) time-to-peak angular velocity (from the onset of APAs to the instant of peak angular velocity), and ii) range of motion of the thigh (calculated from the integrated sagittal angular velocity), respectively, approximate indicator of the velocity and length of the first step.

Statistical analyses

The relation between extracted APA and first step properties was investigated by linear regression analysis, as well as the relation between the UPDRS Motor scores and APA features. For each feature, a separate one-way ANOVA was used to detect differences between the control versus the PD group. For the entire set of statistical analyses the level of significance was set at $p<0.05$. All the analyses were performed with NCSS Software, Kaysville, Utah.

Results

Force plate measures of APAs

The COP trajectory typical for gait initiation (Figure 1B) is maintained in untreated PD subjects, although quantitative changes, especially in lateral COP excursion, were detected.

Peak ML-COP in the PD group is clearly reduced compared to control subjects, while Peak AP-COP is not, as shown in Figure 2-A and 2-C by examples in representative control and PD subjects. Figure 3-A shows the same result for the groups: the mean value of Peak ML-COP in the PD group was significantly smaller than in the control group, $p=0.007$, (mean ± SEM; 24.94 ± 0.79 mm in PD versus 38.21 ± 1.02 mm in control), while Peak AP-COP was not significantly smaller in the PD than control group (mean ± SEM; 21.34 ± 1.1 mm in PD versus 28.7 ± 0.9 mm in control).

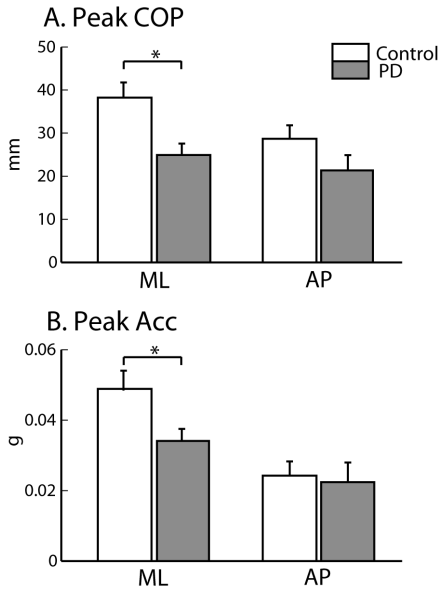

Figure 3*: Comparison of APAs in PD and control subjects. The mean values (±S.E.M) of Peak COP (A) and Peak Acc (B) are presented. Significant differences are showed with * p<0.05.*

Inertial sensor measures of APAs and step kinematics

As expected, the trunk accelerometer detected a pattern for the center of body mass motion reciprocally linked with the COP displacement pattern during the APA; the trunk acceleration showed a medial-forward excursion in correspondence to the lateral-backward displacement of the COP. Similar to the Peak ML-COP, Peak ML-Acc was significantly smaller in PD compared to control subjects, p=0.01, (mean ± SEM; 0.034 ± 0.001 g in PD versus 0.049 ± 0.0015 g in control), while Peak AP-Acc was not (mean ± SEM; 0.022 ± 0.001 g in PD versus 0.024 ± 0.001 g in control). See Figure 2B and 2D for representative subject APA trajectories and Figure 3B for group comparisons.

Unlike APA peak magnitudes, the durations of the APAs were similar between the PD and control groups (mean ± SEM; 0.55 ± 0.01 s in PD, and 0.54 ± 0.01 s in control subjects). Also, time-to-peak APAs, detected from both COP and accelerations in both the ML and AP directions, were similar across the two groups (mean ± SEM from COP; ML direction: 0.40 ± 0.08 s in

PD, and 0.39 ± 0.01 s in control subjects; AP direction: 0.37 ± 0.008 s in PD, and 0.38 ± 0.01 s in control subjects).

Despite the very small peak APA magnitude in subjects with PD, the velocity and length of the first step were not significantly compromised in untreated PD subjects. The time-to-peak forward angular velocity, indicator of step velocity (mean ± SEM; 0.99 ± 0.38 s versus 0.77 ± 0.17 s) and range of thigh motion, indicator of step length, were similar across groups (mean ± SEM; 22.62 ± 0.36° versus 22.66 ± 0.22°).

Correlation between force plate-based and acceleration-based features of APAs

A significant linear correlation was found between COP and acceleration measures of the APA peaks in the ML direction (r=0.84, p=0.00001; Figure 4.A), and in the AP direction (r=0.7, p=0.0004; Figure 4.B).

The time-to-peak forward thigh angular velocity correlated significantly with the magnitude of the APAs: Peak ML-COP (r=-0.52, p=0.01); Peak ML-Acc (r=-0.49, p=0.04); and Peak AP-COP (r=-0.61 p=0.004); Peak AP-Acc (r=-0.58, p=0.006).

However, the Peak ML-COP, Peak AP-COP and Peak ML-Acc, Peak AP-Acc variables were not correlated with the length of the first step. All correlations between Peak ML, AP-COP, or Peak ML, AP-Acc, and UPDRS Motor Section scores were not significant.

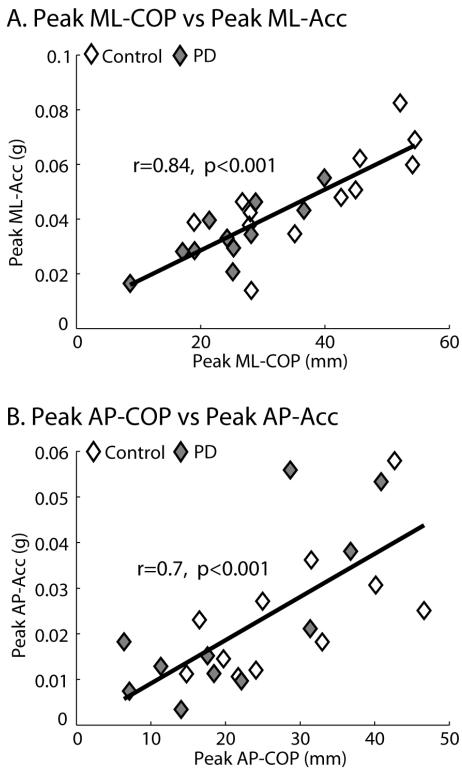

***Figure 4**: Linear correlation between Peak COP and Peak Acc presented for the medio-lateral (A) and antero-posterior (B) directions. Data are combined for PD (grey rhombus) and control subjects (white rhombus).*

Discussion

The results of this study show, for the first time, that lateral APAs are impaired in early, untreated PD, and how wearable inertial sensors can detect this impairment.

APAs are hypometric in the ML direction

Reduced APAs are a specific, primary symptom of PD, responsible for severe balance and mobility problems [13;25;26]. In the current study, we found small peak APAs in subjects with mild PD, even though the velocity and length of their first steps were not slower or smaller than steps of control subjects. These results are consistent with separate, interacting

motor programs for neural control of APAs and the step itself [14;25;27-29]. Early PD may affect the supplementary motor cortex, responsible for APAs before it affects the primary motor cortex and other areas responsible for generating force for stepping [4;14;16;18].

We found a significantly smaller lateral, but not backward, COP displacement during the APAs in subjects with untreated PD, compared to control subjects. This result is in contrast with Carpinella et al. [11] who found a significant reduction of backward displacement of the COP in early PD, but did not report subjects' lateral COP displacements. This discrepancy may be explained by differences in the required task, since our subjects were instructed to take only two steps, whereas their subjects initiated gait, or to differences in the starting foot placement position. We required all subjects to stand with a standard stance width. If the Carpinella's study allowed narrow or self-selected, variable stance width, it would be difficult to detect differences in lateral APAs between groups [6]. In addition, inclusion criteria for PD subjects were different, since all of our subjects were untreated, whereas several subjects in the Carpinella's study were tested on dopaminergic medication. Similar to our results, Carpinella et al. [11] showed similar APA durations for PD and control subjects.

The smaller lateral, but not backward, APA magnitudes suggests that the pathology of PD may have a specific effect on loading/unloading of the legs early in the disease, consistent with abnormal ML, but not AP, sway during quiet stance in PD [30]. Later in the disease, the magnitude of both lateral and backward APAs becomes bradykinetic in PD [18]. Unlike subjects with early PD, healthy elderly subjects show reduced backward, but not lateral, APA magnitudes compared to young subjects, consistent with separate neural control of these two directions of APAs, which have separate functions [11]. Force for lateral APAs come primarily from hip abductors and ankle extensors, so weakness of these muscles could contribute to small lateral APAs in PD. In contrast, force for anterior-posterior APAs come from tibialis anterior muscles, so weakness of ankle dorsiflexors may contribute to small APAs in the elderly. PD subjects also show particularly impaired control of ML sway in quiet stance, consistent with deficits in neural control or proprioception affecting loading and unloading mechanisms that may be important for freezing [31;32]. Since the application of smaller forces to initiate movement results in smaller self-

induced postural perturbations, it is also possible that small lateral APAs represent a strategy to minimize postural instability [11;19;33]. We consider lateral postural instability an unlikely explanation for small lateral APAs because as the disease progresses, PD subjects gradually narrow their stance width to compensate for their inability to scale up the size of their bradykinetic APAs [6].

Although step length and step velocity were not different between groups, first step velocity was significantly correlated with backward and lateral APA magnitude for both groups, consistent with previous studies in healthy subjects [23;34]. Breniere et al., 1987 [35] showed that steady state gait velocity is correlated with the size and duration of backward APAs, but also to differences in the initial posture and proprioceptive availablity on the sole of the foot.

It is unclear whether the magnitude of lateral APAs before step initiation is a good biomarker for PD progression. Although APA magnitude was significantly smaller in early PD, than control, subjects, it was not correlated with their UPDRS Motor Scores (ranging from 7 to 46) or PIDG (Items 27, 28, 29, and 30) or bradykinesia (Items 23, 24, 25, and 26) subscores. This could be due to the fact that APA magnitude may not be a measure of PD severity or bradykinesia, but rather a precursor to freezing. In addition to the small amplitude of lateral APAs observed in our mild subjects, subjects with more advanced PD also show prolonged APA durations, small backward APA amplitude, and significantly slower execution of the first step [4-6;18]. Longitudinal studies are needed to determine which characteristics of postural preparation for step initiation are related to disease progression.

Acceleration sensed at the trunk can detect impaired APAs in untreated PD

Accelerations of the trunk prior to step initiation reliably characterize APAs, similar to a mirror image of COP displacements, as have been measured traditionally. This reflection of trunk acceleration from COP displacements likely reflects center of mass accelerations during the APA phase [14;34]. In addition, our results showed that acceleration-based extracted features in the APA phase can detect the same impairments in untreated PD as the force plate-based extracted features, specifically,

reduced lateral displacement to unload the initial stepping leg. As a compliment to measuring APAs, Breniere et al. [36], demonstrated how to use accelerometers to analyze motions of the hips, shoulders, and estimated body center of gravity before and at heel-off, prior to a step.

Clinicians cannot readily observe small postural preparation or reduced velocity of the first step related to start hesitation. APA detection via accelerometers provides a new, promising application for clinical practice and clinical trials. The acceleration signal via a sensor on a belt is easy to acquire and wireless, portable versions of inertial sensors are becoming available. In this way, step initiation can be measured in a clinical or home environment to monitor progression of start hesitation and sensitivity to interventions, and eventually, to provide biofeedback for preventing freezing of gait.

In conclusion, quantitative analysis of step initiation in untreated PD, with one accelerometer on the trunk, provides useful information for the characterization of patients in early stages of PD, when clinical evidence of start hesitation may not be detectable. Future studies are needed to determine whether patients with the smallest APAs are more likely to later develop freezing with start hesitation.

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Chapter 9

Longitudinal monitoring of posture in patients with early-to-moderate Parkinson's disease

Preliminary results

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Introduction

The defining motor features of Parkinson's disease (PD) are characterized by their insidious onset and inexorable but variable progression. Also, PD can be difficult to diagnose in its early stages, and may be mimicked by other diseases, such as essential tremor, multiple system atrophy (MSA) and progressive supranuclear palsy [1-3].

Reliable and well validated biomarkers for PD to identify individuals "at risk" before motor symptoms, accurately diagnose individuals at the threshold of clinical PD, and monitor PD progression throughout its course would dramatically improve patient care and accelerate research into both PD cause and therapeutics. Further, clinical trials of neuroprotective interventions for PD are lacking accurate, quantitative measures for longitudinal testing of posture and gait that are sensitive to change, even in early stages of the disease.

During the past two decades, much progress has been made in identifying and assessing PD biomarkers, but as yet, no fully validated biomarker for PD is available [4].

Biomarkers are broadly defined as characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [4]. Biomarkers for PD are and may be extremely useful both for disease diagnosis and monitoring, and for drug development.

In considering biomarkers for PD, three crucial issues must be addressed [5]. The first issue is face validity: Is the marker meaningful or relevant to the disease process? Second, what are the performance characteristics of the marker in the relevant subject population under study; for example, diagnostic markers must predict disease in individuals who are not diagnosed. Third, how generalizable is the biomarker? The effect of stage of disease, age, sex, medications, or environment on the biomarker must be carefully assessed.

Our recent studies (see Chapter 8), have shown for the first time that postural control is compromised in subjects with early PD. In particular, postural sway is more affected at the thigh and lower trunk than at the

cervical level in these subjects. Furthermore, it is not known if measures of postural sway show changes that are correlated with the progression of PD in patients early in the disease process.
We hypothesize that the measures that we found altered in early PD, could provide a measure of disease progression since balance control is known to deteriorate across the course of the disease.

Methods

Subjects
We examined 12 PD and 12 healthy, age-matched control subjects. PD subjects were newly diagnosed and were not taking any medications at baseline. All subjects were tested a second time 3-to-6 months after the baseline test (1st measure), and a third time 3-to-6 months after the 1st measure (2nd measure). Those PD subjects who started dopaminergic medication were tested 'off'. Subjects were asked to stand still for 2 minutes staring at an art poster with eyes open. They wore 2 MTX Xsens inertial sensors, mounted with Velcro belts in the middle of the posterior trunk, at the level of L5 and of C7.
We computed several parameters from the 2-D horizontal acceleration signals, including: RMS acceleration (RMS), sway velocity (MV), frequency comprising the 95% of the power (F95%), frequency dispersion (FD), and JERK (see Chapter 8 for details on parameters extraction). The same set of parameters was also computed singularly in antero-posterior (AP) and medio-lateral (ML) direction.
A Linear Mixed Models analysis was used to compare groups and follow-ups.

Results and discussion
Among parameters extracted from the acceleration sensed at L5 level (Fig. 1), JERK, JERK ML, RMS ML, MV ML, FD, FD ML, and FD AP were significantly different between groups ($p<0.05$). In particular, PD showed higher JERK, JERK ML, MV ML, RMS ML at baseline, 1st measure and 2nd measure. Further, JERK ML showed an interaction effect ($p=0.04$), indicating a decline

in jerk from baseline to the 1st measure, while the control group remained constant. Also, FD ML showed an interaction effect (p=0.05) in PD meaning that this parameters is going towards normal values at the 1st measure, but remains higher at baseline and 2nd measure in PD with respect to control subjects.

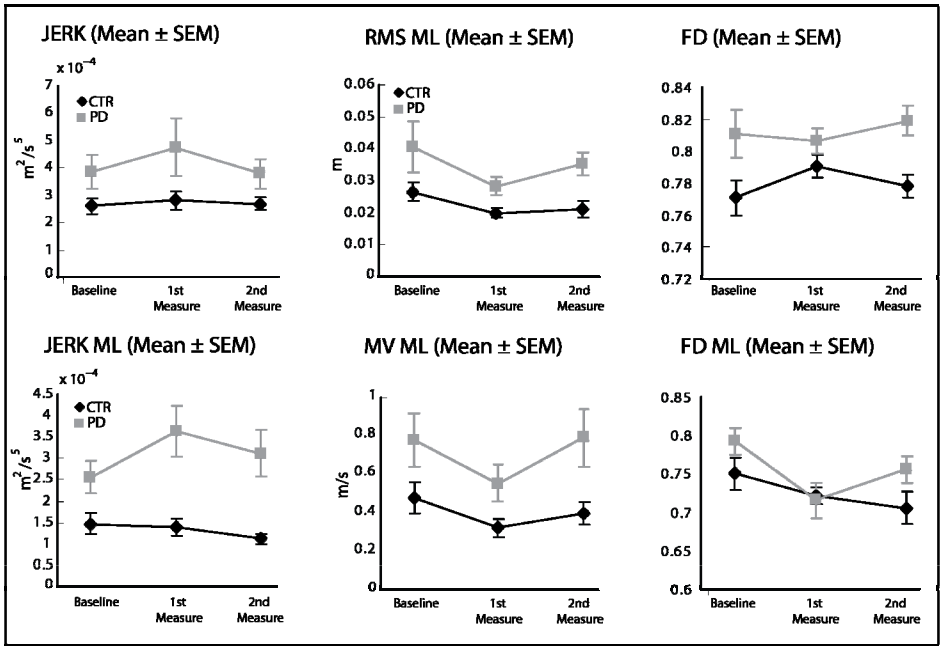

Figure 1

Among parameters extracted from the acceleration sensed at C7 level (Figure 2), JERK ML, RMS ML, MV ML, F95% ML, FD, and FD AP were significantly different between groups ($p<0.05$). In particular, PD showed higher JERK ML from the 2nd measure on ($p=0.01$), while RMS ML and MV ML were higher only at baseline, from the 1st measure on this parameters are similar to controls. In contrast F95 ML showed an interaction effect ($p=0.04$), meaning an increase in PD throughout time.

C7 level

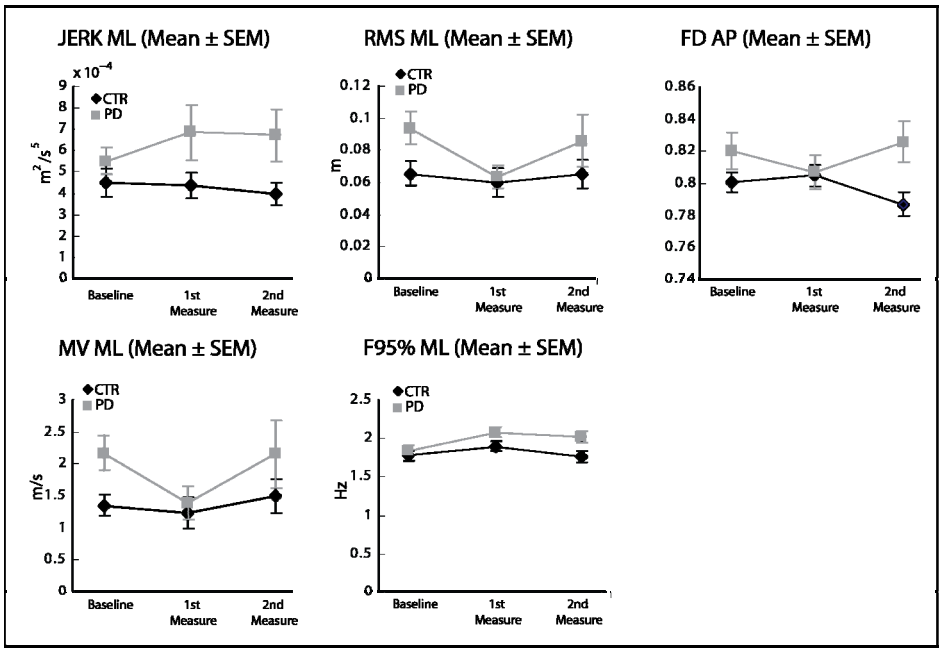

Figure 2

Postural sway is more compromised at lower trunk than at the cervical level in untreated PD subjects and this could be due to an higher rigidity with respect to treated subjects and control. Jerk of postural sway in stance was the most sensitive measure of early, untreated PD. Postural jerk may then be considered for inclusion as a useful biomarker of disease progression in clinical trials of neuroprotective interventions.

Accelerometer-based analysis of spontaneous sway could provide a simple but sensitive tool to cope with mass screening of subjects at risk to develop PD.

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Chapter 10

"Biofeedback for training balance and mobility in older people: a systematic review"
&
"Effect of Audio-Biofeedback in maintaining balance in Parkinson's disease: preliminary results"

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Part of the content of this chapter has been submitted in: A.Zijlstra, M.Mancini, L. Chiari, W. Zijlstra. "Biofeedback for training balance and mobility in older people: a systematic review", Physical Therapy.
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Abstract

Background and Purpose.

The purpose of this systematic review was to assess the effectiveness of applying biofeedback for training of balance and mobility-related activities in older adults.

Methods.

After a broad search, studies in older adults, i.e. mean age ≥ 60 years, were included when they compared the biofeedback-based training to similar training without biofeedback, an educational program or no intervention, and when they used objective measures of balance or mobility as outcomes. Selection of studies and rating of quality, with use of the PEDro scale, was performed independently by 2 reviewers.

Results.

Nineteen studies met the criteria for inclusion. Group sizes were small to moderate and quality scores were mostly moderate. Since large heterogeneity existed in outcome measures, a qualitative analysis was performed. Three studies provided evidence for a positive effect of training balance on a force plate system with visual feedback in 'frail' older adults on the Berg Balance Scale. Based on the results of 2 or more available randomized controlled trials, evidence for larger effectiveness of training with biofeedback than without biofeedback was found for gait rehabilitation in older patients with stroke and in older patients with an injured lower limb, and for training balance in combination with sit-to-stand transfers in older patients with stroke. However, evidence for similar effectiveness of biofeedback-based and conventional balance training was found in older patients with stroke. The included studies do not provide clear indications regarding long-term (non-) added benefit.

Discussion and Conclusion.

Indications exist for positive effects of biofeedback-based therapy, for supporting performance of balance- and mobility-related activities, in the older population. No indications exist for smaller effectiveness of biofeedback-based training compared to regular training.

Introduction

The safe performance of balance- and mobility-related activities during daily life, such as standing while performing manual tasks, rising from a chair and walking, requires intact balance control mechanisms. One-third to one-half of the population over age 65 reports some difficulty with balance or ambulation[1]. The disorders in balance control can be a consequence of pathologies, such as neurological disease, stroke, diabetes disease or a specific vestibular deficit, or can be due to age-related processes, such as a decline in muscle strength[2, 3], sensory functioning[4], or in generating appropriate sensorimotor responses[5].

Balance and mobility disorders can have serious consequences regarding physical functioning (e.g. leading to fall-related injuries) as well as psycho-social functioning (e.g. fear of falls leading to activity restriction and social isolation). Because of the high incidence of balance and mobility disorders in older adults and the large negative impact for the individual, interventions are necessary that counteract the deterioration in performance of balance- and mobility-related activities and that specifically target older adults. Existing interventions usually consist of exercise-based training. Beneficial effects of balance and mobility-related task exercise interventions have been demonstrated in older adults[6]. Providing the older adult with additional sensory information on their own motion, i.e. biofeedback information, may enhance training effects. Depending on the functioning of the natural senses that contribute to balance control, i.e. the vestibular, somatosensory, and visual systems[7], the added sensory feedback may be used as a substitute[8] or as an augmentation[9] in fine-tuning the central nervous system's sensorimotor integration[10].

The effects of providing biofeedback information in improving balance and mobility-related task performance have been investigated in experimental studies[11-15] as well as in intervention studies. Meta-analyses on the effects of biofeedback-based training have been conducted primarily for stroke rehabilitation[16-18]. Whether larger improvements are obtained when providing biofeedback information during balance and mobility-related task training in older adults, compared to regular training without biofeedback, is not yet clear.

The *main objective* of this chapter is to analyze available studies that use biofeedback-based exercise programs in population of older adults and patients with Parkinson's disease.

A *second objective* of the present study is therefore to review the practical feasibility of applying biofeedback-based training in older adults and in patients with Parkinson's disease.

Another objective is to present preliminary results on the use of a biofeedback device to maintain balance in PD patients.

Methods

Data Sources and Searches

Relevant studies were searched for in the electronic databases PubMed, EMBASE, ISI Web of Knowledge, Cochrane Central Register of Controlled Trials, CINAHL and PsycINFO. The search was performed in January 2008 and included all citations that were available in the database at that time. In addition, an update search was performed in September 2008. To identify further studies, reference lists of primary articles were reviewed, “Related Articles” search in PubMed, and “Cited Reference Search” in ISI Web of Knowledge was performed. Articles in English, Italian or Dutch were considered. The following search strategy was applied in the PubMed database:

#1 ***Biofeedback (Psychology)*** *OR (biofeedback OR bio-feedback OR "augmented feedback" OR "sensory feedback" OR "proprioceptive feedback" OR "sensory substitution" OR "vestibular substitution" OR "sensory augmentation" OR "auditory feedback" OR "audio feedback" OR audio-feedback OR "visual feedback" OR "audiovisual feedback" OR "audio-visual feedback" OR "somatosensory feedback" OR "tactile feedback" OR "vibrotactile feedback" OR "vibratory feedback" OR "tilt feedback" OR "postural feedback")*
#2 ***Movement*** *OR* ***Posture*** *OR* ***Musculoskeletal Equilibrium*** *OR (movement OR locomotion OR gait OR walking OR balance OR equilibrium OR posture OR postural OR sit-to-stand OR stand-to-sit OR "bed mobility" OR turning)*
#3 ***Middle Aged*** *OR* ***Aged*** *OR ("older people" OR "old people" OR "older adults" OR "old adults" OR "older persons" OR "old persons" OR "older subjects" OR "old subjects" OR aged OR elderly OR "middle-aged" OR "middle aged" OR "middle age" OR "middle-age")*
#4 (1 AND 2 (AND 4))

in which the bold terms are MeSH (Medical Subjects Headings) key terms. The search strategy was formulated with assistance of an experienced librarian. Since the EMBASE, ISI Web of Knowledge, CINAHL and PsycINFO databases do not have a MeSH key terms registry, the depicted strategy was modified for these databases.

Study Selection

Criteria for Considering Studies

(1) Type of intervention: studies were considered eligible for inclusion in the review when they evaluated biofeedback-based training of balance, posture and/or mobility. Biofeedback refers to measuring some aspect of human motion or electromyographic (EMG) activity and providing the subject, in real-time, with feedback information on the measured signal through the senses. Mobility refers to any activity that results in a movement of the whole body from one position to another, such as in transfers between postures and walking. Experimental studies that evaluated a single training session were excluded. (2) Type of study: studies were included when they compared the biofeedback-based training to similar training without biofeedback, conventional rehabilitation, an educational program or no intervention. Both randomized and non-randomized controlled trials were included. Case reports were excluded. (3) Type of participants: studies were

considered when they included older adults. Studies in which the mean age of one of the subject groups was below 60 years were excluded. (4) Type of outcome measures: studies were selected for reviewing when they used an objective measure of balance, posture or mobility in the outcome assessment. Studies that only used measures of muscle force, EMG activity or isolated movements of body segments were excluded.

Selection Procedures

The titles and abstracts of the results obtained by the database search were screened by 2 independent reviewers (AZ & MM). The full-text articles of potentially relevant references were independently retrieved and examined. A third reviewer (WZ) resolved any discrepancies.

Quality Assessment and Analysis of Relevant Clinical Trials

The quality of selected studies was rated with use of the PEDro scale (see table 1 for a description of the different items). The scale combines the 3-item Jadad scale and the 9-item Delphi list, which both have been developed by formal scale development techniques. In addition, "fair" to "good" reliability (ICC = .68) of the PEDro scale for use in systematic reviews of physical therapy trials has been demonstrated[19]. The scale consists of 10 items (items 2-11) that assess the internal and statistical validity of a clinical trial and another item (item 1) that relates to the external validity of a trial. The PEDro score is derived from adding all items on internal and statistical validity (items 2-11). A total score for the external validity was obtained by adding the score on the criterion of the PEDro scale (item 1) to the score on an additional criterion (see table 1, item 12), that was derived from a checklist by Downs & Black[20]. A point was awarded when a criterion was satisfied on a literal reading of the study report. Two reviewers (AZ & MM) independently scored the methodological quality of included clinical trials and a third reviewer (WZ) resolved any disagreements.

Criteria of the PEDro scale:

External validity

1. *Eligibility criteria were specified.*

Internal and statistical validity

2. *Subjects were randomly allocated to groups.*
3. *Allocation was concealed.*
4. *The groups were similar at baseline regarding the most important prognostic indicators.*
5. *There was blinding of all subjects.*
6. *There was blinding of all therapists who administered the therapy.*
7. *There was blinding of all assessors who measured at least one key outcome.*
8. *Measurements of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.*
9. *All subjects for whom outcome measurements were available received the treatment or control condition as allocated, or where this was not the case, data for at least one key outcome were analyzed by "intention to treat".*
10. *The results of between-group statistical comparisons are reported for at least one key outcome.*
11. *The study provides both point measurements and measurements of variability for at least one key outcome.*

Additional criterion external validity:

12. *The staff, places and facilities where the patients were treated, were representative of the staff, places and facilities where the majority of the patients are intended to receive the treatment.*

Table 1: *Criteria that were used in rating methodological quality of relevant studies.*

A standardized form was then developed to extract relevant information from the included articles. A first version was piloted on a subset of studies and modified accordingly. For evaluating whether applying biofeedback during training of balance and mobility-related tasks in older adults leads to larger improvements, studies were considered that compared training with application of biofeedback to similar training without biofeedback or that compared an experimental training with application of biofeedback to conventional training. In analyzing the intervention outcomes, measures were considered that rate some aspect of balance, posture or mobility; overall functioning; balance confidence and number of falls.

Results: older healthy adults

Search Results

A flow diagram of the search and selection process is depicted in figure 1. A number of studies did fulfill the criteria for type of intervention and population but did not meet the other criteria and were excluded[21-34]. An overview of these excluded studies is given in table 2. In total, 19 controlled trials[35-55] met all of the criteria and were selected for reviewing. The descriptive characteristics are summarized in table 3.

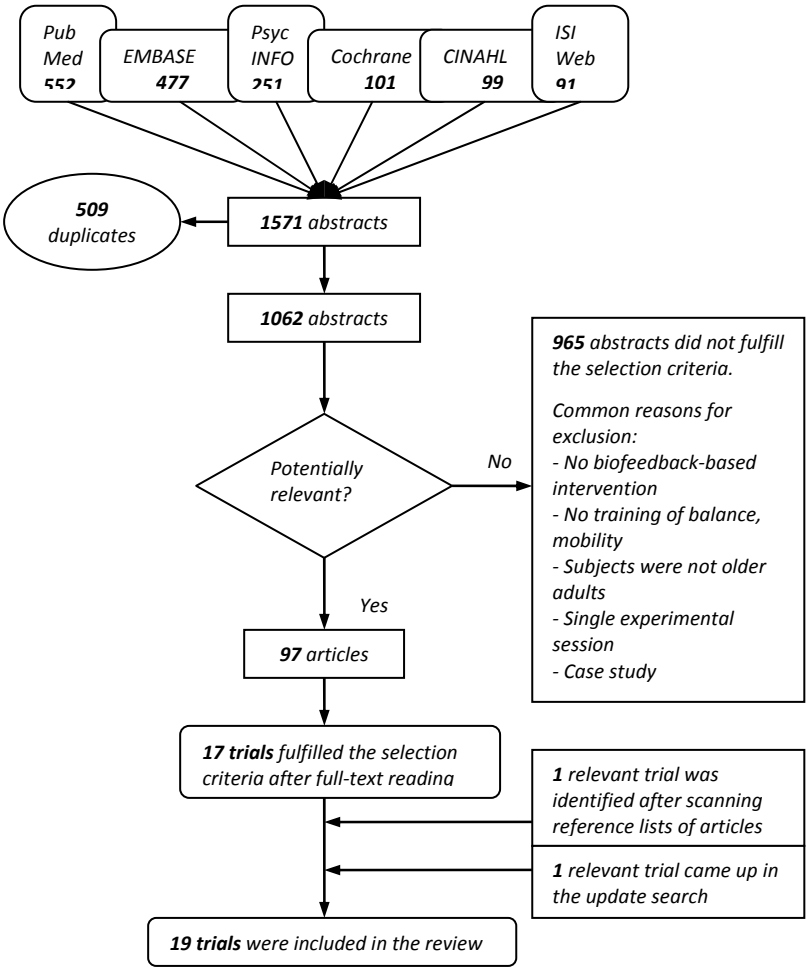

Figure 1: *Procedure for the study selection with utilized databases for the literature search.*

Authors	*Reason for exclusion*
Bisson et al[21]	*Comparison of biofeedback vs. virtual reality training*
Burnside et al[22]	*No objective measure of balance, posture or mobility*
Eser et al[23]	*No objective measure of balance, posture or mobility*
Fields[24]	*No objective measure of balance, posture or mobility*
Gapsis et al[25]	*No objective measure of balance, posture or mobility*
Hamman et al[26]	*No control group with older adults*
Kuiken et al[27]	*No control group*
Lindemann et al[28]	*BF training was compared to home-based exercise*
Mudie et al[29]	*Training of sitting balance*
Santilli et al[30]	*No objective measure of balance, posture or mobility*
Ustinova et al[31]	*No control group with older adults*
Wissel et al[32]	*No objective measure of balance, posture or mobility*
Wolf et al[33]	*No objective measure of balance, posture or mobility*
Wolfson et al[34]	*Comparison does not allow for evaluating BF-part*

BF = biofeedback

Table 2: *Excluded studies with reasons for exclusion*

Sixteen studies were randomized controlled trials (RCTs). The number of subjects in the experimental group was small to moderate, i.e. varying from 3-30 subjects. Twelve studies were in patients with stroke and 4 were in older adults that did not have a specific pathology but, for instance, had a history of falls[48], were relatively inactive[54], or were considered 'frail'[52]. Other type of participants were patients with a below-knee amputation[41]; patients with full weight-bearing instruction[44], i.e. patients with a below- or above-knee amputation, total hip or knee replacement, and femoral neck fracture; and patients with partial weight-bearing instruction[43], i.e. patients with hip arthroplasty, hip nailing, tibial plateau or acetabular surgery.

Six studies evaluated training of gait with application of different types of biofeedback, i.e. auditive feedback of the base of support, step length, the weight on the leg or the knee angle; continuous visual and auditive feedback of EMG activity of trunk and leg muscles. Ten clinical trials studied balance training on a force plate system with continuous visual feedback of performance. Engardt et al[39] evaluated sit-to-stand and stand-to-sit training with auditive feedback of the weight on the paretic leg. The 2 remaining trials studied an intervention consisting of sit-to-stand as well as balance

training and used a force plate system with display to provide visual feedback of weight-bearing on the legs.

Besides parameters of gait and force plate-based measures of balance, rising and sitting down, standard balance and mobility tests were used to assess the effect of the biofeedback-based intervention. These included the Sensory Organisation Test (SOT) and 100% Limits of Stability test (100%LOS), Berg Balance Scale (BBS), Timed Up & Go test (TUG), and maximum gait velocity test. Furthermore, studies estimated the effect on motor function[36, 39, 47, 49], activities of daily living (ADL)[36, 39, 49], physical activity level[51], fear-of-falling or balance confidence[45, 51, 54], and on number of falls during a follow-up period[37, 38, 51].

Table 3: *Characteristics of included (non)-randomized controlled trials that evaluate biofeedback-based training of balance and mobility in older adults.*

A. Training of gait and gait-related activities

Reference Location	Design	Population Mean age (years)	Equipment	Biofeedback type, comparison group(s)	Frequency Duration	Short-term outcomes
Aruin et al[35] 2003 USA	RCT	Patients with stroke and narrow base of support during walking 65	2 sensors placed below knees and next to tibial tuberosity & wearable unit providing signals	Auditive feedback of distance btw knees during conv. therapy vs conv. therapy	2x day, 10 days 25 minutes Total: 500 min	Step width during walking
Bradley et al[36] 1998 UK	RCT	Patients with stroke E1 = 67, E2 = 72, C1 = 77, C2 = 68 [b]	Portable EMG device	Auditive & visual feedback of muscle tone during conv. therapy vs conv. therapy	18x, 6 wks ? minutes	Step length, stride width, foot angle during walking & RMI & Nottingham Extended ADL Index
Hershko et al[43] 2008 Israel	RCT	Patients with a fracture or surgery in a lower limb 68	SmartStep: in-shoe sole	Auditive feedback of weight on affected leg during PWB therapy vs PWB therapy, both followed by by conv. therapy	1x day, 5 days 35 minutes Total: 175 min	Weight on affected leg during walking & TUG
Isakov[44] 2007 Israel	RCT	Patients with a fracture or surgery in a lower limb E = 62, C = 66	SmartStep: in-shoe sole	Auditive feedback of weight on affected leg during FWB therapy vs FWB therapy	2x wk, 2 wks 30 minutes Total: 120 min	Weight on affected leg during walking
Montoya et al[46] 1994 France	RCT	Patients with stroke E = 64, C = 60	Walkway with lighted targets & locometer	Auditive feedback of step length vs same training without feedback, both in addition to conv. therapy	2x wk, 4 wks 45 minutes Total: 360 min	Step length of paretic side during walking
Morris et al[47] 1992 Australia	RCT	Patients with stroke and knee hyperextension E = 64, C = 64	Electrogoniometric monitor	Auditive feedback of knee angle during conv. therapy (phase 1) vs conv. therapy (phase 1), both followed by conv. therapy (phase 2)	1x wk, 4 wks 30 minutes Total: 600 min	Velocity, assymetry and peak knee extension during walking & MAS (gait)

B. Training of static balance[45, 50], dynamic balance[38, 48, 52], static & dynamic balance[41, 42, 53-55]

Reference Location	Design	Population Mean age (years)	Equipment	Biofeedback type, comparison group(s)	Frequency Duration	Short-term outcomes
Cheng et al[38] 2004 Taiwan	CT	Patients with stroke E = 61, C = 61	Balance Master: force plate system with display	Continuous visual feedback of COG & conv. therapy vs conv. therapy	5x wk, 3 wks 20 minutes Total: 300 min	Force plate: maximal stability during standing, varying vision and surface movement & rhytmic weight-shifting
Gauthier-Gagnon et al[41] 1986 Canada	RCT	Unilateral below-knee amputees E = 60, C = 65	Limb Load Monitor: pressure sensitive sole	Auditive feedback of weight on prosthesis during conv. therapy vs conv. therapy	1x day, 8 days 10 minutes Total: 80 min	Force plate: COP during standing, varying vision
Grant et al[42] 1997 Canada	RCT	Patients with stroke 65	Balance Master: force plate system with display	Continuous visual feedback of COG vs conv. balance training, both in in addition to conv. therapy	2to5x wk, max. 8 wks 30 minutes Total: 570 min (average)	Force plate: sway and symmetry during standing, varying vision. BBS, TUG, max. gait velocity test
Lajoie[45] 2004 Canada	CT	Older adults from residential care facilities or living in the community E = 70, C = 71	Force plate system with display	Continuous visual feedback of COP (feedback-fading protocol) vs no intervention	2x wk, 8 wks 60 minutes Total: 960 min	Force plate: COP and RT during standing with feet together. BBS, ABC
Rose & Clark[48] 2000 USA	CT	Older adults with a history of falls 79	Pro Balance Master system: force plate system with display	Continuous visual feedback of COG (feedback-fading protocol) vs no intervention	2x wk, 8 wks 45 minutes Total: 720 min	SOT, 100%LOS, BBS, TUG
Shumway-Cook et al[50], 1988 USA	RCT	Patients with stroke E = 66, C = 64	Force plate system with display	Continuous visual feedback of COP vs conv. balance training, both as part of conv. therapy	2x day, 2wks 15 minutes Total: 300 min	Force plate: sway during standing

Continued.

Reference Location	Design	Population Mean age (years)	Equipment	Biofeedback type, comparison group(s)	Frequency Duration	Short-term outcomes
Sihvonen et al[51, 52] 2004 Finland	RCT	Frail older women living in residential care homes E = 81, C = 83	Good Balance system: force plate system with display	Continuous visual feedback of COP vs no intervention	3x wk, 4 wks 20-30 minutes Total: 240-360 min	Force plate: COP during standing, varying vision and base of support & weight-shifting. BBS, fear-of-falling, activity
Walker et al[53] 2000 Canada	RCT	Patients with stroke E = 65, C1 = 62, C2 = 66	Balance Master: force plate system with display	Continuous visual feedback of COG and weight on the legs vs conv. balance training, both in addition to conv. therapy vs conv. therapy	5x wk, 3-8 wks 30 minutes Total: 450-1200 min	Force plate: sway during standing, varying vision. BBS, TUG, max. gait velocity test
Wolf et al[54] 1997 USA	RCT	Relatively inactive older adults from independent-living center E = 78, C1 = 78, C2 = 75	Chattecx Balance System: force plate system with display	Continuous visual feedback of COP vs Tai Chi chuan training vs educational sessions	1x wk, 15 wks 60 minutes Total: 900 min	Force plate: COP during standing, varying vision and base of support. Fear-of-falling
Yavuzer et al[55] 2006 Turkey	RCT	Patients with stroke E = 60, C = 62	Nor-Am Target Balance Training System: portable force plate system with display	Continuous visual feedback of COG & conv. therapy vs conv. therapy	5x wk, 3 wks 15 minutes Total: 225 min	Walking: time-distance, kinematic and kinetic parameters

C. Training of static balance & sit-to-stand[37]; sit-to-stand[39]; static, dynamic balance & sit-to-stand[49]

Reference Location	Design	Population Mean age (years)	Equipment	Biofeedback type, comparison group(s)	Frequency Duration	Short-term outcomes
Cheng et al[37] 2001 Taiwan	RCT	Patients with stroke E = 62, C = 63	Force plate system with voice instruction system, numerical LED and mirror	Visual feedback of weight-bearing symmetry, as part of conv. therapy vs conv. therapy	5x wk, 3 wks 50 minutes Total: 750 min	Force plate: duration, vertical force measures of sit-to-stand and stand-to-sit [c]
Engardt et al[39] 1993 Sweden	RCT	Patients with stroke E = 65, C = 65	Portable force plate feedback system	Auditive feedback of weight on paretic leg vs same training without feedback, both in addition to conv. therapy	3x day, 6wks 15 minutes Total: 1350 min	Force plate: symmetry of sit-stand and stand-sit. BI (self-care & mobility), MAS (sit-stand)
Sackley & Lincoln[49] 1997 UK	RCT	Patients with stroke E = 61, C = 68	Nottingham Balance Platform: force plate system with display	Continuous visual feedback of weight on the legs vs same training without feedback, both as part of functional therapy and in addition to conv. therapy	3x wk, 4 wks 20 minutes Total: 240 min	Force plate: symmetry, sway during standing. RMA, Nottingham ADL scale

[a] Frequency and duration of biofeedback-based training only

[b] Bradley et al: patients were divided into mild (C1, E1) and severe (C2, E2) subgroups according to their score on the RMI

[c] Cheng et al (2001): subjects were tested at the beginning of training and at 6-month follow-up

ABC = Activities-specific Balance Confidence scale, ADL = Activities of Daily Living, BI = Barthel Index, C = control group, COG = center of gravity, Conv. = conventional, COP = center of pressure, E = experimental group, EMG = electromyographic, 100%LOS = 100% limits of stability test, MAS = Motor Assessment Scale, Max. = maximum, P/FWB = partial / full weight-bearing, (R)CT = (randomized) controlled trial, RMA = Rivermead Motor Assessment, RMI = Rivermead Mobility Index, RT = reaction time, SOT = Sensory Organization Test, TC = Tai Chi group, TUG = Timed Up & Go test

Quality Assessment

Interrater agreement was 76% in assessing external validity and 89% in assessing internal and statistical validity. The main criteria on which disagreement occurred were representativeness of treatment staff, places and facilities; similarity of groups at baseline; and concealment of allocation.

Table 4 shows the total scores for methodological quality of the relevant studies. The eligibility criteria were specified by most authors, except by Cheng et al[37, 38], Aruin et al[35] and Isakov[44]. The places and facilities where the experimental session took place were in most cases representative of the places and facilities where the majority of the target patients are intended to receive the treatment. However, in the study by Rose & Clark[48], the experimental intervention was performed at a research laboratory. Furthermore, Aruin et al[35], Montoya et al[46], Lajoie[45] and Wolf et al[54] did not mention where the experimental sessions took place.

Table 4 : *Total quality assessment scores and summary of main results of included studies*

A. Training of gait and gait-related activities in older patients with stroke

Reference	Type of feedback	Quality[a] E | PEDro	Analysis, Main short-term results
Aruin et al[35] 2003	Auditive	0 | 5	rANOVA, sign. at $p < .05$, Significant difference between groups after the intervention, in favor of experimental group.
Bradley et al[36] 1998	Auditive & Visual	2 | 6	Mixed model rANOVA, sign. at ?, No significant between-group differences in any outcome measure.
Montoya et al[46]	Auditive	1 | 4	Factorial rANOVA [b], sign. at $p < .05$, Significant between-group 1994 difference; significant interaction between beginning/end and group; significant interaction between session and group, all in favor of experimental group.
Morris et al[47]	Auditive	2 | 8	Mann-Whitney *U*-test, sign. at $p < .05$, Significant between-group 1992 differences for motor function of gait after phase 1 and for peak knee extension after phase 2, in favor of experimental group.

B. Training of static balance[50], dynamic balance[38], static & dynamic balance[42, 53, 55] in older patients with stroke

Reference	Type of feedback	Quality[a] E | PEDro	Analysis, Main short-term results
Cheng et al[38]	Visual	1 | 5	rANOVA & post-hoc testing, sign. at $p < .05$, Significant between- 2004 group differences for measures of dynamic balance at posttest, in favor of experimental group.
Grant et al[42] 1997	Visual	2 | 6	rANOVA & post-hoc testing, sign. at $p < .05$, No significant between-group differences in any outcome measure.
Shumway-Cook et al[50] 1988	Visual	2 | 5	Chi-square test, sign. at $p < .05$, Significant between-group difference in change scores for 1 (lateral sway displacement) of 2 measures, in favor of experimental group.
Walker et al[53] 2000	Visual	2 | 7	rANOVA & post-hoc testing, sign. at $p < .05$, No significant between-group differences in any outcome measure.
Yavuzer et al[55] 2006	Visual	2 | 7	Mann-Whitney *U*-test, sign. at $p < .05$, Significant between-group differences in change scores for 2 (pelvic obliquity [c], peak vertical GRF paretic side) of 17 measures, in favor of experimental group.

C. Training of static balance & sit-to-stand[37]; sit-to-stand[39]; static, dynamic balance & sit-to-stand[49] in older patients with stroke

Reference	Type of feedback	Quality[a] E | PEDro	Analysis, Main short-term results [d]
Cheng et al[37] 2001	Visual	1 | 6	Student's *t*-test & Chi-square test, sign. at $p < .05$, Significant between-group differences in improvement [d], in favor of experimental group.
Engardt et al[39] 1993	Auditive	2 | 6	Student's *t*-test, sign. at $p < .01$ & Mann-Whitney *U*-test, sign. at $p <$ 05, Significant between-group differences in improvement for left-right symmetry while rising and sitting down and motor function of sit-stand, in favor of experimental group.
Sackley & Lincoln[49] 1997	Visual	2 | 7	Student's *t*-test & Mann-Whitney *U*-test, sign. at $p < .05$, Significant between-group differences in stance symmetry, ADL performance and motor function at posttest, in favor of experimental group.

D. Training of static balance[45], dynamic balance[48, 52], static & dynamic balance[54] in a population of older adults

Reference	Type of feedback	Quality[a] E | PEDro	Analysis, Main short-term results
Lajoie[45] 2004	Visual	1 | 5	rANOVA & post-hoc testing, sign. at $p < .05$, Significant between-group differences for RT during narrow-based standing and BBS score at posttest, in favor of experimental group.
Rose & Clark[48] 2000	Visual	1 | 3	Doubly multivariate rANOVA & post-hoc testing, sign. at $p < .05$ & between-group pre- to post-intervention effect sizes, Significant interactions between group and time, in favor of experimental group. Group differences were moderate to large.
Sihvonen et al[51, 52] 2004	Visual	2 | 7	rANOVA & Friedman's test, sign. at $p < .05$, Significant interactions between group and time, in favor of experimental group, for 2of6 dynamic- and 4of18 (most difficult conditions) static balance outcomes and the BBS score. Significant improvements in activity level and fear-of-falling in favor of experimental group.
Wolf et al[54] 1997	Visual	0 | 5	rANOVA with baseline balance measures and characteristics as covariates & post-hoc testing, sign. at $p < .05$, Significant between-group differences in improvement for 5of12 balance measures, in favor of experimental group.

E. Training of static & dynamic balance in older amputees[41], gait in older patients with PWB[43] / FWB[44]

Reference	Type of feedback	Quality[a] E | PEDro	Analysis, Main short-term results
Gauthier-Gagnon et al[41], 1986	Auditive	2 | 5	Mann-Whitney *U*-test, sign. at $p < .05$, No significant between-group differences [e].
Hershko et al[43] 2008	Auditive	2 | 6	Student's *t*-test & Chi-square test, sign. at $p < .05$, experimental group improved significantly in PWB and TUG time. Control group only improved significantly in TUG time.
Isakov[44] 2007	Auditive	1 | 5	Student's *t*-test, sign. at $p < .05$, Significant between-group difference in improvement, in favor of experimental group.

[a] E = score external validity (max. 2), PEDro = PEDro score, i.e. score internal and statistical validity (max. 10)
[b] Montoya et al: testing was performed at the beginning and end of each session
[c] Yavuzer et al: authors mentioned possible ceiling effect for pelvic obliquity in the control group
[d] Cheng et al (2001): subjects were tested at the beginning of training and at 6-month follow-up
[e] Gauthier-Gagnon et al: authors reported high inter- and intra-subject variability in sway measures for amputees
ADL = Activities of Daily Living, BBS = Berg Balance Scale, GRF = Ground Reaction Force, P/FWB = partial / full weight-bearing, rANOVA = repeated measures analysis of variance, RT = reaction time, sign. = significance

The PEDro scores ranged from 3 to 8 (out of 10). In 6 RCTs[36, 47, 49, 52, 53, 55], allocation of subjects into their respective groups was concealed. There were no indications that subjects did not receive the treatment or control condition as intended. For 7studies[35, 36, 41, 44, 46, 48, 50] it could not be determined that groups were similar at baseline regarding prognostic indicators. There was 1 study that adjusted for confounding in the analysis. In the study by Wolf et al[54], pre-intervention balance measures and subject characteristics were used as covariates to correct for baseline differences between groups. Blinding of subjects and therapists was not possible in any of the controlled trials. In only 2 articles[47, 55] blinding of assessors was

reported. In 2 studies[46, 55], post-intervention measurements were obtained from less than 85% of the subjects initially allocated to groups. In addition, for 2 other studies[48, 54], it was not clear whether there were any drop-outs. In the studies by Sihvonen et al[51] and Engardt[40], less than 85% of the subjects initially allocated to groups were available for follow-up testing.
Remarks on validity and/or reliability of outcome assessments were made in 10 studies[36, 41, 43, 44, 47-49, 52, 53, 55]. In particular, Isakov[44] conducted a separate study to establish the validity and reliability of the new in-shoe body-weight measuring device before applying it during an intervention. Bradley et al[36] also assessed the reliability of assessments in a pilot study prior to the intervention study. In addition, Sihvonen et al[52] estimated the reliability of dynamic balance tests by administrating the tests twice at baseline, with a 1 week interval. Furthermore, reliability was increased by using the best result out of 5 administrations for the analysis. A similar method was used by Rose & Clark[48] to increase diagnostic tests reliability. In obtaining baseline measures, they conducted the tests twice on consecutive days and only used the scores of the second administration for the analysis.

Short-term Effects of Biofeedback-based Training of Balance and Mobility

In total, 14 of the 19 included studies showed short-term positive effects, in one or more outcome measures, of biofeedback-based training of balance and mobility compared to the control condition(s) (see table 4). Heterogeneity existed in the outcome measures and testing conditions that were used to determine the effectiveness of the intervention. Nevertheless, there were 2 instances in which studies with similar type of subjects, training tasks and feedback used the exact same measure(s). Grant et al[42] and Walker et al[53] evaluated balance training on a force plate system with visual feedback of performance in older patients with stroke, both using the TUG, BBS and maximum gait velocity test as outcome measures. In another case, Sihvonen et al[52], Rose & Clark[48], and Lajoie[45] used the BBS to assess intervention outcome in their sample of older adults. All 3 studies showed positive effects of balance training with visual feedback of performance on the BBS score compared to the control condition(s).

Added Benefit of Applying Biofeedback during Training

Whether applying biofeedback during training of balance and mobility has short-term added benefit could be evaluated in 12 studies. In 3 studies, a wearable biofeedback system was applied during conventional gait rehabilitation in older patients with stroke. Bradley et al[36] did not find any additional effects compared to conventional rehabilitation without biofeedback, whereas Aruin et al[35] and Morris et al[47] did demonstrate added benefit of applying the biofeedback system. Furthermore, Montoya et al[46] showed positive effects of adding biofeedback during a gait training program that was performed in addition to the conventional rehabilitation. In the studies by Grant et al[42] and Walker et al[53], the application of visual biofeedback during additional balance training did not lead to larger effects than training without biofeedback in patients with stroke. However, Shumway-Cook et al[50], who evaluated similar training as part of the conventional therapy, reported larger improvements in a measure of static balance compared to conventional rehabilitation without any biofeedback. Added benefit of applying biofeedback in patients with stroke was also shown for force platform-based training of rising and sitting down[39], and of balance and sit-to-stand[37, 49]. In older patients with a fracture or surgery in a lower limb, addition of auditive feedback of weight on the injured leg during gait rehabilitation led to larger improvements in partial as well as full weight-bearing[43, 44].

Sustainability of Effects

A follow-up test was performed in 10 out of the 19 included studies. The follow-up period ranged from 2 weeks[45] to 33 months[40], with 2 studies[42, 53] that conducted a retest at 1 month; 3 studies[36, 49, 54] at 3 or 4 months; 2 studies[37, 38] at 6 months; and 1 study[51, 52] conducted a retest at 4 weeks and at 1 year.

In the study by Sihvonen et al[52], who included frail older women as subjects, improvements in balance measures after training on a force plate system with visual biofeedback were still maintained after 4 weeks. Similar

results were found in the study by Wolf et al[54] in relatively inactive older adults, in which improvements in 4 out of 5 measures of static balance were maintained after 4 months. In addition, Lajoie[45] demonstrated sustainability of improvements in reaction time during narrow-based standing and in the BBS score at a 2 week retention test. Training on a force plate system with visual biofeedback also led to sustainability of improvements in older patients with stroke. In the study by Cheng et al[38], effects were still maintained at 6 month follow-up in 2 out of 4 dynamic balance measures. In another study by Cheng et al[37], outcomes were not directly assessed after the intervention but were evaluated after 6 months. After 6 months, patients in the experimental group showed larger improvements in sit-to-stand and stand-to-sit performance.

The number of fall incidents during the follow-up period was recorded in 3 studies[37, 38, 51]. In the studies by Sihvonen et al[51] and Cheng et al[37], training with biofeedback led to positive results concerning falls compared to the control condition. The risk of falling and recurrent falls during 12 month follow-up were significantly lower (8% vs. 55%) in a group of older women that had received balance training with visual biofeedback compared to a group of older women that did not receive training[51]. In addition, fall occurences were significantly lower (17% vs. 42%) during 6 month follow-up in older patients with stroke that had received training of static balance and sit-to-stand with visual biofeedback[37].

Whether applying biofeedback during training of balance and mobility has long-term added benefit could be evaluated in 3 studies, all of which were in older patients with stroke. First, larger improvements in sit-to-stand performance and lower number of falls after 6 months were demonstrated for training of balance and sit-to-stand with addition of visual biofeedback in the study of Cheng et al[37]. However, in the study by Sackley & Lincoln[49], a similar type of training program did not lead to larger improvements in ADL performance and motor function after 3 months compared to training without biofeedback. Second, training of sit-to-stand with addition of auditive biofeedback led to larger improvements in movement time but not in weight-bearing symmetry at retesting 2 to 3 years after the intervention[40].

Feasibility of Biofeedback-based Training in Older Adults

One article[52] commented that balance training with visual feedback of the center of pressure is easily adjustable to the health limitations of older adults. On the other hand, Morris et al[47] mentioned that it is unlikely that their used method for providing auditive feedback in correcting knee hyperextension during gait training would be effective for patients with perceptual or cognitive problems. However, another article[49] mentioned that patients with severe, communication problems easily understood the visual feedback information of weight-bearing that was provided during balance and sit-to-stand training. The patients seemed to grasp the concept of the training more effectively than in conventional stroke treatment. In the same study, patients commented that they enjoyed the biofeedback-based training because they knew exactly what they were required to achieve and could judge the results for themselves. Furthermore, the older patients were not frightened by the exposure to the 'new' biofeedback equipment. In 3 studies, on force plate-based training with visual feedback[52, 55] and gait training with EMG feedback[36], the compliance to the training regime was evaluated. All 3 studies reported a high participation rate.

Results: patients with Parkinson's disease

Search Results

Among the excluded studies for the afore-mentioned criteria we selected those studies that treated patients with PD. Five studies evaluated different types of biofeedback in PD subjects, and characteristics are summarized in Table 5.

McIntosh G et al., found that gait velocity, cadence, and stride length improved in PD ON and OFF medication using rhythmic auditory stimulation with respect to a baseline parameters values.
Ioffe ME et al., investigated impairments on the learning of voluntary control of center of pressure using visual feedback in PD and hemiparetic patients. Even if the main aim of this paper was focus on the learning process, they found that during training the rate of displacement of center of pressure and accuracy increase in PD patients, meaning that some degree of learning is still preserved in these patients.
Novak P. Et al., demonstrated that vibration stimulation of the foot soles synchronized with the step increased the walking speed and improved the stride variability in PD subjects. In addition, vibration stimulation prolonged the stride interval and the stride length.
Van Wegen E. Et al., examined the effect of somatosensory cueing on the stride frequency (cadence) of patients with PD finding that rhythmic somatosensory cueing, consisting in a miniature vibrating cylinder attached to the wrist, can effectively be used to lower the cadence while maintaing walking speed, which is equivalent to an increase in stride length.
Nieuwboer A. Et al., demonstrated that nine sessions of cueing training have considerable improvement in gait and gait-related mobility in PD, however these effect were small and specific. Immediately after the training, a significant increase in walking speed and step amplitude accompanied by a tendency to reduce step frequency were found. An important finding of this study regards freezers. In fact, they found a significant change on the Freezing of Gait questionnaire after intervention, signifying a reduction of freezing severity. Although the effects of the

training were maintained after the 3 weeks of training, such effects were not sustained after 6 weeks of follow-up.

***Table 5**:* Characteristics of non included studies on the experimentation of biofeedback systems in PD patients

Reference	*Group size*	*Equipment*	*Biofeedback type*	*Frequency duration*	*Outcome*
McIntosh GC et al., 1997	21 PD OFF&ON 10 CTRL	Foot switch system	Rhytmic auditory stimulus (RAS) matched to each patients baseline cadence.	Four gait trials: 1) Baseline 2) RAS to baseline cadence 3) RAS to 10% faster than baseline 4) no RAS	Spatio-temporal gait parameters.
Ioffe ME et al., 2004	33 PD 20 hemiparesis 13 CTRL	Force plate (Stabilan-01 computer stabiloanalyzer) with visual feedback	Visual feedback (training with two stabilographic games)	Daily repetition for 10 days	Two parameters of voluntary postural control: "performance" and "learning"
Novak P et al., 2006	8 PD ON 8 CTRL	Foot insoles with vibratory devices (VD) embedded.	Vibration stimulos on the sole of the foot upon touch of the heel of forefoot.	Two gait trials: 1) 6 min gait with VD off 2) 6 min gait with VD on	Spatio-temporal gait parameters.
Van Wegen E et al., 2006	17 PD ON	Treadmill	Rhythmic somatosensory cueing and visual flow	Four treadmill walking: 1) Baseline, no visual flow, no RSC 2) Visual flow, no RSC 3) RSC, no visual flow 4) Visual flow with RSC	Stride frequency
Nieuwboer A et al., 2007	153 PD divided in 2 groups: a) early intervention (n=76) b) late intervention (n=77)	Cueing device for gait and gait related activities	Three rhythmic cues modalities: 1) auditory (a beep delivered through an earpiece) 2) visual (light flashes delivered through a ligth emitting diode attached to a pair of glasses) 3) somatosensory (pulsed vibrations delivered by a miniature cilinder worn under a wristband)	Early Intervention: Nine treatment sessions, for 30 min over 3 weeks, immediately followed by 3 weeks in which no training was administered. Late intervention: same treatment reverse order. Follow up of 6 weeks without treatment.	1) Posture&Gait score of UPDRS items (qualitative) 2) Gait & Balance measure (quantitative and qualitative) 3) Activity measures (qualitative) 4) Participation measures (qualitative)

Discussion

The primary aim of the present systematic review was to evaluate the effectiveness of currently available biofeedback methods for training balance and mobility-related tasks in populations of older adults. After a broad literature search, 19 studies were identified that met the criteria for inclusion. Although the present literature review has been conducted as a systematic review, some potential sources of bias, such as language and publication bias, may have influenced the results. In addition, one or more relevant studies may have been overlooked since literature was searched for in a limited amount of sources. Non-reporting of details in the identified articles contributed to a lack of a 100% agreement between raters in scoring methodological quality.

Since no selection criteria were applied regarding type of participants, besides the criterium of a mean age of 60 years or higher, the studies included older adults that had balance and mobility disorders due to a specific medical cause, such as a stroke incident, but also older adults without a specific pathology. A large variety existed between studies in the measures and testing conditions that were used to evaluate improvement after the intervention, therefore a quantitative, statistical pooling of data of different studies was not performed. Since there were also no large-scale RCTs among the included studies, no definitive conclusions can be made. However, some positive indications concerning the effectiveness of biofeedback-based therapy, for supporting performance of balance- and mobility-related activities, in the older population can be identified.

Effect of Visual-feedback Balance Training in Frail Older Adults

Four studies[45, 48, 52, 54] evaluated training of static and/or dynamic balance tasks on a force plate system in older adults. Three of these studies, respectively involving frail older women[52], older adults with a history of falls[48], and older adults from residential care and the community[45], used the BBS to evaluate improvement after the intervention. Based on their results, there are indications for short-term positive effect of visual-feedback

balance training on a clinical measure of balance in different groups of 'frail' older adults. However, since the studies compared the experimental group to a control group that did not receive any training, it cannot be determined whether the improvement was specifically due to biofeedback-based training.

Added Benefit of Applying Biofeedback for Therapy in Older Patients with Stroke

None of the studies that compared biofeedback-based training to similar training without biofeedback demonstrated significantly larger improvements for training without biofeedback. Several remarks on adding biofeedback information during training in older patients with stroke can be made. First, indications for added benefit of training gait with biofeedback were found in 3 of the available studies[35, 36, 46, 47], of which one scored high on methodological quality[47]. Second, based on 3 available studies[42, 50, 53], conventional balance training seems just as effective as biofeedback-based training of balance. Shumway-Cook et al[50] did report significant added effect of biofeedback-based training on lateral sway displacement during standing; however, their study was rated low on quality and was in a small number of subjects. Third, based on positive results of 2 available controlled trials[37, 49], indications for added benefit of applying biofeedback were found for training consisting of balance tasks as well as sit-to-stand exercises. In addition, for older patients with an injury in the lower limb, applying biofeedback information on weight-bearing of the leg during gait rehabilitation seems more effective to train partial or full weight-bearing compared to conventional methods[43, 44]. The available studies do not provide clear indications regarding the long-term (non-) benefit of adding biofeedback for training of balance and mobility in older adults.

Generalization of Training Effects to Functional and Fall-related Measures

Based on results of 4 studies[43, 45, 48, 52], there are indications that positive effects of biofeedback-based training are generalized to improved performance on a clinical test of balance or mobility. In addition, it seems that demonstrated added effect of training with biofeedback is generalized

to measures of motor functioning[39, 49]. However, the included studies do not provide clear indications on whether effects on objective measures of balance and mobility are generalized to measures of fear-of-falling[45, 51, 54] and number of falls[37, 38, 51]. In a large-scale RCT by Wolf et al[33], improvements after balance training with visual biofeedback in community-dwelling older adults were evaluated on the number of falls throughout the study period. Based on their results, training with biofeedback does not seem to lead to reduced fall incidents. However, they did not include objective measures of balance and mobility. It is therefore unclear whether improvements in balance and mobility after biofeedback-based training in older adults are also reflected in a reduced incidence of falls.

Practical Feasibility of Applying Biofeedback-based Training in Older Adults

None of the included controlled trials evaluated the practical applicability of training with biofeedback in older adults with age-related health limitations. In a non-controlled study by Kuiken et al[27], a patient satisfaction survey was used to evaluate user acceptance of wearing a biofeedback goniometer for post-total knee arthroplasty rehabilitation. Application of the device in the older patients appeared feasible. The device was well accepted by the patients and the majority evaluated the auditory feedback as useful and helpful in encouraging exercise.

Despite the lack of feasibility assessments, force plate-based training of balance with visual feedback seems suitable for application in older adults that are living in residential care homes. Sihvonen et al[52] reported high compliance, indicating that participants were motivated to participate and that adherence to the schedule of 3-times-a-week was feasible for them. In addition, training symmetrical weight distribution with use of visual feedback after stroke seems especially suitable for patients that, due to severe communication problems, normally have difficulties in understanding the concept of the training[49]. On the other hand, there are also indications of limited applicability of biofeedback-based training in certain groups of older adults. Both in the study by Sihvonen et al[52] and in the study by Morris et al[47], who studied the addition of auditive feedback of knee hyperextension for conventional gait rehabilitation, older adults with perceptual or cognitive problems were not included. Due to a lack of

feasibility assessments in the available biofeedback studies, there are no clear indications yet regarding the practical suitability of applying biofeedback-based training in geriatric practice.

Conclusions and Future Directions

Based on a qualitative analysis of relevant studies up to september 2008, indications for larger short-term effects with addition of biofeedback were found for training of weight-bearing during walking in older patients with an injury in the lower limb, and for rehabilitation of gait and of balance in combination with sit-to-stand transfers in older patients with stroke. In addition, for older patients with stroke, indications were found for similar effectiveness of biofeedback-based and conventional balance training. No clear indications were found regarding the long-term (non-) added benefit of applying biofeedback for balance and mobility training and regarding the effects in other populations of older adults. Besides applying a control-group comparison of biofeedback-based training to similar training without biofeedback, further studies should 1) optimize the research quality, 2) include a large number of participants, 3) use functional outcome measures of balance and mobility and outcome measures with particular relevance to patients, 4) apply follow-up of participants during at least 6 months to determine the sustainability of any improvement, and 5) evaluate the practical feasibility of the biofeedback-based intervention for application in geriatric practice.

In most of the studies that were included in the review, the effects were determined in a hospital or laboratory setting. Larger effects may be observed when applying biofeedback-based training for a prolonged period of time in the own living environment of patients. The current objectives of EU-funded, 6th framework programme (FP6) projects on Ambient Assisted Living (AAL) require home-based technology systems that comply with criteria of portability and user friendliness. Only 3 studies[35, 43, 44] that were included in the present review, both on gait training, used a biofeedback device that allowed for complete wearability of the system. However, recent progress in technology for wearable, wireless systems to monitor

human motion[56] should facilitate the development of biofeedback systems that can be used in the home environment of target participants.
Based on a qualitative analysis, the authors cannot give evidence-based recommendations for suitable biofeedback modalities. Nevertheless, some directions can be formulated based on practical considerations. For wearable systems, head-mounted displays can be used for providing visual feedback (e.g. virtual-reality goggles[57]). However, a visual display can interfere with normal gazing behavior and therefore create unnatural circumstances. For audio-biofeedback systems, the challenge is to come up with an audio signal that also allows for normal hearing of sounds of the environment. Light, wireless bone-conducting devices may come out as an elected solution in future studies. In avoiding the aforementioned limitations of biofeedback systems based on visual or audio signals, the application of vibro-tactile actuators[58] for providing feedback during therapy could also be considered as an alternative for older adults with intact somatosensory functioning.

Effect of Audio-Biofeedback in maintaining balance in Parkinson's disease: preliminary results

From the amount of studies found in literature it is possible to appreciate the variety of biofeedback designs implemented up to now and the different pathologies they have been tested on.
In particular, regarding augmented-feedback for improving postural stability visual-biofeedback has been extensively used for balance rehabilitation of subjects after stroke[38,42,50,53] in order to reduce postural asymmetry. In addition, visual biofeedback from force plate measurements is the only biofeedback system commercially available and diffused.
In fact, systems made by Neurocom (http://www.onbalance.com/), such as Balance Master, which are currently used for balance training and rehabilitation, are equipped with visual-biofeedback. Recently, the interest in biofeedback design is moving from the visual-biofeedback of force plate measurements to audio- and tactile-biofeedback of inertial sensors measurements[11,59-63]. This new trend in the design is driven by the intent of producing new cost-effective and portable systems for balance training and rehabilitation. In fact, tactile and auditory feedback do not rely on some expensive and cumbersome monitor, and do not require power supply cabling; further, inertial sensors are one thousand times less expensive than force plates and much smaller and portable.

A new audio-biofeedback device (ABF)[64] is currently being tested in PD patients in maintaining balance in static conditions.
Six subjects with PD and 3 age-matched control subjects participated in the study. They were asked to stand quietly with eyes closed. This ABF system uses a palmtop to generate a stereo sound coding the subjects' trunk accelerations sensed by a tri-axial accelerometer (Fig. 2).

***Figure 2**: Subject during the ABF trial*

The postural sway was monitored by the accelerometer. The subject was tested prior (CONDITION: pre), during (ABF), and after (post) the delivery of the ABF. During the trials with ABF, subjects were asked to correct their sway according to the feedback, by keeping the volume as low and as balanced as possible.

A preliminary analysis to study efficacy of ABF to reduce postural sway, was carried out with a main focus on the following parameters, computed from the 2D trunk acceleration: 1) smoothness of sway (JERK), 2) extent of sway (RMS), 3) the frequency below which the 95% of the power of the signal is included (F95%), and 4) direction of maximum sway (Mdir).

Figure 3 shows 2D trunk acceleration in the 3 described condition for a representative PD subject. The amplitude sway was smaller in ABF and post condition with respect to pre condition.

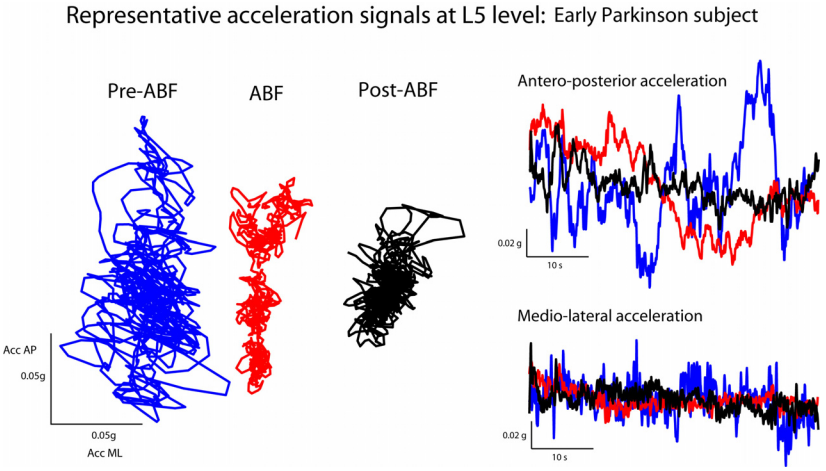

Figure 3: *Trunk acceleration in a representative PD subject in the 3 conditions.*

Jerk in PD is larger with respect to control subjects (Fig. 4). The observed decrease in Jerk in PD in 5 subjects less 1, with ABF treatment, reflects an increased smoothness of movement (more fluid trunk movements); this is preserved even (shortly) after the end of the ABF.

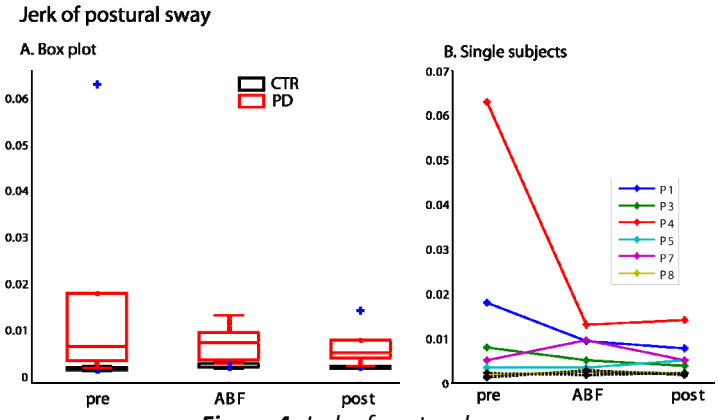

Figure 4: *Jerk of postural sway*

In addition, RMS (Fig. 5), which reflects variability, tends to be reduced in PD during ABF with respect to the pre condition. This suggest that ABF might act to improve regularity of trunk sway; this regularity is only partly maintained after the ABF treatment.

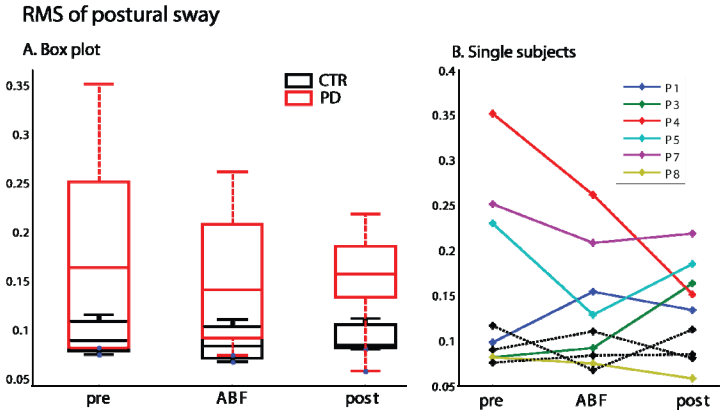

Figure 5: *RMS of postural sway*

PD subjects found the system easy-to-use and adequate, and they were able to correctly follow the audio information, when available. Properties of trunk sway became more physiological (i.e. much closer to CTR sway: smoother and more regular) during trials with ABF.

Although these results are preliminary, they are promising looking forward to an ongoing extended campaign for the clinical validation of the ABF device among the clinical partners of the EU-funded SENSACTION-AAL project.

The development of tele-care exercises to train and facilitate additional motor tasks like gait and postural transfers, that highly impact on the quality of life, are desirable on such population of PD patients and, in general, on elderly people at large, with the aim of improving their mobility and independence, especially in the home environment.

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Chapter 11

Conclusions

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Several factors contribute to postural impairments in PD patients, including disturbed postural reflexes, sensory deficits, posture-kinetic coordination impairments.

PD reduces functional limits of stability as well as the magnitude and velocity of postural preparation during voluntary, forward and backward leaning while standing. Levodopa improves the limits of stability but not the postural strategies used to achieve the leaning (see Chapter 2). Our results highlight the importance of a quantitative approach for postural evaluation in PD. In fact, the lack of correlation between the UPDRS Motor subscale and limits of stability parameters is consistent with poor specificity of the UPDRS Motor subscale for the postural requirements associated with a voluntary lean. Forward voluntary leaning may be a good clinical measure of postural ability in PD by reflecting composite effects of segment orientation, perceived postural stability, fear of falling, whole body kinaesthesia and leg rigidity. Further, ..

In addition, we showed that preparation for step initiation from wide stance was associated with a larger lateral and backward center of pressure displacement than from narrow stance. Subjects with PD did scale up the size of their APA with stance width, they had much more difficulty initiating a step from a wide stance than from a narrow stance, as shown by the greater differences from control subjects in the magnitude of the APA. These results support the hypothesis that PD subjects maintain a narrow stance as a compensation for their inability to sufficiently increase the size of their lateral APA to allow speedy step initiation in wide stance.

Since motor impairments in subjects with PD are strongly time-varying and context-dependent traditional approaches based on sample observations taken in a (movement analysis) laboratory setting may have a limited validity. In order to allow to measure static and dynamic balance without the use of force platform and also outside the laboratory environment we presented an accelerometers-based approach (see Chapter and). Such ambulant measures might be helpful in remote monitoring in elderly or person with balance disorders and also in monitoring progress during balance training at home.

Our studies also showed that balance and anticipatory postural adjustments prior to a step are affected in early, untreated PD (see Chapter and). Quantitative analysis of quiet stance and step initiation by means of

one accelerometer on the trunk could provide useful information for the characterization of patients in early stages of PD, when clinical evidence of start hesitation may not be detectable. Ambulatory monitoring of step initiation is also promising for monitoring patient progression in the home environment, and eventually providing feedback for preventing freezing of gait episodes.

Furthermore, analyzing the literature with a systematic review, we found indications for positive effects of biofeedback-based therapy, for supporting performance of balance- and mobility-related activities, in the older population. Also, evaluating an existing audio-biofeedback device we showed that PD subjects found the system easy-to-use and adequate, and they were able to correctly follow the audio information, when available. Properties of trunk sway became more physiological (i.e. much closer to control sway: smoother and more regular) during trials with ABF. Although our results are preliminary, they are promising looking forward to an ongoing extended campaign for the clinical validation of the ABF device among the clinical partners of the EU-funded SENSACTION-AAL project.

The results and conclusions reported above constitute a brief summary of this thesis. The aforementioned results bring inside new knowledge in order to: i) better understand the central mechanisms that control postural motor performances and how these mechanism are affected in PD patients and with levodopa replacement; ii) quantitative, sensitive measures of postural impairments in PD are needed to characterize the pathology from the early stages of the disease, when the typical symptoms are not yet clearly manifested and not yet evaluable from a naked clinical eye. The merits of such quantitative measures are numerous: - diagnostic, in order to help in early detection of disease; - therapeutic, in order to assess the benefit of tailored treatments in an objective way; long-term, in order to monitor disease progression and improving understanding of the pathophysiology.

A promising area of interest could be the development of tele-care exercises to train and facilitate additional motor tasks like gait and postural transfers, that highly impact on the quality of life, in PD patients and, in general, on elderly people at large, with the aim of improving their mobility and independence, especially in the home environment. These specific exercises might consist of performing functional tasks aided by augmented

feedback and the use of cognitive strategies. By choosing essential mobility related tasks, it is expected that the training will not only results in a better performance of the tasks that were trained, but also in improved performance of other mobility tasks. Then, the outcomes of the feedback training need to be correctly evaluated and compared at the different stage of the rehabilitation program. Obviously, a key requirement is the use of portable sensors in order to provide quantitative measures of daily life motor activities valid in the clinic but also in a home environment.