Parkinson´s Disease and Dual-task: Implications on Motor and Postural Control

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"Sou o resultado da confiança e da força de cada um de vocês"

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ABSTRACT

Parkinson's disease (PD) is considered the second most common neurodegenerative disorder worldwide. PD is being diagnosed earlier and it may even appear in early adulthood. Thus, it is extremely important to learn more about this disease in order to improve the intervention processes, and thus help sustain the autonomy of affected individuals. Although motor skills, whether in movement or in maintaining balance have been considered the primarily affects of PD, an increasing emphasis is now being given to the impairment of cognitive abilities and performance deficits in dual-tasks.

This PhD project focused on two main objectives. The first is related to the importance of intervention using cognitive-motor dual-task training and its benefits on motor and cognitive performance in PD. The second objective is related to the impact that the addition of a cognitive task, i.e. the dual-task, may have in maintaining balance, as well as in performing daily life tasks.

This thesis is organized into two parts: the first part, identified as Part A, introduces the theme, cites the main objectives, provides a brief description about the work developed, indicates the main contributions achieved, presents the findings and indicates prospects for future work. The second part, Part B, consists of seven articles that were produced during this project to answer the objectives defined, and gives further details of the work introduced in Part A.

In order to meet the first objective defined for this project, three articles were produced. The first article presents a systematic review concerning cognitive-motor dual-task interventions. Half of these studies evaluated balance, executive functions and functionality with effective results, but the duration and intervention, particularly in the control group, were not consistent. The second article refers to cognition as a balance predictor. We found explanatory models of balance deficits, which showed that the psychomotor speed, visuospatial skills, attention and working memory can be considered predictors of balance in PD. After this article, we decided that the participants of further studies in this project should not present any cognitive deficits. The third article concerns a randomized clinical trial with a cognitive-motor dual-task intervention in individuals with PD. The results indicated that training with dual-task had better results than single-task training for most of the variables analysed.

The remaining four articles have tried to respond to the second objective, related to the effects of cognitive tasks, defined for this project. The fourth article focuses on the influence of dual-task in maintaining balance. This article shows that static balance in individuals with PD is worse than in controls, particularly when performing dual-task, and that performance depends on the type of cognitive task. The fifth article demonstrates that individuals with PD may have to prioritize tasks, when in the presence of a cognitive task simultaneously with gait initiation. The results suggest that individuals in the early stages of PD may prioritize the motor task (gait initiation), as they have a similar performance to controls, but this decreases the performance of the cognitive task that was significantly lower than in controls. The sixth article refers to the influence of dual-task on postural control in gait initiation. The anticipatory postural adjustments during gait initiation were found to be affected in individuals with PD. This was shown by the failure of the tibialis anterior to activate in single- and dual-task conditions. The seventh and final article studied the postural reorganization of individuals with PD when performing dual-task in the five phases of sit-to-stand-to-sit movement. The individuals with PD showed more difficulties in the performance of 4 of the 5 phases, which became even more evident when they performed a cognitive task simultaneously.

Throughout the development of this PhD project various changes at different levels were found in individuals with PD. The motor and postural control is affected by the addition of a cognitive task, i.e. in performing dual-task. However, this deficit can be improved through dual-task cognitive-motor interventions.

Keywords: Balance, Dual-task, Gait initiation, Motor Control, Sit-to-Stand-to-Sit movement.

RESUMO

A Doença de Parkinson (DP) é considerada a segunda patologia neurodegenerativa mais frequente em todo o mundo. O seu diagnóstico é cada vez mais precoce e surge ainda na idade adulta. Assim, é de extrema importância melhorar os conhecimentos sobre esta patologia de forma a aperfeiçoar a avaliação e intervenção com o objetivo de manter a independência dos indivíduos afetados. Apesar de se ter vindo a considerar que a DP afeta primariamente as capacidades motoras, seja em movimento ou na manutenção do equilíbrio, uma ênfase crescente está a ser dada ao comprometimento da capacidade cognitiva e aos défices de desempenho em dupla-tarefa.

Este projeto de Doutoramento centrou-se em dois objetivos principais. O primeiro está relacionado com a importância da intervenção com recurso a dupla-tarefa cognitivo-motora e os seus benefícios no desempenho motor e cognitivo na DP. O segundo, com o impacto que a adição de uma tarefa cognitiva, isto é a dupla-tarefa, pode ter na manutenção do equilíbrio, assim como na execução de tarefas.

Esta Tese está organizada em duas partes: a primeira parte, designada por *Part A*, introduz o tema deste projeto de Doutoramento, refere os seus objetivos principais, descreve sumariamente o trabalho desenvolvido, indica os principais contributos, apresenta as conclusões e aponta perspetivas de trabalho futuro. A segunda parte, designada por *Part B*, é constituída 7 artigos que foram produzidos para dar resposta aos objetivos definidos e descreve detalhadamente o exposto na *Part A*.

De forma a dar resposta ao primeiro objetivo foram realizados três trabalhos. O primeiro artigo apresenta uma revisão sistemática sobre as intervenções com recurso a dupla-tarefa cognitivo-motora. Verificou-se que metade dos estudos avaliavam equilíbrio, funções executivas e funcionalidade com resultados significativos, mas a duração e a forma de intervenção especialmente no grupo controlo não era consistente. O segundo artigo refere-se a cognição como preditor do equilíbrio. Encontraram-se modelos explicativos dos défices de equilíbrio, que mostraram que a velocidade psicomotora, as competências visuo-espaciais, a atenção e a memória de trabalho podem ser considerados preditores do equilíbrio na DP. Após este artigo considerou-se importante que os participantes deste projeto não apresentassem défice cognitivo. O terceiro artigo consiste num ensaio clínico randomizado de uma intervenção com recurso a dupla-tarefa cognitivo-motora em indivíduos com DP. Os resultados indicaram que o treino

com recurso a dupla-tarefa tem melhores resultados do que o treino com recurso a única-tarefa para quase todas as variáveis analisadas.

Os restantes quatro artigos tentaram dar resposta ao segundo objetivo. Assim, o quarto artigo foca a influência da dupla-tarefa na manutenção do equilíbrio. Demonstrou que o os indivídiduos com DP apresentam maior instabilidade postural do que em controlos e que esta diferença aumenta aquando a realização de dupla-tarefa. O quinto artigo reporta a possível capacidade que os indivíduos com DP têm para priorizar tarefas, aquando a presença de uma tarefa cognitiva em simultâneo com o início da marcha. Os resultados sugerem que indivíduos em estadios iniciais de DP poderão priorizar a tarefa motora (inicio da marcha), onde tiveram um desempenho similar aos controlos, mas isto prejudica o desempenho da tarefa cognitiva que foi significativamente inferior em relação aos controlos. O sexto artigo refere-se à influência da dupla-tarefa no do controlo postural no início da marcha. Verificou-se que os ajustes posturais antecipatórios no início da marcha estão afetados na DP e isso é expresso pela falha de ativação do tibial anterior em tarefa simples e dupla. O sétimo e último artigo apresenta a reorganização postural dos indivíduos com DP aquando a realização de dupla-tarefa, nas cinco fases da tarefa de sentar-levantar-sentar. Os indivíduos com DP apresentaram dificuldades no desempenho de 4 das 5 fases, o que se tornou ainda mais evidente quando tiveram de realizar simultaneamente uma tarefa cognitiva.

Ao longo do desenvolvimento deste projeto de doutoramento verificou-se que existem alterações a vários níveis na DP. O controlo motor e postural é afetado pela adição de uma tarefa cognitiva, isto é, na realização de dupla-tarefa. No entanto, este défice pode ser melhorado através de intervenções cognitivo-motoras.

Palavras-Chave: Equilíbrio, Dupla-tarefa, Inicio de marcha, Controlo Motor, Movimento sentar-levantar-sentar.

CONTENTS

PART A – THESIS OVERVIEW

1. INTRODUCTION

Parkinson's disease (PD) is considered the second most common neurodegenerative disorder worldwide, and is only surpassed by Alzheimer's disease. In Europe, the prevalence of PD ranges from 65.6 to 12,500 cases per 100,000 inhabitants, depending on the region of origin and the diagnostic criteria used (Campenhausen *et al.*, 2005). In Portugal, the National Observatory of Health indicates a prevalence of 392.4 per 100,000 inhabitants (Branco, Nogueira, & Contreiras 2005). Some projections point to a significant increase in cases of PD in the next decades, not only due to the increase in average life expectation, due to earlier diagnoses with more modern techniques (Campenhausen *et al.*, 2005).

Although the causes of PD remain unknown, progress has been made in terms of pathophysiological knowledge. PD results from the death of dopaminergic neurons of the substantia nigra pars compacta that project to the striatum, causing a depletion of dopamine in the basal ganglia (Giroux, 2007; Moroz *et al.*, 2009; Tzedek, Krebs, Shill, Apetauerova, & Arle, 2007). The substantia nigra, striatum, and other structures that constitute the basal ganglia, i.e. the internal and external globus pallidus and subthalamic nucleus, were considered to be predominantly involved in motor control. However, increased knowledge of the basal ganglia has shown that these structures have an additional role in sensory processing, cognition and behaviour. Generally, the disease becomes evident when the neuron loss is about 50% to 69% of the total, which corresponds to when the clinical signs beginning to appear (Joseph Jankovic, 2014; Santens, Boon, Roost, & Caemaert, 2003).

A definite diagnosis of PD necessarily implies the presence of bradykinesia and at least 1 (one) of the following 3 (three) symptoms: rest tremor, rigidity or postural instability (Rana, 2011). Postural instability is one of the most disabling symptoms (Backer, 2006). This deficit can result in falls, loss of mobility and loss of independence, strongly affecting the quality of life and functionality of the individual (Allum, Tang, Carpenter, Oude-Nihuis, & Bloem, 2011; Hass, Waddell, Fleming, Juncos, & Gregor, 2005; McNeely, Duncan, & Earhart, 2012).

Motor control is defined as the ability to perform posture adjustments and direct the body and limbs for the intended activity, referring to the control of the nervous system and the muscular system to achieve efficient and coordinated movements (Haywood &

Getchell, 2009). Postural control emerges from the interaction among the individual, the task and the environment. Thus, it is not a simple reactive response to a sensory stimulus, but as an ability based on experience, intention and adaptation (Shumway-Cook & Woollacott, 2007). During static and dynamic balance, posture is controlled by detecting disturbances in the position of the centre of mass (CoM) and by initiating appropriate responses in order to return the body to a stable position, through the interaction of different systems. Individuals with PD present greater difficulty in the initiation of suitable motor responses (M. Rogers, Takeshima, & Islam, 2003). Balance emerges from the postural control of the individual and therefore, requires three events: the maintenance a specific posture, the adjustment for voluntary movements and the reactions to external disturbances. These events allow the individuals to keep the body in balance in situations of rest (static balance) and of moving (dynamic balance), even when submitted to different stimulus, in order to provide stability and guidance (Nilsson, Fransson, Jarnlo, Magnusson, & Rehncrona, 2009).

The variability and efficiency of functional movement assume an appropriate postural control, which depends on the anticipatory postural adjustments (APAs), in order to maintain stability in the presence of internal and external disturbances, taking into account the context and the task (Aruin, 2002). The APAs occur, as the designation indicates, in anticipation to postural disturbances, particularly during the performance of voluntary movements (Hall, Brauer, Horak, & Hodges, 2013; M. W. Rogers *et al.*, 2011; Yiou, Caderby, & Hussein, 2012). The oscillations are reflected in the centre of pressure (CoP) and have the purpose to generate forces that act to maintain the CoM within the body’s support base (Błaszczyk & Orawiec, 2011; Roerdink, Hlavackova, & Vuillerme, 2011). The APAs begin with an activation pattern of the postural muscles approximately 250 milliseconds (ms) prior to movement and extend until 50 ms after the beginning of the movement (Shiratori & Latash, 2001). They are related to feedforward mechanisms and predicting an integrated postural adjustment in motor programming in higher levels of motor control (Allum *et al.*, 2011; Ganesan, Pal, Gupta, & Sathyaprabha, 2010; Lalonde & Strazielle, 2007). The planning of APAs involves several structures of the central nervous system (CNS), such as the premotor cortex, the supplementary motor area, the basal ganglia and the cerebellum (Jacobs, Lou, Kraakevik, & Horak, 2009; Timmann & Horak, 2001), that, via independent pathways, convey information for the reticular formation, such as the pedunculopontine nucleus, which is an important modulator of APAs (Schepens & Drew, 2004). The fact that the basal ganglia establishes a reciprocal neuronal connection with the pedunculopontine nucleus explains the fact that in individuals with PD the postural control is compromised, reflecting the change in the activation of postural muscles in the form of APAs (Jacobs *et al.*, 2009; Karachi *et al.*, 2010; Purves *et al.*, 2004; Shumway-Cook & Woollacott, 2007).

The ability to maintain balance during static and dynamic activities in various contexts indicates that the postural control system adapts to various task parameters. However, this system suffers a decline with age, resulting in loss of efficacy of the sensory systems, as well as the musculoskeletal system, including the loss of strength and flexibility (Vuillerme, Pinsault, & Vaillant, 2005). Studies have revealed that with the increase of age and as the disease turns more severe, impairment in the postural control system becomes more evident (Nemanich, Duncan, Dibble, Cavanaugh, & Ellis; Paul, Sherrington, Fung, & Canning, 2013). In addition, the duration of the disease, fear of falling and cognitive impairments were found to be related to the balance deficits (M Matinolli *et al.*, 2007).

Although PD has been considered to primarily affect motor skills, there is an increasing emphasis being given to non-motor symptoms such as fatigue, compulsive behaviour, cognitive dysfunction, autonomic dysfunction and sleep disturbance (Camargos, Cópio, Sousa, & Goulart, 2004; Silva & Nakamara, 2013). Several studies have reported cognitive impairments in PD (Aarsland, Bronnick, & Fladby, 2011; Koerts, Leenders, & Brouwer, 2009; Koerts *et al.*, 2011; Merims & Freedman, 2008; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007), even at early stages of the disease (Aarsland *et al.*, 2011; Elgh *et al.*, 2009; Pagonabarraga & Kulisevsky, 2012). Cognitive ability allows a self-directed and intentional behaviour, that enables an adaptive response to new situations (Lezak, Howieson, & Loring, 2004). Impairments in cognitive ability can lead to an exacerbation of the difficulties in dual-task, given the important role of cognition to allocate attention appropriately in tasks that occur simultaneously (Hausdorff *et al.*, 2006; McCloskey & Perkins, 2012; Rochester *et al.*, 2004). Clinical symptoms of PD can compete with the ability to direct the attention, thus contributing to increasing the interference observed with dual-task (Rochester *et al.*, 2004). In fact, situations of dual-task are common in the daily life of any individual, however individuals with PD have difficulties to execute them (Bohnen, Albin, Müller, & Chou, 2011; Conradsson, Löfgren, Ståhle, Hagströmer, & Franzén, 2012; Müller, Jennings, Redfern, & Furman, 2004).

Individuals with PD can perform normal movement patterns when they are focused on the movement performance, i.e. when they focus their attention on the implementation of the intended movements. In this situation, the undamaged premotor cortex is activated, without calling on the injured basal ganglia circuit, thereby facilitating movement. When two tasks are performed simultaneously, there is a competition for limited resources, given that the cortical resources are used to perform motor tasks, resulting in interference of the dual-task and in performance deterioration of one or both tasks (J. Holmes, M. Jenkins, A. Johnson, S. Adams, & S. Spaulding, 2010; V. Kelly, A. Eusterbrock, & A. Shumway-Cook, 2012a; T. Wu & M. Hallett, 2009). Another explanation for the difficulty in dual-task performance for individuals with PD, when compared with individuals without the disease, is related to a lower ability to execute automatic tasks and the existence of deficits in the central executive system, which requires more resources to perform each task individually (T. Wu & M. Hallett, 2009).

The cognitive processes have an important role that increases with age and that should be preserved to ensure a good postural control (Jamet, Deviterne, Gauchard, Vançon, & Perrin, 2007). In the elderly, the age and the deficits related to the postural control system appear to be mainly responsible for the deterioration of the postural control and not for the performance deterioration of the secondary task (Granacher, Bridenbaugh, Muehlbauer, Wehrle, & Kressig, 2011). Biomechanical studies focusing on posture stability have shown that the performance of dual-task has a significant effect on the postural control in individuals with PD (Coppin *et al.*, 2006; Fama & Sullivan, 2002; Springer *et al.*, 2006; Van-Lersel, Kessels, Bloem, Verbeek, & Rikkert, 2008). This suggests that these individuals create a restriction on APAs, in order to focus on the cognitive task without losing balance (J. Holmes *et al.*, 2010; Marchese, Bove, & Abbruzzese, 2003; Nocera, Roemmich, Elrod, Altmann, & Hass, 2013). The interference of dual-task can also be observed in the postural control of individuals with PD when performing a secondary task that significantly compromises the postural stability (Bond & Morris, 2000; M. Morris, 2000; O'Shea, Morris, & Iansek, 2002). The association among changes in parameters related to balance and the performance of secondary tasks is complex, and is not always seen as a consequence of attention load, but maybe due to motor task requirements and hence to increased stiffness (Dault, Yardley, & Frank, 2003).

Based on the previously mentioned assumptions, we can conclude that the efficacy of the dual-task performance (cognitive and motor) is closely related to several factors such as: (1) progression stage of the disease, (2) complexity of the secondary task, (3) limitation of attentional resources, (4) motivational preference, (5) internal focus vs. external attention, and (6) postural confidence (J. Holmes *et al.*, 2010; V. E. Kelly, A. J. Eusterbrock, & A. Shumway-Cook, 2012; Schaefer, 2014).

The most common form of PD treatment is pharmacological with levodopa in order to replace the lost dopamine in the brain. Levodopa is converted to dopamine by the dopa-decarboxylase enzyme, crosses the blood-brain barrier and is rapidly converted into dopamine. Recently, studies with rehabilitative intervention have shown promising results. The reported results indicate a potential for reversing or slowing the progression of the disease, demonstrating that the ability to learn motor skills is relatively well preserved (Chiviacowsky, Wulf, Lewthwaite, & Campos, 2012). In recent years, the positive effect of dual-task training in balance has been shown in various populations, including healthy adults, elderly and individuals with neurological conditions such as stroke (Bherer *et al.*, 2008; Brauer *et al.*, 2011; Kramer *et al.*, 2005; K. Z. Li *et al.*, 2010; Pellecchia, 2005; Silsupadol, Shumway-Cook, *et al.*, 2009; Silsupadol, Siu, Shumway-Cook, & Woollacott, 2006). Several studies have shown that the dual-task cognitive-motor training has a positive effect on gait in the PD population; in particular, in terms of the gait speed, variability and step length (V. Sethi & R. Raja, 2012; Yogev-Seligmann, Giladi, Brozgol, & Hausdorff, 2011). However, the efficacy of interventions based on dual-task cognitive-motor training is still poorly explored.

2. Main Objectives

The key objectives defined for this PhD project were the following:

- To identify existing randomized controlled trials that used cognitive-motor dual-task training and compare its efficacy in relation to single-task training on the balance and executive functions of individuals with PD.

- To compare the postural phase and control strategies when performing single- and dual-task conditions in individuals at early stages of PD (Hoehn and Yahr scale < 3) and in controls when performing static balance, gait initiation and the sit-to-stand-to-sit (STSTS) movement.

To study the topics of these objectives musculoskeletal and cognitive based parameters were used. The dual-task outcomes were always investigated and quantified in both controls and individuals with PD. The results were always interpreted taking into account neurophysiological and biomechanical principles and possible clinical implications.

3. Thesis Organization

This thesis is organized into two main parts. In this first part, Part A, an overview of the research work conducted is presented. Hence, the next section describes briefly the work developed, including the identification of the established objectives, the main results found and the conclusions reached, in addition to the methodological considerations that were taken into account during this project. Then, the main contributions reached with this project are presented. Finally, the last section of this part presents the main conclusions and perspectives for future work.

The second part, Part B, presents the set of articles produced under the scope of this project. It contains seven articles that describe the work conducted in detail, including the methodologies used, the results obtained and their discussion.

4. DESCRIPTION OF THE WORK DEVELOPED

This section provides a brief description of the work conducted during this PhD project, which is fully detailed in the articles included in Part B.

4.1 State-of-art Review

The dual-task performance can be particularly revealing in individuals with PD, since various studies indicate that these individuals are unable to perform simultaneous tasks properly. The influence of secondary tasks, i.e. the dual-task condition, is already well studied in individuals with PD, especially regarding gait and static balance (Ashburn, Stack, Pickering, & Ward, 2001; B.R. Bloem, Grimbergen, Cramer, & Valkenburg, 2000; B.R. Bloem, Valkenburg, Slabbekoorn, & van Dijk, 2001; Bond & Morris, 2000; Camicioli, Oken, Sexton, Kaye, & Nutt, 1998; Jennifer A. Foley, Kaschel, & Sala, 2013; Hausdorff, Balash, & Giladi, 2003; Marchese *et al.*, 2003; Morris, Iansek, Smithson, & Huxham, 2000; Nocera *et al.*, 2013; O'Shea *et al.*, 2002; Rochester *et al.*, 2004; Wild *et al.*, 2013). In general these studies conclude that both gait and static balance performance may deteriorate when a secondary task needs to be performed simultaneously. Furthermore, some of these studies have found that the secondary task was the most demanding, and that it increases the difficulties in terms of postural control (Bond & Morris, 2000; Rochester *et al.*, 2004).

In individuals without PD, the performance of cognitive-motor dual-task implies a division of attentional resources by the two tasks. While the automated motor tasks, like walking on a flat surface at self-selected speed, require little attention, more difficult tasks, such as walking over obstacles or performing a new motor skill, require more attention. Some attention is drawn to the motor domain, and the simultaneous execution of a cognitive task may be compromised (Schaefer, 2014). According to the model proposed by Fitts and Posner (1967), the individuals that acquire a new motor skill usually go through distinct phases that differ in their demand for cognitive resources. In the first phase, called the cognitive phase, most of the movement is controlled consciously, and the execution of the movement is slow and prone to error. The second phase, called the associative phase, consists of a blend of conscious and automated control strategies. After extensive practice, some learner's reach the autonomous phase in which the cognitive control is reduced to a minimum, and the new motor skill can be performed efficiently, consistently and with high precision. According to the same model, individuals that are experts in a motor skill do not decrease their performance when performing that skill simultaneously with a cognitive task; on the other hand, inexperienced people still have to invest some attention on the motor skill performance and may even need to improve the motor performance in single-task. However, individuals with PD have great difficulties in performing automated tasks, and so their learning and training of motor tasks never seem to be enough for good dual-task performance (Koerts *et al.*, 2009; Wu & Hallett, 2008).

Considering the difficulties in performing automated tasks, which makes the motor training insufficient, dual-task training should be included as part of the rehabilitation process of individuals with PD (T. Wu & M. Hallett, 2009), although, until now, no guidelines have been defined for this type of intervention. New paradigms have been studied concerning cognitive-motor dual-task. This type of intervention should be able to improve dual-task performance and/or improve motor and cognitive components individually (K. Baker, Rochester, & Nieuwboer, 2007; Montero-Odasso, Verghese, Beauchet, & Hausdorff, 2012; Silsupadol *et al.*, 2006; Yogev-Seligmann, Rotem-Galili, Dickstein, Giladi, & Hausdorff, 2012). Taking into account the effects of the dual-task on the motor performance, this PhD project started by verifying if an intervention with cognitive-motor dual-task training results in more benefits than the single-task training in individuals with PD. Therefore, a systematic review of randomized clinical trials, addressing training with cognitive-motor dual-task, was prepared: Article 1 – Part B (Fernandes, Lopes, Rocha, & Tavares, Submitted). This study assumes a great importance as there is a need for the standardization of the rehabilitation processes in order to promote the comparison of results and efficiency.

Title: Rehabilitation with dual-task training: A systematic review on randomized controlled trials

Authors: Ângela Fernandes, Daniela Lopes, Nuno Rocha, João Manuel R.S. Tavares

Journal: Submitted to an International Journal

Brief description: The aims of this article were to identify existing randomized controlled trials that used cognitive-motor dual-task training. Three electronic databases were consulted: PubMed®, Scopus® and ISI Web of Science®. Eleven studies were included in the systematic review; the common objective was to discuss the effects of dual-task training. The most studied population were healthy elderly people (38.5%); the skills assessed were: balance, executive functions, falls, gait, mobility and functionality. In general, the interventions had similar exercises; however, they differed in duration (3 to 24 weeks), intensity (30 to 90 min) and frequency (1 to 5 times per week). The cognitive-motor dual-task led to effective results in 53.8% of the studies analyzed for balance, executive functions and functionality. The duration and type of intervention in the control groups appear to be the factors that have the most influence on the results.

As aforesaid, several studies have reported on cognitive impairment in PD (Aarsland *et al.*, 2011; Koerts *et al.*, 2009; Koerts *et al.*, 2011; Merims & Freedman, 2008; Williams-Gray *et al.*, 2007), even at early stages of the disease (Aarsland *et al.*, 2011; Elgh *et al.*, 2009; Pagonabarraga & Kulisevsky, 2012). Approximately 15% to 20% of individuals with PD tend to develop severe cognitive deficits, and their risk of developing dementia is two to three times higher than in controls with similar ages (Leh, Petrides, & Strafella, 2010).

Given that individuals with PD generally present cognitive impairment of some magnitude, it was essential to further understand the extent to which cognition is a determinant for motor and postural control, both in static and in dynamic conditions. The following work in this project identified an exclusion factor that was considered in the posterior works; this factor was the presence of cognitive deterioration. With this exclusion factor, it is possible to assure that the effects on motor and postural control are due to dual-task conditions and not to cognitive deterioration: Article 2 – Part B (Fernandes, Mendes, Rocha, & Tavares, Submitted).

Title: Cognitive predictors of balance in Parkinson's disease

Authors: Ângela Fernandes, Andreia Mendes, Nuno Rocha, João Manuel R.S. Tavares

Journal: Submitted to an International Journal

Brief description: Postural instability is one of the most disabling symptoms of PD that appears to be closely related to cognitive impairments. The aim of this study was to identify the cognitive factors that can predict impairments in static and dynamic balance in PD. The factors studied were combined into two statistically significant models ($p=0.01$, $p=0.03$) that explained 23-28% of the Timed Up and Go variability and 9-11% of the anteroposterior displacement variability. This analysis confirmed that the scores of the Trail Making Test A and the Digit Span Test were statistically significant. Therefore, the cognitive components such as psychomotor speed, visuospatial orientation, attention and working memory can be considered to be important elements to be taken into account for the prediction of balance deficits.

4.2 Interventions with Dual-task Training

Recent studies of specific dual-task training have demonstrated efficacy in various populations, such as the elderly and individuals with neurological diseases, with the most notable improvements in gait and balance (Brauer & Morris, 2010; V. Sethi & R. Raja, 2012; Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009). This intervention was designed specifically to improve gait in individuals with PD, with positive outcomes in gait speed and gait variability (Brauer & Morris, 2010; Yogev-Seligmann *et al.*, 2011). Based on a protocol adapted from Silsupadol, Shumway-Cook, *et al.* (2009), the objective of the following study was to improve balance in individuals with PD using dual-task procedures in a pilot randomized trial. The experimental group received cognitive-motor dual-task training, and the control group received motor training without the cognitive component. This program was chosen as the basis for intervention in individuals with PD due to the significant outcomes that were achieved using a dual-task based intervention. However, other studies and their intervention programs were also taken into account in order to define the frequency, intensity and duration of the sessions and intervention program: Article 3 – Part B (Fernandes, Rocha, Santos, & Tavares, in Press).

Title: Effects of dual-task training on balance and executive functions in Parkinson's disease: A pilot study

Authors: Ângela Fernandes, Nuno Rocha, Rubim Santos, João Manuel R.S. Tavares

Journal: Somatosensory & Motor Research, DOI: 10.3109/08990220.2014.1002605 (in press)

Brief description: The aim of this study was to analyze the efficacy of cognitive-motor dual-task training compared with single-task training on balance and executive functions in individuals with PD. Accordingly, we hypothesized that cognitive-motor dual-task training is more effective at improving balance and executive functions than single-task training in individuals with PD.

The training was run twice a week for six weeks. The control group received balance training, and the PD group performed cognitive tasks simultaneously with the balance training. The results suggest superior outcomes for the dual-task training group compared to the single-task group for static postural control, except with eyes closed in anteroposterior sway. No significant differences were found between the two groups in terms of the executive functions performed.

In conclusion, as was hypothesized for this study, our findings revealed a more positive response with the dual-task intervention compared to the single-task intervention. The motor training with a cognitive task performed simultaneously improved the performance of some parameters related to balance and executive functions of individuals with PD. These observations highlight the strength of rehabilitative interventions based on dual-task training.

After the intervention and the revaluation of the participants, the results were found to be positive, albeit less than what was expected. This led to the decision to carry out further investigations on the effect of dual-task. Individuals with PD have to focus on achieving normal movement patterns by activating the premotor cortex region without using the affected basal ganglia circuit, which is deficient in dopamine. Therefore, in dual-task situations that use the cortical resources to perform motor tasks, the performance of both motor and cognitive components can be compromised (Brauer & Morris, 2010; T. Wu & M. Hallett, 2009).

4.3 Motor and Postural Control during Dual-task

Primary deficits of individuals with PD are in motor performance (Calabresi, Picconi, Parnetti, & Di-Filippo, 2006), and they seem to be more evident in automatic aspects of movement, like the postural adjustments, while more consciously and objectively controlled movements are relatively preserved (Koerts *et al.*, 2009). All behaviours can be regulated automatically or in a controlled, i.e. consciously, way. However, it is assumed that all activities result from a combination of automatic and controlled regulation (Schwarz & Shapiro, 1986).

Individuals with PD have more difficulty to perform automatic movements, as they require more brain processing resources when performing them (Wu & Hallett, 2008). This is in agreement with functional studies focused on achieving automatic movements in PD. Some reports have shown that, in comparison to controls, individuals with PD have increased activity of the cerebellum, premotor cortex, parietal cortex, precuneus and prefrontal cortex during the execution of automatic movements (Wu & Hallett, 2005), whereas no activation was found in the striatum. Instead, in individuals with PD, most of the cortical areas remain activated. This indicates that the expected change of cortical to subcortical areas during the shift from controlled processing to automatic processing does not occur in individuals with PD. Thus, a possible conclusion is that individuals with PD have difficulty to attaining and using automaticity.

The influence of dual-task has been widely investigated, including in individuals with PD. However, these studies have been mainly about gait, and there are few studies regarding other tasks. Thus, the goal of the following work was to study more controlled, i.e., not so automatic tasks like the up and sit tasks or the gait initiation, besides the automatic tasks such as maintaining the standing position. Based on the assumptions made by Schwarz and Shapiro (1986) and on the fact that the complexity of the secondary task influences the motor performance, different cognitive tasks were shown to have an effect on maintaining the upright position in individuals with PD. Thus, in this work the balance in single-task and in two dual-task conditions, between individuals with PD and controls, was verified: Article 4 – Part B (Fernandes *et al.*, Accepted).

Title: Balance under single-task and dual-task conditions in Parkinson's disease

Authors: Ângela Fernandes, Tiago Coelho, Ana Vitória, Augusto Ferreira, Rubim Santos, Nuno Rocha, Lia Fernandes, João Manuel R.S. Tavares

Journal: Submitted to an International Journal

Brief description: This study aimed to compare the static balance in individuals with PD with a control group, under single- and dual-task conditions. The balance was assessed while the participants were standing in an orthostatic position under single-task with eyes open and with eyes closed, and under dual-task while performing two different verbal fluency tasks.

In the early stages of PD, the results are expected to be similar to those of a population without disease. However, significant differences were found for the mediolateral CoP displacement ($p<0.01$) and the anteroposterior CoP displacement ($p<0.01$). Both displacements were significantly higher in the individuals with PD than in the controls. A clear distinction between the single- and dual-task conditions was found. The mediolateral CoP displacement ($p<0.001$) and the CoP displacement velocity ($p<0.001$) were significantly different in single-task condition with eyes open relative to the remaining tests. The anteroposterior CoP displacement ($p<0.001$) was only significantly different in the single-task condition with eyes open in comparison to the same condition but with eyes closed.

This study shows that the static balance of individuals with PD is worse than that of the controls, especially under dual-task conditions. Therefore, in order to promote the functional performance of these individuals, and delay disability, this evidence should be taken into account when designing therapeutic interventions.

After verifying the difficulties the individuals with PD had in maintaining balance, it was decided to explore gait initiation. This choice is linked to the fact that several studies have shown that individuals with PD have difficulties during the stance phase of gait initiation. This is characterized by a backward displacement of the CoP that results from the APAs causing a forward displacement of the centre of gravity (Caderbya *et al.*, 2013; Yiou *et al.*, 2012), which leads to an increased number of falls (V. Kelly *et al.*, 2012a; Schmit *et al.*, 2005). Individuals with PD often have difficulties in generating APAs, particularly in forward propulsion and lateral weight shift when initiating gait (Hall *et al.*, 2013).

In individuals with PD, the dual-task condition restricts the APAs in order to focus on the cognitive task without losing balance (Nocera *et al.*, 2013; Yogev-Seligmann *et al.*, 2010). Because of limited resources and the cognitive nature of neurodegenerative disease, the ability to recruit attentional resources is limited, especially during dual-task, and therefore, performance is impaired. Studies suggest that individuals with PD treat all elements of a dual-task with equal priority (B.R. Bloem, Grimbergen, van-Dijk, & Munneke, 2006). However, individuals after stage 3 of PD have reduced stability in upright standing (Tsutiya *et al.*, 2011). There is no such evidence of this in the early stages of the disease. Thus, the study of motor prioritization capacity in early stages of PD was the focus of the next study developed: Article 5 – Part B (Fernandes, Sousa, Rocha, & Tavares, Submitted-c).

Title: Parkinson's disease and prioritization of tasks: is motor prioritization possible in the early stages of the disease?

Authors: Ângela Fernandes, Andreia S.P. Sousa, Nuno Rocha, João Manuel R.S. Tavares

Journal: Submitted to an International Journal

Brief description: Gait initiation has been demonstrated to be impaired in PD. The aim of this study was to compare the postural phase of gait initiation in single- and dual-task conditions in individuals with PD in the early stages (Hoehn and Yahr scale < 3) and in controls. In contrast to what was expected, no significant differences were observed between the individuals with PD and the controls regarding the anteroposterior and the mediolateral CoP displacement and velocity. However, the mean CoP_{AP} (Figure 1) and CoP_{ML} displacements were lower in the individuals with PD.

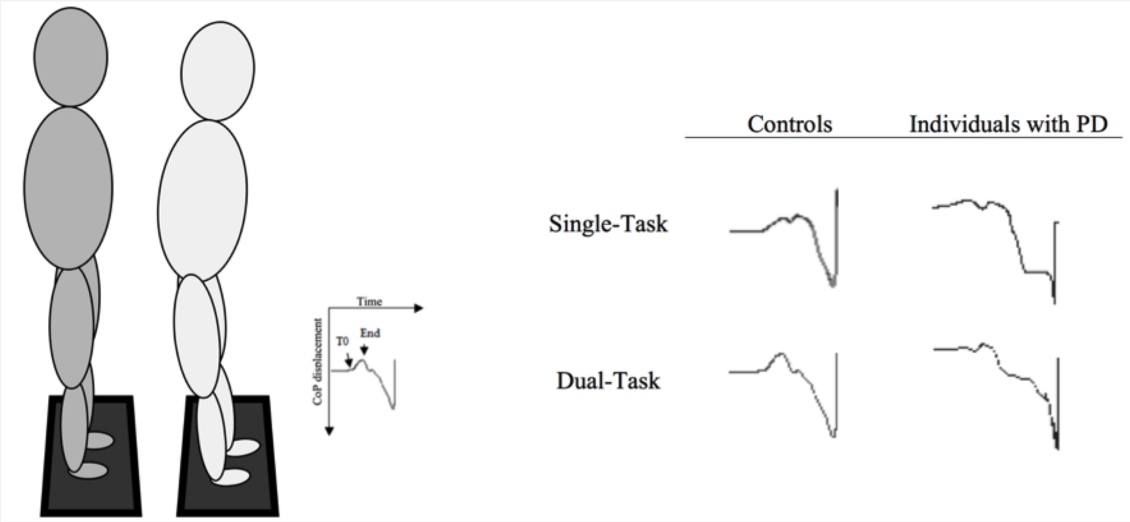

Figure 1. Representation of gait initiation and anteroposterior CoP displacement in single- and dual-task conditions in both groups. (Here, an increment in the CoP value means a posterior CoP displacement, and a decrement an anterior CoP displacement).

Differences were only found in the duration of mediolateral postural phase, $F (1, 16) = 12.494$, $p = 0.003$, that was higher in the individuals with PD than in the controls. The fact that the individuals with PD under study did not show any differences between the single- and dual-task conditions, can also be explained by a greater focus on the motor task, which means that the motor performance is not debilitated despite the worse results in the Stroop test. Most studies that have been conducted to characterize the motor deficits in individuals with PD have used participants in advanced stages of the disease and only in single-task condition. However, most activities of daily living require the simultaneous execution of a cognitive task. Our findings suggest that individuals in the early stages of PD prioritize gait initiation, since their motor performance was similar to that of controls while the number of the colours correctly named was lower in the individuals with PD.

While gait and maintaining balance are traditionally considered "automatic" processes regulated by the basal ganglia and/or the spinal cord, gait initiation is considered a more voluntary and "intentional" task, with a controlled process by higher cortical networks, particularly by the juxtapositional lobule cortex. Thus, for most of the intentional tasks, such as gait initiation, individuals with PD may be able to prioritize them if they perceive them as having greater importance in terms of safety or self-realization than non-automatic tasks (Reetz *et al.*, 2008). Furthermore, the lack of differences between controls and individuals with PD may be due to the fact that the underlying anticipatory muscular synergy was preserved, and the lower CoP displacement and velocity were probably related to the slowness of execution, for instance, to a bradykinetic syndrome (Berardelli, Rothwell, Thompson, & Hallett, 2001). Thus to clarify these questions, the effect of dual-task on the ankle muscle activity of individuals with PD was investigated: Article 6 – Part B (Fernandes, Sousa, Rocha, & Tavares, Submitted-a).

Title: The influence of a cognitive task on the postural phase of gait initiation in Parkinson’s disease: an electromyographic based analysis

Authors: Ângela Fernandes, Andreia S.P. Sousa, Nuno Rocha, João Manuel R.S. Tavares

Journal: Submitted to an International Journal

Brief description: The aim of this study was to compare postural control strategies during gait initiation in single- and dual-task conditions in individuals with early stages of PD (Hoehn and Yahr scale < 3) and in controls. The electromyographic activity of the bilateral ankle muscles, tibialis anterior (TA) and soleus (SOL) were monitored during GI in single- and dual-task conditions. The activation timing of TA was significantly higher for the individuals with PD than for the controls ($p = 0.05$) and a significant interaction between the groups, conditions and limbs was found ($p = 0.027$). Differences between the single- and dual-task conditions were observed for the activation time of the TA ($p = 0.042$) and for the magnitude of SOL ($p = 0.007$), with lower values for the dual-task condition. Furthermore, not all individuals studied followed the previously reported pattern of SOL inhibition followed by TA activation, Figure 2.

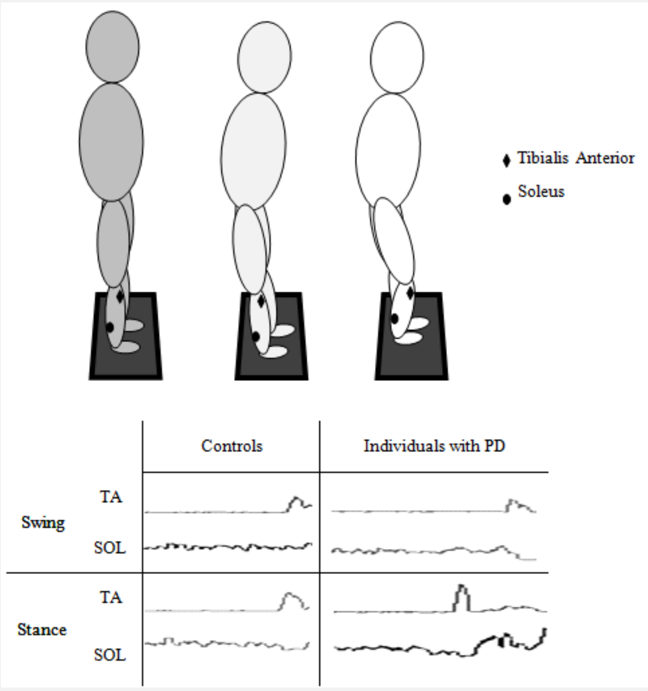

Figure 2. Representation of the gait initiation and electromyographic activity in both limbs of controls and individuals with PD.

The APAs of gait initiation are impaired in PD and are expressed by an activation failure of TA in both single- and dual-task conditions. The knowledge attained from this study should be taken into account in the design of early interventions so that the changes found are minimized along the progress of the disease.

Finally, the influence of the dual-task on a controlled activity, the STSTS movement was investigated; all phases of this task were analyzed. The transitions from sitting to standing and from standing to sitting are essential in activities of daily living that require full postural control, which in turn implies the involvement of APAs (Duncan, Leddy, & Earhart, 2011; Janssen, Bussmann, & Stam, 2002; Mazza, Zokb, & Croce, 2005). The variability and efficacy of functional movements underlined an appropriate postural control that depends on APAs to maintain stability (Aruin, 2002). Thus, the displacement, velocity and duration of the APAs were analyzed: Article 7 – Part B (Fernandes, Sousa, Rocha, & Tavares, Submitted-b).

Title: Influence of dual-task on sit-to-stand-to-sit postural control in Parkinson's disease

Authors: Ângela Fernandes, Andreia S.P. Sousa, Nuno Rocha, João Manuel R.S. Tavares

Journal: Submitted to an International Journal

Brief description: Postural control deficits are the most disabling aspects in PD, leading to decreased mobility and reduced functionality. The aim of this study was to evaluate the postural control of individuals with PD during the STSTS movement when performing single- and dual-task conditions.

The main significant differences between the two groups were the duration in phases 2 ($p=0.029$), 3 ($p<0.001$) and 4 ($p<0.001$), anteroposterior CoP displacement in phases 3 ($p=0.019$) and 5 ($p=0.048$), mediolateral CoP displacement in phase 4 ($p=0.033$), anteroposterior CoP velocity in phases 3 ($p=0.036$) and 4 ($p=0.003$), and for the mediolateral CoP velocity in phase 3 ($p=0.033$). Furthermore, when comparing single- and dual-task conditions in both groups, only a significant difference was found for phase 3 ($p=0.044$). The individuals with PD had more difficulty than controls in performing the STSTS movement, especially when performed simultaneously with a cognitive task, Figure 3.

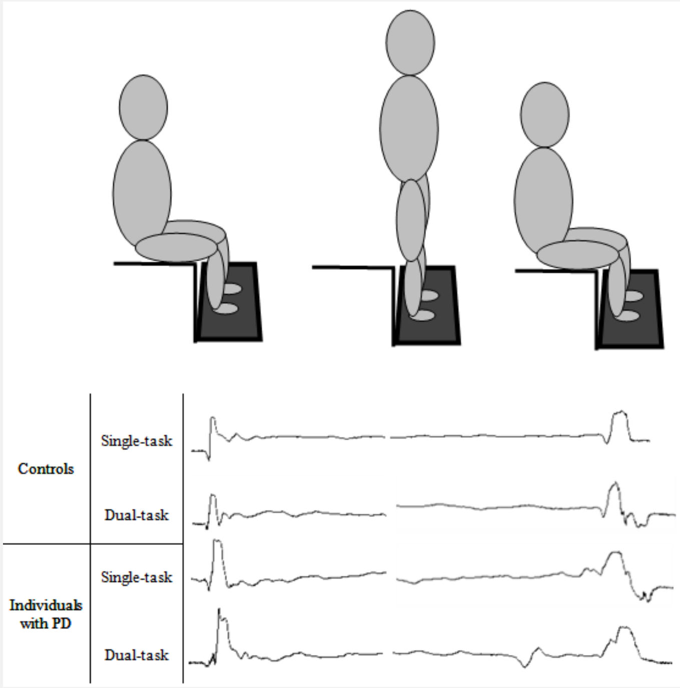

Figure 3. Representation of the anteroposterior CoP displacement in sit-to-stand-to-sit in single- and dual-task in both groups. (Here, an increment in the CoP value means a posterior CoP displacement and a decrement an anterior CoP displacement).

This study assumes particular importance because, by analyzing the five phases of the STSTS movement which are involved in essential tasks of daily life, it shows that individuals with PD have greater difficulty in the stand-to-sit task, which is ignored in most of the studies, than the sit-to-stand task, especially in dual-task condition. In conclusion, it is possible that the individuals with mild PD demonstrated compensatory motor strategies in our study due to a reduced ability to generate force in the lower extremities and a need for greater postural stability during the STSTS movement.

4.4 Methodological Considerations

The options concerning the methodology adopted in each study were made according to the research objectives defined for the PhD project. Although the methodologies, methods and data used are explained in each article included in part B, the reasons for some specific options are not fully justified. Thus, these options are justified here.

4.4.1 Samples

There are various factors that can influence the motor performance and therefore, parameters such as anthropometric, lifestyle, cognitive impairment and treatment using deep brain stimulation that could bias the results were taken into account in these studies.

Studies have shown that individuals with PD who do physical exercises have better balance, strength, posture, gait speed, cardiovascular capacity and stamina compared to those who do not do any physical exercise (Ellis *et al.*, 2011; Salgado, Williams, Kotian, & Salgado, 2013; Speelman *et al.*, 2011; Yousefi, Tadibi, Khoei, & Montazeri, 2009). In addition, acting as a neuroprotective effect that slows the progression of the disease, regular physical exercise has beneficial effects on postural control (Salgado *et al.*, 2013), as the dopaminergic neurons are highly responsive to exercise (Fox *et al.*, 2006). In fact, physical activity promotes increased levels of dopamine, helping to reduce the symptoms of the disease. Based on these facts, it was decided to study sedentary individuals; i.e. with a low level of physical activity (Bennett, Winters-Stone, Nail, & Scherer, 2006). Hence, the individuals in all studies were classified as sedentary or physically active according to the time spent on physical activities, according to Pate *et al.* (1995). Individuals were classified as sedentary when their physical activity was less than three times a week for 20 continuous minutes of vigorous physical activity, or less than 5 times a week for 30 continuous or intermittent minutes of moderate physical activity during, at the least, the last 2 years (Ainsworth *et al.*, 1993; Pate *et al.*, 1995).

The fact that none of the individuals in the studies presented cognitive deterioration was taken into consideration, since it is known that the postural control and cognition are not independent systems (Andersson, Hagman, Talianzadeh, Svedberg, & Larsen, 2003). Furthermore, the intention was to investigate the impact of performing dual-task on the motor and postural control, and knowing that a cognitive task affects the postural stability (Lindholm, Hagell, Hansson, & Nilsson, 2014; Schmit *et al.*, 2005), the presence of cognitive deterioration could exacerbate the difficulties in maintaining the postural control. The cognitive deterioration in individuals with PD is normally associated with an inappropriate prioritization of tasks (V. E. Kelly *et al.*, 2012).

Individuals with PD were excluded from the study if they had undergone deep brain stimulation as it has been verified that there are improvements in patients' performances after such procedures (D. Li *et al.*, 2013; Volkmann, 2007). Consequently, the physical symptoms of individuals who had been submitted to this procedure would have this advantage, other than their medication, which could bias the findings.

There were a total of 147 participants in this PhD project and they were distributed among the studies as shown in Figure 4. Note that the individuals with PD in Article 2 also participated in the study reported in Article 4.

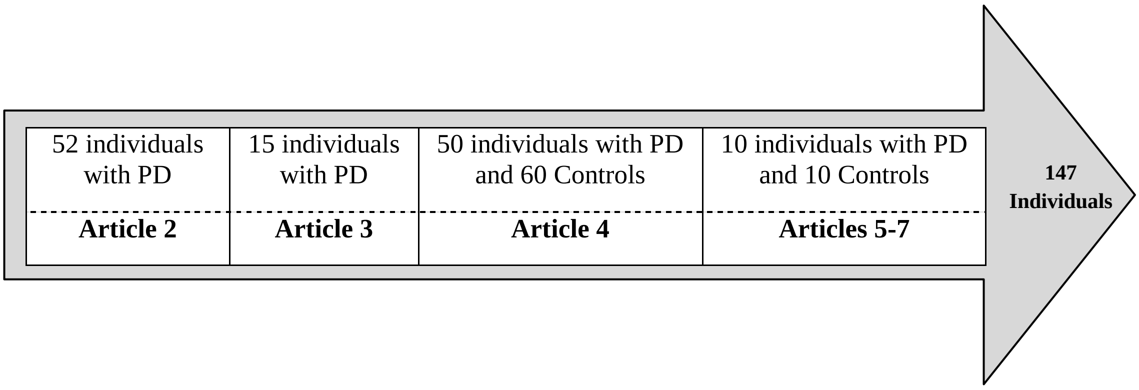

Figure 4. Number of participants and their group in each study conducted during this PhD project.

4.4.2 Dual-task Selection

In this project, the secondary task was always a cognitive task. As we know that the more complex the secondary task is, the greater its influence on the motor control is, we decided to study two different cognitive tasks. In Article 4, phonemic and semantic tasks were used, which are two tasks that activate different parts of the brain and impose different levels of complexity (Meinzer *et al.*, 2009). Recently, studies have shown that old adults and more specifically, individuals with PD, can more easily generate words from a certain letter of the alphabet than generate words belonging to a semantic category (Meinzer *et al.*, 2009; Zec *et al.*, 1999). However, it has also been stated that, the more complex a cognitive task is, the more instability there will be. However, as the results obtained were in line with the findings reported in the literature reviewed and there was a great variability between the individuals in the studies reported in Articles 5, 6 and 7, the Stroop test was select for the secondary task. This test assesses selective attention, inhibitory capacity and concentration (J. Holmes *et al.*, 2010; Romann, Dornelles, Maineri, Rieder, & Olchik, 2012). There are some variations, but the test scores may be set according to the test performance time, number of errors and the number of named items read from or within a certain timeframe (Lezak *et al.*, 2004). In this project, the colour naming test was used, and the number of errors and the number of named items were taken into account. A study by Van der Elst, Van Boxtel, Van Breukelen, and Jolles (2006) using individuals with cognitive impairments but without any pathology, found an inverse relationship between cognitive impairments and increase of errors and reduction of the number of colours specified in the Stroop test; however, in this PhD project, the individuals had no cognitive impairments.

4.4.3 Selected Biomechanical Parameters

<u>Kinematic variables</u>

The most common way to assess postural control is to evaluate the behaviour of the body in a static upright position (Horak, 1987). It is known that when a body remains in the orthostatic position, it oscillates within its corresponding support base; therefore, the amplitude of oscillation could be a good indicator to assess the stability and balance (Ebersbach & Gunkel, 2011; Schmit *et al.*, 2005). Hence, in the studies reported in Articles 2-4, the oscillation of the body and associated variables were assessed using the stabilometric method.

In studies that deal with the postural control, the postural oscillation component of easiest access is commonly explored, i.e. the CoP. This component is obtained using the components of the ground reaction forces and the components of movement. This corresponds to the application point of the vertical forces resultant that are acting on the body’s support surface (Duarte & Sternad, 2008). Hence, the CoP data refer to a measure defined by two coordinates on a force platform surface, according to the postural stability of the assessed individual (Luis Mochizuki & Amadio, 2003). Despite the large number of parameters that can be extracted from stabilometry, such as the direction of the CoP, the area covered by the CoP, range, standard deviation, speed and frequency spectrum of the CoP (Chiari, Rocchi, & Cappello, 2002; Laughton *et al.*, 2003), there are differences between the parameters depending on the different groups and conditions. The literature shows that some parameters can be used as reliable measures of postural stability in PD, like the CoP displacement in the anteroposterior and mediolateral components (Błaszczyk & Orawiec, 2011; Ganesan *et al.*, 2010; J. Holmes *et al.*, 2010). In addition, studies with other populations also rely on anteroposterior and mediolateral displacement velocities to analyze postural stability (Błaszczyk & Orawiec, 2011; Ganesan *et al.*, 2010; J. Holmes *et al.*, 2010; Moghadam *et al.*, 2011; Piirtola & Era, 2006).

<u>Electromyographic activity</u>

The electromyographic activity was used to evaluate the time of muscle activation and the level of muscle activation in the study reported in Article 6. The dynamic normalization method was selected to reduce the variability between individuals and to obtain information about the muscle activation pattern at gait initiation, and also to understand the influence of dual-task on the activity patterns of the relative muscles in the postural phase of gait initiation (Burden & Bartlett, 1999). This dynamic method represents a percentage of the average of both quiet and active periods during the activity. This method reduces the inter-subject variability in relation to other normalization methods, and is helpful for clinical populations that are unable to attempt maximal efforts (D. A. Winter & Yack, 1987). However, this method presents limitations as it trends to produce a normal electromyographic template for a particular task and, therefore, may remove the true biological variation within a group. It may be also more susceptible to systems with low signal to noise ratios and present baseline noise in movements that cause very phasic activations (Sousa & Tavares, 2012).

4.4.4 Selected Cognitive Parameters

During the PhD project, it was also decided to evaluate the cognitive abilities that are documented as being in deficit in individuals with PD. There have been many possible cognitive impairment findings in individuals with PD (Koerts *et al.*, 2009; Koerts *et al.*, 2011; Pagonabarraga & Kulisevsky, 2012; Rodríguez-Ferreiro, Cuetos, Herrera, Menéndez, & Ribacoba, 2010; Watson & Leverenz, 2010; Williams-Gray *et al.*, 2007). Specifically, changes can be found for cognitive flexibility (Koerts *et al.*, 2009; Koerts *et al.*, 2011; Kudlicka, Clare, & Hindle, 2011), divided and selective attention (Elgh *et al.*, 2009; Kudlicka *et al.*, 2011; Watson & Leverenz, 2010), planning (Watson &

Leverenz, 2010), response inhibition (Goldman, Baty, Buckles, Sahrmann, & Morris, 1998; Kudlicka *et al.*, 2011; Watson & Leverenz, 2010), monitoring and codification - working memory (Kudlicka *et al.*, 2011; Watson & Leverenz, 2010), implicit and explicit memory (Watson & Leverenz, 2010), semantic and episodic memory (Elgh *et al.*, 2009), abstract reasoning (Watson & Leverenz, 2010) and conceptualization (Koerts *et al.*, 2011; Kudlicka *et al.*, 2011).

Thus, in the studies presented in Articles 2 and 3, the *Rule Shift Cards Test* of *Behavioural Assessment of the Dysexecutive Syndrome* (RSCardsT) and the Trail Making Test (TMT) A and B were used. The RSCardsT is used to evaluate persevering trends and the ability to shift from a pattern to respond to another, i.e. the cognitive flexibility. This test requires that the participants respond to stimuli (red or black card game) according to one of two rules that are presented consecutively in two different tests: in the first test, the participant has to answer "yes" to a red card and "no" to a black card; in the second test, the individuals have to answer if a card matches or does not match the colour of the previous card shown. The performance is indexed to a profile score ranging from 0 (severely disabled) to 4 (normal performance) taking into account the errors and the time taken to complete the task (Golden, Espe-Pfeifer, & Wachsler-Felder, 2000; Lanfranchi, Jerman, Dal Pont, Alberti, & Vianello, 2010; Wilson, Alderman, Burguess, Hazel, & Evans, 2003). The TMT is composed of two parts: one evaluates the attention and processing speed (Part A), and the other assesses the cognitive flexibility and sequential alternation (Part B). Part A consists in sequencing numbered circles, starting at number one, in order to generate a sequence number as quickly as possible. In Part B, participants must switch between the number and alphabetic modes, linking numbers and characters together. In each part, the score is the total time needed to complete the task (Reitan, 1992; Reitan & Wolfson, 1995).

The Digit Span included in the Wechsler Adult Intelligence Scale test, which can be used to assess attention, working memory and sequential processing, was also used in the study described in Article 3. In this test, the individuals are required to organize and repeat a series of numbers specified verbally. The first task is to arrange the numbers in direct order for a total of 16 trials, grouped in 8 levels, wherein the amount of numbers progressively increases from level to level, the first of which consists of two numbers and the last of 9 numbers. Within each level, the individual must verbalize correctly at least one of the sequences to move on to the next level. The second task of the test is carried out similarly, but the goal is to arrange the numbers in reverse order. For each test being carried out, the correct answers are listed with "1" (one) and the wrong with "0" (zero); at the end, the sum of the quotations of all the answered trials corresponds to the test score (Ostrosky-Solís & Lozano, 2006).

5. MAIN CONTRIBUTIONS ACHIEVED

The main contributions reached with this PhD project are:

- A systematic review about cognitive-motor dual-task intervention that provides important information related to this type of rehabilitation. In fact, it was found that the cognitive-motor dual-task led to effective results in 53.8% of the studies analyzed for balance, executive functions and functionality. The importance of this study is mainly related to the absence of guidelines set for interventions based on cognitive-motor dual-tasks.

- The intervention study with dual-task in individuals with PD reported in Article 3 concluded that this intervention has positive effects, but needs to be modified. The few findings obtained enabled us to understand that it is very difficult to apply a single task-intervention in a control group, because the simple action of talking during an exercise turns the training into a dual-task one. Nerveless, it is believed that this form of intervention is efficient, and this study shows that this type of intervention can be beneficial for individuals with PD.

- The studies concerning the influence of dual-task described in Articles 4 to 7 show that the motor control is impaired in individuals with PD by the introduction of a cognitive task, even in the early stages of the disease. This knowledge is important for understanding the deficits and the strategies used by individuals with PD in balance, gait initiation and the STSTS movement. This project showed that automaticity in individuals with PD is not preserved, and postural instability varies according to the cognitive task. The behaviour in gait initiation was surprising as it was contrary to what was expected. The results obtained suggest that these individuals may be able to prioritize tasks as they arise simultaneously. However, the electromyographic activity based study described in Article 6, which, as far as the authors know, is the first study that has analyzed activities in the dual-task condition electromyography, indicates that the main problem in these individuals does not lie in the deactivation of the SOL, but is expressed by an activation failure in TA in both single- and dual-task conditions. This finding is very important to define successful rehabilitation processes. The study concerning the STSTS movement, reported in Article 7, suggests that individuals with PD have difficulty in all phases defined, except for the phase of preparing for upright position. The preparing for upright position phase is an initial movement, and it was expected that APAs would be less effective in individuals with PD than in controls. It is accepted that the greatest difficulties that individuals with PD have are to remain still and to move from an upright position to a sitting position. Taking into account the prevalence of PD and the expected increase in the coming years with its serious consequences in terms of independence and autonomy, the study of this pathology is important to get a better understanding of performance deficits and potential functional recovery, as well as to develop intervention strategies to maximize recovery. Therefore, the results obtained from this PhD project provide important contributions to define better rehabilitation strategies; particularly by stressing the importance of including cognitive-motor training in the rehabilitation programs in order to improve postural control.

- The articles published in international journals and presented in conferences have disseminated the works carried out here and their findings.

6. Conclusion and Future Work Perspectives

Two main objectives were established for this PhD project. The first was to identify existent randomized controlled trials that used cognitive-motor dual-task training and analyze the efficacy of this training compared with single-task training on balance and executive functions in individuals with PD. The second was to compare the postural phase and control strategies when performing single- and dual-task conditions in controls and in individuals in early stages of PD (Hoehn and Yahr scale < 3) during: static balance, STSTS movement and gait initiation.

Some randomized clinical trials that used cognitive-motor dual-task training were found and, based on their findings it was possible to establish an intervention program for individuals with PD. The motor training with a cognitive task performed simultaneously improved the performance of some parameters related to balance and executive functions of individuals with PD. Therefore, this kind of intervention should be used in this population from the early stages of the disease.

The second objective shows that individuals with PD have more difficulty to achieve suitable postural control when performing dual-task than when performing single-task. The task that showed the best performance in the dual-task condition was the gait initiation, which indicates an ability of individuals with PD to prioritize the motor task. This may be due to the fact that gait initiation requires more care to prevent falls. This is in line with the fact that the dual-task performance can be influenced by postural security. From all the factors that have been mentioned in the literature as decisive for the performance in dual-task, the stage of disease progression, complexity of the secondary task, limited attentional resources and posture confidence were the most determinant for the results achieved in this project.

Although this project has reached several conclusions, other variables should be explored and the findings obtained should be confirmed in larger samples. The use of longer cognitive-motor dual-task interventions are suggested for future studies as well as the follow-up of the results. In addition, the control groups should also undergo a cognitive training with the single-task training, previous to or followed by a balance training to ensure that the dual-task training outcomes are not just due to cognitive training.

Studies on the influence of dual-task in motor control should be based on electromyographic activity, as this activity is closely related to postural adjustments, which would allow further discussion of the results. In addition, studies using more than one dual-task with different degrees of complexity are also suggested.

PART B - ARTICLE 1

Characteristics and efficiency of rehabilitation with dual-task training: A systematic review on randomized controlled trials.

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Submitted to an International Journal

Abstract

Objective: To identify randomized controlled trials in the literature that used cognitive-motor dual-task training and verify the effectiveness of the trainings.

Data Sources: Four electronic databases were used: PubMed®, Scopus®, ISI Web of Science® and Cochrane Library Controlled Trials Register. The search terms were: dual-task, randomized, training and clinical trial. The search was limited to articles concerning humans and written in English.

Study Selection: The articles retrieved for this review from the electronic databases complied with the inclusion criteria: (a) randomized controlled trials, (b) references to randomization and (c) cognitive motor dual-task intervention. The titles and abstracts retrieved were read by two reviewers independently.

Results: 13 studies were included in the systematic review; the common objective was to discuss the effects of dual-task training; the population that has been studied the most is healthy elderly people. The skills assessed were: balance, executive functions, falls, gait, mobility and functionality. In general the interventions had similar exercises; however, they differed in duration (3 to 24 weeks), intensity (30 to 90 min) and frequency (1 to 5 times per week).

Conclusion: The cognitive-motor dual-task led to effective results in 53.8% of the studies analyzed for balance, executive functions and functionality. The duration and type of intervention in the control groups appear to be the factors that have the most influence on the results. The effects of these interventions should be analyzed in specific populations.

Keywords: Dual-task; intervention; controlled clinical trial; systematic review.

Introduction

Dual-task, i.e., performing two tasks simultaneously, is a prerequisite for effective functional performance of anyone's daily life. Thus, the practice of various activities in the context of dual-task is essential for multitask learning and performance, since the training of a single-task limits the coordination of required tasks (V. Sethi & R. Raja, 2012).

Motor performance impairments may result in part from cognitive deficits, particularly in executive functioning and in attention allocation (Coppin *et al.*, 2006; Springer *et al.*, 2006; Van-Lersel *et al.*, 2008). Changes in these processes can lead to an exacerbation of difficulties on a dual- and multi-task level, due to the important role of executive functions with an appropriate allocation of attention in simultaneously occurring tasks (Rochester *et al.*, 2004).

Difficulties in performing two tasks at the same time have been reported associated to several neurological conditions, including multiple sclerosis (Hamilton *et al.*, 2009), Parkinson's disease (T. Wu & M. Hallett, 2009), Alzheimer's disease (J. A. Foley, Kaschel, Logie, & Della Sala, 2011) and stroke (Plummer-D'Amato *et al.*, 2008). So dual-task performance studies have been carried out with patients suffering from neurological conditions as well as healthy elderly (Ohsugi, Ohgi, Shigemori, & Schneider, 2013).

New paradigms have been studied in the area of dual-task interventions and clinical trials designed to determine the effectiveness of the dual-task training, especially compared to single-task training. However, the diversity of protocols and results hamper any clear conclusions (Lussier, Gagnon, & Bherer, 2012; Melzer I & LI, 2004; Pompeu *et al.*, 2012; Silsupadol *et al.*, 2006; Yogev-Seligmann *et al.*, 2012; You *et al.*, 2009).

Therefore, the main aim of this study was to conduct a systematic review of randomized controlled trials with cognitive-motor dual-task training in order to verify the effectiveness of this training. In addition, we wanted to identify and describe the populations involved, the exercises used, the type of sessions, the improvements made and how these were assessed in the relevant studies.

Methods

We performed a systematic review of randomized controlled trials from the 4 databases according to the criteria of the Cochrane Collaboration and PRISMA Statement (Higgins & Green, 2011; Moher, Liberati, Tetzlaff, & Altman, 2009). Only randomized controlled trials with cognitive-motor dual-task intervention were considered, and the search was limited to articles written in English and concerning humans. Randomized controlled trials that had motor-motor dual-task or cognitive-cognitive dual-task as the main intervention and non-randomized controlled trials were not included.

The search strategy was performed by two independent investigators in the following databases: PUBMED (1991-2013), WEB OF SCIENCE (1995–2013), SCOPUS (1985–2013), Cochrane Controlled Trials Register Library (1980-2013). The search strategy used the following MESH terms: dual-task, cognitive-motor task, randomised clinical trial, controlled clinical trial and randomized. In addition, the same researchers performed a manual search of journals in this field.

To allow a direct comparison of the data in the retrieved articles, the data extraction included the following information: authors, year of publication, objectives of the study, population, size (n) of the sample, instruments, skills assessed, characteristics of the intervention (duration, frequency, intensity, exercises, responsible for intervention, type of session), results and conclusions. The information gathered from the included studies was organized descriptively in tables.

To avoid selection bias, the internal validity of the included studies was evaluated by two independent reviewers and as there were no disagreements in the selections made, a third reviewer was not needed. This assessment followed the Cochrane Collaboration Handbook recommendations and items such as: randomization, concealment allocation, blinding of assessment and intention-to-treat analysis were used and were classified as: low risk when clearly described, high risk when not described and unclear when described as indeterminate in the text (Higgins & Green, 2011). For this analyse the Review Manager – Revman 5.2 was used.

Results

From the article selection process, 662 articles were found. After eliminating the duplicate articles (n=250) and excluding the non-relevant ones (n=393), 18 full-text articles were selected for eligibility. A backward citation tracking using Scopus database was performed, i.e., a new search was conducted based on these 18 articles. This resulted in another 225 articles, that after the exclusion of the non-relevant articles (n=221), led to 4 more articles. The 22 articles were then read in full and the articles that did not meet the inclusion criteria were excluded (n=9). Thus, 13 articles were selected for the systematic review, Figure 1.

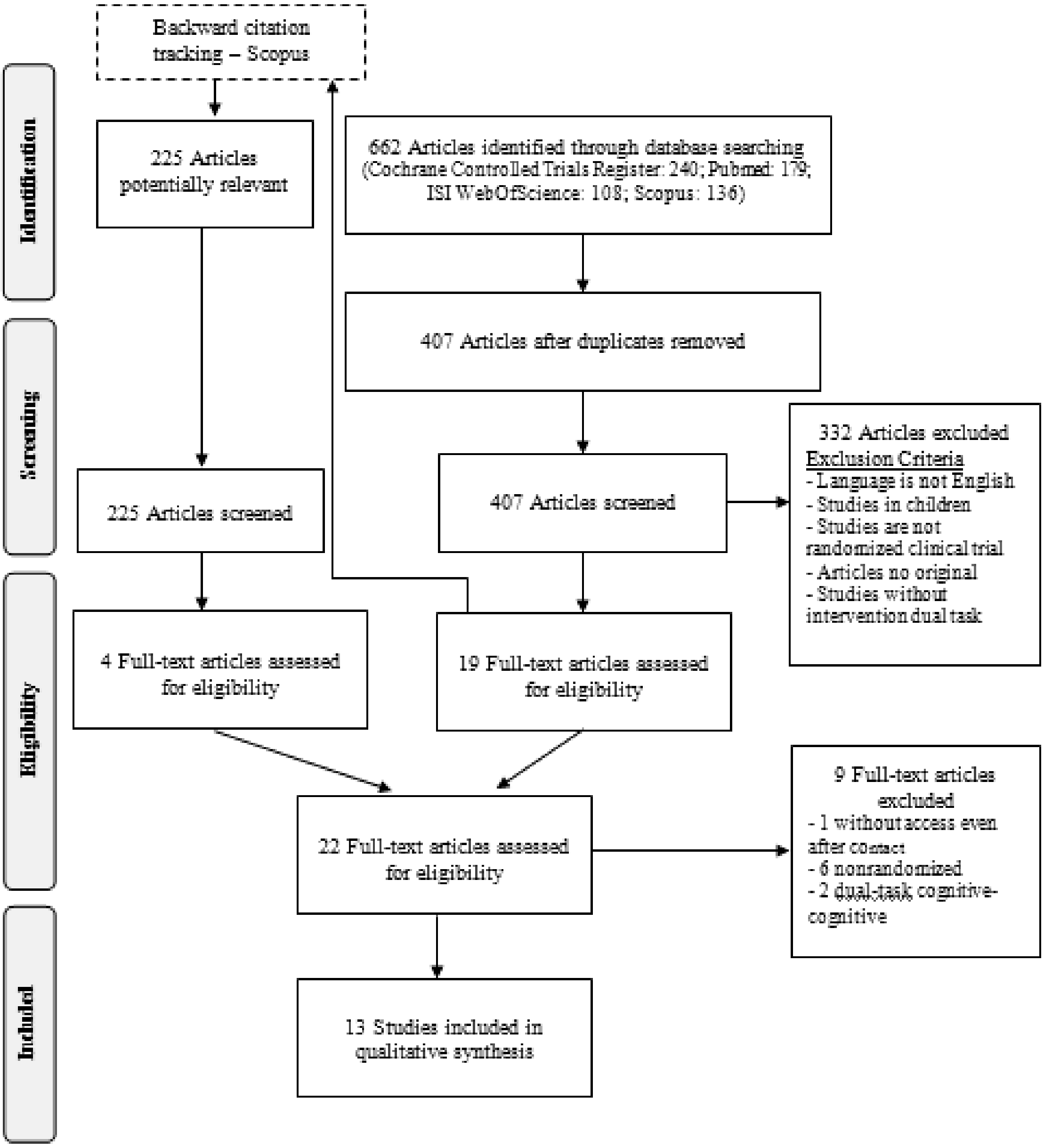

Figure 1. Flowchart of the selection process of the articles included in this review, which was based on PRISMA (Liberati *et al.*, 2009).

The selected articles were published between 2005 and 2012. The 13 articles included a total of 458 participants, of which 54.1% were female. As to the populations addressed, 5 of the studies are related to healthy elderly (de Bruin, van het Reve, & Murer, 2012; 2011; Plummer-D'Amato *et al.*, 2012; Silsupadol, Shumway-Cook, *et al.*, 2009;

Yamada, Aoyama, Tanaka, Nagai, & Ichihashi, 2011), 2 to individuals with stroke (2011; Jiejiao *et al.*, 2012), 1 to elderly with Alzheimer disease (Makizako *et al.*, 2012), 1 to elderly with motor impairment (Silsupadol, Lugade, *et al.*, 2009), 1 to elderly women with osteoporosis (Vaillant *et al.*, 2006), 1 to neurological injury (Evans, Greenfield, Wilson, & Bateman, 2009) and 1 to healthy adults (Pellecchia, 2005). The average age of the participants was around 71.8 years old (Table 1).

Table 1. Information about the articles selected: target populations, samples, gender, ages and instruments.

First Author, Year	Target population	Sample (I/C)	Men/ Women	Age (SD)	Instruments
de Bruin *et al.* (2012)	Healthy elderly	16 (8/8)	I: 2/6 C:3/5	I:79.8 (6.8) C: 75 (8.3)	Timed Up and Go Test; Falls Efficacy Scale; Triaxial accelerometer; International Handheld electronic timer.
Evans *et al.* (2009)	Neurological injury	19 (10/9)	I:9/1 C:8/1	I: 44.4 (8.5) C: 45.1 (9.7)	Walking; Clicking; Sentences; Tone; Counting; Questionnaire regarding activities of daily living.
Hiyamizu *et al.* (2011)	Healthy elderly	36 (17/19)	I: 7/10 C:3/16	I: 72.9 (5.1) C:71.2 (4.4)	The Chair Stand Test; Functional Reach Test; Timed Up and Go Test; Trail Making Test; Force platform; Stroop.
Jiejiao *et al.* (2012)	Chronic Stroke	92 (45/47)	I: 24/21 C:32/15	I:69.1 (5.0) C:71.2 (4.4)	Force Platform.
Pedroso *et al.* (2012)	Alzheimer	21 (10/11)	Not defined	I: 78.3 (7.4) C:77.5 (6.9)	Mini Mental State Examination; Frontal Assessment Battery; Clock Drawing Test; Timed Up and Go Test; Berg Balance Scale.
Plummer-D'Amato *et al.* (2012)	Healthy elderly	17 (10/7)	Not defined	I: 79.6 (5.6) C:76.7 (6.0)	Montreal Cognitive Assessment; Shipley Vocabulary Test; Geriatric Depression Activities-specific Balance Confidence; Timed Up and Go Test.
Makizako *et al.* (2012)	Alzheimer	50 (25/25)	I: 13/12 C:14/11	I: 75.3 (7.5) C:76.4 (6.8)	Mini-Mental State Examination; Wechsler Memory Scale Rev; Logical Memory II; Walking

First Author, Year	Target population	Sample (I/C)	Men/ Women	Age (SD)	Instruments
					speed; Dynamometer; One-leg balance.
Vaillant *et al.* (2006)	Women with osteoporosis	56 (36/20)	Not defined	I: 73.4 (1.7) C:75.6 (1.5)	Timed Up-and-Go test; One-leg balance test on both sides.
Yamada *et al.* (2011)	Healthy elderly	53 I:26 C:27	16/40	I:80.8 (5.4) C: 72.0 (3.9)	Gait speed; Walking cadence; Number of steps; One Leg Balance; Timed Up and Go.
Her *et al.* (2011)	Stroke	38 I:13 C:12+13	I:8/5 C:7/5 C:5/8	I: 63.5 (6.4) C:64.8 (5.2) C:64.5 (4.8)	Gaitview; Berg Balance Scale; Functionality Independence Measurement.
Pellecchia (2005)	Health adults	18 I:6 C:6+6	I:3/3 C:3/3 C:3/3	Not defined	AMTI Accusway system; SWAYWIN.
Silsupadol, Shumway-Cook, *et al.* (2009)	Healthy elderly	21 I:8+6 C:7	I:2/6 I:2/4 C:0/7	I: 74.4 (6.2) I: 76.0 (4.7) C:74.7 (7.8)	Eight-camera motion analysis; Verbal reaction time; Congruency effect;
Silsupadol, Lugade, *et al.* (2009)	Elderly: balance impairment	21 I:8+6 C:7	I:2/6 I:2/4 C:0/7	I: 74.4 (6.2) I: 76.0 (4.7) C:74.7 (7.8)	Gait speed; Berg Balance Scale; Activities specific Balance Confidence Scale.

I: Intervention; C: Control

Table 2 shows the intensity and duration of the interventions. In all studies, the intervention was developed individually or in small groups by technicians with experience or training. The intervention varied from 3 to 24 weeks, the frequency varied from 1 to 5 times per week, and the duration of each session varied from 30 minutes to 90 minutes. Regarding the number of hours of the intervention, 6 studies had less than 10h of intervention (from 3 to 9 h), and 7 studies had more than 21h of interventions (from 21 to 72h).

Table 2. Characteristics of the dual-task interventions, in terms of duration, frequency, intensity and technicians involved, reported in the articles reviewed.

First author, Year	**Characteristics of the interventions**			
	Duration (weeks)	**Frequency (times a week)**	**Intensity (minutes per session)**	**Other information**
de Bruin *et al.* (2012)	12	2	45-60	individually, experienced trainer
Evans *et al.* (2009)	5	10	Not defined	therapist
Hiyamizu *et al.* (2011)	12	2	60	specific physiotherapist
Jiejiao *et al.* (2012)	8	5	40	physical therapist
Pedroso *et al.* (2012)	16	3	60	not defined
Plummer-D'Amato *et al.* (2012)	4	1	45	group circuit in small groups
Makizako *et al.* (2012)	24	2	90	two trained physiotherapists
Vaillant *et al.* (2006)	3	2	Not defined	three physiotherapists with groups of four
Yamada *et al.* (2011)	24	1	50	physiotherapist
Her *et al.* (2011)	6	3	30	physical therapist
Pellecchia (2005)	3	1	Not defined	Individually
Silsupadol, Shumway-Cook, *et al.* (2009)	4	3	45	individually
Silsupadol, Lugade, *et al.* (2009)	4	3	45-50	4 training stations each one with an instructor

Relatively to the number of groups, 9 studies (69.2%) involved two groups; experimental and control groups. The studies of Bruin et al. (2012), Evans et al. (Evans *et al.*, 2009), Hiyamizu et al. (2011), Jiejião et al. (2012), Makizako et al. (2012), Plummer-D’Amato et al. (2012), Vaillant et al. (2006) and Yamada et al. (2011) had interventions with cognitive-motor dual-task in the experimental group and a single-task intervention in the control group. On the other hand, Pedroso et al. (2012) did not have any intervention in the control group, while in the experimental group, a cognitive-motor dual-task intervention was performed. The remaining four studies (30.8%) had three groups: one group for cognitive-motor dual-task and the other two groups had different interventions. Her et al. (2011) applied dual-task in all groups: a cognitive-motor dual-task was applied to one group, cognitive-cognitive dual-task in another group and a motor-motor dual-task in a third group. Pellecchia (2005) applied dual-task to one of the groups, a single-task to another group and the third group did not have any intervention. Finally, Silsupadol et al. (Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009) conducted two studies and in both a cognitive-motor dual-task was applied to the two groups, one with a fixed priority and the other with variable priority, and a single-task was applied to the third group. The exercises, results and conclusions involved in each of the studies reviewed are indicated in Table 3.

Table 3. Groups, results and conclusions of each study.

First author, Year	Group: Results	Conclusions
de Bruin *et al.* (2012)	**ST:** Reaction time hand (p=0.028); TUG§ (p=0.018). **DT:** Fear of falling (p=0.017); reaction time foot (p=0.046); reaction time hand (p=0.048); timed up and go test (p=0.028). No statistically significant differences were found between groups.	Dual-task training reveals high potential to decrease the fear of falling and foot reaction time.
Evans *et al.* (2009)	Statistical significance between groups in sentences (η2¶, p=4.03), walking (η2¶, p=4.46), tones (η2¶, p=5.00), and dual task questionnaire (η2¶, p=3.29).	Some evidence that dual-tasking performance in everyday life was improved after the intervention.
Hiyamizu *et al.* (2011)	**DT:** Rate of stroop task maintaining a standing position higher (p=0.03). **ST:** no statistical differences were found. No statistical differences were found between groups in the Chair Stand Test (p=0.78), Functional Reach Test (p=0.63), TUG§ (p=0.86), Trail Making Test (B–A) (p=0.56) and sway lengths.	Dual-task training in elderly improves dual-task performance during standing.
Jiejiao *et al.* (2012)	**DT:** Anteroposterior balance with eyes open (p=0.000). **ST:** no statistical differences were found. Significant difference was found in mediolateral sway with eyes open and eyes closed (p<0.05).	Dual-task training can produce some beneficial effects on balance function.

First author, Year	Group: Results	Conclusions
Pedroso *et al.* (2012)	**DT:** Mini Mental State Examination (p=0.019); better correlations between executive functions and balance were found: FAB* and TUG§ (r =- 0.67); CDT† and TUG§ (r = -0.64). **ST:** no statistical differences were found. Significant interaction was found between groups and moments in the FAB* (p=0.000), CDT† (p=0.025) and BBS‡ (p=0.045).	DT improved balance and executive functions. The frequency of falls did not present a significant reduction.
Plummer-D'Amato *et al.* (2012)	**DT:** TUG§ and gait speed (p<0.05), ABC‖ scale (p>0.05). **ST:** TUG§ and gait speed (p<0.05), ABC‖ scale (p>0.05). No statistically significant differences were found between groups.	Both groups showed clinically significant changes in gait speed.
Makizako *et al.* (2012)	**DT:** grip strength (p=0.98), OLB¶ (p=0.35); reaction time with balance (p=0.07) and cognitive (p=0.12). **NT:** no training. No statistically significant differences were found between groups.	No significant changes were found in dual-task performances.
Vaillant *et al.* (2006)	<u>2 weeks later</u> **DT:** OLB¶ (p=0.05), TUG§ (p<0.001). **ST:** OLB¶ (p<0.01), TUG§ (p<0.01). <u>3 months later</u> **DT:** OLB¶ (p<0.001), TUG§ (p< 0.0001). **ST:** OLB¶ (p<0.0001), TUG§ (p<0.0001). No statistically significant differences were found between groups.	No additional gains were achieved by adding the cognitive tasks; the improvements were clinically significant and increased over time.
Yamada *et al.* (2011)	**DT:** OLB¶: 6.9 to 10.5; Gait speed: 0.85 to 0.83; Steps: 21.2 to 20.3; Cadence: 105.9 to 112.4; TUG: 11.3 to 10.8 **ST:** OLB¶: 7.3 to 8.7; Gait speed: 0.88 to 0.97; Steps:22.2 to 22.1; Cadence: 108.3 to 103.5; TUG:12.0 to 12.2	Dual-task training improves dual-task performance during dynamic balance.
Her *et al.* (2011)	**DT cognitive-motor:** mean of sway area, Korean BBS‡ and FIM (p<0.05). **DT cognitive:** mean of sway area, Korean BBS‡ and FIM (p<0.05). **DT motor:** mean of sway area, Korean BBS‡ and FIM (p<0.05) Korean BBS‡ and FIM# improvement in the motor cognitive dual-task was significantly different (p<0.05).	Motor and cognitive dual-task training were found to be more effective when implement simultaneously in terms of balance and daily living abilities.

First author, Year	Group: Results	Conclusions
Pellecchia (2005)	**DT:** length of displacement (p>0.05); number of responses on the cognitive task (p<0.01); error rate and number of responses (p>0.05). **NT:** no training. No statistically significant differences were found between groups.	Results suggest that dual-task practice improves dual-task performance.
Silsupadol, Shumway-Cook, *et al.* (2009)	**Fixed Priority DT:** cognitive task p=0.003; response speed (p=0.003). **Variable Priority DT:** cognitive task p=0.02; response speed (p=0.01). **ST:** cognitive task (p=0.72); response speed (p=0.75) No statistical differences were found between groups.	Variable Priority DT was more effective in improving balance and cognitive performance.
Silsupadol, Lugade, *et al.* (2009)	**Fixed Priority DT:** BBS‡ (p=0.001); gait speed (*p*=0.02); gait speed with cognition (*p*=0.001); ABC‖ (*p*>0.05). **Variable Priority DT:** BBS‡ (p=0.001); gait speed (*p*=0.02); gait speed with cognition (p=0.001); ABC‖ (p>0.05). **ST:** BBS‡ (p=0.001); gait velocity (p=0.02); ABC‖ (p=0.001).	Dual-task training was effective in improving gait speed.

DT: Dual-Task, ST: Single-Task

*Frontal Assessment Battery; †Clock Drawing Test; ‡Berg Balance Scale; §Timed Up an Go Test; ‖Activities-specific Balance Confidence scale; ¶One-leg balance; #Functional independence measure

Regarding the Risk of Bias, Figure 2 gives a summary item by item for all studies analyzed and shows that only one study (by Jiejiao *et al.* (2012)) met the assessment criteria in full. The selection bias showed that the risk related to the random sequence generation was considered high in 2 studies, (Hiyamizu *et al.*, 2011; Vaillant *et al.*, 2006), and considered low in the remainder. The relative risk of allocation concealment was classified low in 7 studies (de Bruin *et al.*, 2012; Evans *et al.*, 2009; Hiyamizu *et al.*, 2011; Jiejiao *et al.*, 2012; Makizako *et al.*, 2012; Plummer-D'Amato *et al.*, 2012; Yamada *et al.*, 2011), high in 4 studies (Pellecchia, 2005; Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009; Vaillant *et al.*, 2006), and uncertain in two studies (Her *et al.*, 2011; Pedroso *et al.*, 2012). The performance bias was rated low in 7 studies (de Bruin *et al.*, 2012; Evans *et al.*, 2009; Hiyamizu *et al.*, 2011; Jiejiao *et al.*, 2012; Plummer-D'Amato *et al.*, 2012; Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009), high in 5, (Her *et al.*, 2011; Makizako *et al.*, 2012;

Pedroso *et al.*, 2012; Vaillant *et al.*, 2006; Yamada *et al.*, 2011), and uncertain in 1 study (Pellecchia, 2005). The bias detection was considered low in 6 studies (Hiyamizu *et al.*, 2011; Jiejiao *et al.*, 2012; Makizako *et al.*, 2012; Plummer-D'Amato *et al.*, 2012; Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009), high in 6 (de Bruin *et al.*, 2012; Evans *et al.*, 2009; Her *et al.*, 2011; Pedroso *et al.*, 2012; Vaillant *et al.*, 2006; Yamada *et al.*, 2011), and uncertain in 1 study (Pellecchia, 2005). The attrition bias was ranked low in all studies, except in the study by Plummer D'Amato (Plummer-D'Amato *et al.*, 2012). Finally, the bias description was also considered low in all studies, except those by de Bruin and Silsupadol (de Bruin *et al.*, 2012; Silsupadol, Lugade, *et al.*, 2009).

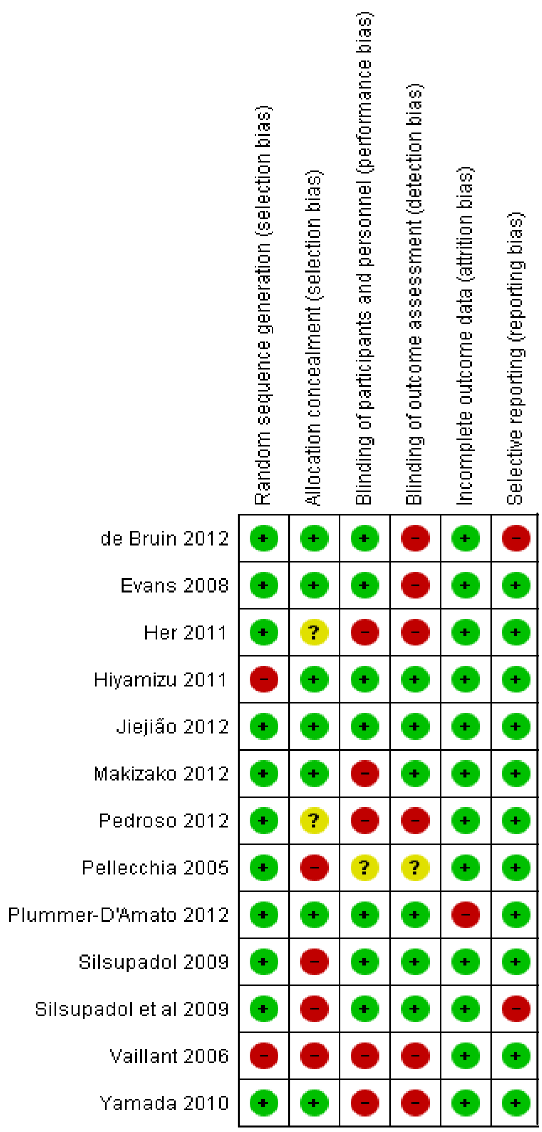

Figure 2. Risk of Bias according to the review authors for each item (- high, + low, ? uncertain).

Discussion

A total of 13 studies were included in the present review, involving a total of 218 participants treated with dual-task training and 240 participants as the controls.

The heterogeneous nature of the studies included in this review challenges the quantitative comparison of results. Thus, it has become essential to analyze the factors that diversify across the studies and may influence the results. Factors related to the sample, evaluation procedures and forms of intervention were analyzed.

Population

The main target populations found were elderly and persons who have had a stroke over 65 years old. These populations reveal noticeable deficits in dual-task activities (J. A. Foley *et al.*, 2011; Plummer-D'Amato *et al.*, 2008). The investigation of Kramer Bherer *et al.* (2006) confirmed that the ability to perform two tasks simultaneously can be substantially improved in the elderly and that plasticity in the control of cognitive attention is possible in old age. In light of the concept of neuroplasticity, it is possible to achieve increased performance in specific cognitive domains, even in individuals who already show some declines (Higgins & Green, 2011). However, individuals do not all have the same level of neuroplasticity. Bherer *et al.* (2006) found that elderly healthy individuals have higher plasticity than elderly with risk of dementia. When comparing elderly and young adults, the most frequently observed pattern is that the young adults improved more than elderly in dual-task training due to higher neuroplasticity (Moher *et al.*, 2009; Yamada *et al.*, 2011).

Intervention: sessions and samples

It is generally assumed that a 10 to 12 h period of intervention is sufficient to obtain positive outcomes. However, there are studies with interventions of longer durations (Evans *et al.*, 2009; Silsupadol *et al.*, 2006) and the results indicate that a higher number of hours may lead to better results. Another factor that may be contributing to detect significant differences in the outcomes is the size of the samples studied. As expected, samples with larger sizes are associated to more expressive outcomes; therefore, studies with larger samples achieved more significant results. With regards to gender, the studies should involve samples with a similar percentage of men and women, as a recent study (Plummer-D'Amato *et al.*, 2012) has shown that in elderly populations, men have a lower stride velocity during dual-task conditions than women. Therefore, men and women may respond differently to the intervention using dual-task procedures, which may also explain the different outcomes reported in the studies analyzed.

As to the programs of intervention, all studies used balance tasks and transfer or change of position exercises, but some also focused on coordination exercises; in terms of the cognitive tasks used, they were very similar. However, the duration, frequency and intensity of the interventions performed were not consistent among the studies reviewed.

Effectiveness

The 13 studies that met the search criteria applied showed that the groups under dual-task training with cognitive-motor exercises improved during the intervention. However, when analyzing the differences between groups, 7 studies showed significant differences. Evans *et al.* (2009) found significant differences between groups in sentences, walking, tone counting and in the dual-task questionnaire. Jiejiao *et al.* (2012) found significant differences between groups in the mediolateral sway with open and closed eyes, and anteroposterior sway with eyes open; Pedroso *et al.* (2012) found group differences in executive functions and balance; Hiyamizu *et al.* (2011) only found differences in rate stroop response. Yamada *et al.* (2011) found group differences in gait speed and walking cadence. Her *et al.* (2011) applied dual-tasks in the three groups, differentiated by the type of procedure, the group with cognitive-motor procedure achieved the best results, with significant differences in terms of sway area in comparison to the motor group, and functionality (functional independence measure) and balance (balance berg scale) compared to the other two groups; and Silsupadol, Lugade, *et al.* (2009) achieved significant results in terms of the ratio of cognitive response and verbal reaction time. These studies had the same number of intervention hours, which is considerably lower than the former three studies; however, satisfactory results were also obtained, probably because the interventions applied to all groups were easier to compare. In the all studies, the best results were for the dual–task interventions. The only parameter that did not get better outcomes with the use of dual-task training was falls, including frequency of falls and confidence levels, which were evaluated in two studies (Jiejiao *et al.*, 2012; Makizako *et al.*, 2012); however, it improved with single-task intervention.

Study Limitations and Future Research

Most of the articles included in this systematic review are pilot studies without solid evidence about the dual-task training efficacy. However, there is a trend for good results in terms of balance, executive functions and functionality. This is even more important given that most of the studies had control groups, which is vital to identify specific treatment outcomes.

In addition, there are several limitations in the research produced so far. For example, most of the dual-task studies have been conducted with elderly individuals and, as already discussed, there is some evidence that younger participants may benefit from such interventions. Furthermore, not all the details provided were sufficient or comparable in the studies. For example, it is crucial to provide a clear description concerning the demographic and clinical characteristics of the participants. Among other benefits, this information would indicate whether such characteristics influence treatment outcomes or not. In addition, the assessment should always be conducted by blinded assessors in order to prevent bias.

There is also an absence of studies reporting follow-up measurements of balance, cognition and functioning, thus ignoring the long term effects of the dual-task intervention. In addition, the long term effects of this training on functional outcomes are important.

Most of the studies reviewed used different treatment plans, especially in terms of the cognitive tasks considered. Hence, the interventions should be described more fully, and the treatment plans should follow common protocols in order to guarantee reproduction and comparison among different studies. Finally, and no less important, the sample size should be sufficient to guarantee adequate statistical power so significant results can be obtained.

This study can be of great importance because as far as the authors know, there is no other review of interventions with dual-task and this type of rehabilitation must be standardized in order to facilitate the comparison of results and their effectiveness.

Implications for practice

Thus, in order to optimize the rehabilitation and reintegration of individuals into their communities and their performance to accomplish daily life activities, it is essential to standardize the form of intervention as well as the objectives. Nyberg and Backman(Nyberg, Backman, & Neely, 2008) suggested that the generalization of skills acquired at a learning center is perhaps the ultimate goal of interventions in order to provide maximum autonomy and independence for each individual.

From the authors' point of view, the positive influences of dual-task interventions have an enormous potential for improving the lives of adults and the elderly. In the face of physical and mental decline with advancing age, dual-task interventions helps to optimize an individual's quality of life, not only by improving health, but also by slowing down or reversing some of the biological effects of the aging process.

PART B - ARTICLE 2

Cognitive predictors of balance in Parkinson’s disease

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Abstract

Background: Postural instability is one of the most disabling symptoms of Parkinson's disease that appears to be closely related to cognitive impairments.

Objective: The aim of this study was to identify the cognitive factors that can predict impairments in static and dynamic balance in Parkinson's disease.

Methods: A sample of 52 individuals with Parkinson's disease was characterized through a sociodemographic questionnaire. The Trail Making Test, Rule Shift Cards Test and Digit Span Test were used to assess the executive functions. The static balance was assessed using a plantar pressure platform, and the dynamic balance based on Timed Up and Go test. The results were statistically analysed using SPSS Statistics software through linear regression analysis.

Results: The factors studied were combined into two statistically significant models ($p=0.01$, $p=0.03$) that explained 23-28% of the Timed Up and Go variability and 9-11% of the anteroposterior displacement variability.

Conclusion: From the findings, we conclude that the psychomotor speed, visuospatial skills, attention and working memory are cognitive component predictors of balance in individuals with Parkinson's disease.

Keywords: Parkinson; Balance; Cognition; Predictors; Plantar pressure.

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease that affects 1% of the world population over 65 years old (Behari, Srivastava, & Pandey, 2005).

Cognitive changes have been addressed by many scientific publications and have concluded that the clinical spectrum of PD is broader than was initially thought (Chaudhuri, Healy, & Schapira, 2006). In PD, deficits are common in several cognitive domains, especially in executive functions (EFs) (Coppin *et al.*, 2006). Recent studies have shown that impairments in EFs are closely related to motor symptoms, particularly with postural instability (Lindholm *et al.*, 2014). This may be due to the important role of these functions in anticipation, planning and coordination (McCloskey & Perkins, 2012).

There are various studies involving cognitive and individual factors with balance impairments; however, none of these studies fully explored if these factors could predict a better or worse balance. Therefore, in this work we intend to identify these factors and see how they explain balance impairments related to PD.

Methods

Study design

A cross-sectional study was designed using a non-probabilistic sample of 52 individuals with PD, aged from 39 to 83 years old. The exclusion criteria were: severe cognitive impairment (screened by Mini Mental State Examination (MMSE)), being unable to stand upright or walk short distances without assistance, severely disabled PD individuals (>3 on the Hoehn and Yahr Scale), individuals with diagnosis of any other neuromuscular disorder, or those who had undergone deep brain stimulation through subthalamic surgery.

The study was approved by the Ethical Review Boards of the Institutions involved in this study and a written informed consent, according to the Helsinki Declaration, was obtained from each participant.

Instruments

The data collected from all participants included sociodemographic characteristics and severity of the impairment motor functions based on the Hoehn and Yahr Scale and part III of the Unified Parkinson's Disease Rating Scale (UPDRS) .

The EFs were also assessed using: the Rule Shift Cards Test, which evaluated the cognitive flexibility and maintenance of information in working memory (Goetz *et al.*, 2004; Lanfranchi *et al.*, 2010; Wilson *et al.*, 2003); the Trail Making Test (TMT) A and B, where TMT A (TMTA) was used to evaluate visuospatial orientation and psychomotor speed, and TMT B (TMTB) to assess cognitive flexibility and divided attention ; the Digit Span was applied to evaluate: attention, working memory and sequential processing (Ostrosky-Solís & Lozano, 2006). Finally, in order to verify the presence of cognitive impairments, MMSE was performed (Dobson, 2010).

An EMED plantar pressure platform, AT 25A model from Novel (Germany), with a sensory area of 380x240 mm^2 and resolution equal to 2 sensors/cm^2 was used for the static balance. The pressure values and stabilometric measurements, such as the centre of pressure (COP) (Maetzler, Bochdansky, & Abboud, 2010; Putti, Arnold, Cochrane, & Abboud, 2008), were acquired with this device at 25 Hz. During the evaluations, the individuals were asked to place themselves on the platform in an upright position, barefoot and looking ahead at a fixed point for a minute. The Timed Up and Go (TUG) test, which measures the functional mobility, was employed to assess the dynamic balance.

Statistical Analysis

Descriptive statistical analysis was performed using proportions, and measures of central tendency and dispersion, according to the nature of the variables.

Linear regressions were conducted in order to investigate the relationship between two or more variables and if one can be predicted from the other(s). Two-tailed tests were used for all analyses and a *p-value* <0.05 was considered statistically significant. The statistical analysis was conducted using SPSS Statistics software, version 22.0 from SPSS Inc. (USA).

Results

Table 1 shows that the sample studied had an average age of 67.3 (±8.9) years old; the mean duration of the disease was 7.9 (±5.5) years, and regarding its severity, 51.9% had the bilateral disease without balance disturbance. The average weight of the individuals of the sample was 72.3 kg (±13.1), and their average height was of 165 (±8.3) cm. In terms of educational levels 65.4% had only 4 years of schooling. The majority of the participants (55.8%) had not suffered any falls during the last year.

Table 1. Sociodemographic and clinical variables of the sample studied (SD - standard deviation).

Variable	n (%)
Age (years), mean (SD)	67.3 (8.9)
Parkinson disease (years), mean (SD)	7.9 (5.5)
Weight (kg), mean (SD)	72.3 (13.1)
Height (cm), mean (SD)	165 (8.3)
Education (years)	
0	3 (5.8)
1-4	34 (65.4)
5-9	9 (17.3)
10-12	1 (1.9)
≥13	5 (9.6)
Falls	
0	29 (55.8)
≥1	23 (44.2)
Disease severity	
Stage 1: Unilateral disease	4 (7.7)
Stage 1.5: Unilateral plus axial involvement	8 (15.4)
Stage 2: Bilateral disease, without impairment of balance	27 (51.9)
Stage 2.5: Mild bilateral disease, with recovery on pull test	9 (17.3)
Stage 3: Mild to moderate bilateral disease; physically independent	4 (7.7)

After checking the correlations among the variables, linear regression analysis was adopted for modelling and to find if there were any possible significant relationships (Table 2). The analysis performed revealed that 23% of the variability found for TUG is explained by the variables of Model 1; however, this increases to 28% when the variables of Model 2 are added, since both are statistically significant. TMTA was the only variable that was found to be statistically significant by itself ($p=0.04$, $R=0.27$).

The variables in Model 1 explained 7% of the variability verified for the mediolateral displacement, and the inclusion of the variables of Model 2 did not modify this result. As for the anteroposterior displacement, the variables of Model 1 explained 9% of the variability, and this increased to 11% when the variables of Model 2 were added.

Table 2. Regression analyses among the TUG, mediolateral and anteroposterior displacements and correlated variables.

		Model 1				Model 2			
		b	95%IC	r	p	b	95%IC	r	p
TUG¶	TMT A	0.04	]0.002;0.068[	0.27	0.04*	0.04	]0.000;0.070[	0.25	0.05*
	MMSE	-0.57	]-1.593;0.460[	-0.14	0.27	-0.48	]-1.536;0.582[	-0.12	0.37
	Digit Span	-0.04	]-0.644;0.561[	-0.02	0.89	-0.10	]-0.708;0.509[	-0.04	0.74
	Walking Aids					-3.62	]-8.659;1.413[	-0.18	0.15
	Age					-0.04	]0.264;0.176[	-0.05	0.69
	Disease Severity					0.71	]-1.113;2.528[	0.01	0.43
	R^2 (p)	0.23 (0.01)				0.28 (0.02)			
ML#	TMTA	0.003	]0.000:0.005[	0.26	0.07	0.002	]-0.001:0.005[	0.23	0.11
	Falls					0.04	]-0.104;0.179[	0.07	0.59
	R^2 (P)	0.07 (0.07)				0.07 (0.16)			
AP§	*Digit Span*	-0.10	]-0.191;-0.006[	-0.29	0.04*	-0.08	]-0.179;0.017[	-0.23	0.10
	Education					-0.12	]-0.343;0.106[	-0.14	0.30
	Height					0.02	]-0.020;0.053[	0.12	0.37
	R^2 (p)	0.09 (0.03)				0.11 (0.11)			

Regression coefficient (b); confidence interval of 95% (95% IC); semi-partial correlation coefficient (r); *p-value <0.05; coefficient of determination (R^2 and p-value for each model); ¶Timed Up and Go test; #Mediolateral displacement; §Anteroposterior displacement.

Discussion

A recent study the Lindholm *et al.* (2014) has shown that cognitive impairments, particularly EFs, are closely related to motor symptoms, especially with postural instability. In fact, the results of the correlations found showed that at least one cognitive test was correlated with balance. In another study, Andersson *et al.* (2003), concluded that postural control and cognition are not independent systems. This may be due to the important role of EFs in anticipation, planning and motor coordination (McCloskey & Perkins, 2012).

Based on the close relationship that appears to exist among postural control and cognitive and individual aspects, the analysis of linear regression revealed that 23% of the variability found for TUG was explained by cognitive tests (TMTA, MMSE and Digit Span), increasing to 28% when the individuals' variables were added (Model 2). Also TMTA was found to be the only statistically significant variable by itself (p=0.04), thus revealing that it can be used as a balance predictor. Physiological studies have provided evidence that the primary motor cortex reflects some aspects of sensory information to guide the motor behaviour. Additionally, the time spent in performing tasks, generally reflects the performance in terms of speed and accuracy. The speed is influenced by the degree of accuracy or insistence on accuracy to reduce error rates, which could result in increased reaction times (Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002).

Concerning the static balance, only the anteroposterior displacement showed a significant model, possibly because regarding the mediolateral displacement, the model was made up of only 1or 2 variables. However, the variables of Model 1 explained 9% of the variability of the variables of the anteroposterior displacement (Digit Span Test), increasing to 11% when the individuals' variables were added. Also Model 1 was shown to be statistically significant (p=0.03), along with Digit Span Test (p=0.04). Andrade *et al.* (2011), concluded that the deterioration in working memory and attention affects balance. In PD, the loss of dopaminergic neurons affects the connection between the basal ganglia and frontal cortex, which interrupts the normal flow of information through these channels, and thus affects the cognitive processes dependent on these areas (Drag, Bieliauskas, Kaszniak, Bohnen, & Glisky, 2009; Owen, 2004). However, PD patients rely heavily on these cortical mechanisms to carry out movements, due to the deficient function of the basal ganglia (Plotnick, Giladi, & Hausdorf, 2010). Bond and Morris (2000), reported that people with PD probably have central processing resources preserved, but the basal ganglia injury means that there is a flaw in the usual shift of attention. So attentional impairments lead to a worsening of balance performance (Marchese *et al.*, 2003).

Conclusion

In this study, two statistically significant models were built and analysed based on linear regression. This analysis confirmed that the scores of the Trail Making Test A and the Digit Span Test were statistically significant. Therefore, it can be concluded that cognitive components such as psychomotor speed, visuospatial orientation, attention and working memory, are important elements to be taken into account for the prediction of balance deficits.

PART B - ARTICLE 3

Effects of dual-task training on balance and executive functions in Parkinson's disease: A pilot study.

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Abstract

The aim of this study was to analyze the efficacy of cognitive-motor dual-task training compared with single-task training on balance and executive functions in individuals with Parkinson's disease.

15 subjects, aged between 39 and 75 years old were randomly assigned to the experimental (n=8) and control (n=7) groups. The training was run twice a week for six weeks. The control group received balance training, and the experimental group performed cognitive tasks simultaneously with the balance training.

There were no significant differences between the two groups at baseline. After the intervention, the results for mediolateral sway with eyes closed were significantly better for the dual-task group and anteroposterior sway with eyes was significantly better for single-task group. The results suggest superior outcomes for the dual-task training compared to the single-task training for static postural control, except in anteroposterior sway with eyes closed.

Keywords: Parkinson's disease, dual-task training, executive functions, balance

Introduction

Parkinson's disease (PD) is considered to be the second most common neurodegenerative disorder affecting currently about 1% of the world population (Andlin-Sobocki, Jonsson, Wittchen, & Olesen, 2005; Campenhausen *et al.*, 2005; Rodrigues de Paula, Teixeira-Salmela, Faria, Brito, & Cardoso, 2006). Some projections point to a large increase in this prevalence over the next decades (Campenhausen *et al.*, 2005) .

PD is clinically defined by motor symptoms such as tremor at rest, rigidity, bradykinesia, as well as postural and gait modifications (Giroux, 2007; Wielinski, Erickson-Davis, Wichmann, Walde-Douglas, & Parashos, 2005); and also by non-motor symptoms such as sleep disorders, cognitive impairment, depression and fatigue, some of which are adverse effects of the dopaminergic medication (Hubert & Fernandez, 2012). Another characteristic feature of PD is the difficulty to perform two tasks simultaneously. This difficulty is because the individuals have to focus on achieving normal movement patterns by activating the premotor cortex region without using the deficient basal ganglia circuit which is deficient in dopamine. Therefore, in dual-task situations that use the cortical resources to perform motor tasks, the performance of both the motor and cognitive components can be compromised (Brauer & Morris, 2010; T. Wu & M. Hallett, 2009). From this point of view, dual-task training should be considered as part of the rehabilitation process of these patients (T. Wu & M. Hallett, 2009), although until now no guidelines have been defined for this type of intervention. New paradigms have been studied concerning cognitive training, such as interventions of cognitive-motor dual-task. This type of intervention should be able to improve dual-task performance and/or improve motor and cognitive components individually (K. Baker *et al.*, 2007; Montero-Odasso *et al.*, 2012; Silsupadol *et al.*, 2006; Yogev-Seligmann *et al.*, 2012).

Regarding specific dual-task training, recent studies have demonstrated its efficacy in various populations such as the elderly and individuals with neurological diseases, with the most notable improvements in gait and balance (Brauer & Morris, 2010; V. Sethi & R. Raja, 2012; Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009). This type of intervention for PD individuals has been focused mainly on gait (Brauer & Morris, 2010; Yogev-Seligmann *et al.*, 2011), and shows improvements in gait speed and gait variability during dual-task training. However, there is no evidence in the literature of the effects of this training on balance and executive functions evaluated independently for PD individuals. On the other hand, such separate evaluation of cognitive-motor dual-task training could be positive and enhance the meaningfulness of this type of training. Thus, considering the positive results of specific cognitive-motor dual-task training obtained in other populations and in other situations that could possibly be reproduced here, we conducted a randomized trial to study the efficacy of a cognitive-motor dual-task training program compared to a single-task program, and evaluated the cognitive and motor components independently, on PD individuals. Accordingly, we hypothesized that cognitive-motor dual-task training is more effective at improving balance and executive functions than single-task training in PD individuals.

Materials and Methods

Participants

Subjects with PD were recruited from the Portuguese Association of Parkinson's Patients. The inclusion criteria used were: capacity to walk ten meters without gait assistance, diagnosis of PD up to Stage 3 according to the modified Hoehn & Yahr scale. The exclusion criteria used were: cognitive deficit confirmed by the Mini Mental State Examination using the following cut-off values according to the education level (≤22 for 0-2 years of literacy; ≤24 for 3-6 years; and ≤27 for ≥7 years (Folstein, Folstein, & McHugh, 1975; Morgado, Rocha, Maruta, Guerreiro, & Martins, 2009)), subthalamic neurosurgery, other neuromusculoskeletal and psychiatric disorders and illiteracy.

The subjects that voluntary accepted to participate were randomized to either the dual-task or single-task training group. The random assignment procedure was performed with numbers generated by a computer program (Microsoft Office Excel 2010), operated by an independent investigator. From a total of 23 eligible subjects, 20 were included in the intervention groups. Before the intervention program started, there were 3 dropouts in the single-task training group (1 for surgery, 1 due to illness and 1 who had various absences) and 2 dropouts in the dual-task training group (1 for personal reasons and 1 due to illness). Hence, 7 subjects were analyzed in the single-task training group and 8 subjects in the dual-task training group. These 15 subjects made up the intervention program as shown in Figure 1.

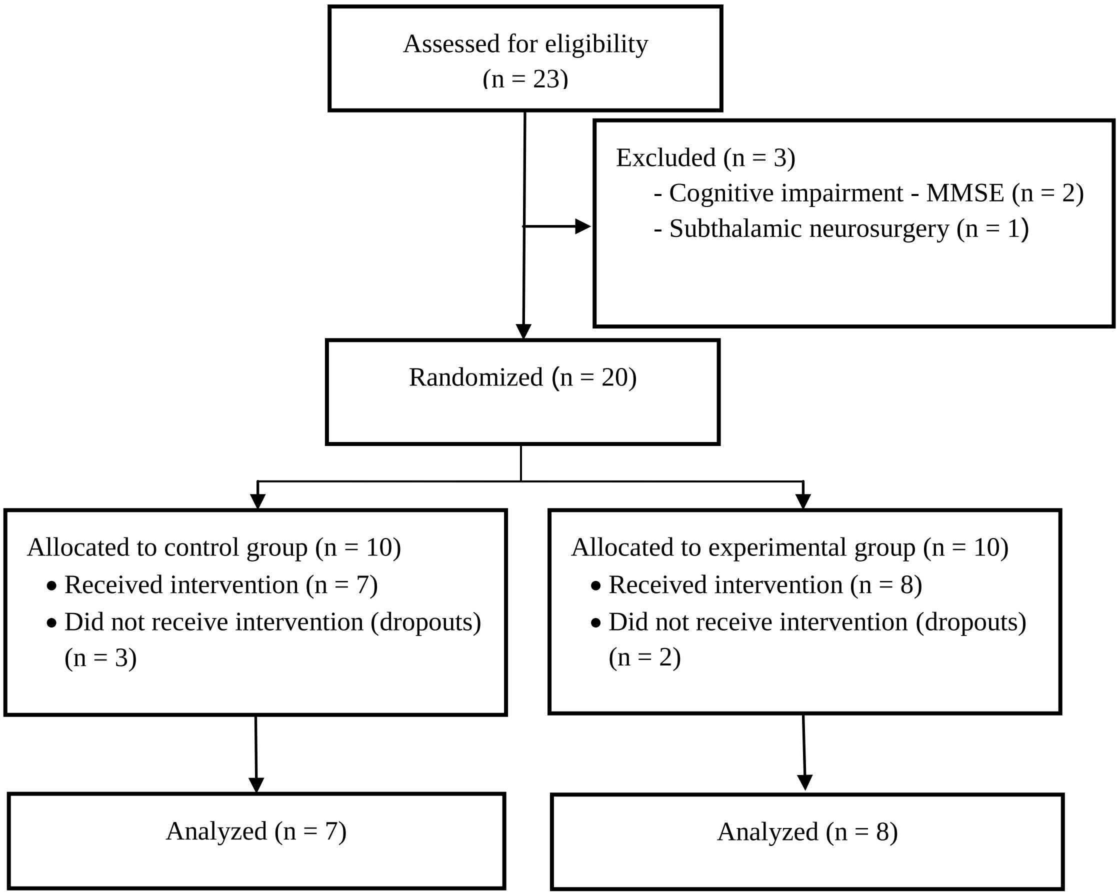

Figure 1. CONSORT (Schulz, Altman, & Moher, 2010) diagram of the recruitment process adopted.

The researcher that evaluated the results was not involved in the training program and had no knowledge to which group the subjects had been assigned, in order to prevent any possible critical judgment and manipulation of the results during the evaluations. In addition, the participants were unaware of the two groups, making this a double-blind study.

The study was explained to each participant according to the intervention group in which they were randomly included. All participants gave their written informed consent in accordance to the Declaration of Helsinki, ensuring data confidentiality and freedom to withdraw from the program at any time. The study was approved by the ethics committee of "Instituto Politécnico do Porto – Escola Superior de Tecnologia da Saúde" and by the directive board of "Associação Portuguesa de Doentes de Parkinson", in Portugal.

Intervention

All participants received balance training that was administered individually twice a week (60 min/session) for six weeks. All participants performed the same motor tasks; however, the participants of the experimental group underwent the cognitive-motor dual-task training program and performed the cognitive tasks simultaneously with the motor tasks, while the participants of the control group only underwent the single-task motor training program, performed the motor tasks. The intervention program was based on an existing training program (Silsupadol *et al.*, 2006). The individual training sessions took place at the "Associação Portuguesa de Doentes de Parkinson" or at the "Instituto Politécnico do Porto – Escola Superior de Tecnologia da Saúde" according to each participant's preference. Each session was organized into 4 stations of intervention, according to Gentile's taxonomy (Gentile, 2000): stability without manipulation activities (e.g. to stand on top of a foam mattress with the eyes closed); gait without manipulation (e.g.: walk on a narrow path); stability with handling activities (e.g. rotate the waist holding a ball) and gait manipulation activities (e.g. walking backwards around objects while holding a basket). The duration of the training sessions was the same for both groups. In the dual-task training, the cognitive activities included digit span (memorize a set of letters or numbers and repeat them in forward or reverse order), N-back (naming a preceding word, letter or number to the one given by the researcher), spelling words (researcher says words to be spelled in the correct order), stroop test (consists of two tasks, reading and naming colour. In both, the stimuli are colour names printed in an incongruent colour), image description (a picture is placed in front of the participant who should describe it with maximum detail), nomination (the participant must say names in a given category: flowers, animals, countries or beginning with a letter of the alphabet), counting (counting in forward and reverse order), description of daily activities and routines (describe the activities that they normally do during a weekday or weekend and describe how do these activities, e.g. what are the stages of taking a shower).

All participants in the experimental group performed the same cognitive activities, but not necessarily in the same order. The complexity of the exercises was increased as the sessions progressed. This increase was based on the addition of obstacles, reduction of the pause time, increasing the complexity of the cognitive task. Each participant received individual training by a professional for 12-15 minutes at each station, which led to a total of 60 minutes per session. Between stations, the participants performed a transition exercise, which was getting up from and sitting down on a chair 15 times. Before beginning the exercises, all procedures were explained to the participant. No reference was made to the tasks the participant should give more importance to.

Outcome Measurements

All outcome measurements were evaluated at baseline and after the intervention for all participants by a clinician who was blinded to the participant's group.

The outcome measurements of motor performance were obtained by Time Up and Go test (TUG), Unified Parkinson's Disease Rating Scale-part III (UPDRS-III) and pressure platform.

The Timed Up and Go test was used to assess the time the participant took to get up from a chair, walk 3 meters and return to the same chair (the total distance walked was 6 meters) and sit down again. The time value chose for each participant was the best, i.e. the lowest value, of three trials performed (Podsiadlo & Richardson, 1991). The test-retest reliability and inter-rater reliability were ICC = 0.80 and r = 0.99, respectively (Lim *et al.*, 2005). UPDRS (Goetz *et al.*, 2003) assesses the signs, symptoms and perception of individuals concerning their performance of activities of daily living (ADLs), based on a self-report and clinical observations; it should be noted that only the motor exploration (UPDRS-III) was applied. This assessment had a high internal consistency (Cronbach's alpha = 0.96) and a satisfactory inter reliability (all items had k > 0.40) (Martínez-Martín *et al.*, 1994). The pressure platform used was an Emed, from Novel (Germany), model AT 25A, with a sensorial area of 380x240 mm^2 and sensor resolution equal to 2 sensors/cm^2. As a stabilometric measurement, the centre of pressure (COP) was evaluated in terms of the mediolateral direction (COPx), the anteroposterior direction (COPy), and the total velocity (Vt) (Błaszczyk & Orawiec, 2011; Ganesan *et al.*, 2010; J. Holmes *et al.*, 2010). The participants were instructed to stand on the platform and remain in a self-selected comfortable upright position. The pressure data was taken twice: first, the subjects were instructed to remain standing on the platform and look towards a fixed point at a distance of 2 meters for 60 seconds with their eyes open (EO); second, the subjects were instructed to remain on the same platform for the same time but now with their eyes closed (EC) (Ebersbach & Gunkel, 2011). The EO/EC order was randomized in order to avoid any possible learning effect. The acquisition frequency of 25 Hz and normalized relative to each subject's body base of support.

The outcome measurements of cognitive performance were obtained by Rule Shift Cards Test (RSCardsT) and Trail Making Test (TMT) A and B. The RSCardsT is used to evaluate perseverance trends and the ability to switch from one pattern to another, by taking into account the errors and the time taken to complete the task (Golden *et al.*, 2000). The TMT (Reitan, 1992) is a test divided into two parts: Part A evaluates attention and processing speed; and part B that assesses the cognitive flexibility and sequential alternation. In each part, the final score is the total time needed to complete the task (Reitan, 1992).

As in other similar studies with this type of population, all tests were carried out when the participants were taking the prescribed medication, denoted as "ON" medication (Conradsson *et al.*, 2012; V. E. Kelly *et al.*, 2012).

Statistical Analysis

According to the nature of the variables under study, descriptive statistical analysis was performed using proportions for the variable gender, and measures of central tendency and dispersion for the variables age, education, hour of physical activity, height, weight, years of disease and intervention outcomes.

For the inferential analysis, the Kolmogorov-Smirnov test was used to assess data normality. Since the normality of the data distribution could not be assumed, we chose to use non-parametric tests. The Mann-Whitney test for independent samples was used to verify the differences between the two groups at baseline and after intervention. In order to analyze which of the interventions was more effective, the change scores (after the interventions relative to baseline) were used. Two-tailed tests were used in all analyses and were considered statistically significant when $p<0.05$. The training effect was calculated using the Cohen's d rule of thumb (Cohen, 1988): low, $0.20 \leq d < 0.50$;

medium, 0.50 ≤ d < 0.80; and high, d ≥ .80. The data collected was conducted using IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The values in Table 1 reveal that there were no significant differences between the two groups in terms of age, gender, education level, weight, height, years of illness and number of falls. Concerning the cognitive performance, there were no significant differences between groups at baseline on the RSCardsT, TMT A and B. As to the motor performance, there were no differences between groups on UPDRS-part III, TUG and COPx, COPy and Vt with eyes open and with eyes closed.

Table 1. Comparison at baseline between the control and dual-task groups.

	Control Group (n=8)	**Dual-Task Group (n=7)**	**p-value**
Age (years)	62.3 (12.9)	63.4 (9.5)	0.862
Gender, male (%)	6 (85.7%)	5 (62.5%)	0.310[a]
Education (years)	10.4 (5.1)	8.6 (6.4)	0.288
Physical activity (hours per week)	1.9 (1.3)	1.3 (0.3)	0.208
Body weight (kg)	67.3 (13.5)	66.8 (13.2)	0.817
Height (cm)	168.3 (8.0)	163.9 (7.4)	0.121
Years of disease	7.7 (7.5)	8.8 (4.3)	0.115
Time Up and Go	11.8 (4.4)	11.3 (3.8)	0.798
UPDRS-part III	14.8 (3.9)	14.3 (4.2)	0.795
Eyes opened			
Mediolateral sway (COPx - cm)	0.938 (0.457)	0.813 (0.249)	0.848
Anteroposterior sway (COPy - cm)	1.084 (0.351)	1.120 (0.527)	0.655
Total velocity (Vt-cm/s)	0.513 (0.426)	0.337 (0.082)	0.898
Eyes closed			
Mediolateral sway (COPx - cm)	0.671 (0.248)	0.813 (0.171)	0.949
Anteroposterior sway (COPy - cm)	1.187 (0.473)	1.133 (0.434)	0.137
Total velocity (Vt - cm/s)	0.578 (0.315)	0.538 (0.447)	0.491
RSCardsT	1.71 (1.38)	2.25 (1.49)	0.475
TMT A	86.33 (69.92)	68.75 (28.40)	0.948
TMT B	186.50 (98.78)	168.75 (55.81)	0.439

Results are: mean and (standard deviation) or (%)

[a] Chi-square test

In order to analyze which of the interventions was more effective, the differences between the two groups were statistically analyzed after the interventions relative to baseline, Table 2. In terms of the motor performance, the only differences were found in COPx and COPy with eyes closed. As to the COPx, the difference between baseline and after intervention was significantly higher for the dual-task group than for the single-task group, U=7.5, p=0.026, with high effect size, d=1.094. The difference between baseline and after intervention in terms of the COPy was significantly lower for the dual-task group than for the single-task group, U=7.5, p=0.029, with high effect size, d=1.43. Nevertheless, the total velocity (Vt) with eyes open and with eyes closed revealed a high effect size (d=0.922 and d=0.902, respectively), and the remaining variables had a medium effect size.

No significant differences were found between the two groups in terms of the executive functions performed. However, the TMT B had a high effect size (d=0.839), the RSCardsT presented a medium effect size (d =0.590) and the TMT A had a small size effect (d=0.324).

Table 2. Comparison between the control and experimental groups after the intervention relatively to baseline.

	Control Group (n=8)	**Experimental Group (n=7)**	**p-value**	**Size Effect**
Time Up and Go	-1.800 (1.127)	-2.900 (3.318)	0.620	0.480
UPDRS-part III	-4.833 (3.764)	-7.000 (2.204)	0.345	0.792
Eyes opened				
Mediolateral sway (COPx - cm)	-0.273 (0.325)	-0.145 (0.093)	0.535	0.581
Anteroposterior sway (COPy - cm)	-0.096 (0.366)	-0.273 (0.257)	0.848	0.605
Total velocity (Vt-cm/s)	-0.148 (0.208)	-0.012 (0.091)	0.128	0.922
Eyes closed				
Mediolateral sway (COPx - cm)	0.112 (0.370)	-0.165 (0.114)	0.026*	1.094
Anteroposterior sway (COPy - cm)	-0.341 (0.465)	0.286 (0.479)	0.029*	1.430
Total velocity (Vt - cm/s)	-0.130 (0.365)	0.096 (0.176)	0.181	0.902
RSCardsT	0.286 (0.489)	1.125 (2.031)	0.336	0.590
TMT A	-11.833 (43.190)	-2,750 (15.416)	0.950	0.324
TMT B	-31.333 (48.980)	-0.250 (32.115)	0.345	0.839

Results are: mean and (standard deviation)

* p-value<0.05

Discussion

Studies have reported the positive influence of targeted interventions for motor training, whether for different cognitive components, including level of attention, processing speed, flexibility and alternating sequential, or for neuromotor issues, mainly in terms of muscle resistance, coordination, balance and agility (L. Baker *et al.*, 2010; Davis *et al.*, 2013; Mirelman *et al.*, 2011; Moher *et al.*, 2009; Tabak, Aquije, & Fisher, 2013; Tanaka *et al.*, 2009). Our research has demonstrated that in a cognitive-motor dual-task training program with 12 sessions, the dual-task training was only statistically more effective than the single-task training for the COPx with eyes closed. A lower oscillation, i.e. smaller COP displacements, corresponds to a higher postural stability (L. Mochizuki, Duarte, Amadio, Zatsiorsky, & Latash, 2006) and thus, in agreement, our results suggested a better balance after the intervention program in the dual-task training group. As to COPy with closed eyes, significant differences were also found, but the dual-task training group presented not as good values as single-task training group. This fact can be explained by the number of years of the disease that was higher in the dual-task training group. The centre of pressure of these participants was shifted to a more posterior position in order to compensate the usual postural deformities caused by high muscular rigidity (J Jankovic, 2008; M Matinolli *et al.*, 2007). This body position, together with the loss of postural reflexes, age-related sensory changes, as well as other features, leads to greater instability in the anteroposterior component (J Jankovic, 2008).

COPx and COPy values with eyes open did not show significant differences between the two groups, but these variables had lower values after intervention in both. Some authors as, for example, (Oie, Kiemel, & Jeka, 2002; Tjernström, Fransson, Hafström, & Magnusson, 2002) defend that vision provides important feedback to the subjects about the physical environment, their spatial interactions and body sway, which complements the information provided by other sensorial receivers. Thus, the eyes open provides important information about postural orientation and helps to optimize the balance control, which may explain the better results found for COP displacement under this condition.

With regard to the Vt, it was found that the results were not statistically significant, but the effect size was high, as in previous studies with elderly individuals (K. Z. Li *et al.*, 2010; Plummer-D'Amato *et al.*, 2012). L. Mochizuki *et al.* (2006) suggested that the lower values of velocity correspond to higher postural stability; however, in our study, the Vt with eyes closed increased in the experimental group, which may be a mechanism to compensate for the lower oscillation.

Based on the Timed Up and Go Test as well as the UPDRS-III test, the difference in terms of mobility was higher in the dual-task training group, with medium effect size, which indicates an improvement of the functional mobility of the individuals. These findings are consistent with other studies in which the average values were better in dual-task training programs, but with no significant results (Her *et al.,* 2011; Jiejiao *et al.*, 2012; Plummer-D'Amato *et al.,* 2012; Vaillant *et al.*, 2006).

Regarding the cognitive components, the TMT A, TMT B and RSCardsT results showed a tendency for improvement in both groups after intervention, likewise in a previous study by Hiyamizu et al. (2011) with healthy elderly individuals. These findings are also in agreement with other studies where visible improvements after dual-task interventions were found, although without statistical significance (Makizako *et al.*, 2012; Pedroso *et al.*, 2012; Pellecchia, 2005; Silsupadol, Lugade, *et al.*, 2009).

The present study, as far as the authors' know, is innovative as it is the first study to assess the outcomes of a dual-task intervention on balance and executive functions in subjects with Parkinson's disease. Nonetheless, there are some limitations that should be discussed. The small size of the studied sample can limit the results, particularly regarding the significance of the statistical tests performed and the generalization of the findings. Hence, this work should be considered as a pilot study that has added knowledge concerning the effects of dual-task training on balance and executive functions in patients with PD. All participants involved were "ON" cholinergic medication, but the effect of the medication on the participants' performance was not taken into account. Therefore, although the intervention adopted was selected based on other closely related studies (Silsupadol, Lugade, *et al.*, 2009; Silsupadol, Shumway-Cook, *et al.*, 2009), it is suggested that future studies should also include a cognitive training before or after the balance training in the control group that undergo the single-task training.

In conclusion, as was hypothesized for this study, our findings revealed a more positive response with the dual-task intervention compared to the single-task intervention. The motor training with a cognitive task performed simultaneously improved the performance of some parameters related to balance and executive functions of individuals with PD. These observations highlight the strength of rehabilitative interventions based on dual-task training.

PART B - ARTICLE 4

Standing balance in individuals with Parkinson's disease during single and dual-task conditions

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Submitted to an International Journal

Abstract

This study aimed to examine the differences in standing balance between individuals with Parkinson's disease (PD) and subjects without PD (control group), under single and dual-task conditions. A cross-sectional study was designed using a non-probabilistic sample of 110 individuals (50 participants with PD and 60 controls) aged 50 years old and over. The individuals with PD were in the early or middle stages of the disease (characterized by Hoehn and Yahr as stages 1-3). The standing balance was assessed by measuring the centre of pressure (CoP) displacement in single-task (eyes-open/eyes-closed) and dual-task (while performing two different verbal fluency tasks).

No significant differences were found between the groups regarding sociodemographic variables. In general, the standing balance of the individuals with PD was worse than the controls, as the CoP displacement across tasks was significantly higher for the individuals with PD ($p<0.01$), both in anteroposterior and mediolateral directions. Moreover, there were significant differences in the CoP displacement based parameters between the conditions, mainly between the eyes-open condition and the remaining conditions. However, there was no significant interaction found between group and condition, which suggests that changes in the CoP displacement between tasks were not influenced by having PD.

In conclusion, this study shows that, although individuals with PD had a worse overall standing balance than individuals without the disease, the impact of performing an additional task on the CoP displacement is similar for both groups.

Keywords: Centre of pressure; dual-task; Parkinson's disease; single-task; standing balance.

Introduction

Parkinson's disease (PD) is a chronic, progressive and neurodegenerative disorder affecting over 4 million people worldwide (Brauer *et al.*, 2011; Matinolli, 2009; Murphy & Tickle-Degnen, 2001). Its symptoms can be categorized as motor and non-motor. The four cardinal features of the disease are predominantly motor: tremor at rest, rigidity, bradykinesia and postural instability (Goldenberg, 2008; J Jankovic, 2008; Murphy & Tickle-Degnen, 2001).

Postural stability and, therefore, balance control is essential components of any locomotion system, and is defined as the ability to maintain the body's centre of gravity over the body's support base while standing still or moving. In individuals with PD, the centre of gravity is usually shifted to a more posterior position, in order to compensate for the postural deformities they acquire, due to a tendency to lean forward (Matinolli, 2009). This body position leads to more instability and the likelihood of falls (Goldenberg, 2008). Additionally, rigidity associated with PD reduces the viscoelastic properties of muscles, which usually serve as a first line of defence against balance perturbations (Matinolli, 2009).

Furthermore, the gait and balance of individuals with PD are understood to deteriorate more when they are performing a second task (Brauer & Morris, 2010; Brauer *et al.*, 2011). Several studies have shown that individuals with PD have serious difficulties in processing simultaneous or sequential tasks adequately (Matinolli, 2009). In fact, when two tasks are performed at the same time, competition for limited resources results in dual-task interference and deterioration in the performance of one or both tasks. This leads to a series of problems in the individuals' daily lives (Brauer *et al.*, 2011; Kara, Genc, Colakoglu, & Cakmur, 2012; V. E. Kelly *et al.*, 2012).

However, it is known that the requirements of a task can influence the balance. Recently, studies have shown that the elderly, and more specifically, individuals with PD, can more easily generate words from a certain letter of the alphabet, than generate words belonging to a semantic category (Brauer & Morris, 2010; Kara *et al.*, 2012). These two tasks activate distinct parts of the brain and represent a different level of complexity for different people (Brauer & Morris, 2010). However, there is a gap with regard to the objective assessment of balance during these tasks. In the early stages of PD such results are expected to be similar to those of a population without PD. Thus, the present study aimed to compare the static balance of individuals with PD with controls, under single- and dual-task conditions.

Methods

Study Design and Participants

A cross-sectional study was designed using a non-probabilistic sample of 50 individuals with PD and 60 controls, aged 50 years old or more. As a previous research has shown that the prevalence of this disease is significantly higher in this age group (Tanner & Aston, 2000), the control group was selected considering the minimum age of the PD group in order to reduce the probability of having significant differences between the groups due to age. The individuals diagnosed with PD were from the São Sebastião Hospital, Santa Maria da Feira, in Portugal, and were referred by their neurologist. The control group was constituted by community-dwelling individuals that volunteered after information regarding the study was disclosed in community institutions in Porto, mainly social, recreation and day care centres.

The exclusion criteria were severe cognitive impairment, screened using the Mini Mental State Examination (Folstein *et al.*, 1975). This exam used the following cut-off points: ≤22 for 0-2 years of literacy; ≤24 for 3-6 years; and ≤27 for ≥7 years(Folstein *et al.*, 1975), which are based on the normative values for Portuguese older adults (Morgado *et al.*, 2009) as its performance varies within the population according to the education level (Crum, Anthony, Bassett, & Folstein, 1993). Exclusion was also for individuals that could not stand upright or walk short distances without assistance; and being unable to speak Portuguese. Severely disabled PD (>3 on the Hoehn and Yahr Scale (Goetz *et al.*, 2004; Hoehn & Yahr, 1967), individuals diagnosed with any other neuromuscular disease, or those who had undergone deep brain stimulation through subthalamic surgery, were also excluded. Controls that self-reported any neuromuscular disorder were also excluded; however, taking into account that the controls were community-dwelling individuals that volunteered to participate in the study, their medical doctor was not consulted. A trained researcher conducted the data collection, using a structured protocol. The individuals with PD were assessed in the São Sebastião Hospital and in the Portuguese Parkinson's Association in Porto. Controls were evaluated in the local community institutions (e.g. recreation centres, learning institutions) through which they had first been contacted in order to be included in the study.

The study was approved by all the Institution's Ethical Review Boards and written informed consent, according to the Helsinki Declaration, was obtained from all participants.

Measurements

The data collected from all participants included sociodemographic characteristics (age, sex and level of education), use of a walking aid, body mass index (BMI), cognitive performance (assessed with MMSE (Folstein *et al.*, 1975)), standing balance in single and dual-tasks (examined by measuring of the CoP displacement using a pressure platform (Emed-AT25 D, from Novel Inc., Munich, Germany)), and number of words enunciated in the dual-task condition. The Modified Hoehn and Yahr Scale (Hoehn & Yahr, 1967) and part III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz *et al.*, 2003) were also used to determine the severity of the impairment regarding the motor function of the individuals with PD. The latter information was provided by the individuals' neurologists immediately before the evaluation conducted in this study.

The participants' standing balance, both under single- and dual-task conditions, was assessed with a pressure platform, containing 4000 capacitive sensors within a sensing area of 380x240 mm2 (sensor resolution of 3 sensors/cm2), capable of acquiring the individual's plantar distribution, both in a static or dynamic form, as well as obtaining stabilometric measures, such as the CoP . Following previous studies (Babič, Petrič, Peternel, & Šarabon, 2014; DiDomenico, Gielo-Perczak, McGorry, & Chang, 2010), the CoP displacement based parameters studied were its maximum displacement (cm) in the anteroposterior (AP) and mediolateral (ML) directions, and its mean velocity (cm/s). For this measurement, each subject was asked to take off his/her shoes, step onto the platform, and maintain an orthostatic position for 60 seconds. The standing balance under single-task condition was assessed in two tasks: with eyes open (looking at a target placed two meters away at the height of the participants' eyes) and with eyes closed. In order to examine the standing balance under dual-task conditions, the participants were asked to maintain an upright standing position while performing two different verbal fluency tasks: semantic fluency task (enunciate the name of as many species of animals as possible) and phonemic fluency task (enunciate as many words as possible beginning with the letter R). These verbal fluency tasks were adapted from a previous study (Cavaco *et al.*, 2013). The order of each test changed randomly, from individual to individual, in order to avoid a learning effect and fatigue. The CoP based parameters were further analysed considering the most stable 30-second period of each test.

The UPDRS (Goetz *et al.*, 2003), which was developed to monitor multiple aspects of PD related to disability and impairment, is made up of four parts, and is the most widely used scale for multicentre clinical trials in PD. Furthermore, this assessment tool has a satisfactory interrater reliability. Only the part III of the UPDRS scale was used in this study for the motor examination. The score given for each item varies from 0-4, from normal to severe; and the part III total score ranged from 0-52. This scale is often accompanied by the Modified Hoehn and Yahr Scale (Hoehn & Yahr, 1967), which evaluates the severity of overall dysfunction in PD. This is a 7-point scale, in which each point is a different stage of the disease (stages 1 to 5, including 1.5 and 2.5). The scale increases with the severity of dysfunction along with the stage of the disease. All tests were carried out with the participants taking their prescribed medications, and were therefore denoted as "ON" medication, as in others studies (Conradsson *et al.*, 2012; V. E. Kelly *et al.*, 2012).

Statistical Analysis

According to the nature of the variables, descriptive statistical analyses were performed using proportions and measures of central tendency and dispersion.

Independent samples t test and chi-square test were performed to examine whether there were significant differences between the two samples, i.e. individuals with PD and controls, for the sociodemographic variables, BMI, use of walking aid, MMSE score, number of words enunciated in each verbal fluency task, and CoP parameters.

The correlation of the CoP based parameters with age and also with the amount of words enunciated in the verbal fluency tasks were also examined using the Pearson correlation.

A Mixed Factorial ANOVA was used for the multivariate analysis between the individuals with PD and controls in the different tests, and all variables were assessed simultaneously taking into account the Bonferroni adjustment for multiple comparisons.

For additional evaluations, the independent samples t test was used to obtain outcomes regarding the differences for the various conditions between the two groups.

Two-tailed tests were used in all analyses and a p-value<0.05 was adopted for statistical significance. All statistical analyses were conducted using IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The PD sample comprised 50 subjects (62% male), with a mean age of 68.3 years old (SD=7.3) and a mean education of 5.2 years (SD=3.9). Most participants were classified in stage 2 of the Modified Hoehn and Yahr Scale, and had a mean UPDRS score of 19.1 (SD=7.9). The control sample comprised 60 individuals (56.7% male), with a mean age of 68.9 years old (SD=10.1), and mean education of 5.8 years (SD=3.8). Independent samples t test and chi-square test showed no statistically significant differences between samples, concerning the sociodemographic variables, BMI, use of walking aid, MMSE score, and number of words enunciated in each verbal fluency task, Table 1.

Table 1. Comparison of both groups regarding the sociodemographic variables, body mass index (BMI), use of walking aid, Mini-Mental State Examination (MMSE) score, and number of words enunciated in each verbal fluency task.

	Individuals with PD (n=50)	**Controls (n=60)**	**p-value**
	M (SD)	**M (SD)**	
Age [years]	68.3 (7.3)	68.9 (10.1)	0.72*
Gender [male], n (%)	31 (62)	34 (56.7)	0.70**
Education [years]	5.2 (3.9)	5.8 (3.8)	0.47*
BMI [kg/cm^2]	26.7 (4.2)	27.5 (4.0)	0.32*
MMSE	27.0 (1.9)	26.4 (3.7)	0.31*
Use of walking aid, n (%)	7 (14)	9 (15)	1.00**
UPDRS	19.1 (7.9)	-	-

	Individuals with PD (n=50)	Controls (n=60)	p-value
	M (SD)	**M (SD)**	
Modified Hoehn and Yahr Scale			
Stage 1, n (%)	3 (6)	-	-
Stage 1.5, n (%)	8 (16)	-	-
Stage 2, n (%)	26 (52)	-	-
Stage 2.5, n (%)	9 (18)	-	-
Stage 3, n (%)	4 (8)	-	-
Verbal fluency tasks			
Semantic task	12.3 (3.8)	11.9 (4.5)	0.55*
Phonemic task	6.5 (2.9)	6.2 (4.3)	0.67*

Modified Hoehn and Yahr Scale: Stage 1 - Unilateral disease; Stage 1.5 - Unilateral and axial disease; Stage 2 - Bilateral disease without impairment of balance; Stage 2.5 - Mild bilateral disease; Stage 3 - Mild to moderate bilateral disease.

* Independent samples t-test and ** chi-square test.

No significant association was found between the CoP based parameters and the age ($0.38 < p < 0.99$ and $-0.08 < r < 0.08$) and also between the CoP based parameters and the amount of words enunciated in the verbal fluency tasks (semantic fluency task: $0.18 < p < 0.98$ and $-0.08 < r < 0.13$; phonemic fluency task: $0.07 < p < 0.64$; $-0.17 < r < -0.05$). Consequently, these variables were not included as covariates in further analyses.

Through the Mixed Model ANOVA (Table 2) analyses, it was possible to ascertain that there were statistically significant differences ($p<0.01$) between the individuals with PD and the controls regarding the maximum CoP displacement (both in AP and ML directions), but not in regard to the mean CoP velocity ($p=0.19$). Overall, the CoP based values were higher for the individuals with PD (Table 3).

Table 2. Results of the Mixed Model (between-within) ANOVA analysis of variance for each CoP based parameter.

CoP parameter	Effect	p-value
Maximum CoP displacement in ML direction	Group (between-subject)	<0.01
	Condition (within-subjects)	<0.01
	Interaction	0.11
Maximum CoP displacement in AP direction	Group (between-subject)	<0.01
	Condition (within-subjects)	0.03

CoP parameter	Effect	p-value
	Interaction	0.32
Mean CoP velocity	Group (between-subject)	0.19
	Condition (within-subjects)	<0.01
	Interaction	0.65

Table 3. Comparison of estimated marginal means of the CoP based parameters between groups.

CoP Parameters	Controls		Individuals with PD		p-value
	M (SE)	95%CI	M (SE)	95%CI	
Maximum CoP displacement in ML direction [cm]	1.87 (0.16)	1.54; 2.19	2.55 (0.18)	2.19; 2.90	<0.01
Maximum CoP displacement in AP direction [cm]	2.11 (0.12)	1.88; 2.34	2.59 (0.13)	2.34; 2.84	<0.01
Mean CoP velocity [cm/s]	1.01 (0.09)	0.90; 1.27	1.27 (0.10)	1.06; 1.47	0.19

Significant differences were also found between the tasks (within-subjects) for the maximum CoP displacement in ML direction (p<0.01), maximum CoP displacement in AP direction (p<0.05), and mean CoP velocity (p<0.01). Post-hoc analysis (Table 4) showed that these differences were between the eyes-open task and the remaining tasks, particularly for the maximum CoP displacement in ML direction and for the mean CoP velocity, and between the eyes-open and the eyes-closed conditions, in particular, for the maximum CoP displacement in AP direction.

Table 4. Comparison of estimated marginal means differences of the CoP based parameters between conditions.

Tasks		Maximum CoP displacement ML [cm]			Maximum CoP displacement AP [cm]			Mean CoP velocity [cm/s]		
		M (SE)	95%CI	p-value	M (SE)	95%CI	p-value	M (SE)	95%CI	p-value
EO	EC	-0.27 (0.09)	-0.52; -0.03	<0.05	-0.39 (0.09)	-0.62; -0.16	<0.001	-0.27 (0.03)	-0.36; -0.18	<0.01
	SF	-0.63 (0.19)	-1.14; -0.13	<0.01	-0.36 (0.15)	-0.78; 0.05	0.12	-0.38 (0.09)	-0.63; -0.14	<0.01
	PF	-0.65 (0.19)	-1.15; -0.14	<0.01	-0.23 (0.13)	-0.59; 0.13	0.51	-0.34 (0.10)	-0.60; -0.09	<0.01

Tasks		Maximum CoP displacement ML [cm]			Maximum CoP displacement AP [cm]			Mean CoP velocity [cm/s]		
		M (SE)	**95%CI**	**p-value**	**M (SE)**	**95%CI**	**p-value**	**M (SE)**	**95%CI**	**p-value**
EC	SF	-0.36 (0.21)	-0.93; 0.21	0.53	0.03 (0.16)	-0.41; 0.47	1.00	-0.11 (0.10)	-0.38; 0.16	1.00
	PF	-0.38 (0.21)	-0.95; 0.20	0.50	0.16 (0.14)	-0.20; 0.53	1.00	-0.07 (0.10)	-0.35; 0.21	1.00
SF	PF	-0.01 (0.10)	-0.27; 0.25	1.00	0.13 (0.09)	-0.12; 0.38	0.94	0.04 (0.03)	-0.05; 0.13	1.00

Eyes-open task (EO), eyes-closed task (EC), semantic fluency task (SF), phonemic fluency task (PF)

On the other hand, no significant interaction was found between group and task, which seems to indicate that the differences in the CoP displacement between tasks were similar for both groups. Therefore, it was found that the effect of performing a more complex task (standing with eyes closed), or an additional task (enunciating words while standing), on standing balance was not significantly different between the individuals with PD and controls (Figure 1).

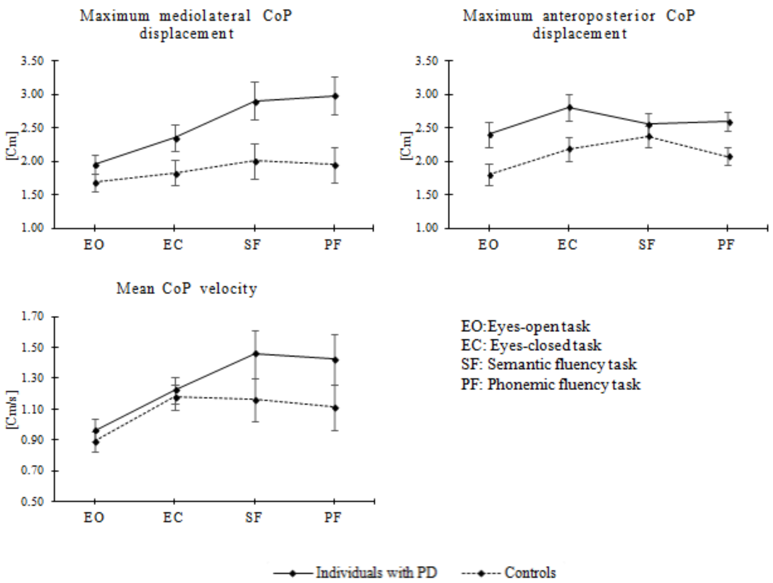

Figure 4. Estimated marginal means and standard errors of the CoP based parameters in each condition and for each group.

Discussion

In general, the standing balance of the individuals with PD was worse (i.e. presented higher CoP displacement values) than those without the disease. For both groups, considering the selected CoP based parameters, the standing balance with eyes closed and under dual-task conditions was worse than the standing balance with eyes open. Furthermore, the differences in standing balance between tasks were not influenced by having PD. In other words, the impact of performing more complex tasks on standing balance was similar for the individuals with PD and the controls, although the standing balance of the individuals with PD was consistently worse.

In comparison with the controls, the individuals with PD had an increased difficulty in maintaining the standing balance. Although only early or middle severity PD individuals were included in the present study, these findings were reasonable considering that postural instability may occur in the early stages of PD (Maarit Matinolli *et al.*, 2007; Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011). Concomitantly, the CoP based values observed were similar to the ones found in previous studies (Morris *et al.*, 2000; Stylianou *et al.*, 2011; Warnica, Weaver, Prentice, & Laing, 2014).

Also as expected, the standing balance was worse when the participants were requested to close their eyes or to perform an additional task. The visual system provides the central nervous system continuous information about the position of the body relative to the environment. Indeed, studies indicate that the postural stability increases with an increasing degree of visual control, as in biofeedback mechanisms (Palm, Strobel, Achatz, von Luebken, & Friemert, 2009). Likewise, the performing of a dual-task can influence the motor performance (Bohnen *et al.*, 2011; Conradsson *et al.*, 2012). Individuals with PD can perform normal movement patterns when they are focused on the movement performance, i.e. when they focus their attention on the implementation of the intended movements. In this situation, the non-injured premotor cortex is activated, without allocating the injured basal ganglia circuit, thereby facilitating the production of movements. When two tasks are performed simultaneously, there is a competition for limited resources, given that the cortical resources are used to perform motor tasks, resulting in interference of the dual-task and in performance deterioration of one or both tasks (J. Holmes *et al.*, 2010). In the present study, clear distinctions were found between the single-task with eyes-open and the other conditions (single-task with eyes-closed and dual-task - while performing two different verbal fluency tasks). Also, the standing balance was found to be worse in more complex tasks (eyes-closed while performing the additional tasks). However, one should argue that the impact of dual-task is related to the complexity of the tasks (V. E. Kelly *et al.*, 2012; V. Sethi & R. Raja, 2012). Regarding the tasks selected for this study, the semantic and phonetic tasks activate different parts of the brain and represent a different level of complexity for different people. The phonetic fluency tasks are more associated with executive function, while the semantic fluency tasks are more closely related to the recovery of information (Azuma *et al.*, 1997; Zec *et al.*, 1999). The fact that the cognitive function of all participants (assessed with MMSE) was relatively preserved might explain why the standing balance in dual-task had values near the eyes-closed single-task condition.

Also, the impact of increasing the complexity of the tasks was relatively similar for the two groups. Although the changes in the CoP based parameters, especially in the maximum CoP displacement in the ML direction and in the mean CoP velocity, across tasks were greater for the individuals with PD, the values of these parameters did not significantly differ from the ones presented by the controls. Some studies (Gobbo, Bergamin, Sieverdes, Ermolao, & Zaccaria, 2014; Targino, Freire, Sousa, Maciel, & Guerra, 2012) have found that individuals with PD have greater standing balance difficulties in dual-task conditions because they need to assign resources previously recruited in order to compensate the deficits in postural control. However, considering that the participants in this study were in early to middle stages of the disease, it is arguable that they did not have the need to recruit significantly more attentional strategies to maintain the postural stability than the controls. Moreover, the added complexity of the dual-task conditions selected for this study might not have been enough to affect these attentional strategies and therefore, the ability of the individuals with PD to maintain the standing balance (Smithson, Morris, & Iansek, 1998). Consequently, one can argue that if more cognitively demanding tasks were selected and/or if the PD participants were in later stages of the disease, the results could have been different. It would also be possible to claim that the results of the present study can be explained by the differences in cognitive status between groups or by different prioritization strategies, i.e. enunciate a reduced amount of words in verbal fluency tasks in order to maintain standing balance; however, no statistically significant differences were found between groups regarding the MMSE score and number of words enunciated in dual-task conditions (Bastiaan R. Bloem, Grimbergen, van Dijk, & Munneke, 2006; V. E. Kelly *et al.*, 2012).

This is the first study that compares individuals with PD to subjects without the disease regarding the changes in the standing balance resulting from performing an additional task. However, some limitations of the study performed can be pointed out. First, the size of the sample and the sampling method could have limited the results in regard to generalizability. Second, the cognitive tasks that were chosen might not have been complex enough to detect the differences between the individuals with PD and the controls. Likewise, the findings could have been different if other CoP based parameters were studied, for example, the length of the CoP path.

Conclusion

The present study showed that the standing balance of individuals with PD is worse than controls. This evidence should provide some guidance for further studies and for the planning of therapeutic interventions, with the aim to improve the functional performance of individuals with PD and delay the oncoming of further disabilities.

Future studies should focus on how different cognitive tasks affect the individual's standing balance, as well as to further investigate the relationship between the single-task condition "eyes closed" and the remaining single- and dual-task conditions. Researchers should also focus on understanding the changes in the CoP based values between single- and dual-task conditions across PD severity and age groups of individuals with PD.

PART B - ARTICLE 5

Parkinson's disease and cognitive-motor dual-task: is motor prioritization possible in the early stages of the disease?

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Abstract

This study aimed to compare the postural phase of gait initiation in single-task (gait initiation) and dual-task (gait initiation plus Stroop test) conditions in healthy subjects and in subjects with Parkinson´s Disease (PD) in the early stages.

The postural phase of gait initiation was assessed through the centre of pressure in single- and dual-task in 10 healthy subjects and 9 with PD.

The analysis indicated that in PD, an additional cognitive task did not affect the displacement of the gait initiation. Differences were found in the duration of mediolateral postural phase that was higher in PD.

The findings suggest that subjects in the early stages of PD prioritize gait initiation, since their motor performance was similar to that of healthy subjects.

Keywords: Dual-task; Stroop test; Gait initiation; Postural phase; Prioritization.

Introduction

The dual-task condition involves the execution of two tasks simultaneously; one being the main task, with a greater focus of attention on it, and the other is the secondary task (V. Kelly, A. Eusterbrock, & A. Shumway-Cook, 2012b; Nocera *et al.*, 2013; Vanshika Sethi & Ravi Raja, 2012). When two tasks are performed simultaneously, the competition for limited resources results in dual-task interference and in the deterioration of the performance of one or both tasks (V. Kelly *et al.*, 2012a; Tao. Wu & Mark. Hallett, 2009b). Biomechanical studies of postural stability have demonstrated that in the dual-task condition, subjects with Parkinson's disease (PD) exhibit impaired postural control. In addition, some authors have suggested that the dual-task condition restricts their anticipatory postural adjustments (APAs), in order to focus on the cognitive task without losing balance (Nocera *et al.*, 2013; Yogev-Seligmann *et al.*, 2010). Postural phase of gait initiation (GI) is associated to the interval between the first vertical impulse, due to the APAs, until the maximum centre of pressure (CoP) displacement backward and toward the first swing limb. It is characterized by a backward displacement of CoP that results from the APAs causing a forward displacement of the centre of gravity (Caderbya *et al.*, 2013; Yiou *et al.*, 2012). Subjects with PD often have difficulties in generating APAs, particularly in forward propulsion and lateral weight shift when initiating gait (Hall *et al.*, 2013). Studies involving subjects with PD have shown that the duration of APAs is extended, the backward and lateral displacements of the CoP are reduced and the length and velocity of the first step are shortened (Burleigh-Jacobs, Horak, Nutt, & Obeso, 1997; Crenna *et al.*, 2006; Gantchev, Viallet, & Aurenty, 1996; Hall *et al.*, 2013; Halliday, Winter, Frank, Patla, & Prince, 1998; M. W. Rogers *et al.*, 2011), increasing the risk of falls (V. Kelly *et al.*, 2012a; Schmit *et al.*, 2005).

Difficulties in performing two tasks simultaneously may be associated with executive dysfunction and attention deficits, which are characteristics of PD (Hausdorff *et al.*, 2006). When individuals with PD focus on the motor performance, they can perform normal patterns of movement by activating the uninjured premotor cortex and not using the injured basal ganglia circuit, thereby ensuring the performance of movements. However, in dual-task condition, the use of cortical resources to carry out motor tasks may compromise or influence the performance of one or both tasks (J. D. Holmes, M. E. Jenkins, A. M. Johnson, S. G. Adams, & S. J. Spaulding, 2010; V. Kelly *et al.*, 2012a; Tao. Wu & Mark. Hallett, 2009b).

Furthermore, several studies have revealed higher instability in upright standing in individuals aged over 65 with and without any pathology that becomes more notorious in the individuals after stage 3 of PD (Tsutiya *et al.*, 2011). However, there is a lack of information about the early stages of PD as well as the influence of the dual-task in GI. Therefore, the aim of this study was to compare the postural phase on GI in single- and dual-task conditions in healthy subjects and in subjects in the early stages of PD (Hoehn and Yahr scale < 3). Therefore, the anteroposterior and mediolateral CoP displacements, the anteroposterior and mediolateral velocities of the CoP displacements and the anteroposterior and mediolateral durations of the postural phase were assessed.

Methods

Participants

A cross-sectional study was implemented using a non-probabilistic convenience sample (Doherty, 1994) of 9 individuals with PD and 10 healthy subjects, aged between 52 and

80 years old. The size of the sample used is in-line with other studies of this kind, such as the studies of Nocera *et al.* (2013) with 13 PD individuals; Halliday *et al.* (1998), with 10 PD individuals; J. Holmes *et al.* (2010), with 12 PD individuals; M. W. Rogers *et al.* (2011), with 8 PD individuals; Schmit, et al. (Schmit *et al.*, 2005) with 6 PD subjects; and the studies of Hiraoka et al. (2006) with 9 PD individuals, and in (2005) with 11 PD individuals. The individuals diagnosed with PD were patients from the Parkinson's Association in Porto, Portugal, while the healthy controls were community-dwelling volunteers mainly from Porto, Portugal.

Subjects were excluded if they presented one of the following factors: incapable of walking independently (based on the Timed Up and Go test (TUG) score until 10 seconds (Podsiadlo & Richardson, 1991)); unable to speak; and severe cognitive impairment (screened with the Montreal Cognitive Assessment (MoCA) (Hoops *et al.*, 2009)). The option for the MoCA test was based on the study by Chou et al. (Chou *et al.*, 2010) who analyzed 5 statistical tests and recommended it as a standard cognitive screening instrument to be used in clinical trials with Parkinson's disease patients. The reasons for this recommendation are that it can be performed quickly and has the potential to identify subtle executive dysfunctions, while covering the major cognitive domains. Severely disabled PD patients (> 3 Hoehn and Yahr Scale (Hoehn & Yahr, 1967)), patients diagnosed with any other neuromuscular disease, or those who had undergone deep brain stimulation through subthalamic surgery or were under cholinergic medication were also excluded. These issues have been made better addressed and justified in the manuscript. Healthy individuals that have been diagnosed as adults with any neuromuscular disorder or that cannot be considered sedentary, according to the Centre for Disease Control for the American College of Sports Medicine, were also excluded (Pate *et al.*, 1995).

A trained researcher conducted the data collection based on a structured protocol. The study was approved by the Ethical Review Board of the "Escola Superior de Tecnologia da Saúde - Instituto Politécnico do Porto", in Portugal. Written informed consent, according to the Helsinki Declaration, was obtained from all participants.

Instruments

The data collected from all participants included sociodemographic characteristics (age, gender, height, weight and level of education), years of disease, cognitive performance (assessed by the MoCA test), functional mobility (evaluated using the TUG test), number of colours correctly named and errors according to the Stroop test, and values in terms of the Hoehn and Yahr scale (1967). Hoehn and Yahr scale is commonly used to assess the severity of overall dysfunction in PD subjects. It is a 7-point scale, in which each point represents a different stage of the disease (stages 1 to 5, including 1.5 and 2.5). The scale increases with the severity of dysfunction along with the stage of the disease (Hoehn & Yahr, 1967).

The values of the vertical, anteroposterior and mediolateral components of the ground reaction forces (GRF) were obtained from a force platform, model FP4060-8 from Bertec Corporation (USA), according to a sampling rate of 1000 Hz (Hanke & Rogers, 1992). The platform was connected to a Bertec AM 6300 amplifier (USA) and in turn, this was connected to an analog-digital converter from Biopac Systems, Inc. (USA), and to an analog board of Qualysis Track Manager (Sweden) that can be used for stabilometric analyses. The force platform signals were digitized and stored for subsequent analysis in Acqknowledge (Biopac Systems, Inc., U.S.A).

Procedures

After an explanation of all the procedures involved, all individuals performed the tasks with shorts and standard shoes (sneakers with laces) that were provided for the study in order to be similar for all individuals. In the single-task condition, the subjects were asked to remaining in the standing position for 30 seconds, looking at a point at eye level two meters away. After this interval, the subjects were instructed to walk three steps at a self-selected speed. In the dual-task condition, the previous procedures were repeated; however, the subjects were required to perform the Stroop test simultaneously, which consisted of naming the colour used to print the name of a different colour (Romann *et al.*, 2012). The order of each condition (single- and dual-task conditions) changed randomly, from individual to individual, in order to avoid a learning effect. There was a one minute rest between each trial, and all necessary repetitions were performed in order to obtain three valid trials to reduce the within-individual variability and increase the statistical power (Mullineaux, Bartlett, & Bennett, 2001). All the experimental data was acquired by the same trained researcher to ensure reproducibility.

The CoP signal was low-pass filtered with a fourth-order Butterworth filter (zero-phase lag) with a cut-off frequency of 8 Hz (D. Winter, 2009). The postural phase was defined as the interval between the starting of the CoP displacement (T0) until the maximum CoP displacement backward and toward the first swing limb. The T0 was identified as the instant when the CoP signal deviated from the baseline (obtained in standing position) plus 3 standard deviations for a minimum interval of 50 ms (Shiratori & Latash, 2001). The end of the postural phase was defined as the instant associated to the first deflection of the CoP displacement (Tsukahara, Kawanishi, Hasegawa, & Sankai, 2010). The values of the anteroposterior CoP displacement (CoP_{AP}) and mediolateral CoP displacement (CoP_{ML}), anteroposterior duration of the postural phase ($Duration_{AP}$) and mediolateral duration of the postural phase ($Duration_{ML}$) and anteroposterior velocity of the CoP displacement (Vel_{AP}) and mediolateral velocity of the CoP displacement (Vel_{ML}) were used for analysis.

Statistical Analysis

According to the nature of the variables under study, descriptive statistical analyses were performed using proportions and measures of central tendency and dispersion. All the variables analysed presented a normal distribution, so MANOVA for repeated measures was used for multivariance analysis between healthy subjects and PD subjects in the single- and dual-task conditions, and all variables were assessed simultaneously. For additional evaluations, the independent samples t test was used to obtain results regarding the differences for the various conditions between groups, while paired samples t test was used to analyse the differences between the single- and dual-task conditions in each group. Two-tailed tests were used in all analyses done and $p < 0.05$ was adopted for statistical significance. All statistical analyses were run using SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The PD sample had 9 subjects (66.7% male), with a mean age of 66 years old (standard deviation (SD) = 8.2), a mean education of 7.7 years (SD = 5.1) and a mean years of disease of 10.22 (SD=5.38). Most of these participants were classified as stage 1 and 1.5 of the Hoehn and Yahr scale with a mean of 8.39 (SD=0.86) seconds in the TUG test. The healthy sample had 10 individuals (50% male), with a mean age of 63.7 years (SD = 7.6) and a mean education of 8.2 years (SD = 4.5). When both groups were compared, statistically significant differences were only found in the number of the colours correctly named on the Stroop test. PD subjects scored less than the healthy subjects, Table 1.

Table 1. Comparison of the sociodemographic and individual variables between the two groups (significant values ($p<0.05$) are indicated in bold).

	Healthy subjects	**Parkinson's subjects**	**p-value**
	M (SD)	**M (SD)**	
Age (years)	63.70 (2.42)	66.00 (2.74)	0.252*
Male, n (%)	5 (50)	6 (66.7)	0.463**
Education (years)	8.20 (1.43)	7.67 (1.69)	0.696*
Weight (Kg)	72.90 (3.14)	69.33 (4.20)	1.000*
Height (m)	1.64 (0.03)	1.65 (0.03)	0.931*
MoCA	26.50 (1.58)	24.78 (5.57)	0.095*
Stroop test: Nº of named colours	24.30 (5.19)	18.17 (5.21)	**0.035**
Stroop test: Nº of Errors	0.63 (0.49)	1.18 (1.45)	0.968*
Hoehn and Yahr scale			
Stage 1, n (%)		3 (33.3)	-
Stage 1.5, n (%)		3 (33.3)	-
Stage 2, n (%)		1 (11.1)	-
Stage 2.5, n (%)		2 (22.2)	-
Years of PD		10.22 (5.389)	-

Hoehn and Yahr scale: Stage 1 - Unilateral disease; Stage 1.5 - Unilateral and axial disease; Stage 2 - Bilateral disease without impairment of balance; Stage 2.5 - Mild bilateral disease; Stage 3 - Mild to moderate bilateral disease.

* Independent samples t-test and

** chi-square test

M – Mean, SD – Standard deviation

The analysis of repeated measures MANOVA, indicated that there were no significant multivariate effects between the healthy and PD subjects studied (F (6.11) = 2.030, p > 0.05, η_p^2=0.525) neither within-subjects independently of their group (F (6, 11) = 0.973, p > 0.05, η_p^2=0.347). Also, no relation was found between the groups and conditions (F (6, 11) = 0.982, p > 0.05, η_p^2=0.349). Univariate analysis between the groups indicated that the $Duration_{ML}$ was significantly higher for the PD subjects than for the healthy subjects, F (1, 16) = 12.494, p = 0.003, η_p^2=0.44). A significant relation was found between the conditions and groups for the $Duration_{ML}$, F (1.16) = 4.717, p = 0.045, η_p^2=0.228).

Although the CoP_{AP} and Vel_{ML} did not present significant differences between the groups, large between-group effects were found, η_p^2=0.07 and η_p^2=0.08, respectively. Considering the within-group univariate analysis, no differences were detected between the single- and dual-task conditions. Nerveless, within the healthy group, large effect sizes (d) were found for the $Duration_{ML}$, $Duration_{AP}$ and Vel_{ML}, and small for the CoP_{AP}, CoP_{ML} and Vel_{AP}. Within the Parkinson’s group, the effect sizes (d) were large for the $Duration_{ML}$, medium for the $Duration_{AP}$ and small for the CoP_{AP} and Vel_{AP}, Table 2.

Table 2. Comparisons between the scores of single- and dual-task conditions for each group. The results are given as the mean (standard deviation), and the significant values (p<0.05) are in bold.

	Healthy Subjects (n=10)		**Parkinson’s subjects (n=9)**		**Effect Sizes**			
	Single-task	**Dual-task**	**Single-task**	**Dual-task**	**F**	**Between Groups η_p^2**	**Within Healthy Group - d**	**Within Parkinson´s Group - d**
CoP_{AP} [cm]	18.08 (11.54)	14.09 (9.65)	10.67 (5.47)	12.83 (7.04)	1.14	0.07	0.38	0.34
CoP_{ML} [cm]	24.16 (12.57)	28.69 (18.54)	23.65 (12.58)	25.76 (13.04)	0.03	0.00	0.29	0.16
$Duration_{AP}$ [seconds]	0.31 (0.11)	0.21 (0.10)	0.26 (0.17)	0.18 (0.08)	0.36	0.02	0.95	0.60

	Healthy Subjects (n=10)		Parkinson's subjects (n=9)		Effect Sizes			
	Single-task	**Dual-task**	**Single-task**	**Dual-task**	**F**	**Between Groups η_p^2**	**Within Healthy Group - d**	**Within Parkinson´s Group - d**
$Duration_{ML}$ [seconds]	0.22 (0.04)	0.17 (0.07)	0.25 (0.05)	0.32 (0.11)	**12.49**	0.44	0.88	0.82
Vel_{AP} [cm/s]	65.67 (53.88)	75.42 (48.81)	61.62 (48.05)	74.60 (35.83)	0.01	0.00	0.20	0.31
Vel_{ML} [cm/s]	107.09 (47.51)	166.16 (92.33)	98.73 (54.79)	96.65 (76.73)	1.43	0.08	0.80	0.03

The significant relations found were explored further. In the dual-task condition, the PD subjects had a significantly higher $Duration_{ML}$ than the healthy subjects, $t(17) = -3.536$, $p = 0.003$). When single- and dual-task conditions were compared, no significant difference was found between the conditions in subjects with PD. However, in healthy subjects, the $Duration_{ML}$ was significantly lower in the dual-task condition than in the single-task condition, $t(9) = -2.496$, $p = 0.034$, Figure 1.

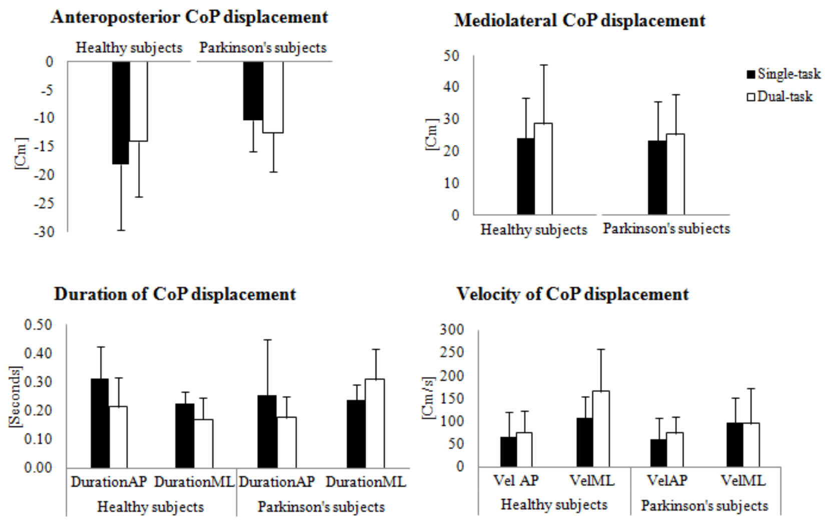

Figure 1. Mean (bars) and standard deviation (error bars) values for anteroposterior, mediolateral, duration and velocity of CoP displacement in healthy and PD subjects during single- and dual-task conditions.

Discussion

The aim of this study was to compare the postural phase of GI in single- and dual-task conditions in healthy subjects and in PD subjects in the early stages of the disease (Hoehn and Yahr scale < 3). In contrast to what was expected, no significant differences were observed between subjects with PD and healthy subjects regarding the CoP_{AP}, $CoP_{ML,}$ $VelCoP_{AP}$ and $VelCoP_{ML}$. However, the mean CoP_{AP} and CoP_{ML} displacements were lower in the subjects with PD. Previous studies of APAs associated with GI have shown that the backward CoP displacement might be significantly reduced in PD subjects (Breniere, Do, & Bouisset, 1987; Elble, Moody, & Leffler, 1994; Nocera *et al.*, 2013). This leads to an extension of the first swing phase and to a decrease in the length of the first step and in the walking speed (Yiou *et al.*, 2012). In this study, the mean values of CoP_{ML} also decreased in PD subjects as was observed in the studies by Yiou *et al.* (2012) and Nocera *et al.* (2013). Also, the mean values of Vel_{AP} and Vel_{ML} found were less in PD subjects, which is in line with those obtained by Halliday *et al.* (1998) and Gantchev *et al.* (1996). Deficits in APAs of PD subjects have been linked to abnormal muscle activation patterns characterized by an extension of excitatory and reduced inhibitory activity as well as a delay in its onset or even loss of muscular activation and/or deactivation (Crenna *et al.*, 2006; Crenna & Frigo, 1991).

Besides the non-existence of statistically significant differences between the healthy and PD subjects, no variable was significantly influenced by the dual-task condition in the PD group. These findings are surprising considering the frequent and consistent negative effect of dual-task on motor performance in PD subjects (B.R. Bloem *et al.*, 2006; J. D. Holmes *et al.*, 2010; Yiou *et al.*, 2012). Some authors have postulated that the nature of this neurodegenerative disease and the cognitive demands of a dual-task condition would limit the performance of one or both tasks (M. Morris, 2000; M. W. Rogers *et al.*, 2011). Thus, before doing this study, it was expected that in GI, the motor performance of the PD subjects would be altered, even in individuals at the initial stage of the disease. Nevertheless, a non-significant difference between the single- and dual-task conditions in GI of PD subjects was also observed in the study by Nocera and co-workers (Nocera *et al.*, 2013).

The non-existence of significant differences between groups obtained in the present study suggests that the PD sample was able to prioritize the motor task in detriment of the cognitive task. This was evidenced by the number of colours correctly named, which was significantly lower in the PD subjects than in the healthy subjects. It is important to note that no differences occurred between the two groups in terms of education and the MoCA test (V. Kelly *et al.*, 2012b; C. O. Souza, Voos, Francato, Chien, & Barbosa, 2013). The MoCA test was applied to both groups to give an indication whether the participants had cognitive deterioration or not and to detect differences of cognitive deterioration between the Parkinson's group and the healthy controls before the evaluation, in order to validate the findings and conclusions of the present study. Moreover, the lack of differences between the healthy and PD subjects may be due to the fact that the underlying anticipatory muscular synergy was preserved and the lower CoP displacement and velocity was probably related to the slowness of execution, i.e. to bradykinetic episodes (Berardelli *et al.*, 2001). In fact, this study found that the CoP_{ML} duration was longer and significantly different for the PD subjects than the healthy subjects. Furthermore, for the healthy subjects the postural phase duration increased in the dual-task condition in relation to the single-task condition. Also these results corroborate other studies suggesting that PD subjects have a lower CoP_{AP}, a higher duration of the postural phase and that the APAs start later during GI in the dual-task condition than in the single-task condition (Carpinella *et al.*, 2007; Nocera *et al.*, 2013; Yiou *et al.*, 2012). In the same subjects, the CoP_{AP} duration tends to decrease from the single- to dual-task conditions. This decrease has been described as an ineffective strategy for maintaining balance, as it causes decreased backward CoP displacements, resulting in higher risk of falls (J. D. Holmes *et al.*, 2010; V. Kelly *et al.*, 2012a; Nocera *et al.*, 2013; Schmit *et al.*, 2005). The fact that the PD subjects under study did not show any differences between the single- and dual-task conditions, can also be explained by a greater focus on the motor task, which means that the motor performance is not debilitated despite the worse results in the Stroop test.

In the literature, most studies to characterize the motor deficits in PD subjects have used subjects in advanced stages of the disease and only in the single-task condition. However, most activities of daily living require the simultaneous execution of a cognitive task. Nevertheless, differences between durations were found. In particular, this study indicates that the behaviour of individuals in the early stages of PD may retain the ability to prioritize tasks and choose the motor task in detriment of the cognitive task. However, it is necessary understand if this prioritization is automatic or it is caused consciously by the individual in order to prevent falls. Therefore, future studies related to the stage of disease in the performance of motor and cognitive tasks independently and simultaneously are essential to clarify this doubt.

Clinical Relevance

This study corroborated that individuals with PD take longer to perform mediolateral displacements, especially in dual-task condition. On the other hand, the mediolateral and anteroposterior displacements found in the individuals with PD were similar to the ones found in the controls. These results indicate that in the early stages of PD, the cognitive performance can be impaired when performing cognitive-motor dual-tasks. Thus, the interventions should not be only focused on the motor performance, which is currently considered the main attention of the interventions, but should also include cognitive training.

Limitations

This study had some limitations. Firstly, the small sample size and the sampling method can limit the results in regard to generalizations, that which leads us to consider it as an exploratory study. Secondly, the potential interference of the experimental environment on the GI of the subjects studied could affect the results obtained. Hence, further studies with larger samples and in different experimental environments are needed.

PART B - ARTICLE 6

The influence of a cognitive task on the postural phase of gait initiation in Parkinson's disease: an electromyographic based analysis

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Abstract

Gait initiation (GI) has been demonstrated to be impaired in Parkinson's disease (PD). The purpose of this study was to compare postural control strategies during GI in single- and dual-task conditions in individuals with early stages of PD (Hoehn and Yahr scale < 3).

The electromyographic activity of the bilateral ankle muscles, tibialis anterior and soleus, of nine individuals with PD and ten control subjects were monitored during the GI in single- and dual-task conditions. The activation timing of tibialis anterior was significantly higher for the individuals with PD than for the controls ($p = 0.05$), and a significant interaction between the groups, conditions and limbs was found ($p = 0.027$). Differences between the single- and dual-task conditions were observed for the activation time of the tibialis anterior ($p = 0.042$) and for the magnitude of soleus ($p = 0.007$), with lower values for the dual-task condition. The duration of the mediolateral CoP displacement was higher in the subjects with PD than in the controls ($p = 0.019$). Furthermore, not all the subjects followed the previously reported pattern of soleus inhibition followed by tibialis anterior activation.

In summary, the anticipatory postural adjustments in GI are impaired in PD and are expressed by an activation failure of tibialis anterior in both single- and dual-task conditions.

Keywords: Dual-task; Postural control; Soleus and tibialis anterior muscles; Patterns of activity

Introduction

Gait initiation (GI) is a transition between an upright posture and gait. On the other hand, the postural phase is defined as the moment of the first vertical impulse, due to the anticipatory postural adjustments (APAs), until the maximum centre of pressure (CoP) displacement backward and toward the first swing limb. In this phase, the CoP moves in the posterior direction, causing the displacement of the centre of gravity forwards (Caderbya *et al.*, 2013; Yiou *et al.*, 2012). This movement involves the coordination of many muscles to support the load on the legs and to produce a forwards movement of the body. The APAs involved in the GI have been seen as an example of muscle synergies of large muscle groups combined with a common motor function (Wang, Shapkova, Siwasakunrat, Zatsiorsky, & Latash, 2007). In young adults, the predominant pattern of muscle activity to produce movement is a bilateral inhibition of the soleus (SOL) activity, followed by a bilateral activation of tibialis anterior (TA) activity occurring almost simultaneously (Crenna & Frigo, 1991; Elble *et al.*, 1994).

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder, with decreased postural reflexes and balance (Błaszczyk & Orawiec, 2011). Individuals with PD often have difficulties to generate APAs leading to impaired forward propulsion and lateral transfer of weight when initiating gait (Hall *et al.*, 2013). Electromyographic (EMG) studies have demonstrated reduced SOL and TA muscle activation during APAs in GI (Gantchev *et al.*, 1996; Rosin, Topka, & Dichgans, 1997). From a neurophysiological point of view, this impairment can be explained by a deregulation of neural pathways between basal ganglia and the pedunculopontine nucleus (Schepens & Drew, 2004) and a higher use of cortical level strategies (Bloem, Grimbergen, Gert van Dijk, & Munneke, 2006; Karachi, et al., 2010; Yarnall, Rochester, & Burn, 2011; Lima-Pardini, et al., 2012). This neuromotor dysfunction can explain the decreased CoP displacement and velocity backward and towards in the first swing limb (Gantchev *et al.*, 1996; Hall *et al.*, 2013; M. W. Rogers *et al.*, 2011) and the increased postural phase duration. In turn, the reduced CoP displacement during the postural phase of the GI contributes to the reduced length and velocity of the first step compromising the GI performance in PD (Burleigh-Jacobs *et al.*, 1997; Crenna *et al.*, 2006; Halliday *et al.*, 1998). Based on the above, it can be expected that in more demanding cognitive conditions the neuromotor dysfunction observed in the postural control phase of the GI in PD would be greater. In fact, in situations of dual-task, the use of cortical resources to perform motor tasks can affect or influence the performance of one or both tasks (J. Holmes *et al.*, 2010; V. Kelly *et al.*, 2012a; V. Sethi & R. Raja, 2012; Woollacott & Shumway-Cook, 2002; Tao. Wu & Mark. Hallett, 2009a). Biomechanical studies of postural stability during GI and walking have clearly demonstrated that the execution of dual-task has a significant effect on postural control among individuals with PD (Nocera *et al.*, 2013; Yogev-Seligmann *et al.*, 2010). However, these studies have accessed the postural control strategies based on kinematic variables which hamper the reasoning about the implications of neural impairment of PD in motor control dysfunction during the GI. The study of the activation timing and magnitude of TA and

SOL and the muscle activation patterns can give significant insights into the comprehension of the motor control dysfunction of the GI in PD. On the top of that, there is a lack of information on the effect of dual-task on the ankle muscle activity during the GI in individuals with PD. Therefore, the aim of this study was to compare the postural phase strategies in GI in single- and dual-task conditions in control subjects and individuals with PD (Hoehn and Yahr scale < 3). Based on previous studies (Nocera *et al.*, 2013; Yogev-Seligmann *et al.*, 2010), it can be hypothesised that the EMG activities of the SOL and TA muscles would be lower in the dual-task condition than in the single-task condition, and that it would be reduced in individuals with PD relative to control subjects.

Materials and Methods

Study Design and Participants

A cross-sectional study was implemented using a non-probabilistic sample of 9 individuals with PD and 10 control subjects, aged between 52 and 80 years old. The individuals diagnosed with PD were patients from the Parkinson's Association, in Porto, Portugal, while the control subjects were community-dwelling volunteers matched in age, gender and limb dominance, mainly from Porto.

Subjects were excluded if they presented one of the following factors: severe cognitive impairment, screened using the Montreal Cognitive Assessment (MoCA) (Hoops *et al.*, 2009), using a cut-off point of ≤26 (Duro, Simoes, Ponciano, & Santana, 2010); unable to walk independently; unable to speak; not sedentary according to the Centre for Disease Control for the American College of Sports Medicine (Thompson, 2001). It should be pointed out here that physical activity promotes improved balance, strength, posture, gait speed, cardiovascular capacity and stamina compared to those who do not do any physical exercise (Ellis *et al.*, 2011; Salgado *et al.*, 2013; Speelman *et al.*, 2011; Yousefi *et al.*, 2009). Severely disabled individuals with PD (> 3 Hoehn and Yahr scale (Hoehn & Yahr, 1967)), diagnosed as adults with any other neuromuscular disease, or those who had undergone deep brain stimulation through subthalamic surgery or were taking cholinergic medication were also excluded. Controls that had been diagnosed with any neuromuscular disorder were also excluded.

A trained researcher conducted the data collection based on a structured protocol. The study was approved by the Ethical Review Board of the "Escola Superior de Tecnologia da Saúde - Instituto Politécnico do Porto" in Porto. Written informed consent, according to the Helsinki Declaration, was obtained from all participants.

Instruments

The data collected included the sociodemographic characteristics age, gender, height, weight and level of education, and years of disease, cognitive performance (assessed by MoCA) (Hoops *et al.*, 2009) and severity of overall dysfunction (Hoehn and Yahr scale) in the PD participants (Hoehn & Yahr, 1967).

The values of the vertical, anteroposterior and mediolateral components of the ground reaction force were obtained using a force platform, model FP4060-8 from Bertec Corporation (USA), according to a sampling rate of 1000 Hz (Hanke & Rogers, 1992). The platform was connected to a Bertec AM 6300 amplifier (USA) and in turn, this was connected to an analog-digital converter from Biopac Systems, Inc. (USA), and to an analog board of Qualysis Track Manager (Sweden) that can be used for stabilometric analyses. The CoP displacement was studied based on the anteroposterior and mediolateral components registered in centimetres (cm). The bilateral (first swing and stance of the limbs) EMG activities of SOL and TA were monitored using surface EMG sensors (model emgPLUX from Plux Ltda, Portugal). The decision to assess TA and SOL was because the inhibition of the posterior muscles, i.e. medial gastrocnemius and SOL, are closely followed by the TA activity, which characterizes the start of gait (Crenna & Frigo, 1991; Elble *et al.*, 1994). Moreover, in comparison to SOL, the medial gastrocnemius activity is clearly asymmetrical, and is less at GI in the stance limb than in the first swing limb (Burleigh, Horak, & Malouin, 1994).

The EMG signals collected with a sampling frequency of 1000 Hz were pre-amplified at the electrodes and then fed into a differential amplifier with an adjustable gain setting (25 - 500 Hz, common-mode rejection ratio (CMRR): 110 dB at 50 Hz, input impedance of 100 MΩ and gain of 1000). For the analogue to digital signal conversion and Bluetooth transmission to the computer, a wireless signal acquisition system (model bioPLUX research, from Plux Ltda (Portugal)) was used. Self-adhesive silver chloride

EMG electrodes, model 505 from Dahlhausen (Germany), were used in a bipolar configuration and with a distance of 20 mm between detection surfaces (centre to centre). The skin impedance was measured with an Electrode Impedance Checker (Noraxon USA, Inc.). The EMG signals were digitized and stored for subsequent analysis in the Acqknowledge software (Biopac Systems, Inc., U.S.A).

Procedures

Skin preparation and electrode placement

The skin surfaces of the mid-belly of the muscles and the patella selected were shaved, and the dead skin cells and non-conductor elements were removed with alcohol and with an abrasive pad to reduce the electrical resistance to less than 5000 Ω.

The EMG electrodes were placed on both limbs according to anatomical references: TA - 1/3 along the line from the tip of the tibia to the tip of the medial malleolus; and SOL - 2 cm distal to the lower border of the medial gastrocnemius muscle belly and 2 cm medial to the posterior midline of the leg and the ground electrode – in the centre of the patella (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000).

Data acquisition

After an explanation concerning the procedures, all individuals performed the tasks with shorts and standard shoes. The foot alignment and the base of support area were maintained constant over the trials. In the single-task condition, the subjects were asked to remain in the upright position for 30 seconds, looking at a point at eye level two meters away. After this interval, the subjects were instructed to walk three steps at a self-selected speed after a verbal command. If a subject asked which leg to start with, the researcher replied ‘‘whatever feels natural for you’’, as lower limb preference plays an influential role on the control of frontal plane body motion during GI (Yamada *et al.*, 2011). However, participants were asked to keep the starting leg consistent for all the trials. In the dual-task condition, the previous procedures were repeated; however, the subjects were required to perform the Stroop test simultaneously (during a total period of 40 seconds). This test assesses selective attention, inhibitory capacity and concentration (J. Holmes *et al.*, 2010; Romann *et al.*, 2012). It should be noted that the Stroop test was only performed in the dual-task condition. There was a one minute rest between each trial, and the necessary repetitions were performed in order to obtain three valid trials for each individual to reduce the within-individual variability and increase the statistical power. The data acquisition was always performed by the same trained researcher to ensure the reproducibility of the technique. The single- and dual-task conditions were performed randomly in order to avoid fatigue and learning effects.

Data processing

The CoP signal was low-pass filtered with a fourth-order Butterworth filter using a zero-phase lag and a cut-off frequency of 20 Hz (D. Winter, 2009). The postural phase was defined as the interval between the beginnings of the CoP displacement (T0) and the maximum CoP displacement backward or toward the first swing limb, associated to the first deflection of the CoP signal, Figure 1. T0 was identified as the instant when the CoP signal deviated from the baseline (obtained in a standing position) plus 3 standard deviations for a minimum interval of 50 ms (Shiratori & Latash, 2001).

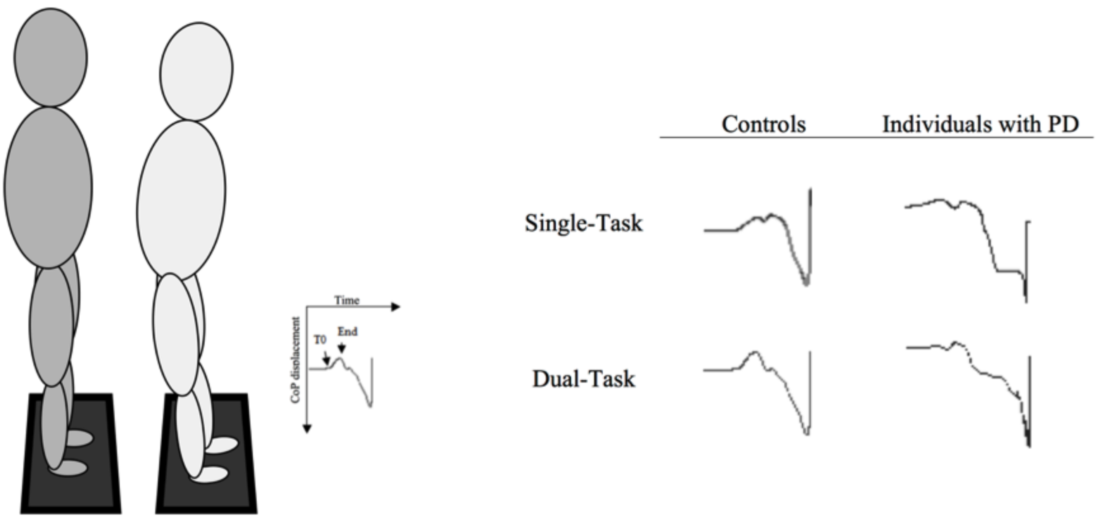

Figure 1. Representation of the anteroposterior CoP displacement for both groups during gait initiation in single- and dual-task conditions. (Here, an increment in the CoP value means a posterior CoP displacement and a decrement in the anterior CoP displacement.)

The EMG signals of both limb muscles were analysed during the postural phase of the GI. The signal was filtered using a zero-lag, second-order Butterworth filter with an effective band pass of 20-450 Hz, and the root mean square was calculated. The magnitude of the signal was calculated for the postural phase and normalized according to the baseline values obtained during upright standing. The activation timing of the TA muscle and deactivation timing of the SOL muscle were detected in a time window from -450 ms in relation to T0 to the end of the postural phase. The latency for each muscle was defined as the instant lasting for at least 50 ms when its EMG amplitude was higher (activation) than the mean of its baseline value plus 3 standard deviations or lower (deactivation) than the mean of its baseline value minus 3 standard deviations, measured from -500 to -450 ms. For each participant, the data of three successful trials were averaged for further analysis. The EMG signal was processed in Matlab (MathWorks, USA).

The score of Stroop test was calculated based on the colour naming test. The number of errors and the number of named items were used for analysis (Lezak *et al.*, 2004) during a pre-defined time (40 seconds) for both groups.

Statistical Analysis

According to the nature of the variables under study, descriptive statistical analyses were performed using proportions and measures of central tendency and dispersion.

MANOVA (group x condition x limb) were used to analyse the multivariance between each group in the single- and dual-task conditions and for swing and stance limbs, when all variables were assessed simultaneously, taking into account the Bonferroni adjustment for multiple comparisons. Two-tailed tests were used in all analyses and $p < 0.05$ was adopted for statistical significance. All statistical analyses were run using IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The PD group had 9 individuals (66.7% male), with a mean age of 66 years old, a mean education of 7.7 years and a mean years of disease of 10.22. Most of these participants were classified as stage 1 (33.3%) and 1.5 (33.3%) of the Hoehn and Yahr scale, and only 11.1% as stage 2 and 22.2% as stage 2.5. The control groups had 10 individuals (50% male), with a mean age of 63.7 years and a mean education of 8.2 years. When both groups were compared, significant differences were only observed in the number of colours enumerated correctly on the Stroop test. The individuals with PD had lower scores than the controls, Table 1.

Table 1. Comparison between the two groups in terms of sociodemographic and anthropometric characteristics. (Significant values ($p<0.05$) in bold.)

	Controls (n=10)	**Individual with PD (n=9)**	**p-value**
	M (SD)	**M (SD)**	
Age [years]	63.70 (2.42)	66.00 (2.74)	0.252*
Male, n (%)	5 (50)	6 (66.7)	0.463**
Education [years]	8.20 (1.43)	7.67 (1.69)	0.696*
Weight [Kg]	72.90 (3.14)	69.33 (4.20)	1.000*
Height [m]	1.64 (0.03)	1.65 (0.03)	0.931*
MoCA test score	26.50 (1.58)	24.78 (5.57)	0.095*
Stroop test: Nº colours named	24.30 (5.19)	18.17 (5.21)	**0.035**
Stroop test: Nº Errors	0.63 (0.49)	1.18 (1.45)	0.968*

* Independent samples t-test

** chi-square test

SD – Standard Deviation

The MANOVA analyses revealed a significant multivariate main effect for the single- and dual-task conditions ($p = 0.033$). Significant univariate main effects for groups were found for all tested variables, but only the activation timing of the TA was significantly higher for the individuals with PD than for the controls ($p = 0.05$). Significant univariate main effects for the conditions were observed for the activation timing of the TA ($p = 0.042$) and for the magnitude of the SOL ($p = 0.007$), with lower values for the dual-task condition than for the single-task condition. The differences between the single- and dual-task conditions occurred in the control group in the magnitude of the TA in the first swing limb, that was significantly lower in the dual-task condition ($p = 0.042$) than in the single-task condition.

In terms of the postural phase duration, a significant relation was found between the conditions and groups for duration of the mediolateral CoP displacement ($p = 0.045$). Specifically, in the dual-task condition, the individuals with PD had a significantly higher duration of the mediolateral CoP displacement than the control subjects ($p = 0.019$). When single- and dual-task conditions were compared, no significant differences were found between the conditions in individuals with PD. However, in the control subjects, the duration of anteroposterior and mediolateral CoP displacements were significantly lower in the dual-task condition than in the single-task condition (p= 0.017 and p = 0.034), table 2.

Table 2. Mean and standard deviation values for the EMG activity of the TA and SOL muscles in first swing and stance limbs and for the duration of the CoP displacements.

First swing limb muscles		Condition	n	Controls M (SD)	p-value	n	Individuals with PD M (SD)	p-value	p-value
TA	Timing [seconds]	Single	10	-0.299 (0.120)	ns	9	-0.041 (0.259)	ns	0.011
		Dual	10	-0.206 (0.200)		8	-0.066 (0.415)		ns
	Relative Magnitude	Single	10	16.899 (25.88)	ns	9	4.538 (4.096)	ns	ns
		Dual	10	9.366 (19.381)		8	2.660 (1.650)		ns
SOL	Timing [seconds]	Single	10	-0.131 (0.307)	ns	9	-0.112 (0.365)	ns	ns
		Dual	10	-0.249 (0.137)		8	-0.164 (0.310)		ns
	Relative Magnitude	Single	10	1.052 (1.001)	0.042	9	0.904 (0.287)	ns	ns
		Dual	10	0.883 (0.480)		8	1.169 (0.287)		ns
Stance limb muscles		**Condition**	**n**	**Controls M (SD)**	**p-value**	**n**	**Individuals with PD M (SD)**	**p-value**	**p-value**
TA	Timing [seconds]	Single	9	0.017 (0.288)	ns	9	-0.112 (0.296)	ns	ns
		Dual	10	-0.240 (0.165)		8	0.295 (0.496)		0.018
	Relative Magnitude	Single	10	12.169 (10.60)	ns	9	2.728 (3.646)	ns	0.022
		Dual	10	9.164 (8.253)		8	3.193 (2.182)		ns
SOL	Timing [seconds]	Single	9	-0.360 (0.449)	ns	9	-0.101 (0.351)	ns	ns
		Dual	10	-0.242 (0.172)		8	-0.266 (0.232)		ns
	Relative Magnitude	Single	10	1.058 (1.235)	ns	9	0.941 (0.441)	ns	ns
		Dual	10	0.578 (0.408)		8	0.566 (0.418)		ns
Postural Phase Duration		**Condition**	**n**	**Controls M (SD)**	**p-value**	**n**	**Individuals with PD M (SD)**	**p-value**	**p-value**
Anteroposterior CoP displacement [seconds]		Single	10	0.312 (0.112)	0.017	9	0.264 (0.204)	ns	ns
		Dual	10	0.190 (0.076)		8	0.188 (0.075)		ns
Mediolateral CoP displacement [seconds]		Single	10	0.225 (0.411)	0.034	9	0.249 (0.052)	ns	ns
		Dual	10	0.170 (0.075)		9	0.274 (0.099)		0.019

SD – Standard Deviation; ns – not-significant

The muscle activation pattern was also analysed. For the first swing limb in the single-task condition, only 20% of the controls deactivated the SOL first and then activate the TA, while in the dual-task condition, 60% of the subjects followed this pattern. In the single-task condition, 56.6% of the individuals with PD followed the SOL-TA sequence, reaching 66.7% in the dual-task condition. For the stance limb in the single-task condition, 90% of the controls followed the SOL-TA sequence, while in the dual-task condition only 50% followed this sequence. In the individuals with PD in the single-task condition, 56.6% of the subjects followed the SOL-TA sequence, while in the dual-task condition the sequence was adopted by 88.9% of the subjects, Figure 2.

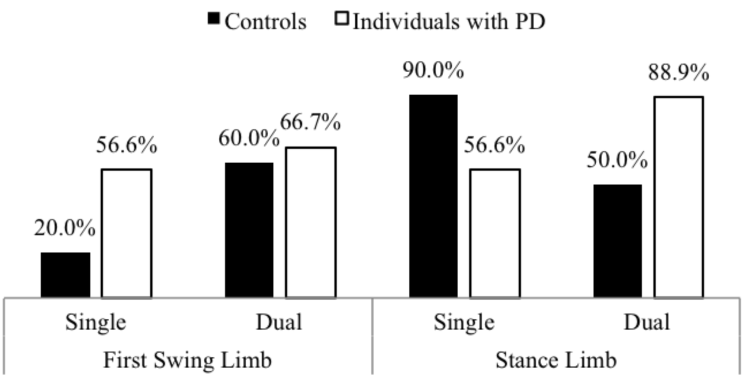

Figure 2. Percentage of individuals that follow the motor activation pattern: deactivation of the SOL followed by activation of the TA, in the first swing and stance limbs in the controls and individuals with PD.

Discussion

This study revealed some differences between individuals with PD and controls in terms of postural control strategies. In the single-task condition in the swing limb and in dual-task condition in the stance limb, the TA activated significantly later for the individuals with PD compared to the controls. The duration of the mediolateral CoP displacement was higher in the individuals with PD than in the controls. Differences between the single- and dual-task conditions were observed only in the control group for the magnitude of soleus and for the duration of the postural phase with lower values for the dual-task condition.

Generally, the differences between groups were more notorious in the TA muscle than in the SOL for both conditions. The TA muscle activated later and with lower magnitude in the individuals with PD in comparison to the controls. The TA is the main muscle to propel the body forward in the postural phase of the GI (Elble *et al.*, 1994), but its activity is usually impaired in individuals with PD (Gantchev *et al.*, 1996) as it tends to become weaker as the disease progresses (Crenna, Frigo, Giovannini, & Piccolo, 1990). This TA impairment can explain the higher duration of mediolateral CoP displacement in individuals with PD compared to control subjects (Carpinella *et al.*, 2007; Nocera *et al.*, 2013; Yiou *et al.*, 2012), and the suggestions that it tends to decrease from the single- to dual-task conditions; however, in our study the difference found between the conditions was not significant. Contrary to the expectations, the SOL onset timing and magnitude of the individuals with PD were very similar to the ones obtained in the controls, indicating that the TA impairment is more related to neuronal dysfunction than with a dysfunction in its antagonist (SOL). However, when comparing the single- and dual-task conditions, it was found that the individuals with PD tended to present decreased SOL deactivation in the swing limb in the dual-task in comparison to the single-task while the reverse situation occurred in the controls. In fact, only the control group presented a decreased duration of CoP displacement during the dual-task relative to the single-task. A lower SOL deactivation in PD can result from a reduction of inhibitory cortical control over the SOL muscle (Massion, 1992; Takakusaki, 2008) and can explain the non-existence of significant differences found between the single- and dual-task conditions in the PD group as to the postural phase duration. However, it has been demonstrated that adding a cognitive task does not change the SOL magnitude significantly (Nadeau, 2007; Reetz *et al.*, 2008). Taking into account that no differences were observed in MOCA between the two groups and that the individuals with PD presented decreased performance in the Stroop test, it can be hypothesised that these individuals prioritized the motor task in detriment of the cognitive task. Unfortunately, our results do not support this hypothesis because the Stroop test was not performed in the single-task condition. Hence, future studies are required on this point. Also this finding should be considered related to that fact that GI alone is seen as a difficult task for individuals with PD (Nadeau, 2007; Reetz *et al.*, 2008).

As to the muscle activation patterns, in a former study, Polync et al. (1998) found that most of the controls and individuals with PD exhibited the previously reported pattern of the SOL inhibition followed by the TA activation in both limbs. However, in the same study, the authors found a significant decrease of the frequency of this pattern of muscle activation in the older individuals. Other studies have suggested that the patterns of muscle activity in elderly subjects for GI are generally consistent, but noticeable inconsistencies were found between the subjects (Mickelborough, van der Linden, Tallis, & Ennos, 2004). In the study of Halliday et al. (Halliday *et al.*, 1998), only three of the 10 individuals with PD showed a TA onset after the SOL inhibition. As no studies about the pattern of muscle activity in individuals with PD were found, and because the amplitudes of the TA did not increase, it was expected that the individuals with PD in this study would present a pattern of motor activation similar to the one of the "normal" subjects. However, only half of the individuals with PD studied followed the pattern of deactivation of the SOL followed by the activation of the TA. These patterns of muscular activation are similar to the aging population and may be due to the fact that the GI is not a fully automatic task, as already mentioned.

Despite some limitations always present in these studies, such as the sample size and the potential interference of the experimental environment in GI, this study assumes particular importance because it describes the EMG analysis of the TA and SOL muscles in GI in the dual-task condition. Also, as far as the authors know, this is the first study to examine the influence of the dual-task condition in individuals with PD using EMG.

Clinical relevance

Contrary to expectations, our findings show that the SOL onset timing and magnitude of individuals with PD were closer to the ones obtained in the controls. This can indicate that the APA's in GI are impaired in PD by an activation failure of the TA in both single- and dual-task conditions. Hence, it is important that during rehabilitation sessions, intervention should concentrate on the TA to improve the functional mobility of individuals with PD.

PART B - ARTICLE 7

Influence of dual-task on sit-to-stand-to-sit postural control in Parkinson's disease

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Abstract

Postural control deficits are the most disabling aspects of Parkinson's disease (PD), resulting in decreased mobility and functional independence. The aim of this study was to assess the postural control stability, revealed by variables based on the centre of pressure (CoP), in individuals with PD while performing a sit-to-stand-to-sit sequence under single- and dual-task conditions.

An observational, analytical and cross-sectional study was performed. The sample consisted of 9 individuals with PD and 9 healthy controls. A force platform was used to measure the CoP displacement and velocity during the sit-to-stand-to-sit sequence. The results were statistically analysed.

Individuals with PD required greater durations for the sit-to-stand-to-sit sequence than the controls ($p<0.05$). The anteroposterior and mediolateral CoP displacement were higher in the individuals with PD ($p<0.05$). However, only the anteroposterior CoP velocity in the stand-to-sit phase ($p=0.006$) was lower in the same individuals. Comparing the single- and dual-task conditions in both groups, the duration, the anteroposterior CoP displacement and velocity were higher in the dual-task condition ($p<0.05$).

The individuals with PD presented reduced postural control stability during the sit-to-stand-to-sit sequence, especially when under the dual-task condition. So it is important to emphasize that individuals with PD have not only deficits in terms of motor performance, but also in terms of cognitive performance when performing the sit-to-stand-to-sit sequence in their daily life tasks. Moreover, both deficits tend to be intensified when two tasks are performed simultaneously.

Keywords: Dual-task; Parkinson's; Postural Control; Sit-to-Stand-to-Sit.

Introduction

Parkinson's disease (PD) is considered the second most common neurodegenerative disorder, affecting about 1% of the world's current population (Andlin-Sobocki *et al.*, 2005; Campenhausen *et al.*, 2005). Some projections indicate a large increase of this prevalence over the coming decades (Campenhausen *et al.*, 2005).

At the moment, the aetiology is explained by genetic predisposition and the presence of toxic environmental factors (Huang, Fuente-Fernández, & Stoessl, 2003; Levy *et al.*, 2005). The majority of individuals with PD present an inadequate interaction between systems responsible for body balance, including the vestibular, visual and proprioceptive systems. Consequently, these individuals tend to shift their centre of gravity forward, and therefore, have difficulty to perform compensatory movements to require balance (Smania *et al.*, 2010). The transition from sitting to standing and standing to sitting are components of some everyday functional tasks that are highly demanding from a postural control perspective. In fact, the sit-to-stand-to-sit (STSTS) sequence implies the involvement of anticipatory postural adjustments (APAs) to movement performance (Duncan *et al.*, 2011; Janssen *et al.*, 2002; Mazza *et al.*, 2005). Hence, the study concerning the STSTS sequence can contribute to clarify postural control requirements during daily activities. The variability and efficiency of functional movements require an appropriate postural control that depends on APAs to maintain stability of internal and external disturbances, taking into account the context and the task (Aruin, 2002). The planning of APAs involves various structures of the central nervous system (CNS), such as the pre-motor cortex, supplementary motor area, basal ganglia and cerebellum (Jacobs *et al.*, 2009; Timmann & Horak, 2001) that, through independent channels, convey information to the reticular formation, such as the pedunculopontine nucleus, which is important to modulate the APAs (Schepens & Drew, 2004). The neural connection between the basal ganglia and the pedunculopontine nucleus is through the corticostriatal-pallidum-pedunculopontine circuit, which is compromised in individuals with PD leading to postural control deficits. This is manifested in the changes in the activation of postural muscles in the form of APAs (Jacobs *et al.*, 2009; Karachi *et al.*, 2010; Purves *et al.*, 2004; Shumway-Cook & Woollacott, 2007). As the CNS is responsible for the motor modulation circuits, which are compromised in individuals with PD, there is a decrease in postural control and consequently, repercussions in the performance of tasks, like STSTS sequences (Bhatt, Yang, Mak, Hui-Chan, & Pai, 2013; O'Shea *et al.*, 2002; Tsukahara *et al.*, 2010). This decreased postural control was demonstrated through CoP displacement variables. The CoP displacement reflects the orientation of body segments and corrective responses that control the centre of mass over the base of support (Prieto, Myklebust, Hoffmann, Lovett, & Myklebust, 1996), resulting from the combination of descending motor commands and the mechanical properties of the surrounding muscles (Baratto, Morasso, & Spada, 2002). In situations of dual-task, the use of cortical resources to perform motor tasks can affect or influence the performance of one or both tasks (J. Holmes *et al.*, 2010; V. Kelly *et al.*, 2012a; Tao. Wu & Mark. Hallett, 2009a). Despite the importance of the postural control stability for the STSTS sequence performance and the impact of PD on the postural control system, few studies have assessed these issues and only the sit-to-stand sequence has been addressed. Additionally, no study has evaluated this task under high cognitive demanding conditions. Based on these facts, the objective of the present study was to analyse the postural control stability in individuals with PD in single- and dual-task conditions. More specifically, the postural stability was assessed through representative CoP displacement variables in the anteroposterior and mediolateral directions (displacements and velocities), in the five phases of the STSTS sequence in single- and dual-task conditions. Based on the results obtained by Bhatt et al. (2013) and on the neural dysfunction involving postural control pathways, a reduced postural control stability in individuals with PD can be hypothesised during the performing of the STSTS sequence. This reduced stability would be amplified in these individuals when the STSTS sequence is performed in the dual-task condition.

Materials and Methods

Study Design and Participants

A cross-sectional study was implemented using a non-probabilistic (Creswell & Clark, 2011) sample of 9 individuals with PD and 9 healthy controls, aged between 52 and 80 years old. The individuals diagnosed with PD were patients from the Parkinson's Association, Porto, in Portugal, while the healthy controls were community-dwelling volunteers, mainly from Porto.

Subjects were excluded if they presented one of the following criteria: severe cognitive impairment (screened using the Montreal Cognitive Assessment (MoCA) test (Hoops *et al.*, 2009)); incapable of performing the sit-to-stand or stand-to-sit sequence independently; and unable to speak. Severely disabled PD patients (> 3 Hoehn and Yahr scale (Hoehn & Yahr, 1967)), patients diagnosed with any other neuromuscular disease, and those who had undergone deep brain stimulation through subthalamic surgery or were taking cholinergic medication were also excluded. Healthy controls that had been diagnosed as adults with any neuromuscular disorder or that could not be considered sedentary according to the Centre for Disease Control for the American College of Sports Medicine, were also excluded (Thompson, 2001).

A trained researcher conducted the data collection based on a structured protocol. The study was approved by the Ethical Review Board of "Escola Superior de Tecnologia da Saúde - Instituto Politécnico do Porto", in Portugal. Written informed consent, according to the Helsinki Declaration, was obtained from all participants.

Instruments

The data collected from all participants included the sociodemographic characteristics age, gender, height, weight and level of education, and years of disease, cognitive performance (assessed using the MoCA test), Hoehn and Yahr scale and the CoP data acquired using a force platform (model FP4060-8 from Bertec Corporation (USA)) under the single- and dual-task conditions.

The scale of Hoehn & Yahr (1967) evaluates the severity of overall dysfunction in individuals with PD. It is a 7-point scale, in which each point represents a different stage of the disease (stages 1 to 5, including 1.5 and 2.5). The scale increases with the severity of dysfunction along with the stage of the disease (Hoehn & Yahr, 1967). The MoCA test consists of eight fields: visuospatial, nomination, memory, attention, language, abstraction, deferred evocation and orientation. The performance of an individual is calculated by the addition of the scores obtained in each of the domains, and the maximum that can be reached is equal to 30 points (Hoops *et al.*, 2009; Romann *et al.*, 2012).

For the evaluation of the postural control, the data from the force platform was acquired at a sampling rate of 1000 Hz (Hanke & Rogers, 1992). The platform was connected to a Bertec AM 6300 amplifier (USA) and in turn, this was connected to an analog-digital converter from Biopac Systems, Inc. (USA), and to an analog board of Qualysis Track Manager (Sweden) that can be used for stabilometric analyses. The stabilometric measurements comprise the assessment of balance in the orthostatic position through body movements, taking into account the anteroposterior (Fx), mediolateral (Fy) and vertical (Fz) components of the ground reaction force. For this, it is necessary to monitor the movement of the CoP in the anteroposterior (CoPAP) and mediolateral (CoPML) directions (Geurts, Nienhuis, & Mulder, 1993). The signal related to the CoP movement was filtered using a fourth-order Butterworth low pass filter with a cut-off frequency of 20 Hz (Schmid, Confortoemail, Camomilla, Cappozzo, & D'Alessio, 2002).

The attention level and consequently, the motor control perturbations were attained through a cognitive secondary task, namely the Stroop colour word test. This test consists in the enunciation of the visual colour instead of the written one. The number of errors and the number of named items were used for analysis (Lezak *et al.*, 2004) during a pre-defined time (60 seconds) for both groups.

Procedures

After an explanation of all the procedures involved, all individuals performed the study with shorts and standard shoes (Kim, Yi, Yoo, & Choi, 2011). The height of the chair seat was adjusted to 100% of the lower leg length (from the knee joint to the ground), and 2/3 of the femur supported on the seat was used as a reference for the subjects to be considered in the sitting position. In the single-task condition, the subjects were asked to rise from sitting with a self-selected speed without using their upper limbs (Dubost, Beauchet, Manckoundia, Herrmann, & Mourey, 2005), then remain for 60 seconds in the standing position, looking at a point two meters away at eye level. After this interval, subjects were instructed to sit, again without any kind of support and at a self-selected speed. In the dual-task condition, all the previous procedures were repeated; however, the subjects were required to perform the Stroop test during the performing of the STSTS sequence (Romann *et al.*, 2012). The test words in different colours were projected on a wall at eye level. The subjects were instructed to name the colour instead of reading the word and no other specific instructions were given. The words were present according to each participant's responses during a pre-defined period of 60 seconds. A one minute rest between each trial was allowed, and the necessary repetitions were performed in order to obtain three valid trials for each subject.

The CoP displacement variables were analysed over the five phases of the STSTS sequence. For this, the sit-to-stand-to sit sequence was divided into five phases: sitting phase - phase 1, sit-to-stand phase - phase 2, standing phase - phase 3, stand-to-sit phase - phase 4, and sitting phase - phase 5. The procedures used to identify the phases are shown in Table 1.

Table 1. Procedures adopted to assess the phases of the sit-to-stand-to-sit sequence, based on Tsukahara et al. (2010).

	Start	**End**
Phase 1	The instant when the CoP signal derived from the baseline (obtained in the sitting position) was greater than 3 standard deviations for a minimum interval of 50 ms.	The instant associated to the first local maximum of the CoP signal from the sit-to-stand sequence.
Phase 2	The instant associated to the first local maximum of the CoP signal from the sit-to-stand sequence.	The instant of the first local minimum of the CoP signal during the sit-to-stand sequence.
Phase 3	The instant of the first local minimum of the CoP signal during the sit-to-stand sequence.	The instant when the CoP signal values were lower than the baseline (obtained in the standing position) plus 3 standard deviations for a minimum interval of 50 ms.
Phase 4	The instant when the CoP signal derived from the baseline (obtained from the standing position) was greater than 3 standard deviations for a minimum interval of 50 ms.	The instant associated to the first local maximum of the CoP signal from the standing-to-sit sequence.
Phase 5	The instant associated to the first local maximum of the CoP signal from the standing-to-sit sequence.	The instant when the CoP signal values were higher than the baseline (obtained in the siting) plus 3 standard deviations for a minimum interval of 50 ms.

The data acquisition was always performed by the same investigator to ensure the reproducibility of the procedures. The data analysis was performed using the Matlab software (MathWorks, USA) and Acqknowledge software (Biopac Systems, Inc. USA).

Statistical Analysis

Descriptive statistical analyses were performed using proportions and measures of central tendency and dispersion.

The independent sample t test and Chi square test were performed to examine whether there were significant differences between the groups in terms of the sociodemographic and anthropometric variables. The multiple analysis of variance (MANOVA) test was used to analyse the interaction between the groups (PD and controls) and the conditions (single- and dual-task). The Bonferroni analysis was used as a post-hoc test to determine the differences in single- and dual- task conditions in each group and to determine for each condition the differences between the groups (PD and controls). The number of errors and the number of correctly named items for the Stroop test were used as covariates in the analysis. Two-tailed tests were used in all analyses, and $p < 0.05$ was adopted for statistical significance. All statistical analyses were conducted using IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The 9 PD individuals (66.7% male) had a mean age of 66 years old (standard deviation (SD) = 8.2), a mean education of 7.7 years (SD = 5.6) and a mean number of years with PD 10.22 (SD 5.38). Most of these participants were classified in stage 1 and 1.5 of the Hoehn and Yahr scale. The 9 healthy controls (44.4% male) had a mean age of 63.9 years (SD = 8.1) and a mean education of 7.8 years (SD = 4.6). The Mann-Whitney test and chi-square test showed no significant differences between the two groups studied, Table 2.

Table 2. Comparison of the sociodemographic and anthropometric variables between the two groups under study.

	Individuals with PD (n=9)	**Healthy Controls (n=9)**	**p-value**
	M ± SD	**M ± SD**	
Age [years]	66.00 ± 8.22	63.89 ± 8.09	0.340*
Gender (male), n (%)	6 (66.7)	4 (44.4)	0.319**
Education [years]	7.67 ± 5.07	7.78 ± 4.58	0.796*
Weight [Kg]	69.33 ± 12.59	74.00 ± 9.86	0.796*

	Individuals with PD (n=9)	Healthy Controls (n=9)	p-value
	M ± SD	M ± SD	
Height [m]	1.65 ± 0.08	1.64 ± 0.08	0.931*
MoCA	24.44 ± 2.24	26.33 ± 1.00	0.063*
Hoehn and Yahr scale			
Stage 1, n (%)	3 (33.3)	-	-
Stage 1.5, n (%)	3 (33.3)	-	-
Stage 2, n (%)	1 (11.1)	-	-
Stage 2.5, n (%)	2 (22.2)	-	-
Years of PD	10.22 ± 5.38	-	-
Stroop test (Nº of naming colours)	30.89 ± 11.19	35.611 ± 17.099	0.489*

Hoehn and Yahr scale: Stage 1 - Unilateral disease; Stage 1.5 - Unilateral and axial disease; Stage 2 - Bilateral disease without impairment of balance; Stage 2.5 - Mild bilateral disease; Stage 3 - Mild to moderate bilateral disease.

* Independent samples t-test and ** chi-square test.

The MANOVA test showed that in phase 1, no significant differences were found between the groups (between-subjects) or conditions (within-subjects) and also no significant interaction was found between group and condition, Table 3.

Table 3. Results of the MANOVA test with p-values of between-subjects, within-subjects and interaction for the duration of each phase and CoP based parameters.

		Covariates adjusted - p-values				
Phase		Duration	CoPAP	CoPML	VelAP	VelML
1	Group (between-subject)	0.267	0.276	0.725	0.662	0.909
	Group (within-subjects)	0.348	0.640	0.817	0.765	0.943
	Interaction	0.712	0.210	0.145	0.513	0.959
2	Group (between-subject)	<0.05	0.088	0.606	0.238	0.496
	Group (within-subjects)	0.149	0.623	0.787	0.408	0.986
	Interaction	0.092	0.120	0.167	0.737	0.932

		Covariates adjusted - p-values				
Phase		Duration	CoPAP	CoPML	VelAP	VelML
	Group (between-subject)	<0.01	<0.05	0.449	0.062	0.054
3	Group (within-subjects)	0.354	0.271	0.625	0.885	0.150
	Interaction	0.606	0.137	0.410	0.614	0.089
	Group (between-subject)	<0.01	0.056	<0.05	<0.01	0.844
4	Group (within-subjects)	<0.01	0.740	0.325	0.822	0.071
	Interaction	0.333	0.499	0.069	0.493	0.108
	Group (between-subject)	0.173	<0.05	0.734	0.077	0.590
5	Group (within-subjects)	0.587	<0.05	0.074	<0.01	0.284
	Interaction	<0.05	0.369	0.125	<0.01	0.795

In phase 2, a significant difference between the groups was found. The individuals with PD presented a greater duration ($p=0.047$) compared to the healthy controls. The Post-hoc analysis showed that these differences occurred only in the dual-task condition ($p=0.005$). However, no differences between conditions or any significant interaction between groups and conditions were found.

In phase 3, the differences between groups were found in terms of the duration and CoPAP displacement. The duration was significantly greater in the PD individuals than in the healthy controls ($p<0.001$). These differences occurred both under single- ($p<0.001$) and dual-task ($p=0.004$) conditions. The CoPAP displacement was significantly higher in the individuals with PD in comparison to the healthy controls (0.015). The Post-hoc analysis showed that these differences occurred under the dual-task condition ($p=0.021$). No differences between the tasks or any significant interaction between group and condition were found.

In phase 4, the differences between the two groups occurred in the duration, CoPML displacement and CoPAP velocity. The duration was significantly greater in the individuals with PD than in the healthy controls ($p<0.001$). Relative to the healthy controls, the CoPML displacement was significantly higher ($p=0.036$) and the CoPAP velocity was significantly lower (p=0.006) in the individuals with PD. The Post-hoc analysis showed that these differences occurred both under the single and dual-task conditions, except in terms of the CoPML displacement that occurred only in the dual-task condition (p=0.015). Also, differences between the two conditions were found in the duration, with a longer duration in the dual- than in the single-task condition (p=0.009). The Post-hoc analysis showed that these differences occurred in the group with PD (p=0.004). Finally, no significant interaction between group and condition were found.

In phase 5, only the COPAP displacement had differences between the two groups, with higher values for the individuals with PD in comparison to the healthy controls. However, significant differences were found between the conditions for the CoPAP displacement (p= 0.043) and velocity (0.010), with higher values for the dual-task condition. Also, no significant interaction between group and condition was found in terms of the duration and CoPAP velocity, which seems to indicate that the differences in the duration and CoPAP velocity were caused by the disease (PD).

The estimated marginal means of the conditions and groups is presented in Figure 1.

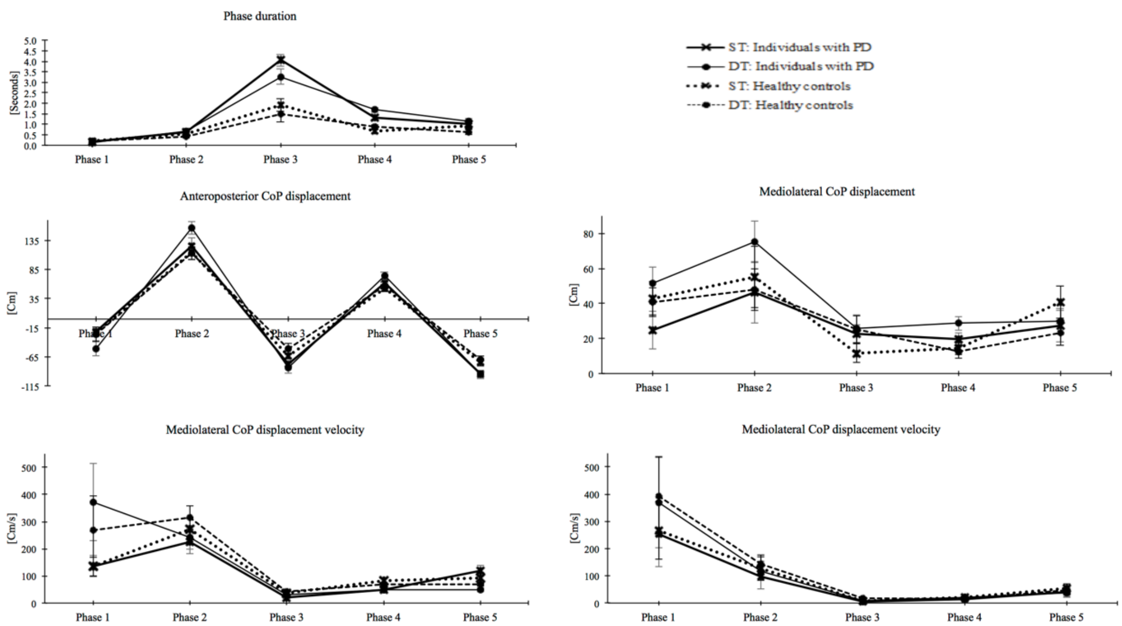

Figure 5. Estimated marginal means and standard error of the phase durations and CoP based parameters under the single- and dual-task conditions for both groups.

Discussion

This study reveals significant differences regarding the postural control of individuals with PD. It is clear that there is a relationship between performing the STSTS sequence and performing a cognitive task.

Comparing the individuals with PD and the healthy controls studied as to the duration of each phase of the sit-to-stand-to-sit sequence, significant differences were found in the single- and dual-task conditions in phases 2, 3 and 4. This finding corroborates previous studies that show a significant increase in the duration of the phases of the STSTS sequence performed by individuals with PD (Bhatt *et al.*, 2013). No difference in the duration of phase 1 was found in the study of Inkster (Inkster & Eng, 2004), where the time to rise from a chair was not significantly different between individuals with PD (ON medication) and controls. The differences found in the duration of phases 2, 3 and 4 between the two groups in both the single- and dual-task conditions can be explained by the pathophysiology of PD. In phase 2, the individuals have to perform a sit-to-stand transfer and the greater duration of this transition in PD individuals compared to healthy controls could be due to the bradykinesia and rigidity present in individuals with PD. Phase 3 corresponds to a stabilization phase that rarely presents any postural deficits in PD. In phase 4, individuals have to control the postural muscles, including the soleus eccentric activity, which is a complex task for individuals with PD (Karachi *et al.*, 2010; Shumway-Cook & Woollacott, 2007).

Comparing the CoPAP and CoPML displacements between the individuals with PD and the healthy controls, significant differences were only found in the dual-task condition, with the former group showing higher CoPAP displacements and a weaker relation for the CoPML displacement. Individuals with PD have superior backward stability resulting from a more anterior CoP position at seat-off (Bhatt *et al.*, 2013). Given these differences in movement patterns, individuals with mild to moderate severity of PD have an exaggerated anticipatory response in the preparation phase in comparison to individuals without PD. This anticipatory response is manifested as an increased momentum that generates a greater forward CoP displacement (Inkster & Eng, 2004). Furthermore, several studies have shown an altered function of the supplementary motor area in individuals with PD due to its indirect connections with the basal ganglia (Cunnington *et al.*, 1996).

Compared to the healthy controls, the individuals with PD had a lower CoPAP velocity in the single-task condition in phases 3 and 4, and also a lower CoPML velocity in phase 3. During the STSTS sequences, these individuals demonstrated a large proportion of co-contraction because they move slower (L. A. P. S. Souza, Curtarelli, Mukherjee, & Dionisio, 2011). However, individuals with PD compensate their slowness and related posterior instability by positioning their CoP forward at seat-off (Mancini, Rocchi, Horak, & Chiari, 2008). The lower velocity could increase the likelihood of backward balance loss at seat-off because of its proximity to their limits of stability (Pai & Lee, 1994).

Comparing the single- and dual-task conditions, only significant differences were found in the CoPML velocity in phase 3. The few differences between the single- and dual-task conditions in individuals with PD may be due to the time of diagnosis of the PD of the individuals studied (10.22 ± 5.38 years), as they may have already acquired, over time, several strategies that assist in carrying out daily life tasks, such as the movements required during the STSTS sequence. These strategies can also justify the similarity with some findings obtained for healthy controls (Wulf, Landers, Leithwaite, & Tollner, 2009), as well as, the fact that the PD group only had a mild severity of the disease (median Hoehn & Yahr score of 1.5). However, a limitation of the study is that the groups did not perform the cognitive task (Stroop test) in single-task condition. This would be useful to discern if the cognitive performance decreased in the dual-task condition, and should be taken into account in future studies.

In this study, we found that the individuals with PD had greater difficulty in the stand-to-sit sequence, which has been ignored in current studies, than in the sit-to-stand sequence, especially in the dual-task condition. Biomechanical studies focusing on posture stability have shown that the performance of dual-task has a significant effect on the postural control in these individuals (Coppin *et al.*, 2006; Fama & Sullivan, 2002; Springer *et al.*, 2006; Van-Lersel *et al.*, 2008). This suggests that they create a restriction on APAs in order to focus on the cognitive task without losing the balance (J. Holmes *et al.*, 2010; Marchese *et al.*, 2003; Nocera *et al.*, 2013). Furthermore, recent studies with rehabilitative intervention in individuals with PD have shown promising results. The reported results indicate a potential for reversing or slowing the progression of the disease, demonstrating that the ability to learn is relatively well preserved

(Chiviacowsky *et al.*, 2012). Several studies have shown that the dual-task cognitive-motor training has a positive effect on gait in the PD population; in particular, in terms of the gait speed, variability and step length (V. Sethi & R. Raja, 2012; Yogev-Seligmann *et al.*, 2011).

Conclusion

The individuals with PD presented reduced postural stability for most of the phases of the STSTS sequence, and this stability was most impaired in the dual-task condition. These findings may suggest that this postural control deficit could lead to compensatory motor strategies in the lower extremities. However, further studies concerning the impact of reduced stability during the STSTS sequence in individuals with PD and their compensatory motor strategies are required.

This study also provides data and guidelines for future research, as well as pointing out the importance of cognitive training. Based on our findings that are in-line with the ones reported by other authors (Brauer *et al.*, 2011; Hiyamizu *et al.*, 2011; Vanshika & Ravi, 2012), it is expected that the stimulation of the cognition can help achieve improvements in terms of motor task performance.

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