Cognitive predictors of balance in Parkinson's disease

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Short-Title: Predictors of balance in Parkinson´s

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Cognitive predictors of balance in Parkinson's disease

Abstract

Postural instability is one of the most incapacitating symptoms of Parkinson's disease and appears to be related to cognitive deficits. This study aims to determine the cognitive factors that can predict deficits in static and dynamic balance in individuals with Parkinson's disease.

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

The results show that a statistically significant model based on cognitive outcomes was able to explain the variance of motor variables. Also, the explanatory value of the model tended to increase with the addition of individual and clinical variables, although the resulting model was not statistically significant The model explained 25-29% of the variability of the Timed Up and Go Test, while for the anteroposterior displacement it was 23-34%, and for the mediolateral displacement it was 24-39%.

From the findings, we conclude that the cognitive performance, especially the executive functions, is a predictor of balance deficit in individuals with Parkinson's disease.

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease that affects 41/100,000 in 40- to 49-year-olds and 1,903/100,000 in persons over 80 years old (Pringsheim, Jette, Frolkis, & Steeves, 2014).

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). In PD, deficits are common in executive functions (EFs) (A Coppin et al., 2006). EFs can be defined as cognitive competences that facilitate the successfully completion of activities in an independent and intentional manner and with the appropriate behaviour (Lezak, Howieson, & Loring, 2004). Examples include inhibition of automated responses, recovery from declarative memory, planning, monitoring, cognitive flexibility and the maintenance of information in the working memory (Schwarz & Shapiro, 1986). Cognitive impairments can have a significant negative influence on carrying out daily life activities and are associated with a lower quality of life (Klepac, Trkulja, Relja, & Babic, 2008).

The cognitive processes have an important role that increases with age and they should be preserved to ensure a good postural control (Jamet, Deviterne, Gauchard, Vançon, & Perrin, 2007). Recent studies have shown that impairments in EFs are closely related to motor symptoms, particularly with postural instability (Lindholm, Hagell, Hansson, & Nilsson, 2014). This may be due to the important role of these functions in anticipation, planning and coordination (McCloskey & Perkins, 2012). Research suggests that abnormal displacements of the centre of pressure are related to balance deficits and consequently, they lead to the occurrence of falls in about 51-68% of individuals with PD. In addition, the duration of illness, fear of falling and cognitive changes were also related to balance deficits, thereby contributing to the independent risk factors for falls (Matinolli et al., 2007).

Individuals with PD frequently use cognitive strategies to maintain balance and postural stability due to their deficits in terms of automaticity (Smithson, Morris, & Iansek, 1998). However, the studies found about cognitive deficits in Parkinson's disease do not establish a relationship between the dynamic and static balance and the different executive functions. Thus, the aim of this study was to define that relationship by identifying the predictors of balance deficit in individuals with PD.

Material and Methods

Study design

A cross-sectional study was designed using a non-probabilistic sample of 52 individuals with PD. The individuals diagnosed with PD were from an outpatient department for movement disorders of a hospital in Portugal. A total of 62 individuals with PD were initially assessed; however, 10 individuals were excluded: 5 for having severe cognitive impairment, 2 due to subthalamic surgery and 3 that could not walk without assistance. Table 1 shows that the sample studied had an average age of 67.3 (±8.9) years old and the mean duration of the disease was 7.9 (±5.5) years. The average weight of the individuals was 72.3 kg (±13.1), and their average height was 165 (±8.3) cm.

< Insert Table 1 about here>

The patients evaluated here were being treated for movement disorders at an outpatient department of a hospital and had been referred by a neurologist based on the score of the modified Hoehn and Yahr scale. All individuals voluntary agreed to participate in this study. The inclusion criteria were: capacity to walk ten meters without gait assistance and diagnosis of PD up to Stage 3 according to the modified Hoehn & Yahr scale (Hoehn & Yahr, 1967); and the exclusion criteria were: 1) the presence of a severe cognitive impairment, screened

using the Mini Mental State Examination (MMSE) test (Folstein, Folstein, & McHugh, 1975), 2), diagnosis of other neuromuscular diseases and 3) history of deep brain stimulation through subthalamic surgery. All participants had good vision; although some of them used glasses. A trained researcher conducted the data collection using a structured protocol.

The Ethical Review Boards of the Institution involved approved this study and each participant signed a written informed consent, according to the Helsinki Declaration.

Instruments

The data collected from all participants included sociodemographic characteristics and the severity of the motor function impairments based on the Hoehn and Yahr Scale and part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Goetz, 2003). UPDRS 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. Here, only the motor exploration (UPDRS-III) was applied; the score of each item varies between 0 (zero) and 4 (four), from normal to severe, respectively, and the total score of UPDRS-III ranges from 0 (zero) to 52. This scale is often accompanied by the Modified Hoehn and Yahr Scale (Hoehn & Yahr, 1967), which evaluates the severity of overall dysfunction in individuals with PD. The scale increases with the severity of the dysfunction along with the stage of the disease. The MMSE test was used adopting the following cut-offs: ≤22 for 0-2 years of formal education, ≤24 for 3-6 years and ≤27 for ≥7 years, which are based on the normative values for older Portuguese adults (Morgado, Rocha, Maruta, Guerreiro, & Martins, 2009), as the exam performance varies within a population according to their educational level.

The EFs were also assessed. The Rule Shift Cards Test (RSCardsT) is commonly 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 involved. The performance profile is indexed to a score based on the number of errors and total time to complete the test

(Golden, Espe-Pfeifer, & Wachsler-Felder, 2000; Wilson, Alderman, Burguess, Hazel, & Evans, 2003). The Trail Making Test (TMT) (Reitan, 1992) is a test divided into two parts: part A (TMTA) evaluates attention and processing speed, and involves sequential linking of numbers from 1 to 25, verbally; and part B (TMTB) 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). The Digit Span Test is a sub-test of both the Wechsler Adult Intelligence Scale and the Wechsler Adult Memory Scale that measures the attention, working memory and sequential processing. In this test, the individuals are required to organize and repeat a series of numbers that have been verbally specified. The first task is to arrange the numbers in direct order with a total of 16 trials, grouped in 8 levels, wherein the amount of numbers specified progressively increases from level to level, the first of which consists of two numbers and the last one of 9 numbers. At each level, the individual must verbalize correctly at least one of the sequences in order to move on to the next level. The second task of the test is similar, but the goal is to arrange the numbers in reverse order (Ostrosky-Solís & Lozano, 2006).

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 to evaluate the static balance. The pressure values and stabilometric measurements, such as the ones based on the centre of pressure (Maetzler, Bochdansky, & Abboud, 2010; Putti, Arnold, Cochrane, & Abboud, 2008), were acquired with this device at 25 Hz.

The participants were instructed to stand on the platform and adopt a self-selected comfortable upright position. Then, the participants 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 (Ebersbach & Gunkel, 2011). The Timed Up and Go Test (TUG), which measures the functional mobility, was employed to assess the dynamic balance. This test was used to assess the time each individual 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 shortest time of three trails was considered the best and therefore was used in the results (Podsiadlo & Richardson, 1991). The test-retest reliability and inter-rater reliability were ICC = 0.80 and r = 0.99, respectively (Lim et al., 2005).

All tests were carried out with the individuals taking their prescribed medication, and were therefore denoted as "ON" medication, as in other studies (Conradsson, Löfgren, Ståhle, Hagströmer, & Franzén, 2012; Kelly, Eusterbrock, & Shumway-Cook, 2012).

Statistical Analysis

Descriptive statistical analysis took into account 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 applied to all analyses and a *p-value* <0.05 was considered statistically significant. The statistical analyses were conducted in SPSS Statistics software, version 22.0 from SPSS Inc. (USA).

Results

Table 2 shows that most of the individuals (51.9%) were classified in stage 2 of the Modified Hoehn and Yahr Scale, and the sample had a mean UPDRS-III score of 18.8 (SD=7.9). In terms of educational levels, 65.4% had only 4 years of schooling. The majority of the individuals (55.8%) had not suffered any falls during the last year.

< Insert Table 2 about here>

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 3). The

analysis performed revealed that 25% of the variability found for the TUG was explained by the variables included in the model built with the cognitive outcomes. In this case, the TMTA was the only cognitive outcome that was found to be statistically significant by itself ($p=0.02$, $r=0.33$). The cognitive outcomes explained 23% of the variability verified for the anteroposterior displacement, and the digit span forward score was the cognitive outcome that was found to be statistically significant ($p=0.03$, $r=-0.32$). As for the mediolateral displacement, the cognitive outcomes explained 24% of its variability. In this case, the TMTA was the cognitive outcome that was found to be statistically significant ($p=0.03$, $r=-0.30$). After these results, the individual variables, like age, weight, height, body mass index and education, and the clinical variables, such as aids, falls, years of disease and severity were added to the model. With these additional variables, the analysis revealed that the variability increased to 29% in TUG, 34% in anteroposterior displacement and 39% in mediolateral displacement, but the resulting model was not statistically significant.

< Insert Table 3 about here>

Discussion

A statistically significant model composed of cognitive outcomes was able to explain the variances of the TUG, anteroposterior and mediolateral displacements. Also, the explanatory value of the model tended to increase with the addition of individual and clinical variables, although the resulting model was not statistically significant. This means that the individual and clinical variables have no significant influence on the motor variables. The model explained 25-29% of the variability of the Timed Up and Go Test, while for the anteroposterior displacement it was 23-34%, and for the mediolateral displacement it was 24-39%.

Although PD affects primarily motor skills, an increasingly emphasis has been given to the cognitive impairment in this disease (Chaudhuri, Healy, & Schapira, 2006). Several studies have also reported cognitive changes in PD, even in the early stages of the disease (Aarsland et al., 2011; Elgh et al., 2009; Koerts et al., 2011; Merims & Freedman, 2008; Pagonabarraga & Kulisevsky, 2012). It is commonly accepted that approximately 30 to 40% of the individuals with PD tend to develop dementia, but some studies indicate that this possibility can vary from 10 to 80% (Aarsland & Kurz, 2010; Aarsland, Zaccai, & Brayne, 2005). Even in cases of early diagnosis of PD, the cognitive decline is about 36% (Foltynie, Brayne, Robbins, & Barker, 2004). In PD, deficits in several cognitive domains, especially with respect to EFs, are common (A. Coppin et al., 2006). In addition, 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, our linear regression analysis revealed that 25% of the variability found for TUG was explained by cognitive outcomes, increasing to 29% when the individual and clinical variables were added. In fact, studies have suggested that for good functional mobility, the individuals need to integrate cognitive components such as psychomotor speed, visual-spatial orientation, attention and working memory (Springer et al., 2006; Van-Lersel, Kessels, Bloem, Verbeek, & Rikkert, 2008).

Concerning the static balance, the variables included led to a statistically significant model that explained 23% of the variability of the anteroposterior displacement and 24% of the variability of the mediolateral displacement, which increased to 34% and 39%, respectively, with the addition of the individual and clinical variables. As to the anteroposterior displacement, the cognitive variables included explained 23% of the variability of the anteroposterior displacement, increasing to 34% when the individual and clinical variables

were added. A recent study (Lindholm et al., 2014) has shown that cognitive impairments, particularly EFs, are closely related to motor symptoms, especially with postural instability. Hence, the results of the correlations found showed that at least one cognitive test was correlated with balance.

For the TUG and the mediolateral displacement, the TMTA was found to be the only statistically significant variable by itself (p=0.02 and p=0.04, respectively), 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).

For the anteroposterior displacement, the Digit Span Test was found to be the only statistically significant variable (p=0.03), and that can also be used as a balance predictor. 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 individuals 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, Bove, & Abbruzzese, 2003).

This work should be seen as an exploratory study with limitations similar to those in other works published in the literature, particularly in terms of the size of the studied sample and the number and type of the assessment tests used. The lack of specific information about gait can be seen as a limitation; however, it should be noted that the mean UPDRS–III score of 18.8 found in the studied sample indicates a good motor performance and a reduced impact of motor performance in assessment of cognitive outcomes. Despite the limitations, the findings in this study enrich our knowledge concerning the relation between cognition and dynamic and static balance in individuals with PD.

The assessment of anxiety and depression could be of particular interest in future studies, since these disorders have a great impact on cognitive outcomes. In addition, the study of other cognitive outcomes and their impact on the motor performance could be important to understand the relationship between cognition and motor performance more precisely.

Conclusion

There are cognitive components that can be assumed as predictors of balance in PD. Here, the scores obtained for the TMTA variable and for the Digit Span Test were those that achieved the greatest statistical significance. Also, the cognitive components such as the psychomotor speed, visual-spatial orientation, attention and working memory were shown to be the most relevant aspects with regard to the prediction of balance deficits. Moreover, the individual variables proved to have more impact on the static balance than on the dynamic balance.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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TABLE CAPTIONS

Table 1. Characterization of the sample studied (SD - standard deviation).

Table 2. Number of falls and clinical variables for the sample studied (SD - standard deviation).

Table 2. Regression analyses among the Timed Up and Go Test (TUG), anteroposterior and mediolateral displacements and related variables (RSCardsT - Rule Shift Cards Test, TMTA - Trail Making Test part A, TMTB - Trail Making Test part B, MMSE - Mini Mental State Examination).

TABLES

Table 1

Sample (n=52)

	Mean (SD)	**Range**
Age [years]	67.3 (8.9)	39-83
Parkinson disease [years]	7.9 (5.5)	1-23
Weight [kg]	72.3 (13.1)	52-103.8
Height [cm]	165 (8.3)	145-182
Gender - men, n(%)	33 (63.5)	

Table 2

Sample (n=52)

Falls, n (%)	
0	29 (55.8)
≥1	23 (44.2)
Disease severity, n (%)	
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)
UPDRS-III, mean (SD)	18.8 (7.9)

Table 3

	TUG			Anteroposterior displacement			Mediolateral displacement		
	b	**95% IC**	**p**	**b**	**95%I C**	**p**	**b**	**95% IC**	**p**
RSCardsT	0.77	]-0.91;2.45[	0.36	-0.30	]-0.61;0.01[	0.06	-0.06	]-0.25;0.13[	0.51
TMTA	0.05	]0.01;0.09[	**0.02**	-0.01	]-0.01;0.01[	0.89	0.01	]0.00;0.01[	**0.04**
TMTB	-0.02	]-0.05;0.01[	0.19	-0.01	]-0.10;0.01[	0.17	-0.01	]-0.01;0.01[	0.11
MMSE	-0.77	]-1.78;0.24[	0.13	0.11	]-0.07;0.30[	0.23	0.10	]-0.15;0.21[	0.09
Digit Span Forward	-0.21	]-1.09;0.67[	0.64	-0.18	]-0.34;-0.02[	**0.03**	-0.03	]-0.13;0.07[	0.56
Digit Span Backward	-0.04	]-1.10;1.02[	0.94	-0.12	]-0.31;0.08[	0.23	-0.12	]-0.24;0.01[	0.06
R^2 (p)	0.25 (0.03)			0.23 (0.05)			0.24 (0.04)		

b - regression coefficient, 95% IC - confidence interval of 95%, R^2 - coefficient of determination, p - p-value (significant values are in bold ($p<0.05$)).