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Investigation of factors impacting mobility and gait in Parkinson disease



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ABSTRACT

Mobility and gait limitations are major issues for people with Parkinson disease (PD). Identification of factors that contribute to these impairments may inform treatment and intervention strategies. In this study we investigated factors that predict mobility and gait impairment in PD. Participants with mild to moderate PD and without dementia ($n = 114$) were tested in one session 'off' medication. Mobility measures included the 6-Minute Walk test and Timed-Up-and-Go. Gait velocity was collected in four conditions: forward preferred speed, forward dual task, forward fast as possible and backward walking. The predictors analyzed were age, gender, disease severity, balance, balance confidence, fall history, self-reported physical activity, and executive function. Multiple regression models were used to assess the relationships between predictors and outcomes. The predictors, in different combinations for each outcome measure, explained 55.7% to 66.9% of variability for mobility and 39.5% to 52.8% for gait velocity. Balance was the most relevant factor (explaining up to 54.1% of variance in mobility and up to 45.6% in gait velocity). Balance confidence contributed to a lesser extent (2.0% to 8.2% of variance) in all models. Age explained a small percentage of variance in mobility and gait velocity (up to 2.9%). Executive function explained 3.0% of variance during forward walking only. The strong predictive relationships between balance deficits and mobility and gait impairment suggest targeting balance deficits may be particularly important for improving mobility and gait in people with PD, regardless of an individual's age, disease severity, fall history, or other demographic features.

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1. Introduction

Parkinson disease (PD) is characterized by both motor and non-motor features, the presence and extent of which vary from individual to individual. In particular, mobility and gait are often impaired in people with PD, as gait requires complex coordination (Jankovic, 2015). The movement difficulty that people with PD experience in their daily lives may be caused by

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a combination of age-related changes, such as decreased muscle strength, impaired balance, and lower visual acuity, as well as disease-related issues. Pathological and compensatory changes in a variety of locomotor brain regions occur in PD and they may lead to increased variability and asymmetry, poor postural control, bradykinesia, rigidity, and freezing of gait (Peterson & Horak, 2016).

While age-related changes and disease severity are commonly known to affect mobility and gait in PD (Dewey et al., 2014; Rodriguez, Rodriguez-Sabate, Morales, Sanchez, & Sabate, 2015), recent evidence suggests that cognitive function may also play a role (Smulders et al., 2013). In contrast to other neurodegenerative conditions which primarily feature cognitive deficits (such as Alzheimer disease), the cognitive profile in PD is more heterogeneous, likely reflecting the more variable underlying neuropathology (Burdick et al., 2014; Lin & Wu, 2015). Among the cognitive impairments present in individuals with PD, executive dysfunction is of particular interest for two reasons. First, executive dysfunction is frequently observed in early stages of the disease (Lanni et al., 2014), and it may precede and foreshadow mobility impairments. Additionally, executive function plays an important role in complex situations, such as dual task walking, that require divided attention (Varalta et al., 2015). Gait performance is known to be affected in various complex situations in people with PD (Amboni, Barone, & Hausdorff, 2013).

Previous studies examined factors that may predict mobility and gait impairment in PD. Different combinations of factors including demographic characteristics, disease severity, fall history, fear of falling, other gait and mobility measures, freezing of gait, balance, balance confidence, muscle power, cognition, and depression, have been identified as significant predictors (explaining up to 30–73% of variance) of gait and mobility performance in single and dual task conditions (Falvo & Earhart, 2009; Lord, Rochester, Hetherington, Allcock, & Burn, 2010; Lord et al., 2014; Nemanich et al., 2013; Paul, Sherrington, Fung, & Canning, 2013; Rochester et al., 2008; Stegemöller et al., 2014; Strouwen et al., 2016; Varalta et al., 2015). All except one of these previous studies measured participants while on anti-parkinson medication, and the single study testing 'off' medication included a relatively small sample (Lord et al., 2010). While medications are known to impact gait and mobility as well as some of these previously identified factors (Hoskovcová et al., 2015), it is unclear whether different factors may be better predictors in the 'off' medication state when motor function is worse. Further, only one study previously examined balance as a potential predictive factor for gait or mobility in PD on medication (Falvo & Earhart, 2009), but predictive value was only assessed for the six minute walk test distance. Balance has been shown to be related to gait, even in the early stages of PD (Yang, Lee, Cheng, Lin, & Wang, 2008). Even knowing the impact that exercise has on gait and mobility (Shen, Wong-Yu, & Mak, 2015; Shu et al., 2014), no previous studies have included measures of levels of physical activity as potential predictors. As a result, balance and physical activity may be key predictors for gait and mobility outcomes, and these factors may explain variance unaccounted for in previous models.

Recognizing that several factors can affect mobility and gait in PD, we further investigated the impact of age, disease severity, balance, balance confidence, fall history, self-report physical activity, and executive function on measures of mobility and gait performance. To our knowledge, this study is the first to evaluate the relationships between common mobility and gait outcomes and key demographic and clinical characteristics, including balance and physical activity, in a large sample of people with PD tested in the 'off' medication state. Improving our understanding of the demographic and clinical factors that may contribute to mobility and gait deficits in PD may inform the development of future targeted interventions and clinical best practices to address impairments.

2. Methods

2.1. Participants

Individuals with idiopathic PD were recruited from the Movement Disorders Center at Washington University School of Medicine. All participants provided informed consent, and the protocol was approved by the Human Research Protection Office. Data were collected from 114 participants with PD during the baseline visit of a larger trial, prior to participation in an exercise intervention (Earhart, Duncan, Huang, Perlmutter, & Pickett, 2015).

This study included community-dwelling participants diagnosed with idiopathic PD (Calne, Snow, & Lee, 1992) with Hoehn & Yahr (HY) Stages I–III (Hoehn & Yahr, 1967), and scores ≥ 24 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). Individuals were excluded if they had a diagnosis of atypical Parkinsonism, had dementia of any kind, or had any other neurological condition. All participants were evaluated in the 'off' medication state (i.e. at least twelve hours since the last dose of PD medication).

2.2. Outcome and predictor variables

This study examined to what extent demographic and clinical features predicted mobility and gait performance outcomes. Mobility was assessed using the Timed Up and Go test (TUG) and the six minute walk test (6MWT). The TUG (Podsiadlo & Richardson, 1991) requires participants to stand up from a seated position, walk 3 m, turn around, walk back, and sit down again. The 6MWT was used to assess endurance by measuring the maximum distance an individual was able to walk within six minutes. For the 6MWT, the participant walked back and forth along a 30 m open hallway. Participants were permitted to stop to rest and/or use their normal assistive device if needed. Time continued to elapse during any rest periods.

Mobility outcome measures were time (s) to complete the TUG and distance (m) covered during the 6MWT. These tests are valid and reliable in people with PD (Falvo & Earhart, 2009; Morris, Morris, & Iansek, 2001; Vance, Healy, Galvin, & French, 2015).

Gait velocity (m/s) was assessed using a 4.8 m GAITRite® instrumented walkway (CIR Systems, Franklin, NJ, USA) during 4 conditions: forward preferred speed (FWD), forward dual task (DT), forward fast as possible (FAST), and backward walking (BKD). We collected three trials for each gait condition, and the order of the conditions was randomized for each participant. Dual task walking occurred at the preferred pace while the participant completed a phonemic listing task using a different letter (H, L or T) for each trial.

The predictors included in this study were: age (years), gender, disease duration (years), daily amount of PD medications converted to levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010), Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS sections I–IV) (Martínez-Martín et al., 1994), Mini-Balance Evaluation Systems Test (Mini-BESTest) (Franchignoni, Horak, Godi, Nardone, & Giordano, 2010), Activities-specific Balance Confidence (ABC) (Powell & Myers, 1995), history of falls (fallers vs. non-fallers, where fallers were defined as having 2 or more self-reported falls in the last 6 months), self-reported physical activity (CHAMPS – non-weighted score) (Stewart et al., 2001), Trail Making test Part B minus Part A (TMT) (Lezak, 1995), Color-Word Interference test inhibition time minus color naming time (CWIT) (Delis, Kaplan, & Kramer, 2001), and Verbal Fluency accuracy in a semantic switching condition alternately naming furniture and fruits (VF) (Delis et al., 2001).

2.3. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS®), version 22.0 for Windows. Descriptive statistics were used to calculate means, standard deviations, and 95% confidence intervals.

We used stepwise multiple regression models (R^2) to assess the relationships between predictors and outcomes. To identify relevant factors for inclusion in each model, we first performed correlations between predictors and outcomes (Pearson for parametric, Spearman for non-parametric variables). Only predictors that were significantly correlated with each mobility outcome measure were included in the respective regression models. The level of significance was set at $p < 0.05$. For each regression model, data were checked to ensure linear relationships, homoscedasticity, independence of observations, normality of regression residuals, and outliers. Values more than 3 standard deviations above or below the mean for predictors and outcomes were classified as outliers and were excluded from analyses.

3. Results

Participants' demographic and clinical characteristics are shown in Table 1.

The initial correlation analyses revealed significant associations between predictors and outcomes as detailed in Table 2.

3.1. Contribution of significant predictors to mobility

The regression models explained 55.7% of the variance in mobility for the 6MWT and 66.9% for the TUG. The Mini-BESTest was the most relevant predictor for both outcomes, followed by ABC and age. The MDS-UPDRS section I (non-motor aspects of experiences of daily living) was a significant independent predictor only for the TUG (Table 3).

Table 1
Demographics and outcomes (mobility and gait velocity) in PD participants.

Characteristic	Mean \pm SD	95% Confidence Interval
Age (years)	66.6 \pm 9.4	64.9–68.4
MMSE (pts)	28.6 \pm 1.4	28.3–28.8
Education (years)	15.7 \pm 2.4	15.3–16.1
Disease duration (years)	5.4 \pm 4.4	4.6–6.2
HY (stage)	2.4 \pm 0.4	2.4–2.5
MSD-UPDRS III (pts)	34.8 \pm 10.4	32.9–36.7
LEDD	810.6 \pm 640.3	691.8–929.4
6MWT (m)	415.9 \pm 111.9	395.1–436.8
TUG (s)	11.6 \pm 4.5	10.7–12.4
Forward walking (m/s)	1.3 \pm 0.3	1.3–1.4
Forward dual task (m/s)	1.1 \pm 0.3	1.0–1.1
Forward fast (m/s)	1.8 \pm 0.4	1.7–1.9
Backward walking (m/s)	0.8 \pm 0.3	0.7–0.8

MMSE: Mini-Mental State Exam; HY: Hoehn & Yahr. MSD-UPDRS III: motor section of the Movement Disorder Society Unified Parkinson's disease Rating Scale. LEDD: Levodopa equivalent daily dose. 6MWT: 6 minute walk test. TUG: Timed up and go. SD: Standard deviation.

Table 2
Correlations between predictors and outcomes.

Predictors	Outcomes					
	6MWT	TUG	FWD	DT	FAST	BKD
Age	−0.363	0.360	−0.291	−0.298	−0.266	−0.431
Gender	−0.196	0.053	−0.012	−0.083	−0.112	−0.177
Fall history	−0.213	0.211	−0.214	−0.229	−0.177	−0.235
Disease duration	−0.139	0.135	−0.207	−0.161	−0.069	−0.129
LEDD	−0.147	0.167	−0.195	−0.128	−0.162	0.025
MDS-UPDRS I	−0.346	0.543	−0.446	−0.407	−0.404	−0.358
MDS-UPDRS II	−0.350	0.551	−0.466	−0.432	−0.370	−0.415
MDS-UPDRS III	−0.420	0.444	−0.443	−0.392	−0.383	−0.391
MDS-UPDRS IV	−0.001	0.037	−0.069	−0.058	−0.041	0.068
Mini-BESTest	0.691	−0.703	0.664	0.588	0.676	0.685
ABC	0.524	−0.652	0.572	0.536	0.535	0.537
CHAMPS	0.010	−0.036	0.103	0.023	0.099	0.100
TMT	−0.073	0.163	−0.200	−0.183	−0.099	−0.151
CWIT	−0.329	0.397	−0.380	−0.352	−0.279	−0.291
VF	0.286	−0.439	0.336	0.337	0.218	0.334

Pearson R or Spearman Rho values are provided for parametric and nonparametric variables, respectively. 6MWT: Six minute walk test. TUG: Timed Up and Go test. FWD: Forward preferred speed. DT: Forward dual task. FAST: Forward fast as possible. BKD: Backward walking. LEDD: Levodopa equivalent daily dose. MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale. Mini-BESTest: Mini-Balance Evaluation Systems Test. ABC: Activities-specific Balance Confidence. CHAMPS: Community Health Activities Model Program for Seniors physical activity self-report questionnaire. TMT: Trail Making test. CWIT: Color Word Interference test. VF: Verbal fluency. Significant correlations are highlighted in bold.

Table 3
Regression coefficients for each mobility outcome.

Mobility	Predictors/Model	R ² (%)	R ² change (%)	Sig
6MWT	Model 1: Mini BESTest	51.6	51.6	0.001
	Model 2: Mini BESTest + ABC	53.7	2.1	0.001
	Model 3: Mini BESTest + ABC + age	55.7	2.0	0.001
TUG	Model 1: Mini BESTest	54.1	54.1	0.001
	Model 2: Mini BESTest + ABC	62.2	8.2	0.001
	Model 3: Mini BESTest + ABC + age	64.9	2.6	0.001
	Model 4: Mini BESTest + ABC + age + UPDRS I	66.9	2.1	0.001

6MWT: Six minute walk test. TUG: Timed Up and Go test. Mini-BESTest: Mini-Balance Evaluation Systems Test. ABC: Activities-specific Balance Confidence. MDS-UPDRS I: Movement Disorder Society Unified Parkinson's disease Rating Scale section I.

3.2. Contribution of significant predictors to gait velocity

The regression models explained up to 52.8% of the variance in gait velocity. Similar to mobility, the Mini-BESTest was the most relevant predictor in all stepwise models for gait velocity. The ABC explained the second highest levels of variance for FWD, DT, and FAST gait velocity, and also contributed to the BKD gait velocity model. Executive function (CWIT) explained a small percentage of the variance in FWD walking velocity, and age was included in both the DT and BKD velocity models (Table 4).

Table 4
Regression coefficients for each gait velocity outcome.

Gait	Predictors/Model	R ² (%)	R ² change (%)	Sig
FWD	Model 1: Mini BESTest	45.1	45.1	0.001
	Model 2: Mini BESTest + ABC	49.8	4.7	0.001
	Model 3: Mini BESTest + ABC + CWIT	52.8	3.0	0.001
DT	Model 1: Mini BESTest	31.3	31.3	0.001
	Model 2: Mini BESTest + ABC	36.7	5.4	0.001
	Model 3: Mini BESTest + ABC + age	39.5	2.8	0.001
FAST	Model 1: Mini BESTest	45.2	45.2	0.001
	Model 2: Mini BESTest + ABC	49.3	4.0	0.001
BKD	Model 1: Mini BESTest	45.6	45.6	0.001
	Model 2: Mini BESTest + age	48.6	2.9	0.001
	Model 3: Mini BESTest + age + ABC	51.4	2.9	0.001

FWD: Forward preferred speed. DT: Forward dual task. FAST: Forward fast as possible. BKD: Backward walking. Mini-BESTest: Mini-Balance Evaluation Systems Test. ABC: Activities-specific Balance Confidence. CWIT: Color Word Interference test.

The unstandardized and standardized coefficients of each predictor entered in the models for mobility and gait velocity are presented in the [Supplementary file](#). The results from Durbin-Watson tests with data ordered according to participant number and from the collinearity statistics ([Supplementary Table 1](#)) reinforce that the data are in accordance with the assumptions required by regression models ([Field, 2009](#)). Correlations between the predictors were also performed ([Supplementary Table 2](#)) to determine the relationships between all potential factors. Bivariate analyses revealed strong associations between Mini-BESTest and ABC, as well as between Mini-BESTest and sections I, II and III of the MDS-UPDRS.

4. Discussion

In this study we investigated the impact of several factors on mobility and gait in non-demented participants with PD. Balance, which had not previously been investigated in models using 'off' medication assessments, was the strongest predictor for all gait and mobility outcomes. Balance confidence, age, executive function, and the MDS-UPDRS subsection for nonmotor aspects of daily living explained smaller portions of the variance for different mobility and gait measures. Understanding how these predictors relate to mobility and gait in PD is important to guide health care professionals in improving independence and potentially reduce risk of falls in this population ([Kerr et al., 2010](#)).

The most salient finding of this study was that balance was the strongest predictor for all gait and mobility outcomes in mild to moderate PD. Balance impairments are present in early disease stages and can even be detected in patients with de novo PD ([Chastan, Debono, Maltête, & Weber, 2008](#); [Mancini et al., 2011](#)). Previously demonstrated strong correlations between measures of balance and gait and mobility measures support our findings ([Paker et al., 2015](#)). Future research should be conducted to determine whether performance in specific domains of balance (e.g. anticipatory postural adjustments, sensory orientation), measured using a tool such as the full BESTest ([Horak, Wrisley, & Frank, 2009](#)), may be driving this relationship and thus would be ideal targets for rehabilitation interventions.

Balance confidence was included in the final regression models for all gait and mobility tasks. The mean ABC score of the participants was relatively high, and many of the items of the instrument inquire about balance confidence during basic gait and mobility tasks similar to the outcome tasks we were measuring. Gait velocity in preferred-pace forward and backward gait was previously shown to be lower in individuals with PD with fear of falling as measured by the ABC (regardless of fall history), and similarly time to complete the TUG was higher in these individuals, supporting the relevance of the ABC for these basic gait and mobility outcomes ([Bryant, Rintala, Hou, & Protas, 2014](#)). Despite not containing turning-specific items, balance confidence was most relevant in predicting TUG, which could potentially be attributed to the presence of turning during this task. Difficulty with turning is common, even in people with mild PD with relatively normal gait ([Crenna et al., 2007](#)). Though the ABC does not include any items specific to turning, self-reported confidence during various complex gait and mobility tasks was an important factor (separate from balance ability) for predicting TUG performance.

Since disease severity is known to affect gait and mobility in PD, we expected disease severity and LEDD (as a surrogate measure of disease severity) would be important predictors. However, the correlations between these variables and all gait and mobility outcomes were weak. This may be attributed to our sample having relatively mild PD. Only section I of the MDS-UPDRS (non-motor aspects of daily living) was included in one of the final models (TUG). More severe non-motor symptoms were associated with worse performance on the TUG. The MDS-UPDRS I contains items measuring cognition and mood which have both been previously identified as relevant factors related to walking tasks ([Lord et al., 2014](#); [Rochester et al., 2008](#)). However, the contribution of MDS-UPDRS I to the TUG model was small (2.1%), compared to the larger contributions of balance (54.1%) and balance confidence (8.2%). The absence of the other sections of the MDS-UPDRS in the regression models may either reflect a lack of relationship with the outcomes (MDS-UPDRS IV) or a significant relationship with the outcomes masked by one or more stronger predictors (MDS-UPDRS II and III). Lack of significant correlation between gait/mobility outcomes and MDS-UPDRS IV may be explained by our mild to moderate sample that did not have substantial motor complications. Sections II and III of the MDS-UPDRS cover activities of daily living and motor signs (including balance and gait-specific items), respectively, which may both have competed substantially with balance in the regression models. Significant associations between the Mini-BESTest and sections II and III of the MDS-UPDRS were confirmed in bivariate analyses ([Supplementary Table 2](#)). It is possible that disease severity measured with the MDS-UPDRS and LEDD would be more strongly related to mobility and gait in samples of participants with more advanced PD.

Our findings supporting the role of age in gait and mobility performance corroborate prior studies ([Falvo & Earhart, 2009](#); [Nemanich et al., 2013](#); [Paul et al., 2013](#); [Rochester et al., 2008](#); [Strouwen et al., 2016](#)). However, our results showed a relatively small impact of age (0–2.9% of variance in outcomes explained) which is on par with some previous studies ([Rochester et al., 2008](#); [Strouwen et al., 2016](#)), but substantially lower compared to others, including one in which age explained 19% of variance in preferred pace and 18% of variance in fast walking velocity ([Nemanich et al., 2013](#)). Differences in results are likely due to the different factors included in the models for each study, as well as differences in the statistical methods used to generate the models. Age was only identified as a significant predictor for a subset of the gait and mobility measures we investigated (6MWT, TUG, DT, and BKD). It is possible that age may be a better predictor for longer duration tasks (6MWT) and more complex tasks (TUG, DT, and BWD) than for simple, shorter duration tasks (FWD and FAST) in people with PD.

Executive function was expected to be associated with mobility and gait given that it is compromised even in early stages of the disease ([Lanni et al., 2014](#)) and because prior work noted that executive function measures explained 6–10.0% of variability in gait velocity during a functional walking test ([Lord et al., 2010](#)). In our study, executive function explained only

3.0% of variance during forward walking velocity and was not a significant predictor for the TUG or dual task walking velocity. Differences between studies might be related to the different outcomes and sets of predictors included in the models. Lord et al. (2010) used a home-based functional walking test, where participants stood up from a chair in their living room, walked to a bench in their kitchen, picked up a tray, and carried it back to the table next to their chair. Their analysis focused on the motor subsection of the MDS-UPDRS and did not include measures of balance. Further, different cognitive tasks were used. We used the Trail Making Test, Color Word Interference Test, and Verbal Fluency, while the previous study used the Brixton Test and elements of the Test of Everyday Attention. It is possible that our cognitive tasks were not as demanding of relevant aspects of executive function as those used by Lord et al. (2010). Inclusion of measures focusing more heavily on attention may have produced different results, particularly for dual task gait. However, balance alone in our forward walking model explained a higher percentage of variability than the combination of executive function plus MDS-UPDRS III in the single task gait model from the previous study. It will be important for future studies to analyze the contributions of executive function and balance predictors in performance of more complex cognitive and walking tasks. Studies with individuals with Parkinson disease and dementia should also be done to clarify if executive function is more strongly related to gait and mobility outcomes in cases of more severe cognitive impairment.

Contrary to our initial hypothesis that physical activity may be a key predictor for gait and mobility performance, self-reported physical activity scores on the CHAMPS were poorly correlated with gait and mobility outcomes. Based on growing evidence suggesting that exercise improves gait and balance in people with PD (van der Kolk & King, 2013), we expected that physical activity would be highly associated with the outcomes. Our results for physical activity should be interpreted cautiously, as there are known limitations with self-report measures of physical activity (Prince et al., 2008). Unbiased, more precise approaches such as accelerometers may be better suited for teasing out potential relationships between real-world physical activity and gait and mobility performance.

4.1. Limitations

The results of this study should be considered in light of some limitations. First, we included only individuals with mild to moderate PD. Further, none of our participants had dementia. Our results may not be generalizable to people with more severe PD or those with dementia. In addition, our regression models could not explain 33.1–44.3% of the variability in mobility and 47.2–60.5% of the variability in gait velocity for different walking conditions. It is possible that adding factors included in prior studies, such as divided attention, muscle power, anxiety, or depression, as well as previously unexplored factors, such as physical fitness, motivation, or joint flexibility, would potentially strengthen the predictive ability of our models.

5. Conclusions

Our results highlight that balance is the most relevant factor for predicting mobility and gait performance in cognitively normal people with mild to moderate PD in the off-medication state. Balance confidence, age, executive function, and non-motor aspects of daily living were also independently associated with the outcomes, but to a substantially lesser extent. Although several factors contributed to the mobility outcomes, the results reinforce that exercise interventions focusing on balance may be best able to impact gait and mobility in PD.

Conflict of interest statement

No conflicts of interest are declared by the authors related to the completion of this project and manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.humov.2016.08.007>.

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