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Determinants of Objectively Measured Physical Functional Performance in Early to Mid-stage Parkinson Disease

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Abstract

Background—Parkinson disease (PD) may lead to functional limitations through both motor and non-motor symptoms. While patients with advanced disease have well-documented and profound functional limitations, less is known about the determinants of function in early to mid-stage disease where interventions may be more likely to benefit and preserve function.

Objective—The objective of the current study was to identify motor, cognitive and gait determinants of physical functional performance in patients with early to mid-stage PD.

Design—Secondary analysis of cross-sectional baseline data from a randomized clinical trial of exercise.

Setting—Tertiary academic medical center.

Participants—121 patients with early to mid-stage PD.

Methods—Our functional performance outcomes included: 1) the Continuous Scale Functional Performance Test (CS-PFP; primary outcome); 2) the timed up and go (TUG) tests; and Section 2 (Activities of Daily Living) of the Unified Parkinson's Disease Rating Scale (UPDRS).

Explanatory variables included measures of disease severity, motor function, cognitive function, balance and gait. Step-wise linear regression models were used to determine correlations between explanatory variables and outcome measures.

Results—In our regression models the CS-PFP significantly correlated with walking endurance (six minute walk; $r^2 = 0.12$, $p < .0001$), turning ability (360 degree turn; $r^2 = .03$, $p = .002$), attention (brief test of attention; $r^2 = .01$, $p = .03$), overall cognitive status (Mini-mental State Examination; $r^2 = .01$, $p = .04$) and bradykinesia (timed tapping; $r^2 = .02$, $p = .02$). The TUG significantly correlated with walking speed (5 meter walk; $r^2 = 0.33$, $p < .0001$), stride length ($r^2 =$

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0.25, $p < .0001$), turning ability (360 turn $r^2 = .05$, $p = .0003$) and attention ($r^2 = .016$, $p = .03$). Section 2 of the UPDRS was significantly correlated with endurance ($r^2 = .09$, $p < .0001$), turning ability ($r^2 = .03$, $p = .001$) and attention ($r^2 = .01$, $p = .03$).

Conclusions—Gait, motor and cognitive function all contribute to objectively measured global functional ability in mild to moderate PD. Subjectively measured functional activity outcomes may underestimate the impact of both motor and non-motor symptoms.

Keywords

Parkinson Disease; physical functional performance; Continuous Scale Physical Functional Performance Test

Introduction

Parkinson disease (PD) is a progressive neurodegenerative illness which typically results in a gradual progression of functional loss and disability due to changes in motor control, gait and non-motor symptoms including fatigue and cognitive dysfunction.(1, 2) In advanced disease individuals may require nursing home placement due to functional limitations, dementia and hallucinations.(3) However, less is known about the determinants of functional limitations earlier in the illness.(1) This is an important area of study as rehabilitation interventions are more likely to have an impact at this stage of the illness and may prevent or slow further functional decline.(4)

Prior studies in this area suggest that postural instability, gait difficulties, bradykinesia, older age and cognitive dysfunction are associated with self-reported functional outcomes.(1, 5, 6) As noted by the authors of these studies, there are several limitations to this literature which merit further research. First, many studies used only univariate analyses which may overestimate the contribution of certain variables, particularly those highly correlated with other explanatory factors. Second, the evaluation of explanatory factors was often limited, for example using only clinician ratings of gait and balance rather than more specific and detailed measures. Finally, functional limitations was inconsistently measured and was assessed using only using self-report scales which have many sources of potential bias.(7)

The Continuous Scale Physical Functional Performance test (CS-PSP) is a robust measure of overall physical functional capacity that was developed and normed on individuals across a wide spectrum of functional capacity from elite athletes to individuals at the threshold for loss of independence.(8) This measure is reliable and valid, both for healthy individuals and those with a variety of disorders, including PD.(8-10) Furthermore, cross sectional data from a large sample of individuals from Hoehn and Yahr stages 1 to 3 indicate that the CS-PFP detects functional loss early in the disease and progressively worsens across stages of PD. (11)

Therefore, the primary objective of this investigation was to examine some of the potential determinants of physical functional capacity using: 1) a variety of explanatory measures to cover demographic (e.g. age, gender, disease duration), motor (e.g. tremor, bradykinesia, rigidity), gait (e.g. speed, balance, turning and endurance) and cognitive function (e.g.

attention, cognitive control, working memory); 2) multivariate models to control for potential correlations amongst variables; and 3) the CS-PFP to objectively measure functional performance abilities. Secondary objectives of this study were to assess the correlation of the CS-PFP with a widely used self-report measure of activities of daily living in PD (Section 2 of the Unified Parkinson's Disease Rating Scale)(12) and an objective measure of functional mobility (the timed up and go test)(13) and to compare the results of our model using the CS-PFP to the self-report and functional mobility based outcomes.

Methods

Participants

The sample for this study was drawn from baseline data of a randomized, controlled trial (RTC) of exercise for people in early and mid-stages of PD.(14) Participants had idiopathic PD, verified by a movement disorder specialist, using UK Brain Bank criteria.(15) They were included in the study if they lived in the community and were able to ambulate without an assistive device. Participants were excluded from the RTC if they had Mini-Mental State Exam (MMSE)(16) score of less than 24, on-state freezing, uncontrolled hypertension, or if exercise was limited by musculoskeletal, neuromuscular (other than PD), or cardiovascular disorders. All participants signed informed consent prior to entering the study, which was approved by our University's Institutional Review Board. Participants in the RTC underwent a comprehensive on-state assessment including the following measures.

Measures of Disease State and Motor Severity

Disease State was rated using the Hoehn and Yahr scale(17) and total score on the Unified Parkinson's Disease Rating Scale (UPDRS)(12). Motor function was examined using the motor subscale of the UPDRS. We also specifically created summary scores for tremor (items 20 and 21), bradykinesia (items 23-26), limb rigidity (limb items of 22) and axial rigidity using the neck rigidity item. Motor function was also assessed using a timed finger tapping task in which subjects were asked to alternately tap with their finger two tally-counters 30 centimeters apart as fast as they could for one minute.(18) Each hand was tested independently and scores were taken from two test trials following a practice trial.

Measures of Cognitive Function and Depression

Cognitive testing included the Mini Mental State Examination (MMSE)(16) to assess overall cognitive function. The Stroop Color Word Test was used to assess cognitive control.(19) To evaluate the cognitive versus speed components of the Stroop test we examined the timed score for word reading and created a cognitive interference score by dividing the color-word time by the word reading time. The Brief Test of Attention was used to assess attentional control.(20) The Spatial Span Backwards was used to assess working memory.(21) These measures were chosen to specifically examine aspects of executive function with minimal confounds of motor or verbal speed. We used the Centers for Epidemiologic Studies Depression Scale (CES-D) to measure depressive symptoms.(22)

Measures of Balance, Gait and Falls

To measure balance we used the forward functional reach task (FR) which quantifies the distance a participant can reach forward without stepping from an initial position of the shoulder flexed at 90°. (23, 24) Within the construct of gait, we specifically measured turning ability using the 360° turn test which measures the time and number of steps required for a participant to turn to the right and to the left when instructed to turn at their normal pace. (25) We measured endurance for gait using the six minute walk in which participants were instructed to walk at a pace that would allow them to cover the greatest distance they could over six minutes. (26, 27) Falling was assessed as a binary event (faller or non-fallers) based on questions 13 and 14 from the UPDRS. (12) We also separated the clinician assessed motor items for gait and balance (pull-test) from the UPDRS for separate analysis. We assessed subjective balance confidence using the activities-specific balance confidence scale (ABC). (28)

Measures of Functional Activities

We defined balance and gait-related function as those functions requiring multiple aspects of balance and gait to successfully complete. To assess basic functions related to gait, we used the timed up-and-go (TUG) which measures the time it takes for a participant to rise from a chair, walk 3 meters, turn 180°, walk back to the chair and sit down. (13, 29) To assess more complex gait related functions important for living independently we had participants complete the Continuous-scale physical functional performance test (CS-PFP). (8, 9) This test includes 16 practical activities, (e.g., climbing stairs, carrying groceries, sweeping a floor), performed consecutively. This test has been validated in PD patients. (10) Participants also completed section 2 of the UPDRS which is a clinician administered survey of 13 patient-reported activities of daily living including ratings of several daily activities (e.g. hand-writing, dressing), gait (e.g. walking, falls) and other symptoms (e.g. tremor, sensory complaints). (12)

Statistical Analyses

Statistical analysis was performed using SAS version 9.2 (SAS Inc., Cary, NC). All data was checked for outliers, distributions and missing values. Student's T-test was used to determine differences between groups. Spearman's correlation was performed to determine the relationship between continuous variables. Stepwise linear regression models were created for balance and gait variables and gait-related functions starting with all potential non-overlapping explanatory demographic, motor and cognitive variables demonstrating a significant correlation with the outcome measure of interest. P-values < .05 were considered significant.

Results

We included 121 subjects with PD in this cohort with a mean age of 64.7 (10.4), 63% males and 92% on dopaminergic medications. Please see Table 1 for demographic, disease, medication, motor, cognitive, gait and functional activity measures for the total sample. Our functional activity outcomes were significantly correlated with each other with the CS-PFP and TUG being highly correlated ($r = -0.83$, $p < .0001$) and other correlations being

moderate (UPDRS-ADL and CS-PFP: $r = -0.36$, $p < .0001$; UPDRS-ADL and TUG: $r = 0.30$, $p = .0007$). Of our functional activity outcomes (CS-PFP, TUG and UPDRS-ADL) only the UPDRS-ADL showed a significant difference between genders (male 9.8 ± 4.8 vs. female 8.0 ± 4.4 , $p = .04$) and we thus included gender as part of our model for UPDRS-ADL below.

Demographic, Motor, Cognitive and Gait Determinants of Functional Activities as Measured by the CS-PFP

To better understand the relationship of the explanatory variables with the CS-PFP we first performed Spearman correlations with our gait outcomes. We then used stepwise linear regression to model determinants of the CS-PFP variable using only those explanatory variables with a significant Spearman correlation. Table 2 summarizes the variables with significant individual correlations with CS-PFP and the results of our final model. Our overall model demonstrated an excellent fit to the data ($r^2 = 0.75$, $p < .0001$) with significant predictors including endurance (the six-minute walk), turning ability (360 degree turn test), bradykinesia (timed tapping), attention (BTA) and overall cognitive function (MMSE).

Demographic, Motor, Cognitive and Gait Determinants of Functional Activities as Measured by the Timed up and Go test (TUG)

As with the CS-PFP models, we began with Spearman correlations and proceeded to stepwise linear regression only for variables with a significant correlation. Table 3 summarizes the variables with significant individual correlations with the TUG and the results of our final model. Our overall model demonstrated an excellent fit ($F = 100.6$, $r^2 = 0.80$, $p < .0001$) with significant predictors including walking speed (Five meter walk), turning ability (360 degree turn test) and attention (BTA). To better understand the contributions of walking speed to TUG performance we repeated our model substituting average step-length and step speed (number of steps divided by time) from the five meter walk and found that step length ($r^2 = 0.25$, $p < .0001$) but not step speed was significantly correlated with the TUG.

Demographic, Motor, Cognitive and Gait Determinants of Functional Mobility and Functional Activities as Measured by the Section 2 of the UPDRS

As with the CS-PFP and TUG models, we began with Spearman correlations and proceeded to stepwise linear regression only for variables with a significant correlation. Table 4 summarizes the variables with significant individual correlations with the ADL-UPDRS and the results of our final model. Our overall model demonstrated an excellent fit ($F = 45.68$, $r^2 = 0.74$, $p < .0001$) with significant variables including endurance (six-minute walk), turning ability (360 degree turn test) and attention (BTA).

Discussion

In this investigation, we examined contributions to three measures of functional activities: a robust objective measure of physical functional capacity, as measured by the CS-PFP, a relatively simple task of balance and gait (the TUG); and a subjective rating of multiple functional activities as measured by the UPDRS ADL Subscale. In all three cases the model

tested demonstrated an excellent fit (r^2 from .74-.8) and all three measures of function demonstrate both motor and non-motor contributions. Notably, these findings demonstrate that a number of factors are uniquely correlated with performance on the CS-PFP compared with the TUG and even compared with the UDPRS ADL Subscale. To understand these findings, it is helpful to consider the differences in construct of these three measures.

The CS-PFP is a robust performance-based measure of physical functional capacity that was developed to objectively assess real world functional abilities in older adults across a wide range of functional abilities using a various activities of daily living (ADLs).(8) Understanding the determinants of physical functional capacity is of particular importance for people with PD because the wide range of impairments seen in isolated gait measures, motor tasks and non-motor tests may not necessarily translate into real world functional limitations. The CS-PFP includes tasks highly dependent on balance and gait (e.g., carrying a suitcase up a simulated bus platform) but also includes tasks that additionally rely heavily on various other capabilities such as motor planning and attention (e.g., putting on a jacket while standing; making a bed; moving laundry from washer to dryer). Thus it is not surprising that the CS-PFP was significantly associated with a range of factors including endurance (the six minute walk test) attention (the BTA), turning ability (360 turn), bradykinesia (timed tapping), and global cognitive status (MMSE).

In contrast, the TUG captures balance and gait only in the context of performing a constrained task of rising from a chair, walking 10 meters turning and sitting back down. Hence it is not surprising that significant contributors to the TUG include speed of movement (The Five Meter Walk test) and turning ability (360 turn). However, it is notable that attention was also correlated with TUG performance which may reflect cognitive contributions to gait and previously reported phenotypic associations between gait and cognitive impairments in PD.(30)

Contributors to function as measured by the CS-PFP also differed from function as measured by the UPDRS ADL Subscale. Specifically, significant contributors to the UPDRS ADL included endurance, turning ability and attention (as for the CS-PFP) but did not include bradykinesia or cognitive status. Several factors may account for the difference in contributors to these two different constructs of functional ability. First, the UPDRS ADL Subscale is based predominantly on self-reported function. It is well known that individuals can overestimate their capabilities by self-report, and likely can underestimate the impact on these abilities from bradykinesia and cognitive status.(7, 31) Secondly, the CS-PFP measures overall capacity and speed in addition to the simple ability to perform individual tasks. There are greater demands for task performance when a series of tasks are performed sequentially and time matters as occurs in the CSPFP which is also reflected in real world situations. Thus the impact of both endurance and bradykinesia would likely be heightened. A third factor is the nature of the tasks that comprise the CS-PFP which includes complex activities such as making a bed, transferring laundry from a washer to a dryer, and getting up from the floor, each of which may be affected by both bradykinesia and cognitive function. In contrast, the UPDRS ADL Subscale focuses on basic activities of daily living.

The results of this study suggest several potential implications for rehabilitation. Clearly measures related to balance and gait were important contributors to overall functional ability. And indeed, much of the emphasis of physical intervention studies has focused on these abilities.(4) Findings from this investigation underscore the importance of including complex tasks that rely on these constructs. Our findings further suggest that stride length may be more functionally relevant than gait speed. In this regard, strategies can be implemented to improve stride length such as those proposed by the intervention referred to as “BIG” and by treadmill training.(32) Although preliminary studies suggest possible benefits of both approaches, robust investigations are warranted to determine whether or not such intervention strategies actually improve balance and gait.

In contrast to gait and balance, relatively little emphasis has been placed on interventions designed to improve endurance, attention, and cognition, which also have significant functional impact. Findings from this investigation, related to attention are consistent with suggestions that strategies should be implemented early in the disorder to assist patients to enhance their ability to perform tasks that require attention, while compensatory strategies should be implemented later in the disease to assist patients to function safely despite attentional demands.(33) Preliminary studies of attentional cueing (34) and dual task training (35) show evidence of potential efficacy and a larger trial of this strategy is currently underway.(36) Recently investigators have demonstrated the long-term (16 month) impact of endurance exercise training for people in early and mid-stages of PD and a current trial is underway to determine the appropriate dosage of treadmill exercise training for people in very early PD (prior to the initiation of pharmacological interventions).(14, 37, 38)

Finally, based on findings from this investigation, outcome measures should include multiple aspects of balance and gait. Commonly used measures of balance and gait (e.g., gait speed, functional reach, Berg Balance) may not fully capture the functional impact of PD and may underestimate the benefits of physical interventions that do not take into account endurance, bradykinesia, and attention, on overall ability to function. Investigations are warranted to determine those measures that best capture the full functional impact of PD and are most sensitive to change.

This study has several important limitations. The study population represented a restricted range of PD severity and also of cognitive dysfunction. It is possible that different factors may be more or less important in patients with late disease and/or more prominent cognitive dysfunction. Because this sample of participants was early in PD and falls and freezing were not significant clinical finding, we did not have an objective measure of these impairments, which may have their own unique determinants. Fatigue likewise was not measured in the parent study, but may be an important determinant of performance on the CS-PFP, given the continuous nature of that task. Finally, our results are a secondary analysis of a pre-existing dataset and dependent on the choice of balance and gait outcomes in the parent study. Prior studies have shown that even among objective tests, not all measures of gait or balance are equally relevant or ecologically valid for PD.(39) Further research is needed to determine which measures of speed, endurance, balance and turns are the most ecologically valid.

Conclusion

Gait, motor and cognitive function all contribute to objectively measured global functional performance abilities in mild to moderate PD and may be considered as targets for future interventional and preventative trials. Subjective functional activity outcome measures and those restricted to gait may underestimate the impact of both motor and non-motor symptoms in patients with early to mid-stage PD.

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Table 1
Demographic Characteristics of Patients: Mean (Standard Deviation)

Age (years)	64.8 (10.4)
Gender (Male/Female)	76/45
Hoehn and Yahr (Mean)	2.4 (0.4)
Hoehn and Yahr (number of participants and percent)	Stage 1: 2 (1.6%) Stage 1.5: 4 (3.3%) Stage 2: 62 (51.2%) Stage 2.5: 41 (33.9%) Stage 3: 12 (9.9%)
UPDRS Motor Score	24.8 (9.8)
MMSE	28.7 (1.3)
Disease Duration (years)	4.4 (3.9)
Levodopa Equivalent Dose	572.15 (468)
Education (years)	15.9 (3.2)
Five Meter Walk (seconds)	3.9 (0.87)
Six Minute Walk (meters)	513.06 (107.3)
360 Degree Turn (seconds)	15.7(4.5)
FR (cm)	13.7 (3.1)
ABC	83.36 (17.40)
CS-PFP	47.7 (16.2)
TUG (seconds)	10.7 (3.0)
UPDRS Section 2 (ADL)	9.1 (4.7)

ABC – Activities of Balance Confidence Scale; ADL – Activities of Daily Living; CS-PFP – Continuous Scale Physical Functional Performance Test; FR – Functional Reach Balance Test; MMSE – Mini Mental State Examination; TUG – Timed Up and Go test; UPDRS – Unified Parkinson Disease Rating Scale; 360 Degree Turn – 360 degree timed turning Test

Table 2
Results of Stepwise Linear Regression for CS-PFP using Demographic, Motor, Cognitive and Gait Variables

Variables used in model (Spearman r and p value)	Significant Results from Stepwise Linear Regression Model
Age ($r = -0.57, p < .0001$) Neck Tone ($r = -0.23, p = .0119$) UPDRS Bradykinesia ($r = -0.3, p = .0007$) UPDRS Motor ($r = -0.45, p < .0001$) MMSE ($r = 0.23, p = .0119$) Stroop Interference ($r = 0.26, p = .0055$) Timed Tapping ($r = 0.63, p < .0001$) BTA ($r = 0.45, p < .001$) SSB ($r = 0.41, p < .0001$) Six Minute Walk ($r = 0.8, p < .0001$) Five Meter Walk ($r = -0.67, p < .0001$) Turning Ability ($r = -0.75, p < .0001$) ABC ($r = 0.42, p < .0001$) FR ($r = 0.62, p < .0001$)	Overall Model Fit: $F = 46.92, r^2 = 0.75, p < .0001$ Significant Variables: Six Minute Walk ($F = 149.65, r^2 = 0.12, p < .0001$) Turning Ability ($F = 24.39, r^2 = .03, p = .002$) BTA Score ($F = 9.38, r^2 = .01, p = .03$) Timed Tapping ($F = 4.8, r^2 = .02, p = .02$) MMSE ($F = 4.28, r^2 = .01, p = .04$)

CS-PFP – Continuous Scale Physical Functional Performance Test; ABC – Activities of Balance Confidence Scale; BTA – Brief Test of Attention; FR – Functional Reach Test of Balance; MMSE – Mini Mental State Examination; Neck tone – neck tone item from UPDRS; SSB – Spatial Span Backwards; Timed Tap - Timed Finger Tapping Test; UPDRS – Unified Parkinson Disease Rating Scale; Turning Ability – 360 Degree Turn Test;

Table 3
Results of Stepwise Linear Regression for the TUG using Demographic, Motor, Gait and Cognitive Variables

Variables used in model (Spearman r and p value)	Significant Results from Stepwise Linear Regression Model
Age ($r = 0.51$, $p < .0001$) Timed Tapping ($r = -0.57$, $p < .0001$) Neck Tone ($r = 0.32$, $p = .0003$) UPDRS-Bradykinesia ($r = 0.36$, $p < .0001$) UPDRS-Motor ($r = 0.42$, $p < .0001$) MMSE ($r = -0.23$, $p = .01$) Stroop ($r = -0.23$, $p = .01$) BTA ($r = -0.28$, $p = .002$) SSB ($r = -0.29$, $p = .002$) 6 Minute Walk ($r = -0.84$, $p < .0001$) 5 Meter Walk ($r = -0.82$, $p < .0001$) 360 turn ($r = 0.71$, $p < .0001$) ABC ($r = -0.43$, $p < .0001$) FR ($r = -0.54$, $p < .0001$)	Overall Model Fit: $F = 100.6$, $r^2 = 0.80$, $p < .0001$ Significant Variables: 5 meter walk ($r^2 = 0.33$, $p < .0001$) BTA ($r^2 = .007$, $p = .07$) 360 turn ($r^2 = .005$, $p = 0.1$) Follow-up model with 5-meter walk replaced by stride length and step speed: $F = 69.15$, $r^2 = .68$, $p < .0001$ BTA ($r^2 = .016$, $p = .03$) 360 turn ($r^2 = .05$, $p = .0003$) Stride Length ($r^2 = 0.25$, $p < .0001$)

ABC – Activities of Balance Confidence Scale; BTA – Brief Test of Attention; FR – Functional Reach Balance Test; MMSE – Mini Mental State Examination; TUG – Timed Up and Go test; UPDRS – Unified Parkinson Disease Rating Scale; SSB – Spatial Span Backwards; 360 Degree Turn – 360 degree timed turning Test

Table 4
Results of Stepwise Linear Regression for Section 2 (ADL) of the UPDRS using
Demographic, Motor, Gait and Cognitive Variables

Variables used in model (Spearman r and p value)	Significant Results from Stepwise Linear Regression Model
Age (r = 0.18, p = 0.47) Gender (male 9.8 ± 4.8 vs. female 8.0 ± 4.4, t-test p = .04) Timed Tapping (r = -0.36, p < .0001) UPDRS-Bradykinesia (r = 0.31, p = .0004) UPDRS-Tremor (r=0.31, p = .0004) UPDRS-Motor (r=0.51, p <.0001) BTA (r= -0.22, p = .02) 6 Minute Walk (r = -0.28, p = .002) 5 Meter Walk (r = 0.26, p =.004) 360 turn (r = 0.21, p = .03) ABC (r = -0.41, p < .0001) FR (r = -0.28, p = .002)	Overall Model Fit: F = 45.68, r ² = 0.74, p <.0001 Significant Variables: BTA (r ² = .01, p = .03) 6 Minute Walk (r ² = .09, p < .0001) 360 Turn (r ² = .03, p = .001)

ABC – Activities of Balance Confidence Scale; BTA – Brief Test of Attention; FR – Functional Reach Balance Test; UPDRS – Unified Parkinson Disease Rating Scale; SSB – Spatial Span Backwards; 360 Degree Turn – 360 degree timed turning Test