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Johnathan Lucas McKay Date

A Cross-Sectional Study of Set Shifting Impairments and Falling in Individuals with and without Parkinson's Disease

By

Johnathan Lucas McKay

Master of Science

Clinical Research

_____

Lena H. Ting, Ph.D.

Advisor

_____

Mitchel Klein, Ph.D.

Committee Member

_____

Beau B. Bruce, M.D., Ph.D.

Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

_____

Date

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By

Johnathan Lucas McKay

Ph.D., Georgia Institute of Technology, 2010

Sc.M., Brown University, 2004

Sc.B., Brown University, 2002

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Abstract

A Cross-Sectional Study of Set Shifting Impairments and Falling in Individuals with and without Parkinson's Disease

By
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BACKGROUND AND OBJECTIVE. Individuals with Parkinson's disease (PD) are at increased risk for falls, and some exhibit characteristic deficits in executive function, including set shifting, which can be measured as the difference between parts B and A of the Trailmaking Test. The objective of this study was to investigate whether impaired set shifting was associated with previous falls in community-dwelling, nondemented individuals with and without PD. METHODS. We conducted a cross-sectional study using existing baseline data of PD patients with and without freezing of gait (n=69) and community-dwelling neurologically-normal older adults (NON-PD) (n=84) who had previously volunteered to participate in rehabilitative exercise programs. Multivariate logistic regression analyses were performed to determine associations between set shifting, PD, and faller status, as determined by ≥1 self-reported falls in the previous 6 months, after adjusting for demographic and cognitive factors and clinical disease characteristics. Individuals with likely dementia (Montreal Cognitive Assessment<18) were excluded. RESULTS. The final study sample after applying exclusion criteria (n=73 NON-PD, n=65 PD) included 51 fallers. PD was associated with substantially increased prevalence of previous falls (OR=4.15 [95% CI 1.65-10.44], P<0.01) after controlling for age, sex, and overall cognitive function. Among PD patients the presence of freezing of gait (FOG) was associated with substantially increased prevalence of previous falls (OR=3.63 [1.22-10.80], P=0.02). Impaired set shifting was associated with previous falls after controlling for age, sex, overall cognitive function, PD, FOG, and PD disease duration (OR=1.29 [1.03-1.60]; P=0.02). Although the strongest associations between set shifting and falling were observed among PD without freezing of gait (OR=2.11) compared to HOA (OR=1.14) and PD with FOG (OR=1.46) in a multivariate model that allowed for interaction between set shifting and PD status, there was insufficient evidence of interaction. CONCLUSIONS. The set shifting component of executive function is associated with previous falls in nondemented older adults with and without PD.

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INTRODUCTION

Falls are the main cause of accidental death in individuals over age 65 (1). Fall risk is increased by about six times in individuals with Parkinson's disease (PD) relative to neurologically-intact individuals (2). Studies of Medicare expenditures in the United States suggest that hip fractures are two to three times more prevalent in individuals with PD and result in two- to three-fold increases in medical charges compared to hip fractures in individuals without PD (3). PD patients also incur approximately 40% higher expenditures in home healthcare (4).

Prospective studies have identified multiple risk factors for falls among individuals with PD – including the presence of freezing of gait (FOG) – but overall causes remain poorly understood. Individuals with PD are subject to many of the same fall risk factors identified in the aging population, including increased age and female sex (5-8), as well as PD-specific factors like FOG. FOG is defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (9) and is prevalent in 38% of PD patients (10). FOG episodes can directly cause falls, and multiple prospective studies have identified FOG as a predictor of fall risk in PD patients (5, 11, 12). Despite these results, falls are acknowledged as extremely difficult to prevent among individuals with and without PD due to their multifactorial causes. As in the case of neurologically intact older adults (8, 13), one of the strongest predictors of fall risk among PD patients remains the presence of previous falls (5), which is of limited clinical utility for directing patients to interventions.

Impaired executive function may play an important role in causing falls in individuals with and without PD. Cognitive impairment is an established risk factor for falls among the elderly (8), and recent prospective studies have demonstrated that impairments in measures of executive function are associated with falls in PD patients (11, 14) and in neurologically-intact older adults (15). Individuals with PD also exhibit characteristic deficits in specific aspects of executive function, including set shifting (16, 17), a subdomain of executive function related to cognitive flexibility

(18, 19). Many studies have estimated set shifting during cognitive tasks as the difference between parts B and A of the Trailmaking Test (19, 20). PD is also associated with impaired set shifting in automatic motor responses during balance (21) and step initiation tasks (22), which suggests that set shifting impairments may cause impaired balance and falls in PD.

To the authors' knowledge, no studies have attempted to relate impairments in the set shifting component of executive function to falling in individuals with or without PD. Many studies examining factors associated with falls are performed either in geriatric settings or in movement disorders clinics and therefore cannot compare these populations. This is a significant limitation because falling in PD is associated with pathophysiology distinct from the dopamine system that may occur in otherwise healthy aging (23). Therefore, in the present study, we examined whether Set Shifting impairments were associated with previous falls in individuals with and without PD.

BACKGROUND

Parkinson's disease is a common neurological disorder with motor and nonmotor symptoms and unknown causes

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (24) and is estimated to affect over 4 million people worldwide, a number that is expected to double by 2030 (25). PD incidence is estimated at 13.4 cases per 100,000 person-years in the United States, with approximately twofold higher rates among men than among women (26). PD incidence rates also increase approximately fourfold between the fifth and sixth decade of life, and continue to increase with advancing age (26).

The causes of idiopathic PD are unknown, although it is clear that degeneration in the dopamine system causes many of the primary motor symptoms. Many PD motor symptoms result from loss of a population of neurons in deep brain regions referred to as the basal ganglia. Consistent with this, basal ganglia damage in primate and rodent models recreate many motor features of parkinsonism (27). There is substantial research into possible environmental causes, as typical Parkinson's disease does not appear to have a strong genetic component (28). It has been hypothesized by many that the reduction in benefit of dopaminergic medications over the course of disease progression may reflect accumulating non-dopaminergic pathophysiology, possibly of the cholinergic system (23); although it may also reflect continuing decline of dopaminergic systems in the basal ganglia. Deeper brain regions including the brainstem have also been implicated in PD pathogenesis. Braak and colleagues suggested a caudal-rostral progression of Lewy-type alpha-synucleinopathy (LTS) during PD progression (29). This hypothesis was recently supported by histological examination of individuals with PD that identified LTS in the brainstem (30).

In addition to the prototypical motor signs of PD, increasing attention has been paid recently to the non-motor features of PD, including cognitive impairments, that may be particularly prevalent

among those with gait and balance problems (31). PD was originally characterized by the four cardinal motor signs of resting tremor, rigidity, bradykinesia, and postural instability and gait dysfunction (32). To exhibit "definite" PD – as defined by Racette and colleagues (33) and used in this study – individuals must exhibit either 1) three or more of: resting tremor, rigidity, slow movement, or postural instability; or 2) two or more of these features with at least one of the first three displaying asymmetry. In addition to these characteristic signs, there has been debate about the impact of PD on cognition since the late 1800s (34-36). More recent research has begun to comprehensively examine the non-motor symptoms of PD, and variation of symptoms among PD phenotype. Cognitive impairment is common among PD patients, with point prevalence of Mild Cognitive Impairment (MCI) and dementia estimated at about 60% and 30%, respectively (37, 38), and dementia incidence 4-6 times that of neurologically-intact individuals (38). Among PD patients, those with axial features such as postural instability are more likely than those with "tremor dominant" symptoms to develop dementia (34). Over the last few decades, substantial research has gone into the idea that motor impairments in PD may result at least in part from non-motor impairments related to impaired attention or executive function, that are revealed during dual-task "walking and talking" paradigms (39).

Freezing of gait (FOG) has been proposed as a "fifth cardinal sign" of PD and is a primary cause of falls

Freezing of gait (FOG) is a Parkinsonian symptom defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (40) that has been proposed as a "fifth cardinal sign" of PD. FOG is prevalent in 38% of PD patients, with prevalence increasing with increasing disease duration (10). In rare cases, FOG can present in the absence of other parkinsonian symptoms as "primary progressive freezing of gait" (41). The pathophysiology of FOG is poorly understood (9), and there are currently no established treatment protocols with clear decision algorithms (42).

FOG episodes can directly cause falls (43), and the presence of FOG in the previous month is associated with two- to three-fold increases in 6-month odds of falling (5). FOG is also associated with impaired static and dynamic balance at times other than during FOG episodes, even after controlling for demographic and clinical factors, suggesting that the presence of FOG may be associated with underlying balance impairments that increase fall risk at times other than during FOG episodes (44). When used as a predictor of fall risk, FOG is typically treated as a dichotomous variable. The presence of any FOG episodes in the previous month is associated with increased fall risk (5). However, FOG severity can also be quantified as an ordinal variable, typically by retrospective report using questionnaires (e.g., 45). More precise methods of assessment exist, including eliciting freezing of gait in a laboratory or clinical setting using a dedicated freezing of gait course (46) or during gait tasks designed to elicit freezing episodes, such as continuous turns-in-place (19).

Impaired aspects of executive function may increase fall risk in individuals with and without PD

Cognitive impairment has long been acknowledged as a risk factor for falls among community-dwelling elderly individuals (8). More recent work suggests that impairments in specific cognitive subdomains – including executive function – may better predict fall risk than overall measures of cognition. A comprehensive review and meta-analysis of studies published between 1988 and 2009 found that while overall measures of global cognitive status (including the Mini-Mental-Status Examination commonly used clinically) were not associated with increased fall risk in community-dwelling older adults, measures of specific cognitive domains including executive function were consistently associated with increased risk (Odds Ratio (OR) 1.44 [1.20, 1.73]) (47).

This result has been supported by more recent prospective studies in individuals with and without PD. In a relatively large five-year prospective study of nondemented community-dwelling

individuals between ages of 70 and 90 (n=256), Mirelman and colleagues (15) identified no significant associations between Mini-Mental Status Examination (MMSE) and future falls (Rate Ratio 1.38 [0.41, 4.60]), but significant associations between estimates of executive function (0.85 [0.74, 0.98]) and attention (0.84 [0.75, 0.94]) assessed with a computerized neuropsychological battery. Similarly, in prospective studies of nondemented PD patients in 2013 (5) and 2014 (14), significant increased odds of future falls were identified for executive function assessed with Mattis Dementia Rating Scale Initiation/Perseveration (MDRS-IP) subtest (OR 0.86 [0.82, 0.91]) but not for MMSE (OR 0.80 [0.63, 1.02]). A third prospective study conducted in 2010 (48) also identified no differences in baseline MMSE scores between fallers and nonfallers.

Set shifting is a component of executive dysfunction that may be particularly impaired in PD

Set shifting is a proposed subdomain of executive function related to cognitive flexibility that is central in many proposed schema of executive function (18, 34, 49). One of the simplest schema, proposed by Miyake and colleagues (18) and Cohen and colleagues (19) divides executive function into three subdomains: shifting between tasks or mental sets, working memory representation monitoring and updating, and prepotent response inhibition. In this schema, set shifting "concerns shifting back and forth between multiple tasks, operations, or mental sets…" – as opposed to perseverance or rumination on a single task (18).

Although no individual test can measure any domain of set shifting exclusively, set shifting can be estimated with many tasks (50), including the difference between parts B and A of the Trailmaking Test (20). This timed test is administered on paper, and requires the participant to quickly connect sequentially numbered dots (part A), or dots alternating between numbers and letters (part B). Performance on each part of the test is assessed with the time required to complete the task, including correcting any errors. Part A is regarded as a measure of visual

search and movement speed, while Part B adds an element of set shifting. Large time differences between parts B and A indicate impaired set shifting. Other measures include the Plus-Minus Task (19) and variants of the Wisconsin Card Sorting Test (51). Example tests for working memory representation monitoring and updating include forward and reverse order recall of digit sequences (52), and example tests for response inhibition include variants of the Stroop conflict resolution and Go-NoGo tests (19).

There is considerable literature on the specific impact of set shifting deficits in PD, both during cognitive and during motor tasks. PD patients have difficulty isolating sequential components of upper-limb motor tasks, which is interpreted as impairment in shifting set from one subtask to another (53), and Cools and colleagues (35) demonstrated in the early 1980s that performance on a broad array of cognitive set shifting exercises was correlated to performance on a motor shifting exercise involving sequence shifting (35). Of particular relevance to falls, during balance tasks, PD patients exhibit postural reflex responses that tend to persevere long after task requirements have changed. For example, in PD patients, muscle responses observed when balance is perturbed while seated are similar to those observed while standing, although individuals without PD are able to effectively and quickly modulate responses across these two conditions (54). Evidence of set shifting deficits in PD has led some to hypothesize – drawing on concepts from psychology – that basal ganglia is associated with impaired "chunking" of motor tasks into constituent components (55).

Notwithstanding the conclusions of many studies that set shifting is particularly impaired in PD, recent studies have used imaging and neuropsychological testing to demonstrate that these impairments may vary across PD phenotypes more than previously thought. Recent studies using neuropsychological testing have demonstrated that set shifting is particularly impaired in PD patients with dopamine-unresponsive FOG (20) and that there is significant variation in subdomains of executive function across PD phenotypes (31). Given that FOG was not reliably

assessed until the mid-2000s, it is therefore possible that Set Shifting deficits are present only in a subset of PD patients, or result from interactions with aging processes rather than primary PD disease processes.

Exercise-based rehabilitation may be the most effective strategy for reducing falls in individuals with and without PD

Falls are difficult to manage through pharmacotherapy among older adults with or without PD, and rehabilitation-based interventions may represent the most effective strategy to reduce fall risk or frequency. Some strategies have been recommended for reducing burden of falls among older adults. Minimization of sedatives such as benzodiazepines (56) has been recommended, and the central nervous system methylphenidate (marketed under the trade name Ritalin) has been proposed to improve executive function and mitigate fall risk (57). However, a meta-analysis conducted by the Rand corporation in 2003 (58) concluded that exercise-based interventions were successful in reducing fall risk (Risk Ratio 0.88 [0.78, 1.00]) and incidence (Incidence Ratio 0.81 [0.72, 0.92]), and that exercise-based interventions were the single most effective strategy for reducing falls.

Among PD patients, so-called “axial” symptoms, including balance and gait abnormalities that may contribute to falls, are difficult to treat with traditional pharmacotherapy (2, 59, 60), and falls in particular have been reported to be unresponsive to modification of dopaminergic medications in PD patients (61). This may reflect, in part, that falls in PD patients are associated with cholinergic rather than dopaminergic dysfunction (23). Early stage trials have tested the ability of the central cholinesterase inhibitor donepezil (a medication used in the palliative treatment of Alzheimer’s disease) on cognitive impairment (62) and on reducing fall risk (63) in PD. Cognitive training has few side effects and has moderate efficacy in improving cognitive measures in PD; however, there is limited research in this area concerning relationships to falling (64).

One rehabilitative intervention that has been repeatedly demonstrated to be safe and effective for improving clinical measures of balance and gait in older adults, individuals with PD, and individuals from other clinical populations is Adapted Tango dance (65-72). Adapted tango consists of simple steps, frequent movement initiation and cessation, multiple directions, unexpected direction changes and varied rhythms. Steps are performed in an adapted traditional ballroom frame, holding the partner's bent elbows. Those with PD or other balance impairment are partnered with a neurologically-intact individual (typically either a spouse or a young healthy volunteer), reducing fall risk. The instructor and assistants are trained in spotting techniques and monitor participants' safety. Although no studies of Adapted Tango have included fall frequency or risk as primary outcomes, the improvements in balance and gait measures observed after Adapted Tango suggest that it may have potential to reduce fall risk or frequency in individuals with and without PD.

METHODS

We used existing baseline measures from two previous exercise-based rehabilitative interventions to assess associations between impaired Set Shifting and previous falls in nondemented, community-dwelling individuals with and without PD. We hypothesized that impaired Set Shifting would be associated with previous falls, and that this association would be modified by the presence of PD or PD and FOG.

Data sources and setting

We performed secondary analyses using existing baseline data of 153 adults with and without Parkinson's disease who had volunteered for exercise-based rehabilitative interventions designed to improve balance and mobility conducted in 2011-2013 and 2014-2015. Participants were recruited through physician referrals, word of mouth, advertisement in the local patient organization newsletters and visits to community support groups and exercise classes. All participants were interviewed for health history and previous falls and assessed with a battery of behavioral and cognitive assessments. Participants with PD were assessed for disease severity with the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (73) and assigned a modified Hoehn & Yahr stage (74) by a Movement Disorders Society-trained examiner or by trained research assistants. All participants met the following inclusion criteria: no diagnosed neurological conditions other than PD, ability to walk ≥3 meters with or without assistance. Participants with PD met the following additional inclusion criteria: diagnosis of idiopathic "definite PD" (33), demonstrated response to antiparkinsonian medications. Exclusion criteria were: significant musculoskeletal impairment as determined by the investigators. Essential details of the rehabilitative intervention and primary outcome measures have been published previously (72, 75-77). Briefly, participants were allocated to intervention arms with Adapted Tango rehabilitative dance classes (65-72) or to control arms comprised of either standard care or health education classes. Some participants were allocated to additional

assessments including imaging and quantitative balance and gait testing using electromyography and motion capture. All participants provided written informed consent according to protocols approved by the Institutional Review Boards of Emory University and the Georgia Institute of Technology.

Participants were excluded from the present analysis due to: presence of neurological conditions other than PD discovered after data collection (n=2), Montreal Cognitive Assessment (MoCA) scores (<18) indicating dementia (78) (n=11), suspected invalid estimates of set shifting due to abnormally long times for Part A of the Trailmaking test (n=2), and suspected invalid estimates of set shifting due to significant tremor artifacts in paper records of the Trailmaking test (n=1). After applying exclusions, there were 138 individuals available for study.

Study Variables

Assessment of primary outcome: Faller Status

The primary outcome was faller status. Participants were classified as "fallers" if they reported 1 or more falls in the prior six months at study entry. A fall was defined as "an event which results in a person coming to rest unintentionally on the ground or other lower level" (79).

Estimation of primary exposure: Set Shifting Score

The primary exposure, Set Shifting Score, was measured as the difference between Parts A and B of the Trailmaking Test (80). This timed test requires the participant to quickly connect sequentially numbered dots (part A), or dots alternating between sequential numbers and letters (part B). This timed test was administered on paper, and numerical scores for each part were truncated to 300 s (20). Test-retest reliability for both parts A and B of ICC $\geq$ 0.79 has been reported in neurologically-normal individuals (81). The difference between parts B and A was used as an estimate of set shifting impairment (19, 20) and is referred to here as Set Shifting Score.

Assessment of secondary exposure: PD Status

The secondary exposure, PD Status, was treated as a dichotomous variable (NON-PD vs. PD, with NON-PD as the reference group) in univariate tests of central tendency, and as a trichotomous variable (NON-PD, PD-FOG, PD+FOG, with NON-PD as the reference group) in multivariate analyses. Participants with PD were classified as PD+FOG if they scored > 1 on item 3 of the Freezing of Gait Questionnaire (FOGQ) (45), indicating freezing of more than once per week (72), and were classified as PD-FOG otherwise. Participants (n=5) for which FOGQ score was unavailable were classified as PD+FOG if they scored > 1 on item 14 of the UPDRS-II, indicating 'occasional' (rather than 'rare') freezing. UPDRS-II item 14 correlates strongly with FOG-specific questionnaires (10). In one participant, UPDRS-II item 14 (indicating non-freezing) was imputed from a later assessment.

Assessment of overall cognitive function

Overall cognitive function was assessed with the Montreal Cognitive Assessment (MoCA), a test which was originally developed to screen for mild cognitive impairment in the general population and is recommended for PD by the Parkinson Study Group Cognitive/Psychiatric Working Group (82). Overall test-retest and interrater reliability ICC are 0.79 and 0.81, respectively (83).

Additional study variables

Additional study variables considered to be relevant for evaluating associations with falling included the demographic and clinical variables moderately or significantly associated with elevated fall risk in PD, including age, female sex, and PD duration measured in years determined by self-report (5). Additional motor domain variables included the Berg Balance Scale (BBS), a 14-item objective instrument designed to assess static and dynamic balance and fall risk in adult populations (84) (test-retest reliability in PD is ICC 0.94 (85)), and self-selected gait speed. Slow gait speed is associated with increased 6-month odds of falling in PD (5) and with increased fall

risk in community-dwelling older adults (6). In one participant, gait speed was imputed from a later assessment.

Missing Data

There was a small amount of missing data: n≤2 for any one study variable. Variables with missing data are detailed in Table 1. Because of the small amount of missing data, complete case analyses were used.

Sample size and power considerations

Due to the exploratory nature of the study no *a priori* power analyses were performed.

Analytic Plan

Descriptive statistics and univariate tests of central tendency across groups

Descriptive statistics (mean±SD, median±IQR, frequencies) were calculated for study variables overall and stratified on PD status. Imbalances across groups were assessed with univariate tests of central tendency (independent sample *t*-tests, Wilcoxon rank sum, chi-squared) between the NON-PD and PD strata, and between the PD-FOG and PD+FOG strata within the PD group. In cases where the assumption of equal variances was unreasonable based on the Folded F statistic, Satterthwaite's formula was applied to estimate variances in each group. In cases where the total sample size was <40, exact Wilcoxon rank sum tests were performed. Exact Wilcoxon rank sum tests were also performed for Parts A and B of the Trailmaking Test, and for Set Shifting Score due to the strong right tail observed in the distribution of these variables. Differences between groups in proportions were assessed with two-tailed chi-squared tests. When expected cell counts were <5, Fisher's exact tests were performed.

Associations between Set Shifting Score and Faller Status

Multivariate logistic regression models were used to estimate associations between the primary exposures Set Shifting Score and PD Status and the primary outcome Faller Status. Associations

were expressed as prevalence ORs of exposure among fallers and nonfallers and corresponding 95% confidence intervals. Set Shifting Score was expressed with respect to the minimum value observed in the sample and scaled to units of 30 seconds, approximately one quartile. ORs were calculated in unadjusted models and in models adjusted for sex, age (in 5-year units), presence of mild cognitive impairment as determined by MoCA score≤27 (mocatest.org), and PD duration (in 5-year units). Variables included in adjusted models were selected based on risk factors for falls known or suspected from previous studies (5, 8). Year variables were centered about the sample median to aid in interpretation of estimated intercepts. Participants in the NON-PD group were coded with value 0 for PD duration after centering and scaling this variable.

Tests of primary study hypotheses

The adjusted multivariate model including primary exposures and covariates was as follows:

$$\begin{aligned}\log\left(\frac{p(Faller=1)}{1-p(Faller=1)}\right) &= \beta_0 + \beta_{SS}\cdot \text{SS} \\ &\quad +\beta_{PD-FOG}\cdot \text{PD-FOG} \\ &\quad +\beta_{PD+FOG}\cdot \text{PD+FOG} \\ &\quad +\beta_1\cdot \text{Age} \\ &\quad +\beta_2\cdot \text{Sex} \\ &\quad +\beta_3\cdot \text{MCI} \\ &\quad +\beta_4\cdot \text{PD duration}\end{aligned} \tag{1}$$

where variable SS indicates Set Shifting Score, indicator variable PD-FOG is 1 for individuals in the PD-FOG stratum and 0 otherwise, and indicator variable PD+FOG is 1 for individuals in the PD+FOG stratum and 0 otherwise. Significance of one-way interactions between Set Shifting Score and age, sex, PD duration, and MCI was assessed with a likelihood ratio test comparing the adjusted model (1) with an adjusted model that also included these one-way interactions.

To test whether impaired Set Shifting was associated with previous falls, the following null hypothesis was evaluated with a Wald test:

$$H_{01}: \beta_{SS} = 0$$

To test whether the association between Set Shifting and previous falls was modified by the presence of PD or PD and FOG, the parameters of a second adjusted multivariate model allowing interaction between Set Shifting Score and PD Status were also estimated:

$$\begin{aligned}\log\left(\frac{p(Faller=1)}{1-p(Faller=1)}\right) &= \beta_0 + \beta_{SS}\cdot \text{SS} \\ &\quad +\beta_{PD-FOG}\cdot \text{PD-FOG} \\ &\quad +\beta_{PD+FOG}\cdot \text{PD+FOG} \\ &\quad +\beta_1\cdot \text{Age} \\ &\quad +\beta_2\cdot \text{Sex} \\ &\quad +\beta_3\cdot \text{MCI} \\ &\quad +\beta_4\cdot \text{PD duration} \\ &\quad +\beta_{SS\cdot PD-FOG}\cdot \text{SS}\cdot \text{PD-FOG} \\ &\quad +\beta_{SS\cdot PD+FOG}\cdot \text{SS}\cdot \text{PD+FOG}\end{aligned} \quad (2)$$

A 2-DOF likelihood ratio test was then employed comparing the full model (2) against the reduced model (1) in order to evaluate the following null hypothesis:

$$H_{02}: \beta_{SS\cdot PD-FOG} = \beta_{SS\cdot PD+FOG} = 0$$

Sensitivity analyses

To minimize the potential for misclassification bias associated with retrospective self-report of previous falls, results of the adjusted model (1) were compared after imposing a more stringent criteria for faller status. In this analysis, participants were classified as "fallers" if they reported ≥2 falls in the previous 6 months.

Sensitivity of the adjusted model (1) to the inclusion of motor domain covariates BBS and gait speed was also assessed. Although motor domain variables have been demonstrated to predict incident falls in prospective studies (5, 6), in this cross-sectional study we could not eliminate the possibility of reversed causality – specifically that impairments in these variables resulted from previous falls (86). Sensitivity to these variables was assessed but this model was not used for primary hypothesis tests. Gait speed was dichotomized about 0.7 m/s, a previously-reported

cutoff for slow gait and elevated fall risk (6). Berg Balance Scale score was dichotomized about 45, indicating functional mobility without the use of a cane (87).

Associations between PD Status and Faller Status without Set Shifting Score

To facilitate comparisons with associations between PD and falling identified in prior studies, multivariable logistic regression models were also estimated with PD Status treated as a dichotomous (PD vs. NON-PD) or trichotomous (PD+FOG, PD-FOG, NON-PD) variable, and with Set Shifting Score omitted.

All reported P-values correspond to 2-tailed tests considered statistically-significant at $P<0.05$. Analyses were performed using SAS University Edition (SAS Studio 3.4 Basic Edition, SAS Release 9.04).

RESULTS

Characteristics of the study population

Demographic and clinical characteristics of the study population stratified on the presence of PD and on the presence of FOG are presented in Tables 1 and 2. Overall prevalence of previous falls was 51/138=40%. A diagram depicting flow of data through the study is presented in Figure 1. Compared to participants without PD, PD patients in the sample were younger (68±10 years vs. 80±11 years), less likely to be female (28/65=44% vs. 52/73=71%), had better overall cognitive function as indicated by MoCA score, had less impaired Set Shifting, and had better static and dynamic balance as indicated by BBS (Table 1). Individuals with PD also had substantially increased prevalence of previous falls (34/65=52% vs. 17/73=23%) (Table 1). Individuals in the PD sample ranged from Hoehn & Yahr stage 1-3.

Among PD patients in the sample, individuals with and without FOG were relatively well-balanced on demographic variables, cognitive function, and disease duration (Table 2). However, among PD patients, freezing of gait was associated with more severe motor symptoms as indicated by UPDRS-III score, poorer static and dynamic balance, more impaired Set Shifting, and increased prevalence of previous falls (18/26=69% vs. 16/39=40%).

Associations between Set Shifting Score and Faller Status

Unadjusted and multivariable-adjusted associations between Set Shifting Score, PD Status, and previous falls are given in Table 3. Contrasting Set Shifting Scores of 30 seconds above the minimum observed in the sample with minimum scores, the prevalence OR for Set Shifting Score was 1.29 (95% confidence interval (CI): 1.03, 1.60; Wald P value: 0.02) after adjusting for PD Status, age, sex, PD duration, and presence of mild cognitive impairment (MCI). This association was stronger, although comparable, to that observed in a model that only included Set Shifting Score and PD Status (OR: 1.19, 95% CI: 0.99, 1.44). The association was statistically significant only in the adjusted model. Strong associations were also observed between PD with and without

FOG and previous falls. Contrasted to the NON-PD group, PD-FOG and PD+FOG ORs were 2.87 and 4.69, respectively. Contrasts between the PD+FOG and PD-FOG groups (OR: 1.64) were not statistically significant.

In the model allowing for interaction between Set Shifting Score and PD Status, the OR for Set Shifting Score was higher among the PD-FOG group (adjusted OR=2.11, 95% CI: 0.94, 4.70) compared to either among the NON-PD group (OR=1.14, 95% CI: 0.86, 1.50) or among the PD+FOG group (OR=1.46, 95% CI: 0.96, 2.23) (Table 4). Compared to the adjusted model without interaction, associations between PD with and without FOG and previous falls were reduced in magnitude by ≈50%, and confidence intervals were substantially wider (PD-FOG vs. NON-PD, OR: 1.08, CI: 0.22, 5.34; PD+FOG vs. NON-PD, OR: 2.2, CI: 0.35, 13.84). Likelihood ratio tests applied to compare models with and without interaction terms (model 2 vs. model 1) produced P values for the interaction that were not statistically significant in either unadjusted (P-interaction=0.34) or adjusted (P-interaction=0.21) models.

Sensitivity analyses

To assess whether the potential for misclassification bias associated with retrospective self-report of previous falls influenced our findings, we performed the analysis with the more restrictive definition of faller status as ≥2 falls in the previous six months (Table 5). When the more restrictive definition was imposed, the OR for Set Shifting Score was essentially unchanged (1.28 in this model vs. 1.29 in the main model); however, ORs for associations between PD with and without FOG were substantially increased in magnitude. The PD-FOG OR increased by 43% and the PD+FOG OR increased by 273%. Unlike the main model, in this model contrasts between PD+FOG and PD-FOG were statistically significant (OR: 4.28, CI: 1.14, 16.16, Wald P value: 0.03).

To assess the sensitivity of the model to the inclusion of motor domain covariates, we also performed the analysis with the inclusion of motor domain covariates BBS and self-selected gait speed (Table 6). Inclusion of these covariates changed ORs by about 10%, with reductions in Set Shifting Score OR (1.21, vs. 1.29) and PD-FOG vs. NON-PD OR (2.66 vs. 2.87) and increases in PD+FOG vs. NON-PD OR (5.06 vs. 4.69) and PD+FOG vs. PD-FOG OR (1.91 vs. 1.64). In this model the number of observations and cases were both reduced (observations, 130 vs. 135, cases, 48 vs. 49) due to missing data. Only the PD+FOG vs. NON-PD OR was statistically significant (Wald P value: 0.02).

Associations between PD Status and Faller Status without Set Shifting Score

In multivariable logistic regression models controlling for age, sex, and overall cognitive function, but without Set Shifting Score, the OR contrasting PD to NON-PD was estimated at 4.15 (CI: 1.65, 10.44) and the OR contrasting PD+FOG to PD-FOG was estimated at 3.63 (CI: 1.22, 10.80).

DISCUSSION

In this cross-sectional study of 138 nondemented individuals with and without Parkinson's disease, impairments in the Set Shifting component of executive function were associated with previous falls after controlling for demographic and clinical variables as well as for overall cognitive function. The results suggested that this association was strongest among those with PD but without freezing of gait (FOG), but the interaction was non-significant likely due to small numbers of PD patients with FOG (n=26).

Observed associations between PD and previous falls – and between FOG and previous falls – were generally consistent with results of prior prospective studies, providing confidence that our sample is similar to those of other studies. In this study, models adjusted for age, sex, and presence of mild cognitive impairment identified ORs contrasting PD to NON-PD (4.15, CI: 1.65, 10.44) consistent with those observed in a large prospective study of falling in individuals with and without PD (6.08, CI: 2.45, 15.05) (2). Similarly, ORs contrasting PD+FOG to PD-FOG (3.63, CI: 1.22, 10.80) were consistent with those observed in a recent prospective study of falling in PD patients (4.11, 2.20, 7.66) (5).

The fact that the estimated OR for PD identified here was smaller than those from prospective studies may reflect systematic biases resulting from the use of retrospectively-assessed fall history. Retrospective self-report of fall history underestimates fall prevalence among PD patients (39% vs. 51%) but overestimates it among individuals without PD (27% vs. 14%) (2). These two biases therefore could have potentially biased the PD OR in our study downward compared to what would have been estimated in a prospective design. Although the PD OR may have been biased downward compared to previous studies, there was no evidence that this was due to misclassification error biasing it towards the null value 1.0. We found essentially the same results when we used a more stringent definition of "faller," consistent with previous observations that risk factors were the same but stronger for multiple falls (8).

One of the issues in all cross-sectional studies is the inability to verify the correct temporal relationships

One of the issues that complicates interpretation of any cross-sectional study is the inability to establish the correct temporal relationship between hypothesized causes and measured outcomes. Here, we found that impaired set shifting was associated with the presence of previous falls in individuals with PD, and in particular – individuals with PD but without freezing of gait. These data are consistent with the hypothesis that set shifting impairments cause falls in PD. We consider the potential for reverse causality in this relationship to be very small, as it is difficult to imagine situations in which a previous fall would impair performance on our measure of set shifting - the difference between parts B and A of the Trail making test. One could speculate that such a reverse causal relationship could potentially exist in the presence of traumatic brain injury or some potential psychogenic manifestation of previous falls - however, in the former case, these individuals would have been excluded from the study, and the latter case seems extremely speculative. Therefore, we consider the most likely interpretation to be that the observed association between impaired set shifting and falling is causal. Although we do not know of any previous studies examining associations between Set Shifting and previous falls, taken together with the results of other studies, these results suggest that impaired executive function, rather than global cognition (e.g. (8)), may be important for predicting fall risk in nondemented individuals. Impaired executive function is associated with increased fall risk in nondemented PD patients (11, 14) and in neurologically-intact older adults (15).

One important difference between this and other studies is that here, we controlled for the presence of mild cognitive impairment using the MoCA, which is recommended over the more common MMSE (88) for assessment of mild cognitive impairment in PD because it includes elements of executive function (78, 83, 89). Recent prospective studies have demonstrated that MMSE scores are not predictive of fall risk in neurologically-normal community-dwelling

individuals (15), and are not associated with increased fall risk in PD patients after adjustment for demographic and clinical covariates (11, 90). Causal links between impaired Set Shifting and falling are unclear, but at least among PD patients, impaired set shifting during motor domain tasks such as reactive balance (21, 91) and step initiation (22) may provide a possible causal pathway between impaired Set Shifting and falling.

The fact that we were unable to identify significant differences in associations between Set Shifting and previous falls across individuals with and without PD casts doubt on the hypothesis that impairments in Set Shifting specific to PD may cause falls. Common shifting difficulties across cognitive and motor tasks have been demonstrated in PD patients for decades (e.g., (35)), and impaired motor domain Set Shifting has been called a "core feature" of PD (22). Among PD patients, FOG is associated with impairments in multiple aspects of executive function (19, 92-94), and levodopa-unresponsive FOG is associated with particularly impaired Set Shifting (20). Based on this evidence, we expected that associations between impaired Set Shifting and falls would be strongest among those with PD and FOG. Therefore, we were surprised that although the worst Set Shifting deficits were observed in the NON-PD group, the strongest associations between Set Shifting and falling were actually among the PD-FOG group. ORs for Set Shifting were highest among individuals with PD but without FOG compared to those in the NON-PD and PD+FOG groups, although estimates were compatible with equal associations across strata. We speculate that one possible explanation for this is that a) individuals in the NON-PD group are able to compensate for Set Shifting deficits sufficient to prevent falls, and b) the influence of Set Shifting on falling in individuals in the PD+FOG group is minimized because of the number of falls caused by freezing episodes.

Strengths

This work has several strengths. To the authors' knowledge this is the first study to relate the Set Shifting component of executive function to falling, either in PD or in healthy older adults. These

results suggest that impaired Set Shifting may contribute to associations between global executive function and falls in both PD patients (14) and in healthy older adults (15), and provide insight into fall risk factors common to both populations. Most studies of fall risk are performed in either geriatric or movement disorders clinics and therefore cannot compare these populations. Because many studies of fall risk factors are performed by movement disorders specialists (14, 20), or geriatricians (15, 95), comparison data from older individuals without PD is often unavailable, making it difficult to apportion identified deficits to PD or to neurologically-normal aging. Although in this sample, the strongest Set Shifting deficits were observed in NON-PD (77±70 s, median±IQR; OR 1.14) and PD+FOG (70±72 s; OR 1.46), the strongest associations with previous falls were observed in PD-FOG (34±44 s; OR 2.11). This suggests that this group could be most likely to benefit from pharmacological or training-based interventions to aimed at improving cognitive function and mitigating fall risk (96).

Limitations

Although we controlled for it in the analysis, we consider one of the strongest limitations of this study to be the potential for residual confounding by age (and related unmeasured covariates) within the NON-PD and PD samples in the source datasets. The healthy participants predominately came from a separate sample than PD participants, and were substantially older overall. Further, the PD sample was drawn largely from active participants in patient advocacy and support groups, who tend to be more highly motivated and less affected overall than PD patients as a whole. The underrepresentation of older individuals among the PD sample may reflect the fact that at least in the case of typical PD progression, individuals in their 80s and 90s are unable to volunteer for the types of intervention from which we sampled the baseline data used here. We speculate that due to the natural history of disease progression and substantial cumulative fall risk in PD, if additional older individuals had been included in the PD sample, the majority would have been fallers and freezers, therefore generally reinforcing the trends observed

here. However - in the absence of such data - the best we can do here is to simply acknowledge this limitation.

We also did not consider years of education in the analysis, which likely influences Set Shifting Scores. For the age ranges observed in this sample, education level < 12 years is associated with an increase of approximately 30 seconds in Trailmaking B time, but minimal changes in Trailmaking A time (97). Therefore, an imbalance in education level between the PD and NON-PD groups could account for some or all of the elevated Set Shifting scores observed in the PD sample. Imbalances in education level could also bias identified ORs for PD downward, as education is negatively associated with falling (7).

As in most studies of PD patients, baseline comparisons between patients with and without FOG were difficult because FOG is usually accompanied by increased disease duration and symptom severity (41). Rather than a clinical assessment of symptom severity such as UPDRS-III score, we chose to use a single marker of PD severity, PD duration, because although fall history is associated with increased UPDRS-III score (23), recent studies demonstrated that PD duration was a comparable (48) or stronger (5) predictor of future falls than UPDRS-III. The use of self-report for FOG status, while a typical procedure, may have introduced misclassification error. It is more accurate to assess FOG in a laboratory setting than by the use of self-report (19). We attempted to minimize this error by using a robust classification for FOG; e.g., FOG had to occur approximately at least weekly to be classified as PD+FOG in this study. However, the potential remains that self-reported FOG status may also have resulted in misclassification error. Finally, using data from volunteers from rehabilitative interventions may result in selection biases of unknown direction and magnitude. Although demographic variables implicated as important for assessing fall risk were included in analyses, the possibility still remains that imbalances in unmeasured and unknown variables may cause confounding. Some studies (e.g., (2)) have minimized this imbalance by recruiting from spouses of PD patients. This approach has the

benefit of improved balancing among internal risk factors for falls – including age and sex – as well as among external risk factors for falls, which may involve the home environment.

Future work

In future work, we will perform a prospective study of fall risk in PD patients with and without FOG to test the ability of measurements based on muscle activity during balance tasks in a laboratory setting to predict incident falls when included as a component of a comprehensive battery of established behavioral (5, 66-68, 98-101) and neuropsychological (14, 20, 102) assessments for fall risk. A prospective design will allow us to establish correct temporal relationships between observed deficits and future falls. In particular, here, we chose not to include motor domain covariates in the main model due to the potential for reverse causality. Although slow gait is a strong fall predictor in individuals with and without PD (5, 6), it can result from previous falls (86). A prospective design will also enable the prediction of fall risk based on the number of previous falls, which is a strong predictor of fall risk in individuals with and without PD (5, 8, 13).

Conclusions

In summary, impaired Set Shifting was associated with previous falls in nondemented individuals with and without PD. The strongest associations were observed among individuals with PD but without FOG, although there was insufficient evidence to distinguish this interaction effect from the null.

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TABLES AND FIGURES

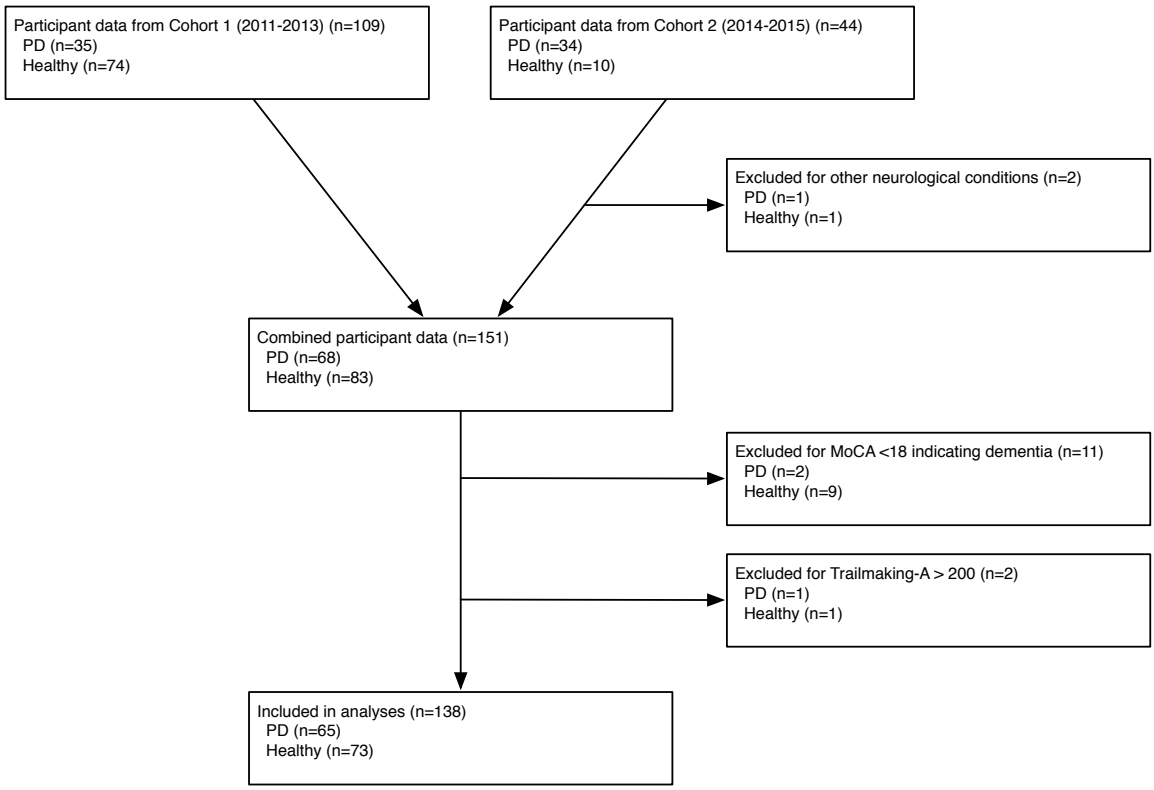

Figure 1. Flow diagram depicting data sources and exclusions.

Table 1. Demographic and clinical features of the study population, assembled from baseline measurements of rehabilitative interventions conducted in 2011-2013 and 2014-2015, overall and stratified on PD Status.

Characteristic	All Participants	NON-PD	PD
N	138	73	65
Age, y (mean±SD)**	75±12	81±11	68±10
Sex**			
Female (N, %)	80 (58)	52 (71)	28 (44)
Male (N, %)	58 (42)	21 (29)	37 (56)
Falling**			
0 falls (N, %)	87 (63)	56 (77)	31 (48)
1 fall (N, %)	22 (16)	12 (16)	10 (15)
≥1 fall (N, %)	51 (37)	17 (23)	34 (52)
≥2 falls (N, %)	29 (21)	5 (7)	24 (37)
Cognitive domain			
MoCA (/30; mean±SD)**	24.5±3.0	23.3±2.8	25.8±2.7
Set shifting			
Trailmaking A (s; median±IQR)**	39.9±23.1[a]	44.7±25.5[b]	36.0±15.3
Trailmaking B (s; median±IQR)**	107.0±92.2[a]	98.1±35.0[b]	77.0±71.0
Trailmaking B–A (s; median±IQR)*	64.9±81.6[a]	76.6±70.4[b]	39.7±66.9
Motor domain			
Berg Balance Scale (/54; mean±SD)**	49.4±7.4[c]	47.6±8.7[d]	51.4±4.8[e]
Gait speed, m/s (mean±SD)	0.98±0.24[f]	0.95±0.24	1.02±0.23[g]
Clinical characteristics			
PD duration, y (mean±SD)			7.3±5.6[e]
UPDRS-III (/108; mean±SD)			32.0±10.6
Freezing of Gait			
Freezer (N, %)			26 (40)
Nonfreezer (N, %)			39 (60)
Hoehn & Yahr stage			
3 (N, %)			20 (14)
2.5 (N, %)			12 (9)
2 (N, %)			26 (19)
1.5 (N, %)			6 (4)
1 (N, %)			1 (2)

Abbreviations: PD, Parkinson's disease; MoCA, Montreal Cognitive Assessment. *P<0.05, **P<0.01, derived from tests of central tendency or homogeneity comparing PD and NON-PD groups. [a]N=137. [b]N=72. [c]N=135. [d]N=71. [e]N=64. [f]N=134. [g]N=63.

Table 2. Demographic and clinical features of PD patients in the study population, assembled from baseline measurements of rehabilitative interventions conducted in 2011-2013 and 2014-2015, stratified on the presence of freezing of gait (FOG).

Characteristic	PD-FOG	PD+FOG
N	39	26
Age, y (mean±SD)	69±8	67±12
Sex		
Female (N, %)	18 (46)	10 (38)
Male (N, %)	21 (54)	16 (62)
Falling*		
0 falls (N, %)	23 (60)	8 (31)
1 fall (N, %)	8 (20)	2 (8)
≥1 fall (N, %)	16 (40)	18 (69)
≥2 falls (N, %)	8 (20)	16 (61)
Cognitive domain		
MoCA (/30; mean±SD)	26.1±2.7	25.4±2.6
Set shifting		
Trailmaking A (s; median±IQR)*	29.8±11.0	41.1±16.3[a]
Trailmaking B (s; median±IQR)*	65.5±54.7	113.1±88.6[a]
Trailmaking B–A (s; median±IQR)*	34.3±44.2	69.8±71.6[a]
Motor domain		
Berg Balance Scale (/54; mean±SD)*	52.9±3.3	49.2±6.0
Gait speed, m/s (mean±SD)	1.06±0.21	0.95±0.26[b]
Clinical characteristics		
PD duration, y (mean±SD)	6.4±5.8	8.5±5.1[a]
UPDRS-III (/108; mean±SD)*	29.4±7.8	35.9±13.0
Freezing of Gait		
Freezer (N, %)	0 (0)	26 (100)
Nonfreezer (N, %)	39 (100)	0 (0)
Hoehn & Yahr stage		
3 (N, %)	9 (23)	11 (42)
2.5 (N, %)	6 (15)	6 (23)
2 (N, %)	17 (43)	9 (35)
1.5 (N, %)	6 (15)	0 (0)
1 (N, %)	1 (3)	0 (0)

Abbreviations: PD, Parkinson's disease; MoCA, Montreal Cognitive Assessment. *P<0.05, derived from tests of central tendency or homogeneity comparing PD+FOG and PD-FOG groups. [a]N=25. [b]N=24.

Table 3. Logistic regression model associations between Set Shifting Score, PD Status, and ≥1 falls in the previous 6 months in the study sample.

	Unadjusted			Adjusted[a]		
	OR	95% CI	P	OR	95% CI	P
Set Shifting Score	1.19	0.99, 1.44	0.07	1.29	1.03, 1.60	0.02
PD-FOG vs. NON-PD	2.90	1.18, 7.14	0.02	2.87	0.92, 8.90	0.07
PD+FOG vs. NON-PD	7.50	2.68, 21.00	<0.01	4.69	1.30, 16.98	0.02
PD+FOG vs. PD-FOG	2.59	0.88, 7.62	<0.01	1.64	0.46, 5.84	0.45
No. Obs		136			135	
No. Events		50			49	
-2•Ln(L)		159.348			137.897	

Abbreviations: PD, Parkinson's disease; FOG, freezing of gait; OR, odds ratio; CI, confidence interval. [a]Adjusted for age, sex, PD duration, mild cognitive impairment.

Table 4. Logistic regression model associations between Set Shifting Score, PD Status, and ≥1 falls in the previous 6 months in the study sample, allowing for interaction between Set Shifting Score and PD Status.

	Unadjusted			Adjusted[a]		
	OR	95% CI	P	OR	95% CI	P
Set Shifting Score (among NON-PD)	1.09	0.83, 1.42	0.62	1.14	0.86, 1.50	0.37
Set Shifting Score (among PD-FOG)	1.60	0.95, 2.69	0.07	2.11	0.94, 4.70	0.07
Set Shifting Score (among PD+FOG)	1.14	0.78, 1.67	0.50	1.46	0.96, 2.23	0.08
PD-FOG vs. NON-PD[b]	1.46	0.38, 5.61	0.58	1.08	0.22, 5.34	0.93
PD+FOG vs. NON-PD[b]	6.30	1.33, 29.88	0.02	2.20	0.35, 13.84	0.40
PD+FOG vs. PD-FOG[b]	4.32	0.91, 20.48	0.06	2.05	0.34, 12.32	0.43
No. Obs		136			135	
No. Events		50			49	
-2•Ln(L)		157.208			134.768	
P-interaction[c]		0.34			0.21	

Abbreviations: PD, Parkinson's disease; FOG, freezing of gait; OR, odds ratio; CI, confidence interval. [a]Adjusted for age, sex, PD duration, mild cognitive impairment. [b]Odds ratio estimated among Set Shifting Score=0. [c]P value versus model without interaction (Table 3), Likelihood Ratio Test.

Table 5. Logistic regression model associations between Set Shifting Score, PD Status, and ≥2 falls in the previous 6 months in the study sample.

	Adjusted[a]		
	OR	95% CI	P
Set Shifting Score	1.28	0.99, 1.66	0.06
PD-FOG vs. NON-PD	4.10	0.90, 18.69	0.07
PD+FOG vs. NON-PD	17.54	3.76, 81.85	<0.01
PD+FOG vs. PD-FOG	4.28	1.14, 16.16	0.03
No. Obs		135	
No. Events		27	
-2•Ln(L)		92.251	

Abbreviations: PD, Parkinson's disease; FOG, freezing of gait; OR, odds ratio; CI, confidence interval. [a]Adjusted for age, sex, PD duration, mild cognitive impairment.

Table 6. Logistic regression model associations between Set Shifting Score, PD Status, and ≥1 falls in the previous 6 months in the study sample, adjusted for motor domain covariates.

	Further Adjusted[a]		
	OR	95% CI	P
Set Shifting Score	1.21	0.95, 1.53	0.12
PD-FOG vs. NON-PD	2.66	0.82, 8.60	0.10
PD+FOG vs. NON-PD	5.06	1.29, 19.87	0.02
PD+FOG vs. PD-FOG	1.91	0.49, 7.43	0.35
No. Obs		130	
No. Events		48	
-2•Ln(L)		129.087	

Abbreviations: PD, Parkinson's disease; FOG, freezing of gait; OR, odds ratio; CI, confidence interval. [a]Further adjusted for age, sex, PD duration, mild cognitive impairment, Berg Balance Scale, and self-selected gait speed.