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Impaired set shifting is associated with previous falls in individuals with and without Parkinson's disease

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Abstract

BACKGROUND—Individuals with Parkinson's disease (PD) are at increased risk for falls, which lead to substantial morbidity and mortality. Understanding the motor and non-motor impairments associated with falls in PD is critical to informing prevention strategies. In addition to motor symptoms, individuals with PD exhibit non-motor deficits, including impaired set shifting, an aspect of executive function related to cognitive flexibility that can be measured quickly with the Trailmaking Test.

RESEARCH QUESTION—To determine whether impaired set shifting is associated with fall history in people with and without PD.

METHODS—We examined associations between set shifting, PD status, and fall history (≥1 falls in the previous 6 months) in data from PD patients (n=65) with and without freezing of gait (FOG) and community-dwelling neurologically-normal older adults (NON-PD) (n=73) who had participated in our rehabilitation studies.

RESULTS—Impaired set shifting was associated with previous falls after controlling for age, sex, overall cognitive function, PD status, FOG, and PD disease duration (OR=1.29 [1.03–1.60]; P=0.02). Consistent with literature, PD and FOG were also independently associated with increased fall prevalence (PD OR=4.15 [95% CI 1.65–10.44], P<0.01; FOG OR=3.63 [1.22–10.80], P=0.02). Although the strongest associations between set shifting and falling were

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observed among PD without FOG (OR=2.11) compared to HOA (OR=1.14) and PD with FOG (OR=1.46), no statistically-significant differences were observed across groups.

SIGNIFICANCE—Impaired set shifting is associated with previous falls in older adults with and without PD. Set shifting may be useful to include in fall risk assessments, particularly when global cognitive measures are within reference limits.

Keywords

Balance; Freezing of Gait; FOG; Executive Function; Frontostriatal

1. Introduction

Falls are a leading cause of accidental death (1), and fall risk is increased by about six times in individuals with Parkinson's disease (PD) (2). In addition to their direct physical sequelae, falls are associated with reduced confidence (3), activity level (4), and quality of life (5), and therefore may indicate the beginning of serious decline in many individuals with and without PD. Despite the significant morbidity and mortality resulting from falls – and the availability of successful fall risk reduction programs (6–8) – identifying candidates for intervention remains difficult, due to the multifactorial causes of falls (9).

Understanding motor and non-motor impairments associated with falls in people with and without PD is therefore critical to informing prevention strategies. In addition to many of the generic or conventional fall risk factors identified in the aging population, such as advanced age and female sex (9), prospective studies have identified multiple disease-specific risk factors for falls among individuals with PD – including the presence of freezing of gait (FOG), an episodic symptom in which patients feel as though their feet are glued to the floor (10). Freezing episodes can directly cause falls; however, the presence of FOG is also associated with poorer static and dynamic balance at times other than during paroxysmal freezing episodes (11), suggesting that pathological changes leading to FOG may impair balance and cause falls at times other than during episodes. However, a comprehensive understanding of the pathologic precursors to falls remains lacking (12). One of the strongest risk factors for falling among those with (13) and without PD (14) remains the presence of previous falls, which is of limited clinical utility for directing patients to interventions.

Many studies have demonstrated associations between impaired executive function and falls in PD and in neurotypical aging, which suggests that measures of subdomains of executive function could be useful in assessments of fall risk. For example, prospective studies have demonstrated elevated fall risk associated with impaired executive function assessed with the multiple-item initiation/perseveration subscale of the Mattis Dementia rating scale in PD (15) or assessed with a computerized testing battery in neurotypical individuals (16). Multiple definitions of and assessment modalities for the construct of executive function have been proposed. However, one subdomain – set shifting – is central to many schemas and can be estimated quickly as the difference between parts B and A of the Trailmaking Test, which can be performed with pencil and paper (17, 18) (see Section 2.2). Set shifting (also referred to as "attention switching," "task switching," or "set switching") is a

component of executive function related to cognitive flexibility. Miyake and colleagues (19) define it as “shifting back and forth between multiple tasks, operations, or mental sets.”

Impaired set shifting, in particular, may be relevant to falls, although potential causal pathways between set shifting and falling remain unknown. Among neurotypical older adults, impairments in set shifting, but not in other components of executive function (i.e., inhibition or memory updating), are associated with increased gait variability during dual task conditions (20), which is an important marker of fall risk (21). Among PD patients, in addition to falls being extremely commonplace, set shifting impairments are common during cognitive and motor tasks. For example, PD patients exhibit impaired ability to shift between sequential voluntary movements (22), to alter balance responses to match task requirements (23) and to (among those with FOG) shift step direction during cued stepping (24). The extent to which dysfunctional basal ganglia or other disease processes in PD cause impairments in cognitive and/or motor set shifting is an area of substantial debate (24, 25). However, it is reasonable that the inability to shift between ongoing motor programs could contribute to falls.

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. Here, we used baseline data of 138 adults with and without PD who had volunteered for exercise-based rehabilitation to test the hypotheses that: 1) impaired set shifting is associated with previous falls, and 2) this association is modified by the presence of PD or PD and FOG.

2. Materials and Methods

2.1. Participants

We assessed associations between impaired set shifting and previous falls using baseline measures of community-dwelling individuals with and without PD from balance and mobility rehabilitative interventions conducted by our group in 2011–2013 and 2014–2015.

Participants provided written informed consent according to protocols approved by the Institutional Review Boards of Emory University and the Georgia Institute of Technology. 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 criterion: diagnosis of idiopathic “definite PD” (26). Participants were excluded based on significant musculoskeletal impairment as determined by the investigators.

Details of the rehabilitative intervention and outcomes have been published previously (27–29). Briefly, participants were interviewed for health history and previous falls and assessed with a battery of behavioral and cognitive outcome measures prior to allocation to intervention arms with Adapted Tango rehabilitative dance classes or to control arms comprised of either standard care or health education classes.

Beginning with n=153 data records initially available, records were excluded due to: presence of neurological conditions other than PD discovered after data collection (n=2),

Montreal Cognitive Assessment (MoCA, (30)) scores (<18) indicating dementia (n=11), suspected invalid estimates of set shifting due to abnormally long times for Part A of the Trailmaking test (>200 seconds; n=2), and confirmed invalid estimates of set shifting due to significant tremor artifacts in paper records of the Trailmaking test (n=1). After applying exclusions, data from n=138 individuals were available for analysis.

2.2. Study variables

The primary outcome was faller status. Participants were classified as “fallers” if they reported ≥1 falls in the last six months at study entry. Falls were defined as “an event which results in a person coming to rest unintentionally on the ground or other lower level” (31). Longitudinal falls data could not be used in this case because most participants were enrolled in fall risk-modifying interventions.

The primary exposure, Set Shifting Score, was measured as the difference between Parts A and B of the Trailmaking Test. This timed test is administered on paper and requires the participant to quickly connect sequentially numbered dots (part A), or dots alternating between sequential numbers and letters (part B), including time required to correct any errors. Numerical scores for each part were truncated to 300 s and the difference between parts B and A was used as an estimate of set shifting impairment (17, 18). A larger difference indicates greater impairment in set shifting.

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) (32), indicating freezing more than once per week (27), and were classified as PD−FOG otherwise. Participants (n=5) for which this FOGQ item was unavailable were classified as PD+FOG if they scored > 1 on item 14 of the Unified Parkinson’s Disease Rating Scale (UPDRS) Part II (33), indicating ‘occasional’ freezing (34).

Global cognitive function was assessed with the MoCA, which has been indicated as a preferred assessment tool among PD due to its inclusion of aspects of overall executive function (30). PD disease severity was assessed with the UPDRS-III (33) by a Movement Disorders Society-trained examiner or by trained research assistants. 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 self-reported PD duration in years (13). Additional motor domain variables included Berg Balance Scale (BBS) (9, 35) and self-selected gait speed (13, 36). MoCA score was dichotomized about 27, with scores ≤26 indicating mild cognitive impairment (mocatest.org). BBS score was dichotomized about 45, indicating functional mobility without the use of a cane (35), and gait speed was dichotomized about 0.7 m/s, a previously-reported cutoff for slow gait (36).

2.3. Statistical approach

Descriptive statistics were calculated for study variables overall and stratified on PD status. Differences across groups were assessed with univariate tests (independent sample *t*-tests, Wilcoxon rank sum, chi-square).

Multivariate logistic regression models were used to estimate associations between Set Shifting Score, PD Status, and the primary outcome Faller Status. Associations were expressed as prevalence odds ratios (OR) ±95% confidence intervals (CI). 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. Odds ratios were calculated in unadjusted models and in models adjusted for sex, age (in 5-year units), MoCA score, and PD duration (in 5-year units).

To test whether Set Shifting score was associated with previous falls, we fit the following multivariate model:

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

where the variable SS indicates Set Shifting Score, the indicator variable PD−FOG is 1 for individuals in the PD−FOG group and 0 otherwise, and the indicator variable PD+FOG is 1 for individuals in the PD+FOG group and 0 otherwise. 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:

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

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

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

Additional analyses were performed as follows. To minimize the potential for misclassification bias associated with retrospective self-report of previous falls, results of the adjusted model (Eq. 1) were compared after imposing a more stringent criterion 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 (Eq. 1) to the inclusion of motor domain covariates BBS and gait speed was also assessed. Finally, to facilitate comparisons with prior studies, additional multivariate logistic regression models were also calculated to estimate prevalence odds ratios for PD vs. NON-PD and for PD+FOG vs. PD−FOG with Set Shifting Score omitted. Due to the exploratory nature of the study no a priori power analyses were performed. All reported P-values correspond to 2-tailed tests considered statistically-significant at $P<0.05$. Analyses were performed using SAS University Edition 9.2.

3. Results

3.1. Demographics

Demographic and clinical characteristics of the study population stratified on the presence of PD and/or FOG are presented in Tables 1 and 2. Overall prevalence of previous falls was 51/138=40%. Participants with PD exhibited significantly increased fall prevalence (34/65=52% vs. 17/73=23%, $P<0.01$) despite being younger, higher functioning cognitively, and less likely to be female than the NON-PD group, all of which are known fall risk factors (9). Among the PD group, individuals with and without FOG were relatively well-matched on demographic variables, cognitive function, and disease duration (Table 2); FOG was associated with more severe UPDRS-III score, poorer BBS score, more impaired Set Shifting, and increased prevalence of previous falls (18/26=69% vs. 16/39=40%).

3.2. Set shifting and Falls

Model (equation 1) demonstrated a significant association between impaired Set Shifting and previous falls (OR: 1.29, 95% CI: 1.03–1.60; P<0.02) after adjusting for age, sex, PD duration, and MoCA score. PD Status was also significantly associated with previous falls (PD+FOG OR: 4.69, 95% CI: 1.30–16.98; P<0.02); however, contrasts between the PD +FOG and PD−FOG groups (OR: 1.64) were not statistically significant. Comparable associations between Set Shifting and previous falls were observed in a model that was unadjusted for age, sex, PD duration, and MoCA score (OR: 1.19, 95% CI: 0.99–1.44); however, associations were statistically significant only in the adjusted model (Table 3).

Likelihood ratio tests comparing Model (equation 2), which allowed interaction between Set Shifting Score and PD Status, to Model (equation 1) demonstrated that the association between Set Shifting and previous falls did not vary in a statistically significant fashion across the NON-PD, PD−FOG, and PD+FOG groups. Results were comparable with (P-interaction=0.21) or without (P-interaction=0.34) adjustments for age, sex, PD duration, and MoCA score. Although not statistically significant, qualitatively stronger associations between Set Shifting and previous falls were observed 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).

3.3. Other analyses

Associations between Set Shifting and previous falls were essentially unchanged when a more stringent definition of faller status was imposed (Table S1; OR: 1.28 vs. 1.29 in adjusted Model 1). Unlike the main model, contrasts between PD+FOG and PD−FOG were statistically significant (OR: 4.28, CI: 1.14–16.16, P<0.03) under a more stringent definition of faller status. Including motor domain covariates BBS and gait speed in the model affected identified odds ratios by ≈10%, reducing odds ratios for Set Shifting (OR: 1.21, vs. 1.29) and PD−FOG (2.66 vs. 2.87) and increasing odds ratios for PD+FOG (5.06 vs. 4.69) (Table S2). In multivariate models controlling for age, sex, and MoCA score, but without Set Shifting, odds ratio contrasting PD to NON-PD was 4.15 (CI: 1.65–10.44) and the odds ratio contrasting PD+FOG to PD−FOG was 3.63 (CI: 1.22–10.80).

4. Discussion

To the authors' knowledge, this is the first study to examine associations between impairments in the set shifting domain of cognitive function and previous falls in individuals with or without PD. Consistent with our hypothesis, we found that impaired set shifting was associated with previous falls in this cross-sectional study of 138 non-demented individuals after controlling for the large effects of PD and FOG, overall cognitive status, and other demographic and clinical variables. Because set shifting can be assessed quickly with the pencil-and-paper Trailmaking Test, it may be an important domain to consider for inclusion in fall risk assessment, particularly when measurements of global cognition fall within reference ranges.

We identified very strong associations between PD, FOG, and previous falls, corroborating the results of prospective studies in the literature. In general agreement with other work (2, 13), in models adjusted for age, sex, and overall cognitive function, odds of previous falls were elevated >4 times among those with PD compared to those without, and >3 times among PD patients with FOG compared to those without. Recent prospective studies have identified generally comparable odds ratios (PD OR: 6.08, CI: 2.45–15.05 (2); PD+FOG OR: 4.11, CI: 2.20–7.66 (13)). Although the odds ratios identified here were biased downward somewhat compared to values from the literature, results were essentially unchanged under a more stringent definition of "faller," suggesting that this bias was not due to the use of self-reported fall history. We speculate that these biases may result from elevated fall prevalence among the NON-PD group, some of whom might have enrolled in the rehabilitative program due to concerns about previous falls.

The association between set shifting score and previous falls observed here supports the hypothesis that impairments in specific subdomains of executive function – rather than overall cognitive function – may be associated with falls in individuals with and without PD. It is possible that this relationship may be observed because set shifting impairments may make motor tasks more challenging. Other measures of executive function have been associated with increased fall risk in non-demented people with (15, 37) and without (16) PD. Causal links between impaired et shifting and falling are unclear, but at least among PD patients, impaired set shifting during motor domain tasks such as reactive balance (23) and step initiation (24) may provide a possible causal pathway between impaired set shifting and falling.

Inconsistent with our hypothesis, we did not find statistically-significant evidence that associations between set shifting and falls were modified by the presence of PD or FOG, which casts doubt on the hypothesis that PD-specific (24) or FOG-specific (17) impairments in set shifting, at least, are associated with falls. Overall, the strongest associations between Set Shifting and previous falls were observed in PD−FOG (OR 2.11). This suggests that people with PD but without FOG could benefit from interventions aimed at improving cognitive function and mitigating fall risk (8). Candidate interventions could include cognitive training, which is beneficial for many aspects of cognition in PD – particularly memory, although efficacy on executive function appears limited in PD (38, 39), or pharmacological agents such as acetylcholinesterase inhibitors, which may potentially reduce falls in PD, either via modifying gait variability or by improving attention or executive function (21, 40, 41). There is also accumulating evidence that exercise rehabilitation is beneficial for cognition in PD (42). Importantly, we could not reject the null hypothesis that associations between set shifting and falling were constant across study groups, leaving unresolved the question of who would best benefit from intervention. This important question could be addressed in a larger, prospective study.

Due to the retrospective nature of the study we were unable to consider relationships between specific cognitive subdomains of executive function other than set shifting (e.g., inhibitory control, monitoring and updating of working memory, etc.) and falls. Although we controlled for overall cognitive ability with MoCA score, we were unable to examine other cognitive predictors. To at least partially address the possibility that these results are not

specific to Set Shifting per se, but that similar results would be observed with other measures related to executive function, we performed univariate t-tests post-hoc to compare outcomes derived from the Trailmaking Test (Part A score, Part B score, and Parts B–A) between fallers and non-fallers.

We found that only Trailmaking B–A and Trailmaking B discriminated fallers from non-fallers among PD patients; scores were increased in fallers compared to non-fallers by 81% (P=0.02) and 36% (P=0.01) for B–A and Part B, respectively. In contrast, among the Non-PD sample, stronger associations with previous falls were observed for Part A, a measure of visuomotor speed (31%, P=0.10), than for Parts B or B–A (15%, P=0.23, and 11%, P=0.54, respectively). These additional results provide some evidence that associations between Set Shifting and falling in the main analyses of this work are indeed specific to Set Shifting per se, rather than executive function in general. Future prospective studies should investigate relationships between other cognitive domains (i.e. inhibitory control, visuospatial control, etc.) and falls to comprehensively test whether this relationship is specific to Set Shifting.

Although we identified associations between impaired set shifting and falling – the strongest of which were observed in individuals with PD but without FOG – potential causal pathways between impaired set shifting and falls remain speculative. One hypothesis that is consistent with these results is that among non-freezers, impaired set shifting was associated with (or potentially caused) transient motor blocks that were not recognized as fully-developed freezing episodes, but that nevertheless were pronounced enough to cause falls. This is in accord with the “cognitive” model of FOG, which states that deterioration of response conflict processes can induce motor blocks (24, 43). Although total FOG-Q scores were unavailable for these analyses, it is likely that many of the individuals with impaired set shifting who were classified as non-freezers for the purposes of this study likely had non-zero FOG-Q scores, because set shifting is significantly associated with total FOG-Q score in PD patients with some self-reported freezing (44). Among freezers and neurotypical individuals, it could be expected that set shifting impairments would be less strongly associated with fall history due to the competing risk factor of FOG and protective factors associated with healthy aging, respectively.

This study has some additional limitations of note. First, although we attempted to minimize misclassification error associated with self-report of FOG status by using a robust classification for FOG, this process was likely imperfect and may have reduced power to discriminate between groups. Second, although motor domain variables such as BBS and gait speed have been demonstrated to predict incident falls in prospective studies (13, 36), we were unable to control for these variables in the main models of this cross-sectional study because of the potential that impaired performance on these measures could be the result of, rather than cause of, previous falls (45). Although we found that the results were not strongly affected by these variables in sensitivity analyses, this remains a limitation that should be addressed in prospective studies. Finally, it is notable that although identified associations between set shifting and falls were statistically significant (OR≈1.3); they were substantially smaller in magnitude than associations between PD and falls (OR≈4.6). Although relationships between set shifting and falls were in the same qualitative direction across all models tested, the limited size of this association meant that identified odds ratios

varied between statistically-significant (P=0.02) and only marginally significant (P=0.07–0.12) depending on which covariates were included. This difference in magnitudes may explain the fact that the NON-PD group included fewer fallers despite more impaired set shifting compared to the PD group.

Conclusion

In summary, impaired set shifting was associated with previous falls in non-demented individuals with and without PD. Set shifting may therefore be useful to include in fall risk assessments in older adults with and without PD, particularly when global cognitive measures are within reference limits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Impaired executive function predicts falls in older adults with and without PD.
- We measured the “set shifting” part of executive function with the Trail Making Test.
- Impaired set shifting was associated with prior falls in those with and without PD.
- The strongest associations were among PD patients without freezing of gait.
- Set shifting may be important in fall risk screening when total cognition is normal.

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)
Education, y (mean±S D) *	16±2	15±3[b]	16±2[g]
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)
Education, y (mean±SD)	16±2[c]	16±2[a]
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±S D)	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.

[c] N=38.

Table 3

Associations between Set Shifting Score, PD Status, and ≥1 falls in the previous 6 months in the study sample (Model 1).

	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, MCI.

Table 4

Associations between Set Shifting Score and ≥1 falls in the previous 6 months, and between PD Status and ≥1 falls in the previous 6 months, in the study sample (Model 2).

	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)		159.348			137.897	
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, MCI.

[b]Odds ratio estimated among Set Shifting Score=0.

[c]P value versus model without interaction (Table 3), Likelihood Ratio Test. Note that this model (Model 2) allows for interaction between Set Shifting Score and PD Status.