



## Full length article

# 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 ( $\geq 1$  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 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.

## 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

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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  $\geq 3$  m 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 ( $> 200$  s;  $n = 2$ ), 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  $\geq 1$  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  $\leq 26$  indicating mild cognitive impairment (mocatst.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)  $\pm$  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 s, 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).

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