

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

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Introduction

Falls lead to significant morbidity and mortality – but causes remain poorly understood

- Falls are a leading cause of accidental death [1] and fall risk is increased by ≈6 times in Parkinson's disease (PD) [2].
- There are multiple PD-specific fall risk factors, e.g., the presence of freezing of gait (FOG) in addition to non-disease-specific fall risk factors identified in neurotypical aging [3]. More work is needed to identify causes and appropriate interventions for falls.

Impaired executive function may cause falls, particularly in PD

- Some people with PD have impaired subdomains of executive function, including set shifting [4, 5, 6, 7]. PD is associated with impaired Set Shifting during balance [8] and step initiation [9], suggesting that it may cause falls in PD.

We tested whether impaired Set Shifting was associated with previous falls in people with and without PD

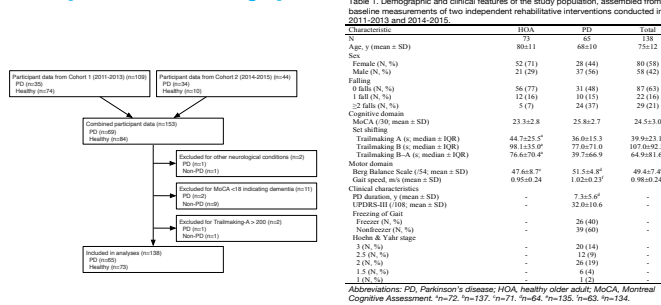
- Hypothesis 1**) Impaired set shifting would be associated with previous falls.
- Hypothesis 2**) The association would be modified by the presence of PD and/or PD+FOG.

Methods

Data sources and setting

- We used baseline measures of community-dwelling individuals with and without PD from two previous balance and mobility interventions.
- Participants were interviewed for health history, previous falls, and assessed with a behavioral and cognitive outcome measure battery prior to allocation to Adapted Tango rehabilitative dance classes or to control arms (either standard care or health education classes) [10-14].
- Inclusion criteria: no diagnosed neurological conditions other than idiopathic "definite PD" [15], ability to walk ≥3 meters with or without assistance. Exclusion criteria: significant musculoskeletal impairment as determined by the investigators.

Participant flow and demographics



Study variables

- Primary outcome: Faller Status.** Participants were classified as "fallers" if they reported ≥1 falls (defined as "an event which results in a person coming to rest unintentionally on the ground or other lower level" [16]) in the prior six months at study entry.
- Primary exposure: Set Shifting Score.** Set Shifting Score was measured as the difference between Parts A and B of the Trailmaking Test. 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 [7, 17].
- Secondary exposure: PD Status.** Participants were classified according to PD Status (NON-PD, PD-FOG, PD+FOG) in multivariate analyses. Participants with PD were classified as PD+FOG according to Freezing of Gait Questionnaire (FOGQ) Q3 [18] or the Unified Parkinson's Disease Rating Scale (UPDRS) Part II item 14 [19].
- Additional clinical, demographic, motor covariates.** Age; sex; UPDRS-III score; disease duration; MCI status (Montreal Cognitive Assessment [MoCA]<27 [20]); Berg Balance Scale (BBS) score [3, 21]; self-selected gait speed [22, 23].

References

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Analysis

Multivariate regression approach

- Hypothesis 1.** To test whether set shifting score was associated with previous falls, we fit the following multivariate model:

$$\log\left(\frac{p(Faller=1)}{1-p(Faller=1)}\right) = \beta_0 + \beta_{SS} \cdot SS + \beta_{PD-FOG} \cdot PD-FOG + \beta_{PD+FOG} \cdot PD+FOG + \beta_1 \cdot Age + \beta_2 \cdot Sex + \beta_3 \cdot MCI + \beta_4 \cdot PD \text{ duration}$$
$$H_{01} : \beta_{SS} = 0$$

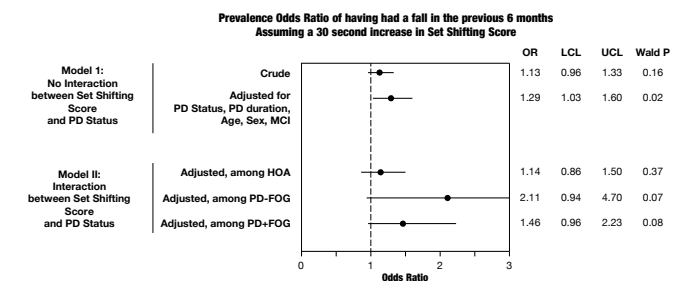
- Hypothesis 2.** To test whether the association between Set Shifting and previous falls was modified by the presence of PD or PD and FOG, we fit the following multivariate model, which allowed for interaction between Set Shifting and PD Status:

$$\log\left(\frac{p(Faller=1)}{1-p(Faller=1)}\right) = \beta_0 + \beta_{SS} \cdot SS + \beta_{PD-FOG} \cdot PD-FOG + \beta_{PD+FOG} \cdot PD+FOG + \beta_1 \cdot Age + \beta_2 \cdot Sex + \beta_3 \cdot MCI + \beta_4 \cdot PD \text{ duration} + \beta_{SS \cdot PD-FOG} \cdot SS \cdot PD-FOG + \beta_{SS \cdot PD+FOG} \cdot SS \cdot PD+FOG$$
$$H_{02} : \beta_{SS \cdot PD-FOG} = \beta_{SS \cdot PD+FOG} = 0$$

Results

Impaired set shifting was associated with previous falls

- Impaired set shifting was associated with previous falls (OR=1.29 [1.03-1.60]; P=0.02) after adjusting for age, sex, MCI, PD, FOG, and PD disease duration.
- In models adjusted for age, sex, and MCI, PD (OR=4.15 [95% CI 1.65-10.44], P<0.01) and FOG (OR=3.63 [1.22-10.80], P=0.02) were associated with previous falls.



The association was not significantly modified by the presence of PD or PD+FOG

- The strongest associations between set shifting and previous falls were among PD-FOG (OR=2.11) compared to HOA (OR=1.14) or PD+FOG (OR=1.46). However, there was insufficient evidence to reject the null hypothesis of no interaction.

Discussion

- Consistent with our hypotheses, impaired set shifting was associated with previous falls** after controlling for demographic/clinical variables and cognitive function.
- PD and FOG were strongly associated with previous falls, corroborating previous studies.** Odds of previous falls were elevated >4 times among PD vs. NON-PD and >3 times among PD+FOG vs. PD-FOG, in agreement with the literature (PD OR: 6.1 [2.5-15.0 [2]; PD+FOG OR: 4.1 [2.2-7.7] [22]).
- There was only qualitative evidence that associations between set shifting and falls were modified by disease state,** suggesting that set shifting is a non-disease-specific risk factor for falls.
- Additional sensitivity analyses:** <https://doi.org/10.1101/146332>.

Conclusions

- Impaired set shifting is associated with previous falls in non-demented individuals with and without PD. Associations may be strongest among those with PD but without FOG, suggesting that these individuals might best benefit from intervention. However, there is insufficient evidence to distinguish this interaction effect from the null. Overall, these results support the hypothesis that impairments in subdomains of executive function – rather than overall cognitive function – may be associated with falls in individuals with and without PD.