



Full length article

Non-motor predictors of freezing of gait in Parkinson's disease

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ARTICLE INFO

Keywords:

Parkinson's disease
Freezing
Gait
Cognition
Sleep

ABSTRACT

Background: The etiology of freezing of gait in Parkinson's disease (PD) is yet to be clarified. Non-motor risk factors including cognitive impairment, sleep disturbance and mood disorders have been shown in freezing of gait.

Research question: We aimed to determine the predictive value of non-motor features in freezing of gait development.

Methods: Data were obtained from the Parkinson's Progression Markers Initiative. Fifty PD patients with self-reported freezing of gait, and 50 PD patients without freezing of gait at the fourth year visit were included. Groups were matched for Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III scores. Several cognitive and non-cognitive tests were used for non-motor features at baseline and over time. Executive function, visuospatial function, processing speed, learning and memory tests were used for cognition. Non-cognitive tests included sleepiness, REM sleep behavior disorder, depression and anxiety scales.

Results: Patients with freezing of gait had higher scores on sleepiness, REM sleep behavior disorder, depression and anxiety scales. However, predictor model analysis revealed that baseline processing speed, learning and sleepiness scores were predictive of self-reported freezing of gait development over time.

Significance: Our findings suggest that specific cognitive deficits and sleep disorders are predictive of future freezing of gait. These features may be helpful in identifying underlying networks in freezing of gait and should be further investigated with neuroimaging studies.

1. Introduction

Freezing is a debilitating symptom affecting gait, movement and speech in Parkinson's disease (PD) [1]. Freezing of gait (FOG) is described as a short, temporary loss or significant reduction of moving the feet forward despite the intention to walk [1]. In early PD, 26% of the patients suffer from FOG and the frequency may increase up to 80% as the disease progresses [2,3]. Current treatment options are usually insufficient in the management of FOG in PD (PD-FOG). The etiology of PD-FOG remains unclear. Imaging studies suggest an imbalance between subcortical and cortical activations may be responsible [4]. Pedunculopontine nuclei (PPN) and locus coeruleus dysfunction has been shown to play a central role in FOG development [5,6]. Thus deficits arising from dysfunction in these regions, such as sleep disorders and autonomic nervous system dysfunction, can be expected to co-occur with PD-FOG [7,8].

There are few longitudinal studies assessing risk factors for PD-FOG. The akinetic-rigid PD subtype has been found as a motoric risk factor for PD-FOG, whereas the tremor dominant PD subtype places patients at a lower risk [9]. External cueing is known to improve gait control [10], which suggests that there are also non-motor risk factors for PD-FOG. Correspondingly, cognitive tasks such as dual-task performance and set-shifting deficits are frequently associated with PD-FOG [11,12]. A cognitive task while walking worsens FOG and the severity of FOG correlates with the extent of cognitive impairment [13]. However, not all cognitive domains are related to freezing in PD. Overall cognition assessed by Mini Mental Status Examination and memory have not been found to be predictive of later development of PD-FOG [14]. Differences may emerge later: Executive measures have been reported to decline over two years in PD patients with FOG, whereas PD without FOG was not associated with any decline [15]. Therefore while assessing the relationship between FOG and cognition, different cognitive

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<https://doi.org/10.1016/j.gaitpost.2018.12.009>

Received 15 August 2018; Received in revised form 25 October 2018; Accepted 5 December 2018

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domains should be assessed separately and over time to better understand the link.

In addition to cognition, other non-motor symptoms may be associated with later development of FOG. Zhang and colleagues [16] reported that mood and sleep disturbances as well as cognitive impairments are associated with FOG development in PD. Anxiety has been shown to be a good predictor of development of PD-FOG within 15 months of the initial PD diagnosis [17]. REM sleep behavior disorder is also more common in PD-FOG compared to PD without FOG [18].

In order to identify non-motor risk factors of FOG, we identified PD patients with FOG at the four year follow up period from the Parkinson's Progression Markers Initiative (PPMI) database, and retrospectively analyzed risk factors for PD-FOG based on their baseline testing. We aimed to determine which cognitive and/or non-cognitive deficits can be used as early symptoms to predict FOG onset later in the disease, in the hope that treatment approaches targeting these deficits might prevent FOG development.

2. Material and methods

2.1. Participants

Data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/data). The methodology and details of the study has been published elsewhere [19], and up-to-date information on the study can be found on the PPMI website (www.ppmi-info.org). This database includes longitudinal data of unmedicated, de novo PD patients diagnosed using established motor criteria with dopamine transporter deficit on SPECT imaging during their baseline visits as well as healthy subjects. All subjects undergo comprehensive longitudinal clinical and imaging evaluations, and bio-sampling. Following the screening/baseline evaluations, assessments occur at 3 month intervals during the first year, and then every 6 months. Although the aim was to enroll PD subjects who would not require symptomatic treatment for at least six months, subjects requiring treatment before this time point were treated and retained in the study. All participating PPMI sites undergo training to ensure standardization of data acquisition. Each site received ethics approval before the start of the study and written informed consents were obtained from all participants.

In our study, two patient groups were formed based on the presence or absence of FOG at the fourth year visit. FOG was assessed using the patient reported value from Movement Disorders Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II. This item is normally scored from 0 to 4; however, this was converted to a binary scale to simply determine whether FOG was present or not (0=no FOG, > 1 = FOG). Overall 50 PD patients with self-reported FOG and 50 PD patients without FOG were included. Groups were matched for motor impairment assessed by MDS-UPDRS Part III during the baseline visit.

2.2. Clinical assessments

Non-motor symptoms and MDS-UPDRS Part III scores were evaluated at baseline and the fourth year. Scores during each year's visit are included for each cognitive domain and available noncognitive data considered to have a potential predictive value for FOG. Cognitive tests were; Montreal Cognitive Assessment (MoCA), phonemic fluency (F words from MoCA), semantic fluency (animals), Letter Number Sequencing (LNS), judgment of line orientation (JLO), symbol digit modalities test (SDMT), Hopkins Verbal Learning Test, total learning tasks 1–3 (HVLTL). Non-cognitive tests consisted of; Epworth Sleepiness Scale (ESS), REM Sleep Behavior Disorder Screening Questionnaire (RBD-SQ), Geriatric Depression Scale (GDS), and State Trait Anxiety Inventory (STAI) total.

Used as a brief global cognitive assessment with high sensitivity and

specificity to detect mild cognitive impairment and mild Alzheimer's disease, the MoCA evaluates several cognitive domains including executive functions, attention, working memory, language, visuospatial functioning, learning, memory, and orientation [20]. Fluency tests, where participants are asked to produce as many words as possible in one minute within a semantic category (semantic fluency, animals) or starting with a given letter (phonemic fluency, F words from MoCA), measure verbal functioning and executive control [21]. For LNS, the participant reads a sequence of numbers and letters, then recalls the numbers in ascending and the letters in alphabetical order. This test measures executive functioning, attention, working memory, processing speed, and cognitive flexibility [22]. The JLO is used to assess visuospatial functioning by requiring the participant to match the angular positions of target line pairs to a reference figure on top of the page [23]. In the SDMT, the participant fills the space below the row with digit using the corresponding symbol based on the key pairing single digits with nine symbols on top of the page. This test measures attention and processing speed [24]. The HVLTL, used to measure verbal learning and memory, is a three-trial list learning and free recall test comprised of 12 words from three semantic categories (four words from each semantic category) [25]. The ESS measures daytime sleepiness by questioning the probability of falling asleep on a scale from 0 to 3 during eight different daily activities [26]. The RBD-SQ is a brief self-report assessing sleep behavior with a high sensitivity and good specificity for RBD diagnosis [27]. The GDS is a reliable and valid screening tool for depression where participants answer each item with "yes" or "no". The shorter version is used in the PPMI due to time restriction [28]. The STAI evaluates two types of anxiety; state and trait with 20 different questions for each anxiety type [29]. Each question is rated on a scale of 4, and higher scores indicate more severe anxiety.

2.3. Statistical analysis

SAS (v. 9.4) and R (v. 3.4.2) were used for statistical analysis. The R package MatchIt function was used to create case controlled matches from the larger non-FOG group [30]. Demographics and disease features were compared between groups using dependent sample *t*-test and McNemar test. Using baseline and fourth year test scores, the main group effect was determined by repeated measures analysis of variance. The Tukey-Kramer approach was used for post hoc tests. All numerical data are reported as mean (standard deviations); unless stated otherwise. $p < 0.05$ was considered statistically significant.

The initial logistic regression model was built based on backward stepwise selection including all of the test scores to determine the significant-tests. The outcome variable was presence or absence of FOG at the fourth year visit. The test scores were the independent variables in the initial logistic regression model. The threshold of *p*-value was set as 0.2 in the backward stepwise selection method. The variable with the largest *p*-value was removed from the model first, and then the logistic regression model was used again to fit the data using the remaining independent variables. This procedure was continued until the largest *p*-value of the variables was below 0.2. This initial regression model was used to reduce the number of variables, using a data driven approach. The independent variables from the last model selection step were then used in the predictive model. Collinearity was investigated between scores included within the model. Then, a receiver operating characteristic (ROC) curve was created to assess sensitivity and specificity of the predictive model.

3. Results

3.1. Demographics and clinical assessments

Demographics and disease features of both PD group are presented in Table 1. Age, gender, years of education, handedness, and disease features including dominantly affected side and MDS-UPDRS Part III

Table 1
Demographics and disease features of the patient groups.

	nFOG (n = 50)	FOG (n = 50)	p value
Age	60.74 (7.20)	60.46 (11.61)	0.884
Years of education	15.80 (2.39)	16.08 (2.74)	0.580
Sex, female	20 (40%)	12 (24%)	0.088
Handedness, right	41 (82%)	41 (82%)	1.000
Dominantly affected side, right	25 (50%)	33 (66%)	0.102
MDS-UPDRS Part III score at 4 th year	29.73 (13.22)	34.23 (12.14)	0.053

All variables are reported as mean (standard deviation) or number (percentage) where appropriate. nFOG = Patients without FOG, FOG = Patients with FOG, MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale.

during the baseline visit were similar between groups.

Non-motor test scores during baseline and fourth year visits for each PD group are summarized in Table 2. Amongst the cognitive tests; MoCA, phonemic fluency, semantic fluency, LNS, JLO, and HVLTL scores were not different between the nFOG and FOG groups. The only cognitive test that differed between the PD groups was the SDMT. All non-cognitive test scores differed between the nFOG and FOG groups. The only difference between the groups during baseline was ESS. The FOG group had higher ESS scores than the nFOG group. In year four; the FOG group had lower SDMT scores and higher ESS, RBD-SQ, GDS and STAI total scores compared to the nFOG group.

3.2. Predictive value of non-motor test scores

Given that only the SDMT, HVLTL and ESS had p values ≤ 0.2 in the initial logistic regression model, only these were included in the final predictive logistic regression model. Colinearity assessment indicated that all values were within acceptable ranges with VIF < 1.5 for all these covariates included in the final model. The results are summarized in Table 3. SDMT and ESS were significant and there was a slight trend for HVLTL which did not reach a significant level. Exp (B) value indicates that for each significant scale, a raise by one point doubles the likelihood that the individual will have FOG complaint at year four. The SDMT, HVLTL and ESS scores at each time point for both PD groups are depicted in Figs. 1–3. The area under the ROC curve was 0.78 for the final model.

4. Discussion

In this study, we investigated the predictive value of several non-motor features of PD which could potentially contribute to the

Table 2
Baseline and fourth year visit test scores of the patient groups.

	nFOG (n = 50)		FOG (n = 50)		Main group effect	Baseline nFOG vs FOG	Year four nFOG vs FOG
	Baseline	Year four	Baseline	Year four			
MoCA	26.90 (2.02)	26.34 (2.50)	26.92 (2.51)	25.10 (5.04)	ns		
Phonemic fluency	14.18 (3.41)	14.24 (4.84)	12.82 (4.03)	12.96 (5.20)	ns		
Semantic fluency	21.10 (4.89)	20.28 (4.41)	21.58 (5.13)	19.79 (5.86)	ns		
LNS	10.62 (2.70)	10.26 (2.17)	10.32 (2.44)	9.58 (3.87)	ns		
JLO	13.16 (1.73)	12.71 (2.06)	12.52 (2.20)	12.38 (2.00)	ns		
SDMT	43.18 (9.09)	42.84 (9.56)	38.92 (9.36)	36.30 (12.93)	0.005*	ns	0.013*
HVLTL	23.98 (4.61)	25.58 (4.74)	25.20 (5.08)	23.81 (7.51)	ns		
ESS	4.94 (3.52)	6.74 (4.87)	7.56 (3.74)	9.78 (4.71)	0.000*	0.014*	0.003*
RBD-SQ	4.24 (2.76)	4.38 (2.96)	5.42 (3.20)	6.12 (3.19)	0.009*	ns	0.022*
GDS	2.18 (1.90)	1.86 (1.78)	2.96 (2.89)	3.59 (2.87)	0.003*	ns	0.002*
STAI total	64.38 (16.74)	58.46 (11.96)	68.74 (18.39)	70.33 (18.90)	0.010*	ns	0.005*

Significance is marked with * for p < 0.05. All variables are reported as mean (standard deviation).

nFOG = Patients without FOG, FOG = Patients with FOG, MoCA = Montreal Cognitive Assessment, LNS = letter number sequencing, JLO = judgment of line orientation, SDMT = symbol digit modalities test, HVLTL = Hopkins Verbal Learning Test, total learning tasks 1–3, ESS = Epworth Sleepiness Scale total, RBD-SQ = REM Sleep Behavior Disorder Screening Questionnaire, GDS = Geriatric Depression Scale, STAI = State Trait Anxiety Inventory, ns = not significant.

Table 3
The final predictive model for FOG.

	df	Estimate	Standard error	Wald Chi-square	Pr > ChiSq
SDMT	1	-0.0944	0.0318	8.8261	0.0030
HVLTL	1	0.0815	0.0500	2.6602	0.1029
ESS	1	0.2289	0.0667	11.7887	0.0006

SDMT = symbol digit modalities test, HVLTL = Hopkins Verbal Learning Test, total learning tasks 1–3, ESS = Epworth Sleepiness Scale total.

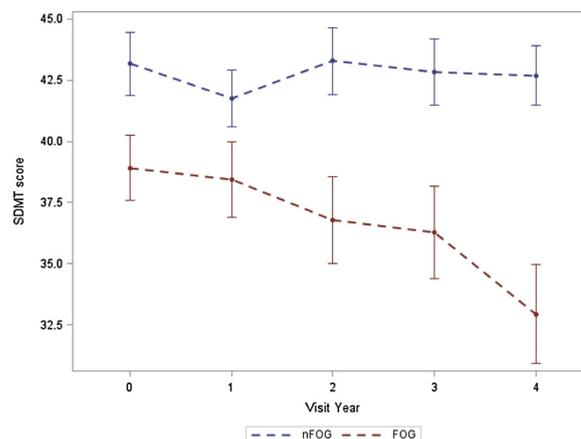


Fig. 1. Symbol Digit Modalities Test (SDMT) scores during each time point in nFOG and FOG patients.

development of FOG. Although the ESS, RBD-SQ, GDS and STAI were higher in the PD-FOG group at baseline, only the ESS, SDMT, and HVLTL were predictive of later development of patient-reported FOG.

The underlying neural structures responsible for increased sleepiness have been found to be correlated with both PD and FOG in previous studies. Degeneration of the locus coeruleus and the ascending reticular activating system are correlated with the development of excessive daytime sleepiness [31], and Lewy body pathology is found in both areas in PD [32]. The locus coeruleus, the largest group of noradrenergic neurons, is part of a catecholaminergic cell population and secretes noradrenaline [33]. Noradrenergic deficits due to locus coeruleus cell loss have been associated with poor balance, falls, and possibly FOG [34]. Studies evaluating the utility of methylphenidate, which directly effects discharge activity of the locus coeruleus and increases synaptic levels of noradrenaline and dopamine, have shown some utility in decreasing FOG in PD patients (post deep brain

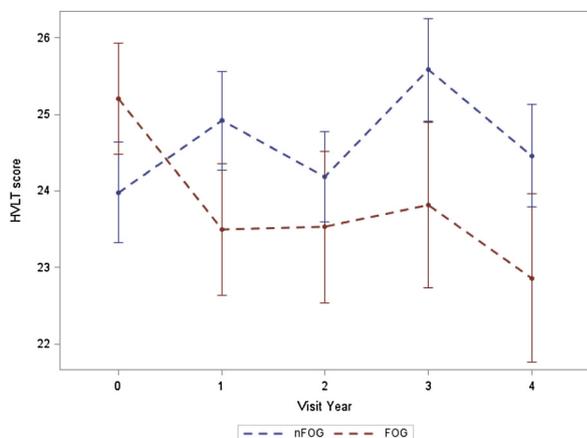


Fig. 2. Hopkins Verbal Learning Test, total learning tasks 1–3 (HVLTL) scores during each time point in nFOG and FOG patients.

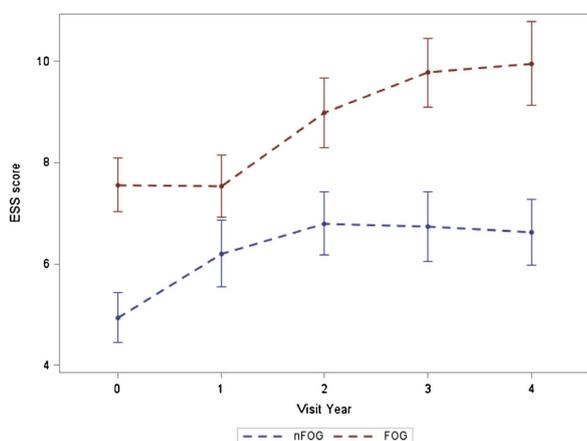


Fig. 3. Epworth Sleepiness Scale total (ESS) scores during each time point in nFOG and FOG patients.

stimulation of the subthalamic nucleus) with FOG [35], but not in patients with advanced PD [36]. In other studies methylphenidate has been shown to improve daytime sleepiness in PD [37]. Atomoxetine, a noradrenergic agent with unique effects on the phasic: tonic discharge ratio of the locus coeruleus, warrants further investigation in the treatment of FOG [38].

Prior articles have noted the role of executive dysfunction in PD-FOG [39]. The current study found that tests of attention and learning, each of which have an executive component, predicted FOG. In line with these findings, the SDMT assesses divided attention, visual scanning, tracking, and motor speed, all of which may contribute to the development of FOG. The HVLTL, a measure of memory which assesses overall learning of a word list over a total of three trials, has been found to correlate with development of and severity of the postural instability/gait disorder (PIGD) subtype of PD [40]. The PIGD subtype of PD, as compared to the tremor predominant PD subtype, is widely considered to be more commonly associated with PD-FOG [41]. Specifically, deficiencies in memory as measured by the HVLTL have been found to be associated with greater postural instability [40].

The lack of relationship between FOG development and anxiety is inconsistent with prior studies [1,17]. Similarly, none of the analyzed cognitive symptoms contributed significantly to the later prediction of FOG. Reasons for the differences seen may include the test battery employed. While earlier studies have found differences in tasks involving set shifting (e.g., trail making test part B) and working memory tests such as digit span backwards to be associated with FOG, the Letter-Number Sequencing task did not emerge as a significant predictor, and

is perhaps a less sensitive measure of these cognitive abilities than some other tests. However, these earlier studies sometimes include the confound of overall disease severity or lack a comparison group [11,12]. Future prospective matched studies should include such measures in order to understand the specific contribution of these cognitive measures.

There are several reasons why our findings may differ from others. The two PD groups were matched by MDS-UPDRS part III, ensuring that there was at least some degree of similarity in severity of symptoms. This is important as, in earlier studies, presence or emergence of FOG is sometimes confounded by overall severity of motor symptoms [13]. In addition, the PPMI sample is newly diagnosed at baseline, and thus the patients in this sample may have been at an earlier stage in their disease than those studied in other samples. However, the group was also quite well educated, suggesting a high level of cognitive reserve that may not have been shared by other samples. Hence, the current group may be less susceptible to early development of cognitive symptoms. The battery of cognitive tests used in the PPMI may not be as sensitive to later development of symptoms, notably others have found the trail making test and digit span tests to be more difficult for patients with FOG. These tests are not part of the PPMI battery.

The true presence of FOG may not always be detected by patient report, thus we may not have included all cases of true FOG, or there may be some selection bias in our sample. Similarly the clinician observation period of gait on the MDS-UPDRS is quite brief, perhaps accounting for the high levels of disparity between patient-reported and clinician-observed FOG in this sample. More sensitive measures of assessing FOG exist, and should be implemented in future, prospective studies.

Comprehensive assessment of each non-motor domain is not feasible due to time restriction during the visits in the PPMI. Although the comprehensive assessment for a mild cognitive impairment diagnosis in PD require at least two tests for each domain (attention and working memory, executive, language, memory, visuospatial) [42], the cognitive battery in PPMI covers the cognitive domains affected in PD and meet the criteria for abbreviated assessment. Additionally, the MoCA was shown to be a reliable and valid screening tool for cognitive dysfunction in PD population [43]. Impairment on the MoCA is considered sufficient for the abbreviated assessment of PD-MCI [42]. Besides the cognitive tests, PPMI provides longitudinal data on multiple non-cognitive tests. The GDS is a reliable and valid screening tool for self-rated depression in PD [44]. The STAI has been shown to be useful in PD for anxiety assessment [45]. The ESS has been extensively used in movement disorders and is recommended for screening of daytime sleepiness in PD [46]. The RBD-SQ is a useful tool in PD for the screening of REM sleep behavior disorder [47]. Future studies assessing the effects of each non-motor domain more specifically would benefit from including more detailed assessment of the domain of interest and focusing on item-level data on the scales.

In summary, the limitations of this study are the small number of patients, retrospective analysis, using self-reported FOG to classify patients based on FOG presence, and investigating FOG development over a short period of time. Including a greater number of patients with a longer follow up period, using clinical assessment of FOG to determine the presence of FOG in a prospective study may yield more reliable findings. A prospective study aiming to investigate the effects of cognitive and non-cognitive features on FOG can include a more detailed assessment which can provide more reliable findings. Future studies designed to understand FOG should further investigate its relationship with sleep disorders, as well as cognitive symptoms particularly vulnerable to the underlying networks. Neuroimaging studies combining structural and functional connectivity, specifically, will be useful in potentially identifying early therapeutic targets.

Declaration of interest

None.

Conflict of interest

The authors have no conflict of interest to report.

CRediT authorship contribution statement

Sarah J. Banks: Writing - original draft, Writing - review & editing.
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Guogen Shan: Writing - original draft, Writing - review & editing.
Denise R. LaBelle: Writing - original draft, Writing - review & editing.
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Acknowledgments

This work was supported by grant funding from the National Institute of General Medical Sciences (grant: P20GM109025).

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson’s Research and funding partners, including Abbvie, Avid, Biogen, Bristol-Myers Squibb, GE Healthcare, Biologend, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Sanofi Genzyme, Servier, Takeda, Teva and UCB (<http://www.ppmi-info.org/fundingpartners>).

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