Explaining Freezing of Gait in Parkinson’s Disease: Motor and Cognitive Determinants

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ABSTRACT: Freezing of gait (FOG) is part of a complex clinical picture in Parkinson’s disease (PD) and is largely refractory to standard care. Diverging hypotheses exist about its origins, but a consolidated view on what determines FOG is lacking. The aim of this study was to develop an integrative model of FOG in people with PD. This cross-sectional study included 51 Parkinson subjects: 24 patients without FOG and 27 with FOG matched for age, gender, and disease severity. Subjects underwent an extensive clinical test battery evaluating general disease characteristics, gait and balance, nongait freezing, and cognitive functions. The relative contribution of these outcomes to FOG was determined using logistic regression analysis. The combination of the following four independent contributors provided the best explanatory model of FOG ($R^2 = 0.49$): nongait freezing; levodopa equivalent dose (LED); cognitive impairment; and falls and balance problems. The model yields a high-risk profile for FOG ($P > 95\%$) when Parkinson patients are affected by at least one type of nongait freezing (e.g., freezing of other repetitive movements), falls or balance problems during the last 3 months, and a Scales for Outcomes in Parkinson’s Disease-Cognition score below 28. A high LED further increases the risk of FOG to 99%. Nongait freezing, increased dopaminergic drug dose, cognitive deficits, and falls and balance problems are independent determinants of FOG in people with PD and may play a synergistic role in its manifestation. © 2012 Movement Disorder Society

Key Words: Parkinson’s disease; gait disorders; cognitive disorders; postural control; freezing of gait

Freezing of gait (FOG) is a disabling gait disorder defined as a “brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk.”¹ Longer disease duration and greater disease severity increase the likelihood of developing FOG, although not all patients ultimately do so.² FOG is accompanied by motor and cognitive abnormalities, but it is currently unclear how these aspects interact and which factor is the most determining in the development of FOG. Important motor correlates of FOG are postural instability, which causes falls,³ and impaired regulation of rhythmic stepping movements.¹,⁴,⁵ In addition, recent work has shown that spatiotemporal dyscontrol and freezing episodes were reported beyond the gait network during writing and repetitive finger movements.⁶–⁹ Freezing during movements other than gait is henceforth called “nongait freezing.” In the cognitive domain, components of
executive functioning\textsuperscript{10} (e.g., conflict resolution\textsuperscript{11} and set-shifting\textsuperscript{12}) and visuospatial abilities\textsuperscript{13,14} were reported as impaired in patients with FOG. Unlike the cardinal symptoms of Parkinson’s disease (PD), FOG is less efficiently improved with dopaminergic medication.\textsuperscript{15} This suggests that FOG has a unique neuro-pathology that exceeds typical dopaminergic regions and requires adequate alternative therapeutic approaches.\textsuperscript{16} Although neuroprotective therapy is still under investigation, early risk identification of FOG may improve its treatment in the near future.\textsuperscript{17}

Therefore, we performed a cross-sectional regression analysis to investigate potential risk factors in having FOG from four domains: demographic and disease characteristics; gait and balance variables; nongait freezing; and cognition. The study aim was to develop an integrative model of the factors determining FOG and to obtain a clinically applicable prediction equation to estimate its probability. Second, we aimed to investigate which factors were most closely associated with FOG severity.

Materials and Methods

Participants

Fifty-one PD patients were recruited from the Movement Disorders Clinic of the University Hospital Leuven (Leuven, Belgium). A score $\leq 1$ on the New FOG-Questionnaire (NFOG-Q) classified 27 patients as freezers, and a score $< 1$ categorized 24 as nonfreezers.\textsuperscript{18} All patients had previously undergone a gait test in the context of other studies.\textsuperscript{6,7,19} Patients were identified as definite freezers when freezing episodes were observed during this gait analysis. Using the algorithm of Snijders et al.,\textsuperscript{20} self-reported freezers were identified as definite freezers when freezing episodes were observed during this gait analysis. Therefore, we performed a cross-sectional regression analysis to investigate potential risk factors in having FOG from four domains: demographic and disease characteristics; gait and balance variables; nongait freezing; and cognition. The study aim was to develop an integrative model of the factors determining FOG and to obtain a clinically applicable prediction equation to estimate its probability.

Clinical Assessment

All patients underwent an extensive clinical test battery while “ON” medication.

1. General disease characteristics: UPDRS,\textsuperscript{21} H & Y staging, and L-dopa equivalent dose (LED) intake (mg/day).\textsuperscript{23}
2. Gait and balance tests: Timed Up and Go Test (TUG),\textsuperscript{24} a short version of the Berg Balance Scale (BBS; items 8, 11, 13, and 14),\textsuperscript{25} the NFOG-Q,\textsuperscript{18} and a questionnaire assessing falls and near falls during the last 3 months, according to Ashburn et al.\textsuperscript{26} This questionnaire contained four items: falls caused by FOG; falls independent of FOG; near falls caused by FOG; and near falls independent of FOG. To address intrinsic balance problems, only fall and near fall scores not induced by FOG episodes were analyzed. Patients scored 1 (or 0) if they had (or had not) experienced falls and/or near falls independent of FOG during the last 3 months.
3. A nongait freezing score was used to assess freezing during eight known freezing-sensitive movements from daily life (i.e., writing, tooth brushing, stirring while cooking, screw driving, feet wiping, typing, cutting food, and talking) or during another self-reported movement. Patients scored 1 (or 0) when reporting at least one type of (or no) nongait freezing.
4. Cognitive outcomes: Mini–Mental State Examination (MMSE) and the cognitive section of the Scales for Outcomes in PD (SCOPA-COG).\textsuperscript{28} A SCOPA-COG $\leq 28$ identified subjects with or without cognitive problems (1/0).\textsuperscript{29} A binary SCOPA-COG score was preferred over its total score for purposes of model simplicity and clinical use.

Statistical Analysis

All analyses were performed using SAS 9.3 and SAS Enterprise Guide software (SAS Institute Inc., Cary, NC).\textsuperscript{30} Kolmogorov-Smirnov’s distribution analysis was carried out to determine the appropriate test for group comparison of all clinical variables: chi-square tests for binary outcomes; Wilcoxon’s nonparametric two-sample tests for ordinal and not normally distributed interval/ratio data; and two-sample $t$ test for normally distributed ratio data. Correlations between variables that differed significantly between groups and their relation to the decision variable Group (freezers/nonfreezers) were calculated using point biserial (interval/ratio predictors) and rank biserial (ordinal predictors) correlation coefficients.\textsuperscript{31} Variables that correlated highly ($R > 0.30$) with Group, but weakly with other predictors (avoiding colinearity), were examined in a univariate logistic regression analysis (RA). Variables with high univariate predictive accuracy ($R^2$) were entered in the full-model, multivariate logistic RA.\textsuperscript{32} A prediction model for FOG was obtained using the formulas below, the logistic regression equation (Equation 1) and the prediction model (Equation 2):

\begin{equation}
\log(Y) = A + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + ... + \beta_nX_n
\end{equation}

\begin{equation}
P(FOG) = P(Y = 1) = \frac{e^{(A + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + ... + \beta_nX_n)}}{1 + e^{(A + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + ... + \beta_nX_n)}}
\end{equation}
where \( Y \) represents the decision variable Group (freezers/nonfreezers), \( A \) the regression intercept, and \( b_1x_i \) the weighted predictors. Significance testing of predictors was based on Wald's chi-square statistics.

The relationship between predictors and FOG severity was examined in the freezer population using the same approach, but employing a linear regression model. The summed score of items 2 to 6 of the NFOG-Q18 on frequency and duration of FOG episodes served as outcome of freezing severity. \( P \) values <0.05 were considered significant.

### Results

From the 27 reported freezers, 23 had shown FOG episodes during the gait tests. Four probable freezers were thus not retained in the analysis. All definite freezers experienced FOG in OFF. In 9 confirmed freezers, FOG was also observed during clinical assessment in ON. There were no clinical differences in patients in whom FOG had been observed during OFF and ON versus in OFF only (\( P = 0.10; \) Supporting Appendix 1).

The final dataset included 47 patients. Table 1 shows the group comparisons for all clinical, gait and balance, nongait freezing, and cognitive variables. No differences were found for gender, age, H & Y stages, and UPDRS (III) total and subscores. Freezers had longer disease duration and higher LED than nonfreezers. Freezers had similar TUG scores with and without dual tasking (DT), but scored significantly worse on the BBS than nonfreezers. Falls or near falls (irrespective of FOG) were reported by 52% of freezers, compared to 21% of nonfreezers. An important distinguishing variable was the presence of nongait freezing reported by 83% of freezers and 33% of nonfreezers. Of the eight items, freezing while feet wiping (present in 57% of freezers and 8% of nonfreezers), talking (44% of freezers and 13% of nonfreezers), and writing (30% of freezers and 13% of nonfreezers) occurred most frequently. All other items were reported by at least 2 freezers. Cognitive (MMSE and SCOPA-COG) scores were lower in freezers than nonfreezers. Based on the SCOPA-COG cut-off score, 60% (\( N = 14 \)) of freezers were identified as having...
cognitive problems versus 21.7% (N = 5) of nonfreezers.

A Model for FOG Occurrence

Variables with significant group differences were examined using Pearson’s correlation derivatives for binary outcomes. To avoid overfitting, no more than four candidate predictors could enter the multivariate logistic model of FOG. All variables correlated significantly (R > 0.30; P < 0.05) with decision variable Group (Supporting Appendix 2). LED, disease duration, BBS, nongait freezing, and the binary SCOPA-COG had the strongest correlations with Group. Disease duration correlated with LED (R = 0.54; P < 0.01) and Group, but not with motor or cognitive variables. LED had a stronger correlation with Group than disease duration (R = 0.47, P < 0.01 versus R = 0.31, P = 0.03). Because the BBS showed evidence of collinearity, only the falls/near falls score (irrespective of FOG) was adopted in the model. Univariate predictive accuracy (R2) was examined for LED, disease duration, falls/near falls, nongait freezing, and SCOPA-COG (0/1) (Table 2). Nongait freezing had the largest R2 (R2 = 0.23; P < 0.01). The odds of having FOG in patients with nongait freezing symptoms, compared to patients without this feature, was 9.5 (95% confidence interval [CI]: 2.51–37.37). LED values were converted from mg to dg (100 mg) to aid interpretation of the odds ratios (ORs). LED explained 21% of the variability (OR, 1.69; CI: 1.17–2.43; P < 0.01), SCOPA-COG 15% (OR, 5.6; CI: 1.53–20.49; P = 0.01), and falls/near falls 10% (OR, 4.15; CI: 1.15–14.92; P = 0.03). Given the stronger correlation of LED with Group (freezer/nonfreezer) and higher R2 than disease duration (R2 = 21% versus 9.8%), only LED was included in the multivariate model.

LED, nongait freezing, falls/near falls, and SCOPA-COG (0/1) were entered into the multivariate logistic regression model to determine FOG. These four contributors jointly explained 49% of variability between freezers and nonfreezers (Table 3). Having falls or near falls was the least important factor (P = 0.06).

Given these β estimations, a prediction model for FOG could be determined, as shown in Equation 3:

$$P(\text{FOG}) = \frac{e^{(-3.5 - 1.21 \text{Non-gait freezing} + 0.69 \text{LED} - 1.06 \text{SCOPA-COG} - 1.03 \text{Falls/near falls})}}{1 + e^{(-3.5 - 1.21 \text{Non-gait freezing} + 0.69 \text{LED} - 1.06 \text{SCOPA-COG} - 1.03 \text{Falls/near falls})}}$$

(3)

Figure 1 compares the contribution of the predictor variables to the presence of FOG at three levels of LED (first quartile, median, and third quartile of the test population). As depicted, risk of FOG in patients receiving a median LED of 587 mg, who were free from nongait freezing, falls/near falls, and cognitive problems, was estimated at 6%. Risk of FOG increased dramatically to 98% for patients with LED suffering from nongait freezing, falls/near-falls, and cognitive problems. Estimated probability of FOG was similar between LED levels for patients with either a 0
### A Model for FOG Severity

Linear RA was applied to test the influence of descriptive, motor, and cognitive features on FOG severity in freezers (N = 23). FOG severity correlated highly with the falls/near-falls questionnaire (R = 0.51; P = 0.01) and moderately with the total score of the nongait freezing items (R = 0.29; P = 0.18). Only falls/near falls had a significant univariate explanation of FOG severity (R² = 27%; P = 0.01). A multivariate RA was therefore not required.

### Discussion

FOG is a complex gait disorder in which disease characteristics and motor and cognitive factors may play a convergent role. This is the first study that has aimed to identify the unique contribution of some of these factors in a multideterminant model of FOG. A combination of nongait freezing, LED, falls/near falls, and cognitive impairment provided the best prediction of FOG in PD patients of equal disease severity. Some of these factors have previously been associated with FOG, but were often regarded as single contributors. Combining these factors in an integrative model of FOG is novel. Only patients with observed FOG ("definite freezers") were included in the freezer group, which adds strength to the model. The findings substantiate the view that a breakdown of multiple neurological systems may be involved in the occurrence of FOG.

Earlier studies reported increased gait asymmetry, problems in gait rhythmicity, and left-right coordination as motor correlates of FOG. In addition, our group and others showed that motor features beyond gait, such as freezing in repetitive hand and feet movements, were associated with FOG. The nongait freezing questionnaire used in this study had the highest univariate predictive value of FOG. Because a validated tool to assess nongait freezing in daily activities has yet to be developed, a self-report bias cannot be fully excluded, pointing to a limitation in the present study. Nongait freezing episodes were reported most often during wiping of the feet. Other items of the questionnaire, particularly hand writing, were also found to be freezing-provoking. Interestingly, patients commented that they tended to avoid these activities in daily life. The nongait freezing questionnaire was predictive of FOG, but not the finger tapping and other repetitive movement items embedded in the UPDRS. Although these items can also induce freezing, scoring is mainly based on the observed slowing and reduction of movement amplitude. In contrast, when we assessed patients using the nongait freezing questionnaire, we explicitly asked whether actual motor blocks occurred that resembled FOG.

The role of reduced cognitive resources, either as a primary or a compensatory factor contributing to the

### Table 2. Results of univariate logistic regression analysis on factor Group (nonfreezers and freezers)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
<th>R²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nongait freezing, 1 versus 0</td>
<td>9.50</td>
<td>2.41 37.47 0.23</td>
<td>&lt;0.01*</td>
<td></td>
</tr>
<tr>
<td>LED, dg</td>
<td>1.69</td>
<td>1.17 2.43 0.21</td>
<td>&lt;0.01*</td>
<td></td>
</tr>
<tr>
<td>Cognitive problems, 1 versus 0</td>
<td>5.60</td>
<td>1.53 20.49 0.15</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>Falls and balance problems, 1 versus 0</td>
<td>4.15</td>
<td>1.15 14.92 0.10</td>
<td>0.03*</td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>1.18</td>
<td>1.00 1.38 0.10</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

ORs indicate the increase in odds for FOG resulting from a one-unit change in effect parameters: 1 dg (100mg) for LED, or from 0 to 1 (problem absent to problem present) for falls and balance problems, nongait freezing, and cognitive problems. For example, for a one-unit increase in LED score (100mg), there is a 69% increase in the odds of developing freezing. All variables except disease duration had a significant univariate predictive accuracy (R²; *P < 0.05).

### Table 3. Results of multivariate logistic regression on factor Group (nonfreezers and freezers)

\[ \text{Log (Y)} = a + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 \]

<table>
<thead>
<tr>
<th>Effect</th>
<th>Intercept</th>
<th>Nongait Freezing (0/1)</th>
<th>LED (dg)</th>
<th>Cognitive Problems (0/1)</th>
<th>Falls and Balance Problems (0/1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β estimate</td>
<td>-3.50</td>
<td>-1.21</td>
<td>0.69</td>
<td>-1.06</td>
<td>-1.03</td>
</tr>
<tr>
<td>Standard error</td>
<td>1.42</td>
<td>0.51</td>
<td>0.26</td>
<td>0.49</td>
<td>0.56</td>
</tr>
<tr>
<td>Wald chi-square</td>
<td>6.13</td>
<td>5.65</td>
<td>7.18</td>
<td>4.63</td>
<td>3.44</td>
</tr>
<tr>
<td>P Value</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>0.03</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Overall explained variance between nonfreezers and freezers: R² = 0.49

Variables with significant univariate predictive accuracy were entered in the multivariate logistic regression model. LED, nongait freezing, cognitive problems, and falls and balance problems were found to be significant independent contributors and jointly explained 49% of variability between nonfreezers and freezers. β estimations allow one to determine the prediction equation for FOG. (Note that negative β estimations are the result of the class level design of 1/0 for 0/1 response variables in the SAS system.)
motor abnormalities of freezers, is a matter of debate. Additionally, it is currently not known which cognitive function is principally involved. One of the cognitive hypotheses of FOG states that freezing is a consequence of frontal executive dysfunction based on evidence that freezers demonstrated reduced cognitive flexibility and verbal fluency, as compared to nonfreezers.\textsuperscript{1,10} Recently, Tessitore et al.\textsuperscript{11} underscored these behavioral findings by showing gray-matter and resting-state MRI changes in frontoparietal regions in freezers\textsuperscript{12,13} Accordingly, our results confirm that the SCOPA-COG significantly contributes to the presence of FOG in synergy with motor symptoms. However, cognitive decline in freezers was unrelated to freezing severity. In particular, attention and memory functions were impaired in freezers, unlike visuospatial function, which was comparable to nonfreezers. The latter finding contradicts recent work that suggests a visuospatial perception deficit in freezers; this may be explained by the fact that the figure assembly task included in the SCOPA-COG is insufficiently sensitive to discriminate between freezers and nonfreezers.\textsuperscript{13,14} This points to the general limitation that studying the cognitive correlates of FOG is highly dependent on the choice of cognitive measures, indicating a cautious interpretation.

The SCOPA-COG was used to investigate the role of global cognitive decline (score <28) in FOG. Using the recently described cut-off score for PD dementia (PDD) (SCOPA-COG <23),\textsuperscript{37} 1 nonfreezer and 5 freezers would have been classified as having PDD. The possible presence of early dementia in our subject sample (mostly freezers) could well be a study limitation, but it is nonetheless an inherent feature of the population under investigation, where cognitive decline evolves faster with time.\textsuperscript{38} Factor et al.\textsuperscript{39} recently explored the risk factors of FOG in PD patients of the postural instability/gait disturbance (PIGD) subgroup. The MMSE was not discriminative between two PIGD subtypes: a group with postural instability and falls (but no FOG) and a group with FOG. However, patients with PIGD and FOG had more-frequent psychotic symptoms that have been linked to cognitive deterioration. Genetic differences were most convincing in distinct profiles for PIGD subtypes with and without FOG. This is in contrast to our finding that falls and balance problems per se contributed to the presence of FOG, albeit the least important factor (P = 0.06). In addition, falls/near falls was the only determinant of FOG severity, confirming an overlap in neuropathology.\textsuperscript{40} Although a failure to couple balance and voluntary locomotor synergies was recently found to be related to FOG, the exact nature of the postural deficits underlying FOG is not yet understood.\textsuperscript{40,41}

LED was significantly higher in freezers than nonfreezers, which may reflect a higher dose needed to alleviate FOG than other symptoms, especially in later disease stages.\textsuperscript{15,42} Patients were matched for UPDRS scores and H & Y stage in ON, but not for disease, duration. Thus, a higher LED may have masked a greater underlying disease severity in freezers and may explain why LED discriminated between freezers and nonfreezers. However, LED had a stronger correlation with the presence/absence of FOG, compared to disease duration, and the explained variance was twice as high as that of disease duration. This suggests that LED captures differences in disease profiles between freezers and nonfreezers that are additional to those merely reflecting increased duration/severity. The l-dopa-dependent element of FOG remains difficult to interpret, because freezers more often receive l-dopa-therapy as an initial drug than nonfreezers.\textsuperscript{43} Chronic medication intake leading to reduced synaptic dopamine (DA) sensitivity could be a possible explanation for FOG in later stages,\textsuperscript{44} and may also explain that, once FOG exists, its severity is not adequately alleviated by l-dopa. In the present study, some patients also demonstrated FOG during clinical assessment while they were otherwise optimally medicated. These patients showed no clinical differences with freezers in whom FOG was only observed during OFF and most likely presented “pseudo-ON-freezing” (i.e., FOG that persists in the ON state, but may be alleviated by a higher dose of dopaminergic medication).\textsuperscript{15} This is consistent with the idea that the therapeutic threshold for FOG may be higher than for other DA-responsive symptoms.\textsuperscript{14} Reduced DA sensitivity does not explain FOG in early-PD patients. The latter is more suggestive of neural depletion outside the nigrostriatal motor pathway.\textsuperscript{16} Ample studies support a nondopaminergic origin for FOG, with the brainstem locomotor regions as key structures (as reviewed elsewhere).\textsuperscript{1} The risk profile for FOG yielded by our study underscores this hypothesis, because cognitive problems, falls, and balance problems are also typically observed as poorly responsive to dopaminergic treatment and are indicative of cholinergic depletion in the pedunculopontine nucleus.\textsuperscript{45} Studies that examine the influence of DA therapy on nongait freezing are lacking, but impaired bimanual coordination, which was associated with upper limb freezing,\textsuperscript{7} does not seem to improve with DA replacement.\textsuperscript{46} Therefore, satisfactory treatment of FOG may require a tight regulation of dopaminergic and, possibly, cholinergic levels.

The determinant model derived from the current study explained only 48% of the variance and did not take into account the contribution of emotional factors (e.g., depression and anxiety) to FOG.\textsuperscript{47} However, it provides fresh evidence for the multifaceted character of FOG, a notion that had not been tested in a single, integrative study before. The assessment of nongait freezing, cognitive impairment, LED, and
falls/near falls is not time-consuming, adding to the clinical utility of the model. Longitudinal evidence is needed to validate whether the identified determinants predict the occurrence of FOG over time.

**Conclusion**

Nongait freezing, increased dopaminergic drug dose, falls/near falls, and cognitive problems are independent determinants of FOG in people with PD. In contrast to earlier studies that focused on a single mechanism to explain freezing in PD, our data indicate that dopaminergic, motor, postural, and cognitive deficits play a synergistic role in the manifestation of FOG.

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**References**


