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ORIGINAL COMMUNICATION

The major impact of freezing of gait on quality of life in Parkinson's disease

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Abstract Freezing of gait (FOG) is a disabling motor symptom experienced by a large proportion of patients with Parkinson's disease (PD). While it is known that FOG contributes to lower health-related quality of life (HRQoL), previous studies have not accounted for other important factors when measuring the specific impact of this symptom. The aim of this study was to examine FOG and HRQoL while controlling for other factors that are known to impact patient well-being, including cognition, motor severity, sleep disturbance and mood. Two hundred and three patients with idiopathic PD (86 with FOG) were included in the study. All patients were between Hoehn and Yahr stages I–III. A forced entry multiple regression model evaluating the relative contribution of all symptoms was conducted, controlling for time since diagnosis and current dopaminergic treatment. Entering all significantly correlated variables into the regression model accounted for the majority of variance exploring HRQoL. Self-reported sleep–wake disturbances, depressive and anxious symptoms and FOG were individually significant predictors. FOG accounted for the highest amount of unique variance. While sleep–wake disturbance and mood have a significant negative impact on HRQoL in PD, the emergence of FOG represents the most substantial predictor among patients in the earlier clinical stages of disease. This finding presumably reflects the disabling loss of independence and fear of injury associated with FOG and underlines the importance of efforts to reduce this common symptom.

Keywords Parkinson's disease · Freezing of gait · Quality of life · Depression · Anxiety · Sleep

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder [1] in which the combination of both motor and non-motor symptoms has a significant and negative impact on patients' quality of life. Health-related quality of life (HRQoL) is the most typically used outcome measure representing an assessment made by patients about the detrimental impact of disease and its consequences on their life. This is a crucial aspect of modern medicine given the importance of applying biopsychosocial models to treatment [2].

Many studies have now assessed HRQoL in PD, most commonly using the Parkinson's Disease Questionnaire (PDQ-39) [3]. These studies have revealed that disease severity, motor complications and dopaminergic treatment all appear to contribute to HRQoL [4–6]. However, a recent large-scale multicenter study showed that the combined effect of non-motor symptoms was the most significant predictor of HRQoL, when compared to the motor aspects of the disease [7]. More specifically, the study identified mood disturbance and sleep problems/fatigue as having the strongest negative impact on HRQoL. Indeed,

this is a finding that replicates those shown previously in the literature [8, 9]. Given the frequency with which non-motor symptoms occur [10], understanding their significant impact on individuals with PD is critical for effective patient management.

While appreciating the significant impact of non-motor aspects of PD is important, the same is true of freezing of gait (FOG), which is a symptom also experienced by many patients as their disease progresses. The phenomenon of FOG presents as the sudden inability to generate effective stepping and forward progression despite the intention to do so [11]. The occurrence of FOG significantly increases a patient's likelihood of falling and subsequent nursing home placement [12]. While research into this symptom is growing in interest, treatment options for FOG are presently limited [13] representing the currently incomplete understanding of the underlying pathophysiology [14].

Given the functional impact of FOG it is not surprising that it has previously been linked to reduced HRQoL in PD patients [15–17]. Moore and colleagues [17] have demonstrated that FOG has a strong and significant impact on HRQoL, irrespective of more general disease severity measures. Similarly, Rahman and colleagues [16] have also reported that FOG negatively impacts on HRQoL, although this study used a non-validated questionnaire to identify freezing and did not include this measure in their main regression analyses. In a very recent study, Perez-Lloret et al. [15] have also been able to correlate FOG with HRQoL. They used logistic regression to show that this relationship occurred irrespective of disease severity and duration, in addition to motor complications.

Thus, previous studies exploring the impact of FOG on HRQoL have not controlled well for variables outside of disease and motor severity when assessing the impact of this symptom, which represents a significant limitation in interpreting the relative strength of these findings. Problems with depression [18], anxiety [19] and sleep [20] have been related to FOG but are also large contributors to HRQoL in PD more generally [7].

The aim of the current study was to assess whether severity of self-reported FOG still independently predicted HRQoL, after controlling for the contribution of other factors within PD. The current study introduced new factors which have not previously been considered concurrently with FOG to determine the specific effects on HRQoL. Based on previous findings in the field, we chose to analyze key variables of generalized cognition, mood, sleep disturbance and motor function [6–9]. It was hypothesized that the combination of these measures would account for a high proportion of variance in HRQoL scores. However, our primary goal was to explore the unique contribution of FOG to HRQoL while controlling for the combined impact of these other key variables.

Methods

Sample

Data was collected from the baseline assessment of patients at the 'Parkinson's Disease Research Clinic' at the Brain and Mind Research Institute, University of Sydney. Participants included were assessed between December 2008 and November 2013. The diagnosis of idiopathic PD was based on the UK Brain Bank clinical criteria [21] and was confirmed by a neurologist (SJGL). Patients with an MMSE of less than 24 were excluded due to possible dementia and thus questionable validity of their self-report questionnaires. Patients did not meet MDS criteria for PD with dementia [22]. To explore the impact of FOG on patients in the earlier clinical stages of disease where paroxysmal limitation on mobility was more likely to be of daily significance and impact, the sample was restricted to those patients rated as Hoehn and Yahr (H and Y) stages I–III [23]. This research was approved by the Human Research Ethics Committee of The University of Sydney, and written informed consent was obtained from all participants.

A sample of 285 patients met criteria for inclusion in the study. However, 78 were removed due to missing data for questionnaire or clinical variables. During initial data screening, four participants were further removed from the analysis due to being strongly significant outliers. Therefore, a sample of 203 patients was included in the study. Of these, 86 reported a score of 1 or higher on 'Question 3' of the Freezing of Gait Questionnaire (FOG-Q) ["Do you feel that your feet get glued to the floor while walking, making a turn, or trying to initiate walking (freezing)?"], which has been shown to be a reliable screening tool to identify freezers [24]. As such, 43 % of the sample was deemed to experience FOG by subjective report. Patient characteristics are shown in Table 1.

Measures

We assessed HRQoL using the scaled index of the PDQ-39 [3]. This questionnaire consists of 39 multiple choice items covering eight dimensions of 'mobility', 'activities of daily living', 'emotional well-being', 'stigma', 'social support', 'cognitions' 'communication' and 'bodily discomfort'. Scores are scaled between 0 and 100 with higher scores suggesting poorer HRQoL. To assess FOG severity, we used the FOG-Q [24]. The FOG-Q consists of six multiple choice questions which assess a patient's severity and frequency of freezing. Scores range from 0 to 24, with higher scores suggesting more severe FOG. Section III of the Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [25] was used to

Table 1 Clinical characteristics of sample

	Mean	Standard deviation
Age (years)	66.77	8.9
Gender (*n*)		
Male	139	
Female	64	
Time since diagnosis (months)	61.30	61.3
Hoehn and Yahr stage (*n*)		
1	39	
1.5	7	
2	98	
2.5	39	
3	20	
DDE (mg/day)	615.81	487.8
UPDRS III	27.60	15.1
MMSE	28.35	1.6
PDQ-39	21.21	14.0
SCOPA-S day	4.29	3.5
SCOPA-S night	4.67	4.2
BDI-II	9.77	7.0
HADS-anxiety	3.95	3.4
FOG-Q total	5.34	5.7

$n = 203$, *DDE* dopamine dose equivalence, *MDS-UPDRS III* Movement Disorder Society Unified Parkinson's Disease Rating Scale (Motor subsection), *MMSE* Mini-Mental State Examination, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *SCOPA-S* Scales for Outcomes in Parkinson's Disease (Sleep), *BDI-II* Beck Depression Inventory 2nd Edition, *HADS* Hospital Anxiety and Depression Scale (Anxiety scale), *FOG-Q* Freezing of Gait Questionnaire

assess for motor severity. This assessment is conducted by a clinician and contains 33 scores over 18 items. Scores range from 0 to 132 with higher scores indicating worse motor symptoms. Global cognitive functioning was assessed using the Mini-Mental State Examination (MMSE) [26]. The second edition of the Beck Depression Inventory (BDI-II) [27] was used to measure depressive symptom severity. This self-report questionnaire comprises 21 items and yields a total score ranging from 0 to 63. Higher scores suggest more severe depressive symptoms. Anxiety was measured using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-anxiety) [28]. The scale consists of 7 questions, with scores ranging from 0 to 21. Higher scores suggest worse symptoms of anxiety. The SCOPA-Sleep (SCOPA-S) [29] was used to measure nighttime and daytime disturbance. Scores range from 0 to 15 for nighttime sleep and 0–18 for daytime sleepiness, with higher scores indicating poorer sleep quality. For medically treated patients, dopamine dose equivalence scores (DDE) were calculated (mg/day) [30]. Time since diagnosis was calculated in months from date of diagnosis to date of assessment.

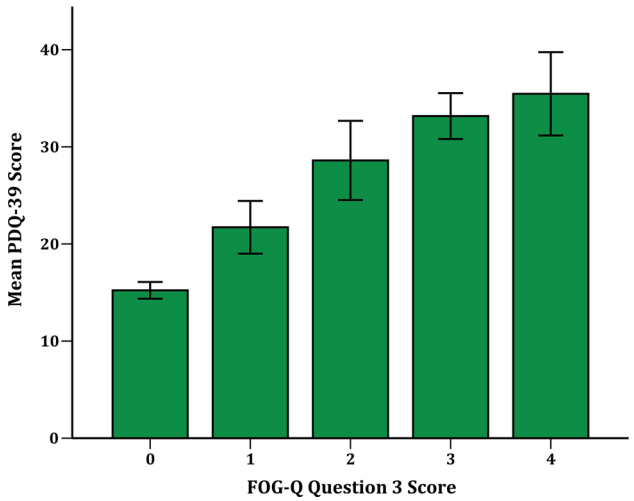

Fig. 1 Mean PDQ-39 scores for patients responding at differing severity levels to Question 3 of the FOG-Q. *Error bars* represent 1 standard error

Statistical analyses

Data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 21. All analyses used an alpha of 0.05 and were two tailed. Pearson bivariate correlations were employed to assess for relationships between the predictor and the outcome variables for regression. Significantly correlated predictor variables were entered at once into a two-block multiple linear regression model to assess their contribution to PDQ-39 scores. Statistical assumptions of normality and heteroscedasticity were not met in some variables included in the model. For this reason, we performed more conservative bootstrapping [31] with bias corrected and accelerated confidence intervals for regression analyses. One thousand bootstrap samples were implemented. The multicollinearity assumption was met, assessed by correlations and collinearity statistics.

Results

Patients defined as freezers scored higher on the PDQ-39 ($M = 29.57$, $SD = 15.29$) than those defined as non-freezers ($M = 15.22$, $SD = 9.36$). More specifically, average PDQ-39 scores across responses to FOG-Q Question 3 are illustrated in Fig. 1. This figure shows that higher scores on this question show a linear relationship with worsened PDQ-39 scores.

Table 2 Pearson correlations between PDQ-39 and initial predictor variables

	PDQ-39	Time since diagnosis	DDE	Age	Gender	MDS-UPDRS III	MMSE	SCOPA-S day	SCOPA-S night	BDI-II	HADS-anxiety	FOG-Q
PDQ-39	–	0.374**	0.371**	0.093	0.092	0.313**	−0.178*	0.522**	0.299**	0.615**	0.554**	0.628**
Time since diagnosis		–	0.467**	0.111	−0.043	0.319**	−0.221*	0.242**	−0.001	0.147*	0.054	0.493*
DDE			–	0.028	−0.066	0.160*	−0.194**	0.351**	0.149*	0.144*	0.091	0.344**
Age				–	−0.054	0.342*	−0.271**	0.141*	0.001	0.046	−0.155*	0.200**
Gender					–	−0.100	0.164*	−0.010	0.131	0.146*	0.136	0.022
MDS-UPDRS III						–	−0.103	0.185**	0.013	0.195	0.037	0.419**
MMSE							–	−0.124	−0.028	−0.078	−0.041	−0.218**
SCOPA-S day								–	0.356**	0.309**	0.226**	0.303**
SCOPA-S night									–	0.209**	0.208**	0.050
BDI-II										–	0.561**	0.293**
HADS-anxiety											–	0.202**
FOG-Q												–

* $p \leq 0.05$

** $p \leq 0.01$

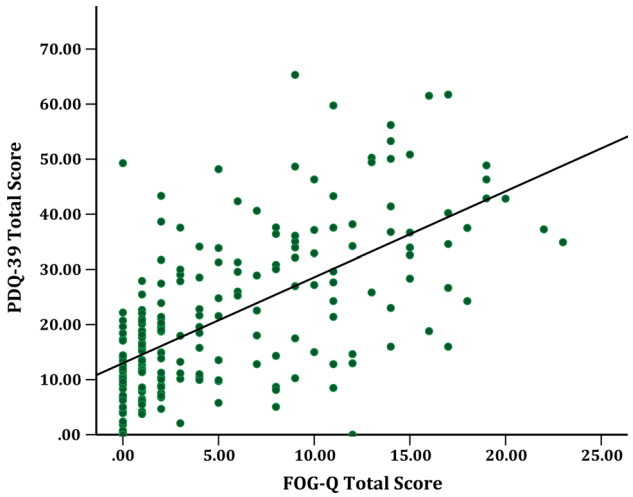

Fig. 2 Scatterplot displaying individual FOG-Q and PDQ-39 scores

Pearson bivariate correlations are displayed in Table 2 and show that PDQ-39 scores were significantly correlated with our control variables of time since diagnosis and DDE. Age and gender did not show significant correlations with the PDQ-39 and were not included in the regression model. All remaining predictor variables (i.e., MMSE, MDS-UPDRS III, FOG-Q, BDI-II, HADS-anxiety, SCOPA-S day and SCOPA-S night) correlated significantly with the PDQ-39. The strongest relationship was between FOG-Q and PDQ-39 scores, and this correlation is illustrated in Fig. 2. Expanding on this, Table 3 also displays

Table 3 Correlations between FOG measures and PDQ-39 subscales

	FOG-Q total	FOG-Q question 3
Mobility	0.801**	0.665**
Activities of daily living	0.560**	0.526**
Emotional well-being	0.352**	0.278**
Stigma	0.254**	0.210**
Social support	0.352**	0.303**
Cognitions	0.279**	0.250**
Communication	0.424**	0.441**
Bodily discomfort	0.369**	0.309**

* $p \leq 0.05$

** $p \leq 0.01$

correlations for measures of FOG with each of the eight domains of the PDQ-39, showing that FOG significantly correlated with all.

To control for time since diagnosis and dopaminergic medication use, these variables were first force entered into the model as a block. These variables alone significantly predicted 17.8 % of the variance in PDQ-39 scores ($F_{2,202} = 21.651$, $p < 0.0001$). However, once the additional predictors were entered at the second stage, a ΔR^2 of 54.4 % was found, suggesting a considerably stronger model (72.2 % of total variance in HRQoL explained). At this stage, however, time since diagnosis, DDE and MDS-UPDRS III all became non-significant predictors, while the

Table 4 Linear model predictors of PDQ-39 scores showing bootstrapped beta scores with the corresponding standard error, significance values, and semi-partial correlations

	Beta	Std. error of beta	Significance value	Semi-partial correlation
Model 1				
Time since diagnosis	0.052	0.017	0.003	0.203
DDE	0.008	0.002	0.002	0.234
Model 2				
Time since diagnosis	0.005	0.011	0.652	0.017
DDE	0.002	0.001	0.078	0.068
MDS-UPDRS III	0.020	0.040	0.622	0.019
MMSE	−0.051	0.383	0.874	−0.006
SCOPA-S night	0.283	0.148	0.044	0.077
SCOPA-S day	0.842	0.179	0.001	0.178
BDI-II	0.527	0.098	0.001	0.210
HADS-anxiety	1.041	0.211	0.001	0.206
FOG-Q	0.955	0.142	0.001	0.306

predictor variables of FOG-Q, BDI-II, HADS-anxiety and both SCOPA-S scores were significant contributors to the model. MMSE was not a significant predictor. This model's overall predictive power was statistically significant ($F_{9,202} = 57.696$, $p < 0.0001$).

We next analyzed semi-partial correlations of the significant contributors to account for the unique variance in PDQ-scores that could be attributed to each of the significant predictors in the full model. While accounting for the other variables in the model, FOG-Q scores uniquely contributed 9.4 %. The contribution of BDI-II to the model was 4.4 % and HADS-anxiety was 4.2 %. SCOPA-S day scores contributed 3.2 % while night scores contributed less than 1 %. Table 4 displays beta values along with other relevant statistics from the regression models.

Motor phenotype analysis

As an additional analysis, we calculated motor phenotype scores for 'tremor', 'non-tremor' and 'rigidity', as described elsewhere [32, 33]. Tremor scores showed a weak correlation with PDQ-39 ($r = 0.145$, $p < 0.05$), non-tremor showed a medium to strong correlation ($r = 0.447$, $p < 0.01$), while rigidity did not significantly correlate ($r = 0.120$, $p > 0.05$). Importantly, however, non-tremor scores were strongly correlated with FOG-Q ($r = 0.597$, $p < 0.01$) and given this likely confound were not considered appropriate for inclusion in the regression model.

Discussion

The results of the current study have shown for the first time that the independent contribution of FOG-Q scores represents the strongest predictor of HRQoL in the earlier clinical stages of PD, after accounting for the contribution of other key variables (general cognition, sleep disturbance, mood problems and motor severity). The variance that could be independently attributed to FOG was more than double that of depression, anxiety and sleep disturbance scores. The contribution of general cognition, motor severity, dopaminergic medication use and time since diagnosis was minimal when considering these variables. These findings consolidate the work of Moore et al. [17], Rahman et al. [16] and Perez-Lloret et al. [15] who found FOG to be related to HRQoL. However, the current results significantly extend these findings by introducing additional clinical factors known to strongly contribute to HRQoL, and illustrate that FOG still remains the most significant predictor.

These results also confirm the hypothesis that measures of self-reported FOG, mood and sleep disturbance all contribute significantly to HRQoL in PD. This finding is directly in agreement with previous studies highlighting the importance of these factors in patient well-being [6–9, 15–17]. The study also confirmed previous findings that non-motor aspects of PD appear to have a more significant impact on HRQoL than broad measures of motor severity [7], with MDS-UPDRS III scores being a non-significant contributor when included in the second stage of the regression model.

While it might seem initially surprising that FOG can be more disabling to HRQoL than sleep and mood disturbance, or motor severity, previously strong arguments have been made for why this may be the case [17]. For example, FOG is an episodic, paroxysmal phenomenon that can occur in public or dangerous situations, which are stress provoking (e.g., crossing roads or entering crowded spaces) [34]. Thus, the disabling impact of a freezing episode can occur at times which significantly impact patients' sense of safety, fear of falling and feeling of independence. Such events can be embarrassing and frustrating and may lead to patients feeling isolated and of burden to their carers and/or family [35]. Thus, negative responses could be anticipated in a HRQoL assessment and indeed the correlations in Table 3 of domains such as 'activities of daily living', 'social support' and 'emotional well-being' support these notions. In addition, our sample consisted of patients in the

earlier clinical stages of the disease. The loss of independence may be one of the most significant challenges for these patients to cope with, possibly contributing to changes for example in social engagement or early retirement.

Depression and anxiety were the next most important predictors of HRQoL. Initial correlational analyses showed that FOG was significantly correlated with these variables. These relationships provide further support for the argument above that FOG may have its negative impact on patient well-being by making patients feel isolated and of burden to their nearest and dearest [17]. The impact of sleep disturbance on HRQoL was less strong. Interestingly, it was daytime sleep disturbance that showed the stronger contribution, with night problems having a minimal impact in the model. Our results suggest that duration of disease and dopaminergic medication use do not strongly impact on HRQoL relative to these other clinical measures.

Currently, treatment options for FOG are poor. Classically, pharmacological intervention and cueing therapies have been employed; however, deep brain stimulation has increasingly grown in appeal [36]. Unfortunately, the effects of cueing and pharmacological options are often short lived, while deep brain stimulation is invasive and unfortunately often suitable for only a small number of patients [13]. It has previously been suggested that computerized cognitive training and virtual reality training may be a beneficial option for the treatment of FOG and gait disorders [13, 37]. However, the current results also provide strong support for the role of more rounded remediation techniques employing concurrent group-based psychoeducation, for example [38]. Such interventions have been proposed as important factors in possibly improving quality of life and well-being [39]. Patients with FOG could be presumed to benefit from these interventions.

Limitations

It is important to consider the limitations to this study. Primarily, we assessed freezing using self-report questionnaire, the most accessible and widely used research tool, and the results are uncompromisingly strong in favor of the contribution of the FOG-Q to HRQoL, suggesting a very significant relationship. However, where resources allow, correlating actual measures of freezing episodes [e.g., 40] would be beneficial in future work. Secondly, MMSE showed little impact on HRQoL, however, given the role of cognitive impairment in FOG [e.g., 41, 42], a more detailed cognitive assessment may have influenced the model. Future studies could explore this impact more precisely. Finally, we had a much higher proportion of male participants, but this is typically reflective of the disease [43].

Conclusions

The current results have shown that self-reported FOG severity is a strong independent contributor to HRQoL in individuals with PD. This is likely to stem from the daily impact of FOG on mobility and independence, causing stress and anxiety in addition to individuals perceiving caregiver burden [35]. Follow-up studies to examine the specific effect of FOG relative to these predictors in caregiver QoL would be beneficial. These results highlight the increasing need for a more solid understanding of pathophysiological mechanisms underlying FOG leading to better treatment options. Clinicians in the field of neurology must show increased awareness to the impact of FOG for optimal management of PD patients.

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Conflicts of interest The authors declare no conflict of interest.

Ethical standard This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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