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Anxiety is associated with freezing of gait and attentional set-shifting in Parkinson's disease: A new perspective for early intervention

K.A.Ehgoetz Martens[a,*], J.M. Hall[a,b], M. Gilat[a], M.J. Georgiades[a], C.C. Walton[a], S.J.G. Lewis[a]

[a] Parkinson's Disease Research Clinic, Brain and Mind Centre, University of Sydney, 100 Mallet Street, Camperdown, New South Wales, 2050, Australia
[b] School of Social Sciences and Psychology, Western Sydney University, Horsley Rd & Bullecourt Road, Milperra New South Wales, 2214, Australia

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ABSTRACT

Previous research has shown that anxiety in Parkinson's disease (PD) is associated with freezing of gait (FOG), and may even contribute to the underlying mechanism. However, limited research has investigated whether PD patients with FOG (PD + FOG) have higher anxiety levels when compared directly to non-freezing PD patients (PD-NF) and moreover, how anxiety might contribute to FOG. The current study evaluated whether: (i) PD + FOG have greater anxiety compared to PD-NF, and (ii) anxiety in PD is related to attentional set-shifting, in order to better understand how anxiety might be contributing to FOG. In addition, we explored whether anxiety levels differed between those PD patients with mild FOG (PD + MildFOG) compared to PD-NF. Four hundred and sixty-one patients with PD (231 PD-NF, 180 PD + FOG, 50 PD + MildFOG) were assessed using the Freezing of Gait Questionnaire item 3 (FOG-Q3), Hospital Anxiety and Depression Scale (HADS), Digit Span Test, Logical Memory Retention Test and Trail Making Tests. Compared to PD-NF, PD + FOG had significantly greater anxiety ($p < 0.001$). PD + MildFOG, however, demonstrated similar levels of anxiety as the PD + FOG. In all patients, the severity of anxiety symptoms was significantly correlated to their degree of self-reported FOG on FOG-Q3 ($p < 0.001$) and TMT B-A ($p = 0.039$). Similar results were found for depression. In conclusion, these results confirm the key role played by anxiety in FOG and also suggest that anxiety might be a promising biomarker for FOG. Future research should consider whether treating anxiety with pharmacological and/or cognitive behavioural therapies at early stages of gait impairment in PD may alleviate troublesome FOG.

1. Introduction

Anxiety disorders such as generalized anxiety disorder, panic disorder and phobias have been argued to be one of the earliest manifestations of Parkinson's disease (PD) [1–3]. Patients with PD and their caregivers rank anxiety and falls as the top two symptoms that require better management in order to improve quality of life [4,5]. One of the most common causes of falls in PD is freezing of gait (FOG), which is characteristically described as a transient cessation of gait, where patients report feeling as though their feet become glued to the floor [6]. A relationship between generalized symptoms of anxiety and severe gait impairments has been noted [7–9], and mood disorders (such as generalized anxiety or depression) have also been suggested to be more common in those with PD who experience FOG [7,10]. Panic attacks are also often associated with freezing episodes [11,12], and recent findings have shown that walking in threatening situations which provoke anxiety, also provoke more FOG episodes [9].

Although, the underlying pathophysiological mechanisms of FOG are still unclear, recent research has proposed that anxiety might contribute to the underlying mechanism of FOG [9,11,13], by overloading the capacity of the basal ganglia to process competing yet concurrent inputs (i.e. cognitive, sensorimotor, emotional) [13,14]. Interconnections between the limbic and motor circuits within the basal ganglia (nucleus accumbens) permit emotional input to interfere with motor outputs (resulting in FOG) [9].

Attention and executive function deficits are also features of basal ganglia pathology even in early PD. Attentional set-shifting deficits, which reflect disturbance in the fronto-striatal pathway [14–17], are often worse in PD + FOG compared to PD-NF [18–21]. These cognitive impairments are especially detrimental to those who have severe gait impairments, since they rely on attention to compensate for their movement impairment [22]. Given that individuals with PD, especially PD + FOG, rely on attention to

* Corresponding author.
E-mail address: Kaylena.ehgoetzmartens@sydney.edu.au (K.A.E. Martens).

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compensate for their gait impairments (i.e. loss of automaticity), anxiety might also contribute to FOG by consuming attentional resources [23–25]. As a result, anxiety may interfere with executive processes (e.g. attentional set-shifting) that are needed in order to compensate for severe gait impairments [9,26,27]. Therefore, anxiety might play a key role in the development of FOG, and as such may be important to consider for early interventions and future therapies to delay or prevent the onset of FOG.

The aim of the current study was to evaluate (i) whether PD + FOG have greater levels of anxiety compared to PD-NF, (ii) whether anxiety in PD is associated with attentional set-shifting deficits, and (iii) whether anxiety might be a useful predictor of those who develop FOG. In addition, we explored whether anxiety levels differed between those patients with PD in the early stages of gait impairment (PD + MildFOG) compared to PD-NF. We hypothesized that both the PD + FOG and PD + MildFOG groups will demonstrate higher clinical levels of anxiety compared to the PD-NF group. We also expected that attentional set-shifting deficits will be related to the severity of anxiety in PD. Finally, it was expected that the severity of anxiety might predict those who experience FOG. By addressing these questions, we hope to extend previous research by examining the relationship between FOG, anxiety and attentional set-shifting, in order to provide insight as to the feasibility of using anxiety as a FOG biomarker and as a potential target for early interventions and future FOG therapies.

2. Methods

2.1. Subjects

The subjects included in this study were recruited from a larger cohort of cases prospectively evaluated between 2008 and 2015 at the PD Research Clinic at the Brain and Mind Centre, University of Sydney. All participants have a confirmed diagnosis of idiopathic PD (based on the United Kingdom Brain Bank clinical criteria) by a trained neurologist (SGJL), and all patients gave written informed consent to the study, which was approved by the University of Sydney Human Research and Ethics Committee. Four hundred and sixty-one PD patients were included in this study. Participants were divided into three groups (PD-NF, PD + FOG, PD + MildFOG) based on their score on the FOG-Questionnaire item 3 (FOG-Q3) ("Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?") [28]. This measure is a reliable screening tool to identify 'freezers'[29]. Two hundred and thirty-one patients were classified as PD-NF (scored 0-"Not at all" on FOG-Q3), 180 patients were classified as PD + FOG (scored between 2 and 4: 2-"rarely, about once a week"; 3-"often, about once a day"; 4-"always, whenever walking" on FOG-Q3), and 50 patients were classified as PD + MildFOG (scored of 1-"Very rarely, about once a month" on FOG-Q3). Exclusion criteria included: the presence of neurological diseases other than PD, psychiatric disorders other than an affective disorder, and/or mini-mental state examination (MMSE) score below 24 indicating dementia. One hundred and twenty-nine patients (62 PD-NF; 54 PD + FOG; 13 PD + MildFOG) in this study were taking anti-depressants and/or anxiolytic medications.

2.2. Data collection and analyses

To evaluate anxiety and depression separately, the Hospital Anxiety and Depression Scale was administered. The 'Anxiety' subscale (HADS-A) and 'Depression' subscale (HADS-D) was subtotalled and compared between groups. FOG-Q3 was selected to reflect FOG severity rather than the total FOG-Q score, based on findings by Shine and colleagues which demonstrated that item 3 from the FOG-Q was most strongly associated with actual behavioural freezing events compared to the total score of the FOG-Q [29]. To evaluate attentional and executive functions participants also completed the Trail Making Test Parts A (TMT-A) and B (TMT-B), as well as the Digit Span Test (backwards and forwards). The primary measure of set-shifting ability was the difference in time to complete Parts A and B of the Trail Making test (TMT B-A). Whereas, attention and working memory was assessed by the forward and backward Digit Span respectively (refer to Table 1). In order to demonstrate a *selective* relationship between anxiety and executive functions, a Logical Memory Test (LM% retention) was also carried out. Since this test is not an executive function, it was not expected to be related to anxiety or FOG and thus acted as a control measure to assess whether the relationship between anxiety, FOG and cognition is specific to executive functioning. Finally, global cognitive functioning was examined with MMSE. Participants were assessed on their regular dopaminergic medication.

An ANOVA was conducted across the three groups and significant findings were further analysed using Tukey's post hoc tests. Due to the group differences in MMSE, UPDRS-III and Disease duration at baseline, a covariate analysis was also conducted.

Pearson's correlations were performed to test associations between neuropsychiatric, neurocognitive, and clinical variables (reported in Table 2). Stepwise multiple regression analyses were performed to examine the relative contribution of neuropsychiatric, neurocognitive and disease related variables to FOG in PD.

In order to determine whether HADS anxiety score might be a useful measure to predict FOG, we collapsed the PD + MildFOG and PD + FOG into one PD + FOG group (N = 230), compared to the PD-NF group (N = 231). Then patients were categorized as having anxiety and/or depression if they scored 8 or above on the HADS-A and/or HADS-D section. Using this criterion, the PD-NF group had 24 patients with anxiety and 207 without, as well as 23 patients with depression, and 208 without (10 of the patients in the PD-NF group had both anxiety and depression). In the PD + FOG group there were 65 patients with anxiety and 165 without, and 66 patients with depression and 164 without 39 of the patients in the PD + FOG group had both anxiety and depression. Odds ratio, positive predictive values and negative predictive values were reported.

3. Results

3.1. Group differences in anxiety

A significant main effect of group was found for anxiety ($F(2,458) = 17.97$, $p < 0.001$). PD + FOG had significantly greater levels of anxiety compared to PD-NF ($p < 0.001$). However, PD + MildFOG was not significantly different from PD + FOG ($p = 0.18$) (see Fig. 1). Notably, even when UPDRS-III, disease duration and MMSE were entered as covariates, the group effect remained significant ($F(2,371) = 11.92$, $p < 0.001$). This group effect also remained significant when depression (HADS-D) was added as a covariate ($F(2,368) = 4.23$, $p = 0.015$), and likewise when TMT B-A and backwards Digit Span were added as covariates ($F(2,257) = 3.03$, $p = 0.05$).

3.2. Group differences in executive functioning

A significant main effect of group was found for the time to complete TMT-A ($F(2,289) = 8.27$, $p < 0.001$), TMT-B ($F(2,281) = 8.62$, $p < 0.001$) and TMT B-A ($F(2,281) = 7.22$, $p = 0.001$). PD + FOG ($p = 0.001$) and PD + MildFOG ($p = 0.041$) took