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Early phenotypic differences between Parkinson's disease patients with and without freezing of gait

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ABSTRACT

Background: Previous studies have associated freezing of gait in Parkinson's disease with the presence of specific phenotypic features such as mood disturbances, REM sleep behavior disorder and selective cognitive impairments. However, it is not clear whether these features are present in the earlier stages of disease or simply represent a more general pattern of progression. To investigate this issue, the current study evaluated motor, cognitive, affective and autonomic features as well as REM sleep behavior disorder in Parkinson's disease patients in the early stages of the condition.
Methods: Thirty-eight freezers and fifty-three non-freezers with disease duration of less than five years and a Hoehn and Yahr stage of less than three were included in this study. The groups were matched on a number of key disease features including age, disease duration, motor severity and dopamine dose equivalence. Furthermore, patients were assessed on measures of motor, cognitive, affective and autonomic features, as well as REM sleep behavior disorder.
Results: Compared to non-freezers, patients with freezing of gait had significantly more non-tremor symptoms and a selective impairment on executive functions, such as set-shifting ability and working memory. Freezers and non-freezers did not differ on measures of tremor, autonomic function, REM sleep behavior disorder, mood or more general cognition.
Conclusion: These results suggest the pathophysiological mechanisms underlying freezing of gait in the early clinical stages of Parkinson's disease are likely to be related to specific changes in the frontostriatal pathways rather than being due to brainstem or more diffuse neuropathology.

1. Introduction

Freezing of Gait (FOG) is a common, disabling symptom of Parkinson's disease (PD) that typically manifests as a sudden inability to move increasing the risk of falls and reducing independence [1]. Freezing episodes can be often be triggered by specific events such as the navigation of narrow spaces, turning and when dual-tasking, which suggests that the phenomenology lies beyond a simple motor problem [1].

Although the precise cause of FOG remains unclear, several distinct hypotheses have been proposed [1]. Previous studies have demonstrated that patients with FOG are unable to generate normal stride length or velocity, leading to the suggestion that FOG is associated with a disturbance of the rhythmic control of gait and the reduced ability to control amplitude [2]. In addition, others have recognized that FOG is associated with abnormalities in the normal postural preparation for the swing phase of a step [3]. Such observations have led to the suggestion that FOG arises from pathological processes within the brainstem structures controlling normal gait including the pedunculopontine nucleus (PPN) [3]. Indeed, this proposition has led to the development of deep brain stimulation surgery targeting the PPN with some positive responses reported [4]. Additionally, previous work has shown that during a motor imagery task, freezers showed increased activity in the mesencephalic motor region, which was associated with subjective FOG severity [5].

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If FOG is indeed the result of a pathological process within the brainstem then it might be expected that patients with freezing would also be likely to experience a broader range of deficits associated with brainstem pathology including autonomic, sleep and affective dysfunction [6]. In keeping with this suggestion, relationships between FOG and autonomic nervous system dysfunction, as well as Rapid Eye Movement (REM) sleep disturbances have been reported [7,8]. Furthermore, a body of evidence derived from functional neuroimaging has demonstrated targeted brainstem pathology across monoaminergic pathways [9,10], which have been linked to the high incidence of depression and anxiety in patients with FOG [1].

In contrast to the potential role of brainstem pathology, the occurrence of FOG has also been associated with more specific "corticostriatal" deficits. A range of executive functional impairments including deficits in attention, 'conflict' resolution and verbal fluency have been described in patients with FOG [11,12] More specifically, freezing behavior has been strongly correlated with the impaired ability to set-shift under temporal pressure [13]. Such findings support the hypothesis that FOG and executive functions have common neurobiological underpinnings, namely a disturbance in cotricostriatal pathways [14,15].

To date, much of the research conducted in FOG has been limited by the inclusion of patients in the advanced stages of the disease. Thus the relationships reported above may have been confounded by the widespread distribution of pathology. To investigate the relative contributions of brainstem and corticostriatal pathology in freezing behavior, this exploratory study investigated ninety-one PD patients in the early clinical stages of the disease. It was hypothesized that if FOG was differentially linked to pathophysiology in the brainstem or across the frontostriatal networks then phenotypic differences should exist between those patients with and without FOG.

2. Methods

2.1. Subjects

The subjects included in this study were recruited from a larger cohort of cases prospectively evaluated between 2008 and 2013 at the Parkinson's Disease Research Clinic at the Brain and Mind Research Institute, University of Sydney. The diagnosis of idiopathic PD was based on the United Kingdom Brain Bank clinical criteria, and was confirmed by a trained neurologist (SJGL). Ninety-one PD patients with a Hoehn and Yahr (H&Y) stage under III and disease duration of five years or less were included. Patients were divided into two groups based on their score on the FOG-Questionnaire item 3 ("Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?"). This measure has previously been shown to be a reliable screening tool to identify 'freezers' [16]. Thirty-eight patients were classified as freezers based on a positive score on the FOG-Questionnaire item 3 whilst the remaining 53 were classified as non-freezers based on a score of 0 on this item. Exclusion criteria included the presence of other neurological diseases or other conditions that would impair gait and dementia as rated by the Movement Disorder Society (MDS) Task Force criteria [17]. There were no age restrictions. All patients were assessed on their regular medication. All patients gave written informed consent to the study, which was approved by the University of Sydney Human Research and Ethics Committee.

2.2. Data collection

An autonomic symptom sub-score was derived from 6 corresponding items (questions 10, 11, 12, 13, 15 and 16) of the MDS-UPDRS parts I and II targeting urinary and constipation problems, light-headedness when standing, fatigue, excessive saliva and difficulties with chewing and swallowing. REM sleep behavior was measured by the REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ) total score. Moreover, a sub score of four questions from the RBDSQ that are specifically about movements during REM sleep (question 4: "I know that my arms and legs move when I sleep"; question 5: "It thereby happened that I (almost) hurt my bed partner or myself"; question 6: "I have had the following phenomenon during my dreams: speaking, shouting, swearing, laughing loudly, sudden limb/movements, "fights", gestures, complex movements, that are useless during sleep, e.g., to wave, to salute, to frighten mosquitoes, falls off the bed, things that fell down around the bed, e.g., bedside lamp, book, glasses"; and question 7: "It happens that my movements awake me".; from now on referred to as RBDSQ4). Finally, affective symptoms were assessed with the Hospital Anxiety and Depression Scale.

To compare tremor and non-tremor symptoms, we calculated a 'Tremor score' and a 'Non-Tremor score' based on an approach used by others [18]. The tremor score was derived from the sum of items 23 and 50–59 of the MDS-UPDRS, divided by the number of items. This score represented the severity of subjective tremor (MDS-UPDRS II) as well as objective tremor at rest and during movements (MDS-UPDRS III). The non-tremor score consisted of the sum of items 14, 16, 22, 24 and 25 from the MDS-UPDRS section II and items 27–49 from section III divided by the number of items. This measure included speech, swallowing, facial expression, the ability to turn in bed, walking and posture, postural stability, rigidity and global spontaneity of movement.

To evaluate cognitive function, the following tests were administered: the Mini-mental State Examination (MMSE) for global cognitive functioning, the Logical Memory sub-test of the Wechsler Memory Scale – III to measure verbal memory; the Digit Span forward and backward sub-tests (total score) of the Wechsler Memory Scale – III to assess attention and working memory; the Controlled Oral Word Association Test to test phonemic (letters F, A, S) and semantic (animal) Verbal Fluency and the Trail Making Test (TMT) parts A (TMT_A) and B (TMT_B) to measure psychomotor speed and set shifting ability. Detailed descriptions of the aforementioned tests have been previously reported [19].

2.3. Statistical analysis

All data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 19. Group differences with regard to demographic and cognitive characteristics were analyzed with an independent *t*-test or the Mann Whitney *U* Test depending on the distribution of the data. Age scaled scores were calculated for the Logical Memory tests. *Z*-scores were calculated from the raw scores of the Verbal Fluency tests and the TMT and the cut-off score for TMT was set at −3.0. *Z*-scores based on normative data were not computed for Digit Span Forward and Backward tests, as normalized data was not available for these scores individually. All analyses used an alpha of 0.05 and were two-tailed.

3. Results

Demographical and clinical characteristics of the two patient groups are displayed in Table 1.

Participants did not differ in terms of age, years of education, disease duration or severity, dopamine dose equivalence and MDS-UPDRS scores.

3.1. Clinical motor symptoms, affective and autonomic function and REM sleep behavior disorder

Patients with FOG had significantly higher mean non-tremor scores than non-freezers but the incidence of tremor did not differ between the groups. No differences were found between groups for the autonomic sub-scale of the MDS-UPDRS, the RBDSQ or for the RBDSQ4. Furthermore, despite higher means on both the HADS anxiety and depression scores, no statistically significant

Table 1
Demographic and clinical characteristics of freezers (n = 38) and non-freezers (n = 53).

	Freezers mean ± SD	Non-freezers mean ± SD	t (df)/U	p-value
Gender (% male)	71	66	−0.504[b]	0.615
Age, years	65.20 ± 9.00	64.58 ± 8.63	−0.332 (89)	0.741
Education, years	13.75 ± 3.43	14.08 ± 3.58	0.651 (89)	0.517
Disease duration, years	1.91 ± 1.40	1.69 ± 1.26	−0.769 (89)	0.444
H & Y stage	2.00 ± 0.42	1.85 ± 0.44	−1.635 (89)	0.106
DDE	452.96 ± 454.19	325.33 ± 244.52	−1.191[b]	0.234
MDS-UPDRS total[a]	43.21 ± 24.56	34.49 ± 15.26	−0.976[b]	0.329
MDS-UPDRS III[a]	25.66 ± 14.11	20.85 ± 10.70	−1.075[b]	0.282

FOG = freezing of gait, H&Y stage = Hoehn and Yahr stages, DDE = dopamine dose equivalence (mg/day), MDS-UPDRS total = total score on Movement Disorder Society Unified Parkinson's Disease Rating Scale, MDS-UPDRS III = motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale.

[a] N = 37.

[b] Mann–Whitney *U* test was used to determine level of significance.