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Freezing of gait in Parkinson's disease: The paradoxical interplay between gait and cognition

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ABSTRACT

Background: Freezing of gait is a disabling episodic gait disturbance common in patients with Parkinson's disease. Recent evidences suggest a complex interplay between gait impairment and executive functions. Aim of our study was to evaluate whether specific motor conditions (sitting or walking) influence cognitive performance in patients with or without different types of freezing.
Methods: Eight healthy controls, eight patients without freezing, nine patients with levodopa-responsive and nine patients with levodopa-resistant freezing received a clinical and neuropsychological assessment during two randomly performed conditions: at rest and during walking.
Results: At rest, patients with levodopa-resistant freezing performed worse than patients without freezing on tests of phonological fluency ($p = 0.01$). No differences among the four groups were detected during walking. When cognitive performances during walking were compared to the performance at rest, there was a significant decline of verbal episodic memory task (Rey Auditory Verbal Learning Test) in patients without freezing and with levodopa-responsive freezing. Interestingly, walking improved performance on the phonological fluency task in patients with levodopa-resistant freezing ($p = 0.04$).
Conclusions: Compared to patients without freezing, patients with levodopa-resistant freezing perform worse when tested while seated in tasks of phonological verbal fluency. Surprisingly, gait was associated with a paradoxical improvement of phonological verbal fluency in the patients with levodopa-resistant freezing whilst walking determined a worsening of episodic memory in the other patient groups.

1. Introduction

Until recently, gait has been viewed as an automated motor task requiring minimal higher-level cognitive function. However, growing evidence suggests a complex interplay between gait disturbances and cognition, especially executive and attentive functions [1]. Freezing of gait (FOG) is a disabling gait disorder, defined as "an episodic inability to generate effective stepping in the absence of any known cause other than parkinsonism or high-level gait disorders [2]. In patients with Parkinson's disease (PD), FOG is most often observed during the "off" periods and shows amelioration to dopaminergic therapies (in our study we will refer to this subtype of dopamine responsive FOG as "OFF-FOG"). However, PD patients also experience FOG resistant to dopaminergic therapy, occurring during both "off" and "on" periods and therefore particularly disabling [3] (we will refer to this subtype of FOG as "ON + OFF FOG"). Patients may also experience FOG only during "on" period (pure ON-FOG) [4], however – since this subtype is very rare – it will not be the focus of this study.

Recently, ON + OFF FOG PD patients were found to display more severe impairment of executive cognitive functions, as compared to patients without FOG with comparable disease duration and severity [5,6]. Hence, it has been hypothesized that FOG may be related to the dysfunction of frontal neural circuits with a positive correlation between the severity of FOG and executive dysfunction.

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This hypothesis is in keeping with the clinical observation that dual tasks frequently trigger FOG [7]. Cognition in FOG patients is still not well characterized [8]: while rough indexes such as Mini Mental State Examination (MMSE) did not differ among PD patients with or without FOG, a significant difference in performance may be observed on neuropsychological tasks assessing executive functions. In the study by Amboni et al. [5], ON + OFF FOG patients performed significantly worse than patients without FOG on the Frontal Assessment Battery (FAB), on a task of phonemic verbal fluency, on the Ten Point Clock Test (TPCT), and the Stroop test part II. In another recent study, Naismith et al. found that set-shifting ability may be specifically related to FOG, since higher scores on the FOG questionnaire (FOG-Q) were significantly related to poorer performance on Trail Making Test part B, while performance on other tasks sensitive to frontal lobe dysfunction (planning or rule acquisition and reversal, working memory, verbal fluency) was not significantly related to FOG [6]. More recent imaging studies [9,10] confirmed an involvement of the "executive-attention" network in patients with FOG compared to patients without FOG.

As part of the executive functions model, attentive resources might play an important role in the etiology of FOG, accordingly it has been suggested that they contribute to the maintenance of a consistent and accurate antiphase left–right stepping [11]. Along this line of reasoning, Shine et al. have recently suggested that an inability to shift between competing attentional demands might be responsible for the occurrence of FOG [12].

In PD patients, independently from the occurrence of FOG, cognitive functions (and especially executive functions and attention) progressively decline with disease progression [13]. Therefore, the main limitation of the aforementioned studies is that they do not unequivocally show a close relationship between the impairment of executive functions and the occurrence of FOG, particularly because all the enrolled patients were evaluated in static conditions (i.e. seated). In addition, some PD patients with severe FOG may still perform normally in tests assessing executive and attentive functions [14], thus pointing to motor circuits (such as the locomotor center in the reticular ponto-mesencephalic region) as main determinants in the pathophysiology of FOG [15]. If cognitive impairment plays a causative role in the pathogenesis of FOG, this would be detected particularly during gait. Therefore, aim of the present study is to evaluate whether different motor conditions (such as being seated in resting condition or walking) influence the cognitive abilities in PD patients without and with different subtype of FOG, namely OFF-FOG and ON + OFF FOG.

2. Methods

2.1. Patients

Twenty-six patients, recruited at our movement disorders out-patient clinic and fulfilling UK Brain Bank diagnostic criteria for PD [16], were enrolled and agreed to participate to the study. Eight PD patients never experienced FOG (noFOG); the remaining 18 patients presented FOG, as revealed by a score ≥ 2 on item 3 of the FOG-Q [17]. Among them, 9 presented a levodopa-responsive FOG occurring either in the morning before taking medication or during wearing-off periods (OFF-FOG); the remaining 9 patients presented FOG during both the "off" and "on" periods and were considered to have levodopa-resistant FOG, at least at the therapeutic doses that were used clinically (ON + OFF FOG). Exclusion criteria were: educational level <5 years, Hoehn and Yahr stage > III, MMSE score <24, other disorders interfering with gait, poor visual acuity, unstable medical treatment regimen, history of psychiatric or neurological illnesses (other than PD), head trauma, neuroleptic exposure or substance abuse; depressive symptoms as revealed by a score > 17 on the Beck Depression Inventory (BDI). Patients with pure ON-FOG were also excluded. Eight subjects were recruited as healthy controls (HC); the aforementioned exclusion criteria (with the exception of a PD diagnosis) were also adopted for HC. All the subjects signed an informed consent form. The local ethical committee approved the study protocol.

2.2. Study design

All subjects were evaluated by the same neuropsychologist and a movement disorders expert, 60–90 min after the first levodopa intake. Patients were assessed at baseline and in two subsequent experimental conditions (lasting about 45 min each – Table 1) in random order: 1. *resting*: while seated, 5 m from the wall on which images for visual tests were projected (Fig. 1A); 2. *walking*: patients were instructed to walk without interruptions along a circular path with a diameter of 4 m; for tests requiring wall projection, images were only presented during the time required for the subject to walk along the 4-meter pathway delimited by the two stripes (Fig. 1B). One of the examiners stood close to the patient for safety reasons. Measures of assessment (including gait velocity and the neuropsychological battery) are listed in Table 1.

As a measure of gait performance we calculated for each subject the time spent to walk 4 m distance while performing a simple-task (Stroop test subtest color naming) and a complex-task (Stroop test subtest interference).

Table 1
Testing protocol.

Domain	Test	Note
Baseline		
Motor assessment	UPDRS-III [18]	Only performed at baseline
	GFQ	
	FOG-Q	
	Simple-task gait velocity (m/s)	4 m walking during Stroop test subtests color naming
	Complex-task gait velocity (m/s)	4 m walking during Stroop test subtests interference
Overall cognitive measures	MMSE	Only performed at baseline
	FAB	
Mood assessment	BDI	
Resting/walking		
Tests sensitive to frontal lobe dysfunction[a]	Stroop test[a] (subset: interference)	Resting and 4 m walking
	Verbal Digit Span forward[a] and backward[a]	Resting and continuous walking
	Phonological verbal fluency[a] (letters F, A, S or E, C, M, 1 min each)	
	PASAT[a]	
Tests less sensitive to frontal lobe dysfunction[a]	Semantic verbal fluency[a] (birds and furniture, or wild animals and transportation means, 1 min each)	Resting and continuous walking
	RAVLT immediate recall[a]	
	BADA noun naming[a]	Resting and 4 m walking
	BADA verbs naming[a]	
	VOSP[a] (subsets: dots counting, objects discrimination, dots discrimination)	

Abbreviations: BADA: Battery for the Analysis of the Aphasic Deficit; BDI: Beck Depression Inventory; FAB: Frontal Assessment Battery; FOG-Q: Freezing of Gait Questionnaire; GFQ: Gait and Fall Questionnaire; MMSE: Mini-Mental State Examination; PASAT: Paced auditory serial addition test; RAVLT: Rey's Auditory Verbal Learning Test; UPDRS-III: motor part of the Unified Parkinson's disease Rating Scale VOSP: the Visual Object and Space Perception Battery.

[a] For tests performed twice (in the two experimental conditions resting and walking) parallel forms were used in order to minimize the effect of learning (practice effect).

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