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Virtual reality walking and dopamine: Opening new doorways to understanding freezing of gait in Parkinson's disease

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ABSTRACT

Freezing of gait (FOG) is a disabling form of gait disturbance that is common in the advanced stages of Parkinson's disease (PD). Despite its prevalence, methods of studying and assessing FOG are limited. We have previously shown that a virtual reality paradigm was able to distinguish between those who report FOG ("freezers") and those who do not report FOG ("non-freezers"). In this paradigm, 'freezers' were found to have prolonged footstep latency in response to known triggers of FOG including doorways, sliding doors and dual-tasking. In this study, we employed the same paradigm to assess performance of 27 freezers and 14 non-freezers in their clinical 'on' and 'off' medication states. In this study, only participants in the freezing group demonstrated statistically significant increases in latencies experienced in the 'off' state compared to the 'on' state in response to wide and narrow doorways and the opening of a sliding door. By contrast, these behavioral differences were not apparent in non-freezers. Furthermore the delay was specific to environmental cues and was not due to generalized slowing in the 'off' state. The findings suggest that this motor delay when processing environmentally salient cues is specific to freezers and is partially mediated by dopamine-dependent neurocircuitry.

1. Introduction

Freezing of gait (FOG) is an abrupt and involuntary cessation of stepping that affects over half of patients with advanced Parkinson's Disease (PD) [1,2]. In this disabling form of gait disturbance, patients report their feet as being suddenly 'glued to the floor' as they try to initiate or maintain locomotion, resulting in a significantly increased risk of falls and nursing home placement [3,4].

The clinical features and triggers of FOG have been well characterized and notably FOG is precipitated by salient environmental cues, such as navigating narrow doorways [5,6]. It is also well recognized that freezing occurs with increased frequency and severity when patients are in their 'off' state, implicating a role for dopamine in FOG [7]. Additionally, a number of other behavioral and motor disturbances have been found in patients who experience FOG such as impaired set-shifting ability, reduced step-length and altered timing of gait, which are all thought to contribute to the mechanisms underlying freezing [6,8,9].

The pathophysiology of FOG is not well understood (for reviews see [2,10,11]) and the neural mechanisms underlying environmentally-provoked freezing have yet to be elucidated. This is in part been due to a general inability to reproduce FOG or its associated features in a controlled but ecologically valid manner. To address this issue, we used an experimental paradigm in which patients with FOG navigate a virtual environment by the use of foot-pedals [12]. This has now been successfully shown in several recent studies to be a valid and useful method for investigating freezing behavior [12–14]. In these reports, prolonged foot stepping latency was used as an indicator of motor delay that correlates with freezing behavior in PD patients. A recent study has shown that a cohort of PD patients who self-reported FOG ('freezers') experienced significantly longer foot-step latencies following the passing of virtual doorways compared to non-freezers and control subjects [15]. However, as all the PD patients were tested in the 'on' medication state, the influence of dopamine on this specific phenomenon was not explored. Previous kinematic studies have shown that doorways are more likely to trigger freezing especially in the absence of dopaminergic medication [16,17].

The aim of the present study therefore, was to compare performance between the on- and off-states within freezer and non-freezer groups as a novel means of exploring the role of dopamine in doorway-provoked freezing. In keeping with the results of earlier studies, we hypothesized that footstep latencies within the VR task would be increased in the 'off' state relative to the 'on' state and that this effect would be specific only to the freezer group.

2. Experimental procedures

2.1. Patients

A total of 41 patients with PD were recruited from the Brain and Mind Research Institute (BMRI) PD research clinic. All patients satisfied

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the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank criteria [18]. The study was approved by the Human Ethics Research Committee of the University of Sydney and written informed consent was obtained from all patients. All patients were tested both 'on' and 'off' their regular medications (see Table 1 for dopamine dose equivalence) on two separate occasions at least two weeks apart. Testing order was randomized. Demographic details are presented in Table 1. All patients underwent neurological examination and were rated on section III of the Unified Parkinson's Disease Rating Scale (UPDRS; [19]).

Of the 41 patients, 27 patients were classified as 'freezers' (those who report FOG) and 14 'non-freezers' (those who do not report FOG) according to a positive response (score 1–4) on item three on the FOG questionnaire (FOGQ-3: "*Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*"; [20]). The response to this question has previously been shown to be a reliable screening tool for patients with FOG [21]. Patients who answered positively to this question, went on to have clinically confirmed FOG through demonstration of one or more episodes of stepping cessation during a standardized assessment of gait incorporating rapid 180° turns. Depressive symptoms were self-rated using the Beck Depression Inventory-II (BDI-II; [22]) and cognition was assessed using the mini mental state examination [23]. Patients with overt clinical depression as assessed by a neurologist (S.J.G.L.) and neuropsychologist (S.L.N.) were excluded from the study. Color-blind and vision-impaired patients were also excluded from the study. Performance results are provided in Table 1.

2.2. Virtual reality (VR) paradigm

Subjects were tested using the Virtual Gait Laboratory, a software environment consisting of a three dimensional corridor presented in first person perspective [24]. In this paradigm the participant is stationary with left and right feet positioned over respective foot pedals and the virtual environment is displayed on a monitor in front. Gait initiation ("WALK" presented in green) and stopping cues ('STOP' presented in red) are displayed on the screen at predefined intervals described in detail elsewhere [15]. To navigate the virtual environment, the patient is required to step on the pedals, alternating between left and right to simulate natural gait. This action produces corresponding forward stepping movements on screen accompanied by realistic auditory feedback through speakers. On-screen, patients take steps through a virtual corridor along which they encounter a number of narrow and wide doorways presented at randomized intervals. The time-points of each step made are automatically recorded along with the time point coinciding with the passing of a doorway. Out of sequence steps (i.e. left–left or right–right) were recorded but were not associated with on-screen movement.

Table 1
Patient characteristics. FOGQ, Freezing of Gait Questionnaire; FOGQ3, FOGQ Item 3; BDI-II, Beck Depression Inventory-II; UPDRS-III, Unified Parkinson's Disease Rating Scale (motor section); MMSE, mini-mental state examination; DDE, dopamine dose equivalence. Values stated as mean ± standard error. *P < 0.05; **P < 0.01; ***P < 0.001, independent samples *t*-test.

	Freezers	Non-freezers	P value
N	27	14	–
Age (yrs)	65.8 ± 1.8	62.6 ± 7.9	0.275
Hoehn and Yahr Stage	2.3 ± 0.9	1.8 ± 0.1	0.098
FOGQ***	11.6 ± 0.9	1.2 ± 0.4	<0.001
FOGQ3***	2.5 ± 0.2	0 ± 0	<0.001
BDI-II	13.1 ± 2.5	6.6 ± 1.4	0.056
UPDRS-III*	34.7 ± 3.0	24.1 ± 3.3	0.032
MMSE	28.0 ± 0.4	29.1 ± 0.3	0.072
DDE (units)	881 ± 119	603 ± 149	0.164

2.3. Behavioral analysis

The primary measure of the paradigm is 'footstep latency', defined as the time taken between two alternate (left–right or right–left) steps resulting in forward progression in the virtual environment. In order to characterize the effect of environmental stimuli on footstep latency, the outcome of interest used in this study was the maximum foot step latency (MFSL) occurring within three steps of the environmental cue in question. Since we were looking to compare deviations from natural rhythm of stepping between subjects, the MFSL was further scaled to each subject's own mode footstep latency. The mode latency was calculated by distributing all latencies throughout the paradigm within 0.1 second bins and then taking the most frequent. The mode footstep latency is taken as a more robust measure of the cadence of natural stepping than the average footstep latency which is skewed by the intermittent episodes of prolonged latencies which we were attempting to detect. The scaled MFSL has been used previously to reliably differentiate between freezers and non-freezers with respect to salient stimuli in the paradigm [15].

We examined the scaled MFSLs in response to three environmental cues — the triggering of a sliding door to open and passing through a wide doorway or narrow doorway. These were averaged across the entire run and a statistical comparison between the 'on' and 'off' performances was made for each patient using a non-parametric paired sign test. Comparison of demographic data between 'freezer' and 'non-freezer' groups was performed using an independent samples *t*-test. Data analysis was performed using Statistical Package for the Social Sciences Version 17 (SPSS; Chicago, IL, USA). An alpha level of 0.05 was used with two-tailed tests. Scaled mean MFSL was expressed as mean ± standard error unless otherwise specified.

3. Results

3.1. Modal latency

No statistically significant difference was observed in modal footstep latency in patients in their 'off' state when compared to their 'on' state in either freezers (0.48 ± 0.09 s *vs* 0.49 ± 0.09 s respectively; P = 0.75) or non-freezers (0.56 ± 0.06 s *vs* 0.57 ± 0.04 s respectively; P = 1.00). Thus any statistically significant differences in scaled footstep latency reported below would not be due to differences in the scaling factor (mode) and are unlikely to represent non-specific generalized motoric changes in footstep latency present throughout the whole paradigm.

3.2. Stimulus evoked footstep latency

In patients who were classified as freezers (n = 27) the scaled MFSL was significantly longer in the 'off' state with respect to all environmental cues compared to the 'on' state. Specifically, on comparison of the 'off' versus 'on' state we found a statistically significant increase in scaled MFSL in response to wide doorways (2.27 ± 0.44 *vs* 1.36 ± 0.26; P < 0.01), narrow doorways (2.69 ± 0. 51 *vs* 1.38 ± 0.27; P < 0.01) and upon triggering the opening of a sliding doorway (2.91 ± 0.56 *vs* 1.40 ± 0.27; P < 0.05) (Fig. 1).

In those patients classified as non-freezers (n = 14), no significant change in scaled MFSL was detected between the 'off' and 'on' states in response to wide doorways (1.19 ± 0.10 *vs* 1.16 ± 0.11; P = 0.58), narrow doorways (1.17 ± 0.09 *vs* 1.22 ± 0.14; P = 0.58), nor the opening of a sliding doorway (1.20 ± 0.12 *vs* 1.32 ± 0.17; P = 1.00) (Fig. 2).

4. Discussion

This study involved comparisons of foot-step latency in response to virtual environmental cues between the 'on' and 'off' states in a sample of freezers and non-freezers. In freezers, an increase in maximum footstep latency was found in the 'off' state compared to the 'on' state when passing through wide and narrow doorways and upon the triggering a