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Modeling freezing of gait in Parkinson's disease with a virtual reality paradigm

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ABSTRACT

Freezing of gait is a paroxysmal and disabling symptom that commonly affects patients in the latter stages of Parkinson's disease, however the intermittent nature of this symptom makes it difficult to study in the clinical setting. Our research group has previously reported a correlation between self-reported freezing of gait symptoms and performance on a seated virtual reality gait task. In this study, we sought to determine whether behavioral measures recorded on this task were correlated with actual clinical measures of freezing of gait recorded in a cohort of 38 Parkinson's disease patients whilst in their clinically defined 'off' state. Firstly, patients with freezing of gait had a significantly larger frequency of spontaneous motor arrests recorded on the virtual reality gait task than 'non-freezers'. In addition, in those 24 patients with clinically proven freezing of gait, the number and percentage of time spent with freezing on the virtual reality task were both moderately correlated with the duration of freezing of gait recorded on the timed up-and-go tasks. These findings suggest that the freezing behavior observed during a virtual reality gait task may share similar neural substrates to freezing of gait. Such a relationship could offer a potential avenue for modeling the phenomenon of freezing of gait in Parkinson's disease, allowing for the exploration of the neural correlates of freezing.

1. Introduction

Freezing of gait (FOG) is a paroxysmal motor block that affects patients with Parkinson's disease (PD), particularly in the advanced stages [1], leading to falls, high morbidity and subsequent nursing home placement [2,3]. The pathophysiology underlying FOG is poorly understood [4–6], however a number of consistent clinical observations have been described, such as difficulty in navigating tight spaces and impairments with dual-task performance [7]. Previous studies have also shown a direct link between freezing of gait and impairment on cognitive tasks that measure attentional set-shifting impairment under temporal pressure [8–10]. Whilst most frequently affecting gait, the phenomenon of freezing has also been observed in upper limb function and speech [11–13] suggesting that there may be a common pathophysiology across motor activities rather than being specific to walking.

Our research group has previously developed a virtual reality (VR) gait paradigm to be used for the exploration of freezing behavior in PD [14], offering a means of safely reproducing freezing behavior in a clinical setting that can also be combined with functional neuroimaging. Specifically, the VR task models normal walking and dual-task performance using a set of footpedals to navigate a realistic three-dimensional environment presented on a computer screen in the first person, all whilst seated. Patients are required to respond to both simple and complex pre-learned cognitive cues, which determine periods of walking and stopping in the VR task and also lead to fluctuations in cognitive load, which we predict will lead to impairments in motor performance. The presence of these motor arrests have previously been shown to correlate with self-reported freezing behavior in PD when patients were tested in their 'On' state [14]. The paradigm has also been utilized in conjunction with fMRI to evaluate the neural correlate of the freezing phenomenon in PD [15]. However, no previous study has attempted to determine whether performance on the VR gait task correlates with actual episodes of FOG in patients with PD. In this experiment, we sought to investigate whether measures of VR freezing behavior distinguish between those patients screening positive and negative for FOG and in addition, whether measures of freezing on the VR paradigm are correlated with actual episodes of FOG elicited during timed up-and-go (TUG) tasks?

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2. Methods

2.1. Sample

43 patients (Hoehn and Yahr (H&Y) stage II–III) were consecutively recruited from the Parkinson's Disease Research Clinic at the Brain and Mind Research Institute in Sydney, Australia. All patients were diagnosed according to UKPDS Brain Bank criteria [16]. Each participant was also assessed on the MDS UPDRS-III, the Freezing of Gait Questionnaire (FOG-Q) [17] and the New Freezing of Gait Questionnaire (NFOG-Q) [18]. None of the patients were deemed as having dementia according to MDS PD Dementia criteria [19]. Patients were also administered the Trail Making Test parts A and B, allowing for the calculation of a score (TMT_{B-A}) that reflects impaired attentional set-shifting score which has previously been correlated with self-reported FOG [14]. The study was approved by The University of Sydney Human Research and Ethics Committee and written informed consent was obtained. Demographic details for all patients are presented in Table 1.

2.2. Medication

All patients were assessed in the practically defined 'Off' state having withdrawn from treatment overnight. None of the patients described an increase in freezing behavior following the administration of dopaminergic therapy. Details of the medication regimens can be found in Supplementary Material.

2.3. Virtual reality task

As described previously, the VR paradigm consisted of a straight corridor with environmentally salient features (such as doors) and WALK and STOP cues presented in the first person on a computer screen (see Fig. 1) [14,16]. Patients performed the task seated in front of a computer screen with their left and right feet positioned over corresponding response pedals which encoded binary information related to left and right 'footsteps'. These pedals needed to be alternately depressed ('left–right–left–right') to enable forward motion on the screen. Steps taken out of sequence (such as 'right–right') did not allow forward progression on the screen. Before commencing the VR gait task, patients were trained to respond to simple direct cues (such as 'WALK' or 'STOP') that appeared on the screen as they progressed along the corridor. In addition, patients were trained on a complex pre-learned rule where congruent color-words (e.g. 'BLUE' written in blue) indicating 'WALK' and incongruent color-words (e.g. 'BLUE' written in green) indicating a cue to 'STOP' also appeared on the screen (see Supplementary material for video footage of the VR task). After displaying competency on the task, patients performed a single 10-min trial of this paradigm navigating a straight corridor with no turns, during which they responded to 90 WALK cues (45 simple and 45 complex) and 30 STOP cues (15 simple and 15 complex).

2.4. Virtual reality outcome measures

Motor arrests on the VR task were defined as any period where the temporal gap between two alternate footsteps was greater than twice the patient's modal footstep latency. The modal footstep latency was derived from an individual's most frequent footstep latency, as grouped in bins of 0.1 s. This measure is more sensitive to the detection of long-latency footsteps, as any estimate of the average footstep of these samples would be skewed motor arrests, and is a close corollary of 'step time' or cadence. In order to control for impaired cognitive processing, any motor arrest occurring within three steps of the presentation of a cognitive cue was removed from the analysis. The number and duration of each motor arrest was calculated for each patient, leading to the calculation of the percentage of time spent frozen, which a more robust measure of clinical freezing than the number of freezing events [20].

As described previously [14], we also collected a number of other specific outcome measures from the VR task:

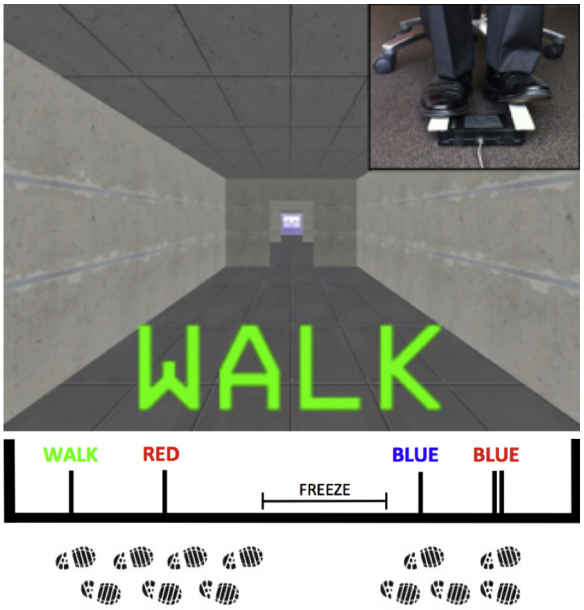

Fig. 1. The top image in the figure is from a screen capture of the presentation of the virtual reality environment during the presentation of a WALK cue with the configuration of the foot pedals shown in the top right corner inset. The bottom image is a graphical depiction of the virtual reality task, complete with simple (WALK) and complex Walk (RED written in *red*) and Stop (BLUE written in *red*) cues. Underneath the depiction of the task is an example of a patient's footstep pattern, with a sample of 'modal' footstep walking (on the left and right of the image) and a motor arrest (labeled 'FREEZE'), which is defined as any between-footstep latency of greater than two times the patient's modal footstep latency. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

Table 1
Demographic details and virtual reality outcome measures. UPDRS III, Unified Parkinson's Disease Rating Scale Motor Sub-score. All test statistics are from *t*-tests with equal variance assumed except for: §Mann–Whitney *U*-test and #*t*-test with unequal variance; $^{*}p<0.05$; $^{**}p<0.01$; and $^{***}p<0.001$. Normal data are presented with mean ± standard deviation and data with a non-parametric distribution are reported with the median score and the intra-quartile range (in parentheses).

	Freezers	Non-freezers	Test statistic
Demographics			
Number	24	14	
Age (years)	69.5 ± 7.3	64.0 ± 8.2	2.12*
Hoehn and Yahr, stage§	2.5 (2.5–3.0)	2.0 (1.0–2.0)	4.13***
UPDRS III score	39.8 ± 11.1	23.5 ± 12.5	4.16***
Disease duration (years)§	6.0 (4–9)	3.5 (3–6)	2.71**
Dopamine dose equivalence (mg/day)	1026.0 ± 476.4	564.0 ± 531.9	2.76*
Freezing of Gait questionnaire§	12.0 (11–14)	1.0 (0–3)	5.07***
Freezing of Gait Questionnaire, Q3§	3.0 (3.0–3.3)	0.0 (0.0–0.0)	5.07***
New Freezing of Gait Questionnaire	18.7 ± 5.7	0.0 ± 0.0	5.23***
Trail Making Test, Part B–Part A#	110.3 ± 71.7	54.7 ± 47.6	2.86**
Timed up-and-go tests			
Clinical freezing episodes§	16.0 (9.0–35.0)	0.0 (0–0)	5.07***
Percent time spent frozen (%)§	9.9 (40.4–26.0)	0.0 (0–0)	4.86***
Virtual reality outcome measures			
Modal footstep latency (s)	0.5 ± 0.3	0.6 ± 0.2	0.83
Longest start hesitation (s)#	4.9 ± 2.6	1.8 ± 0.7	5.06***
Longest out-of-sequence (s)§	3.53 (1.9–5.4)	0.91 (0.7–1.4)	2.94**
Longest motor arrest (s)§	7.2 (4.3–9.0)	1.6 (1.3–3.9)	3.63***
Virtual reality motor arrests#	49.4 ± 37.5	21.5 ± 23.0	2.84**
Percent time spent frozen (%)§	26.04 (10.6–44.5)	2.68 (0.5–5.8)	4.06***