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Editor's comment: Editor's comment: Investigating PD by means of virtual reality (VR) was introduced by Albani et al in 2002. In this interesting article, VR was utilized to explore mechanisms of freezing of gait (FOG) during which subjects interacted with a virtual environment, emphasizing the role for deficits in attention and visuospatial processing in the development of FOG. The authors found that delayed response latencies would be exacerbated by particular stimuli requiring resolution of a Go-No Go task, and also by environmental features requiring increased processing, suggesting that FOG is associated with impaired regulation of automatic behaviour, and additionally demonstrating the utility of VR for the evaluation of gait disorders in PD.

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Using virtual reality to explore the role of conflict resolution and environmental salience in Freezing of Gait in Parkinson's disease☆

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ABSTRACT

Background: The freezing phenomenon is among the most disabling symptoms of Parkinson's disease (PD) manifesting most commonly as Freezing of Gait with a paroxysmal cessation of effective stepping. Recent studies have suggested that freezing is related to both impairments in conflict resolution as well as the processing of environmentally salient information.

Methods: In this study, we utilized a virtual reality gait paradigm to investigate differences in motor outflow between PD patients with ($n = 36$) and without ($n = 37$) Freezing of Gait, as well as age-matched healthy controls ($n = 18$). Subjects were required to navigate a realistic on-screen environment with the use of foot pedals to simulate stepping whilst responding to either cues associated with conflict resolution (congruent 'Red', 'Green' or 'Blue') or environmental salience (wide, narrow and sliding doorways). Footstep latency was used as a measure of motor output.

Results: Significantly increased stepping latencies were observed in freezers compared to non-freezers ($p = 0.004$) and controls ($p = 0.016$) in response to stimuli requiring the inhibition of implicitly cued behavior ('red' cue). Patients with Freezing of Gait also demonstrated increased motor latency compared to non-freezers and controls specifically in response to environmentally salient triggers including narrow doorways ($p = 0.03$ and 0.01 respectively) and the opening of a sliding door ($p = 0.036$ and 0.048 respectively). Performance on the paradigm in relation to these triggers correlated significantly with self-reported freezing severity.

Conclusion: These results suggest that deficits in conflict resolution and visuospatial processing may reflect some of the neural mechanisms associated with freezing behavior and that these can be probed in a virtual reality environment.

1. Introduction

Freezing of Gait (FOG), defined as a brief episodic absence or marked reduction of forward progression of feet despite the intention to walk [1], is one of the most debilitating and least understood symptoms of Parkinson's disease (PD), affecting over 50% of patients with advanced disease [2]. It is well recognized that the freezing phenomenon can be precipitated by cognitive triggers such as dual

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tasking [3] and environmental factors like passing through narrow doorways [4,5]. These observations have prompted a number of pathophysiological models of FOG that emphasize dysfunction across the neural networks required for the effective processing of common triggers (for reviews see Refs. [1,6]). Much of this work has highlighted the executive dysfunction observed in FOG and in particular the role of attentional [7–9] and visuospatial processing [10,11].

It has been proposed that freezing events may be triggered by a lack of neural reserve across complementary yet competing neural pathways from differing functional domains across the corticostriate networks [7]. Extending this proposal, one study using an attentional network task has demonstrated that patients with FOG show impairments in conflict resolution compared to non-freezers, suggesting that freezing may relate to a paroxysmal breakdown in the synchronization of automatic and controlled processes [12].

In addition to the contribution of disrupted attention in FOG, failure in visuospatial processing has also been highlighted as playing a likely role. Recent work has identified that deficits in visuospatial perception and reasoning discriminated freezers from non-freezers [10] and a further study investigating visual angle discrimination has suggested that processing deficits may selectively relate to pathophysiology in the dorsal stream, thus implicating occipitoparietal networks that link primary visual cortex with primary motor cortex [11].

The validation of such models and elucidation of the neural networks underlying FOG has proven difficult given the practical limitations of assessing gait whilst simultaneously assessing factors like conflict resolution and visuospatial perception in a standardized manner. Recently, the use of Virtual Reality (VR) environments has been proposed as a possible method for addressing these questions [13,14]. Subjects use pedals to control their movement within a non-immersive realistic three-dimensional environment, permitting the investigation of both conflict resolution and visuospatial processing in an ecologically valid gait-simulation paradigm. Although performance on this VR paradigm has previously been correlated with self-reported FOG symptoms [13], it has not been used to specifically address the influence of these specific freezing triggers.

In this experiment, we employed the VR paradigm to explore the effect of conflict resolution and salient environmental stimuli on performance of a concurrent motor task in freezers, non-freezers and age-matched healthy controls. We predicted that in freezers stimuli associated with greater conflict resolution and environmental features requiring increased processing (i.e. narrow and sliding doors) would be associated with significantly delayed motor outflow compared to non-freezers and controls.

Table 1
Demographic, neurological and neuropsychiatric patient data for freezers, non-freezers and controls.

	Freezers	Non-freezers	Controls	*F/t*	*p*
N	36	37	18	–	–
Age (years)	66.2 ± 9.6	63.2 ± 8.8	69.3 ± 7.6	3.0	0.06
FOG-Q[a]	10.4 ± 5.3	1.1 ± 1.2	–	−11.1[b]	<0.001
FOG-Q3	2.4 ± 1.1	–	–	–	–
UPDRS-III[a]	29.4 ± 12.6	21.03 ± 11.2	–	−2.9[b]	0.005
UPDRS-III (non-gait subscore)	25.0 ± 1.9	23.2 ± 1.9	–	−0.7[b]	0.516
UPDRS III (toe tapping)	3.4 ± 1.9	2.7 ± 1.6	–	−1.6[b]	0.11
Hoehn and Yahr[a]	2.3 ± 0.9	1.6 ± 0.7	–	−3.7[b]	0.001
BDI-II[a]	12.8 ± 11.6	6.2 ± 5.5	4.2 ± 4.1	9.1	<0.001
MMSE	28.2 ± 1.8	28.8 ± 1.8	28.6 ± 1.2	1.0	0.38
DDE (mg)[a]	748.1 ± 424.0	381.9 ± 367.9	–	−3.7[b]	<0.001

Data is displayed as Mean ± SD. UPDRS-III, Unified Parkinson's Disease Rating Scale (Motor section); FOG-Q, Freezing of Gait Questionnaire; FOG-Q3, FOG-Q item three; BDI-II, Beck Depression Inventory II; MMSE, Mini-Mental State Examination; DDE, Dopamine Dose Equivalence.

[a] Significant differences between one or more groups.

[b] The *t* value is shown for comparisons made between two groups (Student's *t*-test).

2. Materials and methods

2.1. Participants

This study recruited 73 PD patients from the Brain and Mind Research Institute (BMRI) PD research clinic and 18 healthy controls. Patients satisfied the UKPDS Brain Bank criteria [15] and all were assessed on their regular medication as part of their clinical assessment. The study was approved by the Human Ethics Research Committee of the University of Sydney and written informed consent was obtained from all subjects. Demographic details are presented in Table 1. Patients were rated on section III of the Unified Parkinson's Disease Rating Scale (UPDRS [16]) and were between Hoehn and Yahr (H&Y) stages I–IV.

Patients were classified as "freezers" or "non-freezers" based on item three of the FOG questionnaire [17] (FOG-Q): "*Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*" This item (FOG-Q3) has previously been shown to be a reliable screen for FOG [18]. This categorized 37 patients as non-freezers and 36 patients as having some degree of freezing. Patients with major depression were excluded from the study, sixteen patients were taking antidepressants and a measure of affective disturbance was attained using the Beck Depression Inventory-II [19] (BDI-II). Participants performed a Mini-Mental State Examination (MMSE [20]) and none were deemed to have dementia according to the *Movement Disorders Society* PD dementia criteria [21]. Dopamine Dose Equivalence (DDE) was calculated for all patients.

2.2. Virtual reality paradigm

The VR paradigm displays a realistic three-dimensional corridor presented in the first person. All testing was conducted with the subject sitting in front of the screen with left and right feet positioned over corresponding response pedals that controlled left and right stepping movements on the display screen. The use of foot pedals here, in contrast to the use of hand buttons in an earlier study [13], is in keeping with recent work that has reported that alternate stepping in place is a sensitive and specific approach for capturing arrests in motor output in freezers [10]. All pedal responses were recorded but the software was configured such as to disallow any forward progression on the screen with "out of sequence" steps (i.e. left–left or right–right). Thus on-screen movement and accompanying auditory feedback was only associated with alternating left–right pedal sequences.

The conflict resolution color-word task consisted of the words "GREEN", "BLUE" and "RED" being presented on the lower third of the screen in varying colors (green, blue or red). Participants were required to continue 'walking' using the foot pedals if the color-word was congruent (e.g. "BLUE" written in blue), or stop, if the word appeared in an incongruent color (e.g. "BLUE" written in green). Subjects practised the paradigm prior to recording to ensure they had understood the task. Instructions were repeated until acquisition of the rules had been satisfactorily achieved by each subject as demonstrated by an appropriate response to all possible stimuli.

Color-word combinations were deliberately chosen as red, blue and green given the implicit valence of these colors (i.e. red-stop, blue-neutral and green-walk). The implicit valence of red and green was reinforced by the intermittent presentation of the simple commands "WALK" written in green and "STOP" written in red, in place of the color-word cues. Subjects were presented counterbalanced color-word cues and simple commands in a pseudo-