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

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\textbf{A B S T R A C T}

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.

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\section{1. Introduction}

Freezing of gait (FOG) is a paroxysmal motor block that affects patients with Parkinson's disease (PD), particularly in the advanced stages of PD\textsuperscript{[1]}, leading to falls, high morbidity and subsequent nursing home placement\textsuperscript[2,3]. The pathophysiology underlying FOG is poorly understood\textsuperscript[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\textsuperscript[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\textsuperscript[8–10]. Whilst most frequently affecting gait, the phenomenon of freezing has also been observed in upper limb function and speech\textsuperscript[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\textsuperscript[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 set-pedals 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\textsuperscript[14]. The paradigm has also been utilized in conjunction with fMRI to evaluate the neural correlate of the freezing phenomenon in PD\textsuperscript[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 (NFQG-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 arrest 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:

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 inter-quartile range (in parentheses).

<table>
<thead>
<tr>
<th></th>
<th>Freezers</th>
<th>Non-freezers</th>
<th>Test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Number</td>
<td>24</td>
<td>14</td>
<td>2.12*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.5 ± 7.7</td>
<td>64.0 ± 8.2</td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr, stage</td>
<td>2.5 (2.5–3.0)</td>
<td>2.0 (1.0–2.0)</td>
<td>4.13***</td>
</tr>
<tr>
<td>UPDRS III score</td>
<td>39.8 ± 11.1</td>
<td>23.5 ± 12.5</td>
<td>4.16***</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.0 (4–9)</td>
<td>3.5 (3–6)</td>
<td>2.71**</td>
</tr>
<tr>
<td>Dopamine dose equivalence (mg/day)</td>
<td>1026.0 ± 476.4</td>
<td>564.0 ± 531.9</td>
<td>2.76**</td>
</tr>
<tr>
<td>Freezing of Gait Questionnaire</td>
<td>12.0 (11–14)</td>
<td>1.0 (0–3)</td>
<td>5.07***</td>
</tr>
<tr>
<td>Freezing of Gait Questionnaire, Q3</td>
<td>3.0 (3.0–3.3)</td>
<td>0.0 (0.0–0.0)</td>
<td>5.07***</td>
</tr>
<tr>
<td>New Freezing of Gait Questionnaire</td>
<td>18.7 ± 5.7</td>
<td>0.0 ± 0.0</td>
<td>5.23***</td>
</tr>
<tr>
<td>Trail Making Test, Part B–Part A</td>
<td>110.3 ± 71.7</td>
<td>54.7 ± 47.6</td>
<td>2.86**</td>
</tr>
<tr>
<td><strong>Timed up-and-go tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical freezing episodes</td>
<td>16.0 (9.0–35.0)</td>
<td>0.0 (0–0)</td>
<td>5.07***</td>
</tr>
<tr>
<td>Percent time spent frozen (%)</td>
<td>9.9 (4.0–26.0)</td>
<td>0.0 (0–0)</td>
<td>4.86***</td>
</tr>
<tr>
<td><strong>Virtual reality outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modal footstep latency (s)</td>
<td>0.5 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>0.83</td>
</tr>
<tr>
<td>Longest start hesitation (s)</td>
<td>4.9 ± 2.6</td>
<td>1.8 ± 0.7</td>
<td>5.00***</td>
</tr>
<tr>
<td>Longest out-of-sequence (s)</td>
<td>3.53 (1.9–5.4)</td>
<td>0.91 (0.7–1.4)</td>
<td>2.94**</td>
</tr>
<tr>
<td>Longest motor arrest (s)</td>
<td>7.2 (4.3–9.0)</td>
<td>1.6 (1.3–3.9)</td>
<td>3.63***</td>
</tr>
<tr>
<td>Virtual reality motor arrests*</td>
<td>49.4 ± 37.5</td>
<td>21.5 ± 23.0</td>
<td>2.84**</td>
</tr>
<tr>
<td>Percent time spent frozen (%)</td>
<td>26.04 (10.6–44.5)</td>
<td>2.68 (0.5–5.8)</td>
<td>4.06***</td>
</tr>
</tbody>
</table>

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).

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2.5. Clinical assessment of freezing

In the second part of the study, patients performed a series of eight timed up-and-go (TUG) tasks on a 5-m standardized course similar to that described previously [21]. Although TUG tasks are not the most sensitive means of invoking FOG [22], they do provide an effective clinical measure of FOG [21,23]. As the VR did not contain any turns, we excluded any FOG episodes that occurred during the turning portions of the TUG tasks. The TUG trials were videotaped for post hoc analysis of freezing episodes, which were defined as the paroxysmal cessation of a patient’s normal footstep pattern [21,23] and ended when the patient performed an effective step. The freezing episodes were logged according to their time of onset and offset by experienced clinical raters (JMS and SG): single-measure intra-class correlation = 0.914 and 0.907 for frequency and duration of FOG events, respectively. Patients were divided into two groups: those who were witnessed to suffer from at least one episode of freezing during clinical assessment; and those who neither self-reported FOG nor were witnessed to have an episode of freezing during the clinical assessment. Any patient that self-reported FOG (FOG-Q3 score $> 0$ [17]) but did not suffer from clinical FOG during the TUG trials was discarded from the analysis ($n = 5$), leaving a total of 38 patients in the final study.

2.6. Statistical analyses

The Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL) was used for all analyses. To examine between-group differences, two-sample $t$-tests or Mann–Whitney U-tests were performed, depending on the distribution of the data. The second stage of the analysis included only those patients that suffered from FOG in the TUG tasks. Bivariate Spearman’s correlations were utilized to explore the relationship between motor arrests from the VR task, performance on the FOG-Q and NFQOG and the amount and duration of FOG whilst performing TUG tasks. All analyses were two-tailed, with an alpha level of 0.05.

3. Results

Demographic information for the patients is presented in Table 1. Patients with FOG were older ($t = 2.0, p = 0.057$), with longer disease duration ($t = 3.5, p = 0.002$) and had more advanced disease, as measured by H&Y stage ($t = 5.0, p < 0.001$) and UPDRS-III scores ($t = 4.2, p < 0.001$). In keeping with previous research [6], patients who displayed FOG showed worse performance on the TMTB-A ($t = 2.2, p = 0.038$). Despite these demographic differences, the two groups did not differ with respect to their modal footstep latency ($t = 0.8, p = 0.432$) and there were no significant differences in the “toe-tapping” segments of the UPDRS-III (item 40: Mann Whitney $U = 0.68, p > 0.500$; and item 41: $U = 0.72, p > 0.500$). As such, any observed differences in performance on the VR gait task were likely unrelated to generally impaired motor function.

Patients who screened positive for FOG showed significantly longer maximum start hesitation latency ($t = 5.1, p < 0.001$), maximum out-of-sequence latency ($U = 2.94, p = 0.002$); longest spontaneous motor arrest ($U = 3.63, p < 0.001$), as well as the number of spontaneous motor arrests ($t = 3.4, p = 0.002$) and percentage time spent with freezing on the VR task ($U = 4.86, p < 0.001$). The number of motor arrests in the first and last minute were strongly correlated across the cohort ($rho = 0.616, p = 0.001$), suggesting the absence of a ‘fatigue effect’.

3.1. Clinical assessment of freezing

24 of the 38 patients (63%) displayed FOG on the TUG tasks. The total number of FOG events in these patients during the TUG tasks was 237, averaging 9.9 per patient (SD 14.0, range 1–51 and median 4.5). The mean percentage of time spent with FOG during TUG tasks was 5.8% (SD 10.5, range 0.2–39.9% and median 1.3%). No measures of actual FOG events during TUG tasks were significantly correlated with scores on either the FOGQ or the NFQOG, a finding that has previously been reported [20]. There was no fatigue effect observed during the TUG tasks.

3.2. Comparison of motor arrests and TUG freezing behavior

The percentage of time spent with motor arrests on the VR task was positively correlated with the percentage of time frozen during TUG assessments (Spearman’s $rho = 0.506, p = 0.011$; see Fig. 2a). There was also a moderate positive correlation between the number of motor arrests and the percentage time spent with freezing (Spearman’s $rho = 0.478, p = 0.018$; see Fig. 2b) during TUG assessment. The number of motor arrests on the VR task was not correlated with the number of FOG events on the TUG tasks (Spearman’s $rho = 0.381, p = 0.066$), nor the percentage of time spent frozen ($rho = 0.355, p = 0.088$), however each analysis showed a trend for significance.

The duration of the longest spontaneous motor arrest on VR was positively correlated with the percentage of time spent frozen on the TUG tests (Spearman’s $rho = 0.407, p = 0.048$), however no other VR outcome measure was significantly correlated with TUG performance and none of the VR outcome measures were significantly correlated with either the NFQOG or the FOGQ (see Supplementary Material).

4. Discussion

The results presented extend those reported in an earlier study [13], which was conducted in a smaller sample of patients in their ‘On’ state. Specifically, measures such as the longest spontaneous motor arrest and the number and the duration of motor arrests on
the VR task were all significantly greater in PD patients who displayed clinical FOG. As such, it appears that the VR gait task may be able to reliably detect motor impairment in PD patients with FOG.

The second part of this study demonstrated that motor arrests on the VR task were significantly associated with the presence and severity of FOG recorded during a series of TUG tasks. Specifically, there was a positive correlation between the percentage of time frozen on the VR task and the percentage of time frozen during the TUG tasks. In addition, the number of motor arrests in the VR paradigm was also positively correlated with the percentage of time spent frozen on the TUG tasks. Interestingly, the number of motor arrests was not significantly correlated with the number of TUG FOG events, questioning the utility of this measure as a clinical tool. However, the number of motor arrests was correlated with the percent time frozen on the TUG tasks and a recent study that compared clinical ratings of different measures of FOG showed that the percentage of time spent frozen was a more robust measure of FOG across clinicians [20].

As expected, patients from the two groups in this study differed significantly on a number of clinical measures, such as disease duration and disease stage, however these measures have been previously shown to form inseparable aspects of the clinical phenotype of FOG in PD [4], suggesting that it is not possible to study FOG without their concomitant influence. Despite these clinical differences, the two groups displayed similar modal footstep latencies whilst performing the VR gait task and had similar impairments on foot-tapping movements as measured during the UPDRS-III assessment. Therefore, these clinical similarities suggest that any of the paroxysmal breakdowns on the VR task were not related to general motor performance but rather to specific pathophysiological mechanisms associated with freezing behavior.

The higher frequency of motor arrests observed during the VR gait paradigm may be due to the differences between the two tasks and the way in which freezing behavior is recorded. It has previously been reported that independent raters show more consistent ratings on TUG tasks when measuring percentage time frozen as opposed to the number of episodes [20], likely due to some raters classifying several brief episodes of FOG occurring in rapid succession as one extended event, with others marking them as multiple short events. The use of an objective measure of motor arrest derived from modal stepping latency in our VR paradigm may therefore be capturing an increased number of brief motor arrests. The presence of a small amount of freezing behavior in the ‘non-freezer’ cohort supports this notion, suggesting that each individual motor arrest in the VR environment may not be specifically due to freezing behavior, possibly occurring secondary to motor fatigue or an incorrect response to the task. Despite these caveats, the percentage time spent frozen on the VR task was significantly correlated with the percentage time frozen on the TUG tasks, suggesting that the two tasks are measuring related phenomena.

The VR gait task was specifically designed to trigger freezing behavior in susceptible individuals. Therefore the frequency of motor arrests in the VR task may also have been inflated by the presence of dual-tasking, an ability which is impaired in all patients with PD but is especially poor in patients with FOG [8,10]. Furthermore, the VR environment contains other distinct triggers in the form of environmentally salient features, such as doorways that were not assessed in the TUG tasks. It is therefore possible that the events identified by the VR paradigm may not represent true ‘motor freezing’ but rather some related phenomenon common to the sample of patients with PD that were studied. The long latencies recorded as motor arrests could represent a delay in cognitive processing. Indeed, a number of independent studies have confirmed the link between dual-task performance and FOG [6,7,24] with evidence suggesting that susceptible patients preferentially increase their focus on cognitive tasks to the detriment of effective walking [5]. In this context, motor arrests on the VR task could be viewed as the cognitive manifestation of the freezing phenomenon. However, only a small proportion of the freezing behavior recorded occurred immediately following the presentation of a cognitive cue (<8%) and these events were all removed prior to our analysis. As such, it seems highly unlikely that these motor arrests represent impaired cognitive processing but rather a more specific dysfunction in patients with FOG. Despite these conclusions, the goal-directed nature of the VR task, in which patients must keep a pre-learned rule in working memory, suggest that it is not possible to effectively remove the cognitive elements of the task altogether. As such, the results of this study are unable to definitively conclude that motor arrest within the VR paradigm does not also represent a cognitive phenomenon and indeed, it is likely that these processes share common neural pathways [25].

Due to the fact that the VR paradigm was designed to manipulate cognitive and limbic load [14], these results also support the notion that freezing behavior is due to dysfunction within neural networks supporting non-motor functions, such as the Cognitive Control Network [26] and the Salience Network [27]. This interpretation is consistent with a number of recently reported studies [8–11,25], as well as an fMRI study that implicated frontoparietal dysfunction in FOG [15]. Thus, these results provide further support for the hypothesis that freezing in PD is due to a failure to effectively integrate information through cortical and sub-cortical regions within neural networks underlying executive function [25,28–30].

5. Conclusion

The results of this study show that a behavioral surrogate of FOG can be measured in a virtual environment whilst seated, minimizing the influence of gravity and the neural centers that control posture. Clearly, the VR paradigm is qualitatively distinct from gait, however the task primarily probes motor function. As such, the intimate relationship between motor arrests in the VR paradigm and the severity of freezing during standardized clinical assessment suggests that the VR task can accurately model freezing behavior in PD.

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The patients in this study formed the basis of a separate study that was recently published in Parkinsonism and Related Disorders [21].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.gaitpost.2012.10.026.

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