Duration of step initiation predicts freezing in Parkinson’s disease


Objectives – In some individuals with idiopathic Parkinson’s disease (PD), freezing of gait episodes develops as the disease progresses. The neural mechanism underlying freezing in PD is poorly understood. Here, we report a 2-year follow-up on the novel discovery of prolonged step initiation duration as a potential marker of impending freezing.

Methods – Non-freezing PD participants in stages 2.5–4 of the Hoehn and Yahr disease severity scale were recruited from an earlier study which determined the effect of semi-virtual cues on walking. Responders were those who completed the first step faster in the presence of the virtual cues while non-responders either did not change or took longer to complete the first step. Both groups of participants were interviewed 2 years later to determine who had developed freezing of gait.

Results – Participants in the responder group had a 13-fold risk of developing freezing of gait within 2 years following the cueing study (OR = 13.3, 95% CI = 1.1–167). A cutoff score of −2.6% (i.e., a decrease in the duration of the first step with visual cues by 2.6% relative to no cues) gave a sensitivity and specificity of 100% and 89%, respectively.

Conclusions – To the best of our knowledge, this is the first novel discovery of a physical predictor of freezing in PD. The time to complete the first step is a simple test to administer in the clinic or at home and may therefore be easily incorporated into a fall prevention training program for PD before the inception of freezing.

Introduction

Freezing of gait develops in 30–60% of individuals in the advanced stages of idiopathic Parkinson’s disease (PD) (1–3). It is a feature of the disease that is not as commonly included in the description of the disease progression compared to the more well-known motor symptoms of postural instability, bradykinesia, tremor, rigidity, and dyskinesia (4, 5). Freezing can significantly increase the risk of falling as it can sometimes occur unexpectedly. In instances where freezing is predictable, patients often do not have the knowledge or skills to anticipate and adapt to it (6). High levels of anxiety, stress, or fatigue seem to increase the severity of freezing (7). One way to better understand freezing is to look for features of walking performance which might indicate that a patient is likely to develop freezing soon.

Intervention programs in the form of education and training can then be implemented before the patient starts to experience it.

For reasons that are still unclear, individuals with PD who experience freezing episodes improve their walking in the presence of external cues. Among the various sensory augmentations, visual cueing appears to be the most widely studied modality (8–10). Visual cues may serve to compensate or substitute for the so-called automatic gait initiation and walking patterns that is defective in PD when freezing of gait is present (8). We hypothesize that individuals who are predisposed to develop freezing of gait acquire this compensatory mechanism before the onset of freezing can be detected or perceived. The ability to predict which individual may be at risk for freezing of gait would be an important step toward a better understanding of its occurrence.
We previously reported the findings of a study in which participants who had not yet developed freezing of gait walked in the presence or absence of semi-virtual visual cues (8). Some participants initiated the first step faster in the presence of the cues while others either showed no change or started slower. Although this finding appears to be consistent with a random distribution of varying walking performance, we hypothesized that the beneficial effect of the visual cues may be a symptom of impending freezing which may be detected by the duration of the first step. Here, we report a 2-year follow-up pilot study on those participants. To our knowledge, this is the first time that a potential physical marker of freezing in PD has been discovered.

**Material and methods**

**Participants**

The study was approved by the Institutional Review Board. Participants gave verbal consent to be included in the phone survey study. A total of 17 participants participated. They comprised non-freezing participants with idiopathic PD from a previous study (8) who were rated 2.5–4 on the Hoehn and Yahr (H and Y) disease severity scale (11). The median stage was 3.

**Procedure**

**Previous study** – In the previous study, participants in their usual anti-Parkinson drug regime walked 10 m per trial while wearing a semi-virtual reality cueing goggle (44, 45). When it was turned On, two stripes of alternating black and white squares were projected along the subject’s nasal field of view while the landscape surrounding the subject remained unobstructed (Fig. 1). The goggle was connected to a sensor unit that is worn on one side of the waist. It sensed the subject’s forward walking speed and scrolls the tiles backwards at the same speed as the subject’s walking. This produced the impression that the squares were stationary and the subject perceived that they were stepping over the tiles. The tiles remained stationary when the subject was not walking (i.e., sitting or standing). In the Off condition, subjects continued wearing the goggle and viewed the surrounding scene through the lens of the goggles but without the tiles. The On–Off conditions were alternated thrice each. Timing started when the ‘go’ command was given to the subjects to start walking. To test the true effect of the visual cues, participants underwent the two cueing conditions without the benefit of practice trials. Walking performance including duration of step initiation, walking speed, step length, and cadence was measured.

**Current study** – In this study, these participants were assigned to one of two groups based on the duration of their step initiation from the previous study. Responders (n = 9, 6 men and 3 women, median H and Y = 3) were those who completed the first step faster with the visual cues (relative to no cues) either in the first trial, the average of three trials, or both (1.2 ± 0.3 s without cues compared to 1.0 ± 0.2 s with cues, P = 0.0009). Non-responders (n = 8, 5 men and 3 women, median H and Y = 3) were participants who completed the first step that was either of similar or slower duration either with or without the visual cues (1.2 ± 0.5 s). A summary of the participants’ disease characteristics and walking performance is presented in Table 1. Note that all the attributes were similar between the groups except for the duration of the first step (P < 0.001, Fig. 2). The step length for both groups averaged 0.48 ± 0.16 m, speed was 0.84 ± 0.3 m/s, and cadence was 104.2 ± 17.4 per minute. The Folstein test for dementia (12) in both groups was within normal limits. There was a trend in the responder group to have a longer-duration diagnosis and more severe motor symptoms than the non-responder group, but they did not reach statistical significance. There were four participants from the earlier study who were not

![Figure 1](image.png)  
Figure 1. The visual cueing device (44, 45). The contrasting squares take up a small strip of the subject’s field of view and do not block the landscape. They are enlarged for illustration only. Refer to the text for details.
included in this study. Two were lost to follow-up and two withdrew consent.

During the interview, the phenomenon of freezing of gait (17, 18) was carefully explained to the participants in both groups to determine whether they had developed the condition since their participation in the previous visual cueing study 2 years ago (8) and to ensure that they did not misconstrue their bradykinesia or postural instability as freezing (19, 20). The FOG-Q freezing questionnaire was administered to participants who experienced freezing (17).

Statistics

A one-tailed chi-square analysis for a 2 × 2 contingency table was used to test the hypothesis that the beneficial effect of visual cueing portends the development of freezing within 2 years of the visual cueing test. Measures of effect size (odds ratio), sensitivity, and specificity were also calculated. A receiver operating curve (ROC) comparing the percent change in duration of the first step (average of three trials) between the responders and non-responders was created to visualize its diagnostic potential. The area under the curve (AUC) and 95% confidence intervals were also calculated. The cutoff score and its 95% confidence interval were determined by choosing the highest likelihood value to achieve the optimal trade-off between sensitivity and specificity. The alpha level for significance testing was set at 0.05 for all analyses.

Results

In the responder group, 88.9% (eight of nine participants) developed freezing within 2 years following the previous visual cueing study (8) whereas in the non-responder group, freezing occurred in 37.5% (three of eight participants), χ² (1, N = 17) = 4.9, P = 0.013 (Fig. 3). Responders had a 13-fold risk for developing freezing within 2 years. The sensitivity and specificity of the visual cueing test for the time to complete the step initiation were 73% and 83%, respectively (Table 2). The severity of freezing based on the

![Figure 2](image-url)  
Figure 2. Percent change in duration of first step with the cueing device turned On (average of three trials). *P < 0.001.

![Figure 3](image-url)  
Figure 3. Two-year follow-up of responders and non-responders.
FOG-Q questionnaire in the responder group was 17.4 ± 5.4 and 20.7 ± 2.1 in the non-responder group.

A summary of the receiver operating curve (ROC) analyses, including the area under the curve (AUC), sensitivity, specificity, and cutoff score for the percent change in duration of the first step (average of three trials) between the responders and non-responders is presented in Table 3, along with the corresponding 95% confidence intervals. A plot of the ROC is shown in Fig. 4. At a cutoff score of -2.6% (i.e., a decrease in the duration of the first step with visual cues by 2.6% relative to no cues), the sensitivity and specificity were 100% and 89%, respectively.

Table 2 Acquisition of freezing

<table>
<thead>
<tr>
<th></th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (%)</td>
<td>88.9%</td>
</tr>
<tr>
<td>Non-responders (%)</td>
<td>37.5%</td>
</tr>
<tr>
<td>Strength of association</td>
<td>13 (1.1–167)</td>
</tr>
<tr>
<td>Sensitivity and specificity</td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>73 (39–94)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>83 (36–100)</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>89 (52–100)</td>
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<tr>
<td>Negative predictive value (%)</td>
<td>63 (25–92)</td>
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</table>

The results of the study suggest that a decrease in the duration of the first step when visual cues are present is potentially a reliable physical predictor of the development of freezing of gait in PD.

It is important to note that a shorter duration of the first step (in the presence of visual cues) can mean at least two things. First, the patient’s step length could be the same relative to the no-cues condition but is moving the feet faster. It may also indicate that the patient is taking a shorter step while moving at the same speed. Both cases produce a shorter duration of the first step. In the first instance, there could be a subtle presence of hesitation in gait initiation which is removed with visual cues, thereby resulting in a shorter first-step duration. The second instance could be where the patient exhibits festination, whereby the patient takes shorter and quicker steps and eventually either stops walking or falls.

We stress here that neither of these possibilities was grossly evident during the study. We did not observe, nor were they reported by the subjects that they had already acquired freezing of gait episodes at the time of the study. Classically, step initiation includes the automatic postural adjustment and step execution (swing phase) components. Unfortunately, we did not use a computerized motion capture system to test our subjects. Knowledge of these parameters may be useful to better understand the mechanisms behind the increased duration of step initiation in patients with PD who are at risk for developing freezing of gait.

The mechanism of freezing of gait in PD remains controversial. While some researchers ascribe the frontal executive functioning areas of the brain to be the source of the freezing (3, 21), possibly due to depleted frontal dopamine output (22), other neurotransmitter systems (23, 24), long-term levodopa therapy (4, 25), or hemispheric asymmetry (26), other studies have not found support for some of these hypotheses (27–29). Abnormal inhibition of the thalamus and pedunculopontine regions which produces an increase in synchronization of the striatal networks is also thought to contribute to freezing (30, 31). Patients with PD who develop freezing may represent a special classification of the disease condition that is yet to be discovered or characterized (24, 27, 32–34).

Certain features of PD may increase the likelihood of the appearance of freezing. These include initial walking difficulty, severity of the disease...
(walking, balance control, and speech), cognitive decline, and depression (20). Interestingly, older age at onset of diagnosis does not appear to increase the odd of developing freezing (20), although freezing is more commonly experienced in older patients (20). Off-freezing may be addressed by changing the medication regimen. However, it is the on-freezing which is most bothersome because of its resistance to anti-PD medications (6, 18, 27, 35–37).

Although these variables have been shown to associate with the appearance of freezing of gait, none of them provide the prospective and quantitative physical parameters needed to preempt its inception. The results of the current study are promising despite the small and biased sample. A larger study may possibly allow us to identify more or correlated physical markers of freezing, for example, executive or postural set-shifting difficulties (8, 38–42). The ultimate goal is to refer at-risk patients to adaptive training for fall prevention (43).

References

27. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson’s disease: a review of