

Gait freezing in Parkinson's disease and the stride length sequence effect interaction

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Freezing of gait (FOG) has been identified as one of the main contributors to gait disturbances in Parkinson's disease. While the pathophysiology remains enigmatic, several factors such as step length and the sequence effect (step to step reduction in amplitude) may lead to the occurrence of FOG. It was hypothesized that by reducing step length, FOG episodes would present more frequently if a significant sequence effect (measured as a regression slope) was co-existent in the subject. Twenty-six participants with Parkinson's disease were separated clinically into a freezing (PD + FOG, $n = 16$) and non-freezing (PD – FOG, $n = 10$) group, with 10 age-matched control participants. Testing involved walking trials where preferred step length was set at 100%, 75%, 50% and 25% of normalized step length. The number of FOG episodes increased in the 50% condition and further increased in the 25% condition compared to other conditions. The participants with FOG also demonstrated a larger average regression slope, with significant differences in the 75%, 50% and 25% conditions when compared to the PD – FOG and control groups. There were no significant differences when comparing the slope of the PD – FOG and control group, indicating the reduced step length and the sequence effect may have led to the occurrence of FOG. These findings support the possible dual requirement of a reduced step length and a successive step to step amplitude reduction to lead to FOG.

Keywords: Parkinson's disease; freezing of gait; sequence effect

Abbreviations: FOG = freezing of gait; FOG-Q = freezing of gait questionnaire; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Examination

Introduction

Freezing of gait (FOG) is a paroxysmal phenomenon commonly seen in advanced Parkinson's disease. Freezing episodes are transient, generally lasting for a few seconds (Fahn, 1995). They tend to increase in frequency as the disease progresses (Lamberti *et al.*,

1997; Giladi, 2001). Environmental constraints requiring a change in the gait speed, pattern or direction, such as negotiating an obstacle, walking in confined spaces or on reaching a destination, will often trigger a freezing episode (Fahn, 1995; Giladi, 2001). Freezing episodes may also occur spontaneously when walking in an open space, even with the absence of FOG-provoking stimuli,

particularly in the later stages of Parkinson's disease (Schaafsma *et al.*, 2003). FOG is also influenced by cognitive factors, such as stress, anxiety and attention (Giladi and Hausdorff, 2006).

The causes of FOG are poorly understood. Nieuwboer *et al.* (2001) suggested that freezing whilst walking could stem from failure to generate normal amplitude in step length. Bloem *et al.* (2004) suggested that falls and FOG have been linked as interconnected gait disturbances in Parkinson's disease and may share a common pathophysiology. Parkinson's disease patients with FOG display differences in their gait, particularly in stride-to-stride variability, compared with those that do not experience freezing; these differences are present even between freezing episodes (Hausdorff *et al.*, 2003; Bloem *et al.*, 2004). Stride-to-stride variability further increases (magnitude of stride-to-stride fluctuations) in patients with Parkinson's disease who experience FOG in the 'off' state (Hausdorff *et al.*, 1998, 2003; Iansek *et al.*, 2006).

Iansek *et al.* (2006) suggested that FOG during walking was possibly due to the presence of the 'sequence effect' (gradual step to step reduction) in combination with an overall reduced step length which, if small enough, would eventually lead to freezing. That hypothesis was, however, based on the duality of basal ganglia function and malfunction in Parkinson's disease in the elaboration of automatic movement in conjunction with the supplementary motor area. It has been suggested previously that the basal ganglia maintains cortically selected motor set in the supplementary motor area and provides internal cues to the supplementary motor area in order to enable each sub movement to be correctly linked together (Iansek *et al.*, 1995). Iansek *et al.* (2006) examined the sequence effect in FOG subjects and found that contrary to hypokinesia, the sequence effect did not respond to medication or attention strategies. It did disappear with the use of external cues in that study, however, no evidence was provided to support the hypothesis that FOG was due to the presence of the sequence effect (gradual step to step reduction) in combination with an overall reduced step length.

The aim of this study was to test the hypothesis that FOG, during walking, results when the sequence effect is superimposed on a reduced step length. The progressive reduction in step to step amplitude (sequence effect), measured by a linear regression slope, was compared between Parkinson's disease participants who experienced freezing (PD+FOG), those who did not experience freezing (PD–FOG), as well as a group of elderly control participants (control). It was hypothesized that participants in the PD+FOG group would exhibit FOG more frequently when step length was significantly reduced. In addition, the participants in the PD+FOG group who froze were expected to have the sequence effect when compared to the non-freezing control groups (PD–FOG and control). This study focused purely on FOG during walking (defined herein as coming to a complete stop during walking), excluding initiation difficulties.

Method

Participants

Twenty-six participants with Parkinson's disease were recruited as a sample of convenience, from the Kingston Centre Movement

Disorders Program, and clinically identified by a neurologist as presenting with FOG, or an absence of such episodes. This was done on the basis of observation and by the participant's verbal account of whether they had experienced freezing. Power analysis could not be performed as only one previous study reports regression slope data (Iansek *et al.*, 2006) and a comparative group was not included. Further review of studies reporting on FOG failed to report spatiotemporal data needed for power analysis. Participants who experienced freezing (PD+FOG) ($n=16$; males=14) were initially identified, then matched for age with participants who did not experience FOG (PD–FOG) ($n=10$; males=9). All were tested whilst they were 'off' medication. There was an additional control group of participants with no family history of Parkinson's disease ($n=10$; males=9). Overall there was no difference in age across the three groups, $F(2,33)=0.18$, $P>0.05$.

Participants were included if able to walk a total of 250 m unaided, had no history of other neurological conditions, orthopaedic surgery or any musculoskeletal disorders that could affect gait, had a Mini-Mental State Examination score $>24/30$ (MMSE, Folstein *et al.*, 1975) and a Geriatric Depression Scale score (GDS; Brink *et al.*, 1982) of <20 (scores of 0–9 indicating normal, 10–19 mild depressive and 20–30 as severe depressive) (Spren and Strauss, 1998).

Clinical measures included the motor section (III) of the Unified Parkinson Disease Rating Scale (UPDRS, Fahn and Elton, 1987), disease duration, Hoehn and Yahr staging (H&Y, Hoehn and Yahr, 1967) and the FOG questionnaire (FOG-Q, Giladi *et al.*, 2000).

Materials

To measure the spatial and temporal gait parameters, an electronic walkway GAITRite® (CIR Systems Inc. Clifton, NJ 07012) was employed. Measuring 8.3 m long and 0.89 m wide, the GAITRite® collects data through pressure sensors embedded into the carpet. The GAITRite® has been found to produce highly reliable measurements, particularly with walking speed, cadence and step length (intra-class correlations between 0.82 and 0.92 and coefficients of variation between 1.4% and 3.5%) (Menz *et al.*, 2004). The retest reliability is excellent at preferred and fast speed for speed, cadence and stride length (ICC 3.1=0.92–0.97) and remains high at slow speed (ICC 3.1=0.78–0.91) in healthy adult participants (Bilney *et al.*, 2003). GAITRite® has also been shown to discriminate between the footstep patterns of people with Parkinson's disease and healthy controls (Nelson *et al.*, 2002).

The GAITRite® was positioned in the centre of the laboratory so that there was a minimum of 5 m of open space at either end and a minimum of 2 m either side. This arrangement provided sufficient open space to minimize environmental stimuli that may have provoked freezing (Fahn, 1995). Tape was placed on the gait laboratory floor 2 m from either end of the mat to mark the commencement and finishing points for the walking trials to avoid acceleration and deceleration while walking on the mat.

The participants' gait was recorded on videotape to facilitate observational analysis. A full body view of the sagittal plane of motion was recorded at 25 frames per second by a remote controlled panning video camera (Panasonic Combination Camera, model WV-CS50, Matsushita Electrical Industrial Co., Ltd Osaka, Japan) positioned at the middle of the walkway. This information was used to score the incidence of freezing episodes and allowed

repeat viewing, therefore increasing the accuracy of reporting (Lord *et al.*, 1998).

FOG was defined as an unintentional and temporary phenomenon where the feet failed to progress (Schaafsma *et al.*, 2003). An episode of freezing was considered to have ended when the participant took at least two steps at or near their normal step length (Schaafsma *et al.*, 2003) or, in this study, at the step length set for that walking trial. FOG has been reported to be variable and occur in a variety of situations in people with Parkinson's disease (Giladi *et al.*, 1992). Five subtypes of freezing have been identified and include: (i) start hesitation at initiation of walking; (ii) freezing on turning; (iii) freezing in restricted areas; (iv) destination freezing; and (v) open space hesitation in the absence of stimuli likely to result in FOG (Schaafsma *et al.*, 2003). It remains unclear if the pathophysiology of the freezing subtypes is different (Schaafsma *et al.*, 2003). Therefore, to understand the mechanisms of FOG, it is important to restrict the paradigms to control the variables. The frequency of freezing in open spaces was reported to be high in the people with Parkinson's disease in their 'off' state (Schaafsma *et al.*, 2003), therefore only episodes of FOG during open space walking were recorded for this study. Freezing during open space walking was defined as an unintended stop to stepping during the middle 6.3 m of the GAITRite®.

Procedure

The research was given approval by the Southern Health Research Ethics Committee, in conjunction with the Monash University Human Research Ethics. All data were collected at the Gait Laboratory at the Kingston Centre, Cheltenham, with each testing session lasting for ~2 h. Written informed consent was obtained from participants prior to testing, and the participant's mental status and ability to give consent was confirmed. Participants took their last dose of anti-parkinsonian medication at least 12 h before testing, to study freezing in the 'off' state. Participants' height and weight were recorded and leg length was measured in order to calculate normalized step length (normalized step length = $0.8 \times \text{leg length}$) (Hof, 1996). From this calculated value of step length (100%), further reductions of 75%, 50% and 25% of normalized step length (in centimetre) were calculated for each individual and marked out on the floor.

The gait measurements were captured by the GAITRite® in which walking trials consisted of five conditions: (i) preferred step length; (ii) 100% normalized step length (SL100); (iii) 75% normalized step length (SL75); (iv) 50% normalized step length (SL50); and (v) 25% normalized step length (SL25). A total of 20 walking trials were collected from each participant. Conditions were not counterbalanced in order to examine the effect of gradually reducing the step length and to avoid any difficulties faced when walking in the smaller step length conditions as this could present as a confounding variable. Subsequent to data analysis, a subgroup of six subjects, who experienced FOG, were retested with randomization of the SL conditions to ensure fatigue was not a contributor to freezing episodes.

Visual cues in the form of multiple white strips were placed on the floor at the calculated normalized step length to demonstrate the required step length at which to walk. Participants were given

an opportunity to practice each step length before completing four walks in each condition. For each walking trial except SL25, the white strips were placed over the 2 m before the start end of the mat at the required normalized step length, in order to cue the correct step length for each condition. In the SL25 condition, the white strips were placed only 1 m before the start end of the mat due to the increased number of steps. White strips were not placed on the GAITRite® mat to avoid visual cues that may have influenced FOG during data capture. Participants were given standardized instructions before each walking trial. Participants were instructed to walk at a self selected pace using the prescribed step length to the line marked 2 m beyond the end of the mat to minimize the risk of slowing down.

The video recording was viewed independently by two assessors to count the number of FOG episodes. To familiarize the assessors with the counting, a training session was conducted to determine when a single block started and finished. When differences in scores were identified, the video was observed concurrently by the assessors until a consensus was reached.

Data analysis

One-way analysis of variance (ANOVA) was employed to compare group descriptive data and gait characteristics for the three groups. The coefficient of variability was calculated for all groups and all conditions to determine step length variability. One-way ANOVA was used to compare the coefficient of variability for the three groups. The number of freezing episodes for each condition in the PD+FOG group was totalled together and a one-way ANOVA applied to determine possible associations between step length and the number of freezing episodes. The percent of FOG episodes (i.e. the number of freezing episodes in each condition divided by the total number of freezing episodes) was also calculated for comparison between conditions.

GAITRite® software was used to analyse the temporal-spatial data of each trial. To extract step to step data, Microsoft Access was used. In trials where FOG occurred, the footsteps leading up to the motor block were identified and the section with the greatest number of steps, with a required minimum of six steps, was used in the temporal-spatial analysis for that trial. The footsteps recorded at the time of the freezing episode were not included in the temporal-spatial analysis.

When calculating the regression slopes for trials where FOG did not occur, step length data for all footsteps was used. When freezing episodes did occur, the section of the walking trial with the greatest number of steps, with a required minimum of six steps, was used in the analysis. The benefit of using the time period where the greatest number of steps was taken is that there were more data points for calculating the regression line and so the standard errors around the slope were reduced. One regression slope was calculated for each walking trial.

The regression slope (β), representing the decrease or increase in step length for each individual walk, were averaged to formulate group mean average slopes, which were compiled for each condition (preferred, SL100, SL75, SL50 and SL25). This was done by examining the four walking trials for each condition individually in which step length was plotted against step number in each trial

to formulate a linear regression. These were compared between groups using a one-way ANOVA and Tukey honestly significant difference (HSD) *post hoc* test.

The individual β -values for each walking trial in the preferred condition were examined and related to the presence or absence of freezing episodes. Pearson's correlation coefficient (r) was conducted between these FOG episodes and β -values, as well as between freezing episodes and the clinical measures (UPDRS, H&Y, MMSE, GDS and FOG-Q). β -values were also correlated using Pearson's r and the relationship between clinical measures for the PD+FOG and PD–FOG groups. The power of the correlation was determined by criteria suggested by Cohen (1988): $r=0.10$ to 0.29 : small, $r=0.30$ to 0.49 : medium, $r=0.50$ to 1.0 large. P -values <0.05 indicated a significant difference.

To determine whether variation in the number of steps taken affected differences in regression slopes between groups, the same number of steps in each group were analysed for the preferred and SL25 conditions.

Results

Scores for the UPDRS (Section III) ranged from 16 to 36 (mean = 23.25, SD = 5.42) for the PD+FOG group; the duration of Parkinson's disease ranged from 3 to 23 years (mean = 12.44, SD = 5.00). For the PD–FOG group, the scores for the UPDRS (Section III) ranged from 9 to 21 (mean = 15.9, SD = 3.67), with a duration of Parkinson's disease from 1 to 8 years (mean = 2.30, SD = 2.45).

No significant differences were found between the groups for the MMSE [$F(2,33) = 3.26$, $P > 0.05$], however, there were significant differences in GDS scores across groups [$F(2,33) = 17.64$, $P < 0.001$], with the PD+FOG group scoring significantly higher than the PD–FOG and control group. These scores still fell within an acceptable range (see Table 1).

The PD+FOG group scored significantly higher on the UPDRS III [$t(24) = 3.77$, $P < 0.05$] and H&Y [$t(24) = 5.96$, $P < 0.05$] indicating a more severe level of disability compared with the PD–FOG group which may be associated with the significant difference in duration of disease [$t(24) = 5.92$, $P < 0.05$] between the two groups.

Only participants in the PD+FOG group displayed freezing, and therefore analysis investigating the number of freezing episodes across the step length conditions was restricted to those participants.

The PD+FOG group walked with a significantly smaller step length [$F(2,33) = 28.66$, $P < 0.05$] and velocity [$F(2,33) = 33.88$, $P < 0.05$] to the PD–FOG group. *Post hoc* tests revealed that these differences were present between the PD+FOG group and the other two groups. The PD–FOG and control group did not differ in step length and velocity mean values. There was no significant difference in mean cadence values across groups [$F(2,33) = 0.63$, $P > 0.05$] (see Table 2).

PD+FOG group had significantly greater variability in step length. *Post hoc* analysis showed these differences were in the preferred, 25% and 50% conditions ($P < 0.01$) (Table 3). There was no difference in step length variability between the PD–FOG

Table 1 Means and standard deviations of screening measures and characteristics for PD + FOG, PD – FOG and control groups

Group characteristics	PD + FOG (n = 16) Mean (SD)	PD – FOG (n = 10) Mean (SD)	Control (n = 10) Mean (SD)
Age	68.06 (1.73)	68.40 (8.41)	69.7 (5.03)
MMSE	28.19 (1.72)	28.20 (1.48)	29.60 (0.97)
GDS	12.00 (3.78)**	7.30 (4.30)	3.30 (2.75)
Disease duration	12.44 (5.01)*	2.30 (2.45)	–
FOG-Q	14.88 (3.44)**	1.80 (1.32)	–
UPDRS	23.25 (5.42)*	15.90 (1.16)	–
Section III (motor)			
Hoehn & Yahr Stage	3.88 (0.81)*	2.10 (0.61)	–

Dashes indicate where descriptives were not applicable.

Hoehn & Yahr Stage = Hoehn and Yahr Staging of Parkinson's Disease

**Significant < 0.001 ; *significant < 0.05 .

Table 2 Spatiotemporal characteristics of gait in preferred condition for each group

Spatiotemporal variables	PD + FOG (n = 16) Mean (SD)	PD – FOG (n = 10) Mean (SD)	Control (n = 10) Mean (SD)
Cadence (steps/min)	118.38 (21.59)	113.40 (6.07)	111.92 (7.92)
Velocity (cm/s)	69.97 (30.37)*	121.67 (11.17)	141.80 (16.78)
Step length (cm)	37.76 (18.18)*	64.40 (5.86)	76.13 (8.62)

*Significant < 0.05 .

and controls. The PD+FOG also had significantly greater step length variability in the 75% condition ($P < 0.05$) compared with the control group. Greater variability was found in the 100% condition for PD+FOG group but *post hoc* analysis showed no significant differences between groups.

Analysis for PD + FOG group: number of freezing episodes

All participants in the PD+FOG group reported freezing through the FOG-Q (mean = 14.88, SD = 3.44) although five failed to demonstrate freezing during the actual testing session. A total of 245 freezing episodes were counted in the PD+FOG group. The total number of freezing episodes in each condition is illustrated in Fig. 1A.

Participants were more likely to experience FOG episodes in conditions with the smaller step length (i.e. SL25), particularly participants who demonstrated freezing during the preferred condition. When the background step length was increased in the PD+FOG group, from the preferred to SL100, the freezing

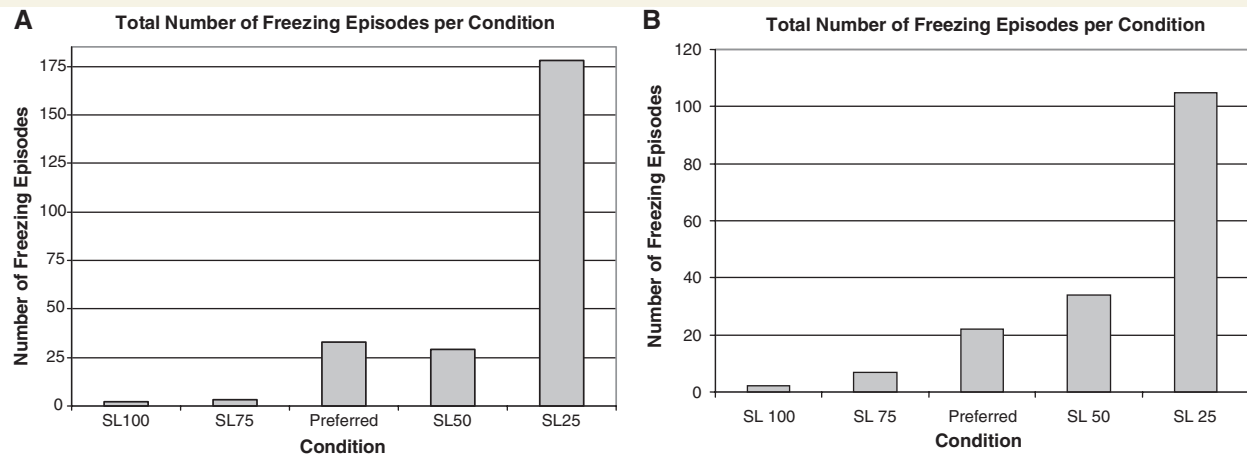


Figure 1 (A) Number of freezing of gait episodes in each condition in the PD+FOG group. (B) Number of FOG episodes in each condition, in the subgroup of six participants with randomized conditions.

Table 3 Summary of average step length and coefficient of variability (COV%) values for the three groups across conditions for each group

Condition	Group					
	PD + FOG (n = 16)		PD – FOG (n = 10)		Control (n = 10)	
	Mean (SD)	COV%	Mean (SD)	COV%	Mean (SD)	COV%
Preferred	37.76 (18.18)	12.84**	64.40 (5.36)	3.52	76.13 (8.62)	1.36
SL100	58.75 (11.42)	4.42	72.37 (5.11)	2.52	77.71 (5.85)	2.00
SL75	49.34 (9.40)	5.57*	61.55 (5.5)	2.94	63.28 (4.11)	1.95
SL50	32.77 (8.02)	8.47**	45.84 (5.36)	4.31	44.78 (4.84)	3.78
SL25	14.17 (4.81)	16.72**	21.53 (3.89)	6.99	23.25 (4.74)	8.28

*Significant < 0.05; **significant < 0.01.

episodes were effectively eliminated. Figure 1B demonstrates the number of FOG episodes for the subgroup of six participants with randomized conditions. It can be seen that the 25% SL condition still resulted in the maximum number of freezing episodes, suggesting fatigue was not related to the number of episodes.

Analysis based on average slopes (β) in each condition across all groups

The sequence effect, as measured by the regression slopes, of all three groups was included in this section of the analysis. One participant in the PD+FOG group, who experienced severe blocking, was excluded in this analysis because individual footsteps could not be identified in all four trials. Regression slope for one trial in the preferred condition could not be calculated for another participant in the PD+FOG group.

Table 4 demonstrates that the slopes (β) for the PD+FOG group were substantially greater than those in the PD–FOG and control groups across conditions, particularly at the reduced step length. Using scores for UPDRS (Section III), H&Y, GDS and disease duration (years) as covariates in the analysis, there were no significant differences between groups reported in the

preferred and SL100 conditions [$F(2,32)=1.41$, $P>0.05$ and $F(2,32)=1.05$, $P>0.05$, respectively]. However in the SL75, SL50 and SL25 conditions the PD+FOG group demonstrated a significantly higher β -value [$F(2,32)=3.34$, $P<0.01$, $F(2,32)=2.66$, $P<0.05$ and $F(2,32)=5.56$, $P<0.01$, respectively] compared to the PD–FOG and control group. Tukey's HSD test confirmed the difference in β was located in the PD+FOG group, when compared with the PD–FOG and control group. The PD–FOG and control group did not differ in the β -values across conditions.

To examine whether these observed differences were still evident with better matched subgroups, participants in the PD+FOG group ($n=5$) who experienced freezing during testing and had lower UPDRS III scores (mean=18.4, SD=2.30) were compared with a subgroup of PD–FOG ($n=7$) with similar UPDRS III scores (mean=17.7, SD=2.06). The slopes (β) for the PD+FOG subgroup were significantly different for SL50, $t(11)=3.75$, $P<0.01$ and SL25, $t=-2.20$, $P<0.05$. The slopes (β) were not significantly different between subgroups in the preferred, SL100, and SL75 conditions.

Figure 2 displays the regression slopes for walking trials 1 and 3 in the SL25 condition, for a single age-matched participant in

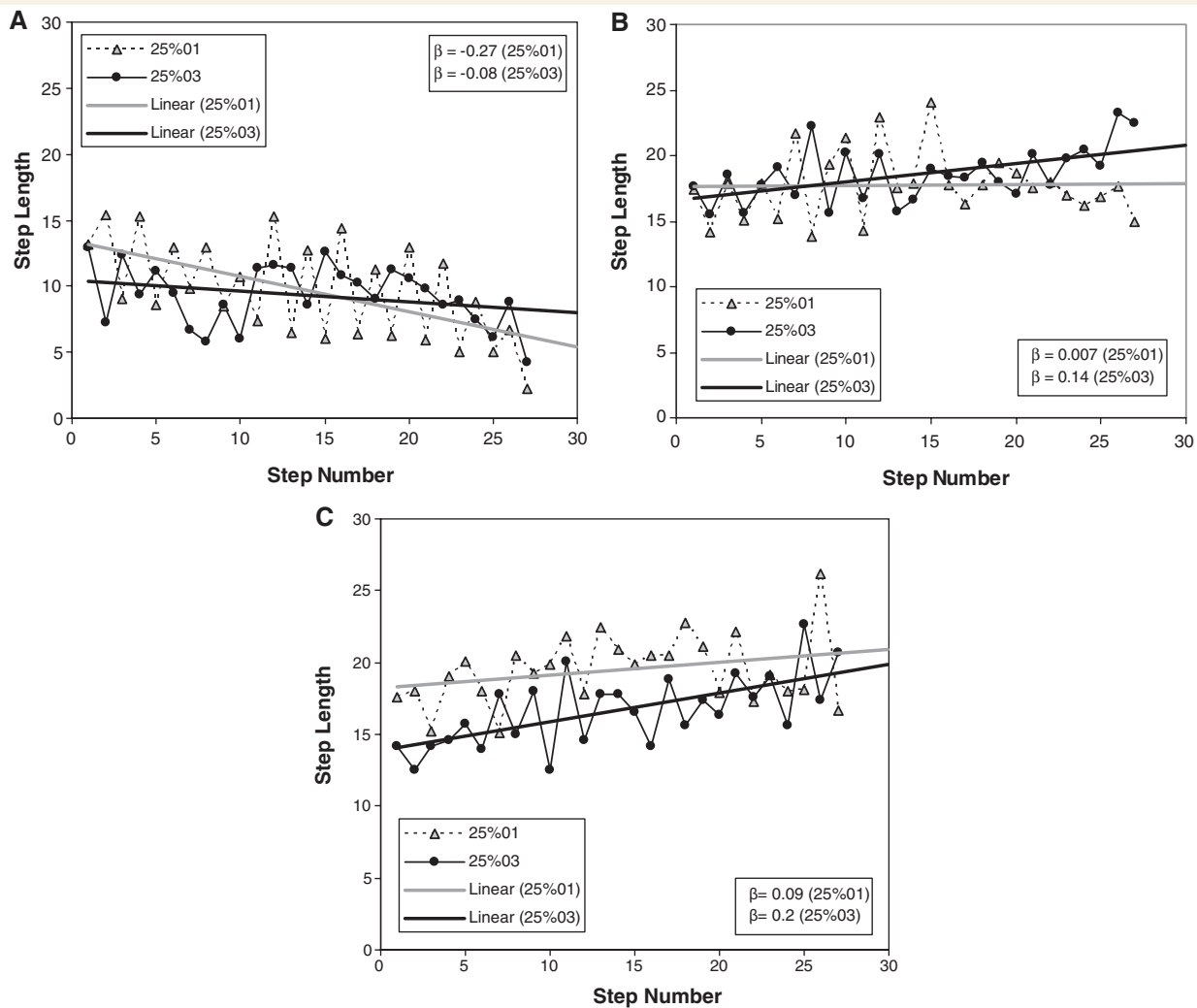


Figure 2 (A) Relationship between step length and step number for a single PD+FOG participant in the SL25 condition. (B) Relationship between step length and step number for a single PD – FOG participant in the SL25 condition. (C) Relationship between step length and step number for a single control participant in the SL25 condition.

the PD+FOG group (Fig. 2A), PD – FOG group (Fig. 2B) and control group (Fig. 2C).

Figure 2A shows the participant with PD+FOG had a negative slope within each walking trial, indicating the presence of the sequence effect. Figure 2B and C demonstrate the PD – FOG participant and the control participant were able to maintain a stable step length.

Analysis of slopes (β) in preferred condition for PD+FOG group and its relation to freezing of gait episodes

To address the hypothesis that the negativity of the sequence effect (β) could predict freezing episodes, the preferred and SL25 conditions were compared for the presence of FOG, as most of the freezing episodes occurred in the SL25 condition. The SL100, SL75 and SL50 conditions were not included in the subsequent analysis as the majority of PD+FOG participants did

not exhibit FOG in these conditions. There was a significant negative relationship between the number of freezing episodes and the preferred average slope [$r(13) = -0.85$, $P < 0.01$], indicating the number of episodes increased as the β -value of the slope in the preferred walking trials decreased (i.e. were negative) (Table 5).

Further correlation analyses were conducted comparing the total number of FOG episodes with clinical measures (H&Y, UPDRS III, MMSE, GDS and FOG-Q). It was found that freezing in SL25 correlated strongly with duration of disease ($r = -0.82$, $P < 0.01$). The remainder of the results demonstrated that the number of freezing episodes did not correlate significantly with H&Y, UPDRS III motor scores, FOG-Q, MMSE or GDS scores.

Discussion

This study examined the hypothesis that FOG during walking, in people with Parkinson's disease, is dependent upon both the

Table 4 Summary of average slope (β) values for the three groups across conditions for each group

Group	Mean β -value (SD)				
	Condition				
	Preferred	SL100	SL75	SL50	SL25
PD + FOG ($n = 15$)	−0.41 (0.41)	−0.63 (0.46)	−0.36 (0.29)**	−0.18 (0.33)**	−0.17 (0.28)**
PD − FOG ($n = 10$)	−0.13 (0.18)	−0.40 (0.33)	−0.07 (0.22)	0.19 (0.23)	0.07 (0.10)
Control ($n = 10$)	−0.28 (0.36)	−0.30 (0.13)	0.02 (0.16)	0.09 (0.16)	0.03 (0.08)

SL = Step length.

**Significant < 0.01

Table 5 Summary of β -values for PD + FOG group and significance in preferred condition and associated freezing episodes

Participant (PD + FOG)	Walks in preferred condition Slope (β)				FOG in preferred	FOG in SL25
	1	2	3	4		
1	−0.81**	−0.86**	−0.84**	0.62*		
2	0.10	−0.79**	−0.77**	−0.78**	•	•
3	−0.32*	−0.40	−0.16	−0.33	•	•
4	−0.04	−0.70**	−0.49	−0.09		
5	−0.83**	−0.52*	−0.88**	−0.80**	•	•
6	−0.62*	0.06	0.06	−0.32		
7	−0.74**	−0.52**	−0.81	–	•	•
8	0.23	−0.20	0.10	−0.09		•
9	−0.57*	−0.32	−0.02	−0.51		•
10	−0.13	−0.37	−0.11	−0.19		
11	−0.37*	−0.59**	−0.36	−0.31	•	•
12	−0.04	−0.33	0.07	0.10		
13	0.21	−0.27	−0.07	0.16		•
14	−0.57**	−0.46	−0.74**	−0.54**	•	•
15	−0.80**	−0.45*	−0.70**	−0.42	•	•
16	−0.44	−0.81	−0.77**	−0.16		•

Dash indicates data not obtained.

SL = Step Length; • = FOG exhibited.

*Significant < 0.05; **Significant < 0.01.

presence of the sequence effect and an adequately reduced step length to enable the step to step reduction of the sequence effect to lead to a motor block. Step length was artificially reduced and the number of motor blocks increased dramatically from the 50% normalized step length reduction to the 25% normalized step length reduction. These motor blocks occurred only in the PD + FOG group who demonstrated a significant sequence effect as measured by β -values on regression analysis. The other groups (PD − FOG and control) failed to demonstrate any motor blocks in any of the conditions and had insignificant β -values on regression analysis. These results confirm our hypothesis and provide an explanation for FOG that has previously been a difficult clinical phenomenon to elucidate.

The results also strengthened previous findings which showed a reduction in step length as a contributing factor to FOG (Nieuwboer *et al.*, 2001; Iansek *et al.*, 2006). The majority of participants in the PD + FOG group were observed to freeze when their step length was reduced in the SL25 normalized condition. As noted earlier, all of the participants who experienced freezing in the preferred condition continued to freeze when

placed in the SL25 normalized condition. For those PD + FOG individuals that did not freeze in the preferred walking trials, FOG could be induced by reducing their step length. This finding suggests that when the step length is artificially reduced, the same effects are observed as when there is an automatic reduction in step length during normal walking in a variable environment requiring different amounts of conscious attention.

The sequence effect seen in the PD + FOG group is likely to be due to a progressive decrease in step length during walking, which can be represented by a regression slope. When the average slopes were compared across all three groups for each condition, there was a significant difference in the SL75, SL50 and SL25 normalized conditions, with *post hoc* results locating the differences in the PD + FOG group only. There were no significant differences when comparing the PD − FOG and control groups; this lends support to the hypothesis that a predicted slope (sequence effect), will be present only for those that experience FOG during walking. Interestingly, no significant difference between groups was present in the preferred condition; this could be attributed to the variability observed when participants

walk at their normal pace and step length. Within individual regression analyses the slopes in the preferred condition were observed to be highly inconsistent, a feature that was also highlighted by Iansek and colleagues (2006).

In support of the argument that both step length and the sequence effect contribute to freezing, a defining pattern was observed within the PD+FOG group, regarding the size of the slopes leading to a freezing episode. When the slopes of participants who did not freeze were compared to those who had experienced FOG the latter group's slopes tended to be larger, indicating that their steps were becoming smaller and smaller. The contribution of the sequence effect to freezing is further supported by the coefficient of variability results. Participants in the PD+FOG group had greater step length variability in the conditions when freezing episodes were more frequent—preferred, 50% and 25%. The presence of the sequence effect may explain the greater step length variability. Previous research has demonstrated that there is a progressive decrease in the three steps before a freezing episode, (Nieuwboer *et al.*, 2001), indicating a relationship between FOG and a sequence effect. The study by Iansek *et al.* (2006) suggested that the dual causation of hypokinesia and shortening of steps led to the occurrence of FOG during walking, on the basis that the sequence effect was present before the onset of freezing. Therefore, it was anticipated that there would be a relationship between the freezing episodes and the average slopes (β), particularly in the conditions with smaller step lengths. However, this was only shown to be significant in the preferred condition, indicating the presence of multiple contributory factors to FOG (Iansek *et al.*, 2006) that should be explored more thoroughly.

Other possible explanations for FOG include the dysfunctional execution of internally generated motor sequences in gait (Giladi *et al.*, 2001a). These authors thought that freezing was probably related to the reduction in the amplitude of movements (seen in the decreased stride length) as well as a gait disturbance in terms of rhythmic control (Nieuwboer *et al.*, 2001). The theory that rhythmic control may play a role is implicitly supported from research on asymmetric motor function of gait. Plotnik *et al.* (2005) found gait asymmetry in PD+FOG patients, in which the variability in the timing of motor commands differed for each leg. As this was not observed in PD–FOG patients, the authors hypothesized that FOG could be related to asymmetric gait; i.e. when this un-coordination reaches threshold level, gait becomes disarrayed and freezing occurs. This is compatible with our current understanding of the basal ganglia deficit which results in corruption of cues provided to the supplementary motor area, resulting in the step to step amplitude reduction. Such a timing disorder, manifesting in amplitude deregulation, may form an alternative explanation for the findings of Plotnik *et al.* (2005).

The PD+FOG group demonstrated a significantly greater duration of disease, higher FOG-Q scores, UPDRS motor and H&Y scores compared to the PD–FOG group. In concert with the more severe disease, the PD+FOG group had a significantly shorter step length compared to the PD–FOG and control groups. These findings are consistent with previous reports (Nieuwboer *et al.*, 2001). A strong association between FOG and disease progression concurred with previous findings,

although this was not reflected in correlations with H&Y scores. However, when the individual scores of the H&Y stage were compared in the PD+FOG group, it was observed that those who could be classified as severe freezers (those who experienced FOG in preferred and SL25 conditions) were attributed higher H&Y stages. This may suggest that freezing is coincident with disease progression, however, comparison between subgroups of similar disease severity supports the findings that decreased step length, in combination with the sequence effect, provides evidence of a causal relationship with FOG.

The difficulty of evaluating FOG in a test situation is a major obstacle in studying the phenomenon (Schaafsma *et al.*, 2003) and this was demonstrated in the current study; although all participants in the PD+FOG group reported freezing in the FOG-Q, five failed to freeze during the testing session. The participants' desire to perform and the heightened arousal from the test situation could explain this failure of freezing (Nieuwboer *et al.*, 2001; Bricchetto *et al.*, 2006). Another possible explanation is that increased awareness resulted in increased 'background' step length, therefore, decreasing the risk of freezing when the sequence effect was present. It must be noted that attention does not influence the regression slope (Iansek *et al.*, 2006).

The variation in the severity of freezing also remains an issue when attempting to investigate FOG. In the current study, patients were observed blocking so severely that they were unable to continue, thereby minimizing the potential total number of freezing episodes. The difficulty of clinically evaluating FOG results is a reliance upon the subjective answers obtained by the patient through questionnaires, such as the FOG-Q, which has been compared against other dimensions of gait disturbances and found to have predictive validity (Giladi *et al.*, 2005). In the findings of the current study the number of freezing episodes did not correlate with the scores on the FOG-Q. This study focused on the number of freezing episodes and not their duration. The FOG-Q had only one question relating to frequency of freezing and three questions measuring duration. This tool does not measure the same entity as that recorded in this study. Therefore, it is reasonable to expect that the number of FOG episodes did not correlate with the scores on the questionnaire.

Most participants with Parkinson's disease are exposed to some type of technique training to improve their walking and performing everyday tasks, with the primary aim of keeping them mobile (Bloem *et al.*, 2004). People who experience FOG commonly use 'rescue' techniques such as imagery or inverted walking sticks; one theory is that this use of visual information bypasses the basal ganglia and a normal step length is produced. The effectiveness of visual cues was evident in this study, with only one participant experiencing FOG in the SL100 condition. Overall most participants showed a vastly improved gait when visual cues were set for a normal step length.

Although the anatomical basis of FOG is not yet known, it appears that freezing is related to dopamine deficiency, as levodopa therapy does have some effect on alleviating it. Schaafsma and colleagues (2003) found that all subtypes of FOG improved with the application of levodopa, specifically by decreasing the frequency and duration of freezing episodes. The FOG response

to levodopa has been found to correlate highly with overall improvement in gait. The current study did not investigate the effect of medication on freezing, since all Parkinson's disease participants were tested 'off' medication; however it is apparent that the artificial reduction in background stride length is responsible for a motor block during walking if the sequence effect is also present. Medication acts to increase background stride length (Morris *et al.*, 2005) and as such would make the sequence effect less significant with an anticipated reduction in motor blocks. In the current study *almost* no motor blocks occurred in the PD+FOG group at ideal step length demonstrating the dramatic influence of background stride length in alleviation of motor blocks in this condition. By corollary, it can be anticipated that a good response to medication would have a similar effect in motor blocks in PD+FOG.

Several limitations should be acknowledged. A small sample size may account for the non-significant differences in β between groups in the preferred condition, despite the fact that there were prominent visible differences in the slopes. The use of a regression line to measure the sequence effect is difficult as the significance of the slope is greatly affected by the variation in the number of steps taken. To assess this potential affect (in the preferred and SL25 condition) the same number of steps in each group were analysed, with little to no difference on the slope of the sequence effect. Therefore, application of this method appears appropriate. While the groups were evenly matched for age and individual normalized step length was calculated to maintain standardization, there was a considerable difference in the reported disease duration, disease severity, H&Y and GDS scores for participants with Parkinson's disease. However, the results suggest the slopes are independent of these variables which supports the hypothesis that FOG is a result of decreased step length in the presence of the sequence effect.

Although this study only measured FOG during straight line walking in open space, the results may contribute to understanding why people with Parkinson's disease commonly experience freezing when performing dual tasks such as using increased attention to avoid obstacles in confined spaces or turning (Giladi *et al.*, 1992, Schaafsma *et al.*, 2003). It has been reported that step length is reduced during turning, in people with Parkinson's disease, and that this reduction was greater than that shown by young and older healthy adults (Huxham *et al.*, 2008). The present study found that the number of FOG episodes was greatest when step length was reduced which suggests the risk of freezing may increase on turning. Studies have also shown exaggerated amplitude reduction of step length in people with Parkinson's disease during walking and secondary task performance (Rochester *et al.*, 2004). The alteration in step length may be a contributing factor to freezing during everyday tasks which commonly involve dual tasks.

Although participants were encouraged to rest between trials, it is difficult to exclude the factor of fatigue influencing results. This may apply particularly for the severe freezers who experienced a number of FOG episodes, with some displaying up to 10 blocks in one walk. As all participants were tested off medication, considered at their 'worst' state, they became fatigued easily and this possibly affected their walking performance. The possibility

that fatigue played a role in the finding of an increased number of freezing episodes in the SL25 condition was, however, excluded by the randomization of the conditions in a subgroup of six subjects which demonstrated a similar result to the non-randomized design.

Our findings have significant clinical relevance as they support the concept of duality of basal ganglia function and confirm the practicality of the use of motor set mismatch and the sequence effect in examining of motor malfunction in Parkinson's disease. The PD+FOG group walked at a preferred step length very similar to the 50% reduction of ideal step length, a value where the motor blocks became more frequent. This contrasted with the PD-FOG group who walked with a preferred step length between 100% and 75%. Only minor changes in step length would increase the likelihood of motor blocks and such minor changes could be induced by distracted attention, a change in direction, performance of secondary task, impaired cognition or waning of medication effects. Motor blocks did not, however, occur in the PD-FOG group even when the SL was reduced to 25% of the ideal step length. The factors that contributed to a motor block occurred in the PD+FOG group were the sequence effect was combined with a small step length. This reduction of step to step amplitude was associated with the block. The clinical variability of the phenomenon can be explained by the variability of the sequence effect, the preferred step length of the individual, the effect of medication on the background stride length and the capacity of the individual to focus attention on walking. Attention can in turn be distracted by secondary task performance, visual inputs, medication effects on attention span and cognitive decline. Factors which increase preferred step length may equally eliminate FOG and these include focused attention, attentional strategies, medication and visual cues. Only the latter, however, eliminate the sequence effect.

In summary, this study addressed FOG during walking in Parkinson's disease and demonstrated that both a reduced step length and sequence effect may contribute to freezing, although it is not possible to determine the degree to which these induced an effect. Through training PD+FOG participants to walk at smaller step lengths, FOG became more apparent, and this was possibly related to a progressive decrease in their step length. This was only observed in participants who experienced FOG. Overall, these findings support previous research in demonstrating that a reduction in step length is one of the contributing factors to FOG. Rehabilitative techniques should focus on assisting Parkinson's disease patients to concentrate on maintaining step length during walking episodes to prevent gait difficulties.

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