FREEZING OF GAIT IN PARKINSON'S DISEASE: A PERCEPTUAL CAUSE FOR A MOTOR IMPAIRMENT?

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Abstract

While freezing of gait (FOG) is typically considered a motor impairment, the fact that it occurs more frequently in confined spaces suggests that perception of space might contribute to FOG. The present study evaluated how doorway size influenced characteristics of gait that might be indicative of freezing. Changes in spatiotemporal aspects of gait were evaluated while walking through three different sized doorways (narrow (0.675m wide X 2.1m high), normal (0.9m wide X 2.1m high), and wide (1.8m wide X 2.1m high)) in three separate groups: 15 individuals with PD confirmed to be experiencing FOG at the time of test; 16 non-FOG individuals with PD; and 16 healthy age-matched control participants. Results for step length indicated that the FOG group was most affected by the narrow doorway and was the only group whose step length was dependent on upcoming doorway size as indicated by a significant interaction of group by condition [$F(4,88) = 2.73$, $p < 0.034$]. Importantly, the FOG group also displayed increased within-trial variability of step length and step time, which was exaggerated as doorway size decreased [$F(4,88) = 2.99$, $p < 0.023$]. A significant interaction between group and condition for base of support measures indicated that the non-FOG participants were also affected by doorway size (similar to PD FOG), but only in the narrow doorway condition. These results support the notion that some occurrences of freezing may be the result of an underlying perceptual mechanism that interferes with online movement planning.

Abbreviations: PD = Parkinson's disease, FOG = Freezing of gait

Introduction

Although not present in all patients, freezing is perhaps the most debilitating symptom of Parkinson's disease (PD) as it may lead to falls, a decrease in quality of life, and loss of independence (1-3). Nearly one third of PD patients experience some type of freezing episode (4) Freezing of gait (FOG) is characterized by a sudden inability to initiate or continue walking, especially while turning; in stressful time-constrained situations; and upon entrance into and through confined spaces such as doorways (5-9). Increased stride-to-stride variability has recently been identified prior to FOG (compared to PD patients without FOG) during a 20m "stand up and go" walking task (10). Hausdorff et al. demonstrated that the ability to regulate stride-to-stride timing during gait is severely impaired in FOG patients, as compared to other individuals with PD. Hence, analysis of stride-to-stride variability is a useful method of identifying characteristics of gait that are closely linked to freezing. PD patients with FOG also display altered timing, and specifically premature muscle activation and termination patterns prior to a freezing episode, leading to an abnormally long stance phase (11-14). Thus, the evidence for a central timing deficit in PD (15, 16) is growing.

While freezing has been argued to be the result of a motor block (4), recent evidence has suggested other possible factors that may contribute. In their more recent work, Giladi et al. argue that FOG must have a different pathophysiology than typical motor symptoms, since other motor issues are positively influenced by dopaminergic medication, while freezing remains unresponsive (17). While Okuma et al., (6) point out that FOG can be sensitive to medication, most research has supported the notion that FOG is dopa-resistant (9, 18). FOG has also been linked to secondary issues that are common in PD such as anxiety, depression, stress and panic (17, 19-21).

Perception may be the most important alternate mechanisms to consider. While perceptual influences associated with freezing are rarely considered, PD patients are profoundly influenced by awareness of their body (relative to environment) (22). In spatial perception tasks, individuals with PD require a greater number of saccades to create accurate spatial representations (23). While this study concluded that spatial perception is comparable in healthy and PD participants, PD with FOG may be uniquely influenced by space perception.

Importantly, perceptual judgment deficits have been recently identified as a contributing factor to motor impairment in PD (24). Collectively, research suggests that key differences exist in the perceptual processing capabilities of PD patients with FOG specifically, highlighting the potential for a relationship to exist between perception and FOG (25).

Currently, research investigating why freezing occurs while traveling through confined spaces remains incomplete. One possibility is that impaired integration of vision with spatial memory prevents patients with FOG from adapting to confined spaces. In a qualitative study, PD patients reported feeling too large to pass through small spaces, even though they were aware that doorways are designed for human size (26). Lee et al. found that individuals with PD who responded yes to the question "Have you ever had problems walking through narrow spaces?" were also likely to be subject to difficulties with freezing (26). Yet, to our knowledge there is no research quantifying whether an alteration in gait occurs in anticipation of a confined space. By examining changes to

gait prior to a confined space, it may be possible to determine whether a perceptual mechanism might contribute to or trigger FOG.

Thus, the aim of this experiment was to evaluate the effect of doorway size on gait prior to reaching the doorway in two groups of individuals with PD: (i) who experience freezing of gait (PD FOG) and (ii) who experience gait abnormalities but are absent of FOG (PD Non-FOG).

Subjects and methods

Subjects

The study involved 31 participants with PD (15* confirmed to be experiencing FOG at the time of test, 16 absent of FOG) and 16 healthy, age-matched control participants (no significant differences for age, height or symptom severity between groups, for full details of participant characteristics see Table 1) recruited from a database at the Movement Disorders Research and Rehabilitation Centre at Wilfrid Laurier University in Waterloo, Canada. In this database, participants in the PD FOG group were selected based on their self-report of experiencing freezing. Initially, patients would be interviewed by a trained clinician (about their experience of freezing), but only if they had scored a 1 or higher on question 14 of the Unified Parkinson's disease rating scale (UPDRS). This question specifically addresses whether or not freezing was experienced by the participant at the time they enrolled as a research centre participant. Additionally, a trained clinician confirmed the occurrence of freezing in these patients at the time of test (see Procedures below).

All patients that were tested had clinically typical PD as confirmed by diagnosis from at least one movement disorder neurologist, and were known to be responsive to anti-parkinsonian medication. All participants with PD were tested approximately 1 hour after having taken their anti-Parkinson's medication. However, criteria were used to verify that individuals in the FOG group were experiencing episodes of freezing at the time of test (see Procedures below). Participants in the non-FOG PD group scored at least a 1 (out of 4) on the gait portion of the Unified Parkinson's Disease Rating Scale (UPDRS-Motor section III) by a movement disorder specialist and had no self-reported incidents of freezing in their case history. Sixteen healthy control subjects also participated in the study. These individuals were mostly spouses or relatives of the PD participants.

Subjects were excluded from testing if they had a past history of neurological conditions other than PD, or orthopedic or visual disturbances that severely impaired walking ability. Participants were also excluded if they had been previously diagnosed by a neurologist with dementia, had a confirmed score of less than 27 on the Mini Mental State Exam, or had dyskinesias which would alter their gait pattern. Each participant was informed about the requirements of the study and signed institutionally approved consents, according to the declaration of Helsinki (BMJ 1991; 302: 1194).

* Initially, 20 PD patients who had self-reported freezing were recruited for the study. Based on the described screening protocol employed to confirm freezing at the time of test, 5 patients were excluded and are not reported in the current data set.

Table1 Characteristics of the three groups

Group	Age- M (yrs)	Height- M (cm)	UPDRS- M (score)	Years since diagnosed –M (yrs)	Dose of Levodopa - M (mg)	Gender
PD FOG	72.4 +/- 6.79	172.51 +/- 8.51	32.8 +/- 7.34	9.07 +/- 5.29	1013.33 +/- 390.27	13 male, 2 female
PD Non-FOG	72.19 +/- 6.23	170.66 +/- 9.69	28.81 +/- 6.35	5.97 +/- 4.61	725.0 +/- 449.81	10 male, 6 female
HC	70.75 +/- 5.98	167.96 +/- 7.53	n/a	n/a	n/a	6 male, 10 female

Note: M denotes mean

Materials

The room used for data collection was a laboratory containing a metal framed double doorway leading out into an empty hallway. The double doorway acted as the wide doorway condition (i.e. 2 times normal door width), whereas the single doorway was used for the normal doorway condition. A perfectly colour-matched wooden plank was fitted in to the side of the single doorway for the narrow doorway condition. The lighting in both the laboratory and the hallway was maintained at a consistent brightness. Data was collected on a *GAITRite*® carpet (*GAITRite*®, CIR System, Inc., Clifton, NJ, USA) which is 3.96 m long X 0.79 m wide and contains sensors that send information received from the participants' footsteps to an attached computer. A researcher walked alongside (and slightly behind) the participant at all times for safety of the participant during each trial.

Procedure

Pretest Procedure

In addition to the UPDRS assessment of gait (used to confirm the presence of freezing), an additional measure was developed to further establish the experience of freezing at the time of test. Each participant in the PD FOG group performed a modified version (through doorway) of the timed up-and-go test (TUG). This test began with the patient seated in a chair and upon a go signal they proceeded to stand and walk through a doorway to a marker on the ground located three meters from the chair. Once they reached this marker, they turned and proceeded back to the chair to sit down. This was observed by a movement disorder specialist that confirmed the participant was experiencing a sudden inability to initiate or continue walking at some point during the TUG, before continuing to the normal testing procedure. If FOG indicators were absent, the patient was excluded from testing.

Test Procedure

Participants walked the length of the *GAITRite*® carpet that was positioned so that participants would walk through a doorway, in three randomized conditions that were five (blocked) trials each. Each trial commenced with the participant standing with eyes closed, two metres before the start of a *GAITRite*® carpet. This ensured that characteristics of gait initiation were not recorded. Participants were instructed to start walking as soon as they opened their eyes, and walk the length of the *GAITRite*® carpet through the doorway. The three experimental conditions were:

i) Narrow doorway condition in which the participant walked through a smaller than normal (3/4th size) doorway; (0.675m wide X 2.1m high). The wooden plank designed to make the doorway narrow partially overlapped the *GAITRite® carpet in this condition.*
ii) Normal doorway condition acted as the baseline control condition, in which the participant walked through a normal sized doorway (0.9m wide X 2.1m high).
iii) Wide doorway condition in which the participant walked through a double sized doorway (1.8m wide X 2.1m high).

The three conditions in this protocol allowed for the analysis of whether the size of doorway is a contributing factor to the gait alterations and freezing of gait experienced while traveling through confined spaces. Spatiotemporal characteristics of the individuals' gait were analyzed solely preceding the doorway in order to determine the effect of the doorway on gait leading up to the narrowed space. This allowed for the analysis of anywhere from four to seven steps depending on the participants step length. Any foot falls at, or after the doorway were excluded from analysis in this experiment.

Statistical analysis

There were three independent groups in this experiment; individuals with PD experiencing FOG (PD FOG), those with PD experiencing gait abnormalities absent of FOG (PD Non-FOG), and healthy control subjects (Controls). As suggested by Morris et al.,(27) individuals with PD are known to suffer deficits in velocity, step length, step timing and base of support. As such, the primary dependant variables analyzed were gait velocity (cm/s), mean step length (cm) which is equal to the length of a toe off to the opposite foot heel contact, base of support (cm), cadence (steps/min), time spent in double support (s). In addition, Hausdorff et al.(10), have supported the evaluation of step-to-step variability as a precursor of FOG. Hence, two measures of step-to-step variability were calculated for each of the spatiotemporal measures: (i) within-trial standard deviation around each individual participant's mean value for a trial was averaged across participants in a given group, and (ii) the coefficient of variation (CV) within a trial was calculated based on standard deviation (see (i)) divided by the average value for a given trial, in order to account for variability normalized to the mean. Left and right steps were pooled and results were analyzed by the STATISTICA computerized statistical package using a mixed model 3 groups X 3 conditions X 5 trials ANOVA. In order to determine where the significant differences found in the ANOVA's occurred, Tukey's Honest Significant Difference (HSD) post hoc procedure was employed.

Role of the funding source

The funding source behind this research did not have any involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

Results

Participant demographics

To determine whether significant differences existed between the three groups, an ANOVA was performed and found no significant differences between the groups age or

height. A t-test was also performed and found no significant differences between the PD FOG and PD non-FOG group in regards to their years since diagnosed or the amount of levodopa they were taking. There was also no significant difference found with regards to disease progression as indicated by their UDPRS score..

Gait velocity

Individuals who experience FOG were found to walk significantly slower (85.5 +/- 30.0 cm/s) on average as compared to the PD non-FOG (107.3 +/- 18.8 cm/s) and Control (119.3 +/- 12.81 cm/s) groups, as demonstrated by a main effect of group [$F(2,44) = 10.90$, $p < 0.001$). Post hoc analysis confirmed that the PD FOG group walked at a significantly slower velocity as compared to both the PD non-FOG group (20.3% decrease, $p = 0.012$) and Controls (28.3 % decrease, $p < 0.001$). There was no significant interaction of velocity observed with condition. An interaction was identified between group and trial [$F(8,176) = 2.36$, $p < 0.0195$]. This interaction demonstrated that the PD FOG group was the only group to experience a reduced velocity in their first encounter with the doorway. Neither the PD non-FOG nor HC groups altered their velocity through the trials.

Step length

It was also observed that the PD FOG group had a significantly smaller step length (45.9 +/- 13.9 cm) as compared to both the PD non-FOG group (56.6 +/- 7.4 cm) and Controls (63.9 +/- 6.8 cm). This was evident from the observed main effect of group [$F(2,44) = 13.11$, $p < 0.001$]. Post hoc analysis confirmed that the PD FOG group had a significantly smaller step length than the PD non-FOG group ($p < 0.011$) as well as Controls ($p < 0.001$). The PD non-FOG group did not differ significantly from Controls.

More importantly, a significant interaction of step length was found when comparing group and condition [$F(4,88) = 2.73$, $p < 0.034$] (Fig. 1). The Narrow doorway significantly decreased the step length of the PD FOG group, while the other two groups were not affected. This was confirmed through post hoc analysis in which the narrow doorway caused the PD FOG group to shorten their steps (42.5 +/- 15.4 cm) as compared to the normal doorway (46.4 +/- 13.9 cm) by 8.4% ($p < 0.005$) and wide doorway (48.7 +/- 13.5 cm) by 12.7% ($p < 0.001$).

An interaction was identified between group and trial when examining step length [$F(8,176) = 6.08$, $p < 0.001$]. The PD FOG group demonstrated a significantly smaller step length in their first encounter with the doorway (43.4 +/- 15.5 cm) as compared to the other trials ($p < 0.029$). Neither the PD non-FOG nor the Control group altered their step length with respect to trial.

Insert Figure 1 about here

Base of support

A significant interaction of group and condition was found when analyzing base of support [$F(4,88) = 3.96$, $p < 0.053$] (Fig. 2). Base of support did not significantly change with condition in either the PD FOG or Control groups. Also, it was found that the PD FOG group had a significantly larger base of support (on average 29.6% larger) as

compared to Controls ($p < 0.001$) across all conditions. The PD FOG groups' base of support was found to be consistently the widest and the Controls the narrowest. In the wide doorway condition, individuals in the PD non-FOG group were found to behave like Controls, with both of these groups revealing a significantly smaller base of support when compared to the PD FOG group ($p < 0.001$). In the normal doorway the PD non-FOG differed from both groups, with a significantly smaller base of support than the PD FOG group ($p < 0.001$) and a wider base of support than the Control group ($p < 0.004$). Interestingly, when confronted with the narrow doorway condition, the PD non-FOG groups' behaved similar to the PD FOG group and only differed from the control group, who continued to display the narrowest base of support ($p < 0.001$). Solely the PD non-FOG group altered the size of their base of support with respect to doorway as they exhibited a wider base of support when approaching the narrow doorway (19.6 +/- 6.9 cm) as compared to the wide doorway (17.3 +/- 7.7 cm, $p < 0.035$).

Insert Figure 2 about here

Step length variability

When comparing groups for within-trial step length variability, a main effect was found [$F(2,44) = 7.79$, $p < 0.002$]. Post hoc analysis confirmed that the PD FOG group (2.9 +/- 1.5 cm) had significantly greater step length variability as compared to both the PD non-FOG group (1.6 +/- 0.9 cm, $p < 0.004$) and Controls (1.0 +/- 0.5 cm, $p < 0.001$). A significant interaction was also identified between group and condition [$F(4,88) = 2.99$, $p < 0.023$] (Fig.3). The PD FOG group was the only group found to exhibit an increased step length variability in the narrow (3.2 +/- 1.8 cm, $p < 0.001$) and the normal (3.0 +/- 1.8 cm, $p < 0.091$) doorway as compared to the wide (2.4 +/- 1.2 cm,) doorway condition. Neither the PD non-FOG group nor Control group demonstrated a change in step length variability as a result of doorway condition.

In order to normalize against mean values, the CV of step length was analyzed revealing a significant group vs. condition interaction [$F(4,88) = 2.85$, $p < 0.029$] (Fig.4). Solely the PD FOG group was affected by the size of doorway, as they experienced a higher CV with regards to step length in the narrow doorway (0.118, +/- 0.129) as compared to the wide doorway (0.06 +/- 0.048, $p < 0.004$).

Insert Figure 3 about here

Insert Figure 4 about here

Step duration

Without the data being normalized, there were no significant group, condition nor trial effects with regards to step duration. However, the CV of step duration was analyzed and revealed a main effect of group. The PD FOG group was found to have a significantly higher CV (0.085 +/- 0.088) as compared to both the PD non-FOG (0.031

+/- 0.02, $p < 0.015$) and Controls (0.018 +/- 0.007, $p < 0.002$) groups [$F(2,44) = 7.45$, $p < 0.002$]. Also a trend reaching significance was found between group and condition indicating that the PD FOG group were the only participants affected by doorway size (with respect to CV of step duration)

Discussion

The primary objective of the current study was to evaluate the influence of space perception on gait in individuals with PD who experience FOG, other PD patients (absent of FOG), and healthy age matched participants. Freezing is extremely difficult to draw out in experimental settings (28), as was also the case during the current experiment which has been suggested to be caused by a heightened attention due to participation in an experiment (9). However, several studies have shown decreased stride length and increased gait timing variability prior to a freezing episode (10). Therefore, in spite of a lack of actual freezing episodes, the obtained results demonstrate that an upcoming confined space has a profound effect on gait in patients experiencing FOG. Overall, gait of the FOG participants was significantly more variable when compared to the other groups (as demonstrated by CV data for step length and step duration), which is in agreement with previous research demonstrating an increase in gait variability prior to a freeze (10). Perhaps important to note, is that these indicators of freezing are occurring well before arrival at the actual doorway, suggesting that online perceptual processes must be interrupting the initial movement plan to pass through the doorway. Thus, impaired perceptual ability may be an important factor contributing to freezing in PD.

This is the first study to demonstrate that while approaching a narrow doorway; freezers already exhibit alterations to gait (shortened step length, increased gait variability, increased base of support) that are indicative of an upcoming freezing episode. These changes were not evident in non-FOG individuals with PD, or healthy participants. In fact, non-FOG showed a constant deficit in step length (compared to healthy), regardless of doorway size. Our results are in direct contrast to Van Wegen et al who demonstrated that small spaces presented in the form of a virtual corridor had no effect on gait in PD (28). A group by trial interaction reaffirms that the PD FOG group were most affected (in terms of step length and velocity) upon their first encounter with the doorway, whereas the other two groups were unaffected by trial. This may suggest that experience (i.e. practice) helps PD patients improve their spatial perception to confirm a door size, although heightened anxiety level (in a group of patients that are prone to falling) during the first encounter with the narrow cannot be ruled out. Therefore, perceptual judgment of the upcoming doorway, and thus a certain degree of visuospatial ability appears to be more greatly affected in PD patients who experience freezing.

Base of support is generally considered to be a measure of stability, and hence we hypothesized that the PD FOG group might attempt to maximize stability, by increasing base of support in the narrow doorway condition. However, the PD FOG group showed a consistent increase in base of support, that was not significantly influenced by doorway size. Since freezers are substantially more unstable, they may adopt a wide base of support regardless of environmental context. Interestingly, the PD non-FOG group altered their base of support only in anticipation of the narrow doorway (similar to freezers), yet were not affected by the other doorways. In contrast, healthy control

participants have a high level of stability, and hence maintained a normal (and narrower) base of support regardless of condition (compared to both PD groups).

In accordance with Hausdorff et al. (10, 29), the current study found increased within-trial step length and step duration variability in only the FOG group, and this was more profound in the narrow doorway specifically. It should be noted that they were the only group to demonstrate this effect, providing additional support to the hypothesis that perceptual impairments primarily affect individuals with freezing. The increased step length variability is indicative of an unstable gait pattern that may be reflective of an attempt to voluntarily control gait, possibly by increasing the sampling of proprioceptive feedback (16). Freezers were unable to maintain a normal stride, and instead more frequently altered their step length, potentially leading to an increased risk of falling (30). As suggested by Iansek et al (31), the fact that a decreased step length (accompanied by increased variability) can be identified prior to the narrow doorway suggests that attentional or perceptual mechanisms (i.e. involved in processing characteristics of the door) contribute to the occurrence of a freezing episode.

Although perception was not directly evaluated, our work has provided a glimpse of the impact that perceptual mechanisms may have on severe gait deficits such as freezing. Changes in step length, base of support, and within-trial step length and step duration variability all support the notion that patients with FOG alter their gait in response to how they perceive environmental contexts. This may be important to consider since the observed changes in gait can be predictive of an upcoming freezing episode (10, 12). PD patients without FOG were also found to be affected by narrow doorways, suggesting that increased perceptual constraints may lead to gait alterations even in non-freezers. Individuals with PD appear to be unable to accurately evaluate self-motion in relation to upcoming obstacles (22). This may be an important perceptual factor to consider for other situations such as entering an elevator or any other situation in which patients may be approaching confined or crowded spaces. We recognize that there are certain situations which elicit FOG (i.e. turning) that may not be related to perception. Suggestive mechanisms for freezing during turning include asymmetrical gait (32).

As previously mentioned, freezing is extremely difficult to draw out in laboratory settings, thus it is important to consider whether patients categorized as non-freezers may have had the experience of FOG within their own home environment. In the case of the current study, categorization into the non-FOG group was confirmed by a clinician, in addition to self-report (of experience at home), UPDRS (Q. 14) and our modified TUG test. While the possibility exists that the non-FOG patients might progress into FOG, it is unlikely that they would be experiencing any sort of FOG at the present time.

Individuals with PD were tested while “on” dopaminergic medication which is a potential limitation of this study, although it is has been shown that freezing is poorly affected by medication (17). Testing was conducted solely in the “on” state of PD in order to get a true understanding of the perceptual mechanisms that may commonly occur while patients are medicated (as in everyday situations). Future studies might include the testing of individuals with FOG while “off” medication in order to obtain a clearer understanding of basal ganglia contribution to freezing. The use of an eye tracking device in future research could be useful in order to monitor participants gaze directions while approaching the doorway. Future research also should focus on underlying perceptual mechanisms that may be prevalent in FOG (and more generally in PD), in

order to better understand the causes of freezing. Taking these perceptual mechanisms into consideration will be important for the development of effective treatment strategies to combat freezing.

Conflicts of Interest

The authors' of this article state that there are no conflicts of interest with regards to this research.

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Licensing

Figure Captions

Figure 1 Changes in step length over the three conditions in the PD FOG group, PD Non-FOG group, and Controls

Figure 2 Base of support alterations across condition

Figure 3 PD FOG group displays increased step length variability in Narrow condition

Figure 4 Step length coefficient of variation over the three conditions in the PD FOG, PD Non-FOG, and Control groups

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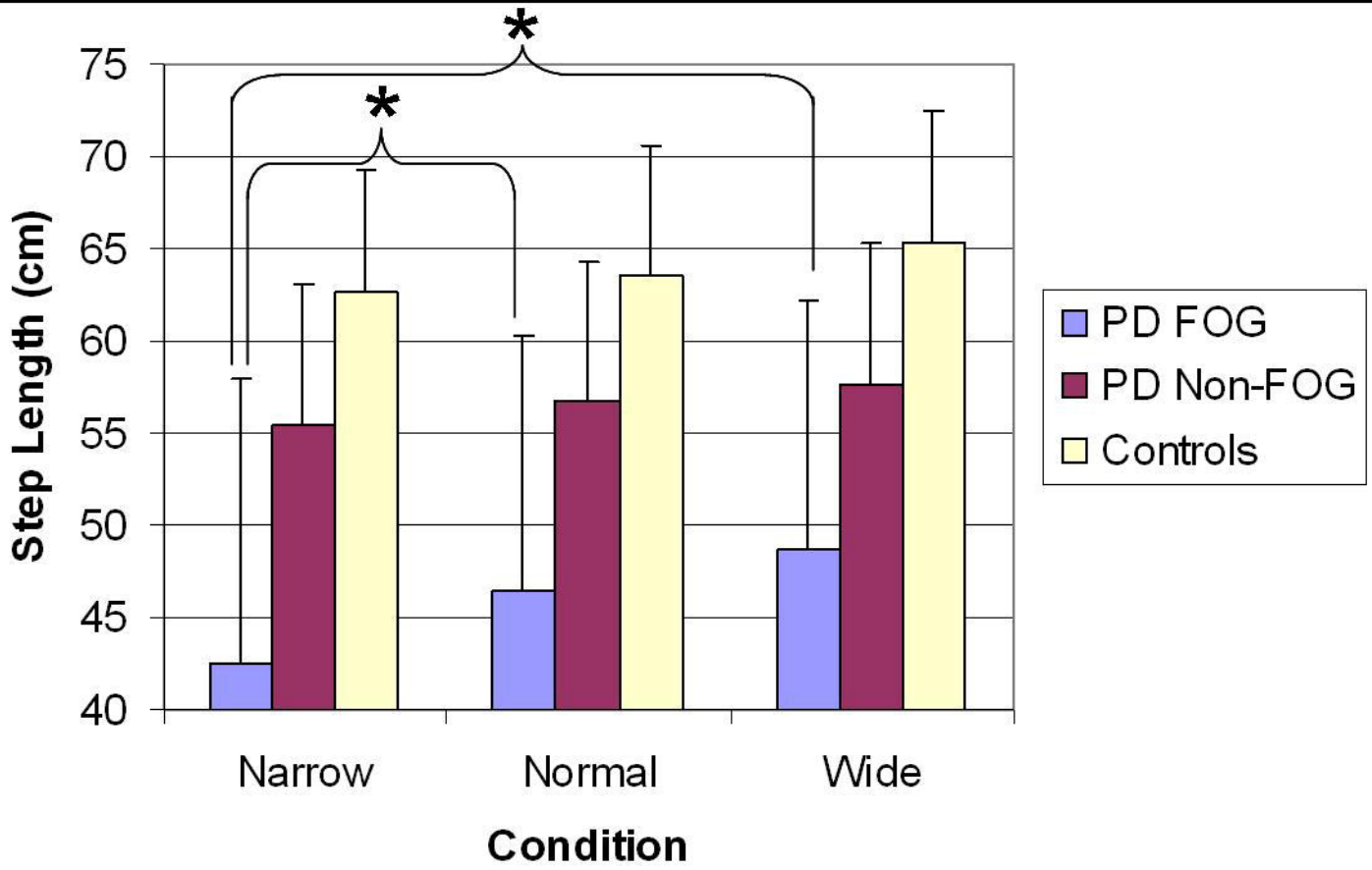
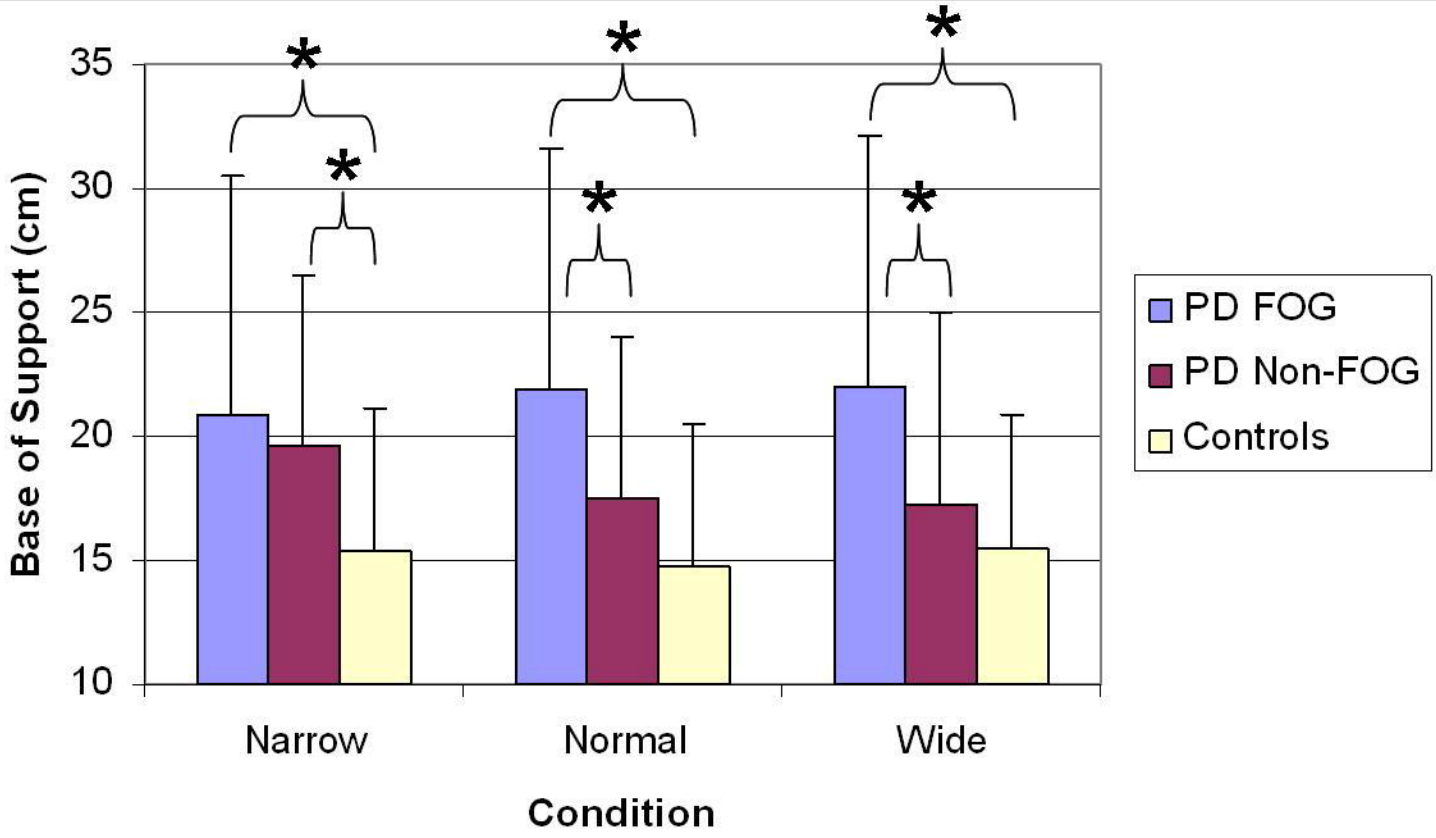
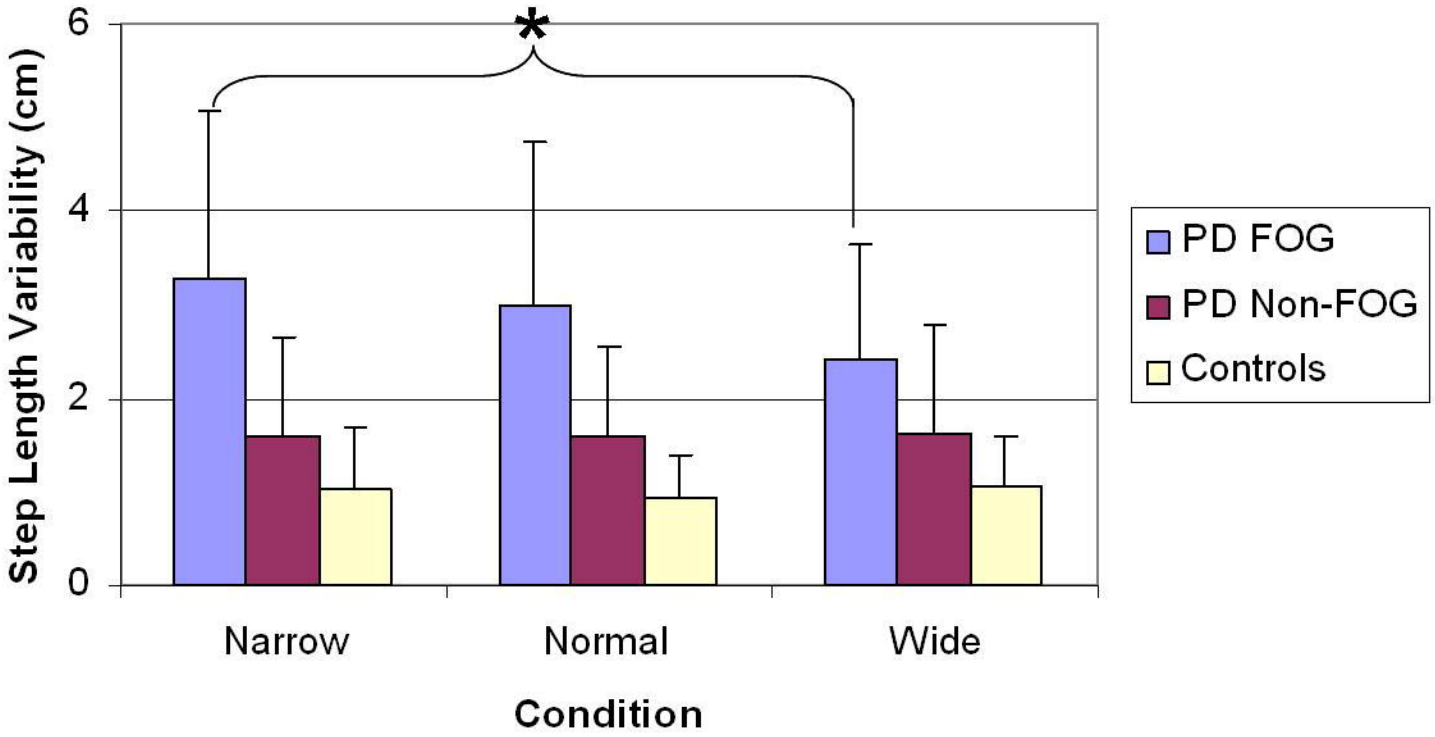
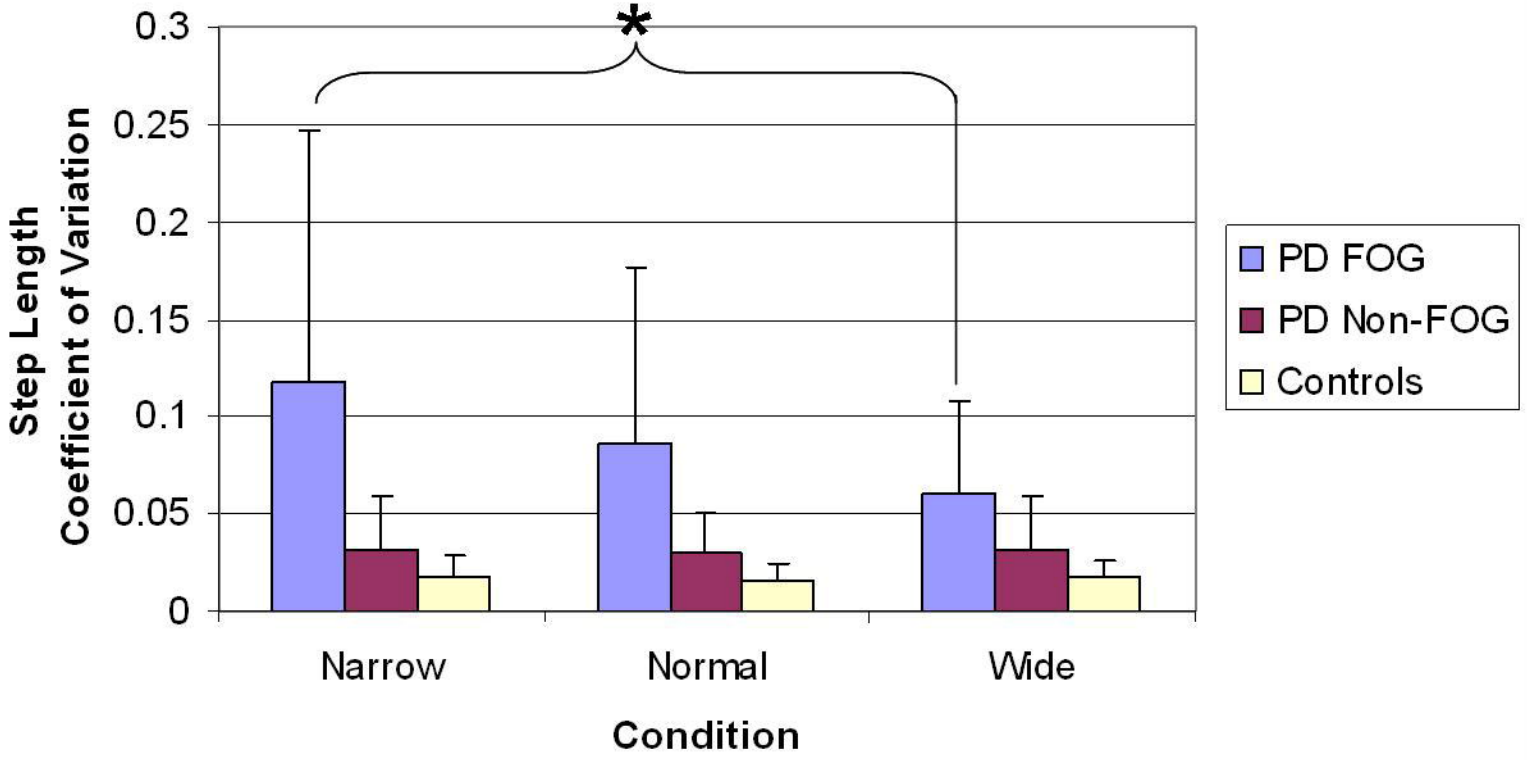

*
*
75
70
65
60
55
50
45
40
Step Length (cm)
Narrow
Normal
Wide
Condition
PD FOG
PD Non-FOG
Controls


35
30
25
20
15
10
Base of Support (cm)
*
*
*
*
*
*
Narrow
Normal
Wide
Condition
PD FOG
PD Non-FOG
Controls


Step Length Variability (cm)
6
4
2
0
*
Narrow
Normal
Wide
Condition
PD FOG
PD Non-FOG
Controls


*
0.3
0.25
0.2
0.15
0.1
0.05
0
Step Length
Coefficient of Variation
Narrow
Normal
Wide
Condition
PD FOG
PD Non-FOG
Controls