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Postural control and freezing of gait in Parkinson's disease

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1. Introduction

Freezing of gait (FOG) in Parkinson's disease (PD) is defined as a “brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk” [1]. The pathophysiology of FOG is not yet fully understood and several

hypotheses about the potential mechanisms behind the symptom exist (for review see Ref. [2]). Postural control is required during gait initiation when the center of mass is shifted on one leg while the other leg initiates the first step. During walking or turning dynamic postural control is involved, especially when turns are performed with a small radius and gait becomes less regular [3]. The relationship between postural control and FOG is not yet assessed in detail.

When analyzing static postural control previous studies have shown that during quiet stance patients with FOG (PD+FOG) do not differ in the average center of pressure (COP) excursion, COP velocity and sway regularity in comparison to patients without FOG (PD-FOG) [4,5]. However, the study conducted by Nantel et al. [5] found a significant correlation between the severity of FOG and average anterior–posterior (AP) COP excursion and medio-lateral COP velocity. The results of both studies have to be interpreted

List of abbreviations: AP, anterior–posterior; CI, confidence interval; EC, eyes closed; FAB, Fullerton Advanced Balance; FOG, freezing of gait; FOGQ, Freezing of Gait Questionnaire; HC, healthy control; H&Y, Hoehn and Yahr; LOS, limits of stability; ML, medio-lateral; PD, Parkinson's disease; PD+FOG, patients with FOG; PD-FOG, patients without FOG; RMS, root mean square; SEn, sample entropy; SI, symmetry index; UPDRS, Unified Parkinson's Disease Rating Scale.

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with caution, as PD+FOG and PD-FOG significantly differed concerning disease duration and disease severity [4,5]. It has been shown that PD+FOG have reduced directional control during voluntary weight shifting [6].

With respect to reactive postural control evidence exist that PD+FOG perform significantly worse in the pull test in comparison to PD-FOG [7]. Smulders et al. [8] analyzed compensatory stepping responses during backward perturbations and showed that PD+FOG have smaller step lengths in comparison to PD-FOG whereas PD+FOG do not differ concerning onset and number of steps. PD+FOG have no deficits in shifting between different postural control sets [8] and postural strategies during sensory manipulations do not differ compared to PD-FOG [6]. As gait asymmetry is related to FOG [9], one study analyzed asymmetry in postural control during stance perturbations but no relationship to FOG was found [10]. It has been shown that the overall balance performance is reduced in PD+FOG compared to PD-FOG [11].

When analyzing gait initiation it has been shown that anticipatory postural adjustments are not different between PD+FOG and healthy control (HC) [12]. Proprioceptive deficits may be one reason why PD+FOG differ in some aspects of postural control in comparison to PD-FOG [13]. It is suggested that FOG and postural instability underlie different pathophysiological mechanisms [14].

Taken together the current literature indicates that PD+FOG differ in some but not all aspects of postural control. Insufficient sample sizes and the lack of age-, disease duration- and disease severity matched groups of some of these studies make it difficult to clearly characterize postural control deficits of PD+FOG.

Postural control is multidimensional and involves static/dynamic and feedforward/feedback processes. The aim of the present descriptive study was to clarify in an explorative approach if and which postural control deficits exist in PD+FOG in comparison to PD-FOG and HC. First, we used a multidimensional clinical balance scale to analyze whether PD+FOG are postural instable in comparison to PD-FOG and HC. We consider clinical balance scales as useful tools to assess overall balance performance as they are able to reflect various dimensions of postural control. Furthermore, by analyzing subitems of the scale we wanted to describe postural control deficits in more detail. To our best knowledge this is the first study using the subitems of a multidimensional clinical balance scale to characterize postural control in PD+FOG in detail. Second, COP measurements were conducted during quiet stance and during maximal voluntary forward and backward leaning. Specifically, beside other COP based outcomes we wanted to analyze the average anterior–posterior COP position during quiet stance and no other study focused on that aspect before. We anticipated that start hesitation may be related to an altered stance position in PD+FOG. Furthermore we aimed to assess postural asymmetry during quiet stance and during maximal forward and backward leaning to see if there is any relationship to FOG.

2. Methods

2.1. Participants

31 PD+FOG, 27 PD-FOG and 22 HC participated in this study. Patients were recruited from the Neurology Department University Hospital Schleswig–Holstein and from the PD support group, Kiel, Germany. The patients' spouses served as healthy control. Evaluations were performed between February 2012 and December 2014. PD patients were diagnosed according Brain Bank Criteria for PD and were classified to be PD+FOG if they scored ≥ 1 point on question three of the Freezing of Gait Questionnaire (FOGQ) [15]. FOG and its subtypes were carefully explained and demonstrated by the examiner before completing the FOGQ. Participants were

encouraged to have another person present to add detail or to confirm the patient's statement. The following exclusion criteria were applied: any other neurological disorders other than PD, deep brain stimulation (PD patients only). PD groups were well balanced for disease duration and motor symptom severity, and all groups were fairly balanced for age. Disease severity was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part 3 and the Hoehn & Yahr (H&Y) scale. The study protocol was approved by the local ethics committee and all participants gave written informed consent prior to participating.

2.2. Testing procedure

Patients were assessed in the ON state of medication. Postural control was assessed as follows:

- (1) The Fullerton Advanced Balance (FAB) scale was performed to assess postural control with a clinical balance scale [16]. The FAB scale is a 10-item test instrument with a 5-point ordinal scale for each item (0–4 points) and a maximal score of 40 points (higher values indicate better performance). The FAB scale is validated for individuals with PD demonstrating excellent interrater and test-retest reliability [17].
- (2) Center of pressure (COP) displacements of postural sway was measured using a Zebris FDM-S force measuring plate (Zebris Medical GmbH, Isny, Germany) with a 100 Hz sampling frequency. The COP is the location of the vertical ground reaction vector on the surface on which the subject stands. Subjects stood barefoot on the plate with their hands on the hip and were instructed to look straight ahead on a white wall. All participants placed their feet with standardized heel-to-heel distance (11 cm) on the same position of the plate using a positioning device which was eliminated before starting the measurement [18]. The analysis consisted of two parts: The first 30 s participants were instructed to stand normal. Thereafter, subjects were required to lean as far forward and as far backward as possible without moving the feet or bending at the hips. Subjects had to hold their limits of stability (forward and backward) for 5 s, respectively. The participants had two attempts at the test, and the trial with the greater limit of stability (LOS) was considered for further analysis.

In order to let the subjects perform each test under the same physical conditions, a seated rest was proposed by the assessor several times. If the assessor gained the impression that a participant suffered from fatigue, a seated rest was given.

2.3. Data analysis

COP data were filtered using a second-order low-pass Butterworth filter (cutoff frequency 10 Hz). Due to the use of the filter, 2915 data points of the first 30 s recording remained to calculate the following variables: (1) average anterior–posterior (AP) COP position expressed as percentage of foot lengths; (2) root mean square (RMS) distance relative to the mean COP position to quantify the magnitude of COP displacements; (3) mean COP velocity and (4) sample entropy (SEn).

We are using SEn to exam the degree of irregularity of postural sway. When the signal is not changing strongly, SEn is lower; if it is irregular, SEn is higher. We proceed SEn refer to the algorithms of Richman [19] as follows:

$$SEn(m, r, N) = -\ln \frac{A^m(r)}{B^m(r)} \quad (1)$$

N presents the input signal in the form of a time series with N data points. m is the length of sequences to be compared, and r is the tolerance.

We set $B = \{(N - m - 1)(N - m) / 2\} B^m(r)$ and $A = \{(N - m - 1)(N - m) / 2\} A^m(r)$, where B is the total number of template matches of template length m and A is the total number of forward matches of template length $m + 1$, and then SEn can be expressed as $-\ln(A/B)$. We have used $m = 2$ and $r = 0.2$.

To analyze the limits of stability, the distance between maximal anterior and minimal posterior COP displacements was calculated and normalized to foot length (LOS peak distance). Additionally, the average COP position during maximal forward/backward leaning was calculated over a time period of 4 s, respectively and expressed as percentage of foot length (LOS average distance).

Postural asymmetry was analyzed in a subgroup of 64 subjects (22 PD+FOG, 20 PD-FOG and 22 HC) by computing the following COP variables for the left and right foot separately: average AP COP position, RMS distance, mean COP velocity, LOS average distance and amount of force (N) resulting on the ground. The absolute symmetry index (SI) was calculated for each of these variables with the following equation [20]:

$$SI = \frac{|V_{left} - V_{right}|}{\frac{1}{2} \times (V_{left} + V_{right})} \times 100 \quad (2)$$

V_{left} and V_{right} represent the variable of the left and right foot. A SI of 0 indicates perfect symmetry.

2.4. Statistical analysis

For statistical analysis SPSS (version 19.0) was used. The variables were tested for normality (Shapiro–Wilk-Test) and equality of variance (Levene-Test). In the case that normality and equality of variance were ensured, a one-way ANOVA was used to compare the differences between the three groups and an independent sample Student's T-Test was conducted to compare two groups. If normality and equality of variance were not assured, a Kruskal–Wallis-H-Test was used to compare the differences between three groups and an independent sample Mann–Whitney-U-Test was performed to analyze two groups.

Within the PD patients, the relationship between FOG and postural control was assessed calculating Spearman's Rho correlation statistics between the severity of FOG (FOGQ total score) and balance related measures.

The pre-defined level of significance was set at $p < 0.05$.

3. Results

Table 1 shows the participants' characteristics. The groups did not differ in age ($p = 0.051$). PD+FOG and PD-FOG had similar disease duration ($p = 0.264$) and disease severity (H&Y: $p = 0.204$; UPDRS part 3: $p = 0.374$). A significant difference was found in the distribution of gender ($p = 0.041$). A comparison between female and male subjects was performed for each group and no significant difference was found for any outcome (see Supplemental Material online for details).

The three groups significantly differed in the FAB scale total score ($p < 0.001$) and in all subitems of the FAB scale except item 1 ($p < 0.05$) (Table 2). Comparing the groups of PD+FOG and PD-FOG resulted in a significant worse performance of the patients with FOG at the FAB scale total score ($p = 0.005$) and at the subitem

“functional reach test” (item 2, $p = 0.01$) and the subitem “standing on foam with eyes closed” (item 7, $p = 0.009$). HC subjects significantly performed better in comparison to PD-FOG in all subitems except item 1 (“standing with feet together eyes closed”).

With respect to the COP analysis, PD+FOG, PD-FOG and HC differed significantly in all variables ($p < 0.05$) (Table 2). During quiet stance, the average anterior–posterior COP position was significantly shifted towards posterior orientation when comparing PD+FOG and PD-FOG ($p = 0.031$) as well as when comparing PD-FOG and HC ($p = 0.025$) (Fig. 1). PD+FOG had significantly reduced LOS peak distances ($p = 0.032$) and showed significantly less ability to voluntarily lean forward as expressed by the LOS average anterior COP displacement ($p = 0.04$) when compared to PD-FOG. PD-FOG and HC significantly differed in any COP outcome variable ($p < 0.05$).

Within the PD patients significant correlations were found between the severity of FOG and the FAB scale total score, subitem “functional reach test” (item 2), subitem “stepping over a bench” (item 4), subitem “standing on foam eyes closed” (item 7), subitem “reactive postural control” (item 10), average anterior–posterior COP position and LOS average anterior COP displacement ($p < 0.05$) (Table 3) (see Supplemental Material online for subitems of the FOGQ).

For the subgroup of participants analyzed for postural asymmetry no significant differences were found between the groups concerning age and disease severity. The three groups did not differ significantly in the symmetry indices of any variable. The degree of asymmetry did not correlate with the degree of FOG (see Supplemental Material online for details of the participant characteristics and results of the subgroup analysis).

4. Discussion

This study shows that PD+FOG have impaired postural control in comparison to PD-FOG and HC as measured with a multidimensional clinical balance scale. PD+FOG not only suffer from FOG but also have postural control deficits and the level of postural instability correlates with the severity of FOG. Both symptoms are two independent risk factors for falls [21] and may explain the high fall rates of PD+FOG [22]. The average score of 21.8 points of PD+FOG at the FAB scale is clearly below the cut off score of 27 points, indicating a high risk for future falls in PD [23]. Analyzing the subitems of the FAB scale revealed that PD+FOG especially perform worse in “functional reach” and “standing on foam with eyes closed” in comparison to PD-FOG. Notably, PD+FOG did not differ from PD-FOG in turning, standing on one leg or tandem walk. Controlled lateral weight shift from one leg to the other as required during these items does not seem to be impaired in PD+FOG. Given the fact, that PD groups and HC are well balanced for demographic characteristics, symptom severity and disease duration, these results reflect the impact of FOG on postural control rather than other clinical signs or symptoms.

This is the first study analyzing the relationship of the average anterior–posterior COP position with respect to foot length and FOG. Our results show that the COP of PD+FOG is significantly displaced towards a posterior orientation in comparison to PD-FOG. The average AP COP position correlates with the severity of FOG indicating that the more the patients exhibit FOG, the more the patients shift their center of gravity towards the heels during stance. Furthermore we found that PD+FOG have a reduced ability to voluntarily lean forward in comparison to PD-FOG as measured clinically by the FAB scale subitem “functional reach test” and by the COP analysis. The inability to voluntarily lean forward significantly correlated with the severity of FOG. Taken together our results show that PD+FOG have an impaired capacity to control the

Table 1
Participant characteristics (n = 80).

	PD+FOG (n = 31)	PD-FOG (n = 27)	HC (n = 22)	p-Value
Age (y)	72.8 (7.7)	72.9 (8.8)	69.1 (5.6)	0.051
Gender (M/F)	22/9	14/13	8/14	0.041 [#]
BMI (kg/m ²)	26.1 (5.2)	26.0 (3.9)	24.9 (2.9)	0.688
Disease duration (y)	9.1 (5.3)	8.1 (6.2)	—	0.264
H&Y stage	2.7 (0.4)	2.6 (0.3)	—	0.204
H&Y stage 2	2	3	—	0.433 [#]
H&Y stage 2.5	14	15	—	0.300 [#]
H&Y stage 3	14	9	—	0.259 [#]
H&Y stage 4	1	0	—	0.534 [#]
UPDRS III	21.3 (8.7)	19.9 (9.5)	—	0.374
FOGQ total score	14.0 (5.0)	3.9 (2.4)	—	<0.001

NOTE. Values are mean (SD) or number of participants; p-value of Kruskal–Wallis-H-Test/Mann–Whitney-U-Test or [#] Chi-Square Test.

Table 2
Results of the Fullerton Advanced Balance scale and COP analysis (n = 80).

	PD+FOG (n = 31)	PD-FOG (n = 27)	HC (n = 22)	p-Value	p-Value PD+FOG vs. PD-FOG	p-Value PD-FOG vs. HC	p-Value PD+FOG vs. HC
FAB scale total score	21.8 (5.8)	25.6 (5.0)	34.9 (2.4)	<0.001 ^a	0.005^b	<0.001 ^b	<0.001 ^b
Item 1 (standing, feet together EC)	3.7 (0.6)	3.9 (0.6)	4.0 (0.0)	0.065 ^a	0.207 ^b	0.197 ^b	0.030^b
Item 2 (functional reach)	2.1 (1.0)	2.8 (1.1)	3.7 (0.9)	<0.001 ^a	0.010^b	0.001^b	<0.001 ^b
Item 3 (360° turning)	1.9 (0.3)	2.0 (0.2)	2.3 (0.7)	0.017^a	0.375 ^b	0.034^b	0.014^b
Item 4 (stepping over a bench)	3.0 (1.2)	3.5 (0.8)	4.0 (0.2)	0.001^a	0.097 ^b	0.013^b	<0.001 ^b
Item 5 (tandem walk)	1.7 (1.3)	2.1 (1.3)	3.6 (0.6)	<0.001 ^a	0.312 ^b	<0.001 ^b	<0.001 ^b
Item 6 (standing on one leg)	1.8 (1.3)	2.0 (1.1)	3.6 (0.8)	<0.001 ^a	0.328 ^b	<0.001 ^b	<0.001 ^b
Item 7 (standing on foam EC)	2.4 (1.5)	3.4 (0.9)	4.0 (0.0)	<0.001 ^a	0.009^b	0.003^b	<0.001 ^b
Item 8 (jump)	2.1 (1.2)	2.2 (1.3)	3.6 (0.7)	<0.001 ^a	0.615 ^b	<0.001 ^b	<0.001 ^b
Item 9 (walk with head turns)	1.6 (1.2)	1.9 (1.4)	3.6 (0.8)	<0.001 ^a	0.383 ^b	<0.001 ^b	<0.001 ^b
Item 10 (reactive postural control)	1.8 (0.9)	2.2 (1.0)	2.9 (1.0)	0.002^a	0.087 ^b	0.044^b	<0.001 ^b
Mean COP position AP (% of foot length)	39.4 (6.6)	42.9 (5.2)	46.6 (5.9)	<0.001 ^c	0.031^d	0.025^d	<0.001 ^d
RMS distance (mm)	9.2 (3.7)	8.1 (4.2)	5.4 (1.9)	<0.001 ^a	0.145 ^b	0.003^b	<0.001 ^b
RMS distance AP (mm)	7.4 (2.8)	6.2 (2.8)	4.5 (1.6)	<0.001 ^a	0.065 ^b	0.016^b	<0.001 ^b
RMS distance ML (mm)	5.1 (3.2)	5.0 (3.6)	2.7 (1.5)	0.001^a	0.963 ^b	<0.001 ^b	0.002^b
Mean velocity (mm/s)	15.0 (9.3)	16.0 (15.2)	7.6 (2.8)	<0.001 ^a	0.668 ^b	<0.001 ^b	<0.001 ^b
Mean velocity AP (mm/s)	10.6 (6.2)	10.8 (7.4)	5.9 (2.2)	0.001^a	0.882 ^b	0.001^b	0.001^b
Mean velocity ML (mm/s)	8.3 (6.3)	9.5 (12.2)	3.7 (1.4)	<0.001 ^a	0.569 ^b	<0.001 ^b	<0.001 ^b
SEn AP	0.90 (0.10)	0.92 (0.12)	0.83 (0.07)	0.009^a	0.528 ^b	0.007^b	0.008^b
SEn ML	0.94 (0.10)	0.91 (0.10)	0.84 (0.08)	0.001^a	0.227 ^b	0.013^b	<0.001 ^b
LOS peak distance (% of foot length)	45.4 (10.7)	51.4 (10.9)	60.4 (7.1)	<0.001 ^a	0.032^b	0.002^b	<0.001 ^b
LOS average distance (% of foot length)	34.6 (11.0)	38.5 (10.8)	50.7 (7.8)	<0.001 ^a	0.346 ^b	<0.001 ^b	<0.001 ^b
LOS average anterior COP position ^e (% of foot length)	61.7 (8.2)	66.6 (8.3)	74.4 (5.8)	<0.001 ^c	0.028^d	<0.001 ^d	<0.001 ^d
LOS average posterior COP position ^e (% of foot length)	27.1 (6.1)	28.1 (5.6)	23.7 (5.0)	0.015^a	0.646 ^b	0.005^b	0.024^b

NOTE. Values are mean (SD); ^a p-value of Kruskal–Wallis-H-Test; ^b p-value of independent sample Mann–Whitney-U-Test; ^c p-value of one-way ANOVA; ^d p-value of independent sample Student's T-Test; ^e average AP COP position (% of foot length) over a time period of 4 s during maximal forward (anterior) or backward (posterior) leaning; bold typed indicate p < 0.05.

COP in forward direction, not only during quiet stance but also during voluntary forward leaning. It remains an open question whether to consider our finding as a cause or consequence of FOG. When initiating gait, the COP is shifted backwards in the direction of the heel of the swing leg's foot to produce a moment of force which moves the center of gravity towards anterior in the direction of the stance foot [24]. A displacement of the COP towards the posterior direction during stance results in a reduced capacity to produce a backward moment of force which is required to initiate forward progression. PD+FOG therefore have a restricted precondition to generate forward progression during gait initiation. Others have shown that PD+FOG perform multiple anticipatory postural adjustments when trying to initiate the first step [12]. The altered COP position may contribute to the abnormal coupling between APA and the step motor program and may be one reason for the occurrence of start hesitation in patients with FOG.

Alternatively the altered COP position may be a consequence of FOG. Most falls in patients with PD occur in forward direction [25]. PD+FOG are predisposed for forward falls when the center of mass moves forward but no steps occur during a FOG episode [26]. The

shift of the COP towards backward therefore may be a compensatory strategy to obtain a safe stance position in order to avoid forward falls. In the current literature inconsistency exists about the COP position during stance in PD. Schieppati and Nardone [27] showed a COP shift backwards in patients with PD in comparison to HC, which is in agreement with our results. However, authors of another study report that patients with PD have a significant shift towards anterior when compared to HC [28]. The latter study analyzed the COP position as the distance (mm) to the tuberosity of the tendocalcaneus without consideration of foot length. We analyzed the average COP position normalized to foot lengths. This may contribute to different findings. In contrast to other studies [27] we could not find any correlation between the AP COP position and disease duration or disease severity (H&Y and UPDRS part III) and no significant differences in COP position were found when comparing less affected (H&Y 1–2.5) with more affected (H&Y 3–4) patients. The lack of these correlations underline the strength of the relationship between FOG and COP position in the present study.

We confirm the results of others [4,5] that PD+FOG and PD-FOG

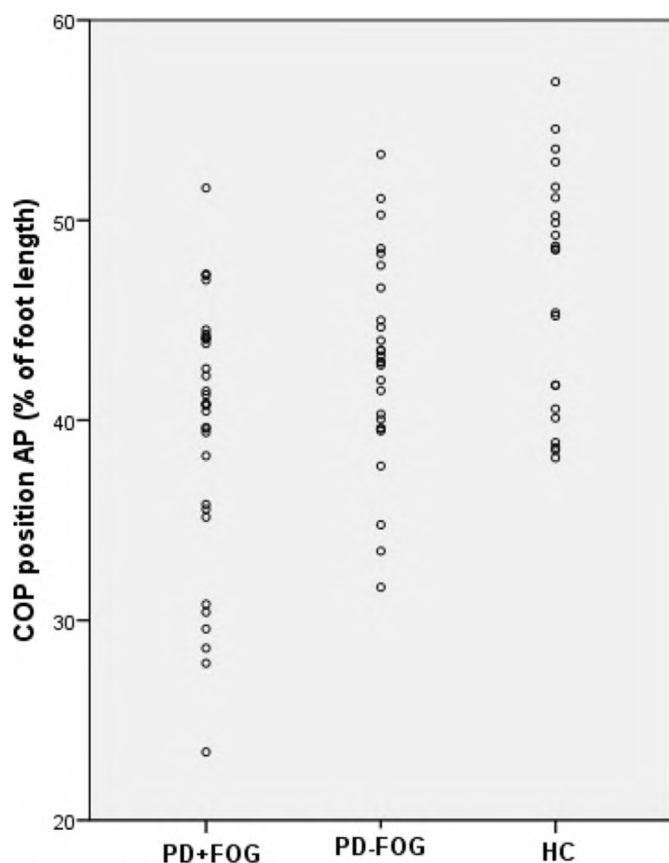


Fig. 1. Participants' anterior–posterior COP position in relation to foot length.

Table 3
Correlation between the severity of FOG (FOGQ total score) and balance related measures within the PD patients (n = 58).

Test	p-Value ^a	Spearman's rho
FAB scale total score	0.001	-0.430
Item 1 (standing with feet together EC)	0.217	-0.165
Item 2 (functional reach)	0.049	-0.259
Item 3 (360° turning)	0.079	-0.232
Item 4 (stepping over a bench)	0.007	-0.350
Item 5 (tandem walk)	0.204	-0.169
Item 6 (standing on one leg)	0.315	-0.134
Item 7 (standing on foam EC)	0.010	-0.335
Item 8 (jump)	0.126	-0.203
Item 9 (walk with head turns)	0.147	-0.193
Item 10 (reactive postural control)	0.001	-0.413
Mean COP position AP (% of foot length)	0.003	-0.382
RMS distance (mm)	0.297	0.139
RMS distance AP (mm)	0.163	0.186
RMS distance ML (mm)	0.753	-0.042
Mean velocity (mm/s)	0.497	0.091
Mean velocity AP (mm/s)	0.583	0.074
Mean velocity ML (mm/s)	0.393	0.114
SEn AP	0.738	-0.045
SEn ML	0.231	0.160
LOS (% of foot length)	0.054	-0.255
LOS av (% of foot length)	0.229	-0.160
LOS ant av (% of foot length)	0.008	-0.346
LOS post av (% of foot length)	0.318	-0.134

NOTE. ^a p-value of Spearman correlation; bold typed indicate $p < 0.05$.

do not differ in COP excursion, COP velocity or sway regularity. While evidence exist that PD+FOG have increased asymmetry during walking [3,29,30] we could not find any differences between

PD+FOG, PD-FOG and HC when compared for postural control asymmetry during stance. This confirms the results by Boonstra et al. [10] who could not find differences in postural control asymmetry between PD+FOG and PD-FOG during stance perturbation.

The following limitations have to be announced. First, the three groups were well matched concerning age, disease duration and disease severity but differed in the distribution of gender. However, as we found no significant difference between female and male subjects in any outcome in any group we consider our findings reliable. Second, postural asymmetry was only analyzed in a subgroup of 64 subjects. Anyway, subgroups did not differ concerning age, disease duration and disease severity and we consider the subgroup's sample size still large enough to detect meaningful differences. Furthermore, when interpreting our findings it has to be taken into account that patients were assessed during the ON state of medication. The execution in the OFF state would give further information about underlying mechanisms leading to FOG. However testing the patients in an ON medication setting is a more realistic assessment of everyday motor functioning. Moreover, we did not measure cognitive function which is relevant for gait. The assessment of cognitive impairment would allow to further interpret our results. Finally, beside the conduction of a clinical balance scale, we focused to analyze postural control during stance and interpreted an altered stance position with respect to start hesitation. It should be kept in mind that FOG during walking or turning might have other underlying mechanisms.

In conclusion our results show that patients with FOG have reduced postural control in comparison to patients without FOG and HC. Specifically, PD+FOG have an impaired ability to voluntary lean forward, difficulties to stand on foam with eyes closed and reduced limits of stability. During quiet stance the COP of PD+FOG is significantly displaced towards posterior in comparison to PD-FOG and this shift significantly correlates with the severity of FOG. Whether this displacement contributes to the occurrence of FOG or whether an altered stance position is a compensatory strategy to avoid forward falls should be assessed in further studies.

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