Influence of cognitive impairment on the freezing of gait in non demented people with Parkinson's disease

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Introduction. Freezing of gait (FOG) is a motor disturbance usually appearing in advanced Parkinson's disease (PD). Cognitive and executive function seems to play an important role in this phenomenon.

Aim. To investigate if cognitive and kinematic parameters correlate with FOG in PD patients without dementia.

Patients and methods. We conducted an observational cross-sectional study. Participants were classified in two groups: freezers and non-freezers. Clinical information was obtained by Hoehn & Yahr scale, Unified Parkinson's Disease Rating Scale and balance test of Short Physical Performance Battery. Cognitive function was evaluated using Minimental Examination and the Fuld Object Memory Evaluation; executive function was assessed with the Frontal Assessment Battery test. Battery kinematic parameters were assessed by means of gait speed, cadence, stride length and stride time.

Results. Twenty-five participants with PD without dementia completed the evaluation. Statistical significant differences between freezers and non-freezers were found in global cognition ($p = 0.02$), memory ($p = 0.04$), executive function ($p = 0.04$), cadence ($p = 0.02$), stride length ($p = 0.04$) and stride time ($p = 0.01$).

Conclusion. Cognitive parameters may have an important contribution to the manifestation of freezing of gait in PD. These results may have important clinical implications for developing future non-pharmacological and cognitive interventions strategies targeted to PD patients with FOG.

Key words. Cognition. Gait. Motor disturbance. Older people. Parkinson's disease.

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Introduction

Freezing of gait (FOG) is a complex and disabling episodic motor phenomenon usually appearing in advanced Parkinson's disease (PD) [1]. FOG consists of an inability to generate steps impairing forward gait that makes the patient remains, literally, glued to the floor [2]. It usually occurs in specific situations such as making turns or walking through a door. FOG does not respond well to dopaminergic medication [3]. It is a definite risk factor for falls and its appearance marks a downturn in the disease course of individuals with PD [4].

The mechanisms underlying this phenomenon are largely unknown and various hypotheses attribute FOG to abnormal gait pattern generation, problems with central drive and automaticity of movement, abnormal coupling of posture with gait, perceptual malfunction and frontal executive dysfunction [5].

FOG may be, in part, a result of dopaminergic down-regulation. Motor disturbances related to gait akinesia seem to be linked to low dopamine striatum uptake [1] and movement initiation can be interfered by striatal dopamine receptor blockade [6]. FOG may be, in part, a result of dopaminergic down-regulation. However, the appearance of this gait disturbance during the parkinsonian on-state and its poor response to levodopa [3] implicates other non-motor and non-dopaminergic factors. Cholinergic areas, including the pedunculopontine nucleus [7] may also be involved in FOG pathophysiology as pharmacological central cholinergic potentiation with antidementia drug rivastigmine lowers the risk of falls. Noradrenergic therapy has also proved to be useful in some PD patients. Increasing evidence recognizes that cognitive and executive function have a center role in the FOG phenomenon [8]. Tasks demanding complex gait adaptations can be compromised if the executive control system is impaired [9]. Moreover, gait anticipatory mechanisms and motor strategic planning are involved since freezing episodes frequently occur in situations when the patient turns, adjusts his gait to a pattern on a crowded area or when a change in gait is prompted by crossing a door or obstacle [10].

Upon an upcoming event, patients with FOG frequently experience impairment and interruptions on their planned movement sequence [11]. FOG episodes may benefit from external sensory cues suggesting that sensory and perceptual pathways are also involved [12,13].

Considering the role of frontal-lobe functions in gait and complex motor behaviors we hypothesize that there is an intrinsic relationship between cognitive impairment in executive function and abnormal posture and gait related to FOG. The aim of this study is to compare kinematic parameters, executive function and cognitive performance in a group of non-demented PD patients with and without FOG.

Patients and methods

Participants

Patients with PD were recruited through personal letters from the Asociación de Párkinson Galicia-Bueu using the following inclusion criteria: PD according to the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank [14]; stages 1-3 on the Hoehn and Yahr (H&Y) scale [15]; and stable doses of antiparkinsonian medication (dopaminergic medication dosage not changed at least one month prior to assessment).

Exclusion criteria were: dementia (DSM-IV criteria); other major neurological disorders, neuropsychiatric comorbidity or acute illness limiting the evaluation protocol; and refusal to participate by the patient or his/her caregiver.

The ethics committee (CEIC 2011/343) approved the study and all participants and/or caregiver gave informed written consent.

Outcome measures

The medical staff of the association was previously trained for all assessment tools and performed the clinical evaluation. The participants were tested approximately one hour after the last dose of antiparkinsonian drug. All were in the 'on' phase.

Clinical parameters

- Demographic information including age, sex, academic level and medical history of each patient were gathered with the database form created for this purpose.
- Clinical staging of PD was measured using the H&Y scale [15].
- Patients' motor condition and disease severity were measured using the Spanish validated version of the Unified Parkinson's Disease Rating Scale (UPDRS) [16,17] in order to assess functional status (subsection II) and motor function (subsection III).
- Postural control was assessed by means of the balance test of the Short Physical Performance Battery (SPPB) [18].

Cognitive parameters

- Global cognition was evaluated by a personal interview of the patient and the Spanish-adapted version of the Mini Mental Status Examination (MEC) [19].
- Frontal cognitive functions were assessed by means of the Spanish validated version of the Frontal Assessment Battery (FAB) [20,21].
- Memory: the Fuld Object Memory Evaluation (FOME) [22] was used to assess immediate and delayed memory function [23]. Two FOME scores namely total storage (range: 0-50) and delayed recall (range: 0-10) were derived to assess encoding and retrieval function respectively, with lower scores indicating more impairment.

Kinematic assessment

Gait speed (m/s), cadence (steps/min), stride length (m), stride time (s), rate single support/double-support were calculated after counting steps and time needed for a 10m walk, turn and walk at the same route back at the patients' preferred speed. All evaluations were recorded with an automatic computerized video motion analysis system (Sports Motion-Pro Trainer DV Motion Analysis). This device allows for a biomechanical gait analysis through of recording spatiotemporal and sagittal plane kinetic and kinematics by means of a video motion system. To this aim, spherical retro-reflective markers were placed on specific anatomical points of the participants' right lower limbs, enabling three-dimensional analysis during the gait cycle.

Design and data collection protocol

This observational cross-sectional study was conducted in two phases. In phase 1, after obtaining the demographic information, education level and medical data the participants were distributed into two groups according to whether FOG was present or not. The allocation of the participants to one of two groups, FOG and non-FOG, was done according to question 14 of the UPDRS (functional subscale, part II) which addresses whether the freezing phenome-

non was experienced at the time of enrollment. Those who scored one or higher were allocated to the FOG group and those who scored 0 were allocated to the non-FOG group. A neurologist assessed all participants in order to confirm/exclude the presence of FOG in these patients at the time of the test [9]. At the end of this phase, the MEC test was administered. In phase two, only those who obtained a score in MEC ≥ 24 and gave consent to participate in further assessment carried out the remaining assessments previously described.

Statistical analysis

Data analysis was performed using the SPSS Statistics v. 20.0 software. Shapiro-Wilk's distribution analysis was applied to determine data distribution and the adequate statistical test according to parametric and non-parametric data. To describe profile sample for all variables, data were presented in frequency tables for categorical data and descriptive statistics were applied for numerical data with means and standard deviation. Chi-square and the Fisher test were used to compare categorical data and one-way ANOVA and Mann-Whitney *U*-test were used for comparisons involving continuous data.

To verify the relationship between cognition and kinematic parameters we conducted a partial correlation controlled by cognitive function, memory, motor condition (UPDRS-III) and academic level. Finally, we performed a multivariate regression analysis to determine a model that allows for identifying the differences between FOG and no-FOG participants. The level of significance for all variables was 5%.

Results

Thirty-four PD patients were initially evaluated. Ten participants were classified as freezers (FOG group) and 24 as non-freezers (non-FOG group). Nine participants of non-FOG group screened positive for probable dementia and were thus excluded. Twenty-five individuals completed all evaluations and were included for data analysis. Figure displays the distribution of the sample and excluded cases. 25 individuals completed all evaluations and were included for data analysis. After performing the specific tests, 15 individuals were classified as non-freezers and were included on the non-FOG group and 10 individuals with freezing of gait characteristics were included on FOG group. There were no individuals with advanced PD treatments such as apomorphine, duodopa or deep brain stimulation.

Table I. Clinical and kinematic profile and group comparison of outcomes for FOG and non-FOG groups (mean ± standard deviation).

		Non-FOG (n = 15)	FOG (n = 10)	p [a]
Clinical parameters	Gender (male/female)	8/7	6/4	–
	Age (years)	69.5 ± 7.99	69.7 ± 5.2	0.93
	Academic level (primary/secondary)	10/5	9/1	–
	Disease duration (years)	8.2 ± 4.2	9.0 ± 5.3	0.73
	Clinical stage, H&Y	2.6 ± 0.6	2.3 ± 0.5	0.34
	Functional, UPDRS II	13.8 ± 4.4	11.8 ± 2.8	0.19
	Motor, UPDRS III	12.2 ± 4.1	15.0 ± 2.0	0.02 [b]
	Balance, SPPB	4.0 ± 0.8	3.1 ± 1.3	0.01 [b]
Cognitive parameters	Global cognition, MEC	31.7 ± 2.3	30.7 ± 2.4	0.02 [b]
	Executive function, FAB	14.3 ± 2.6	13.7 ± 3.0	0.04 [b]
	Memory, FOME	42.3 ± 7.5	40.5 ± 3.7	0.04 [b]
Kinematic parameters	Cadence (steps/min)	96.0 ± 15.4	111.8 ± 13.5	0.02 [b]
	Gait speed (m/s)	1.9 ± 0.5	1.7 ± 0.5	0.43
	Stride length (cm)	62.4 ± 13.8	51.2 ± 10.9	0.04 [b]
	Stride time (s)	1.1 ± 0.1	1.3 ± 0.2	0.01 [b]
	Single support (s)	44.6 ± 6.4	51.0 ± 13.1	0.07
	Double support (s)	39.9 ± 9.5	46.4 ± 15.8	0.21
	Single/double support time	1.1 ± 0.2	1.1 ± 0.2	0.99
	Hip-flexion (degree)	23.9 ± 3.2	23.3 ± 3.8	0.71
	Hip-extension (degree)	33.2 ± 2.8	34.2 ± 3.6	0.47
	Knee terminal state (degree)	16.2 ± 2.6	15.5 ± 3.9	0.63
	Knee-swing phase (degree)	65.4 ± 9.9	67.1 ± 13.1	0.73
	Ankle-dorsiflexion (degree)	4.4 ± 2.1	6.8 ± 2.8	0.25
	Ankle-plantar flexion (degree)	11.1 ± 3.4	9.5 ± 2.5	0.23

FAB: Frontal Assessment Battery; FOG: freezing of gait; FOME: Fuld Object Memory Evaluation; H&Y: Hoehn & Yahr scale; MEC: *miniexamen cognitivo*; SPPB: Short Physical Performance Battery; UPDRS: Unified Parkinson's Disease Rating Scale. [a] Unpaired Student's *t*. [b] Statistically significant values.

Table I shows clinical, cognitive and kinematic characteristics for freezers and non-freezers.

FOG group individuals presented more impaired motor conditions (UPDRS III) (p = 0.02) than non-

Table II. Relationship between executive function (FAB) and kinematic parameters.

			FAB		
			Total (n = 25)	Non-FOG (n = 15)	FOG (n = 10)
Level academic, global cognition, motor (UPDRS III) and memory (FOME)	Gait speed	*r*	0.671	0.715	0.809
		Sig.	0.001	0.110	0.000
	Cadence	*r*	0.536	0.770	0.303
		Sig.	0.003	0.073	0.222
	Stride length	*r*	0.537	0.656	0.795
		Sig.	0.003	0.157	0.000
	Stride time	*r*	0.605	0.592	0.566
		Sig.	0.001	0.216	0.014
	Single support	*r*	0.583	0.704	0.634
		Sig.	0.001	0.118	0.005
	Double support	*r*	–0.583	–0.704	–0.634
		Sig.	0.001	0.118	0.005
	Single/double support	*r*	0.610	0.770	0.664
		Sig.	0.001	0.073	0.003
	Hip-flexion	*r*	–0.027	0.553	–0.223
		Sig.	0.893	0.255	0.373
	Hip-extension	*r*	0.172	–0.150	0.309
		Sig.	0.380	0.777	0.213
	Knee-terminal state	*r*	–0.046	–0.138	–0.166
		Sig.	0.817	0.794	0.510
	Knee-swing phase	*r*	–0.367	–0.346	–0.338
		Sig.	0.055	0.502	0.170
	Ankle-dorsiflexion	*r*	–0.039	0.371	0.338
		Sig.	0.844	0.469	0.171
	Ankle-plantar flexion	*r*	–0.158	–0.298	–0.156
		Sig.	0.421	0.567	0.537

FAB: Frontal Assessment Battery; FOG: freezing of gait; FOME: Fuld Object Memory Evaluation; H&Y: Hoehn & Yahr scale; MEC: *miniexamen cognitivo*; *r*: correlation coefficient Pearson; Sig.: significance; UPDRS: Unified Parkinson's Disease Rating Scale.

Table III. Relationship adjusted coefficient between FOG and non-FOG groups.

	R^2	p
Motor (UPDRS III)	16.0	0.045
Balance (SPPB)	16.2	0.045
Global cognition (MEC)	19.8	0.026
Executive function (FAB)	16.4	0.044
Memory (FOME)	16.3	0.046
Cadence (steps/min)	21.7	0.029
Stride length (cm)	21.7	0.021
Stride time (s)	17.6	0.035

FAB: Frontal Assessment Battery; FOG: freezing of gait; FOME: Fuld Object Memory Evaluation; H&Y: Hoehn & Yahr scale; MEC: *miniexamen cognitivo*; R^2: adjusted point biserial coefficient; UPDRS: Unified Parkinson's Disease Rating Scale.

FOG individuals. Freezers scored significantly worse in global cognition (p = 0.02), executive function (p = 0.04) and memory (p = 0.04). Regarding kinematic parameters, freezers presented significantly increased cadence (p = 0.02), decreased stride length (p = 0.04) and slower stride time (p = 0.01). The combination of small and slow steps with fast cadence resulted in impairments for gait performance on freezers.

Variables with significant differences between both groups were inserted in a Pearson's correlation and were calculated taking into account the binary outcomes. Regarding this analysis score, UPDRS-III, SPPB, MEC, FOME and FAB, as well as cadence, stride length and stride time, were correlated with FOG showing the greatest values of significant correlation ($r > 0.4$; $p < 0.05$).

Values of significant correlation coefficient for each variable are displayed on table II. The results of the univariate analysis performed in order to identify the variables containing significant predictive values are shown on table III.

Multivariate analysis was calculated for motor, balance, global cognition, executive function memory, cadence, stride length and stride time. Results are displayed on table IV. These eight contributors, jointly explained approximately 73.9% of variability between FOG and non-FOG patients (R^2 = 0.581; $p < 0.02$).

Discussion

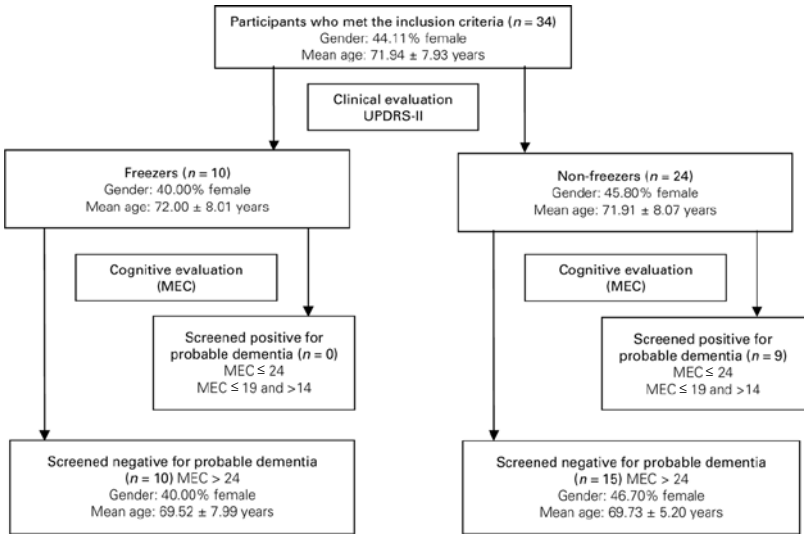
Our study shows that cognitive and motor scores appear to be strongly correlated with FOG in PD patients. Among the cognitive domains considered, global cognition, memory and executive function contribute to FOG. Of the kinematic parameters, the combination of small and fast steps and increased cadence is the pattern impacting on FOG gait performance. Neither age, gender or disease duration seem to contribute to the FOG phenomenon.

Freezing of gait is an intriguing, complex and ominous motor PD phenomenon. Various models have been suggested as theoretical frameworks in understanding the FOG episodes: a threshold model in which the accumulation of motor deficits over time leads to FOG [24], an interference model proposing that FOG is a result of the inability to deal with central processing resources [25], a cognitive model viewing FOG as induced by a failure to process response conflict [26], and the decoupling model that views FOG as a disconnection between central motor programs and motor response [27].

The finding that performance on cognitive tests differentiates freezers from non-freezers supports the notion that cognitive parameters may have an important contribution to the manifestation of freezing of gait in PD.

In the present work, as previously reported [28], freezers showed worse performance on the MEC than non-freezers, suggesting a significant difference in the global cognitive status between the groups. The fact that global cognition may play a determinant role in FOG is not surprising. In fact, the FOG phenomenon has been related to impairments in dual-task performance (the ability to maintain normal walking while performing a secondary task) and attentional shifting [29]. A specific deficit in monitoring for self-made errors under high cognitive load has been recently reported [30]. Freezers performed also significantly worse than non-freezers on specific cognitive tests such as the FAB and the FOME, revealing more impairment in frontal executive functions and in immediate memory function (more difficulty identifying and recalling familiar household objects by touch or visual processing), respectively. Lower scores on cognitive tests related to frontal lobe and executive functions have been previously reported in freezers [31], suggesting that executive function is a significant predictor of FOG. Importantly, both automatic and controlled (frontal executive function) processes have been shown to be more impaired in freezers than in non-freezers in previous studies [32]. Consistent with these results, there is recent neuroimaging evidence revealing that freezers show relatively reduced functional resting connectivity within both executive-attention and visual neural networks [33] and functional decoupling between the right-lateralized cognitive control (executive) network and the basal ganglia nuclei [34].

Figure. Inclusion of participants for data analysis.



Working memory has been shown to be impaired in patients with freezing of gait compared to non-freezers [35]. Immediate memory function, measured by the FOME test, was also significantly lower in freezers than in non-freezers in the present work, suggesting that memory dysfunction may be also an independent determinant of FOG. The role of memory on gait mechanisms, especially in those associated with cadence, has been previously reported [36,37]. When combined with executive dysfunction, memory impairment has been associated with gait speed and predicted longitudinal gait speed decline over five years [38].

The role played by cognitive dysfunction in FOG is also supported by the lack of improvement with levodopa in on-state FOG, suggesting that other neural systems may contribute to its pathogenesis. A study showed that patients with levodopa-unresponsive FOG displayed greater impairments in executive functioning as compared to controls. These findings implicate frontal lobe dysfunction in addition to progression of the pathological process to non-dopaminergic circuits [39]. Several studies have

Table IV. Results of multivariate linear regression between FOG and non-FOG patients.

	Estimate (B)	95% CI	
Constant	–6.20	–12.12	–0.28
Motor (UPDRS III)	0.09	0.05	0.14
Balance (SPPB)	0.20	0.04	0.37
Global cognition (MEC)	0.01	–0.09	0.09
Executive function (FAB)	–0.04	–0.10	0.02
Memory (FOME)	0.01	–0.02	0.004
Cadence (steps/min)	0.02	–0.01	0.04
Stride length (cm)	–0.01	–0.03	0.01
Stride time (s)	2.77	1.31	4.23

95% CI: 95% confidence interval; FAB: Frontal Assessment Battery; FOG: freezing of gait; FOME: Fuld Object Memory Evaluation; H&Y: Hoehn & Yahr scale; MEC: *miniexamen cognitivo*; UPDRS: Unified Parkinson's Disease Rating Scale. Only variables with significant predictive values on univariate analysis were inserted to this model. All of these variables showed an independent contribution to explain partially the variability between FOG and non-FOG outcomes.

explored the involvement of different neurotransmitters in FOG pathogenesis, specially the noradrenergic and cholinergic systems. Noradrenergic deficits due to neuronal loss in the locus coeruleus have been linked to FOG [40]. Methylphenidate, a drug that inhibits dopamine and noradrenaline presynaptic transporters in the striatum and prefrontal cortex, may improve gait parameters and FOG in patients with advanced PD [41]. In addition to this motor effect, methylphenidate is known to improve attention and executive dysfunction in other disorders [42]. The pedunculo-pontine nucleus, a cholinergic area that is part of the mesencephalic locomotor region, may be implicated in many motor deficits relating to locomotion and posture in PD patients**.** Central cholinergic potentiation with rivastigmine, a central acetilcholesterase inhibitor, and nuclear in antidementia pharmacological therapy may reduce the risk for falls [43].

Our study has several limitations. The size of our sample is small and therefore our results should be interpreted with caution. We did not apply depression and anxiety scales, which recently have been an area of focus in the study in FOG. We also did not adjust our results for treatments, which may interfere with motor and cognitive assessments.

In conclusion, our results suggest that FOG is not a pure motor phenomenon and that it may be associated with global and executive cognitive dysfunction. Because cognitive functions can be significantly improved by cognitive training [44], the present results may have important clinical implications for developing future non-pharmacological intervention and cognitive rehabilitation strategies targeted to improve FOG symptoms in PD patients.

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Influencia del deterioro cognitivo en la congelación de la marcha en pacientes con enfermedad de Parkinson sin demencia

Introducción. La congelación de la marcha (CDM) es una alteración motora que suele aparecer en estadios avanzados de la enfermedad de Parkinson (EP). Las funciones cognitivas y ejecutivas parecen tener un papel importante en la aparición de este fenómeno.

Objetivo. Investigar si los parámetros cognitivos y cinemáticos se correlacionan con la CDM en pacientes con EP sin demencia.

Pacientes y métodos. Estudio observacional y transversal. Los participantes se clasificaron en dos grupos: con y sin CDM. La información clínica se obtuvo mediante la escala de Hoehn y Yahr, la *Unified Parkinson's Disease Rating Scale* y la prueba de equilibrio de la *Short Physical Performance Battery.* La función cognitiva se valoró con el miniexamen cognitivo y la *Fuld Object Memory Evaluation,* y la función ejecutiva, con la *Frontal Assessment Battery.* Los parámetros cinemáticos se valoraron mediante la velocidad de la marcha, la cadencia, la longitud del paso y el tiempo del paso.

Resultados. Veinticinco participantes con EP sin demencia completaron el programa. Se encontraron diferencias estadísticamente significativas entre individuos con y sin CDM en cognición global (p = 0,02), memoria (p = 0,04), función ejecutiva (p = 0,04), cadencia (p = 0,02), longitud del paso (p = 0,04) y tiempo del paso (p = 0,01).

Conclusión. Diversos parámetros cognitivos pueden contribuir de forma importante en la aparición de la CDM en la EP. Estos resultados pueden tener implicaciones clínicas relevantes para el desarrollo de estrategias e intervenciones no farmacológicas y cognitivas dirigidas a pacientes con EP y con CDM.

Palabras clave. Cognición. Congelación de la marcha. Enfermedad de Parkinson. Marcha. Personas mayores. Trastorno motor.