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Freezing of gait subtypes have different cognitive correlates in Parkinson's disease☆

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ABSTRACT

Background: Freezing of gait (FOG) is a major concern for Parkinson's disease (PD) patients because it is a leading cause of falls and is associated with poor quality of life. The pathophysiology is unknown but it is hypothesized that it relates to cognitive abnormalities; particularly executive and visuospatial dysfunction. However, prior results have been discrepant. Pharmacologic subtypes of FOG include those that are responsive and unresponsive to levodopa.
Objective: To determine whether executive and visuospatial dysfunction are associated specifically with the levodopa unresponsive subtype of FOG.
Methods: 135 PD subjects completed a single assessment included FOG questionnaire, UPDRS motor scale, comprehensive cognitive battery and measure of hallucinations. Analyses compared unresponsive ($n = 16$), responsive ($n = 20$) and no FOG ($n = 99$) subtypes.
Results: The unresponsive subtype had a significantly older age of onset of PD than the responsive group ($p = .03$) and had worse motor scores ($p = .003$) than the no FOG group. Longer disease duration was associated with the responsive group compared to the no FOG group ($p = .002$). The unresponsive FOG group had significantly poorer visuospatial ability ($p = .001$) and executive functioning ($p = .02$) than both the no and responsive FOG subgroups. These latter groups were not significantly different. The responsive FOG group was associated with the presence of hallucinations.
Conclusion: Aside from pharmacological differences, unresponsive FOG is associated with executive and visuospatial dysfunction implicating frontostriatal pathways while responsive FOG is associated with hallucinations suggesting involvement of posterior cortical regions. Further study and treatment of FOG should include appropriate subtype classification.

1. Introduction

Freezing of gait (FOG) is defined as "brief, episodic absence or marked reduction of forward progression of the feet despite intention to walk" [1]. Patients identify it by their feet feeling glued to the floor. It most often occurs with initiating gait and turning [2]. FOG is common in Parkinson's disease (PD) [3]. It is a leading cause of falls and is associated with loss of independence and poor quality of life with social isolation [4].

FOG has been referred to as a "mysterious" motor feature with its own pathophysiology separate from the cardinal motor features of PD [1]. It has been hypothesized that it relates to cognitive dysfunction, particularly executive and visuospatial abnormalities [1,5,6] and several studies appear to corroborate this notion [7–9]. Furthermore, FOG has also been found to be associated with the presence of hallucinations [10]. While these cognitive and behavioral associations have been generally accepted by the investigative community [5], differences in executive and visuospatial dysfunction between patients with and without FOG have been inconsistent and the reasons for these discrepancies remain to be elucidated.

FOG is a complex issue on several levels. For example, some authors indicate that different types of gait problems such as festination and akinetic FOG represent a continuum [11]. In addition, it is well known that several pharmacological subtypes of FOG exist in PD [11,12]. They can be categorized into those responsive to

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levodopa and those which are unresponsive. "Off" FOG responds to dopaminergic therapy. "On" FOG may be caused by dopaminergic drugs, only occurring in the "on" state (this is rare), while "unresponsive" FOG is not impacted by dopaminergic agents and occurs in the "on" and "off" states. Inconsistencies in cognitive findings among studies may occur because investigators have not considered that these pharmacological subtypes of FOG may have different outcomes. In this study we compared performance on cognitive measures in those with levodopa responsive FOG (RFOG), unresponsive FOG (URFOG) and no FOG. Considering that the subtypes are pharmacologically different and with data from some studies suggesting subtypes are cognitively different [9,13–15] we hypothesized that URFOG would be associated with executive and visuospatial performance while RFOG would not. Furthermore, because of its relation to cognitive change in PD and considering our previous finding of an association with FOG, we explored the relationship of hallucinations with different FOG subtypes.

2. Methods

2.1. Subjects

This study was approved by the Emory University Institutional Review Board (IRB). All subjects signed an IRB approved consent document. Subject recruitment started February 9, 2009 and ended September 14, 2010. One hundred and fifty two subjects were recruited consecutively from the practices of two neurologists (SAF, AF) in the Emory Movement Disorder Center. All subjects met modified UK brain bank diagnostic criteria for PD [16]. Exclusion criteria included advanced stage dementia where subjects were unable to perform activities of daily living independently, the presence of cerebrovascular disease or extensive white matter disease, findings suggestive of atypical parkinsonism (extraocular movement abnormalities, pyramidal tract signs, ataxia), past neuroleptic use, and past history of multiple head injuries.

2.2. Assessments

All subjects were evaluated in a standardized fashion over a five hour period. They were given breaks to take medication and eat lunch. Demographic and clinical information were collected including age, age at diagnosis, duration of disease from diagnosis, gender, ethnicity, education level, handedness, and medications.

2.2.1. Motor function

Motor severity was measured with the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor examination performed in the "on" state. The occurrence of dyskinesia was assessed through UPDRS part IV. The presence of FOG was assessed using the validated Freezing of Gait questionnaire (FOG-Q) [17]. If subjects had a score of >0 on item 3 of the scale based on its occurrence in the previous month then FOG was considered present. After completion of the FOG-Q, subjects were asked if their FOG occurred in the "off" or "on" state, in both states, or if this was unknown. Subjects were then categorized by a binary classification to those with pure "off" or levodopa responsive FOG (RFOG) versus the other categories of response (i.e. those with FOG occurring only in the "on" state or in both "on" and "off" states) referred to cumulatively as the levodopa unresponsive FOG (URFOG) group. This classification is justified because it is well known that the "off" FOG group is levodopa responsive in contrast to the other groups which are not.

2.3. Cognitive functioning

A comprehensive battery of neuropsychological measures [18] was administered by a trained psychometrist, under the supervision of a neuropsychologist (A.B.S., J.O.L.) and completed in the "on" state. The mini-mental status exam (MMSE) was used to assess global cognitive status. Attention was evaluated by the maximum number of correct trials for digits forward and the number of seconds needed to sequence numbers using a pencil (Trailmaking A). Language was examined via the 60-item version of the Boston Naming Test and timed phonemic fluency. The evaluation of memory included verbal episodic memory (delayed story recall and delayed recall of words), visual episodic memory (delayed recall of designs), and semantic memory (timed generation of animal names in 60 s). Visuospatial skills were assessed using a motor free, untimed measure requiring judgment of the angular orientation of lines (JOLO). Finally, executive functioning was measured via set shifting tasks involving mental manipulation of digits and timed alternation of numbers/letters and symbols (Trailmaking B and Digit Symbol) as well as the ability to inhibit a prepotent response (Stroop Color-Word) and to generate hypotheses (Wisconsin Card Sorting Test-WCST).

2.4. Visual hallucinations

Patients were administered the Scale for the Assessment of Positive Symptoms (SAPS) as the primary measure of psychotic symptoms [19]. The hallucinations subscale assesses seven subtypes (auditory, voices commenting, voices conversing, somatic or tactile, olfactory, visual). Each subtype is rated on a scale ranging from 0 (absent) to 5 (severe). In addition, a Global Rating of Severity (ranging 0–5) provides an overall score for the entire domain.

2.5. Statistical analysis

Univariate analyses (analysis of variance-ANOVA, Chi-Square) were performed to examine relationships between the presence of FOG subtypes and demographic characteristics (age, education, gender), clinical disease features (duration, age of onset, UPDRS motor score, and use of PD medications: levodopa, dopamine agonists, amantadine, monoamine oxidase inhibitors) and global cognitive status (MMSE). For cognitive assessments, to reduce the likelihood of making Type I errors, the scores of the tests comprising the domains of attention, language, memory, visuospatial performance, and executive functioning were each converted to z scores based on the performance of the entire group. The z scores were then averaged to form a composite score reflecting performance on each domain. Analyses of covariance (ANCOVA) were conducted to evaluate neurocognitive functioning in each domain, while controlling for potential confounders identified in the univariate analyses including age, education, disease duration, UPDRS motor score, and MMSE score. If the result was significant for the domain ($p < .05$), post hoc analyses were carried out to evaluate which individual measures contributed to differences among the groups. Composite scores were not derived for the visuospatial domain (one test only) or for the number of hallucinations, visual hallucinations, and dyskinesia.

3. Results

Complete cognitive, FOG and hallucination data were available for 135 PD subjects (90%). Forty eight subjects (35%) experienced FOG. Twelve of them did not know which state their freezing occurred in. Of the remaining sample of 36 subjects, 16 had URFOG, and 20 had RFOG. Table 1 shows their demographic and clinical features and global cognitive status. The URFOG group had a significantly greater age of onset of PD than the RFOG group ($p = .03$) and had higher UPDRS scores ($p = .003$) than the no FOG group. Longer disease duration was present in the RFOG group compared to the no FOG group ($p = .002$) but there was no significant difference between the URFOG and RFOG groups. In terms of cognitive status, the MMSE scores were significantly lower (worse) ($p = .001$) in both FOG groups compared to the no FOG

Table 1
Demographic and clinical features of patients with levodopa unresponsive (URFOG), levodopa responsive FOG (RFOG) or no FOG.

	URFOG ($N = 16$)	RFOG ($N = 20$)	No FOG ($N = 99$)	P Value
Mean ± SD; range				
Age (years)	70.3 ± 7.2; 58–81	65.0 ± 9.1; 49–81	64.4 ± 8.8; 38–80	.05
Duration of disease (years)	8.2 ± 5.2; 3–21	10.6 ± 5.2; 3–22[a]	7.0 ± 3.6; 1–22[a]	.002
Age of onset (years)	62.2 ± 9.7; 40–76[a]	54.1 ± 10.1; 33–69[a]	58.0 ± 8.9; 32–80	.03
Education (years)	15.0 ± 2.5; 12–20	15.1 ± 2.5; 12–20	16.0 ± 2.2; 11–20	.07
UPDRS score (points)	22.3 ± 5.7; 12–34[a]	20.7 ± 8.5; 8–41	16.3 ± 7.7; 2–43[a]	.003
MMSE score (points)	27.1 ± 2.1; 21–30[a]	27.4 ± 2.4; 21–30[b]	28.7 ± 1.7; 22–30[a,b]	.001
FOGQ total score	12.2 ± 4.6; 7–23[a]	10.5 ± 4.4; 3–21[b]	1.6 ± 1.2; 0–5[a,b]	.001
Male N (%)	11 (69%)	14 (70%)	65 (66%)	.92

A common superscript indicates a significant difference among the marked groups.