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Journal of the Neurological Sciences 248 (2006) 173 – 176

Journal of the Neurological Sciences

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The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease

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Available online 14 June 2006

Abstract

Freezing of gait (FOG) is a disabling episodic gait disturbance that is common among patients with Parkinsonism. FOG typically lasts a few seconds and is associated with a unique sensation: the patient feels that his feet are glued to the ground, causing him to remain in place despite making a concerted effort to overcome the motor block and move forward. Traditionally, FOG has been viewed as a motor symptom of advanced Parkinson's disease. Here we describe evidence which demonstrates that mental conditions also likely play an important role in the pathogenesis of FOG. Stress, anxiety, depression and cognitively challenging situations are associated with FOG, and may set the stage for and increase the likelihood that FOG occurs. A conceptual model that explains how mental conditions may modulate FOG is developed.
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Keywords: Freezing of gait; Parkinson's disease; Mental function gait

1. Introduction

Freezing of gait (FOG) is a disabling episodic gait disturbance that is common among patients with Parkinsonism. FOG typically lasts a few seconds and is associated with a unique sensation: the patient feels that his feet are glued to the ground, causing him to remain in place despite making a concerted effort to overcome the motor block and move forward. FOG is most often an "OFF" medication phenomenon that responds to levodopa. It is typically seen while turning ("turning hesitation"), at gait initiation ("start hesitation") and in tight quarters such as doorways or during stressful situations [1–3]. FOG causes only mild discomfort in the early stages of Parkinson's disease (PD), but can be a critically important motor complication leading to falls, loss of mobility and curtailed independence as the disease progresses [4]. Furthermore, it has recently been reported that FOG episodes are a major contributing factor for the deterioration in quality of life of patients with PD, even beyond its relation to mobility disturbances [5]. The pathogenesis underlying FOG has yet to be fully explained.

Traditionally, FOG has been viewed as a motor symptom of advanced PD related to disease severity [1,6]. However, the response of FOG to pharmacological interventions suggests that FOG has common as well as disparate properties compared to the classic motor symptoms of PD. Two recent prospective drug studies on patients in the early stages of PD demonstrated that treatment with the dopamine agonists (DA) pramipexole and ropinirole increased the risk of experiencing FOG compared to levodopa [7,8], possibly due to either a relatively milder dopaminergic effect of DA or to a specific yet unexplained negative effect of DA predisposing to the induction of FOG. In addition, the monoamine oxidase B (MAO-B) inhibitors selegiline and,

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0022-510X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2006.05.015

more recently, rasagiline as well as the catechol-*O*-methyl transferase (COMT) inhibitor entacapone have been shown to decrease FOG severity in double blind, placebo-controlled prospective studies [2,6,9,10]. Interestingly, rasagiline and entacapone did not affect the "OFF" state through the same mechanism, thus suggesting that rasagiline affected FOG through a non-dopaminergic mode. As an "OFF" sign, FOG responds to high frequency deep brain stimulation (DBS) of the sub-thalamic nucleus, while "ON" FOG is generally resistant to DBS [11]. These differences between the effects of pharmacologic treatments on FOG and other motor symptoms may in part be explained by accumulative evidence which indicates that FOG is more than simply another motor symptom of PD and that it is strongly influenced by mental function.

This article summarizes the evidence which suggests that mental aspects, emotional as well as cognitive, play an important role in the occurrence and possibly the development of FOG.

1.1. The relationships between stress, anxiety, depression and FOG

1.1.1. Stress

FOG is a unique symptom in many ways, but one of its most striking clinical features is its relationship to stress. On the one hand, FOG is relatively rare when a patient visits the doctor's office or the gait laboratory [12]. A recent survey among 390 patients with PD who experienced FOG found that it occurs most frequently at home and less commonly when walking outdoors [2]. On the other hand, FOG often occurs in stressful situations that are related to time pressures, such as when entering an elevator or crossing the street while the light is green [4]. The dynamics of this sensitivity to certain time-critical situations are of interest. They suggest that externally triggered initiation of locomotion involving temporal constraints may use a gait initiation network that is more susceptible to the development of start hesitation. Recent observations indicate that patients with FOG have disturbed left/right leg synchronization [13]. When an already dys-synchronized network is challenged to perform a task that requires a complete split between the control of one leg and the other, the added stress of time constraints may increase the likelihood of "jamming" the system and predispose to FOG. This may occur during turning or at gait initiation when one leg is used to provide support or pivot and the other leg is supposed to swing forward, as commonly occurs during gait initiation and turning. This proposed mechanism is consistent with the high frequency of FOG in these two situations. The patient may or may not understand the nature of these physiological dynamics, but it is reasonable to suggest that having experienced the difficulties that these situations can and do cause, he will feel some stress each time he confronts time-critical motor challenges; stress that may further predispose to FOG.

1.1.2. Anxiety

The increased frequency of FOG in stressful situations suggests the possibility that FOG may occur in association with increased general anxiety. Lieberman recently studied the relationship between anxiety, as measured using the Hamilton anxiety scale, and FOG, as measured using the FOG-Q, in 109 consecutive PD patients [14]. Twenty-nine patients reported FOG of whom 4 also reported experiencing panic attacks (13.7%), while only 2 of the other 80 PD patients (2.5%) reported experiencing panic attacks ($P<0.05$). The author concluded that anxiety, at least in certain forms, is apparently more common in patients with FOG. His study confirmed previous results by Vazquez et al. who reported a higher frequency of FOG in PD patients with panic attacks when compared to PD patients without panic attacks [15]. Even though panic attacks are fairly common in the "OFF" state, anxiety and panic attacks are considered as non-dopaminergic symptoms or as essentially serotoninergic symptoms of PD. Thus, this relationship between FOG and anxiety/panic attacks may support an idea originally proposed by Narabayashi [16], i.e., that FOG is partly due to decreased serotonin or adrenaline concentration in the brain.

1.1.3. Depression

Two large prospective studies demonstrated an association between FOG and depression. The first is the well-known Deprenyl and Tocopherol Treatment of Parkinsonism (DATATOP) study. This prospective, double blind, placebo-controlled trial assessed the therapeutic effects of deprenyl, tocopherol (vitamin E) and placebo on the early stages of PD, prior to any dopaminergic treatment [17]. FOG was evaluated by using the question on FOG in the activities of daily living (ADL) part of the Unified Parkinson's Disease Rating Scale (UPDRS, item 14) [18]. Depression was assessed using the Hamilton Depression Scale (HAMD) which was given prior to any treatment and at the end of the blinded phase. A higher degree of depression at baseline was associated with earlier development of FOG ($P<0.001$) and a risk factor for the development of FOG during the course of the study (14 months) (Hazard ratio 1.58 [95% CI: 1.11-2.26]). Similarly, the presence of FOG at the end of the study, before the group assignments were revealed, was significantly associated with higher scores on the HAMD at the end of the study ($P<0.05$)[6]. The second prospective trial, a substudy of the LARGO study [19], also demonstrated a relationship between FOG and depression in patients with advanced PD. Four-hundred and fifty-four patients were randomized to three treatment arms: rasagiline (1 mg/day), entacapone (200 mg added to each levodopa dose) or placebo [2]. At baseline and after 10 weeks of treatment, FOG severity was assessed using the Freezing of Gait Questionnaire (FOG-Q) [20]. At baseline, FOG-Q scores were significantly associated with depressive symptoms, as measured with the Beck depression scale ($P<0.01$). In addition, the effect of rasagiline on FOG-Q scores was

significantly lower in patients with more severe depression at baseline ($P<0.05$) [2].

Both of these studies indicate that depression apparently modulates FOG, both in relatively mild and in more severe PD. The relationship between depression and FOG, however, might not be one of simple cause and effect. Frontal lobe dysfunction, common in PD, may influence the scores on the HAMD and Beck depression scales [21]. Thus, while depression is probably related to FOG, the extent to which it influences FOG awaits further study, for example, examining the effect of antidepressants on FOG.

1.2. The relationships between cognitive function and FOG

1.2.1. Dual tasking

The cognitive function of patients with FOG has not been well characterized. While Mini Mental State Exam (MMSE) scores are similar in patients with FOG and age- and disease-matched PD patients who do not report FOG [13], the MMSE provides only a gross measure of cognitive function. Two related phenomena may provide some insight into the potential contribution of cognitive function to FOG. The first is that certain patients with FOG must "stop walking while talking" (SWWT), an observation that has received much interest [22]. Although SWWT and FOG are entirely different entities, they share one key common feature, i.e., the cessation of forward movement despite the desire to move ahead. Stoppage of locomotion can be semi-voluntary, prioritizing the cognitive demand over locomotion if the two cannot run in parallel, as in the case of SWWT, or it can be involuntary. Both SWWT and FOG can occur in the same person and possibly even in the same episode. In fact, it may be difficult to determine how much of the "stop" is voluntary or involuntary. Prioritization is a normal physiological response of the brain to a dual tasking situation [23], but inappropriate prioritization might be hazardous to the individual [24–26]. If the available cognitive resources are inadequate to allow walking and the performance of a second, parallel task, such as talking, the maintenance of upright balance must receive precedence-safety first. Thus, in such a situation, the patient may deal with the non-locomotor task while standing and resume walking only when sufficient resources are freed up to allow concentration on walking, hence SWWT [22]. FOG might also be related to insufficient cognitive resources, however, in contrast to SWWT, FOG is unintentional by definition. Be that as it may, one can speculate that FOG episodes could occur when a patient wishes to perform another task simultaneously. While controlled studies have not yet demonstrated it, our clinical experience indicates that dual tasking frequently provokes FOG in PD patients with a history of FOG.

Furthermore, our clinical observations lead us to speculate that the inappropriate response to dual tasking, namely the effort to free oneself from FOG, may lead to falls. Clearly, many other factors also determine whether FOG results in a fall, but it is noteworthy that FOG is an independent risk factor for falls among patients with PD [27]. Direct confirmation that dual tasking causes FOG is lacking, but indirect evidence supports the idea that dual tasking may not only cause FOG, it might also exacerbate the predisposition to FOG among patients already prone to freezing.

In addition to the treatment with pramipexole [8] and possible other dopamine agonist drugs [7], five factors have been clearly associated with increased FOG severity: 1) the "OFF" state [3]; 2) disease severity [1,5,2]; 3) depression [2,6]; 4) increased gait dys-rhythmicity (stride-to-stride time variation) [27]; and 5) increased right/left leg swing time dys-synchronization [13]. Anything that strengthens the "OFF" state, increases its duration or heightens gait dys-rhythmicity or dys-synchrony may lower the threshold for FOG. Dual tasking (e.g., subtracting serial 7's) both increases gait dys-rhythmicity and asymmetry/dys-synchrony in PD patients [25], suggesting that it might also directly or indirectly pave the way for FOG. Thus, the ring of a telephone may bring about a freezing episode in a patient with a history of FOG. Similarly, FOG may be more likely in a PD patient who has to walk through a doorway and adjust his/her steps accordingly.

The relationship between dual tasking, cognitive function, affect and FOG is complex. The burden of carrying out a second task may provoke stress and anxiety as well, in which case multiple mental aspects could be involved.

2. A suggested conceptual model

Based on the above observations, we propose a conceptual framework that describes the contribution of mental aspects to FOG (Fig. 1). Depression and anxiety may place a chronic load on mental health, and depression has been associated with gait changes, including increased stride-to-stride variability [28,29]. Dual tasking and mental loading increase stride-to-stride variability [25,30], right/left leg dys-synchronization, and asymmetry in PD patients [25], thus lowering the threshold for FOG. In a similar way, depression, stress and mental loading might lead to disturbed inter-hemispheric

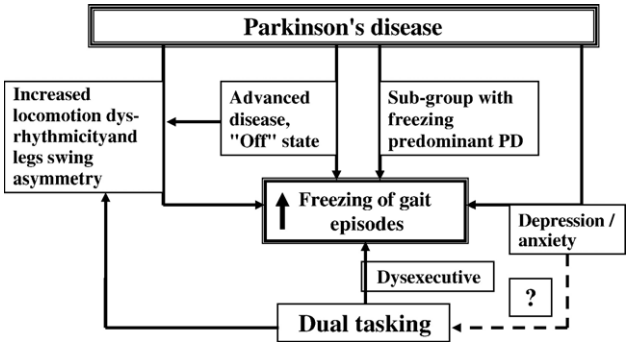

Fig. 1. Conceptual framework relating freezing of gait (FOG) to mental and motor aspects. Advanced Parkinson's disease, depression, stress, anxiety and cognitive challenges in the form of dual tasking may all act to increase gait dys-rhythmicity, dys-synchrony and asymmetry and predispose to FOG.

synchronization, another factor that predisposes to FOG [13]. The combination of these factors together with advanced PD, putative motor disturbances specific to patients with FOG and other yet to be described elements set the stage and heighten the probability that persons with a history of FOG will be even more likely to experience freezing in a stressful or another mentally challenging situation.

FOG is an episodic entity and can be provoked or alleviated by many intrinsic and extrinsic factors. Any attempts to understand the pathophysiology of FOG and to develop treatments must take into account its multifactorial nature. Mental aspects (e.g., both affect and cognition) are likely to play an important role as intrinsic, predisposing factors. Treatment interventions that improve "OFF" symptoms and signs, gait rhythmicity and asymmetry (e.g., levodopa or rhythmic auditory stimulation) have been shown to decrease FOG frequency and severity [3]. If mental dysfunction predisposes to FOG, one could anticipate that improvement of mental function will reduce the frequency and severity of FOG. It remains to be seen whether anti-depressants and other medications that improve mental function can help to alleviate FOG.

Acknowledgments

We thank Esther Eshkol for her editorial assistance and Judith Kna'ani for her secretarial support. This work was supported in part by the National Parkinson Foundation, the Parkinson's Disease Foundation, and by the National Institutes of Health grants AG-14100, RR-13622, HD-39838 and AG-08812.

References

[1] Giladi N, McMahon D, Przedborski S, Flaster E, Guillroy S, Kostic V, et al. Motor blocks ("freezing") in Parkinson's disease. Neurology 1992;42:333–9.
[2] Giladi N, Tal Y, Meiron R, LARGO FOG Sub-Study Group. Validation of the Freezing of Gait Questionnaire (FOG-Q) in Parkinson's disease. Gait Posture 2005;21:S94.
[3] Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur J Neurol 2003;10:391–8.
[4] Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord 2004;19(8):871–84.
[5] Moore O, Peretz C, Giladi N. Freezing of gait has significant effect on quality of life in Parkinson's disease. Mov Disord 2005;20:S115.
[6] Giladi N, McDermott M, Fahn S, Przedborski S, Jankovic J, Stern M, et al. Freezing of gait in Parkinson's disease: prospective assessment of the DATATOP cohort. Neurology 2001;56:1712–21.
[7] Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000;42(20):1484–91.
[8] Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. JAMA 2000; 284(15):1931–8.
[9] Shoulson I, Oakes D, Fahn S, Lang A, Langston JW, LeWitt P, et al. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of Parkinsonism trial. Ann Neurol 2002;51(5):604–12.
[10] Giladi N, Balash Y. Treatment of Parkinsonian gait disturbances. In: Hausdorff JM, Alexander NB, editors. Evaluation and management of gait disorders. Marcel Dekker Inc. p. 273–83.
[11] Krause M, Fogel W, Mayer P, Kloss M, Tronnier V. Chronic inhibition of the subthalmic nucleus in Parkinson's disease. J Neurol Sci 2004; 219:119–24.
[12] Nieuwboer A, De Weerdt W, Dom R, Lesaffre E. A frequency and correlation analysis of motor deficits in Parkinson patients. Disabil Rehabil 1998;20(4):142–50.
[13] Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann Neurol 2005;57:656–63.
[14] Lieberman, A. Freezing of gait, anxiety and panic. J Neurol Sci in press.
[15] Vazquez A, Jimenez-Jimenez FJ, Garcia Ruiz P, Garcia-Urra D. "Panic attacks" in Parkinson's disease. A long term complication of levodopa therapy. Acta Neurol Scand 1993;87:14–8.
[16] Narabayashi H. Clinical analysis of akinesia. J Neural Transm 1980; 16:129–36.
[17] Parkinson Study Group. DATATOP: a multi center controlled clinical trial in early Parkinson's disease. Arch Neurol 1989;46:1052–60.
[18] Fahn S, Elton R, Members of the UPDRS development committee. Recent developments in Parkinson's disease. In: Fahn S, Marsden CD, Calne D, Goldstein M, editors. Vol 2. Florham Park, NJ: Macmillan Health Care Information, 1987:153–163, 293–304.
[19] Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005;365:947–54.
[20] Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with Parkinsonism. Parkinsonism Relat Disord 2000;6:165–70.
[21] Henry J, Crawford JR. A metaanalytic review of verbal fluency deficits in depression. J Clin Exp Neuropsychol 2005;27(1):78–101.
[22] Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. Lancet 1997;349:617.
[23] Woollcott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture 2002; 16(1):1–14.
[24] Bloem BR, Vakenburg VV, Slabbekoorn M, van Dijk JG. The multiple tasks test. Strategies in Parkinson's disease. Exp Brain Res 2001; 137(3–4):478–86.
[25] Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? Eur J Neurosci 2005;22:1248–56.
[26] Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual tasking effects on gait variability: the role of aging, falls, and executive function. Mov Disord in press.
[27] Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. J Neurol Sci 2003;212:47–53.
[28] Hausdorff JM, Peng CK, Goldberger Al, Stoll AL. Gait unsteadiness and fall risk in two affective disorders: a preliminary study. BMC Psychiatry 2004;4:39.
[29] Paleacu D, Shutzman A, Giladi N, Simon ES, Herman T, Hausdorff JM. Gait disturbances in depressed patients: effects of pharmacologic therapy. Mov Disord 2005;20:S60.
[30] Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. J Geriatr Psychiatry Neurol 2003;16:53–8.