



Review

Freezing beyond gait in Parkinson's disease: A review of current neurobehavioral evidence

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ABSTRACT

Besides the continuous motor impairments that characterize Parkinson's disease (PD), patients are frequently troubled by sudden paroxysmal arrests or brief episodes of movement breakdown, referred to as 'freezing'. Freezing of gait (FOG) is common in advanced PD and typically occurs in walking conditions that challenge dynamic motor-cognitive control. Mounting evidence suggests that episodic motor phenomena during repetitive upper limb (e.g. writing), lower limb (e.g. foot tapping) and speech sequences resemble FOG and may share some underlying neural mechanisms. However, the precise association between gait and non-gait freezing phenomena remains controversial. This review aimed to clarify this association based on literature on non-gait freezing published between 2000 and 2013. We focused on clinical and epidemiological features of the episodes and their relevance to current influential models of FOG, including recent neuroimaging studies that used a non-gait freezing paradigm as a proxy for FOG. Although not capturing the full complexity of FOG, the neurobehavioral insights obtained with non-gait freezing paradigms will contribute to an increased understanding of disturbed brain-behavior output in PD.

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Abbreviations: FOG, freezing of gait; FOG-Q, freezing of gait questionnaire; PD, Parkinson's disease; PD + FOG, PD patients with freezing of gait; PD – FOG, PD patients without freezing of gait; UL, upper limb; UPDRS, unified Parkinson's disease rating scale.

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1. Introduction

Parkinsonian motor disturbances are characterized by spatio-temporal control deficits such as bradykinesia, hypokinesia, increased timing and scaling variability and impaired bilateral coordination (Jankovic, 2008). This clinical pattern is especially

observed when patients perform repetitive, sequential movements that recruit motor processes through the dysfunctional basal ganglia and manifest themselves in many daily activities such as walking, writing and speaking. Regarding locomotor control, Giladi et al. (2013) emphasized the distinction between continuous gait impairments that consistently affect the gait pattern, and episodic phenomena that are transient and unpredictable. Freezing of Gait (FOG) is without doubt the best described type of episodic movement breakdown and is defined as a 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' (Nutt et al., 2011). FOG thus refers to both complete gait arrests as well as periods with severely disrupted walking patterns, yielding a nearly complete loss of proficient gait such as shuffling. Clinically, FOG is often accompanied by high-frequency, trembling-like leg movements and festination or hastening phenomena, i.e. rapid steps with an ever decreasing step length (Nutt et al., 2011). Indeed, kinematic analysis of lower limb segments during an episode of FOG, showed highly abnormal rather than completely absent movement patterns, which differentiates the episode from continuous abnormalities, voluntary stops and fatigue (Bloem et al., 2004; Hausdorff et al., 2003; Nieuwboer et al., 2001; Schaafsma et al., 2003). FOG is a debilitating phenomenon that negatively impacts on mobility, falls and quality of life in patients with Parkinson's disease (Moore et al., 2007; Kerr et al., 2010).

FOG research has largely been driven by two important approaches. Firstly, although FOG is a common gait disorder (Macht et al., 2007), it does not affect all patients equally, suggesting that the comparison of patients with FOG (PD + FOG) and patients without FOG (PD – FOG) may aid in the search for neurobehavioral markers of the symptom. Secondly, patients typically freeze in response to increased motor, cognitive and limbic load, such that triggers of FOG have been extensively investigated (Nutt et al., 2011; Nieuwboer and Giladi, 2013). These insights have catalyzed the development of a number of topical papers that have linked FOG to a combination of exaggerated motor impairments (see Plotnik et al., 2012; Heremans et al., 2013a for review) and reduced cognitive resources that involve executive functioning (see Heremans et al., 2013b; Shine et al., 2013d; Vandebosscche et al., 2012 for review). How these factors influence the underlying mechanisms of FOG may depend on the specific situation or 'type' of FOG, for example at gait initiation or during ongoing locomotion but this is currently unclear (see Nieuwboer and Giladi, 2013 for review).

Giladi et al. (1992) proposed the general term 'motor blocks' for the episodic motor phenomena inherent to PD, irrespective of the type of movement and the effectors involved. Early studies reported that finger tapping provokes 'manual motor blocks' (Ziv et al., 1999) and 'finger festination' (Nagasaki et al., 1996), which showed correlations with patients' gait abnormalities. Similarly, Ackermann et al. (1993) provided circumstantial evidence for 'speech freezing' in one akinetic-rigid patient who demonstrated abnormally fast speech repetitions with reduced articulatory amplitude during an oral diadochokinetic task. Since then, the number of publications on episodic phenomena during repetitive upper limb, lower limb and speech motor control has continued to increase. Moreover, these non-gait freezing phenomena are currently being used as proxies for freezing of gait in neuroimaging experiments, as directly studying walking itself is not possible in a scanning environment (Shine et al., 2013a,b,c; Vercruyse et al., 2013). However, the overlap between clinical and epidemiological characteristics of non-gait freezing problems and FOG is still a matter of debate. In addition, it is currently unclear whether the recent motor-cognitive models that explain the emergence of breakdown during gait (see Nieuwboer and Giladi, 2013 for review), translate to similar breakdowns in motor control that is not associated with gait.

1.1. Aim and scope of the review

The primary aim of this review was to critically examine the link between FOG and non-gait freezing phenomena based on literature published between January 2000 and October 2013. We will therefore describe and illustrate episodic phenomena in studies that examined motor control involving the lower limbs (Section 2.1), upper limbs (Section 2.2) and speech (Section 2.3) in patients with Parkinson's disease. In keeping with the FOG definition by Nutt et al. (2011), we aimed to discuss all non-gait freezing-like behavior including actual arrests as well as motor phenomena that are tightly interlinked with FOG (e.g. festination and hastening). As the existence of 'subtypes' of FOG is still a matter of debate, we included non-gait freezing phenomena at the beginning as well as during ongoing movement. We specifically discuss their clinical manifestation, the behavioral constraints that triggered the episode and the kinematic properties during the episode, which will be highlighted in overview figures. In addition, we report the evidence pro or contra the co-occurrence of non-gait freezing and FOG within patients. The parallels between lower limb, upper limb and speech freezing are then combined (Section 2.4) in order to explore their relevance to current conceptual models of FOG (Nieuwboer and Giladi, 2013).

As a secondary aim, we summarized the results of recent neuroimaging studies that adopted a non-gait freezing motor paradigm to unravel the brain mechanisms related to episodic breakdown in PD (Section 3). The novel insights will be discussed against a background of core involvement of basal ganglia networks in regulating sequential motor tasks and in dynamically integrating motor-cognitive processes.

Finally, the last section (Section 4) provides tentative conclusions regarding the evidence and relevance of non-gait freezing in relation to FOG.

2. Current evidence on non-gait freezing

In the upcoming paragraphs, we outline the main characteristics of episodic motor phenomena that were described in PD patients during the performance of experimental or functional tasks involving the lower limbs (but not gait), upper limbs and speech control. We used PubMed to search for literature of which the title and/or abstract made mention of an episodic failure termed 'motor block(s)', 'motor arrest(s)', 'hesitation', 'freezing', 'freezing of gait', 'gait freezing', 'akinesia/akinetic', 'festination', 'hastening' or 'movement breakdown' in combination with one of the search terms covering the types of movement under investigation ('upper limb', 'lower limb', 'hand(s)', 'finger(s)', 'feet/foot', 'stepping' or 'articulation/articulatory', 'oral', or 'speech'). Next, articles were screened for relevance based on their abstract and main text. Other relevant references cited by these papers were also explored. After exclusion of (1) papers not written in English, (2) review articles, (3) studies on continuous motor deficits without description of an episodic event and (4) articles published before January 1st 2000, 33 articles were maintained (nine on lower limb phenomena, 17 on upper limb phenomena, four on speech disturbances and two on more than one type of non-gait freezing).

2.1. Episodic motor phenomena in lower limb movements

The first part of Table 1 summarizes the evidence on episodic motor phenomena during lower limb movements in PD patients. Abe et al. (2003) investigated rotational velocity waveforms in order to assess inter-limb coordination deficits during semi-passive pedaling movements in PD and control subjects. The bicycle ergometer allowed for uncoupled pedaling of left and right legs. The authors found that whereas healthy subjects oscillated the

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