REVIEW

Characterizing Freezing of Gait in Parkinson's Disease: Models of an Episodic Phenomenon

Alice Nieuwboer, PhD,[1]* and Nir Giladi, MD[2]

[1]*Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium*
[2]*Movement Disorders Unit, Department of Neurology, Tel-Aviv Medical Center, Sackler School of Medicine, Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel*

ABSTRACT: Freezing of gait (FOG) is a very disabling and common gait disorder in Parkinson's disease (PD). The first aim of this article was to provide a methodological and critical review of the most common research approach to understand FOG, ie, comparing the behavior of freezers with that of non-freezers. The review demonstrates that studies often fall short in clearly defining the freezer\non-freezer groups and in controlling for disease severity and other confounders. These problems complicate data interpretation on FOG. The second aim of this article was to summarize the literature on the potential mechanisms behind the episodic nature of FOG in the following four models: (1) The *threshold model* assumes that FOG occurs when the accumulation of various motor deficits reinforce each other to a point of motor breakdown; (2) the *interference model* proposes that FOG represents an inability to deal with concurrent cognitive, limbic, and motor input, causing an interruption of locomotion; (3) the *cognitive model* views FOG as induced by a failure to process response conflict, leading to behavioral indecision; and (4) the *decoupling model* sees FOG as a disconnection between preparatory programming and the intended motor response as a result of which automatic movement generation gets stuck. These four theoretical premises are still incomplete and do not fully explain FOG. The depletion of motor and cognitive reserves and an increasingly complex response to levodopa with disease progression will also have an impact on the emergence of FOG episodes. © 2013 International Parkinson and Movement Disorder Society

Key Words: freezing of gait; Parkinson's disease; executive function; gait

The problem of freezing of gait (FOG) in Parkinson's disease (PD) is an important target for investigation in movement disorders gait research. A freezing episode is not only fascinating to the observer but signifies a very distressing experience for the patient.[1] Between 21% and 27% of patients in the early stages of PD report experiencing FOG.[2,3] In the later stages, this number increases up to 80%.[3,4] It is interesting to note that not all patients with PD develop FOG,[4] but the possibility that it will appear in all advanced PD patients after a long enough washout period of levodopa (L-dopa) has never been ruled out. FOG is tightly associated with synucleinopathies like PD and multiple system atrophy.[5] However, it is observed frequently and even earlier in the course of other pathologies like progressive supranuclear palsy, high-level gait disorders, and vascular parkinsonism.[5,6]

The episodic nature of FOG makes it difficult to study its underlying mechanisms.[7] A way to bypass this problem is to examine how the motor and cognitive profiles of freezers differ from those of non-freezers. Although this research paradigm has led to some useful insights, the first aim of this article was to critically examine the drawbacks of comparing groups with and without FOG based on an analysis of the literature between 2008 and March 2013. The second aim was to summarize current thinking on the intermittent nature of FOG in four models and reflect on how these models may relate to the various types of FOG in the clinical setting.

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Dr. Alice Nieuwboer,: KU Leuven, Faculty of Kinesiology and Rehabilitation Sciences, Department of Rehabilitation Sciences, Tervuursevest 101, 3001 Leuven, Belgium; alice.nieuwboer@faber.kuleuven.be

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Between Group Comparisons: Are There True Freezers and Non-freezers?

In Table 1, we summarize 35 studies[8–42] that were carried out over the past 5 years in which groups with and without FOG were compared. We included studies that were specifically designed to provide insight into the motor and non-motor symptoms and the neural networks underlying FOG, excluding psychometric and effect studies. We also disregarded studies that contrasted freezers with healthy controls because of the difficulty of isolating disease-specific from freezing-specific findings in these designs. Studies were critically reviewed by two independent reviewers on the following 3 criteria: subgroup classification, how L-dopa was taken into consideration, and how control was implemented for subgroup differences.

Subgroup Classification

Table 1 indicates that, in most publications, the freezer classification was based on the patient's retrospective self-assessment of FOG over a period of time using various questionnaires. Patients who had the symptom outside this arbitrarily chosen time zone were classified as non-freezers. Snijders et al.[43] suggested a decision tree to refine freezer/non-freezer classification by identifying 3 categories: (1) a "self-reported freezer," (2) a "probable freezer" when FOG is confirmed by a third person (caregiver), and (3) a "definite freezer" when freezing is actually observed during formal objective testing. To enhance the FOG specificity of the findings, it would make sense to compare definite freezers with non-freezers. However, achieving comparability between such groups for other disease characteristics would be a difficult task. In addition, excluding probable or self-reported freezers limits the generalizability of the findings, because patients may actually experience FOG but suppress it during testing. In 11 of the 35 studies, comparisons were based on definite freezers. In 6 studies, mixed groups were included, and 18 investigations were based on self-reported freezers.

Relation With Levodopa

Table 1 lists the 14 freezer/non-freezer studies that were carried out with patients *on* medication when FOG may have been suppressed. The relation between FOG and dopamine depletion is notoriously complex and non-linear.[44] The spectrum of response can range from *"off"* FOG, when freezing episodes are completely relieved by L-dopa, to *"on"* FOG, when the blocks are induced or exacerbated by L-dopa.[45] "L-Dopa–unresponsive" FOG may indicate an intermediary subtype in which the effect of dopaminergic stimulation is not strong enough to prevent FOG even if other parkinsonian motor signs are improved in the *"on"* state. A recent study[46] demonstrated that, when subthalamic nucleus (STN)-stimulated patients with *"off"* FOG were contrasted to those who had "L-dopa–unresponsive FOG," executive function was more impaired in the latter group, likely reflecting greater pathology in non-dopaminergic circuits. We observed that 23 studies in Table 1 did not report proportions of L-dopa–responsive or L-dopa–unresponsive freezers and that, in 15 studies, the L-dopa equivalent dose (LED) was not provided.

Control for Confounders

Freezer/non-freezer differences are likely with respect to disease severity and duration[47] as well as non-motor symptoms, such as cognitive ability and depression.[26,48] Table 1 also lists 23 studies in which freezer subgroups were not well matched for several aspects of disease state. In 12 of those studies, mismatching was apparent for disease duration and severity, as expressed by Unified Parkinson's Disease Rating Scale-motor part (UPDRS III_ scores) or Hoehn and Yahr stage. In addition, summed disease severity scores mask the possibility that freezers and non-freezers may have different disease phenotypes, ie, postural instability and gait deficit (PIGD) and tremor-dominant subtypes.[49,50] Except for one study in which this was not reported,[12] all studies used groups that were well matched for age. In 11 studies, groups differed in terms of global cognitive scores; and, in another 11 studies, cognitive descriptors were not reported. Table 1 indicates that eight studies applied statistical corrections to account for the confounding variables, and five studies[2,8,9,14,32] reported insignificant correlations between the confounders and primary outcomes. Overall, the fact that disease severity and cognitive impairment were different between groups or were unknown in a large number of studies implies that drawing direct inferences from these results to FOG must be done cautiously.

Based on the above analysis and the awareness of how difficult it is to elicit FOG frequently and consistently in research laboratories,[7] the freezer/non-freezer comparison remains a useful paradigm for hypothesis generation. To optimize the paradigm and enhance data interpretation, we recommend the following: (1) define subgroups according to the Snijders et al. algorithm,[43] (2) use a validated and standardized clinical protocol to observe and rate FOG,[43,51–53] (3) develop consensus criteria for defining non-freezers, (4) report LED and cluster patients according to FOG L-dopa–responsiveness, (5) match patients for disease severity and global cognitive capacity, and (6) use sample sizes that allow for statistical correction for additional confounders. Nutt et al.[54]questioned whether the dichotomy between freezers and non-freezers was better replaced by a continuous spectrum ranging from absent to severe FOG. This approach can be adopted in future studies when measurement tools that permit time-varying

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TABLE 1. Studies comparing characteristics in freezers and non-freezers

Included studies	Groups	FR definition	Classification method	Not matched[a]	Not reported	*On/off*
Comparison of motor function						
Plotnik et al., 2008[8]	21 FR/13 NFR	Self-reported	FOG-Q item 3	—	LED, % on/off FR	*On/off*
Chee et al., 2009[9]	16 FR/10 NFR	Definite	Interview, clinical assessment, observation	DD, H&Y, UPDRS III, GDS	LED, % on/off FR	*Off*
Nieuwboer et al., 2009[10]	10 FR/10 NFR	Self-reported	FOG-Q item 3	DD, UPDRS III, LED	—	*Off*
Almeida and Lebold, 2010[11]	15 FR/16 NFR	Definite	UPDRS II item 14 observation	Cognitive tests not reported	—	*On*
Delval et al., 2010[12]	8 + 2 FR/10 NFR	Definite/self-reported	FOG-Q item 3, observation	Not reported	LED, % on/off FR	*Off*
Lebold and Almeida, 2010[13]	15 FR/16 NFR	Definite	UPDRSII, observation	LED: Cognitive tests not reported	—	*On*
Spildooren et al., 2010[14]	14 FR/14 NFR	Self-reported	NFOG-Q	MMSE, SCOPA-Cog	LED, % on/off FR	*Off*
Cohen et al., 2011[15]	11 FR/13 NFR	Self-reported	FOG-Q	H&Y, UPDRS: Cognitive tests not reported	LED, % on/off FR	*Off*
Nanhoe-Mahabier et al., 2011[16]	5 + 7 FR/15 NFR	Self-reported/definite	NFOG-Q, observation	—	LED	*Off*
Okada et al., 2011[17]	10 FR/7 NFR	Self-reported	FOG-Q item 3	LED: Cognitive tests not reported	—	*On*
Danoudis et al., 2012[18]	16 FR/10 NFR	Definite	FOG-Q item 3, clinical assessment	DD; H&Y; UPDRS III[c]	LED, % on/off FR	*Off*
Peterson et al., 2012[19]	12 FR/19 NFR	Self-reported	FOG-Q item 3	Cognitive tests not reported	LED, % on/off FR	*Off*
Vercruysse et al., 2012[20]	11 FR/12 NFR	Self-reported	NFOG-Q	SCOPA-Cog	% On/off FR	*Off*
Vercruysse et al., 2012[21]	11 FR/12 NFR	Self-reported	NFOG-Q	MMSE	% On/off FR	*Off*
Bhatt et al., 2013[22]	10 FR/10 NFR	Definite	Interview, observation, clinical assessment	Cognitive tests not reported	LED, % on/off FR	*On*
Frazzitta et al., 2013[23]	30 FR/30 NFR	Definite	Observation	UPDRS II; Cognitive tests not reported	—	*On*
Nanhoe-Mahabier et al., 2013[24]	5 + 2 FR/7 NFR	Definite/self-reported	NFOG-Q, observation	—	LED, % on/off FR	*Off*
Spildooren et al., 2013[25]	13 FR/14 NFR	Self-reported	NFOG-Q	MMSE	LED, % on/off FR	*Off*
Comparison of nonmotor function						
Amboni et al., 2008[26]	13 FR/15 NFR	Self-reported	FOG-Q item 3	UPDRS II	% On/off FR	*On*
Maidan et al., 2010[27]	10 FR/10 NFR	Self-reported	FOG-Q item 3		LED, % on/off FR	*Off*
Tan et al., 2011[28]	12 FR/12 NFR	Definite	Interview, observation, clinical assessment	UPDRS[c]: Cognitive tests not reported	LED, % on/off FR	*On*
Vandenbossche et al., 2011[29]	11 FR/11 NFR	Self-reported	NFOG-Q	MMSE	% On/off FR	*On/off*
Knobl et al., 2012[30]	10 FR/10 NFR	Probable	UPDRS II (14), interview	DD, UPDRS: Cognitive tests not reported	LED, % on/off FR	*On*
Lord et al., 2012[31]	27 FR/27 NFR	Self-reported	FOG-Q item 3	Cognitive tests not reported; UPDRS III[c]	% On/off FR	*On*
Nantel et al., 2012[32]	18 FR/11 NFR	Definite	FOG-Q item 3, SIP task	DD, UPDRS III (axial items), cognitive tests	LED	*Off*
Vandenbossche et al., 2012[33]	14 FR/14 NFR	Self-reported	NFOG-Q	DD[c], MMSE, SCOPA-Cog	% On/off FR	*On*
Vercruysse et al., 2012[34]	23 FR/24 NFR	Definite	NFOGQ, observation	MMSE, SCOPA-Cog	—	*On*
Vandenbossche et al., 2013[35]	14 FR/14 NFR	Self-reported	NFOG-Q	—	% On/off FR	*On*

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TABLE 1. *Continued*

Included studies	Groups	FR definition	Classification method	Not matched[a]	Not reported	*On/off*
Comparison of neural function						
Snijders et al., 2011[36]	3 + 9 FR/12 NFR	Probable/ definite	NFOG-Q, observation, clinical assessment	—	LED	*Off*
Thevathasan et al., 2011[37]	8 FR[b]/8 NFR	Self-reported or probable (unclear)	FOG-Q item 3	UPDRS III (27–30)	—	*Off*
Imamura et al., 2012[38]	21 FR/34 NFR	Self-reported	UPDRS II (14)	Levodopa	% On/off FR	*Off*
Kostic et al., 2012[39]	17 FR/20 NFR	Definite	FOG-Q item 3, clinical assessment, observation	UPDRSIII[c], MMSE[c], HADS, cognitive tests[c]	% On/off FR	*Off*
Tessitore et al., 2012[40]	16 FR/13 NFR	Self-reported	FOG-Q item 3, clinical assessment	UPDRS II & III (PIGD), BDI, cognitive tests[c]	% On/off FR	*On*
Tessitore et al., 2012[41]	12 FR/12 NFR	Self-reported	FOG-Q item 3, clinical assessment	UPDRS II, FAB, cognitive tests[c]	% On/off FR	*On*
Shine et al., 2013[42]	14 FR/15 NFR	Definite	FOG-Q item 3, observation	UPDRS item 46, HADS[c]	—	*Off*

[a]Patients were not matched for parameters that were not primary or secondary outcomes.
[b]It is not clear whether patients had freezing of gait and/or postural instability.
[c]Analyses were statistically corrected for group differences.
FR, freezers; NFR, non-freezers; FOG-Q, Freezing of Gait Questionnaire; LED, levodopa equivalent dose; DD, disease duration; H&Y, Hoehn and Yahr stage; UPDRS III, Unified Parkinson's Disease Rating Scale-part III (clinician scored motor evaluation): UPDRS II, Unified Parkinson's Disease Rating Scale-part II (self-evaluation of activities of daily living); GDS, Geriatric Depression Scale; NFOG-Q, New Freezing of Gait Questionnaire; MMSE, Mini-Mental State Examination; SCOPA-Cog, Scales for Outcomes in Parkinson's Disease-Cognitive part; SIP, stepping in place; HADS, Hospital Anxiety and Depression Scale; PIGD, postural instability and gait deficit; BDI, Beck Depression Inventory.

FOG assessment are robust and valid.[55–58] Regardless of whether FOG is continuous or binary, we focus this report on the one thing that is without question and in need of further elucidation: the episode itself.

Definition and Episodic Nature of FOG

FOG is defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk."[54,59] The phenomenology of an episode as well as its precipitating and alleviating factors have been described extensively,[54] whereby high-frequency oscillations and festinating steps before and during FOG have been delineated as important markers.[60,61] Figure 1 illustrates the various ways in which freezing disrupts locomotion. In the figure, we have also included examples of freezing of repetitive upper limb movement due to their demonstrated similarities with FOG.[21] However, differences between FOG and freezing in other effectors also are apparent. Most notably, FOG, and not finger freezing, depends on posture and balance control and on dynamic gait adaptation in the face of obstacles.

Figure 1A demonstrates *akinetic freezing*,[62] typically occurring at movement initiation, in this case, of a repetitive flexion-extension sequence of the fingers. Even in this most akinetic example of freezing, ineffective movement attempts were registered, suggesting that, even in an *involuntary* phenomenon, there is voluntary effort embedded to overcome the block. Hence, the onset and termination of the episodes are intricately linked with the intention to execute a motor task. Unlike some other forms of triggered episodic neurological phenomena, such as epilepsy (ie, photosensitive) and paroxysmal dyskinesias (ie, the kinesiogenic and kinetic forms), freezing episodes never occur at rest but at "the wish to move." This intention to engage in voluntary action combined with the need to adjust movement to external circumstances or to internal motor commands seems to jam the system.

Figure 1B-D shows templates of *motor freezing*, which is defined as arrests in gait or other motor sequence progression without a clear external circumstance other than an alteration of the motor pattern itself, as far as can be interpreted by the observer. As stated above, internal motor commands may also alter during motor freezing. Typically, it presents itself during gait on an open runway (Fig. 1B) and during performance of a turn (Fig. 1C) or when performing movement sequences (Fig. 1D). In contrast, Figure 1E,F provides examples of FOG when triggered by external circumstances, ie, when reaching a destination (Fig. 1E) or passing through a doorway (Fig. 1F). Figure 1E,F depicts the erratic behavior of FOG and the complexity of its signal output when derived from movement registration in complex circumstances. Sometimes FOG (Fig. 1F) produces high-frequency oscillations and, at other times, unilateral attempts to come out of the block (Fig. 1E).

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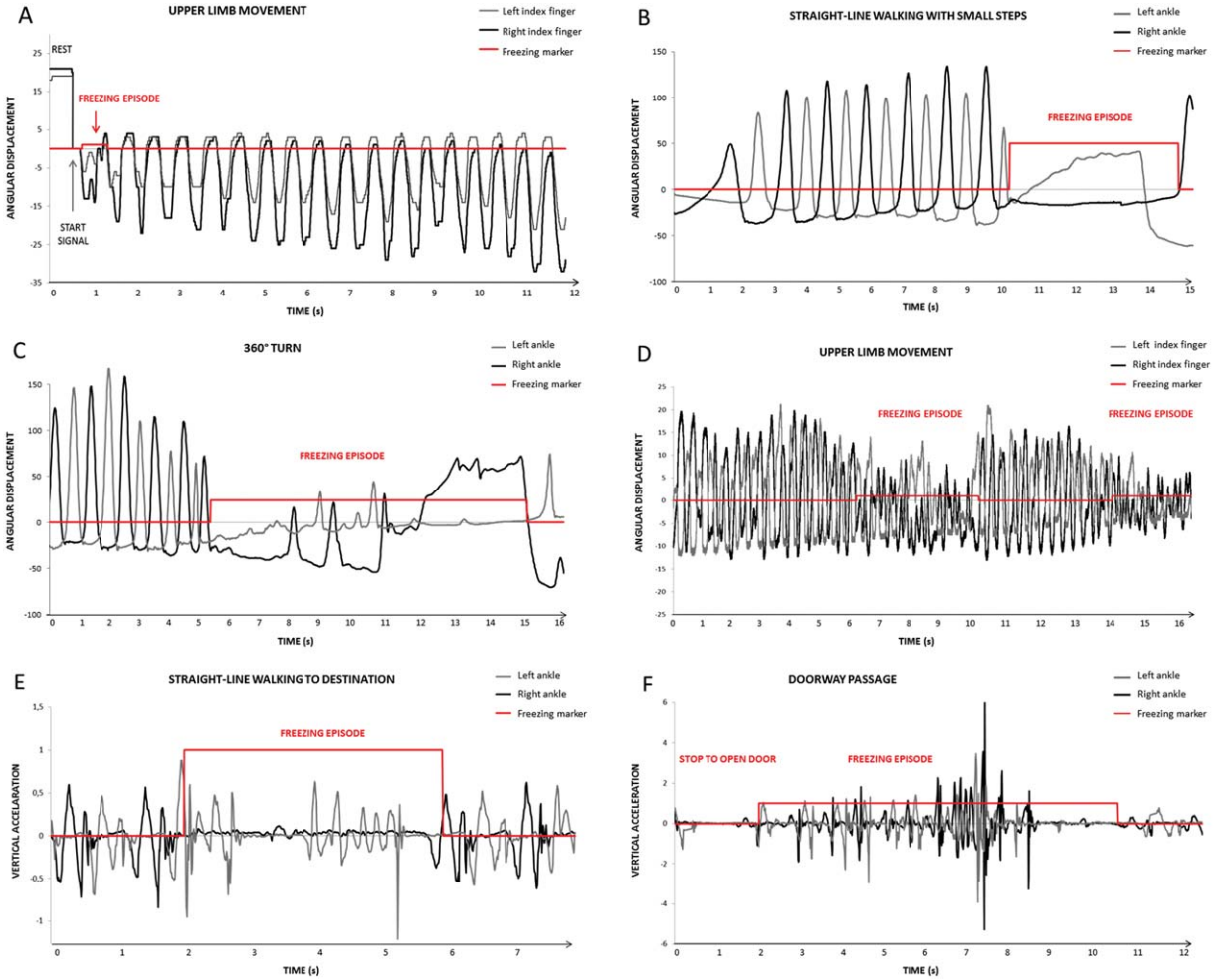

FIG. 1. Examples of freezing of gait (FOG) traces are shown. (**A**) In an example of akinetic freezing, angular displacement of the right (black line) and left (gray line) index finger is traced during a bilateral movement (in-phase) trial. Movement was performed while the patient was lying in a 3-Tesla magnetic resonance scanner during periods of movement alternating with rest periods. Data from the first 12 seconds of a 30-second trial are shown. Data were retrieved via shaft encoders fixed to the rotation axis of the orthoses, which was aligned with the metatarsophalangeal joint axis of the index finger. The red marker demarcates when freezing of the upper limb took place: immediately after the start signal, when the patient attempted to initiate repetitive movement after a period of rest (no video available). (**B**) In this example of motor FOG, angular displacement of the right (black line) and left (gray line) ankle is traced during straight-line walking. The patient was instructed to walk with small steps on an open runway. Data were retrieved using a VICON data-capturing system (Workstation 612; Vicon Motion Systems, Inc., Centennial CO), which was positioned around a 10-meter walkway. After 9.5 seconds, the patient experiences a freezing episode (red marker), during which cyclic ankle movements are completely absent (see also Video 1). (**C**) In this example of motor FOG, angular displacement of the right (black line) and left (gray line) ankle is traced during walking and while turning 360 degrees. Again, data were retrieved using the VICON data-capturing system positioned around a 10-meter walkway. After 3 seconds, the patient starts turning toward the left side, making smaller, stepping movements. A few seconds later, the patient has a freezing episode (red marker) and is clearly unable to produce rhythmic ankle movements. Intermittent larger movements are produced, but an effective step is only achieved 10 seconds later (see also Video 2). (**D**) In this example of motor freezing, angular displacement of the right (black line) and left (gray line) index finger is traced during a bilateral movement (anti-phase) trial. Movement was performed while sitting. Data from the last 16 seconds of a 30-second trial are shown. Data were retrieved via angular encoders placed on the rotation axis of the index fingers. The red marker demarcates two freezing episodes of the upper limb that are characterized by abnormally small movements with rapid, irregular frequency (no video available). (**E**) In this example of triggered FOG, vertical acceleration of the right (black line) and left (gray line) ankle is traced during straight-line walking toward a chair. Data were retrieved via accelerometers attached between ankle and knee joints of the right and left leg. The patient experiences balance problems and enters a freezing episode (red marker). After trying to get out of the block for 2 seconds, he enters into a total freeze on both sides. For about 2 seconds, the patient attempts to overcome the freeze. At the 5.8-second time mark, a large step of the right leg reintroduces normal walking (see also Video 3; note that the video and figure are not synchronized). (**F**) In this example of triggered FOG, vertical acceleration of the right (black line) and left (gray line) ankle is traced during straight-line walking toward a chair. Data were retrieved via accelerometers attached between ankle and knee joints of the right and left leg. After opening the door and walking through it with a tray, the patient has a freezing episode (red marker), which intensifies as he tries to continue walking, almost leading to a fall (see also Video 4; note that the video and figure are not synchronized).

Although different FOG types may appear in the same patient under varying circumstances, the diversity of the episodes calls for disassociating the various types if we are to understand the neural origins of FOG. The sections below present four models that have been described in the recent literature explaining the episodic nature of FOG. Figure 2 provides an overview of these 4 models.

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Four Models of Freezing Episodes

The "threshold model" of FOG

Plotnik et al.[63] suggested a "threshold model" to explain the transient occurrence of FOG. Even in normal coupled, cyclical movement, imposed temporal or spatial motor changes within the same motor effectors will reach a critical threshold of coordination instability.[64] In the face of parkinsonian gait, a highly coupled, bilateral motor task, such as walking, may deteriorate even more, reaching a threshold of locomotion breakdown earlier and with greater consequences. Why this occurs in freezers rather than in non-freezers is because, in the former group, gait between episodes is more disturbed and more susceptible to breakdown. Greater gait abnormalities were observed in freezers compared with non-freezers when *off* L-dopa in (1) step scaling,[9,18,65] (2) gait rhythmicity,[66] and (3) bilateral step coordination[8] and symmetry.[67]

Figure 2 shows that the threshold model predicts that it is possible to drive the motor system toward the freezing state when some of these critical gait deficits are exaggerated. Indeed, it was demonstrated that experimentally minimizing stride length[9]or increasing cadence during gait or repetitive stepping in place[68,69] provoked FOG episodes. Furthermore, the combination, rather than each separate manipulation, of step amplitude and rhythm induced a greater freezing-related, coordination deficit, although no actual FOG episodes were elicited.[70] Even in bilateral upper limb movements, which are less strongly coupled than gait, the threshold model holds. Time series of repetitive finger movement showed deterioration just before freezing, and finger freezing episodes were exacerbated by imposing small-amplitude and high-frequency constraints (see Fig. 1C).[20,21,71]

Because turning poses a greater demand on locomotion control by requiring asymmetrical step sizes and adjustment of bilateral coordination, the model may also explain FOG during this motor task.[14] It is interesting to note that FOG episodes tended to occur at the end of turning[25] and were more prominent during 360-degree turns compared with 180-degree turns,[43] although a clean comparison between turning angles was not made in the latter study. Contrary to non-freezers, freezers had increased step time variability,[22] higher cadence,[14] and disordered bilateral coordination[19] during turning, deficits that were correlated with a greater number of episodes among freezers. Cadence-reducing cues alleviated FOG[72] during turning, suggesting that rhythmic priming prevented patients from reaching the freezing threshold.

The threshold-driven, accumulative pattern of motor abnormality described above is likely to be distinct from motor fatigue. Progressive amplitude reduction or sequence breakdown during repetitive upper limb motion showed no correlation with clinical fatigue[73] and was solely dependent on frequency manipulations.[71] However, the distinction between motor fatigue and freezing needs further elucidation.

The "interference model" of FOG

Lewis and Barker[74] put forward an "interference model" to conceptualize a freezing interval. Although not termed as such by the authors, the term *interference* is used here for its resemblance with the construct of dual task interference. The model explains

Models of FOG	Principle	Prediction of FOG-episodes
Threshold[63]	Accumulation of motor deficits until threshold is reached and freeze occurs	Increase motor cycle frequency Decrease amplitude Increase coordination complexity
Interference[75]	Competition for common central processing resources induces breakdown	Increase number concurrent tasks Increase difficulty level tasks Increase load of external input
Cognitive[82]	Deterioration in processing of response conflict induces block	Increase incongruency level Increase response speed Increase load on executive function
Decoupling[90]	Decoupling between motor programs and motor response induces block	Increase strength startle stimuli Increase frequency startle stimuli Increase postural load or instability

FIG. 2. This chart summarizes the four models for the episodic appearance of freezing of gait (FOG).

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FOG as a momentary breakdown of concurrent information processing of cognitive and limbic load during motor tasks. It contends that decreased neural reserve in the segregated basal ganglia circuits—the oculomotor, sensorimotor, associative, and limbic loops[75]—leads to neuronal crosstalk between these circuits. Consequently, internal pallidal outflow becomes abnormal, inducing a temporary inhibition of the pedunculopontine nucleus (PPN), giving rise to FOG.[74] The model incorporates the idea that interference between neural circuits can be suspended or *reset* by focusing on goal-directed behavior or an external cue.[74,76]

Figure 2 indicates that, in contrast to the threshold model, the interference model would predict that FOG can be induced by increasing the number of concurrent tasks and their difficulty level. Several studies support the idea that loading both the motor and the cognitive systems, such as when exposed to environmental challenges, increases the likelihood of FOG[14,77] or FOG-like episodes.[11,30,77,78] The association between FOG and increased heart rate dynamics just before freezing and during actual episodes points to a possible limbic contributor to FOG.[27] However, none of those studies explicitly demonstrated the exact temporal coupling between the cognitive or limbic load and the onset of episodes.[14,30,77,78]

Recent imaging studies[42,79] support and extend the interference model, demonstrating that networks beyond the basal circuitry are involved in faulty processing of multimodal information. Shine and coworkers[42] compared brain activity in freezers and non-freezers during performance of alternating depression of left and right foot pedals in a virtual reality environment with low and high cognitive load. High cognitive load required suppression of incongruent responses and led to more delayed pedal responses in freezers. In these high-load conditions, freezers showed reduced activations in the mesolimbic frontostriatal areas and the left STN relative to non-freezers.[42] In addition, a regions-of-interest analysis demonstrated that the mesencephalic locomotor region was altered both structurally and functionally in freezers, and these changes were correlated with freezing severity.[36,79] Compared with continuous pedaling, increased activity in frontoparietal regions and reduced activity in some basal ganglia nuclei were observed during freezing of pedalling.[79] Although these delays were moderately correlated with FOG,[78] it is not clear whether these episodes reflect freezing or related cognitive processing lags, because it was demonstrated that the full pedaling motion inherent to bicycling was protective against FOG.[80]

The "cognitive model" of FOG

Vandenbossche et al.[81] proposed a "cognitive model" of FOG, conceptualized as a conflict-resolution deficit evident in situations requiring a response decision and exacerbated by global freezing-related executive dysfunction (see Fig. 2). Response selection and inhibition of unwanted responses require both implicit (automatic) and consciously controlled mechanisms.[82] Freezers and non-freezers exhibited impaired conflict resolution during neuropsychological congruency tests, but only in freezers was this significantly different from controls.[29] Set-shifting under time pressure, as measured by the Trail Making Test, also appeared to be related to FOG and not to other disease markers.[83,84] Furthermore, freezers demonstrated stronger automatic activation of incorrect responses and less efficient suppression of conflicting responses during incongruent trials.[33] These deficits were most prominent when the opportunity to allocate controlled input to compensate for these deficits was reduced, implying that executive dysfunction could enhance the risk of FOG.[33]

The frontostriatal circuits are considered central to mediating action selection and response inhibition in conjunction with the hyperdirect pathway, involving the STN and the right inferior frontal cortex.[85,86] These areas are implicated in signaling when a conflict is present and temporarily prevent premature action by raising the globus pallidus internus decision threshold, such that response selection is delayed until conflict is resolved.[87] Motor arrests provoked by incongruent response decision tasks were indeed associated with decreased blood oxygenation level-dependent (BOLD) responses in these subcortical regions, consistent with the cognitive model.[42]

Although the precise distinction between the inhibitory and automatic response generation components of the model needs further investigation, with current knowledge, Figure 2 puts forward that, by imposing faster response decisions and greater incongruence, FOG is induced. Also, the model predicts that FOG frequency would be correlated to executive dysfunction. It has been observed that freezers demonstrate more pronounced problems in several domains of executive dysfunction compared with non-freezers (for review, see Heremans et al.[88]). Brain imaging work also suggests that structural damage and reduced functional connectivity in the frontal and parietal cortices may underlie exaggerated executive dysfunction in freezers relative to non-freezers, but those results need further confirmation.[39–41]

The "decoupling model" of FOG

Jacobs et al.[89] proposed a "decoupling model" of FOG, whereby episodes are characterized by a decoupling between pre-planned motor programs and the release of an inherent movement or step at gait initiation. Overall, studies of voluntary gait initiation have shown delayed and under-scaled steps in PD, but these deficits proved surprisingly unrelated to freezing.[17,90,92] Equally, anticipatory postural adjustments

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(APAs), the preparatory phase of step initiation during which pressure increases under the swing limb to enable displacement of the center of mass over the stance limb,[89] were prolonged and more variable in PD[91] irrespective of FOG.

An experimental setup, whereby platform perturbations were meant to elicit automatic compensatory stepping reactions to avoid falling, demonstrated for the first time a freezing-specific problem.[89] Unlike healthy controls, patients with FOG had multiple dysfunctional APAs, resembling freezing-like, oscillatory behavior of the knees. These repeated loading-unloading cycles were accompanied by delayed or failed generation of stepping, which was interpreted as a malfunction in coupling an APA with a step. The fact that this decoupling mechanism was observed during automatically triggered responses is of critical importance. The discrepancy between a failure of an unconscious preparatory process and perceived movement intention may explain why patients describe FOG as having "their feet glued to the floor."

Okada et al.[17] reported that double limb support time of the first step during gait initiation was prolonged in freezers relative to non-freezers, possibly indicating compensatory behavior for increased postural instability and/or decoupling. A link between balance impairment, postural preparation, and movement decoupling in FOG is likely. During repetitive stepping in place, underscaled and inefficient weight transfers between both legs were highly correlated to FOG severity.[69] However, although FOG and postural instability coexist, currently, their shared mechanisms are poorly understood.[26]

Thevathasan et al.[92] provided preliminary evidence for the possibility of a decoupling model of freezing during automatic movement initiation through a startle-react paradigm. They demonstrated that patients with freezing and/or falling responded with a delayed startle response in axial muscles to auditory stimuli of varying loudness and proposed that the lack of these preprogrammed responses may be analogous to what happens during FOG. This was further supported by the finding that PPN stimulation restored these startle responses and improved turning times in freezers.[37] Using spectral analysis of local field potentials from implanted PPN electrodes, it was shown that α oscillations in the caudal PPN were attenuated just before and at the onset of a FOG episode,[93]; whereas α power increased when gait was normalized, pointing to a central role of the PPN in FOG.

Discussion and Future Directions

In this review, we have presented four possible models of the episodic nature of FOG as separate entities (see Fig. 2). However, it is probable that there may be various degrees of interplay between these explanatory models, partially explaining the heterogeneity of FOG. We speculate that the decoupling mechanism, together with the cognitive model, probably underlies akinetic FOG, which is mostly apparent at start hesitation, especially when a response decision is awaited. It is noteworthy that freezers reportedly had greater variability in deciding which swing limb to use when initiating gait relative to non-freezers, suggesting that a response selection deficit may interfere with motor coupling.[17] As such, abnormal pre-movements at gait initiation may express inadequately inhibited, prepotent responses during conflict resolution or failed attempts to generate motor programs, possibly even through "alternative networks," while trying to overcome the block. What exactly constitutes or brings on decoupling in the brain is still unclear and will require further unraveling.

During motor FOG, eg, when turning or walking on an open runway, both the threshold model and the decoupling model may be at play. When incremental gait abnormalities cross the freezing threshold and lead to a freezing episode, it may be more difficult to generate a normal preparatory motor response and release a stepping movement. Hence, the threshold and decoupling models probably reinforce each other.

All models are likely to play a role in triggered FOG, when freezing occurs in complex situations. In this case, external input from the environment may bring on processing difficulties of these concurrent, multiple inputs. This, alone or in conjunction with conflict resolution problems, may provoke FOG. Interference can further drive an already unstable motor system toward the freezing threshold,[63] after which the decoupling mechanism may preclude normal gait reinitiation. Hence, the decoupling and threshold models seem to play a part in most of the FOG types. The cognitive and interference models probably contribute to this to a greater or lesser extent. The interference and cognitive models also do not account for the high-frequency oscillations so commonly co-occurring with FOG.

What has not been discussed so far is that FOG episodes will occur against a background of motor and cognitive (functional) reserve, which fuels the chances that an episode will arise the more these resources become depleted with disease progression. This compensatory reservoir is determined by the underlying gradient of pathology, affecting critical locomotor circuits in different places.[54] Background cognitive capacity is also likely to have an impact on the susceptibility for FOG. Figure 2 acknowledges that cognitive impairment may lower the freezing threshold and negatively affect the processing capacity of concurrent input. Two recent multivariate studies confirmed that global cognitive impairment was an independent contributor to FOG.[34,76] Finally, the response to medication is another crucial factor in determining the breeding ground for FOG.

Previously, we demonstrated that freezer versus non-freezer comparisons fall short in fully enlightening the

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background risk factors of FOG. Therefore, it is encouraging that methodologies to measure even very subtle episodes on a continuous scale and with a high temporal resolution are advancing. A number of validation studies using movement registration sensors during walking demonstrated that the calculation of spectral analysis-derived measures hold promise for future FOG severity indexes.[55–58] This possibility means that power-based, multivariate studies of FOG are within reach. To develop drug treatment and behavioral strategies that may protect against FOG or delay its onset, a better understanding of the factors that lead up to motor-cognitive system failure and its possible compensatory mechanisms is needed. For this aim, the onset of the FOG symptom has to be measured prospectively as well as its motor, cognitive, affective, and neural correlates using structural and functional connectivity brain-imaging methods.

From the above, it is evident that none of the models presented provide an overarching or full explanation of FOG, and refinements and extensions are required. Future studies need to explicitly identify which underlying FOG model is being adopted to enable accurate data interpretation. For instance, the only two functional magnetic resonance imaging studies of FOG-like episodes used an interference-cognitive model[79] and a motor threshold model of FOG[94]; consequently, altered activity in mainly cognitive[79] and motor[95] neural networks were reported, respectively.

The BOLD response is a slow method for studying short freezing events and generates limited statistical power. Recent work is pointing to the feasibility of using electroencephalographic signals to detect FOG episodes with sufficient temporal resolution through wavelet transform analysis techniques.[96] A drawback of this method is that critical areas, notably, the mesencephalic locomotor region and basal ganglia, cannot be accessed. Preliminary data indicated that wavelet energy changed 5 seconds before FOG and produced electroencephalographic signals that were distinct from those derived in Alzheimer's disease or epileptic seizures.

To conclude, we have presented four possible explanatory concepts of FOG, mostly of motor and cognitive origins, that are intertwined to a greater or lesser extent in different situations in which FOG occurs. These models need further validation and testing, but we suggest that this theoretical framework, as well as the precise measurement of FOG and its epiphenomena, will pave the way to a better understanding and characterization of the episodes.

Legends to the Videos

Video 1. Freezing in a gait laboratory: The patient is represented by a stickman. He was instructed to walk with small steps on an open runway. Data were retrieved using a VICON data-capturing system (Workstation 612; Vicon Motion Systems, Inc., Centennial CO) positioned around a 10-meter walkway. Motion registration is captured in Figure 1B of the article.

Video 2. Freezing in a gait laboratory during turning: The patient is represented by a stickman. Data were retrieved using the VICON data-capturing system (Workstation 612; Vicon Motion Systems, Inc.) positioned around a 10-meter walkway. Motion registration is captured in Figure 1C of the article.

Video 3. Freezing during straight-line walking toward a chair: Data were retrieved using accelerometers attached between ankle and knee joints of the right and left leg. When seeing the chair, the patient has a freezing episode and experiences balance problems. After trying to get out of the block for 2 seconds, he enters into a total freeze of movement on both sides. Motion registration is captured in Figure 1E of the article.

Video 4. Freezing in a doorway while carrying a tray: Data were retrieved using accelerometers attached between ankle and knee joints of the right and left leg. After opening the door and walking through it with a tray, the patient has a freezing episode, which intensifies as he tries to continue walking, almost leading to a fall. Motion registration is captured in Figure 1F of the article. ■

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