Title: Characterising freezing of gait in Parkinson's disease: models of an episodic phenomenon.

Abbreviated title: Freezing of gait: models of the episodes

Authors: Nieuwboer A, PhD[1], Giladi N, MD[2]

Affiliations: [1]KU Leuven –University of Leuven, Department of Rehabilitation Sciences, 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

Corresponding author: Alice Nieuwboer, Address: KU Leuven, Faculty of Kinesiology and Rehabilitation Sciences, Department of Rehabilitation Sciences, Tervuursevest 101, 3001 Leuven, Belgium, E-mail: alice.nieuwboer@faber.kuleuven.be, Phone: +32-16-32.9119 ; Fax: +32-16-32.91.97

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Abstract

Freezing of gait (FOG) is a very disabling and common gait disorder in Parkinson's disease (PD). The first aim of this paper is to provide a methodological and critical review of the most common research approach to understand FOG, i.e., comparing the behaviour of freezers with that of non-freezers. The review shows 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 paper 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 behavioural 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 impact upon the emergence of the FOG-episodes.

Introduction

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 21-27% of patients in the early stages of PD report to have FOG.[2,3] In the later stages, this number increases up to 80%.[3,4] Interestingly, not all PD patients develop FOG[4], but the possibility that it will appear in all advanced PD patients after a long enough washout period of levodopa has never been ruled out. FOG is tightly associated with synucleinopathies like PD and multiple system atrophy.[5] It is, however, frequently and even earlier observed in the course of other pathologies like progressive supra-nuclear 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 non-freezers. While this research paradigm has led to some useful insights, the first aim of this paper is 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 is 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.

Between group comparisons: are there true freezers and non-freezers?

In Table 1, we summarize 35 studies[8-42] carried out over the past five years, which compared groups who have FOG to those who do not. We included studies specifically designed to give 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- from freezing-

specific findings in these designs. Studies were critically reviewed by two independent reviewers on the following 3 criteria: subgroup classification, how levodopa was taken into consideration and how control was implemented for subgroup differences.

Subgroup classification

Table 1 shows 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. (2011)[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. Besides, excluding probable or self-reported freezers limits the generalizability of the findings as subjects 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.

Relationship with levodopa

Table 1 shows that 14 freezer/non-freezer studies were carried out on-medication when FOG might have been suppressed. The relationship 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 levodopa, to "on" FOG when the blocks

are induced or exacerbated by levodopa.[45] "Levodopa-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] showed that when subthalamic nucleus (STN) stimulated patients with "off-FOG" were contrasted to those with "levodopa-unresponsive FOG", executive function was more impaired in the latter group, likely reflecting greater pathology in non-dopaminergic circuits. We found that 23 studies in Table 1 did not report proportions of levodopa-responsive or unresponsive freezers and that in 15 the Levodopa Equivalent Dose (LED) was not provided.

[Insert table 1 here]

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 shows that in 23 studies freezer subgroups were not well-matched for several aspects of disease state. In 12 of these studies, mismatching was apparent for disease duration and severity as expressed by UPDRS III scores or Hoehn & Yahr stage. In addition, summed disease severity scores mask the possibility that freezers and non-freezers may have different disease phenotypes, i.e., 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 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 in a large number of studies disease severity and cognitive impairment were different

between groups or unknown 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 to: 1) define subgroups according to the Snijders et al. algorithm[43]; 2) use a validated and standardised 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 levodopa-responsiveness; 5) match patients for disease severity and global cognitive capacity; and 6) use sample sizes which allow for statistical correction for additional confounders. Nutt et al. (2011)[54]questioned whether the dichotomy between freezers and non-freezers is 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 FOG assessment are robust and valid.[55-58] Regardless of whether FOG is continuous or binary, we focus this paper 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 prior and during FOG have been delineated as important markers.[60,61] Figure 1 illustrates the various ways in which freezing disrupts locomotion. In this figure, we 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 are also 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 (i.e., photo-sensitive) and paroxysmal dyskinesias (i.e., 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 show templates of 'motor freezing', by which is meant: 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 (Figure 1B) and during performance of a turn (Figure 1C) or when performing movement sequences (Figure 1D). In contrast, figure 1E-F show examples of FOG when triggered by external circumstances, i.e., when reaching a destination (Figure 1E) or passing through a doorway (Figure 1F). Figures 1E and F depict the erratic behaviour of FOG and the complexity of its signal output when derived from movement registration in complex circumstances. Sometimes FOG shows (Figure 1F) high frequency oscillations and other times unilateral attempts to come out of the block (Figure 1E). 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 following sections will 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.

[Insert figure 1 here]

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 found in freezers compared to non-freezers when off-levodopa in: 1) step scaling[9,18,65], 2) gait rhythmicity[66], 3) bilateral step coordination[67] and symmetry[68]. Figure 2 shows that the threshold model predicts that it is possible to drive the motor system towards the freezing state, when some of these critical gait deficits are exaggerated. Indeed, experimentally minimising stride length[9]or increasing cadence during gait or repetitive stepping in place[69,70] was shown to provoke 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.[71] 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 prior to freezing and finger freezing episodes were exacerbated by imposing small amplitude and high frequency constraints (see Figure 1C).[20,21,72]

As turning poses a greater demand on locomotion control by demanding asymmetrical step sizes and adjustment of bilateral coordination, the model may also explain FOG during this motor task.[14] Interestingly, FOG-episodes tended to occur at the end of turning[25] and were more prominent during 360° compared to 180° turns[43], although a clean comparison between turning angles was not made in the latter study. Contrary to non-freezers, freezers showed increased step time variability[22], higher cadence[14] and disordered bilateral coordination[19] during turning, deficits, which were correlated with a higher number of episodes in freezers. Cadence-reducing cues alleviated FOG[73] during turning, suggesting that rhythmic priming prevented patients from reaching the freezing threshold.

The above described threshold-driven accumulative pattern of motor abnormality 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[74] and was solely dependent on frequency manipulations[72]. However, the distinction between motor fatigue and freezing needs further elucidation.

[Insert figure 2 here]

The 'interference model' of FOG

Lewis and Barker[75] put forward an 'interference model' to conceptualise 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 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[76] leads to neuronal crosstalk between these circuits. As a result, internal pallidal outflow becomes abnormal, inducing a temporary inhibition of the pedunculopontine nucleus (PPN), giving rise to FOG.[75] The model incorporates the idea that interference between neural circuits can be suspended or 'reset' by focusing on goal-directed behaviour or an external cue.[75,77]

Figure 2 illustrates 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[14,78] or FOG-like episodes[11,30,78,79]. The association between FOG and increased heart rate dynamics just prior to freezing and during actual episodes points to a possible limbic contributor to FOG.[27] However, none of these studies explicitly demonstrate the exact temporal coupling between the cognitive or limbic load and the onset of the episodes.[14,30,78,79] Recent imaging studies[42,80] support and extend the interference model showing that networks beyond the basal circuitry are involved in faulty processing of multimodal information. Shine and co-workers[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, regions of interest analysis showed the MLR to be both structurally and functionally altered in freezers and these changes were correlated with freezing severity.[36,80] Compared to continuous pedalling, increased activity in frontoparietal

regions and reduced activity in some basal ganglia nuclei were found during freezing of pedalling.[80] Although, these delays were found to be moderately correlated with FOG[79] it is not clear whether these episodes reflect freezing or related cognitive processing lags, as full pedalling motion inherent to bicycling was show to protect against FOG.[81]

The cognitive model of FOG

Vandenbossche et al.[82] 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 figure 2). Response selection and inhibition of unwanted responses require both implicit (automatic) and consciously controlled mechanisms.[83] Freezers and non-freezers showed 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 related to FOG and not to other disease markers.[84,85] 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.[86,87] 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.[88] Motor arrests provoked by incongruent response decision tasks were indeed associated with decreased 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 predicts 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. Freezers have been shown to demonstrate more pronounced problems in several domains of executive dysfunction compared to non-freezers (for review)[89]. 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 these results need confirmation.[39-41]

The' decoupling model' of FOG

Jacobs et al.[90] proposed a 'decoupling model' of FOG, whereby episodes are characterised by a decoupling between pre-planned motor programmes and the release of an inherent movement or step at gait initiation. Overall, studies of voluntary gait initiation have shown delayed and underscaled steps in PD, but these deficits proved surprisingly unrelated to freezing.[17,91,92] Equally, anticipatory postural adjustments (APA's), the preparatory phase of step initiation during which pressure increases under the swing limb to enable displacement of the centre of mass over the stance limb[90], were prolonged and more variable in PD[92] irrespective of FOG.

An experimental setup, whereby platform perturbations were meant to elicit automatic compensatory stepping reactions to avoid falling, showed for the first time a freezing-specific problem.[90] Unlike healthy controls, patients with FOG showed multiple dysfunctional APA's, resembling freezing-like oscillatory behaviour of the knees. These repeated loading-unloading cycles were accompanied by delayed or failed generation of stepping, interpreted as a malfunction to couple an APA with a step. The fact that this decoupling mechanism was

found 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 perceive FOG as having 'their feet glued to the floor'.

Okada et al.[17] found that double limb support time of the first step during gait initiation was prolonged in freezers relative to non-freezers, possibly indicating compensatory behaviour 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.[70] However, while FOG and postural instability co-exist its shared mechanisms are at present poorly understood.[26]

Thevathasan et al.[93] provided preliminary evidence for the possibility of a decoupling model of freezing during automatic movement initiation through a startle-react paradigm. They showed that patients with freezing and/or falling responded with a delayed startle response in axial muscles to auditory stimuli of varying loudness. They 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 alleviated turning times in freezers.[37] Using spectral analysis of local field potentials from implanted PPN electrodes, it was shown that alpha oscillations in the caudal PPN were attenuated just before and at the onset of FOG episodes[94] while alpha power increased when gait was normalized, pointing to a central role of the PPN in FOG.

Discussion and future directions

We have presented in this review four possible models of the episodic nature of FOG as separate entities (see figure 2). It is, however, probable that there may be varying degrees of interplay between these explanatory models, explaining the heterogeneity of FOG. We

speculate that the decoupling mechanism together with the cognitive model probably underlies akinetic FOG, mostly apparent at start hesitation, especially when a response decision is awaited. Interestingly, it was shown that freezers had greater variability in deciding with which swing limb gait initiation was started 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 needs further unravelling.

During motor FOG, e.g., when turning or walking on an open runway, both the threshold and the decoupling models 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 towards the freezing threshold[63] after which the decoupling mechanism may preclude normal gait re-initiation. 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 impact on the susceptibility for FOG. Figure 2 acknowledges that cognitive impairment may lower the freezing threshold and negatively affect processing capacity of concurrent input. Two recent multivariate studies confirmed that global cognitive impairment was an independent contributor of FOG.[34,77] Finally, the response to medication is another crucial factor in determining the breeding ground for FOG.

Earlier, we showed that freezer versus non-freezer comparisons fall short in fully enlightening the 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 showed that the calculation of spectral analysis-derived measures hold promise for future FOG-severity indexes.[55-58] This possibility makes power-based multivariate studies of FOG within reach. To develop drug treatment and behavioural 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 presented models provide an overarching or full explanation of FOG and refinement 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 fMRI studies of FOG-like episodes utilized an

interference-cognitive[80] and a motor threshold model of FOG[96] and as a result altered activity in mainly cognitive[80] and motor[96] neural networks were found, respectively.

The BOLD-response is a slow method for studying short freezing events, generating limited statistical power. Recent work is pointing to the feasibility of using electroencephalographic (EEG) signals to detect FOG-episodes with sufficient temporal resolution through wavelet transform analysis techniques.[95] A drawback of this method is that critical areas, notably the MLR and basal ganglia, cannot be accessed. Preliminary data showed that wavelet energy changed 5 seconds before FOG and produced EEG-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 better understand and characterize the episodes.

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Comparison motor function							
1.	Plotnik M et al. 2008	21 FR 13 NFR	Self-reported	FOG-Q item 3	-	LED % ON/OFF FR	ON OFF
2.	Chee R et al. 2009	16 FR 10 NFR	Definite	Interview, Clinical assessment, Observation	DD, H&Y, UPDRS III, GDS	LED % ON/OFF FR	OFF
3.	Nieuwboer A et al. 2009	10 FR 10 NFR	Self-reported	FOG-Q item 3	DD, UPDRS III, LED	-	OFF
4.	Almeida QJ et al. 2010	15 FR 16 NFR	Definite	UPDRS II item 14 Observation	Cognitive tests not reported	-	ON
5.	Delval A et al. 2010	8+2 FR 10 NFR	Definite/ Self-reported	FOG-Q item 3 Observation	Not reported	LED % ON/OFF FR	OFF
6.	Lebold CA et al. 2010	15 FR 16 NFR	Definite	UPDRS II Observation	LED; Cognitive tests not reported	-	ON
7.	Spildooren J et al. 2010	14 FR 14 NFR	Self-reported	NFOG-Q	MMSE, SCOPA-COG	LED % ON/OFF FR	OFF
8.	Cohen RG et al. 2011	11 FR 13 NFR	Self-reported	FOG-Q	H&Y, UPDRS; Cognitive tests not reported	LED % ON/OFF FR	OFF
9.	Nanhoe-M. W et al. 2011	5+7 FR 15 NFR	Self-reported/ Definite	NFOG-Q Observation	-	LED	OFF
10.	Okada Y et al. 2011	10 FR 7 NFR	Self-reported	FOG-Q item 3	LED; Cognitive tests not reported	-	ON
11.	Danoudis M et al. 2012	16 FR 10 NFR	Definite	FOG-Q item 3 Clinical assessment	DD; H&Y; UPDRS III[#]	LED % ON/OFF FR	OFF
12.	Peterson DS et al. 2012	12 FR 19 NFR	Self-reported	FOG-Q item 3	Cognitive tests not reported	LED % ON/OFF FR	OFF
13.	Vercruysse S et al. 2012	11 FR 12 NFR	Self-reported	NFOG-Q	SCOPA-cog	% ON/OFF FR	OFF
14.	Vercruysse S et al. 2012	11 FR 12 NFR	Self-reported	NFOG-Q	MMSE	% ON/OFF FR	OFF
15.	Bhatt H et al. 2013	10 FR 10 NFR	Definite	Interview, Observation, Clinical assessment	Cognitive tests not reported	LED % ON/OFF FR	ON
16.	Frazzitta G et al. 2013	30 FR 30 NFR	Definite	Observation	UPDRS II; Cognitive tests not reported	-	ON
17.	Nanhoe-M. W et al. 2013	5+2 FR 7 NFR	Definite/ Self-reported	Observation NFOG-Q	-	LED % ON/OFF FR	OFF
18.	Spildooren J et al. 2013	13 FR 14 NFR	Self-reported	NFOG-Q	MMSE	LED % ON/OFF FR	OFF
Comparison non-motor function							
19.	Amboni M et al. 2008	13 FR 15 NFR	Self-reported	FOG-Q item 3	UPDRS II	% ON/OFF FR	ON
20.	Maidan I. et al. 2010	10 FR 10 NFR	Self-reported	FOGQ item 3	-	LED % ON/OFF FR	OFF
21.	Tan T et al. 2011	12 FR 12 NFR	Definite	Interview, Observation Clinical assessment	UPDRS[#]; Cognitive tests not reported	LED % ON/OFF FR	ON
22.	Vandenbossche J et al. 2011	11 FR 11 NFR	Self-reported	NFOG-Q	MMSE	% ON/OFF FR	ON OFF
23.	Knobl P et al. 2012	10 FR 10 NFR	Probable	UPDRS II (14) Interview	DD, UPDRS; Cognitive tests not reported	LED % ON/OFF FR	ON
24.	Lord S et al. 2012	27 FR 27 NFR	Self-reported	FOG-Q item 3	Cognitive tests not reported; UPDRS III[#]	% ON/OFF FR	ON
25.	Nantel J et al. 2012	18 FR 11 NFR	Definite	SIP task FOG-Q item 3	DD, UDPRS III (axial items), Cognitive tests	LED	OFF
26.	Vandenbossche J et al. 2012	14 FR 14 NFR	Self-reported	NFOG-Q	DD[#], MMSE, SCOPA-cog	% ON/OFF FR	ON
27.	Vercruysse S et al. 2012	23 FR 24 NFR	Definite	Observation NFOG-Q	MMSE, SCOPA-cog	-	ON
28.	Vandenbossche J et al. 2013	14 FR 14 NFR	Self-reported	NFOG-Q	-	% ON/OFF FR	ON
Comparison neural function							
29.	Snijders AH et al. 2011	3+9 FR 12 NFR	Probable/Definite	NFOG-Q, Observation, Clinical assessment	-	LED	OFF
30.	Thevathasan W et al. 2011	8 FR** 8 NFR	Self-reported or probable (unclear)	FOGQ item 3	UPDRS III (27-30)	-	OFF
31.	Imamura K et al. 2012	21 FR 34 NFR	Self-reported	UPDRS II (14)	L-DOPA	% ON/OFF FR	OFF
32.	Kostic VS et al. 2012	17 FR 20 NFR	Definite	FOG-Q item 3, Clinical assessment, Observation	UPDRS III[#], MMSE[#], HADS, Cognitive tests[#]	% ON/OFF FR	OFF
33.	Tessitore A et al. 2012	16 FR 13 NFR	Self-reported	FOG-Q item 3 Clinical assessment	UPDRS II,III (PIGD), BDI, Cognitive tests[#]	% ON/OFF FR	ON
34.	Tessitore A et al. 2012	12 FR 12 NFR	Self-reported	FOG-Q item 3 Clinical assessment	UPDRS II, FAB, Cognitive tests[#]	% ON/OFF FR	ON
35.	Shine JM et al. 2013	14 FR 15 NFR	Definite	FOG-Q item 3 Observation	UPDRS item 46, HADS[#]	-	OFF

Legends of tables and figures

Table 1 Studies comparing freezers and non-freezers characteristics

*Exclusion of effect studies and measurement studies of FOG; ** Not matched = considered for parameters outside primary and secondary parameters of interest;

***= not clear whether patients had FOG and/or postural instability; %[#] = % on/off FRs; DD= disease duration; H&Y= Hoehn & Yahr stage; LED= Levodopa Equivalent Dose; GDS = Geriatric Depression Scale; BBS= Berg Balance Scale, HADS=Hamilton anxiety and depression rating scale; SIP=stepping in place; BDI = Beck Depression Inventory.

FIGURE 1 EXAMPLES OF FOG TRACES

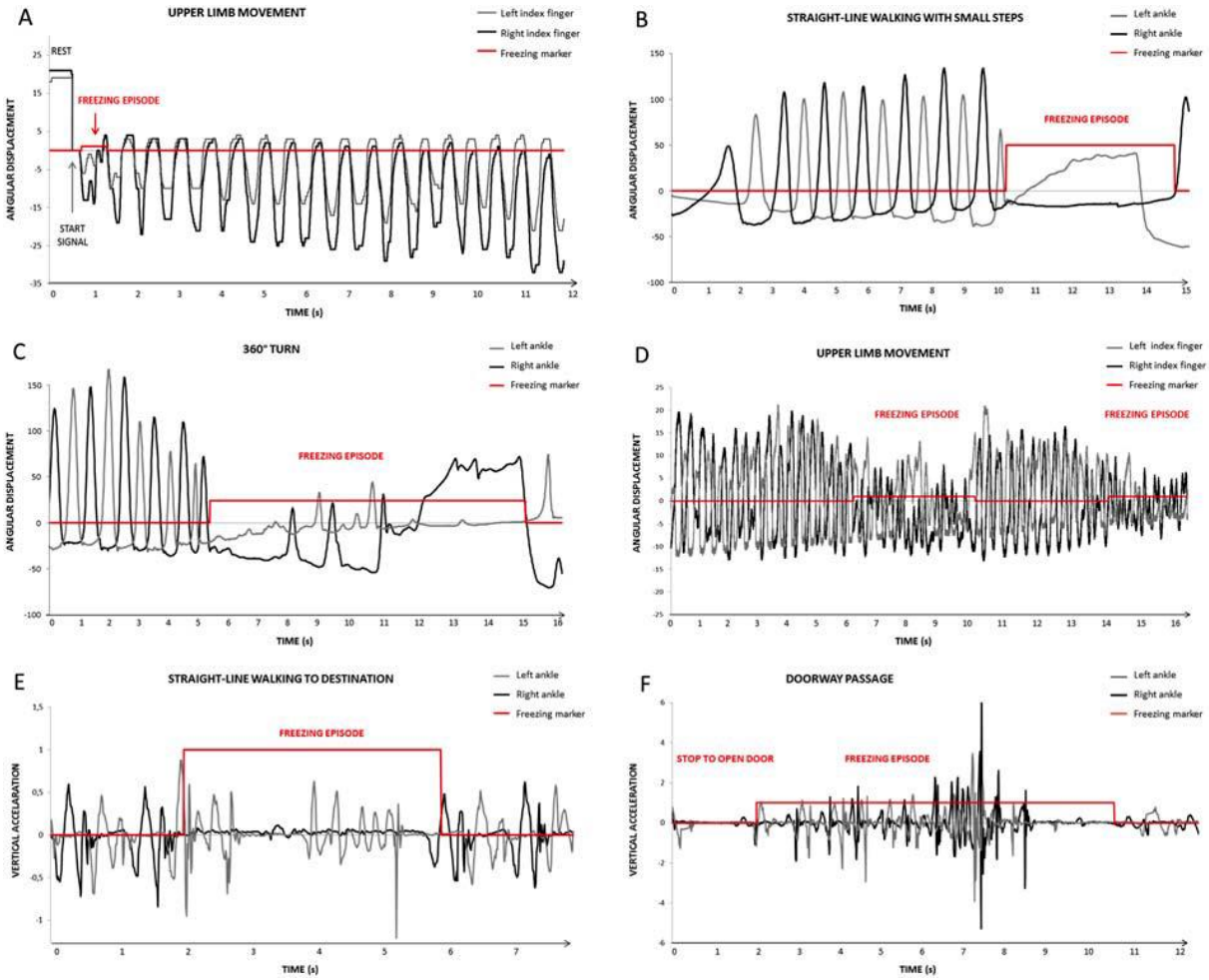

FIGURE 1A. Example Akinetic freezing
Angular displacement of the right (black line) and left (gray line) index finger during a bilateral movement (in-phase) trial. Movement was performed while lying in a 3T MR scanner where periods of movement alternated with rest periods. Data of the first 12 seconds of a 30 second trial are shown. Data was 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 the initiation freeze, i.e. 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.

FIGURE 1B. Example Motor FOG
Angular displacement of the right (black line) and left (gray line) ankle during straight-line walking. The patient was instructed to walk with small steps on an open runway. Data was retrieved via a VICON data capturing system (Vicon Motion Systems, Workstation 612) that was positioned around a ten meter walkway. After 9,5 seconds, the patient experiences a freezing episode (red FOG marker) during which cyclic ankle movements were completely absent. See also Video 1.

FIGURE 1C. Example Motor FOG
Angular displacement of the right (black line) and left (gray line) ankle during walking and turning 360 degrees. Data was retrieved via a VICON data capturing system (Vicon Motion Systems, Workstation 612) that was positioned around a ten meter walkway. After 3 seconds, the patient starts turning over the left side, making smaller stepping movements. A few seconds later, the patient has a

freezing episode (red FOG 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.

FIGURE 1D. Example Motor freezing
Angular displacement of the right (black line) and left (gray line) index finger during a bilateral movement (anti-phase) trial. Movement was performed while sitting. Data of the last 16 seconds of a 30 second trial are shown. Data was 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.

FIGURE 1E. Example Triggered FOG
Vertical acceleration of the right (black line) and left (gray line) ankle during straight-line walking towards a chair. Data was retrieved via accelerometers attached between ankle and knee joints of the right and left leg. The patient experienced 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 seconds time mark, a large step of the right leg re-introduces normal walking. See also Video 3. Note that the video and figure are not synchronized.

FIGURE 1F. Example Triggered FOG
Vertical acceleration of the right (black line) and left (gray line) ankle during straight-line walking towards a chair. Data was 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 becomes more intensive as he tries to continue walking leading to almost falling. See also Video 4. Note that the video and figure are not synchronized.

FIGURE 2 SUMMARY OF FOUR MODELS FOR THE EPISODIC APPEARANCE OF FOG

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 external input
Cognitive[82]	Deterioration in processing of response conflict induces block	Increase incongruency level Increase response speed Increase load 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

Video legend 1

Freezing in gait laboratory. The patient is represented by a stickman. He was instructed to walk with small steps on an open runway. Data was retrieved via a VICON data capturing system (Vicon Motion Systems, Workstation 612) positioned around a ten meter walkway. Motion registration is captured in Figure 1B of the manuscript.

Video legend 2

Freezing in gait laboratory during turning. The patient is represented by a stickman. Data was retrieved via a VICON data capturing system (Vicon Motion Systems, Workstation 612 positioned around a ten meter walkway. Motion registration is captured in Figure 1C of the manuscript.

Video legend 3

Freezing during straight-line walking towards a chair. Data was retrieved via 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 manuscript.

Video Legend 4

Freezing in a doorway while carrying a tray. Data was 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, which becomes more intensive as he tries to continue walking leading to almost falling. Motion registration is captured in Figure 1F of the manuscript.

Author's Roles:

Alice Nieuwboer

Manuscript Preparation: A. Literature Review, B. Conceptualization, C. Writing of the first draft, D. Review and Critique.

Nir Giladi

Manuscript Preparation: A. Conceptualization, B. Review and Critique.