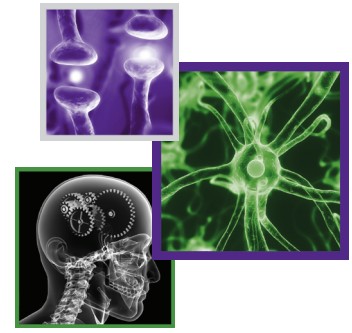
REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Neurodegenerative Disease Management



Freezing of gait in Parkinson's disease: from pathophysiology to emerging therapies

Alberto Cucca*[1,2], Milton C Biagioni[1], Jori E Fleisher[1], Shashank Agarwal[1], Andre Son[1], Pawan Kumar[1], Miroslaw Brys[1] & Alessandro Di Rocco[1]

Practice points

- The interplay between the basal ganglia and cerebral cortex seems to play a crucial role in freezing of gait pathogenesis.
- The optimization of dopaminergic therapy is the first step to relieve off-related freezing of gait.
- Multiple sessions of dedicated physical therapy usually provide significant yet transient benefits.
- A growing body of evidence indicates noninvasive brain stimulation as a promising option for these patients in the near future.

Freezing of gait (FOG) is 'an episodic inability to generate effective stepping in the absence of any known cause other than parkinsonism or high level gait disorders'. FOG is one of the most disabling symptoms in Parkinson's disease, especially in its more advanced stages. Early recognition is important as FOG is related to higher fall risk and poorer prognosis. Although specific treatments are still elusive, there have been recent advances in the development of new therapeutic approaches. The aim of this review is to present the latest knowledge regarding the phenomenology, pathogenesis, diagnostic assessment and conventional treatment of FOG in Parkinson's disease. A review of the evidence supporting noninvasive brain stimulation will follow to highlight the potential of these strategies.

First draft submitted: 28 April 2016; Accepted for publication: 3 August 2016; Published online: 7 September 2016

KEYWORDS
- freezing of gait
- neurorehabilitation
- noninvasive brain stimulation

Freezing of gait (FOG) is defined as 'an episodic inability to generate effective stepping in the absence of any known cause other than parkinsonism or high level gait disorders' [1]. FOG classically presents as a severe, sudden, gait dysfunction and patients may describe it as if their feet were glued to the floor [2]. The duration of FOG is generally a couple of seconds. Occasionally, it may last more than 30 s and even, up to a few minutes [2–4]. Gait can be limited to extremely short steps or, in some cases, the patient may be completely unable to move in any direction [5]. A significant proportion of patients with Parkinson's disease (PD) may experience FOG, and for those who do, it is one of the most disabling symptoms. In a survey conducted with 990 PD patients, FOG episodes have been observed in 32% of the sample [6]. Furthermore, FOG can occur in many forms of parkinsonism, including atypical parkinsonian disorders such as multiple system atrophy-parkinsonism type and, in particular, progressive supranuclear palsy – pure akinesia type, in which FOG is the fundamental clinical manifestation [5,7]. FOG episodes have been also described in patients suffering from acute carbon monoxide intoxication [8] as well as in neurodegeneration with brain iron accumulation [9] and pallido-nigro-luysian atrophy [10].

[1]Department of Neurology, The Marlene & Paolo Fresco Institute for Parkinson's & Movement Disorders, New York University School of Medicine, New York, NY 10016, USA
[2]Department of Medicine, Surgery & Health Sciences, University of Trieste, Clinica Neurologica, Trieste, Italy
*Author for correspondence: Tel.: +1 646 5014 864; cucca.alberto@libero.it

Future Medicine part of fsg

Due to its complexity, diversity of etiologies and unclear physiopathology, FOG has been dubbed a 'mysterious phenomenon' [11]. The episodic nature of FOG suggests a transient, functional disruption of the complex system responsible for locomotion, yet a unified pathogenetic mechanism has not been identified. FOG episodes typically start insidiously and their frequency slowly increases with disease duration and clinical progression. Rarely, however, it can begin or even reverse acutely after vascular events [12,13]. Early recognition of FOG in clinical practice is particularly important as it is significantly related to increased risk of falling and decreased survival [7]. Although a specific and effective treatment is still lacking, advances in the development of new therapeutic approaches have been made in the past years, particularly in noninvasive brain stimulation and deep brain stimulation (DBS).

The aim of this review is to present the latest knowledge regarding the phenomenology, pathogenesis, diagnostic assessment and conventional treatment of FOG in PD. A review of the evidence supporting noninvasive brain stimulation will then follow to highlight the potential of these novel neuromodulatory strategies.

Clinical phenomenology, pathogenesis & diagnosis

• Clinical phenomenology & natural history

FOG can be classified according to several criteria. One classification scheme involves the phases of walking. When occurring at the beginning or at the end of gait, FOG can be clinically defined as 'start hesitation' or 'destination hesitation', respectively. Commonly, FOG is observed during changes in trajectory thus being defined as 'turning hesitation'. Finally, FOG can be encountered while walking through narrow and obstructed spaces. This latter form is also known as 'tight quarters hesitation' [14].

Furthermore, particularly in PD, FOG is strongly associated with motor fluctuations. Freezing in the off-medication state in PD is the most common setting for FOG, with episodes characterized by longer duration, higher frequency and significant improvement following dopaminergic medication adjustments. In contrast, freezing in the on-medication state is rare, usually of brief duration, and sometimes showing an unpredictable or paradoxical response to adjustments of medications [15].

FOG can also be categorized by the patient's most prominent motor features: shuffling forward, trembling in place or total akinesia. 'Shuffling forward' refers to minimal forward progression with tiny steps of decreased amplitude and speed. 'Trembling in place' is characterized by the onset of a tremulous activity involving the lower limbs. Finally, the least common subtype of FOG, total akinesia, is identified as a sudden interruption of voluntary movements in the lower limbs with a complete impairment in gait progression. While the first two subtypes are found during both on- and off-states in PD, total akinesia seems to be an exclusive off-state phenomenon [16].

FOG episodes are profoundly affected by cognitive engagement, external attentional cueing and anxiety levels, which can trigger freezing (i.e., dual-task performance during gait execution, gait under time constraints or in narrow spaces) as well as improve it (i.e., visual or auditory external cueing) [17,18]. In addition, FOG can be symmetric or asymmetric, affecting one lower limb in a greater proportion.

In patients with a long history of PD and chronic dopaminergic exposure, the overall estimated prevalence of FOG is between 20 and 60% [19]. FOG appears with highest frequency in Hoehn and Yahr stages III and IV. Nevertheless, FOG can represent the most prominent feature in unmedicated, early-stage patients. Indeed, contrary to what was previously believed, early occurrence of FOG is not sufficient *per se* to suggest an atypical parkinsonism (DATATOP study group, 1989). In early PD, FOG is briefer and less frequent, mainly presenting as start and turning hesitation [6]. Results of the DATATOP study show that the early onset of axial symptoms such as gait, posture and language disturbances is associated with a greater risk of developing FOG [20]. FOG also correlates with longer disease duration, higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS), higher daily levodopa-equivalent daily doses and previous exposure to anticholinergic medications [21]. Cognitive impairment – particularly executive dysfunction – and apathy are also well-recognized comorbid factors [22]. In PD, FOG shows a correlation with other axial symptoms, including postural instability and speech disturbances [23]. In contrast, FOG seems not to correlate with two of the cardinal symptoms of the disease, that is, bradykinesia and tremor [24]. Indeed, the lack of association between bradykinesia and FOG challenged the original hypothesis that this phenomenon could be interpreted

as the extreme end of the hypokinetic spectrum of parkinsonian symptoms [24]. Accordingly, the tremor-predominant phenotype of PD seems to display a lower risk of developing FOG.

With PD progression, FOG may become a pervasive and devastating symptom, potentially occurring even in relatively open and accessible spaces and leading to a significant risk of falls [19]. Most freezers are confined to a wheelchair after an average of 5 years from the onset of the symptom [7]. The higher risk of falling significantly hampers patient mobility and autonomy in everyday activities, drastically reducing quality of life [21]. In general, patients affected by parkinsonism with gait and balance disturbances are also burdened by a higher mortality, with a median life expectancy of about 7 years when recurrent falls are present [25,26]. These data have been reproduced in a PD population of more than two hundred patients, in whom the presence of gait disorders was a significant predictor of decreased survival [27].

Another peculiar aspect is the relationship between FOG and gait festination, the latter defined as the generation of increasingly rapid and small sequential steps usually occurring in proximity to the destination [28]. Since festination precedes most gait interruptions, it has been proposed that FOG represents the main manifestation of the same spectrum of symptoms, characterized by a varying degree of gait disruption [11]. However, festination can present independently from FOG. Although festination of speech correlates with gait festination [29], a definitive relationship between gait festinatino and FOG has not yet been demonstrated [11].

Observing motor interruptions similar to FOG during the execution of various repetitive rhythmic acts, such as writing or speaking, raises the question of whether the different topographic distribution of the same disease could influence its clinical manifestation. Freezing of speech, defined as an episodic interruption of the normal verbal flow, is significantly associated with the presence of FOG. In particular, anomalies of speed, cadence and step length are related to the number of verbal interruptions and repetitions [30]. Freezing of the upper limbs is also reliably associated with the presence and severity of FOG and, like the latter, is ameliorated by visual and acoustic cueing. Not all of the kinematic parameters observed in freezing of the upper limbs are, however, comparable with those of FOG, in particular the space–time and coordination anomalies [31]. Intuitively, the execution of repetitive manual movements does not reflect the same level of functional complexity as that of the system responsible for locomotion, and it is therefore difficult to directly compare these motor programs [32].

• Pathogenesis

The pathogenesis of FOG is still debated due to its clinical complexity, variety of coexisting pathologies and lack of a clear neuropathological substrate on postmortem examinations [33]. FOG is not exclusive to PD and the response to dopaminergic therapy, if compared with that observed for the cardinal symptoms of the disease, is almost always suboptimal. This suggests the involvement of nondopaminergic circuits and other anatomical structures in the CNS [34]. Indeed, gait is a unique, semiautomatic, learned motor act based on the hierarchical integration of multiple neural systems, which differ by topography, phylogenetic origin and genetic programming [7]. Three elements are required to ensure locomotion: maintaining balance and posture, generating an autonomous cyclic pattern that subserves basic locomotion and, finally, a hierarchically superior system integrating locomotion with proprioceptive, visual–spatial, acoustic and vestibular information to select the most appropriate motor pattern [7]. The main areas responsible for supraspinal control of gait are the pontomedullary reticular formation, the mesencephalic locomotor region (MLR), the basal ganglia, the cerebellum and associative and motor cortices [11]. An alteration of this system, at virtually any level, can disrupt gait. Various etiopathogenic theories have been proposed, none of which are mutually exclusive.

One hypothesis suggests that the cause of FOG is to be found within the spinal generator of the gait cycle [35]. This center consists of neuronal groups that can rhythmically stimulate the muscles of the lower limbs and, therefore, automatically initiate and maintain gait propulsion [11]. These pacemaking cellular groups are in reciprocal synaptic connection with their contralateral counterparts through inhibitory interneurons. They receive continuous sensory impulses from muscle-tendon peripheral afferents and are, therefore, able to generate immediate responses to sudden gravitational changes without the need for suprasegmental control [36]. The abnormalities in the rhythm of gait experienced by freezers seem to support the hypothesis

of a spatial-temporal disintegration in the activation of such centers [37]. Freezers show a greater interstep variability than controls together with a typically arrhythmic walking pattern even in the absence of FOG episodes [38]. Some interesting etiopathogenic considerations can be drawn from the 'trembling in place' phenomenon, which is not an irregular movement of the lower limbs, but rather a structured muscular activity during which ankle flexors and extensors reciprocally contract. While 'trembling in place', the patient's legs fluctuate in an oscillatory pattern of 5–8 Hz. Spectral analysis of this tremulous activity has made it possible to clearly distinguish it from the typical PD tremor [38]. This seems to suggest that an independent generator supports such activity, but it is not clear whether the latter is the expression of local pathological activation or an expression of liberation from a higher level inhibitory control. Electromyography studies on patients with FOG have shown that the activity of tibialis anterior and plantar flexor muscles begins and terminates prematurely during the dynamic phase of the gait cycle, however, constantly maintaining the normal reciprocal interaction [39]. These features indicate that the cyclic activity of walking in FOG subjects is pathologically influenced by an altered suprasegmental drive [40].

An alternative hypothesis of FOG posits a deficit in normal anticipatory postural adjustments. When starting to walk, the integration between postural control and the spinal generator is crucial. The center of gravity is laterally displaced on one foot to allow the contralateral limb to be lifted and pushed forward. An abnormal association between posture and gait can be an important factor causing FOG. Through integrated systems of gait analysis it has been observed that freezers show a deficit in normal anticipatory postural adjustments [41]. According to a recent study, freezers need more time to associate the head–neck axis with the pelvic axis when turning [42]. 'Trembling in place' could therefore be a hypercompensatory manifestation of the patient's failure to adapt his posture when changing direction [43]. The merit of this theory is that it provides a plausible explanation of the correlation between FOG and the risk of falls. Furthermore, the anatomical substrate of FOG may then reside in the pontomedullary reticular formation, at which level posture is coordinated with locomotion [44].

Another possibility is that freezing originates from a loss of automation in the central drive for internally generated movements [45]. In this case, the basal ganglia and brainstem both play a crucial role. In the vast majority of cases in PD, FOG is experienced during the off-state and optimization of dopaminergic therapy can reduce it significantly [46]. This indicates that the symptom is, at least partially, related to a central hypodopaminergic state in PD [3]. In conditions of reduced dopamine reserves, the functional overuse of the basal ganglia due to increased cognitive, motor or limbic activation, seems to increase the inhibitory firing by the globus pallidus interna and substantia nigra pars reticulate (SNr) toward brainstem structures involved in the activation and maintenance of gait [47]. Of these brainstem structures, the MLR seems to play a key role in connecting the central motor drive with spinal generators [48]. The MLR consists of the pedunculopontine nucleus (PPN), and cuneiform and subcuneiform nuclei. The PPN is a heterogeneous group of cells located in the caudal mesencephalic tegmentum that receives bilateral inhibitory GABAergic projections from the subthalamic nucleus the ventral and dorsal striatum, the pallidum and the SNr. The PPN extends excitatory cholinergic and glutamatergic efferents to major output structures in the striatum (globus pallidus interna and SNr). The pathological involvement of cholinergic neurons of the PPN has been demonstrated in PD patients suffering from gait and posture impairment [49]. However, DBS of the PPN in patients with FOG has produced controversial results so far [50]. In any case, the loss of automatism is consistent with the episodic nature of FOG, which can indeed emerge in situations causing a functional overload of the basal ganglia. Moreover, this hypothesis explains the benefits obtained through external cueing, which appear to bypass the interruption of the caudate nucleus–thalamus–prefrontal cortex motor loop through alternative pathways. An abnormal motor response to altered visuospatial feedback could partially explain the occurrence of FOG in particular situations, that is, when passing through a semi-open door or approaching a destination [51].

The hypothesis that FOG episodes could be triggered by a specific impairment in negotiating spatial obstacles has recently been supported by voxel-based morphometry data in freezers showing a particular pattern of gray matter atrophy of areas intimately related to visuospatial functions, such as the left inferior frontal gyrus, precentral

gyrus and inferior parietal gyrus [52]. More recently, the gray matter volume was found to be significantly reduced in the inferior parietal lobe and angular gyrus in freezers as compared with nonfreezers [53]. However, the hypothesis that visual misperception drives FOG was recently tested by comparing the kinematic profile and visuospatial judgement of PD patients with and without FOG, with healthy subjects while walking through doors of different widths. Interestingly the visuospatial judgment of freezers did not significantly differ from that of healthy controls, which has therefore called this hypothesis into question [54]. The visuospatial hypothesis posits that stress resulting from the need to solve space–time conflicts is critical in generating FOG. Based on that premise, the logical deduction has been to study the connections between the prefrontal cortex and the basal ganglia, as these areas are critically involved in problem solving, set-shifting and the inhibition of unwanted responses.

Numerous studies have shown that freezers experience a deficit in executive functions compared with controls [55,56]. In the past few years, several neuroimaging studies took advantage of motor imagery and virtual reality paradigms in the attempt to identify potential neural correlates of FOG. Among these, task-related functional MRI provides interesting information about the task-specific recruitment of specific brain regions by comparing the dynamic changes in their blood oxygenation level dependent signal between the task-activated state and the control state. A task-related functional MRI study with gait imagery in patients with FOG has demonstrated a reduction in the blood oxygenation level dependent signal response of some mesial frontal regions, including the supplementary motor area, as compared with controls [57]. More recently, using a virtual reality gait task, Shine and coauthors reported a defective recruitment of specific cortical and subcortical regions in freezers when compared with nonfreezers when responding to indirect cognitive cues [58]. A recent study using functional near infrared spectroscopy measured frontal activation, that is, oxygenated hemoglobin (HbO_2) levels in Brodmann area 10 before and during FOG; results showed temporal abnormalities in frontal activation highlighting transient motor-cognitive failures in FOG [59]. Finally, an *in vivo* PET study reported that extranigral pathological conditions combining diminished neocortical cholinergic innervation and β-amyloid deposition are common in PD with FOG, consistent with a role for cortical dysfunction in FOG [60]. Overall, evidence suggests that the functional disruption of some cortical networks plays a crucial role in the pathogenesis of FOG. Some issues have not, however, been solved yet. For example, not all freezers show executive dysfunction, and morphostructural imaging data have yielded mixed results thus far [61].

In conclusion, despite the significant progress made in recent years, a unifying and reproducible theory explaining the pathogenesis of FOG has yet to be proven. There is widespread recognition that the disconnection between the basal ganglia, the prefrontal cortex and frontoparietal association areas is a critical element inducing FOG. In parallel, the subcortical involvement of certain areas responsible for the suprasegmental control of locomotion, such as the MLR, seems to result in a disconnection of the centers automatically generating gait from their hierarchically superior structures. When compared with controls, freezers show specific signs of gait impairment even outside of freezing episodes, such as an increased variability in the duration of each step, poor motor coordination of the lower limbs and reduced length of steps [40]. Furthermore, prior to the FOG onset, the kinematic gait profile of these patients often reveals a large set of stereotyped abnormalities, including a decreased range of movement of the ankles and hips in the sagittal plane, a significant reduction in the length of strides, a reduced dissociation between knees and hips in the swing phase and sometimes an overall disarray in the temporal control of gait cycles which can be difficult to differentiate from that occurring in gait festination [62]. Overall, these observations suggest that FOG may have a specific, independent pathogenic substrate characterized by a spatiotemporal disruption of the gait pattern due to the involvement of the complex hierarchical system responsible for locomotion [45].

• Diagnostic assessment

The assessment of FOG is complicated by its episodic, unpredictable and variable clinical presentation as well as its complex relationship with medications. In clinical practice, detection of FOG relies on history and examination. However, FOG questionnaires have been designed and validated to not only detect FOG but to quantify its severity together with its

impact on quality of life and functional autonomy in every day settings [1]. One item in the UPDRS section on activities of daily living specifically inquires about the presence and frequency of FOG and falls. However, item 14 of the 'old UPDRS' does not differentiate FOG-induced falls from those occurring independent of a FOG episode. Clinically, the sensitivity of this item for recognizing FOG seems quite poor. A more recent version of the UPDRS developed by the movement disorders society (MDS) task force includes the most common circumstances associated with the onset of FOG, as well as the severity and frequency, ranging from episodic and transient FOG occurring only upon initiation or turning, to a persistent FOG which can appear even in open and unobstructed paths [63]. Since some PD patients may not recognize or endorse FOG, the UPDRS part III also aids in the detection of otherwise unrecognized FOG through the clinician's objective physical examination.

The first questionnaire specifically developed for FOG assessment is the FOG-Q by Giladi *et al.* [4]. It is a six-item scale investigating the presence, frequency and duration of FOG together with a general survey of the patient's gait function. In particular, the third item explicitly refers to the patient's experience of feeling his own feet glued to the floor. If the patient does not fully comprehend the question, the examiner is asked to perform a practical demonstration. The scale ranges from 0 to 24 points, with higher scores indicating greater severity and impairment. According to the FOG-Q validation conducted on patients enrolled in the LARGO study, the third item is at least as reliable as the corresponding item in the UPDRS in detecting the presence of FOG [64]. The FOG-Q demonstrated both high test–retest reliability and internal consistency, and adequate correlation with UPDRS Motor and activities of daily living sections [64]. Moreover, when directly compared with item 14 of the UPDRS, item 3 of FOG-Q was able to identify almost twice as many PD patients as 'freezers', thus indicating a higher sensitivity [64]. Recently, a new version of FOG-Q (NFOG-Q) has been validated. It includes a demonstration video to improve FOG recognition by the patient and caregiver. The NFOG-Q has been shown to be reliable not only in assessing the presence of FOG but also in evaluating temporal change [65]. However, all of these tools are dependent upon the patient's ability to recognize FOG and discriminate it from other relatively similar symptoms such as gait festination or body bradykinesia, and also on the patient's willingness to report FOG to the clinician [66]. Further complicating accurate detection and reporting by patients is the fact that the vast majority of FOG usually occurs in advanced PD during off-states, and among patients with high levels of comorbid apathy [21]. It is often difficult to elicit FOG during an outpatient evaluation or in a gait analysis laboratory. To enhance the detection rate of FOG in these settings, one can increase the cognitive load by asking the patient to perform serial subtraction, for example, or by simultaneously testing verbal fluency [67]. The administration of a dual task challenge during gait execution is associated with a progressive reduction in step speed and amplitude, leading to the appearance of FOG [68]. In addition to addressing cognitive and attentional strategies, the clinical examination of the patient could involve a videotaped analysis of all gait phases, including sudden changing in direction, turning in place, overcoming multiple obstacles, passing through tight spaces, taking very short steps and repetitively stopping and starting [3]. In 2010, a standardized clinical protocol was developed by Ziegler and co-authors to assess the severity of FOG and festination through a fast, reproducible, highly feasible rating tool [69]. The study was conducted with 29 patients with different underlying pathologies for FOG, including PD, MSA-type P and subcortical vascular encephalopathy. This tool involves the execution of the three walking maneuvers commonly associated with FOG (starting, turning and passing through doors) on three levels of growing complexity, with the administration of single and multiple tasks. Ziegler's protocol showed excellent interrater and test-retest reliability. A moderate correlation with FOG-Q was found while no correlation with the motor section of UPDRS was demonstrated. Additionally, the standardized, brief Timed Up and Go test can help to quantify the degree of FOG in the clinical setting. The Timed Up and Go test directs the clinician to measure the time required by the patient to arise from a chair, take a 3-m-long walk (10 ft), turn around and return to the starting point [70].

Objective measurements of kinematic parameters associated with FOG are currently available only in dedicated laboratories. With the use of various detection systems, such as

sensor-equipped insoles and pressure-sensitive motorized treadmills, it is now possible to collect important quantitative and qualitative parameters of a patient's gait, both during and between FOG episodes. The qualitative data analysis usually includes gait pattern variability together with rhythmicity, consistency and regularity of steps. In particular, FOG-affected patients show a greater stride-to-stride variability, a lower step smoothness, a lower rhythmicity and a decreased lower limb coordination as compared with controls [71]. In this context, a promising system involves the continuous recording of the patient's locomotion in his or her home environment through sensors applied to the body [72]. This technique shows a double benefit: the extended recording (72 h) can detect a greater number of FOG episodes which, as described above, often escape detection during a single outpatient visit. Second, the registration of locomotion during home-based activities provides a more ecological approach to fully elucidating the patient's gait dysfunction in his everyday life. This form of recording may become the standard for objective FOG measurement in the future.

Summary

The complex phenomenology of FOG reflects the anatomical and functional complexity of the system responsible for bipedal locomotion which is a semiautomatic, learned function requiring a sophisticated, dynamic integration between various neural structures at multiple levels. A unified etiopathogenetic theory is still lacking. The diagnostic assessment of FOG may be a real challenge due to its episodic and unpredictable nature. Kinematic profiling allows more objective determination of some FOG-related parameters but is not commonly available at bedside. The FOG-Q and the NFOG-Q are sensitive questionnaires to retrospectively detect and follow-up this phenomenon; video demonstration of FOG could be interestingly useful for patient's better appraisal of the phenomena. In clinical practice, a video-taped gait analysis where attentional, cognitive and physical constrains are administered to evoke FOG is currently the most effective way to assess it.

FOG treatments

• Pharmacological therapies

Approximately 90% of FOG in PD occurs during off-states, suggesting a partial relation to the hypodopaminergic state of the basal ganglia [3]. Accordingly, the optimization of dopaminergic therapy is the first critical step in pharmacologic treatment targeting FOG [46]. Indeed, most dopaminergic drugs that have shown efficacy in reducing the severity and duration of off-periods have also shown beneficial effects on FOG. From a practical point of view, the therapeutic options commonly considered to treat wearing-off phenomena, like the adjustment of the L-dopa doses during the day and the co-administration of catabolic inhibitors, may have a beneficial outcome also on FOG episodes, particularly those occurring during the off-state [73]. However, FOG may nonetheless be suboptimally responsive, if at all, to dopaminergic therapy, similar to other poorly L-dopa responsive symptoms such as postural instability and speech disturbances. The ELLDOPA study showed a lower occurrence of FOG in patients receiving L-dopa as compared with controls [74]. It remains unclear if this correlation reflects purely the symptomatic effect or if it may also indicate an underlying neuroprotective mechanism and delay in FOG worsening [75]. In addition, some evidence suggests that the prompt initiation of L-dopa therapy can delay the onset of FOG [74]. To date, L-dopa is the only drug with a Class A recommendation with IA level evidence for these patients [76]. The management of on-FOG remains a major issue as it occurs in patients with otherwise satisfactory control of bradykinesia, rigidity and tremor. There are also patients who experience FOG when transiting from off- to on-state. In these cases, FOG may have been induced or exacerbated by the administration of dopaminergic therapy, making its treatment challenging.

The effect of dopamine agonists on FOG is particularly complex. In theory, since these drugs are effective in reducing off-time in most patients, a beneficial effect on FOG should be expected. However, a large prospective randomized controlled trial (RCT) conducted in early-stage PD showed that the progression of FOG is significantly greater in patients treated with dopamine agonists as compared with patients treated with L-dopa [77]. This echoes the findings of an older study by Ahlskog and colleagues reporting the onset of FOG following administration of a D2-receptor agonist [78]. Therefore, in the absence of further studies, the administration of these drugs in freezers should be avoided.

Selegiline, a selective inhibitor of the monoamine oxidase-B (MAO-B) enzyme, has proved

effective in reducing the incidence of FOG as an exploratory outcome in a prospective RCT. These findings have been replicated in a subsequent 2-year longitudinal follow-up study [49,79]. Interestingly, the induction of metamphetaminoid metabolites has been proposed as an explanation for these findings [80]. Rasagiline, another MAO-B inhibitor, also mildly reduced FOG [81].

Conflicting evidence surrounds the effect of amantadine in subjects with FOG. The administration of this drug seems to extend the survival rate of PD patients [82]. Amantadine could act by improving motor symptoms but also by modulating patients' cognitive performance [83]. According to one small retrospective study in advanced PD, amantadine was associated with a decreased appearance of FOG [20]. However, a subsequent study found contradictory results [84].

Gurevich *et al.* reported a single case of dramatic improvement in FOG following the administration of botulinum toxin in the calf of a PD patient [85], leading the authors to propose a dystonic mechanism as a potential contributor to FOG. However, subsequent prospective studies have failed to reproduce this observation [86].

Given the key role played by some brainstem noradrenergic nuclei in locomotion and their significant involvement in PD pathogenesis [48], a few studies have investigated the effects of the norepinephrine precursor L-threo-dihydroxiphenylserine (L-DOPS) in freezers. The results to date have not demonstrated significance [87]. Nevertheless, in a recent small study Fukada and co-authors demonstrated that the co-administration of L-DOPS with entacapone could ameliorate FOG. To explain this effect, the authors posited that the blockage of the catechol-o-methyl transferase enzyme may be critical to boost the efficacy of L-DOPS by reducing its peripheral metabolism, thereby enhancing its CNS distribution [88].

Methylphenidate is an amphetamine-derived molecule that significantly enhances central monoaminergic transmissions by inhibiting both dopaminergic and noradrenergic reuptake. In some open-label studies, methylphenidate has been associated with greater overall mobility among PD patients, particularly with respect to some FOG-related parameters such as stride-to-stride variability [89]. However, an RCT conducted on 23 PD patients receiving up to 80 mg/day of methylphenidate showed worsened scores in the FOGQ and UPDRS [90].

Given the underlying loss of cholinergic function in patients suffering from FOG, the administration of cholinergics has been recently tested as a therapeutic option. According to a recent RCT, rivastigmine is effective in improving gait stability in PD patients. Even though a specific effect on FOG was not demonstrated, promising results have been reported on some closely related phenomena, including fall frequency and step variability [91]. Finally, encouraging results on FOG have been described in a single patient treated with donepezil, another acetylcholinesterase inhibitor, specifically affecting attention and executive functions [92].

• Rehabilitation

Given the limited effectiveness of current pharmacotherapy in the management of FOG, a growing number of studies have employed various nonpharmacological approaches. In general, patient-centered physical therapy programs for people with PD based on compensatory strategies, strategies to improve motor learning and fall education as well as on assisting people to make lifelong changes in physical activity habits are generally recommended [93]. Dibble *et al.* conducted a systematic review of exercise-based interventions to improve balance in PD and determined that there is moderate evidence to support the efficacy of exercise in improving postural instability and balance task performance; however, it remains unclear as to which specific types and dosages of exercise are optimal for the management of balance disorders specially in those patients with high levels of gait disorders [94].

In clinical practice, rehabilitative sessions of treadmill training are commonly performed to improve gait. The efficacy of this practice in the treatment of some FOG-related parameters has been reported by various studies [95,96]. Unfortunately, the therapeutic effects are not commonly sustained over time, requiring periodic repetition of multiple sessions. This phenomenon could be explained by progressive impairment of the internal loop of the basal ganglia which is involved in the automation of learned movements [97]. For this reason, growing attention has been paid toward additional strategies based on external reinforcement and cueing. As different motor and sensory tricks can be effective approaches in overcoming FOG, many patients develop their own individualized cueing strategies to overcome freezing episodes

(e.g., marching to a command or a rhythmic song, stepping over an inverted cane, picturing a stick in the path and aiming to step over it, shifting body weight from side to side, or stepping backward) which all aim to provide external sensory-motor drive in order to overcome freezing [98]. More controlled application of sensory cueing was found effective in improving gait pattern among PD patients. Indeed, most rehabilitative interventions for gait disorders in PD take advantage of highly integrated attention-based strategies in which the use of external cues (visual, acoustic or cognitive) is coupled with the decomposition of complex actions into sequential execution of single movements [99]. In subjects with FOG, visual cues are effective in counteracting stride amplitude abnormalities and reducing step-to-step asymmetry. Auditory cues seem to be effective in improving gait rhythmicity [17]. The combination of external cueing and treadmill may be more effective in reducing FOG than cueing strategies alone. Indeed, it has been assumed that the treadmill itself could act as an additional cue by imposing an external rhythmic pattern and focusing the patient's attention [100]. However, a recent RCT did not show significant changes in NFOG-Q scores after a physical rehabilitation program based on multiple home sessions of cued exercises [101].

• Deep brain stimulation

DBS is known to significantly improve motor symptoms and quality of life in PD patients by extending the duration of unhampered motor function [102]. However, the effect of DBS on FOG and other axial symptoms is controversial as some studies report a greater number of falls and deterioration of gait and balance [103–105]. The underlying mechanisms of these adverse events are still debated, but could be directly related to the DBS procedure. Alternatively, the restoration of a greater level of activity due to an overall improved motor function may result in a higher risk of falling. Given these caveats, only a few, small studies have directly investigated the effects of DBS on FOG. Some benefits, mainly for off-related FOG episodes, have been reported after stimulation of the ventral intermediate thalamic nucleus (Vim) [106] and the subthalamic nucleus [107,108]. It has also been suggested that PPN stimulation may be beneficial, notwithstanding a great deal of interindividual variability [109,110]. However, no improvements in other axial symptoms such as postural instability and lower limb dystonia were observed after PPN stimulation, minimizing the overall impact of this intervention on gait functions [109].

• Noninvasive brain stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are noninvasive methods of brain stimulation used for the study and treatment of neurological and psychiatric disorders. Both TMS and tDCS are safe and largely well-tolerated interventions, which can effectively modulate regional brain

Table 1. Methodology of noninvasive brain stimulation studies for freezing of gait.

Main parameters	TMS			tDCS
Study (year)	Rektorova *et al.* (2007)	Lee *et al.* (2014)	Kim *et al.* (2015)	Valentino *et al.* (2014)
Parameters	10 Hz, 90% MT, 1350 pulses	10 Hz, 90% MT, 1000 pulses	10 Hz, 90% MT, 1000 pulses	Anodal, 2 mA, 20 min
Location	DLPFC and MC (Leg)	DLPFC, MC (Leg), SMA	MC (Leg)	MC (Leg)
Number of treatment sessions	1	1	5	5
Sham arm and type	No	Yes, coil held at 90°	Yes, coil held at 90°	Yes, DC stimulator turned off at 30 s
Number of completed participants	4	19	17	10
Main findings	No significant effect on off-related FOG	M1-LL and DLPFC improved some FOG outcomes	Improvement in UPDRS-III and in 'turn steps' but not in FOG-Q	Improved gait and occurrence of FOG episodes. Modest improvements on MDS-UPDRS, FOG-Q score and Gait and Falls Questionnaire
Ref.	[117]	[118]	[119]	[120]

DC: Direct current; DLPFC: Dorsolateral prefrontal cortex; FOG: Freezing of gait; FOG-Q: Freezing of gait questionnaire; MC: Motor cortex; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; MT: Motor threshold; SMA: Supplementary motor area; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation.

activity by influencing the bioelectric state of neurons [111,112]. Most clinical trials to date have shown some beneficial effects of repetitive TMS (rTMS) or tDCS on symptoms of PD [113–116]. However, the evidence for treating PD axial symptoms, including FOG, is limited **(Table 1)**.

Transcranial magnetic stimulation

According to a systematic review of 10 RCTs, TMS is effective in relieving motor symptoms of PD, particularly when high frequency stimulations are applied over the primary motor cortex (M1) [121]. More recently, Chou *et al.* reviewed 20 sham-controlled RCTs totaling 470 PD patients confirming modest efficacy of this technique on UPDRS outcomes. Importantly, at the subgroup analysis a significant effect was reached only after high frequency stimulation was applied over M1 or when low frequency stimulation was delivered to alternative frontal targets [122]. Moreover, another review of TMS side effects in PD has confirmed its safety and tolerability in PD patients [123].

Despite the amount of data regarding the efficacy and safety of this technique in relieving motor symptoms of PD, rTMS has not yet been systematically assessed as a potential treatment for FOG. An initial report by Retkorova and colleagues found no significant effect on off-related FOG in six PD patients treated with five sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) and primary leg

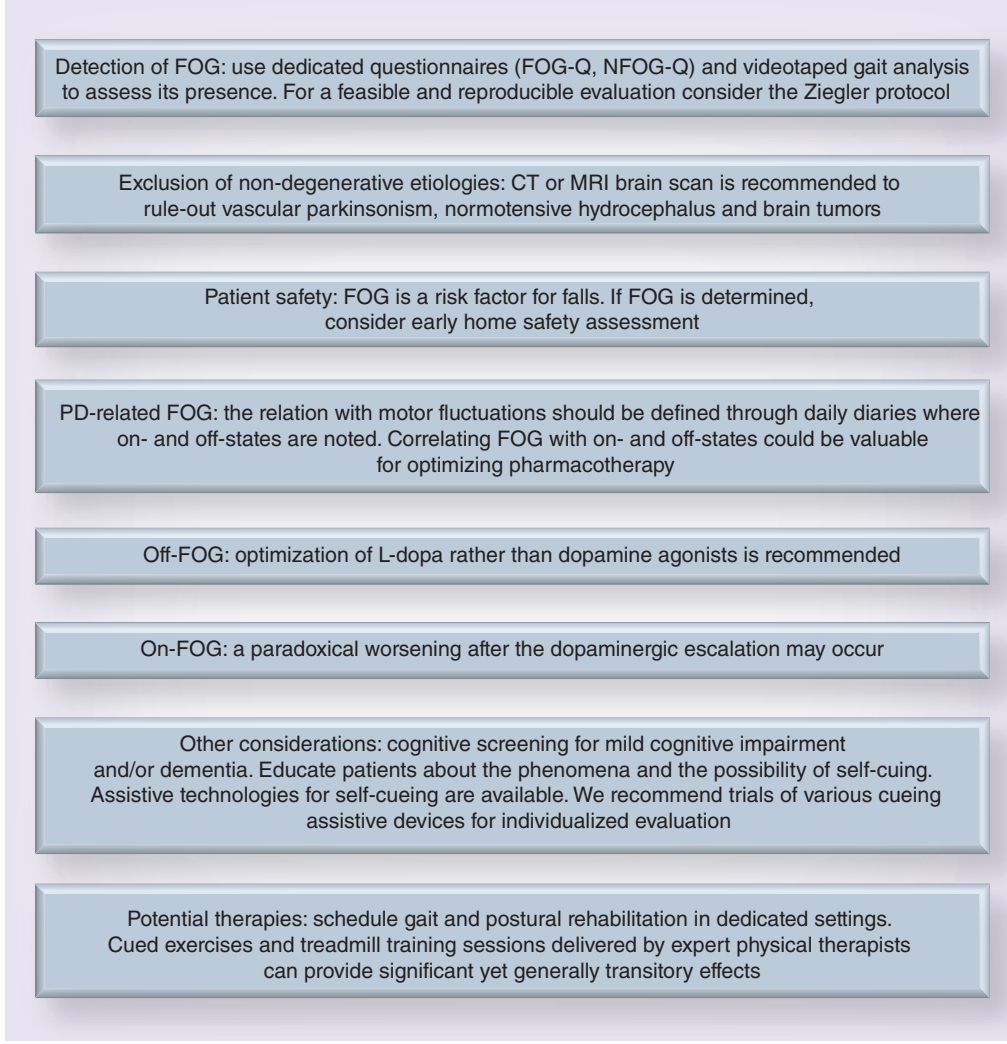


Figure 1. Practice management proposed flow chart.
CT: Computerized tomography; FOG: Freezing of gait; FOG-Q: Freezing of gait questionnaire; NFOG-Q: New freezing of gait questionnaire.

Table 2. Most relevant modalities of rehabilitation and emerging therapies.

General treatment modality	Intervention	General remarks	Ref.
Physical rehabilitation	Physical therapy	Systematic review and meta-analysis showed moderate evidence for recommendation	[93,94]
	Treadmill training	Temporal benefits were obtained. Combined therapies (i.e., cueing) seem to hold a greater potential for FOG rehab	[95,96]
	External cueing combined therapies	Several studies. Positive results have led to moderate evidence for recommendation	[17,99–101]
Invasive brain stimulation	DBS	Conflicting results still unclear best lead location and stimulator parameters	[102–110]
Noninvasive brain stimulation	TMS	Early stage of development, small studies, safe intervention, two positive and one negative study	[117–119]
	tDCS	Early stage of development, one cross-over study improved FOG with no adverse events	[120]

DBS: Deep brain stimulation; FOG: Freezing of gait; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation.

motor area (M1LL) [117]. However, a later double-blind cross-over study on 20 patients with FOG investigating the effects of a single session high frequency rTMS did suggest efficacy [118]. Three different cortical areas were explored in a cross-over design: most affected lower limb motor area (M1-LL), DLPFC and supplementary motor area along with sham TMS stimulation. The overall result of the study was that high frequency TMS over M1-LL and DLPFC were associated with improvement in some FOG-related outcomes, especially after M1-LL stimulation. In order to determine if this paradigm could provide further cumulative long-lasting effects, the same group explored multisession (five daily sessions) high-frequency rTMS over the M1-LL versus sham TMS in a cross-over design. The results showed a slight improvement in UPDRS-III and in 'turn steps' (on a modified Standing Start 180 Turn Test) but not in FOG-Q **(Table 1)** [119]. The authors proposed that the favorable impact on FOG could be due to rTMS correcting basal ganglia dysfunction through corticobasal ganglia-thalamo-cortical circuits, indirectly triggering striatal hyperactivity and/or rTMS-mediated activation of dopaminergic neurons in the striatum. The different results of these studies may be attributable to technical factors since the studies used different TMS coils, different total number of pulses and different outcome measurements.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is another promising noninvasive cortical stimulation technique involving the application of a constant, low intensity (i.e., 1–2 mA), direct current through surface electrodes applied to the scalp. The electric flow induces changes in cortical excitability with enhanced activity in the area under the anode, and decreased activity under the cathode [124]. These low-amplitude direct currents are strong enough to modify membrane potentials but, in contrast to TMS, without triggering the depolarization of neurons [124,125]. Moreover, to date, the use of conventional tDCS protocols has not produced any reports of a serious adverse effect which makes this particular technology safer than TMS and highly appealing for therapeutic applications [126,127]. A recent, double-blind, crossover, randomized, sham-controlled study investigated the efficacy of five daily sessions of tDCS on severity of FOG in ten PD patients [120]. Electrical current was delivered for 20 min at an intensity of 2 mA through the anode applied over M1LL and the cathode placed over the contralateral orbitofrontal cortex. The cortical side for the M1LL target was selected according to the first leg usually used by the patient to restart his gait after a FOG episode. Intriguingly, only PD patients with FOG persisting in the on-state were enrolled, thus partially controlling the potential confounding effect related to the on-restoration of other motor symptoms like bradykinesia. Following anodal tDCS, significant improvements were reported in the active but not sham groups, as evidenced by the Stand Walk Sit test used to evaluate gait and occurrence of FOG episodes in different contexts. Also, more modest improvements were reported in secondary outcomes MDS-UPDRS total and motor scores, FOG-Q score, and score on the Gait and Falls Questionnaire. Significant effects persisted for the 4-week follow-up period. No adverse effects were reported.

Despite some evident limitations of sample sizes and design, it should be recognized that FOG is still devoid of optimal treatments and is associated with a devastating burden on both patients and their caregivers. Therefore, the use of such noninvasive, highly safe and reproducible techniques seems to merit further investigation in the attempt to provide these patients with additional therapeutic options **(Table 1)**.

Summary

Despite the objective shortage of treatments specifically addressing this phenomenon, FOG may be significantly relieved by optimization of the dopaminergic therapy. Furthermore, patients can already take advantage of highly integrated rehabilitative strategies combining different paradigms of treadmill training and cued exercises (see **Figure 1**, practice management proposed flow chart). The contribution of noninvasive brain stimulation alone or combined with neurorehabilitation still needs to be systematically assessed through well-powered, well-designed and reproducible studies **(Table 2)**.

Future perspective

FOG is not just an episodic, stereotyped symptom arising from different neuropathological substrates but rather a discrete pathological entity with its own natural evolution and a peculiar association with specific comorbid factors. Even though a unified etiopathogenetic theory is still lacking, a growing awareness regarding the central role of the abnormal connectivity between different cortical areas and some subcortical structures, including basal ganglia and brain stem, gradually emerged in these past few years. We are convinced that a more precise understanding of all cognitive and psychiatric-behavioral aspects underlying locomotion will significantly contribute to the pathophysiological definition of FOG and its treatment. In the near future, highly integrated rehabilitative interventions combining different paradigms of locomotion exercise and cueing strategies (behavioral cueing, wearable technologies for cueing, among others) will emerge with adequate evidence for further recommendation. The contribution of noninvasive brain stimulation alone or combined with neurorehabilitation seems a particularly promising therapeutic option. Nevertheless, the potential of these new techniques still needs to be systematically assessed through well-powered, well-designed and reproducible studies. The episodic nature of FOG seems to suggest a precipitating event occurring in a chronic context of greater individual vulnerability. Such an event appears to be related to the need to solve sudden space–time conflicts related to locomotion. In patients with FOG, such a challenge can temporarily interrupt the proper orchestration of the information stream which is normally processed through the interplay between the basal ganglia and cerebral cortex. In our species, bipedal locomotion is learned when the cycle characterized by a constant alternation of balance and loss of balance becomes automatic. Like any other learned function, locomotion is indeed subject to neurodegeneration. This should lead to consider locomotion not a mere motor function but rather a superior integrated function where the role played by cerebral cortex is crucial.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Giladi N, Nieuwboer A. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. *Mov. Disord.* 23(Suppl. 2), S423–S425 (2008).

2 Fahn S. The freezing phenomenon in parkinsonism. *Adv. Neurol.* 67, 53–63 (1995).

3 Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur. J. Neurol.* 10(4), 391–398 (2003).

4 Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with Parkinsonism. *Parkinsonism. Relat. Disord.* 6(3), 165–170 (2000).

5 Giladi N, Kao R, Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. *Mov. Disord.* 12(3), 302–305 (1997).

6 Giladi N, Mcmahon D, Przedborski S *et al.* Motor blocks in Parkinson's disease. *Neurology* 42(2), 333–339 (1992).

7 Jankovic J. Gait disorders. *Neurol. Clin.* 33(1), 249–268 (2015).

8 Lee MS, Lyoo CH, Choi YH. Primary progressive freezing gait in a patient with CO-induced parkinsonism. *Mov. Disord.* 25(10), 1513–1515 (2010).

9 Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. *J. Mov. Disord.* 8(1), 1–13 (2015).

10 Wong JC, Armstrong MJ, Lang AE, Hazrati LN. Clinicopathological review of pallidonigroluysian atrophy. *Mov. Disord.* 28(3), 274–281 (2013).

11 Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* 10(8), 734–744 (2011).

12 Kuo SH, Kenney C, Jankovic J. Bilateral pedunculopontine nuclei strokes presenting as freezing of gait. *Mov. Disord.* 23(4), 616–619 (2008).

13 Nakajima A, Ueno Y, Shimura H *et al.* Acute transient freezing of gait in a patient with posterior reversible encephalopathy syndrome. *BMC Neurol.* 13, 79 (2013).

14 Okuma Y. Freezing of gait and falls in Parkinson's disease. *J. Parkinsons. Dis.* 4(2), 255–260 (2014).

15 Julia VR, Roberta B, Angelo A. Therapy-resistant symptoms in Parkinson's disease. *J. Neural. Transm.* 123(1), 19–30 (2015).

16 Okuma Y, Yanagisawa N. The clinical spectrum of freezing of gait in Parkinson's disease. *Mov. Disord.* 23(Suppl. 2), S426–S430 (2008).

17 Nieuwboer A. Cueing for freezing of gait in patients with Parkinson's disease: a rehabilitation perspective. *Mov. Disord.* 23(Suppl. 2), S475–S481 (2008).

18 Ehgoetz Martens KA, Ellard CG, Almeida QJ. Does anxiety cause freezing of gait in Parkinson's disease? *PLoS ONE* 9(9), e106561 (2014).

19 Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov. Disord.* 19(8), 871–884 (2004).

• **Valuable paper providing an accessible and wide overview on the complexity of the phenomenon as well as on its relationship with falls.**

20 Giladi N, Mcdermott MP, Fahn S *et al.* Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology* 56(12), 1712–1721 (2001).

•• **Seminal paper studying the occurrence of freezing of gait (FOG) in a large cohort of Parkinson's disease patients, providing robust informations about several factors associated to the onset and the severity of the phenomenon.**

21 Perez-Lloret S, Negre-Pages L, Damier P *et al.* Prevalence, determinants, and effect on quality of life of freezing of gait in Parkinson disease. *JAMA Neurol.* 71(7), 884–890 (2014).

22 Factor SA, Higgins DS, Qian J. Primary progressive freezing gait: a syndrome with many causes. *Neurology* 66(3), 411–414 (2006).

23 Schlenstedt C, Muthuraman M, Witt K, Weisser B, Fasano A, Deuschl G. Postural control and freezing of gait in Parkinson's disease. *Parkinsonism. Relat. Disord.* 24, 107–112 (2016).

24 Bartels AL, Balash Y, Gurevich T, Schaafsma JD, Hausdorff JM, Giladi N. Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia. *J. Clin. Neurosci.* 10(5), 584–588 (2003).

25 Wenning GK, Litvan I, Jankovic J *et al.* Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. *J. Neurol. Neurosurg. Psychiatry* 64(2), 184–189 (1998).

26 Wenning GK, Ebersbach G, Verny M *et al.* Progression of falls in postmortem-confirmed parkinsonian disorders. *Mov. Disord.* 14(6), 947–950 (1999).

27 Pinter B, Diem-Zangerl A, Wenning GK *et al.* Mortality in Parkinson's disease: a 38-year follow-up study. *Mov. Disord.* 30(2), 266–269 (2015).

28 Fasano A, Bloem BR. Gait disorders. *Continuum (Minneap Minn)* 19(5 Movement Disorders), 1344–1382 (2013).

29 Moreau C, Ozsancak C, Blatt JL, Derambure P, Destee A, Defebvre L. Oral festination in Parkinson's disease: biomechanical analysis and correlation with festination and freezing of gait. *Mov. Disord.* 22(10), 1503–1506 (2007).

30 Park HK, Yoo JY, Kwon M *et al.* Gait freezing and speech disturbance in Parkinson's disease. *Neurol. Sci.* 35(3), 357–363 (2014).

31 Nieuwboer A, Vercruysse S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. *Eur. J. Neurosci.* 29(7), 1422–1430 (2009).

32 Yanagisawa N, Hayashi R, Mitoma H. Pathophysiology of frozen gait in Parkinsonism. *Adv. Neurol.* 87, 199–207 (2001).

33 Muller J, Seppi K, Stefanova N, Poewe W, Litvan I, Wenning GK. Freezing of gait in postmortem-confirmed atypical parkinsonism. *Mov. Disord.* 17(5), 1041–1045 (2002).

34 Bonnet AM, Loria Y, Saint-Hilaire MH, Lhermitte F, Agid Y. Does long-term aggravation of Parkinson's disease result from nondopaminergic lesions? *Neurology* 37(9), 1539–1542 (1987).

35 Plotnik M, Hausdorff JM. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. *Mov. Disord.* 23(Suppl. 2), S444–S450 (2008).

36 Takakusaki K, Habaguchi T, Ohtinata-Sugimoto J, Saitoh K, Sakamoto T. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. *Neuroscience* 119(1), 293–308 (2003).

37 Moore ST, Macdougall HG, Ondo WG. Ambulatory monitoring of freezing of gait in Parkinson's disease. *J. Neurosci. Methods* 167(2), 340–348 (2008).

38 Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Exp. Brain Res.* 149(2), 187–194 (2003).

39 Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Janssens L, Stijn V. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. *Brain* 127(Pt 7), 1650–1660 (2004).

40 Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Mov. Disord.* 16(6), 1066–1075 (2001).

41 Cohen RG, Nutt JG, Horak FB. Errors in postural preparation lead to increased choice reaction times for step initiation in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 66(6), 705–713 (2011).

42 Spildooren J, Vercruysse S, Heremans E *et al.* Head-pelvis coupling is increased during turning in patients with Parkinson's disease and freezing of gait. *Mov. Disord.* 28(5), 619–625 (2013).

43 Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. *Exp. Neurol.* 215(2), 334–341 (2009).

44 Schepens B, Stapley P, Drew T. Neurons in the pontomedullary reticular formation signal posture and movement both as an integrated behavior and independently. *J. Neurophysiol.* 100(4), 2235–2253 (2008).

45 Lewis SJ, Barker RA. A pathophysiological model of freezing of gait in Parkinson's disease. *Parkinsonism Relat. Disord.* 15(5), 333–338 (2009).

46 Holloway RG, Shoulson I, Fahn S *et al.* Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch. Neurol.* 61(7), 1044–1053 (2004).

47 Lewis SJ, Shine JM. The next step: a common neural mechanism for freezing of gait. *Neuroscientist* 22(1), 72–82 (2014).

48 Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. *Brain* 123(Pt 9), 1767–1783 (2000).

49 Giladi N, Treves TA, Simon ES *et al.* Freezing of gait in patients with advanced Parkinson's disease. *J. Neural. Transm.* 108(1), 53–61 (2001).

50 Morita H, Hass CJ, Moro E, Sudhyadhom A, Kumar R, Okun MS. Pedunculopontine nucleus stimulation: where are we now and what needs to be done to move the field forward? *Front. Neurol.* 5, 243 (2014).

51 Almeida QJ, Lebold CA. Freezing of gait in Parkinson's disease: a perceptual cause for a motor impairment? *J. Neurol. Neurosurg. Psychiatry* 81(5), 513–518 (2010).

52 Kostic VS, Agosta F, Pievani M *et al.* Pattern of brain tissue loss associated with freezing of gait in Parkinson disease. *Neurology* 78(6), 409–416 (2012).

53 Herman T, Rosenberg-Katz K, Jacob Y, Giladi N, Hausdorff JM. Gray matter atrophy and freezing of gait in Parkinson's disease: is the evidence black-on-white? *Mov. Disord.* 29(1), 134–139 (2014).

54 Cowie D, Limousin P, Peters A, Day BL. Insights into the neural control of locomotion from walking through doorways in Parkinson's disease. *Neuropsychologia* 48(9), 2750–2757 (2010).

55 Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. *Mov. Disord.* 25(8), 1000–1004 (2010).

56 Amboni M, Cozzolino A, Longo K, Picillo M, Barone P. Freezing of gait and executive functions in patients with Parkinson's disease. *Mov. Disord.* 23(3), 395–400 (2008).

57 Snijders AH, Leunissen I, Bakker M *et al.* Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. *Brain* 134(Pt 1), 59–72 (2011).

58 Shine JM, Matar E, Ward PB *et al.* Differential neural activation patterns in patients with Parkinson's disease and freezing of gait in response to concurrent cognitive and motor load. *PLoS ONE* 8(1), e52602 (2013).

59 Maidan I, Bernad-Elazari H, Gazit E, Giladi N, Hausdorff JM, Mirelman A. Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures. *J. Neurol.* 262(4), 899–908 (2015).

60 Bohnen NI, Frey KA, Studenski S *et al.* Extra-nigral pathological conditions are common in Parkinson's disease with freezing of gait: an *in vivo* positron emission tomography study. *Mov. Disord.* 29(9), 1118–1124 (2014).

61 Heremans E, Nieuwboer A, Vercruysse S. Freezing of gait in Parkinson's disease: where are we now? *Curr. Neurol. Neurosci. Rep.* 13(6), 350 (2013).

62 Alice N, Fabienne C, Anne-Marie W, Kaat D. Does freezing in Parkinson's disease change limb coordination? A kinematic analysis. *J. Neurol.* 254(9), 1268–1277 (2007).

63 Goetz CG, Tilley BC, Shaftman SR *et al.* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov. Disord.* 23(15), 2129–2170 (2008).

64 Giladi N, Tal J, Azulay T *et al.* Validation of the freezing of gait questionnaire in patients with Parkinson's disease. *Mov. Disord.* 24(5), 655–661 (2009).

•• **Validates the first questionnaire specifically developed to assess FOG.**

65 Nieuwboer A, Rochester L, Herman T *et al.* Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture* 30(4), 459–463 (2009).

66 Nieuwboer A, Giladi N. The challenge of evaluating freezing of gait in patients with Parkinson's disease. *Br. J. Neurosurg.* 22(Suppl. 1), S16–S18 (2008).

• **Highlights the importance to take advantage of combined diagnostic methodologies to properly assess FOG.**

67 Rahman S, Griffin HJ, Quinn NP, Jahanshahi M. The factors that induce or overcome freezing of gait in Parkinson's disease. *Behav. Neurol.* 19(3), 127–136 (2008).

68 Morris ME, Iansek R, Matyas TA, Summers JJ. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain* 119(Pt 2) 551–568 (1996).

69 Ziegler K, Schroeteler F, Ceballos-Baumann AO, Fietzek UM. A new rating instrument to assess festination and freezing gait in Parkinsonian patients. *Mov. Disord.* 25(8), 1012–1018 (2010).

70 Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* 39(2), 142–148 (1991).

71 Moe-Nilssen R, Aaslund MK, Hodt-Billington C, Helbostad JL. Gait variability measures may represent different constructs. *Gait Posture* 32(1), 98–101 (2010).

72 Weiss A, Herman T, Giladi N, Hausdorff JM. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait: insights using a body-fixed sensor worn for 3 days. *J. Neural. Transm.* 122(3), 403–410 (2014).

73 Horstink M, Tolosa E, Bonuccelli U *et al.* Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: late (complicated) Parkinson's disease. *Eur. J. Neurol.* 13(11), 1186–1202 (2006).

74 Fahn S, Group PS. Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J. Neurol.* 252(Suppl. 4), IV37–IV42 (2005).

75 Fahn S, Oakes D, Shoulson I *et al.* Levodopa and the progression of Parkinson's disease. *N. Engl. J. Med.* 351(24), 2498–2508 (2004).

76 Giladi N. Medical treatment of freezing of gait. *Mov. Disord.* 23(Suppl. 2), S482–S488 (2008).

•• **A remarkably accurate overview on the currently available pharmacological strategies to address FOG.**

77 Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N. Engl. J. Med.* 342(20), 1484–1491 (2000).

78 Ahlskog JE, Muenter MD, Bailey PA, Stevens PM. Dopamine agonist treatment of fluctuating parkinsonism. D-2 (controlled-release MK-458) vs combined D-1 and D-2 (pergolide). *Arch. Neurol.* 49(5), 560–568 (1992).

79 Shoulson I, Oakes D, Fahn S *et al.* Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of

parkinsonism trial. *Ann. Neurol.* 51(5), 604–612 (2002).

80 Zuniga C, Lester J, Cersosimo MG, Diaz S, Micheli FE. Treatment of primary progressive freezing of gait with high doses of selegiline. *Clin. Neuropharmacol.* 29(1), 20–21 (2006).

81 Rascol O, Brooks DJ, Melamed E *et al.* Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* 365(9463), 947–954 (2005).

82 Uitti RJ, Rajput AH, Ahlskog JE *et al.* Amantadine treatment is an independent predictor of improved survival in Parkinson's disease. *Neurology* 46(6), 1551–1556 (1996).

83 Inzelberg R, Bonuccelli U, Schechtman E *et al.* Association between amantadine and the onset of dementia in Parkinson's disease. *Mov. Disord.* 21(9), 1375–1379 (2006).

84 Macht M, Kaussner Y, Moller JC *et al.* Predictors of freezing in Parkinson's disease: a survey of 6620 patients. *Mov. Disord.* 22(7), 953–956 (2007).

85 Gurevich T, Peretz C, Moore O, Weizmann N, Giladi N. The effect of injecting botulinum toxin type a into the calf muscles on freezing of gait in Parkinson's disease: a double blind placebo-controlled pilot study. *Mov. Disord.* 22(6), 880–883 (2007).

86 Wieler M, Camicioli R, Jones CA, Martin WR. Botulinum toxin injections do not improve freezing of gait in Parkinson disease. *Neurology* 65(4), 626–628 (2005).

87 Narabayashi H, Yokochi F, Ogawa T, Igakura T. Analysis of L-threo-3, 4-dihydroxyphenylserine effect on motor and psychological symptoms in Parkinson's disease. *No To Shinkei* 43(3), 263–268 (1991).

88 Fukada K, Endo T, Yokoe M, Hamasaki T, Hazama T, Sakoda S. L-threo-3, 4-dihydroxyphenylserine (L-DOPS) co-administered with entacapone improves freezing of gait in Parkinson's disease. *Med. Hypotheses* 80(2), 209–212 (2013).

89 Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin. Neuropharmacol.* 29(1), 15–17 (2006).

90 Espay AJ, Dwivedi AK, Payne M *et al.* Methylphenidate for gait impairment in Parkinsondisease: a randomized clinical trial. *Neurology*76(14), 1256–1262 (2011).

91 Henderson EJ, Lord SR, Brodie MA *et al.* Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, Phase 2 trial. *Lancet Neurol.* 15(3), 249–258 (2016).

92 Yener GG, Kaya GC, Ozturk V, Akdal G. Improvement in Tc-99m HMPAO brain SPECT findings during donepezil therapy in a patient with pure akinesia. *Ann. Nucl. Med.* 19(7), 607–609 (2005).

93 Morris ME, Martin CL, Schenkman ML. Striding out with Parkinson disease: evidence-based physical therapy for gait disorders. *Phys. Ther.* 90(2), 280–288 (2010).

94 Dibble LE, Addison O, Papa E. The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *J. Neurol. Phys. Ther.* 33(1), 14–26 (2009).

95 Lo AC, Chang VC, Gianfrancesco MA, Friedman JH, Patterson TS, Benedicto DF. Reduction of freezing of gait in Parkinson's disease by repetitive robot-assisted treadmill training: a pilot study. *J. Neuroeng. Rehabil.* 7, 51 (2010).

96 Hong M, Earhart GM. Rotating treadmill training reduces freezing in Parkinson disease: preliminary observations. *Parkinsonism. Relat. Disord.* 14(4), 359–363 (2008).

97 Curra A, Berardelli A, Agostino R *et al.* Performance of sequential arm movements with and without advance knowledge of motor pathways in Parkinson's disease. *Mov. Disord.* 12(5), 646–654 (1997).

98 Okuma Y. Freezing of gait in Parkinson's disease. *J. Neurol.* 253(Suppl. 7), Vii27–Vii32 (2006).

99 Morris ME. Movement disorders in people with Parkinson disease: a model for physical therapy. *Phys. Ther.* 80(6), 578–597 (2000).

100 Frazzitta G, Maestri R, Uccellini D, Bertotti G, Abelli P. Rehabilitation treatment of gait in patients with Parkinson's disease with freezing: a comparison between two physical therapy protocols using visual and auditory cues with or without treadmill training. *Mov. Disord.* 24(8), 1139–1143 (2009).

101 Martin T, Weatherall M, Anderson TJ, Macaskill MR. A randomized controlled feasibility trial of a specific cueing program for falls management in persons with Parkinson disease and freezing of gait. *J. Neurol. Phys. Ther.* 39(3), 179–184 (2015).

102 Okun MS, Foote KD. Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Rev. Neurother.* 10(12), 1847–1857 (2010).

103 Russmann H, Ghika J, Villemure JG *et al.* Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. *Neurology* 63(10), 1952–1954 (2004).

104 Umemura A, Oka Y, Okita K, Toyoda T, Matsukawa N, Yamada K. Predictive factors affecting early deterioration of axial symptoms after subthalamic nucleus stimulation in Parkinson's disease. *Parkinsonism Relat. Disord.* 16(9), 582–584 (2010).

105 Weaver FM, Follett K, Stern M *et al.* Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 301(1), 63–73 (2009).

106 Limousin P, Krack P, Pollak P *et al.* Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N. Engl. J. Med.* 339(16), 1105–1111 (1998).

107 Xie T, Vigil J, Maccracken E *et al.* Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. *Neurology* 84(4), 415–420 (2015).

108 Yokoyama T, Sugiyama K, Nishizawa S, Yokota N, Ohta S, Uemura K. Subthalamic nucleus stimulation for gait disturbance in Parkinson's disease. *Neurosurgery* 45(1), 41–47; discussion 47–49 (1999).

109 Ferraye MU, Debu B, Fraix V *et al.* Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain* 133(Pt 1), 205–214 (2010).

110 Moro E, Hamani C, Poon YY *et al.* Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain* 133(Pt 1), 215–224 (2010).

111 Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int. J. Neuropsychopharmacol.* 14(8), 1133–1145 (2011).

112 Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120(12), 2008–2039 (2009).

113 Fregni F, Simon DK, Wu A, Pascual-Leone A. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. *J. Neurol. Neurosurg. Psychiatry* 76(12), 1614–1623 (2005).

114 Wu AD, Fregni F, Simon DK, Deblieck C, Pascual-Leone A. Noninvasive brain stimulation for Parkinson's disease and

dystonia. *Neurotherapeutics* 5(2), 345–361 (2008).

115 Kamble N, Netravathi M, Pal PK. Therapeutic applications of repetitive transcranial magnetic stimulation (rTMS) in movement disorders: a review. *Parkinsonism Relat. Disord.* 20(7), 695–707 (2014).

116 Nitsche MA, Cohen LG, Wassermann EM *et al.* Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.* 1(3), 206–223 (2008).

117 Rektorova I, Sedlackova S, Telecka S, Hlubocky A, Rektor I. Repetitive transcranial stimulation for freezing of gait in Parkinson's disease. *Mov. Disord.* 22(10), 1518–1519 (2007).

118 Lee SY, Kim MS, Chang WH, Cho JW, Youn JY, Kim YH. Effects of repetitive transcranial magnetic stimulation on freezing of gait in patients with Parkinsonism. *Restor. Neurol. Neurosci.* 32(6), 743–753 (2014).

119 Kim MS, Hyuk Chang W, Cho JW *et al.* Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. *Restor. Neurol. Neurosci.* 33(4), 521–530 (2015).

120 Valentino F, Cosentino G, Brighina F *et al.* Transcranial direct current stimulation for treatment of freezing of gait: a cross-over study. *Mov. Disord.* 29(8), 1064–1069 (2014).

121 Elahi B, Elahi B, Chen R. Effect of transcranial magnetic stimulation on Parkinson motor function-systematic review of controlled clinical trials. *Mov. Disord.* 24(3), 357–363 (2009).

122 Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol.* 72(4), 432–440 (2015).

123 Vonloh M, Chen R, Kluger B. Safety of transcranial magnetic stimulation in Parkinson's disease: a review of the literature. *Parkinsonism Relat. Disord.* 19(6), 573–585 (2013).

124 Brunoni AR, Nitsche MA, Bolognini N *et al.* Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 5(3), 175–195 (2012).

125 Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. *Annu. Rev. Biomed. Eng.* 9, 527–565 (2007).

126 Brunoni AR, Fregni F. Clinical trial design in non-invasive brain stimulation psychiatric research. *Int. J. Methods Psychiatr. Res.* 20(2), e19–e30 (2011).

127 Bikson M, Grossman P, Thomas C *et al.* Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul.* doi:10.1016/j.brs.2016.06.004 (2016) (Epub ahead of print).