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Expert recommendation

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Management of freezing of gait — mechanism-based practical recommendations

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Abstract

Freezing of gait (FOG) is a debilitating motor symptom that commonly occurs in Parkinson disease, atypical parkinsonism and other neurodegenerative conditions. Management of FOG is complex and requires a multifaceted approach that includes pharmacological, surgical and non-pharmacological interventions. In this Expert Recommendation, we provide state-of-the-art practical recommendations for the management of FOG, based on the latest insights into the pathophysiology of the condition. We propose two complementary treatment flows, both of which are linked to the pathophysiology and tailored to specific FOG phenotypes. The first workflow focuses on the reduction of excessive inhibitory outflow from the basal ganglia through use of dopaminergic medication or advanced therapies such as deep brain stimulation and infusion therapy. The second workflow focuses on facilitation of processing across cerebral compensatory networks by use of non-pharmacological interventions. We also highlight interventions that have potential for FOG but are not supported by sufficient evidence to recommend for clinical application. Our updated recommendations are intended to enable effective symptomatic relief once FOG has developed, but we also consider potential targets for preventive approaches. The recommendations are based on scientific evidence where available, supplemented with practice-based evidence informed by our clinical experience.

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Our dear colleague Nir Giladi sadly passed away shortly after submission of this manuscript. Nir was one of the very first people to draw attention to freezing of gait. Throughout his career, much of his work remained focused on gaining a better understanding of this mysterious motor phenomenon. Alongside the many other important contributions that he made, Nir was one of the inspirational drivers behind the new International Freezing of Gait Society. We dedicate this manuscript to his memory.

Introduction

Freezing of gait (FOG) is defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk"[1]. FOG can occur in several neurological disorders[2–6] but is most common in Parkinson disease (PD) and atypical forms of parkinsonism[7–9], and is considered to be among the most debilitating motor symptoms[10]. The prevalence of FOG is higher among people with more advanced disease; approximately 50% of people with advanced PD experience FOG[8,11,12]. FOG increases the risk of falls and fall-related injuries, and leads to a decline in functional mobility and independence, with negative effects on quality of life[13,14].

Management of FOG is challenging and requires a multifaceted approach that includes pharmacological, surgical and non-pharmacological treatments. We proposed a treatment algorithm a decade ago that is now widely used[15], but knowledge of the mechanisms that underlie FOG has advanced considerably, and novel treatments have emerged[16–20]. In this Expert Recommendation, we therefore present revised guidance for the management of FOG in PD on the basis of the latest insights into the underlying pathophysiology.

We first summarize the presumed pathophysiological substrate of FOG, which provides the basis for designing targeted therapies tailored to the needs of individuals. We then introduce two complementary treatment flows: one focuses on dopaminergic medication, deep brain stimulation (DBS) and infusion therapies, and the other focuses on non-pharmacological treatment. Importantly, both workflows start with characterizing the type of FOG to devise a personally tailored treatment strategy. We conclude by highlighting other pharmacological, surgical and non-pharmacological interventions that could be beneficial in FOG but are not supported by sufficient evidence to include in our recommendations.

Our updated recommendations are largely intended to enable symptomatic relief (that is, ameliorate FOG once it has emerged), but we also touch upon potential targets for preventive approaches. The recommended interventions are based on scientific evidence where available, combined with practice-based evidence informed by our clinical experience (Table 1). We interpret the scientific evidence cautiously where FOG was not the primary outcome in studies of therapeutic strategies and consider the fact that FOG is not measured objectively in all studies, because assessment remains difficult in the absence of standardized, responsive and reliable measures of severity[21–25].

Pathophysiology of FOG

The pathophysiology of FOG in PD is complex — the presumed mechanisms (Fig. 1) involve dysfunction across multiple and variable neural circuits[16,26]. The available evidence suggests that FOG ultimately results from paroxysmal failure to regulate the amount of GABAergic inhibition from basal ganglia outputs that affect activity in brainstem locomotor centres — the circuitry between these two regions is the so-called final common pathway of FOG[27,28]. Moreover, failure to compensate for loss of automatic gait control through goal-directed motor function probably contributes to FOG[29,30].

Excessive inhibitory basal ganglia outflow

Supraspinal gait control is necessary to adapt the gait pattern during gait initiation or termination, turning or when walking through doorways or crowded environments. This adaptive control mechanism enables navigation through an ever-changing environment[31]. Most of these contexts recur frequently and initiate automatized and fast gait adjustments that are effortless in healthy people. In PD, however, degeneration of nigral dopaminergic neurons that project to the posterior putamen affects the cortical–basal ganglia–thalamo–cortical posterior motor circuit, which is involved in automatic motor control[32]. The net result is tonic over-inhibition of the posterior motor circuit, leading to de-automatization of motor control. Initially, this over-inhibition can be overridden by bursts of dopaminergic signalling to enable selective self-generated motor actions[33,34], but with disease progression and further dopaminergic denervation of the caudate and putamen, the ability to selectively self-generate motor actions becomes increasingly impaired[35]. During challenging locomotor tasks in particular, the intermittent lack of dopamine and consequent lack of dopamine type 1 receptor stimulation in locomotor programmes in the direct pathway result in gait breakdown or an inability to initiate gait[27,36,37]. Examples of such motor tasks — gait initiation, turning and gait termination — are established triggers of FOG[38,39].

Failure of compensation for loss of gait automation

In contrast to the posterior motor circuit, which involves the ventrolateral putamen, the anterior cortical–basal ganglia–thalamo–cortical circuit, which involves the rostromedial striatum, is relatively spared in PD[40]. This anterior motor circuit is involved in goal-directed motor control, so it provides a mechanism to compensate for the loss of automatic gait control[41].

Adequate goal-directed gait control relies not only on the integrity and function of cortical–striatal motor loops, but also on compensatory input from cognitive, sensory and limbic systems[24,42–45]. To effectively integrate these distinct compensatory brain networks, a minimum level of activity in the noradrenergic ascending arousal system is probably required, but this system is impaired to varying degrees in PD with FOG[46–48]. Indeed, lower concentrations of noradrenaline in the cerebrospinal fluid have been associated with greater severity of posture and gait disturbances in PD[49]. Furthermore, imaging studies have shown that the volume and surface area of the noradrenergic locus coeruleus are decreased and thalamic noradrenaline transporter binding is reduced in people with FOG relative to people without, and these measures correlate with FOG severity[47,48]. When noradrenergic activity is suboptimal, compensatory brain networks are thought to remain too segregated to enable adequate gait compensation[50], whereas during moments of heightened arousal, when noradrenergic activity is supraoptimal, brain networks are thought to become overly integrated, inducing a conflict that results in paroxysmal gait dysfunction and possibly FOG[27,51–54].

Besides impaired integration of cerebral compensatory networks, the ability to adjust for loss of automatic gait control via goal-directed motor control might also be diminished in PD and FOG by the inevitable degeneration of compensatory cortical areas that occurs as the disease progresses[55]. With increasing disease duration, cognitive impairment — in particular, executive dysfunction — becomes more prevalent, especially in people who experience FOG[56]. Given that the

Table 1 | Interventions recommended for freezing of gait in Parkinson disease

Approach	Treatment	Effect[a]	Level of evidence[b]
Reduction of inhibitory basal ganglia outflow			
Optimizing dopaminergic medication	Levodopa	Improvement	Level B[65,78]
	Dopamine agonists	Can worsen and improve FOG Insufficient data[c] Inconsistent data[d]	Level D[79,80]
	Monoamine oxidase-B inhibitors (rasagiline and selegiline)	Improvement Reduced risk of developing FOG	Level B[192–196]; level A2[11,197]
	Apomorphine	Improvement Insufficient data[c]	Level C[111,112]
DBS and infusion therapies	STN DBS	Improvement	Level A1[89]
	GPi DBS	Improvement	Level A1[95]
	PPN DBS	No improvement Inconsistent data[d]	Level D Level C[98,100,101,262]
	Levodopa–carbidopa intestinal gel infusion	Improvement	Level C[107–109]
	Levodopa–entacapone–carbidopa intestinal gel infusion	Improvement Insufficient data[c]	Level C[113]
Facilitation of compensatory networks			
Physical training and fall prevention	Exercise	Improvement Insufficient data[c]	Level A1[24]
	Physiotherapy (for example, gait, balance and turning training)	Inconsistent data[d] Insufficient data[c]	Level A1[24,25]
	Occupational therapy (for example, home adjustment, help with daily planning)	Improvement Insufficient data[c]	Level D
	Use of walking aids (for example, wheeled walker, Nordic walking poles, wheelchair for long distances)	Improvement Insufficient data[c]	Level D
Applying compensation strategies	Expert education on complex strategies (e.g., negotiating a doorway)	Improvement Insufficient data[c]	Level D
	Compensation strategies (for example, cueing, weight shifting, action observation)	Improvement Insufficient data[c]	Level A1[157]
	Device-aided cueing strategies (for example, laser shoes, vibrating socks, augmented reality glasses)	Insufficient data Inconsistent data[d]	Level C[163,164,168]
	Other device-aided interventions (for example, soft robotic apparel)	Insufficient data[c]	Level C[166]
Targeting non-motor symptoms associated with FOG	Dual-task gait training	Improvement Insufficient data[c]	Level A2[c142,176]
	Cognitive behavioural therapy	No improvement Insufficient data[c]	Level B[178]
	Antidepressants (SSRIs)	Insufficient data[c] Inconsistent data[d]	Level C[c182,183]

[a]Refers to the overall effect on FOG unless otherwise specified; information regarding specific subtypes of FOG is often unavailable and where specific FOG subtypes are reported, a description of how the subtype was determined is usually lacking. [b]Level A1, meta-analysis that includes at least some trials with an evidence level of A2 and consistency between trial results; level A2, good-quality randomized double-blind controlled trials of sufficient size with consistent results between trials; level B, moderate-quality randomized clinical trials of insufficient size or other types of comparative trial (for example, nonrandomized trials, cohort studies or case–control studies); level C, non-comparative trials; level D, expert opinion. [c]Consensus among the authors was that evidence is solely derived from few and/or inconsistent level B, C or D evidence studies or from studies in which FOG was not the primary outcome measure. [d]Consensus among the authors was that evidence is derived from multiple studies with a similar level of evidence but contradictory results. DBS, deep brain stimulation; FOG, freezing of gait; GPi, globus pallidus internus; PPN, pedunculopontine nucleus; SSRI, selective serotonin reuptake inhibitor; STN, subthalamic nucleus.

cognitive network regulates goal-directed gait, situations that demand simultaneous cognitive and motor processing cause a conflict for attentional resources that is detrimental to gait control, particularly given that people with PD typically prioritize cognitive tasks over motor control[57]. Indeed, dual tasking while walking can provoke FOG[58–61].

In addition, cholinergic deficiencies are thought to contribute to FOG by altering executive function and attentional mechanisms that are involved in goal-directed gait control[62]. Similarly, degeneration of striatal cholinergic interneurons can disrupt cortical–striatal information flow, thereby hampering goal-directed gait control and

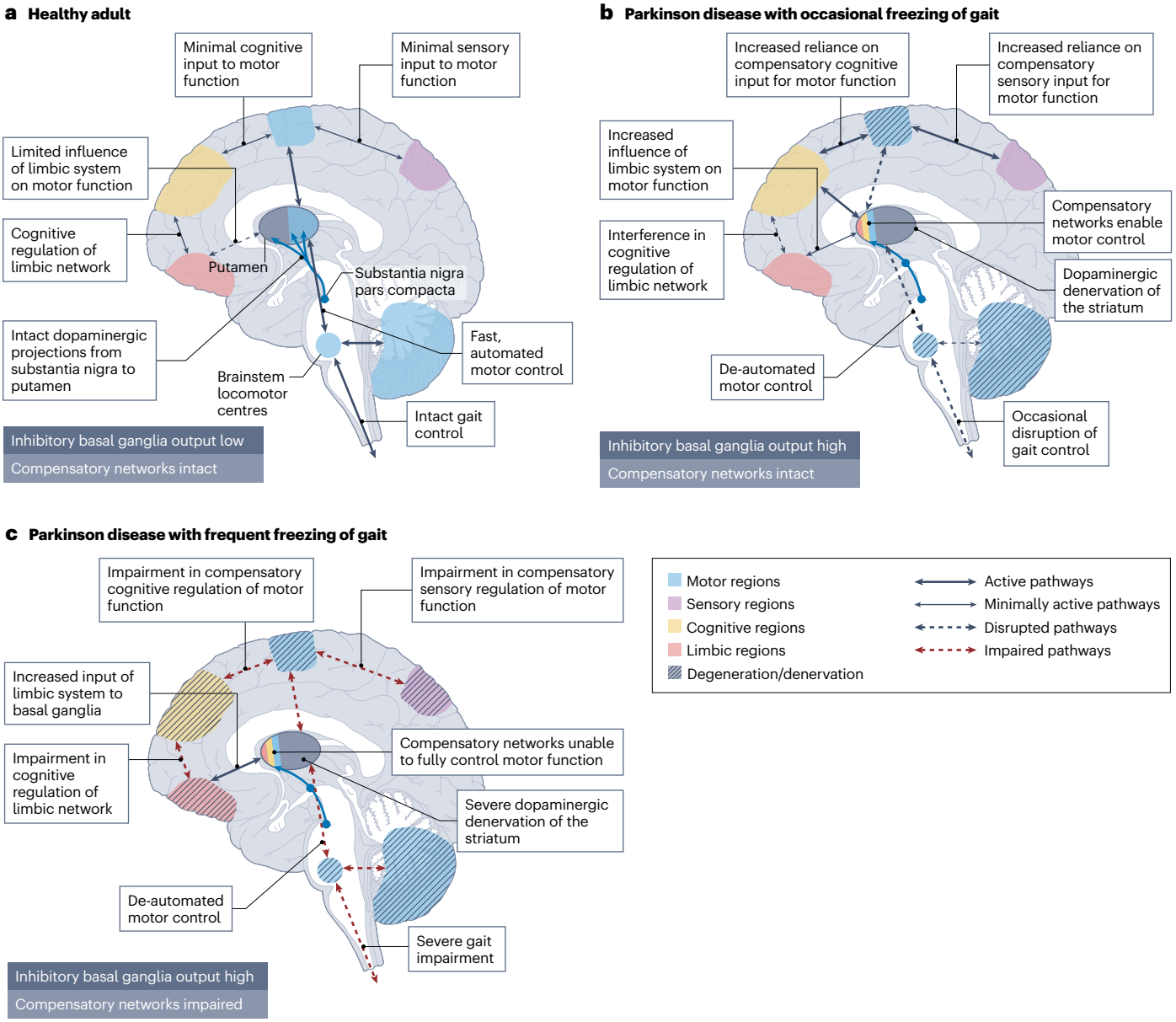


Fig. 1 | Proposed pathophysiological mechanisms of FOG in Parkinson disease. a, In health, supraspinal gait control is essential for adaptation of gait that enables navigation of an ever-changing environment. Most flexible gait situations frequently recur, and adjustment of gait to these situations has been automated and occurs fast and effortlessly. Consequently, only limited cognitive and sensory input is required to regulate walking during situations that necessitate a high degree of adaptation. Intact dopaminergic innervation of the basal ganglia from the substantia nigra pars compacta ensures that the need for adaptation causes limited interference with minor effects on gait performance. The cognitive network is also free to process additional tasks that demand attention (dual tasking) and to regulate limbic input. Consequently, situations that increase arousal (for example, stress or a threat) have only a limited effect on gait performance. **b**, Alterations to networks in Parkinson disease that lead to occasional freezing of gait (FOG). Owing to dopaminergic denervation in the basal ganglia, basal ganglia inhibitory output to the brainstem locomotor centres is increased and motor function is de-automated. As a result, reliance on compensatory cognitive (attention) and sensory (mostly visual) input is increased. This reliance on compensatory networks affects gait performance and increases the risk of interference during situations that require a high degree of adaptation. In moments of insufficient dopamine availability, the basal ganglia lose the ability to process compensatory inputs, further increasing inhibition and leading to occasional breakdown of gait and FOG. The requirement for the cognitive network to regulate gait together with interference in attention during dual tasking can lead to dysregulation of limbic input, which further increases the risk of FOG in the context of stress. **c**, Alterations of networks that lead to frequent FOG. As the pathology of Parkinson disease progresses, dopaminergic denervation of the basal ganglia worsens, and denervation and degeneration of cortical areas also occurs. Therefore, the need for compensation remains but the compensatory networks and regulation of limbic input become increasingly impaired. The consequence is severe gait disability and frequent FOG.

sensorimotor integration, so this is a plausible mechanism of altered network function that underlies FOG[63,64].

Pathophysiology-based management

Though the mechanisms described above are not an exhaustive explanation for the full heterogeneity of FOG, they do provide a foundation on which to build a targeted treatment strategy. On the basis of this presumed pathophysiology, optimal management of FOG should consist of at least the following two pillars: reducing excessive inhibitory outflow of the basal ganglia and facilitating gait via processing across compensatory networks. In addition, preventive approaches should be explored to reduce the risk of developing FOG throughout the course of the disease. We elaborate on these concepts in the sections that follow.

Reduction of inhibitory basal ganglia outflow

Excessive inhibitory outflow of the basal ganglia can be reduced through dopamine replacement therapy (including infusion therapies) and DBS. We propose a pharmacological and surgical management approach that is tailored according to classification of FOG on the basis of its response to dopaminergic stimulation.

Establish the response to dopaminergic stimulation

The relationship between FOG and dopaminergic medication is complex (Fig. 2). FOG most commonly occurs in the dopaminergic OFF state — that is, when the effect of medication has worn off. In this case, FOG can generally be improved by dopaminergic medication. We refer to this type of FOG as OFF-state FOG[65]. However, FOG can also occur during what seems to be the ON state — that is, when the upper limb manifestations of PD are well controlled. In this scenario, the ON state is incomplete because the lower limbs are insufficiently controlled. This type of FOG is the result of suboptimal dosing and can therefore be ameliorated by higher dosages of dopaminergic medication. We refer to this type of FOG as pseudo-ON-state FOG[36]. A third type of FOG is more or less equally severe in both the ON state and the OFF state, and is unresponsive to changes in dopaminergic medication. We refer to this as dopa-unresponsive FOG, also known as dopa-resistant FOG[66,67]. This type of FOG often occurs when non-dopaminergic lesions are prominent, such as in atypical parkinsonism or late-stage PD. The term ON–OFF FOG is sometimes used to refer to FOG that occurs in both the ON state and the OFF state — we have not adopted this term because it could be interpreted to mean either pseudo-ON-state FOG or dopa-unresponsive FOG.

Much rarer forms of FOG include biphasic FOG[68,69] and ON-state FOG[36,70,71]. Biphasic FOG manifests in the transitional phases between the ON state and OFF state; for example, shortly after intake of dopaminergic medication or just before the next scheduled dose. In ON-state FOG[36,70], FOG is absent or less severe during the OFF state (for example, immediately after waking up) but seems to be induced by dopaminergic stimulation.

This classification of FOG on the basis of its response to dopaminergic medication guides the clinician towards the strategy that optimizes dopamine replacement therapy. Importantly, intermediate types of FOG can exist. Furthermore, the response of FOG to treatment can evolve over time; for example, FOG that was initially dopa responsive can become partially responsive or dopa unresponsive. Renewed evaluation is advised if the selected treatment approach becomes less effective over time; we recommend evaluation at least once per year, and more frequently on indication.

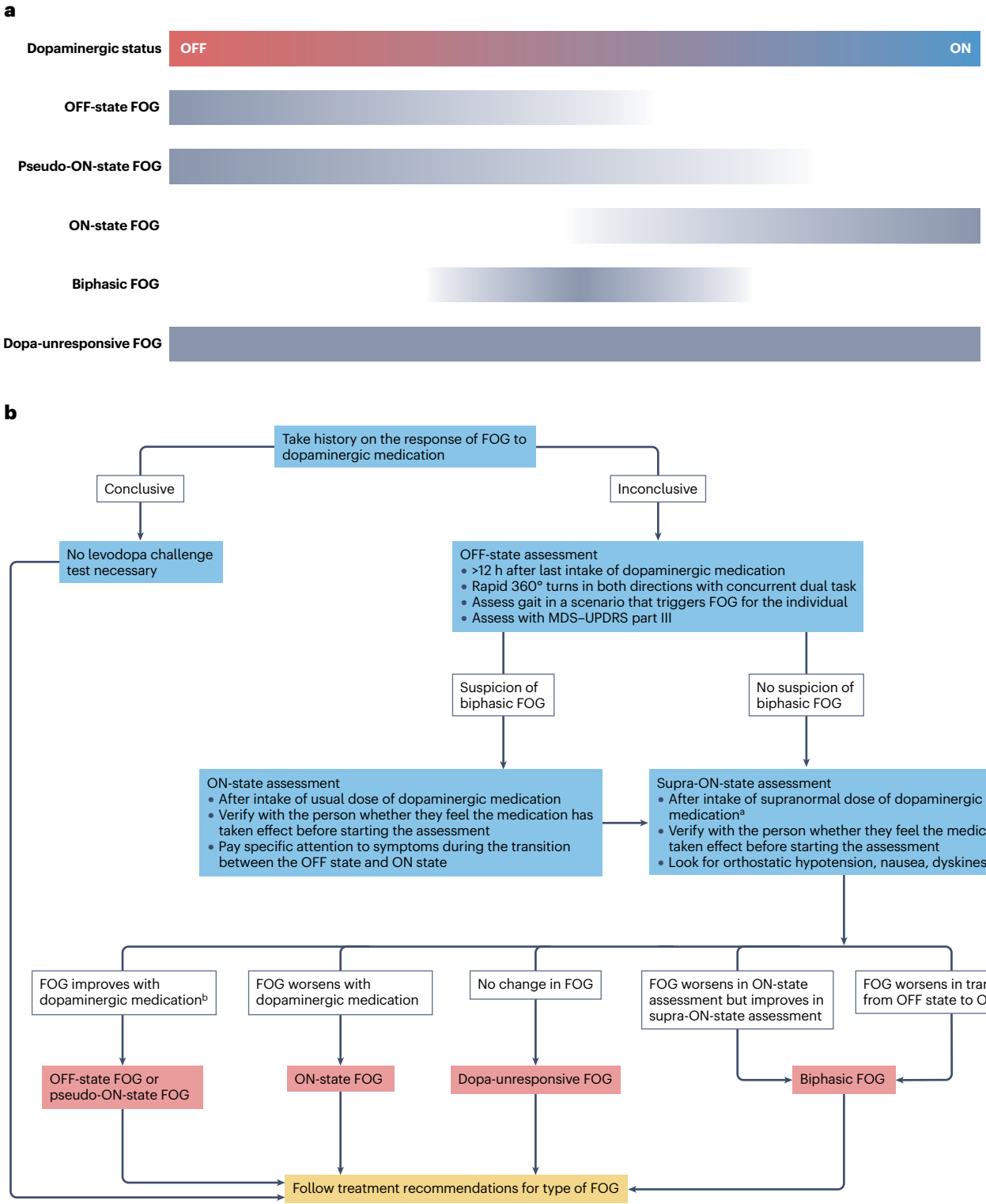
To establish the pharmacological classification of FOG, the person with FOG can be asked questions to determine whether FOG occurs predominantly in the dopaminergic OFF state, ON state, in the transitional phases between the ON state and OFF state, or equally in both states. For example, asking the individual and their caregiver about the presence of FOG in the first few minutes after waking up in the morning (when patients are typically in the OFF state) can be informative, as ON-state FOG is usually absent after waking in the morning, whereas OFF-state FOG is often at its worst. However, in our experience, people with FOG are not always aware of the effects of their medication or able to distinguish between the ON state and OFF state, especially those with more advanced disease[72]. Therefore, use of a levodopa challenge test (Fig. 2) is usually warranted for objective verification of how FOG responds to dopaminergic medication. A levodopa challenge can be particularly helpful to determine the presence of types of FOG other than OFF-state FOG, which can often be identified with sufficient certainty on the basis of history alone[71]. The indications, commonly used protocols and potential complications of an acute levodopa challenge test have previously been reviewed in detail elsewhere[73].

Objectively verifying the presence of FOG in the consulting room can, however, be very challenging for various reasons[74]. Several tools have been proposed for the identification of FOG and assessment of its severity — technology for such objective assessment has previously been reviewed by the International Consortium of Freezing of Gait[75]. The task that seems most sensitive for detection of FOG is rapid 360° turns in both directions, preferably with a concurrent task, though we recommend additional use of other tests that can provoke FOG, such as walking through a narrow doorway, for optimal sensitivity[76,77]. A consensus-based proposed protocol for provocation of FOG — known as the Giladi protocol — was published in 2025[75]. This protocol includes eight behavioural tasks that involve combinations of walking, turning and shuffling, sometimes while performing cognitive tasks. The authors of the Giladi protocol acknowledge that key details are likely to change as part of ongoing validation and refinement.

Optimize dopaminergic medication

Once the FOG phenotype has been established, the most appropriate pharmacological approach can be selected (Fig. 3). For OFF-state FOG and pseudo-ON-state FOG, reducing daily time in the OFF state through conventional oral dopaminergic medication should be the first step. For treatment-naive individuals who experience FOG, we recommend starting with levodopa, which can reduce freezing severity in both phenotypes[64,65,78]. Though dopamine agonists might have some advantages over levodopa, such as the ability to dose once daily, they are less effective for controlling motor symptoms of PD[16], so levodopa is our preferred recommendation for dopaminergic treatment of FOG. For individuals who are already receiving levodopa, we recommend considering an increase in the dosage or addition of a monoamine oxidase type B (MAO-B) or catechol-*O*-methyltransferase (COMT) inhibitor to increase availability of levodopa, depending on tolerability. Amelioration of FOG can require higher doses of levodopa than the doses needed to suppress other cardinal signs of PD (as illustrated by the phenomenon of pseudo-ON-state FOG)[36].

For people who are already receiving dopamine agonists alone, the most straightforward approach would seem to be to increase the dose of the dopamine agonist, but our recommended strategy is to start adjuvant levodopa. This recommendation is informed by several considerations. First, uncertainty exists about whether dopamine



agonists can induce or aggravate FOG. Two clinical trials have suggested that monotherapy with dopamine agonists increases the risk of developing FOG in comparison with levodopa monotherapy[79,80]. We suspect that relative underdosing with dopamine agonists so that OFF-state or pseudo-ON-state FOG is not sufficiently suppressed could explain these findings. Indeed, relative underdosing was indicated by differences in Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS–UPDRS) part III scores, which were higher in the agonist arm than the levodopa arm, suggesting poorer control of PD symptoms. Nevertheless, until the uncertainty is resolved definitively,

Fig. 2 | Pharmacological classification of FOG. a, The relationship between freezing of gait (FOG) types and dopaminergic status. People receiving dopaminergic medication can be in the ON state (medication is effectively controlling symptoms), the OFF state (medication ineffective or worn off) or in transition between the two states (top bar). The grey bars indicate where along this spectrum of dopaminergic status each type of FOG is most likely to occur. A stronger grey colour indicates a higher likelihood that FOG will occur. **b**, The procedure for the levodopa challenge test for objective verification of FOG type. [a]Different strategies can be applied to determine the dose; for example, 140–200% of the levodopa equivalent dose or the usual dose plus a pragmatic dose of 250 mg levodopa or benserazide (dispersible). The choice of strategy should be based on individual characteristics (for example, baseline dyskinesia). We advise that local protocols are followed if available. [b]Improvement that is clinically meaningful to the individual. MDS–UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale.

caution with dopamine agonists remains warranted if FOG seems to worsens after increasing the dose.

Interestingly, long-term levodopa treatment has also been associated with an increased risk of developing FOG relative to the risk with progression of PD, possibly because the intermittent oral intake is associated with non-physiological dopaminergic stimulation that somehow elicits FOG[70,81,82]. Further investigation remains necessary to definitively untangle the contribution of non-physiological dopaminergic stimulation to the development of FOG from the concurrent contribution of spreading neuropathology owing to disease progression[83]. However, we recommend that the possibility does not deter use of levodopa as the first-choice treatment for OFF-state FOG or pseudo-ON-state FOG, as current evidence suggests that the benefit outweighs the risk.

For OFF-state FOG and pseudo-ON-state FOG, the treatment regime should be optimized to minimize response fluctuations and dyskinesias. One strategy for this is to prevent fluctuations through dose fractionation or adjuvant therapy with an oral MAO-B inhibitor or COMT inhibitor[84]. Alternatively, fluctuations can be treated ad hoc by use of rescue medication. Detailed instructions for the management of response fluctuations in people with PD are available elsewhere[85,86].

Management of dopaminergic treatment response fluctuations is particularly important in biphasic FOG. This type of FOG is uncommon, and no studies of its management are available. However, we can draw from knowledge about the treatment of biphasic dyskinesia, which is a related and more common phenomenon. On this basis, extended release formulations of dopaminergic medications should be avoided so that the transitions between the ON state and OFF state are not prolonged. Fast-acting rescue treatments, such as inhaled levodopa or sublingual or subcutaneous apomorphine, can be considered to shorten transition times.

For ON-state FOG, we recommend that dopaminergic medication is reduced, though this reduction should be balanced against worsening of other dopa-responsive symptoms; for example, bradykinesia, which can affect walking ability beyond the occurrence of FOG. In our experience, prolonging the interval between doses can also be successful; the extent to which the interval should be prolonged depends on the number of doses and the tolerability. If tapering of dopaminergic medication is hampered by the emergence of debilitating symptoms that are controlled by oral dopaminergic medication, then DBS or infusion therapies[87] could be considered to enable further dose reductions (see the section 'DBS therapies and infusion therapies').

Given that non-dopaminergic pathways are presumed to contribute to dopa-unresponsive FOG, various pharmacological approaches beyond dopamine replacement therapy have been proposed, though evidence for their efficacy is limited or inconclusive[88] (see the section 'Interventions under investigation'). Our main recommendation for the management of debilitating dopa-unresponsive FOG is the use of non-pharmacological interventions (see the section 'Facilitation of compensatory networks').

DBS and infusion therapies

When non-invasive approaches do not sufficiently ameliorate FOG (for example, if dose-limiting adverse effects or uncontrollable fluctuations in response occur), DBS or infusion therapies can be considered. These therapies are primarily intended to treat motor fluctuations that cannot be managed adequately with oral dopaminergic treatments[87] in OFF-state and pseudo-ON-state FOG, so establishing the response of FOG to levodopa is crucial for predicting outcomes of these therapies.

Strong evidence demonstrates that DBS of the subthalamic nucleus (STN) improves FOG[89], especially with bilateral implants[90] (Table 1). In a secondary analysis of the EarlyStim trial, in which STN DBS was compared with 'best medical treatment', 52% of individuals who did not receive DBS experienced FOG during 3 years of follow-up, compared with 34% of individuals who received STN DBS[91]. However, long-term follow-up studies suggest that the effects of STN DBS on balance and gait tend to diminish, presumably as a result of disease progression and development of non-dopaminergic symptoms[92,93]. In one study, 64% of people who had received STN DBS for >20 years started to report falls and a higher prevalence of axial and dopa-resistant symptoms[94]. DBS of the globus pallidus pars interna (GPi) can also improve OFF-state FOG, but is less effective for movement impairments than STN DBS overall, and the majority of evidence favours targeting the STN[95,96]. Owing to its efficacy for dyskinesias, however, GPi DBS is a viable option for pseudo-ON-state FOG, as it is generally compatible with higher doses of levodopa than is STN DBS.

Studies of DBS of the pedunculopontine nucleus (PPN) for FOG have yielded mixed results[97–101]. Most studies of PPN DBS have included small numbers of participants, methodology has varied greatly between centres, and there is considerable controversy around the optimal target and stimulation parameters. Overall, we consider PPN DBS to be ineffective for FOG.

In some cases, DBS at high frequencies can worsen FOG, and low-frequency (60–80 Hz) STN stimulation can be helpful in this scenario[102,103]. However, low-frequency stimulation can lead to worsening of appendicular signs, particularly tremor[104,105]. Variable-frequency stimulation, which involves cycling between high and low frequencies, has been proposed as an alternative to mitigate this effect, though this option is currently available in only some countries[106]. In addition, when and in whom to use low-frequency stimulation remains unclear. In one retrospective study, 85 individuals were switched to stimulation at frequencies <100 Hz at an average of 3.8 years after surgery, but 36% were switched back to high-frequency stimulation within 6 months. The most common reported reasons for switching back were worsening of appendicular signs, a lack of clinical benefit and further worsening of axial signs. Axial motor scores on medication before surgery and the *y*-axis coordinate of the active contact were independent predictors of whether individuals would retain use of low-frequency stimulation[103].

If people with FOG are ineligible for DBS or prefer to avoid brain surgery, levodopa–carbidopa intestinal gel infusion (LCIG) can be

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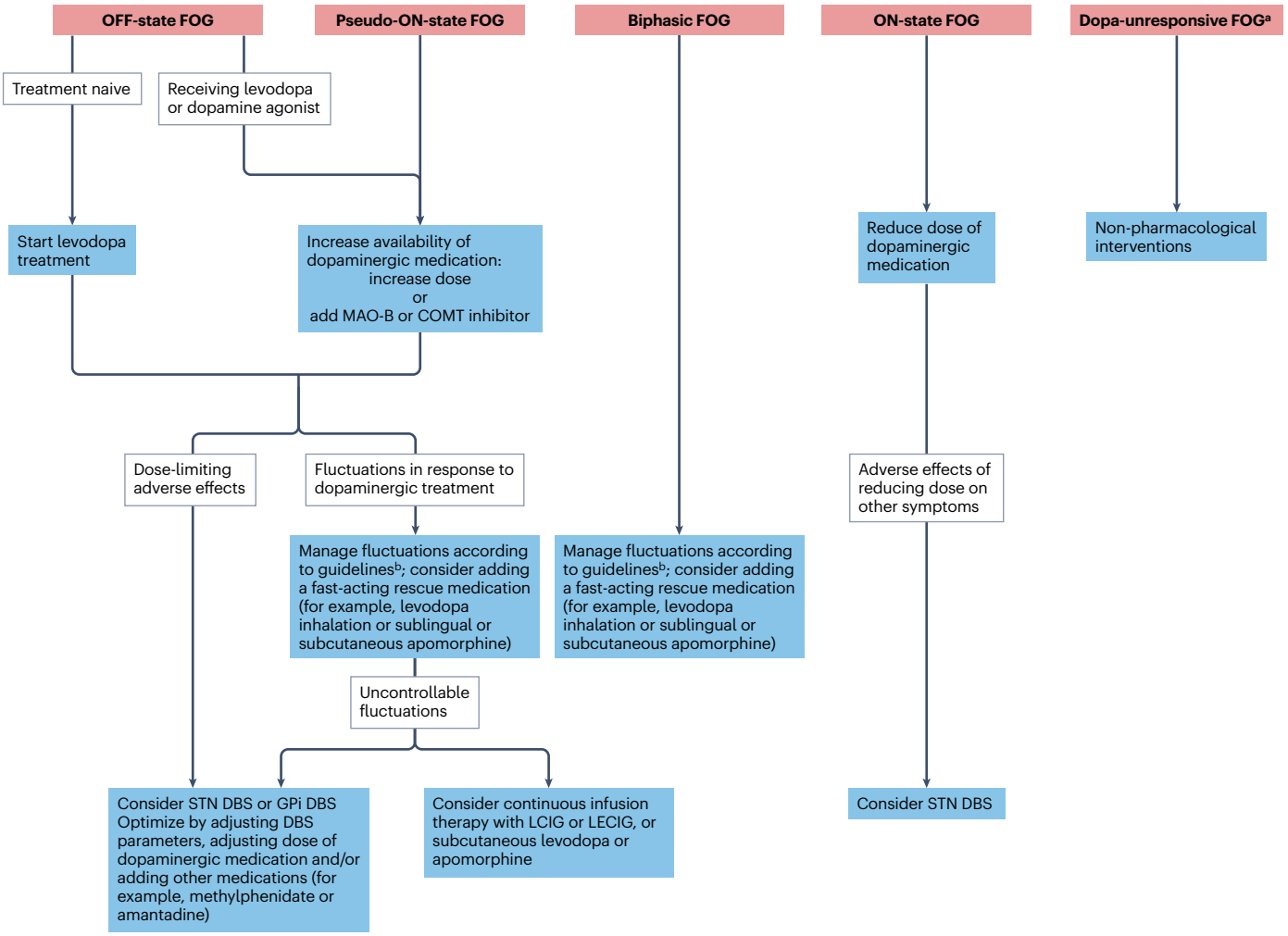

Fig. 3 | Recommended interventions for reduction of excessive basal ganglia inhibitory outflow in FOG. For optimal management, these recommendations should be combined with the recommended interventions for facilitation of cerebral compensatory networks (Fig. 4). [a]Also known as dopa-resistant or ON–OFF freezing of gait (FOG). [b]Refs. 85,86. COMT, catechol-*O*-methyltransferase; DBS, deep brain stimulation; GPi, globus pallidus internus; LCIG, levodopa–carbidopa intestinal gel; LECIG, levodopa–entacapone–carbidopa intestinal gel; MAO-B, monoamine oxidase-B; STN, subthalamic nucleus.

considered for OFF-state FOG and pseudo-ON-state FOG. Benefits of continuous LCIG on gait speed, stride length and FOG severity were demonstrated in a 6-month prospective observational study[107–109]. Increases in the infusion rates can improve FOG, though the infusion rate might be limited by disabling treatment-induced dyskinesias in some individuals[110]. Continuous subcutaneous apomorphine infusion and intestinal infusion of levodopa–entacapone–carbidopa gel could also be effective for management of OFF-state FOG and pseudo-ON-state FOG[111–113] — from clinical experience, these treatments reduce time in the OFF state, though they have not been studied specifically in the context of FOG. Similarly, subcutaneous infusions of levodopa or foslevodopa–foscarbidopa reduce time in the OFF state and could also be effective, though studies of these treatments are lacking owing to their recent introduction.

Studies of DBS and infusion therapies in biphasic FOG and ON-state FOG are scarce owing to the rarity of these types of FOG. Anecdotal experience suggests that STN DBS can be effective for ON-state FOG, as it enables dopaminergic medication to be reduced substantially. Notably, ON-state FOG has been identified as an issue for people receiving STN DBS that has been overlooked and could be easily managed by adjusting the stimulation parameters or lowering the dose of adjuvant oral dopaminergic medications[114]. Clinical experience has shown that GPi DBS is not effective in ON-state FOG, as it does not typically enable dopaminergic medication to be reduced. However, if ON-state FOG is a manifestation of peaks in plasma levels of dopaminergic medication, use of infusion therapies could be effective[115], as they enable more accurate control of levodopa levels to within 2 g/h.

Dopa-unresponsive FOG does not seem to respond to any of the DBS approaches discussed above, but some evidence suggests that LCIG can improve dopa-unresponsive FOG[110,116–118], especially when infusion is around the clock (24 h LCIG)[119]. Multiple, non-mutually exclusive hypotheses have been proposed for the underlying reasons for the benefit, including that delivery of dopamine is more physiological, sleep and/or mood are improved, and oral treatment is simplified. Another

reasonable explanation is that the individuals who benefit never had dopa-unresponsive FOG and the infusion therapy more effectively treats what was always OFF-state FOG. Regardless, we do not recommend use of 24 h LCIG as a standard procedure for dopa-unresponsive FOG, as it remains difficult to predict whether a given individual would benefit and FOG has been aggravated by LCIG therapy in some instances[115].

Facilitation of compensatory networks

The aim of the second pillar of FOG treatment is to improve gait by facilitating processing across cerebral compensatory networks. This approach primarily involves non-pharmacological interventions (Fig. 4). To guide non-pharmacological treatment decisions, we categorize individuals into three groups: those without FOG, in whom the aim is to prevent its occurrence, those with occasional FOG and those with frequent FOG. Given that FOG is likely to progress during the course of the disease, we again recommend re-evaluation of treatment options at least annually, and more frequently upon indication.

Regardless of severity, FOG is highly associated with falls[120,121], so mitigating the risk of falls is a central consideration in clinical decision-making. Cognitive ability and how this interacts with learning and the availability of compensatory resources is another central theme[56,122]. Given these challenges in relation to FOG, we advocate referral to specialized physiotherapists if available, especially when FOG becomes prominent.

Towards prevention of FOG

Optimal management of FOG in PD should not only include symptomatic therapies, but also aim to delay or prevent FOG. A growing body of work based on multivariable modelling has identified several factors that predict the development of FOG[123–125]. These studies consistently show that non-modifiable factors, such as age, disease duration and disease severity, influence the development of FOG. However, several specific motor and non-motor features that precede the onset of FOG are also relevant because they can be modified by training. The most important predictors in the motor domain are motor sequence deterioration[124], reduced balance[123], a decline in step length at the onset of turning[126] and a general decline in spatiotemporal gait parameters[125]. Non-motor predictors include cognitive impairment, depression, anxiety and sleep disturbances[123,124].

No studies have investigated primary or secondary prevention of FOG. Whether exercise can delay the onset of FOG is uncertain, but a substantial body of work indicates that training can improve gait[127,128], balance[127,129], cognition[130], depression[131] and, to a lesser extent, anxiety[131]. Therefore, we recommend that physical activity and generic exercise programmes are prescribed to all people with PD, as they affect motor symptoms favourably when started early and maintained at a moderate to vigorous rate[127,132]. Moreover, early initiation of such programmes predicts prolonged exercise habits, which is an important advantage for individuals whose mobility can become severely restrained once FOG is frequent[133]. When FOG is established, training needs to become more specific to address the multitude of associated motor and non-motor deficits.

Physical training and fall prevention

An increasing number of studies suggest that aerobic exercise attenuates progression of motor symptoms in PD[134,135]. In one MRI study that included 130 people with PD, aerobic exercise increased functional connectivity of the anterior putamen with the sensorimotor cortex relative to connectivity of the posterior putamen with the sensorimotor cortex, and increased functional connectivity in the frontoparietal network[136]. These changes were proportional to improvements in fitness[136]. Theoretically, if the resilience of the neural circuitry within, or closely intertwined with, the locomotor pathways is increased through exercise, then the probability of episodic gait breakdown might be expected to decrease. This hypothesis is supported by the findings of a meta-analysis of studies in which training specifically targeted networks relevant to FOG[24]. The analysis revealed that training that was intended to improve cognition, cognition–motor integration, balance, gait and obstacle avoidance had a moderate effect size on the self-reported severity of FOG, whereas generic exercise had a smaller effect that was

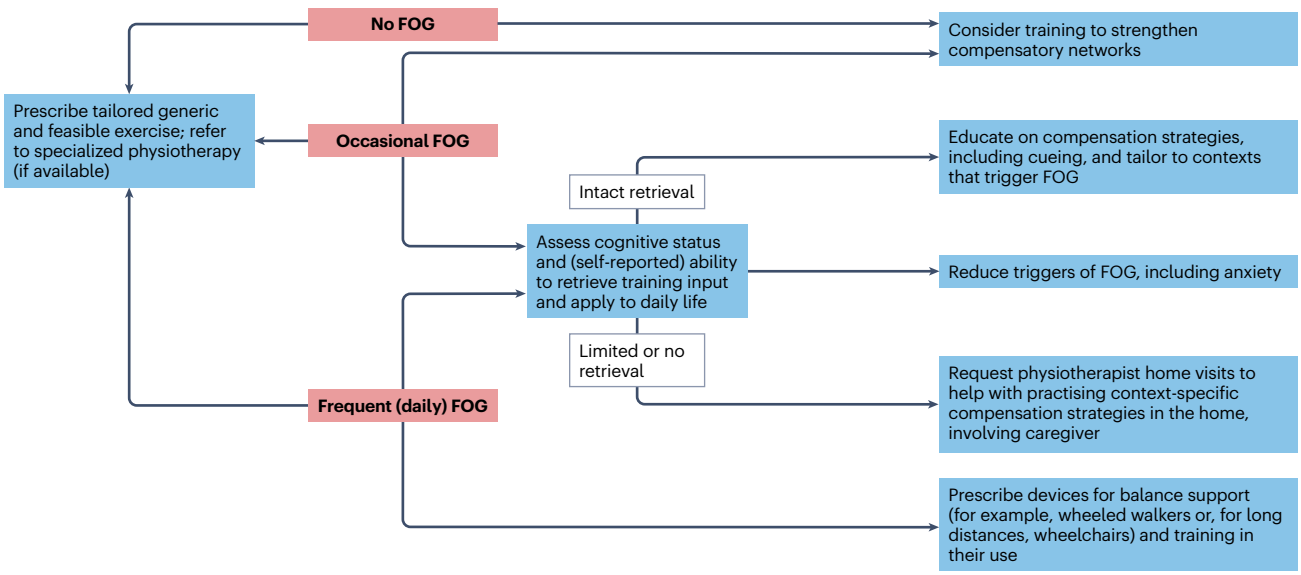

Fig. 4 | Recommended interventions for facilitation of cerebral compensatory networks in freezing of gait. For optimal management, these recommendations should be combined with the recommended interventions for the reduction of excessive basal ganglia inhibitory outflow (Fig. 3). Multiple interventions can be considered simultaneously. FOG, freezing of gait.

not statistically significant. By contrast, another review of the effects of physiotherapy indicated only small and uncertain benefits on FOG[25].

People with FOG have a more pronounced loss of automatic gait control than people with PD but no FOG[17,122]. This loss is likely to contribute to faster decline of gait parameters over time[125], including greater step length regression upon reaching destinations[126,137], greater turning difficulties[138,139] and a larger impact of dual-task interference[38,122]. Though direct effects on FOG itself have not been demonstrated, adaptive walking programmes administered over ground (not on a treadmill)[137], on a split-belt treadmill[140,141] and on a virtual reality dual-task treadmill[142] can improve gait quality and gait adaptation[38,140–142]. Besides loss of automated gait control, people with FOG have more pronounced postural instability than those without, which is closely intertwined with gait disturbance and the risk of falls[143]. Dynamic and reactive balance are particularly affected, as is the ability to produce mediolateral weight shifts[144] and anticipatory postural adjustments[145]. These postural features respond to training with repeated platform perturbations[146] and resistance exercises on unstable surfaces[147], and virtual reality dual-task training reduces fall rates in people with and without FOG[142].

Though learning to avoid situations that can lead to falls at home reduced the fear of falling, it did not reduce risk of falls among people with PD, particularly those with FOG[148]. Therefore, in conjunction with gait and balance training, we advise thoughtful and timely prescription of walking aids for people with FOG[149]. For people with occasional FOG, Nordic walking poles can be safe and acceptable for outdoor walking[150]. For individuals with frequent FOG, we suggest the use of wheeled walkers for outdoor and indoor mobility, as this type of aid elicits the fewest episodes of FOG[151]. In addition, we urge the prescription of dedicated training in the proper use of walkers in complex environments to reduce FOG[151]. Knowing that both FOG and falls are affected by constraints in the physical environment, we also recommend education about domestic adaptations that, for example, minimize the need to manoeuvre through narrow spaces, reduce household clutter and tripping hazards, and optimize lighting. Occupational therapists can advise on optimization of the home setting. Finally, manual lightweight wheelchairs could be prescribed for covering long distances outdoors; occupational therapists can also help with the prescription process for these[149].

Another important aspect to consider in FOG is the prevention of fall-related injuries, particularly fractures. Screening of bone health can be considered for people who are at risk of falls as part of good clinical practice[152].

Compensation strategies

Another strategy to achieve improvements in walking in people with PD is to engage compensatory cortical networks by allocating more attention to gait, thereby reducing reliance on the automatic gait control system[44,153,154]. The aim of this approach is to use cues in training and daily ambulation to facilitate the use of goal-directed gait control to compensate for loss of automated gait control[155–158]. An ambulatory EEG study of people with PD and gait impairment has demonstrated that activation of the sensorimotor cortex and frontal and parietal cortical areas is greater during gait with cues (for example, walking to the pace of a metronome) than during gait without cues, suggesting a successful switch from automatic to goal-directed control of gait[44].

A multitude of compensation strategies are possible; a comprehensive overview of seven categories of patient-identified compensation strategies has previously been published[159,160]. Examples include conscious use of motor programmes such as skating or side-stepping when approaching a trigger. Though this variety testifies to the resilience and creativity of people with FOG, these strategies are highly unique to individuals and might not generalize[160]. Expert education on complex strategies, such as negotiating a doorway in a stepwise fashion, and practising these strategies seems to be beneficial for people with intact cognition[161]. Action observation and mental rehearsal of manoeuvres is known to improve their retention[161,162]. An online video repository of compensation strategies to facilitate education is available from Walking with Parkinson.

Innovative devices are also being developed to facilitate compensation; for example, laser shoes and augmented reality glasses to generate visual cues[163,164], vibrating socks and insoles to provide tactile cues[162,163], smartphone apps to deliver auditory cues[156,158,165], and soft robotic apparel to facilitate hip flexion[166]. These methods have a positive effect on some spatiotemporal parameters of walking and turning in people with FOG but, as is the case for compensation strategies in general, the effects are variable and temporary[155,157,158,167]. Development of novel devices based on wearable sensors that can automatically provide on-demand or adaptive cueing in real time upon detection of FOG will further facilitate these approaches[168,169]. In one study, on-demand cues had sizeable effects on the duration of FOG episodes in conjunction with medication[169]. However, repeated exposure to these on-demand cues in daily life did not result in implicit learning of how to avoid conditions that trigger FOG. Controlled trials are needed to determine the utility and feasibility of these devices for gait facilitation in people with FOG.

Individuals with intact cognition can learn and retain how to re-initiate gait once an episode of FOG occurs. People can be successfully taught to consciously release the motor intent and induce a voluntary stop to reduce the risk of falling, then focus attention on increasing the amplitude of the mediolateral weight shift to re-initiate stepping[170,171]. Verbal counting and auditory or visual cues can also be effective for undoing hypometric anticipatory postural adjustments and facilitate gait initiation[157]. Such recoupling after an episode of FOG might be achieved by reducing the processing conflicts within neural pathways that are involved in FOG and redirecting attention towards goal-directed gait control[170].

An important consideration in the context of compensation strategies is that global cognition is generally impaired in individuals with FOG compared with those without[56,172,173], which could limit the learning and use of compensation strategies. A meta-analysis has shown that people with FOG not only have reduced global cognitive function, but specific cognitive deficits in executive, memory and visuospatial domains[56]. Therefore, we recommend an initial evaluation of whether remembering compensatory strategies and integrating them into personal routines would be feasible for individuals. If time allows, we recommend systematically gauging whether compensatory strategies are being memorized and retained in daily life through self-reports from people with FOG and their caregivers as part of the routine follow-up. For individuals with limited retrieval or low cognitive function, compensation strategies can be practised in the home environment to target specific contexts in which FOG occurs frequently. Though caregiver burden is higher for people with cognitive impairment as well as an increased risk of falls[174,175], involvement of caregivers to reinforce compensation strategies can be helpful.

Targeting non-motor symptoms

We recommend interventions to directly address non-motor impairments that are related to FOG, including cognitive impairment, anxiety,

depression, orthostatic hypotension and sleep disturbances. Training the motor–cognitive interplay through dual-task gait training and enriched multicircuit training programmes is beneficial for people with FOG, leading to improvements in executive function, dual-task gait speed and FOG severity[142,162,176]. In addition, personalized and computerized training programmes that target executive function have shown promise for reduction of FOG during the ON state, though not during the OFF state, albeit with limited cognitive benefits[177,178].

Some individuals with FOG have higher levels of anxiety and/or a reduced ability to cope with anxiety-provoking situations compared with people without FOG, and anxiety is heightened during episodes of FOG[54,159,179]. Moreover, conditions that trigger FOG or the fear of falling can invoke anxiety that worsens FOG through dysfunctional crosstalk between motor, cognitive and limbic pathways or the redirection of attention away from gait control[50,51,54,159]. These complex relationships between arousal, attention and anxiety and the impacts of these interactions on adaptive behaviour require careful consideration in clinical reasoning[50]. Behavioural strategies for managing FOG-related anxiety are insufficiently developed[170]. Cognitive behavioural therapy does not seem to reduce FOG[178]. A randomized controlled trial to determine the effects of tailored behavioural strategies to reduce FOG related to anxiety and stress is ongoing[180].

Among people with PD, those with depression have a greater risk of developing FOG than those without[11,181]. Adequate treatment of depression might, therefore, be expected to decrease the risk of FOG. However, studies of antidepressants in the context of FOG to date are scarce and have produced inconsistent results[182,183].

Interventions under investigation

Several pharmacological and non-pharmacological treatment modalities — mostly approved therapies for PD — could be beneficial in the management of FOG but have not been included in our recommendations because the scientific and practice-based evidence for their benefit is currently limited or inconclusive (Table 2). We discuss several of these treatments below to highlight their potential, the current evidence and the research needed to determine their clinical value.

Pharmacological approaches

Non-dopaminergic agents could theoretically be beneficial in FOG by facilitating processing in cerebral compensatory networks. Robust evidence to support this hypothesis is currently lacking, but some non-dopaminergic treatments have been investigated.

Methylphenidate influences dopaminergic and noradrenergic transmission in striato-frontal circuits, so it has the potential to improve FOG. In one study, methylphenidate had positive effects on attention and FOG, but only in people receiving STN DBS[184]. Furthermore, in a randomized, double-blind, placebo-controlled study with a follow-up period of 6 months, methylphenidate did not improve FOG in 27 people with PD without STN DBS[185].

Improvements in FOG have been reported in studies of L-thyreo-3,4-dihydroxyphenylserine (known as droxidopa or L-DOPS), which is a prodrug of noradrenaline[186,187]. Indeed, a study published in 1987 led to approval of its use for FOG in Japan[188]. However, this work has not been verified elsewhere; two small negative studies were not published[189]. A trial of co-administered droxidopa and the COMT inhibitor entacapone demonstrated a beneficial effect in dopa-resistant FOG, whereas entacapone or droxidopa alone has no effect[190]. A large trial being conducted in the USA has been designed to explore the effect of droxidopa on axial motor signs, including FOG, in PD[191].

Improvement of FOG has also been reported in studies of other drugs that increase noradrenergic transmission, such as the MAO-B inhibitors rasagiline and selegiline[192–196]. Selegiline has also been associated with a reduced risk of developing FOG[11,197]. Furthermore, a pilot double-blinded randomized trial of the selective norepinephrine reuptake inhibitor atomoxetine in five people with PD and dopa-unresponsive FOG demonstrated a trend towards improvement[198]. However, atomoxetine treatment did not change patient-reported FOG severity scores as measured with the Freezing of Gait Questionnaire (FOG-Q, a commonly used measure of FOG) in another open-label 8-week pilot study that involved ten people with PD and dopa-unresponsive FOG[199].

Targeting the cholinergic system is another approach that is being explored in the context of FOG. Loss of cholinergic neurons in the nucleus basalis of Meynert and the PPN can be detrimental to balance and attention and therefore contribute to an increased risk of falls[200,201]. Accordingly, anticholinergic medication increases the risk of falls in older people and could increase the risk of FOG in people with PD[202]. Conversely, acetylcholinesterase inhibitors reduce the risk of falls in at least a subset of people with PD (people with PD and dementia for galantamine and people with PD and a history of falls for rivastigmine)[203,204]. Nevertheless, in a randomized double-blind, placebo-controlled trial in 130 people with PD without dementia, the acetylcholinesterase inhibitor rivastigmine did not improve self-reported FOG after 32 weeks of treatment[205]. Preliminary results of a randomized double-blind, placebo-controlled trial to test the effect of rivastigmine on fall rates in 600 people with PD without dementia are anticipated[206]. Acetylcholinesterase inhibitors might not be expected to have a dramatic beneficial effect on FOG, as the brainstem and forebrain cholinergic hubs are affected even before the development of dementia[64,207]; the resulting denervation reduces the likelihood of beneficial effects from inhibition of acetylcholinesterase. Indeed, these drugs have been used in clinical practice for many years to improve cognition; among people who have received these drugs and happened to also have FOG, no tangible beneficial effects on FOG have been reported. By contrast, the cholinergic agonist nicotine bitartrate (an oral formulation of nicotine) seemed to significantly reduce FOG and falls in one study of 65 people with PD who were treated for 10 weeks[208]. However, this phase I–II trial was designed to assess effects on levodopa-induced dyskinesia, and the effects on FOG were identified in an exploratory retrospective re-analysis of the data, so further studies with longer treatment periods and objective measures of FOG as a primary outcome are necessary to establish the potential of nicotine bitartrate for the management of FOG.

The NMDA receptor antagonist amantadine is used to treat levodopa-induced dyskinesias, and anecdotal experience suggests some effect on FOG, but study results have been mixed. In the prospective NS-Park cohort study, 1,585 people with PD and FOG were treated with amantadine at a median dose of 200 mg/day, and no significant effect on FOG was seen[209]. By contrast, an open-label retrospective study of intravenous amantadine in 30 people with advanced parkinsonism of various aetiologies indicated an improvement of FOG and fewer falls[210]. Treatment was initiated with a loading dose of 200–400 mg/day for 5 days, followed by a maintenance dose of 200–400 mg every 1–3 weeks for an average of 15.1 months[210]. In a randomized, double-blind, placebo-controlled, multicentre trial, intravenous amantadine administered twice daily for five consecutive days did not improve total FOG-Q scores, though some parameters, such as freezing item scores on the UPDRS part II, had improved 1 month after treatment[211]. Well-powered trials with FOG as the primary outcome

Table 2 | Interventions with potential for treatment of freezing of gait in Parkinson disease

Treatment	Effect[a]	Level of evidence[b]
Pharmacological approaches		
Methylphenidate	Improvement only in selected people receiving STN DBS	Level B[184,185]
Droxidopa	Insufficient data[c] Inconsistent data[d]	Level C[c188,189]
Droxidopa with entacapone	Improvement Insufficient data[c]	Level C[190]
Atomoxetine	Insufficient data[c]	Level B–C[198,199]
Acetylcholinesterase inhibitors (galantamine and rivastigmine)	Inconsistent data[d] on FOG Reduction of fall rate	Level A2–B[c204,205]
Nicotine bitartrate	Improvement Insufficient data[c]	Level A2[c208]
Amantadine (oral or intravenous)	Improvement Inconsistent data[d]	Level D Level A2–C[209–211]
Istradefylline	Improvement Insufficient data[c]	Level C[215,216]
Surgical approaches		
Fields of Forel DBS	Improvement Insufficient data[c]	Level C[c219]
STN–SNr DBS	Inconsistent data[d]	Level A2[218,220–222]
Adaptive DBS	Insufficient data[c]	Insufficient data
MRgFUS of the STN	Insufficient data[c]	Insufficient data
MRgFUS of the GPi	Insufficient data[c]	Insufficient data
Epidural spinal cord stimulation	Inconsistent data[d] Insufficient data[c]	Level A1–B[c237–239]
Patterned and individualized dorsal root stimulation	Insufficient data[c]	Level C[240,241]
Invasive vagus nerve stimulation	Insufficient data[c]	Insufficient data
Non-invasive neuromodulation		
Transcutaneous vagus nerve stimulation	Inconsistent data[d]	Level B[c245–250]
rTMS of the primary motor cortex and supplemental motor area	Improvement Insufficient data[c]	Level B[251]
rTMS of the posterior parietal cortex	Improvement Insufficient data[c]	Level B[252]
rTMS of the dorsolateral prefrontal cortex	Insufficient data[c]	Level B[251]
rTMS of the premotor cortex	Insufficient data[c]	Insufficient data
rTMS of the cerebellum or spinal cord	Insufficient data[c]	Insufficient data
tDCS of the primary motor cortex and dorsolateral prefrontal cortex	Inconsistent data[d] Insufficient data[c]	Level B[255,256]
tDCS of the cerebellum	Insufficient data[c]	Insufficient data

[a]Refers to the overall effect on FOG unless otherwise specified; information regarding specific subtypes of FOG is often unavailable and where specific FOG subtypes are reported, a description of how the subtype was determined is usually lacking. [b]Level A1, meta-analysis that includes at least some trials with an evidence level of A2 and consistency between trial results; level A2, good-quality randomized double-blind controlled trials of sufficient size with consistent results between trials; level B, moderate-quality randomized clinical trials of insufficient size or other types of comparative trials (for example, nonrandomized trials, cohort studies or case–control studies); level C, non-comparative trials; level D, expert opinion. [c]Consensus among the authors was that evidence is solely derived from few and/or inconsistent level B, C or D evidence studies or from studies in which FOG was not the primary outcome measure. [d]Consensus among the authors was that evidence is derived from multiple studies with a similar level of evidence but contradictory results. DBS, deep brain stimulation; FOG, freezing of gait; GPi, globus pallidus internus; MRgFUS, MRI-guided focused ultrasound; rTMS, repetitive transcranial magnetic stimulation; SNr, substantia nigra; STN, subthalamic nucleus; tDCS, transcranial direct current stimulation.

measure are needed to further explore the potential of intravenous amantadine.

Finally, adenosine receptor antagonists are under investigation for FOG. These drugs, which include caffeine and istradefylline, have antiparkinsonian effects owing to suppression of the indirect GABAergic inhibitory striatopallidal pathway[212,213]. These effects seem to be mediated by an antagonistic interaction between adenosine A2A receptors and dopamine D2 receptors[214]. In two open-label studies of

istradefylline in 14 and 31 patients with PD, FOG-Q scores improved after 4 and 12 weeks of treatment, respectively[215,216]. In line with these findings, a post hoc analysis of pooled data from eight randomized, placebo-controlled phase IIb or phase III trials of istradefylline in a total of 2,165 people with PD with axial motor problems indicated that treatment with 40 mg/day for 12 or 16 weeks was associated with significantly lower UPDRS II/III axial-related scores, suggesting that istradefylline for treatment of FOG should be pursued in future studies[217].

Surgical approaches

Electrodes with multiple contacts offer the opportunity to simultaneously stimulate regions surrounding the STN, and these regions have been explored as targets in FOG[218]. One study has shown that stimulation of the fields of Forel improves levodopa-unresponsive gait and balance disorders[219]. Given that excessive inhibition of brainstem nuclei induced by the substantia nigra pars reticulata (SNr) is thought to contribute to PD-related gait disorder, stimulation of this brain region has been investigated in several studies. A randomized controlled trial showed that combined STN–SNr stimulation had a significant effect on FOG in 12 participants[220], and efficacy of combined STN–SNr DBS for FOG has been replicated in independent studies[218,221]. In another study in 10 people with PD, combined STN–SNr DBS did not have a beneficial effect on FOG beyond that of STN DBS alone, but improvements in spatiotemporal gait parameters were observed in individuals[222]. A multicentre randomized controlled trial of STN–SNr DBS for FOG has been completed but results are not yet available[223].

Advances in totally implantable bidirectional neural prostheses offer the possibility of adaptive (closed-loop) DBS based on real-time sensing of neural activity during stimulation[224–227]. In contrast to conventional DBS with fixed stimulation parameters, adaptive DBS can adjust to fluctuations in activity or symptom severity throughout the day. Examples of peripherally induced adaptive DBS include STN DBS that is triggered by wearable devices that detect FOG[228], though cerebral recordings of gait phases are considered to be more reliable biomarkers[229,230]. For individuals who still require moderate doses of medication to optimally treat FOG while receiving DBS, adaptive DBS can facilitate coordination between medication and stimulation therapy by reducing stimulation during the ON state and increasing it during the wearing-off period on the basis of stimulation-entrained gamma oscillations in the STN and cortex as markers of high and low dopaminergic states[231]. Furthermore, stimulating on demand is likely to minimize the detrimental effects of DBS on gait circuits — a similar benefit has already been demonstrated for DBS-related speech impairments[232].

MRI-guided focused ultrasound (MRgFUS) of the STN (that is, non-invasive subthalamotomy) could, in theory, improve OFF-state FOG and pseudo-ON-state FOG, though its adoption remains limited and it is typically performed unilaterally. Pallidotomy with MRgFUS has been approved for clinical use, but its role in treating FOG is largely unexplored. Bilateral pallidotomy is feasible[233] and is likely to maximize efficacy. DBS, MRgFUS and other lesional techniques that target the thalamus have no effect on FOG[234].

Preclinical experiments have shown that epidural spinal cord stimulation desynchronizes cortico–striatal beta oscillations and can improve akinesia, abnormal gait, posture and bradykinesia in rodent and primate models of PD[235,236]. Anecdotal experience of beneficial effects in a limited number of people with PD undergoing spinal cord stimulation for pain has inspired trials of spinal cord stimulation for FOG. In a systematic review and meta-analysis of 11 studies that included 76 participants, modest but significant reductions of axial subscores were seen, although the greatest benefit was in pain reduction[237]. Interestingly, spinal cord stimulation has improved FOG in people who had previously been treated with DBS, though findings on the sustained benefit over time are inconsistent[238,239]. Overall, the results should be interpreted with caution owing to several limitations, including study heterogeneity (for example, inclusion of people with and without pain), open-label designs and small sample sizes.

Although still in the early stages of development, a promising approach for treatment of FOG is patterned and individualized dorsal root stimulation to induce locomotion. This technique was initially developed for spinal cord injury[240], but also had a positive effect in the primate model of PD and in one person with PD and dopa-unresponsive FOG who was also receiving STN DBS[241]. In the animal model, stimulation was triggered by cortical control, but clinical stimulation was triggered by either a button press on a walker or by a wearable device. Future development of this approach is likely to include implantation of cortical sensors that can trigger spinal stimulation automatically.

Vagus nerve stimulation has also been considered as a possible treatment of FOG on the basis of its ability to modulate brainstem physiology and noradrenergic pathways. Invasive vagus nerve stimulation, which is approved for treatment of epilepsy and depression, involves surgical implantation of a generator that delivers electrical pulses to the left cervical vagus nerve. This stimulation initially affects deep brain areas such as the nucleus solitarius and locus coeruleus, but subsequently affects the limbic cortex. Notably, vagus nerve stimulation could also modulate dopamine metabolism in subcortical networks, offering a promising avenue for alleviating other motor features of PD[242,243]. Preclinical studies have shown that invasive vagus nerve stimulation can improve the structural and functional aspects of PD, as it can affect the ascending cholinergic and noradrenergic pathways[244]. However, vagus nerve stimulation in people with PD and FOG has so far only been attempted with non-invasive vagus nerve stimulation[245–250].

Non-invasive neuromodulation

Transcutaneous auricular and transcutaneous cervical vagus nerve stimulation have been tested in PD. Three sham-controlled trials with variable designs in terms of stimulation parameters, timing and type of assessment have shown that auricular transcutaneous vagus nerve stimulation has a positive effect on PD gait[245–247]. However, another sham-controlled study of auricular stimulation identified no benefit on many outcome measures, including FOG-Q scores[248]. Two studies of transcutaneous cervical vagus nerve stimulation have demonstrated a beneficial effect on gait variability in PD[249,250].

Studies of high-frequency repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex, especially the areas that control leg movement, and the supplementary motor area have indicated promising effects on FOG[251]. One study has also shown that rTMS of the posterior parietal cortex reduced FOG owing to the role of this area in visuospatial processing and locomotion[252]. rTMS of the dorsolateral prefrontal cortex and premotor cortex has produced less convincing outcomes, and experience with spinal or cerebellar rTMS is limited[251,253,254]. Transcranial direct current stimulation (tDCS) is more widely available and practical than rTMS, but tDCS of the primary motor cortex with or without stimulation of the dorsolateral prefrontal cortex had a smaller effect on FOG than did rTMS[255,256]. Unilateral cerebellum closed-loop tDCS synchronized with the gait cycle has had beneficial effects on walking in people with PD[257], but its relevance in the management of FOG remains to be explored.

Overall, these non-invasive neuromodulatory approaches exert their effects through transient changes in cortical plasticity, which means that they are safe but seem to have short-lasting effects on FOG[258]. Homeostatic brain processes and impairment of plasticity itself further hamper non-invasive stimulation for the treatment of PD[259]. Nevertheless, these approaches could be promising tools when combined with rehabilitation or to explore the potential of new targets for invasive neuromodulation[260].

Conclusions

We present state-of-the-art practical recommendations for the management of FOG that are guided by the presumed underlying mechanisms (Figs. 3 and 4). We hope that our approach will help clinicians to make treatment decisions, thereby improving the mobility and quality of life of individuals with this debilitating condition. Moreover, we hope that the knowledge gaps identified will inspire researchers to conduct well-designed clinical trials of treatments for FOG and will inform the design of trials for prevention of FOG among people who are at risk of developing the condition. The field is currently hampered by the lack of a universal, reliable outcome measure for FOG, but this constraint will hopefully be addressed by the recently published Giladi protocol, which is currently being validated by an international consortium.

With respect to future clinical trials, we encourage researchers to consider that FOG is a highly heterogeneous condition and that participants in clinical trials should be characterized carefully. This characterization should include not only the response of FOG to dopaminergic medication but also whether episodes are predominantly provoked by motor, cognitive or limbic triggers[261]. We envision that by building on these recommendations, the personalized treatment of individuals with FOG will undergo substantial further improvements in the next 10 years.

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