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Review article

Freezing of gait: Promising avenues for future treatment

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ABSTRACT

Freezing of gait is a devastating symptom of Parkinson's disease and other forms of parkinsonism. It poses a major burden on both patients and their families, as freezing often leads to falls, fall-related injuries and a loss of independence. Treating freezing of gait is difficult for a variety of reasons: it has a paroxysmal and unpredictable nature; a multifaceted pathophysiology, with an interplay between motor elements (disturbed stepping mechanisms) and non-motor elements (cognitive decline, anxiety); and a complex (and likely heterogeneous) underlying neural substrate, involving multiple failing neural networks. In recent years, advances in translational neuroscience have offered new insights into the pathophysiology underlying freezing. Furthermore, the mechanisms behind the effectiveness of available treatments (or lack thereof) are better understood. Driven by these concepts, researchers and clinicians have begun to improve currently available treatment options, and develop new and better treatment methods. Here, we evaluate the range of pharmacological (i.e. closed-looped approaches), surgical (i.e. multi-target and adaptive deep brain and spinal cord stimulation) and behavioural (i.e. biofeedback and cueing on demand) treatment options that are under development, and propose novel avenues that are likely to play a crucial role in the clinical management of freezing of gait in the near future. The outcomes of this review suggest that the successful future management of freezing of gait will require individualized treatments that can be implemented in an on-demand manner in response to imminent freezing. With this review we hope to guide much-needed advances in treating this devastating symptom of Parkinson's disease.

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1. Introduction

Freezing of gait (FOG) affects more than half of all patients with Parkinson's disease (PD) and various types of parkinsonism [1]. It is defined as a sudden inability to initiate or continue gait, often described by patients as if their feet are “stuck to the floor” while their upper body continues its original trajectory [2]. FOG occurs on a paroxysmal basis, although certain motor (e.g. turning), cognitive (e.g. dual-tasking), affective (e.g. threatening situations) and environmental (e.g. narrow doorways) features can often trigger freezing [2–4]. Freezing episodes are characterized by leg trembling, short shuffling steps, or a complete motor block; and usually last 1–2 s, although longer (>10 s) events can be experienced [2,3].

Current management of FOG involves a multidisciplinary approach with pharmacological and surgical treatment options, as well as non-pharmacological treatment including physiotherapy and occupational therapy. In addition, co-morbidities that are known to exacerbate FOG (e.g. anxiety [4]; or cognitive decline [5]) should be managed. For information on the current treatment options for FOG, see Ref. [6]. However, despite ‘optimal’ medical management and personalized rehabilitation strategies, freezing often results in falls and fall-related injuries [6,7] and surgical options are at best, partially efficacious [8]. As such, the development of new and more effective treatments for FOG is an important research priority and the rational of the present review.

Unfortunately, FOG has a complex pathophysiology that

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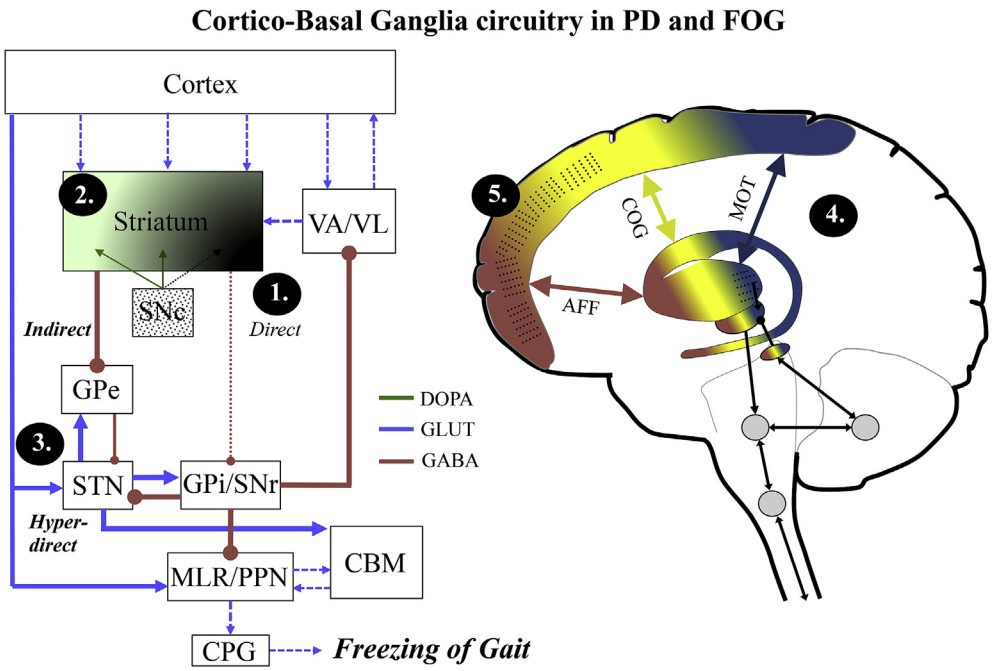

Fig. 1. Schematic representation of the complex pathophysiology underlying FOG.
FOG has a complex pathophysiology that remains poorly understood (for reviews please see Refs. [9] and [10]). Figure 1 depicts five non-exclusive pathophysiological mechanisms that are hypothesized to underlie the manifestation of FOG. **(1)** The dopaminergic insult in PD is most severe in the sensorimotor striatum causing an over-activation of the inhibitory GPi/SNr that in turn sends strong GABAergic projections to the brainstem and thalamic locomotor regions, thereby disrupting efficient processing of gait; **(2)** The associative striatum and frontal-parietal cortices are relatively spared early in the disease course, allowing PD patients to operate gait through goal-directed strategies. However, as a result, their gait becomes less automated and vulnerable to interference from consecutive task demands that can paroxysmally disrupt gait control; **(3)** The hyper-direct pathway likely becomes engaged as a result of increased response conflict, activating the GPi/SNr while also disrupting cerebellar processing involved with automated gait modulation. Altered 5–7 Hz oscillations between the STN and GPi may also underpin the characteristic '*trembling in place*' often observed during FOG; **(4)** Processing across competing yet complementary motor, cognitive and limbic cortico-basal ganglia loops likely results in cross-talk between competing inputs and further depletion of the gait-related sensorimotor striatum of dopaminergic resources thereby disrupting gait; **(5)** Extra-nigral pathology impairs compensatory attentional gait strategies and contributes to L-dopa resistant FOG, especially as PD progresses. AFF = Affective, COG=Cognitive, MOT = Motor, DOPA = Dopamine, GLUT = Glutamate, GABA = Gamma-aminobutyric acid, SNc = Substantia nigra pars compacta, SNr = Substantia nigra pars reticulata, GPe = Globus pallidus externus, GPi = Globus pallidus internus, VA/VL= Ventral anterior and ventral lateral nuclei of the thalamus, STN=Subthalamic nucleus, MLR = Mesencephalic locomotor region, PPN=Pedunculopontine nucleus, CBM=Cerebellum, CPG=Central pattern generators.

remains poorly understood. However, recent theoretical frameworks have suggested that transient over-activation in the inhibitory striatal output nuclei projecting to the motor thalamus and brainstem locomotor regions, as well as dysfunctional cortical and cerebellar projections to these subcortical and brainstem regions, may be ultimately involved in the manifestation of FOG in PD [9,10]. This notion implies that any neural circuitry that increases the firing rate of the striatal output nuclei (e.g. through altered cortico-basal ganglia processing) or impairs the cortical-brainstem and cerebellar-brainstem connections (e.g. due to extra-nigral pathology) could be involved in the manifestation of FOG in PD (see Fig. 1) [9]. The interaction of multiple failing neural circuits may in fact underlie the heterogeneity of the freezing phenomenon [9], which in turn may demand more individualized approaches to treatment.

Regardless of the neural complexity, our growing comprehension of freezing together with upcoming technological advances that allow for management in an 'on-demand' manner, have begun to provide novel options to improve treatment and perhaps even prevent development of FOG. The aim of this review is thus to evaluate several promising avenues, including pharmacological, surgical and behavioural interventions, and to propose a common theme to guide the development of improved treatments for this devastating symptom of Parkinson's disease. The level of evidence for the key studies described will be indicated in superscript according to the gradation in Box 1.

Box 1
Level of Evidence

I	Meta-analysis containing trials with evidence II, with consistency in trials results;
II	Good quality randomised comparative clinical trials (randomised double-blind controlled trials) of sufficient size and consistency (Phase I, II or III);
III-1	Moderate (weak) quality randomised clinical trials of insufficient size or other comparative trials (non-randomised trials, cohort studies, patient-control studies) of sufficient size;
III-2	Moderate (weak) other comparative trials (non-randomised trials, cohort studies, patient-control studies) of insufficient size;
IV	Non-Comparative trials;
V	Expert opinion or protocol development

2. Pharmacological treatments

Simply optimizing conventional oral dopaminergic medication can reduce off time and reduce FOG severity [3][III–1]. New ways to deliver dopaminergic medication more reliably are therefore

theoretically attractive for treating FOG, at least to the extent that dopaminergic pathology plays a causative role in the disorder. Indeed, a Rotigotine transdermal patch as an adjunct to oral dopamine may reduce the likelihood for FOG in patients with wearing off [11][III−2]. Furthermore, continuous 24 h levodopa-carbidopa intestinal gel administration could alleviate what otherwise appeared to be levodopa-resistant FOG [12][III−2] and pseudo-on FOG [13][III−2]. There is also interest in a newly developed aerosolized form of levodopa particles that improved motor functions and achieved rapid improvement and daily reduction of OFF states in a recent randomised placebo-controlled phase III RCT in 86 Parkinson patients [14][II]. The hope is that this promising form of inhalational levodopa (with its short maximum concentration time of 20 min) [15] may act as an ad hoc rescue for sudden 'off' periods [14], thereby reducing the risk of FOG during those periods.

Closed-looped approaches for on-demand dopamine administration also have potential to reduce motor fluctuations and off state freezing, much like existing insulin devices for treating Type I diabetes that tailor dosage according to real-time sensor glucose concentration in order to maximize benefits and minimize side-effects [16]. Indeed, a prototype that uses the electrochemical technique of fast scan cyclic voltammetry to measure dopamine levels in vitro and control dopamine infusion pumps has already been developed [17][V]. Also, a 'neurochemostat' for closed-loop regulation of electrically evoked brain dopamine release in anesthetized rats has been developed [18][V]. However, these promising technologies are invasive procedures that may not suit all individuals with freezing, and whether both methods actually ameliorate FOG has yet to be tested.

Dopamine-resistant FOG may involve extra-nigral brain pathology, e.g. in the frontal lobe, noradrenergic locus coeruleus or cholinergic portion of the pendunculopontine nucleus (PPN) [6]. Several studies have therefore trialled non-dopaminergic drugs, but so far with limited beneficial effects (Table 1). This treatment failure (at the group level) may in part reflect disease heterogeneity, with multi-level neural system deficits that could well be different across different subjects. Future studies should therefore develop new methods that can tailor the pharmacological management to the pathophysiological and neurochemical profile of individual patients, e.g. using machine learning techniques [19] or genetic characteristics [20].

For instance, knowledge on inherited genetic variations that influence drug efficacy and/or toxicity may assist clinicians to guide pharmacotherapy [20]. One example is the influence of a Catechol-O-methyltransferase (COMT) polymorphism on dopamine levels in the brain. COMT is one of the main enzymes accounting for metabolic degradation of dopamine in the prefrontal cortex [21,22]. Inter-individual variability in COMT enzyme activity has been shown to affect prefrontal dopamine levels and executive functioning (including attention) in patients with Parkinson's disease [21,23]. In addition, the effectiveness a COMT inhibitor (Entacapone) on levodopa ON-time was influenced by the PD patient's type of COMT polymorphism in a randomised cross-over clinical trial [23][II]. Given that dopaminergic denervation of fronto-striatal networks and executive dysfunctions have been implicated in the aetiology of freezing of gait [2,24], this makes testing patients with Parkinson's disease on the COMT polymorphism a potential future endeavour to inform clinical management [25]. For instance, patients with low basal dopaminergic prefrontal activity due to high COMT enzyme activity might need more dopaminergic stimulation to reduce FOG [25][V]. However, further investigation is needed to determine the precise level of clinical translation that can be achieved by testing patients with FOG for the COMT gene, as well as for other pharmacogenetic variants [21].

3. Surgical treatments

Conventional Deep Brain Stimulation (DBS) of the subthalamic

Table 1
Non-dopaminergic pharmaceutical therapies trialled for FOG in PD.

Cl Class	Drug(s)	Effects	Ref	Level of evidence*	Clinical Recommendation**
Acetyl-cholinesterase inhibitor	Rivastigmine	Rivastigmine did not reduce FOG	[106]	II	Acetylcholinesterase inhibitors are currently not recommended for the treatment of FOG
N-methyl D-aspartate receptor antagonist	Amantadine	Inconclusive results	[1]	IV	Oral amantadine can be considered in addition to dopaminergic treatment for patients with dopamine-responsive FOG, although results remain inconclusive. Given the high bioavailability of oral amantadine we do not recommend IV delivery
			[107]	IV	
			[108]	IV	
			[109]	III-2	
			[110]	III-1	
			[111]	III-1	
Central nervous system stimulant	Methyl-phenidate	Reduced FOG in PD patients with STN-DBS but not in patients without STN-DBS	[25]	III-1	Patients with optimally tuned STN stimulation and levodopa treatment who continue to experience FOG could be eligible for a judicious trial of 1 mg/kg/day of MPH. Future studies are needed to test effects of MPH on FOG in patients without STN stimulation as effects remain unconvincing
			[112]	III-1	
			[113]	IV	
			[114]	III-1	
Norepinephrine precursor	Droxidopa (L-DOPS)	Insufficient results; Increased NE and DA concentrations in CSF and reduced FOG in combination with Entacapone	[115]	III-2	Consider in combination with entacapone in patients with dopamine-resistant FOG
			[116]	III-2	
			[117]	III-2	
Adenosine receptor inhibitor	Caffeine Istradefylline	Insufficient results; Caffeine improved akinesia subtype of FOG and istradefylline reduced subjective FOG in a small open-label prospective study	[118]	III-2	Large scale clinical trials are needed to define appropriate dosage schemes for adenosine receptor inhibitors. As such, caffeine and istradefylline should be reserved for research settings
			[119]	III-2	

NOTE: * Level I = Meta-analysis containing at least some trials with evidence II, with consistency in trials results; Level II = Good quality randomised comparative clinical trials (randomised double-blind controlled trials) of sufficient size and consistency (Phase II or III); Level III-1=Moderate (weak) quality randomised clinical trials of insufficient size or other comparative trials (non-randomised trials, cohort studies, patient-control studies) of sufficient size; Level III-2=Moderate (weak) other comparative trials (non-randomised trials, cohort studies, patient-control studies) of insufficient size; Level IV=Non-Comparative trials; Level V = Expert opinion or protocol development. NOTES: Ref = References, FOG=Freezing of Gait, PD=Parkinson's disease, IV=Intravenous administration, MPH = methylphenidate; STN-DBS = Deep brain stimulation of the subthalamic nucleus, L-DOPS = L-threo-3, 4-dihydroxyphenylserine, NE = norepinephrine, DA = Dopamine, CSF= Cerebrospinal fluid; **Expert opinion based on current evidence.

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nucleus (STN-DBS) or globus pallidus internus (GPi-DBS) currently do not offer satisfactory control of FOG [6,8,26][IV]. This has prompted efforts to discover alternative targets [27]. The PPN is part of the mesencephalic locomotor region in the brainstem, which consists of glutamatergic and cholinergic neurons that are involved in the initiation and modulation of gait [28]. This notion motivated studies to evaluate PPN-DBS as a potential treatment for FOG, especially when not responsive to dopamine [28]. However, a recent meta-analysis showed inconsistent findings across small-sampled studies, without overall improvement in FOG [29]. The observed heterogeneity in clinical effects could relate to variability in the exact site where this large and diffuse nucleus is being stimulated [6,27]. For this reason, alternative MRI-based targeting has been proposed as a more accurate approach than relying on traditional brain atlas targeting [27,30]. Alternatively, stimulation of the PPN may require selective targeting of particular frequency bands. Indeed, recent work using simultaneous magnetoencephalography and local field recordings from PPN-DBS electrodes in Parkinson patients has shown that different regions of the PPN use unique frequencies to couple with the attentional and motor networks implicated in FOG [31].

Multi-target strategies, allowing modulation of cortico-basal ganglia loops, are another option [27]. Targeting multiple sites could synchronize these circuits and promote neuroplasticity [32]. Furthermore, the functional and episodic nature of FOG suggests that its pathophysiology cannot be localized to any single neural structure [9]. Instead, FOG is hypothesized to result from multiple failing neural circuits that involve transient disruptions of cortico-basal ganglia projections to the brainstem (e.g. PPN) and cerebellar locomotor regions (Fig. 1) [9,24]. This notion is partly supported by several small studies, where combined PPN and STN stimulation appeared to have beneficial effects on gait and postural instability [33][III−2] and FOG [34][IV] that exceeded the effect seen following stimulation at either single target alone. Larger clinical trials therefore seem warranted. Other multi-target combinations, such as the STN and the substantia nigra pars reticularis (which are both major inhibitory output structures of the basal ganglia) have also shown promise to reduce FOG [35][III−1].

Currently, high-frequency STN stimulation (~130 Hz) is used conventionally in many DBS centres as it reliably improves cardinal motor symptoms [36]. However, this stimulation setting has little or sometimes even unfavourable effects on FOG severity [6,8,36,37]. Several studies have now shown however, that changing the settings to 60 Hz can reduce freezing severity [37,38][III−1], although sometimes at the expense of worsening tremor at the lower DBS frequencies [36]. An elegant solution would be to utilize novel closed-looped adaptive DBS systems that automatically adjust the output stimulation based on the ongoing neural activity of a reference structure that contributes to the temporal evolution of FOG [32,36,39–41]. Indeed, using predefined continuous stimulation parameters that remain static over time necessarily limits DBS effectiveness for treating paroxysmal symptoms, such as FOG [32]. The effects of one such closed looped adaptive DBS system on FOG was tested as a proof-of-concept in four patients with Parkinson's disease postoperatively [42][III−2]. This study used a unilateral, ambulatory brain-computer interface controlled adaptive DBS of the STN to provide stimulation (on/off) only when local field potentials (recorded directly from the stimulation electrodes) exceeded a predetermined level of beta power [42]. This approach resulted in an average reduction in clinical FOG severity whilst delivering less than 50% of the stimulation, which in turn would prolong battery life [42]. Such adaptive DBS might also minimize stimulation-induced side effects [32,42]. Currently there is no direct comparison with conventional DBS, so it remains unclear if these findings were related to adaptive DBS *per se* [42].

Another type of adaptive DBS was recently tested in a case study using bilateral STN-DBS in combination with a wearable device that analysed local field potential beta band power of the STN [43][III−2]. This allowed voltage stimulation to be continuously adapted linearly during each second [43], which is different from the previously described on-demand (i.e. on/off) strategies [42]. The initial results showed similarly effective outcomes for axial motor signs (i.e. posture, gait and postural stability) as compared to conventional DBS, but with improved control of stimulus-evoked side effects [43]. Future studies are now required in order to optimise the algorithm used to reduce FOG [43], perhaps benefiting from invasive electrocorticography [44,45] or non-invasive EEG recordings [46,47] from cortical regions that have been associated with freezing [48,49], and similarly from body-worn wearable sensors that can be used to predict imminent FOG [50,51] as further described below. Finally, researchers are developing novel ways to detect intraoperative fluctuations in neurochemical concentrations. For instance, by using the fast-scan cyclic voltammetry technique, researchers were able to detect sub-second dopamine fluctuations in the striatum during performance of a reward-based task in 17 PD patient undergoing DBS surgery [52]. Others are developing a Wireless Instantaneous Neurochemical Concentration Sensor that can detect dopamine, adenosine, serotonin and glutamate levels at near-real time (millisecond) resolution [53][V]. If the use of in vivo neurochemical sensors in humans became established, such techniques could improve our understanding of how DBS underlies clinical benefits [53] and offer potential to improve FOG by programming future smart DBS systems to deliver desired stimulation parameters based on fluctuating neurotransmitter levels [27][V].

Electrical spinal cord stimulation, a treatment conventionally used to alleviate chronic pain, has also received recent interest for its potential to alleviate motor symptoms of PD [54]. Based on animal experiments, Yadav and Nicolelis (2017) [54] hypothesize that high frequency stimulation of the dorsal column ascending fibers could disrupt supraspinal pathological oscillations. Specifically, it could desynchronize the prominent inhibitory beta band oscillations in the basal ganglia of PD as well as modulate firing rates of the PPN and motor thalamus, thereby resulting in the alleviation of PD motor symptoms [54]. Although most studies thus far have been open label case reports warranting cautious interpretation, altogether there appears to be a trend towards improved postural instability and gait measures in PD patients following high frequency spinal cord stimulation [54]. Importantly, aberrant beta band oscillations in the basal ganglia have also been implicated in the pathophysiology underlying FOG [55,56], making spinal cord stimulation an attractive future avenue to treat FOG. Indeed, a recent study found a 56% improvement in subjective FOG along with improved objective gait measures following high frequency (300 Hz) spinal cord stimulation at the upper thoracic (T2-T4) level in 4 PD patients that were treated with bilateral STN-DBS for 7–8 years prior but whom still experienced troublesome postural instability and gait freezing at the time of enrolment into the study [57][III−2]. The beneficial effects of spinal cord stimulation on freezing in these patients remained for the 6 months duration of the study [57]. This minimally invasive intervention could be considered relatively safe and may become an important adjunct to enhance the effectiveness of other treatments for FOG (e.g. adaptive DBS) by phase locking oscillations across cortical and subcortical structures to create a brain state that is more permissible for locomotor control [9,54,57][V].

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4. Behavioural interventions

4.1. Cueing

Cueing is one of the best-known behavioural "tricks" used to overcome FOG [58]. However, the positive effects of continuous cueing are often lost over time [59,60]. This probably occurs when the control of gait shifts back from a goal-directed strategy to automatically being processed by the malfunctioning basal ganglia network [24,59,61]. In addition, it is particularly difficult to deliver cueing as an ambulatory intervention that can assist patients regardless of where they are [62]. To this end, novel devices are being developed that help the efficient delivery of cues. For instance, a laser-shoe that tunes the cue presentation into the patient's own step frequency was recently introduced, showing beneficial effects [62,63][III−1]. Furthermore, efforts are being made to develop on-demand systems that 'know' when a cue should be presented in an attempt to preserve a cue's novelty and thus effectiveness [50,51].

4.2. FOG detection and prediction systems for effective FOG avoidance

Probably the best way to deliver a cue at the appropriate time is to develop an integrative system between a putative cueing device and a reliable physiological measure of imminent FOG [50,51,64]. For instance, by analysing the 'freezing index' (a ratio of high to low frequency movements) using body-worn sensors that can operate in real-time [50,65–68]. Indeed, subjective improvements in FOG have been found when patients were equipped with an accelerometer-based real-time FOG detection system that incorporated external acoustic cues when FOG was detected [50,51][III−2].

Researchers have also started to develop FOG detection and prediction systems that utilize physiological signals that originate from the brain itself, for instance by using functional near infrared spectroscopy [69] or electroencephalography [48,49]. Although more work is needed to make these techniques operate in real-time, detecting the earliest signals of imminent FOG from the brain would offer a valuable time window for FOG prevention when coupled with an activated intervention as a form of dynamic biofeedback. For instance, such systems could be used to activate adaptive cueing or modulate stimulation parameters during periods of imminent freezing (see Fig. 2)[V]. To realize daily implementation, researchers will need to consider the practicality and aesthetics of their design when developing such systems. To this end, Ly et al. (2016) recently showed that the input from just two EEG-channels, which would be more practical and easier to conceal for patients, could predict FOG with comparable performance as the input from a full 32-channel EEG montage [70].

4.3. Smart glasses

Smart glasses, which are wearable computers embedded within spectacles can also be used to deliver on-demand cueing [71]. A remarkable feature of these devices is the ability to augment reality by visually overlaying pertinent information on top of the patient's visual field [71,72]. This is of particular interest to patients with FOG that seem to benefit more from 3D cues over 2D cues [73][IV]. However, a prototype of smart glasses that projected 3D augmented cues recently failed to improve FOG [74][III−1]. Based on user experience the authors of that study postulated that the device was too heavy and uncomfortable, which may have distracted patients in a manner similar to cognitive dual tasking [74]. Furthermore, the bulky construction of the glasses narrowed the field of

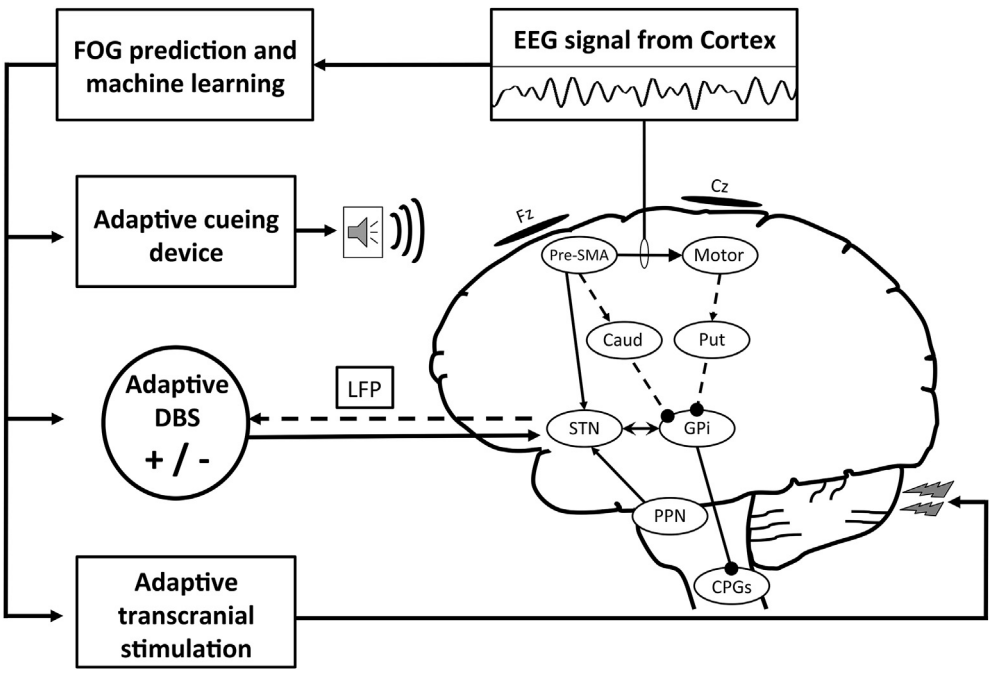

Fig. 2. Representation of future closed-looped FOG prediction and avoidance systems.
Systems that detect physiological signals of imminent FOG could allow for the timely activation or modulation of adaptive cueing and stimulation devices in an attempt to prevent episodes of FOG from occurring. Although such systems could be developed using many classifiers (including those obtained from body-worn sensors), EEG and DBS was chosen for this figure as these methods allow for the detection of the earliest signals implicated in the cause of FOG (namely those originating from the brain itself) that would offer an optimal time window for such 'closed-loop' interventions. It is hoped that the brain of PD patients at this time is not yet in a state of freezing and therefore will still be able to benefit from treatment strategies, such as cueing, to avoid the occurrence of clinical FOG. FOG=Freezing of gait, EEG = Electroencephalography, DBS = Deep brain stimulation, LFP = Local field potential. Figure adapted with author's permission from Shine et al.,. (2014) [49].

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Table 2
Portable computing devices to improve freezing of gait in Parkinson's disease.

Applications	Cueing (on-demand) • Visual (augmented) cues • Auditory cues • Tactile cues (vibration) Object recognition • Using the embedded camera to detect upcoming environmental triggers of freezing (e.g. doorways) Instructions • Aid spatial navigation • Alert about changes in objective gait measures (i.e. biofeedback) • Instructions for timely medication intake Telemedicine • Off-site clinical consultations, physiotherapy and occupational therapy • Healthcare accessibility for patients in rural areas
Operational tips	Usability • Simple operation system with easy instructions • Voice or gesture operations for patients with tremor • Accommodate need for prescription glasses • Option to present cues in either the center of visual field or periphery • Reduce blue light emission in the evenings to prevent sleep deficiency and fatigue • Log performance to aid personalized rehabilitation and inform large scaled research
Safety considerations	Training • Training and supervision by an expert are recommended prior to self-usage Perception • Stimuli should not interfere with complex daily tasks such as driving and crossing the street Limit cognitive load • Simple instructions • Prevent visual conflict between actual and augmented stimuli Limit limbic load • No sudden presentation of stimuli • Only present stimuli after patient has stopped walking Privacy • Adhere to laws governing healthcare data (e.g. record de-identified data)

view and may have blocked sensory visual feedback that patients relied on for gait control [74]. Developers of new mobile cueing devices, such as smart glasses, therefore need to carefully consider the contraindications of the device on FOG that may overshadow the benefits of cueing (for recommendations, see Table 2). Interestingly however, the potential of smart glasses and other portable computing devices is not limited to external cueing (Table 2). For instance, they could aid future e-health technologies, such as telemedicine [75], where the device is used to provide additional off site and multidisciplinary health care (e.g. physiotherapy or occupational therapy) to improve FOG [7,72][V].

4.4. Behavioural and cognitive training

Behavioural training interventions hold promise for reducing FOG [7]. For example, a motor learning based intervention using a combination of auditory cueing and gait training showed beneficial effects on FOG that were retained for up to four weeks after the intervention [76][III−2]. This indicates that patients equipped with closed looped cueing systems as described above may benefit from an initial behavioural training period to ensure optimal long-term therapeutic benefits. Action observation training may represent another innovative adjunct to rehabilitation as it was recently shown to prolong the retention effects of physical training on FOG for a duration of 1–3 months compared to physical training alone [77–79][III−1]. The addition of task-related sounds during action observation further increased the positive gain effects of physical training on subjective FOG in PD, possibly as the multisensory information allowed patients to recognize the correct spatial (action observation) as well as temporal (sounds) aspects of the movement [79][III-1]. Moreover, task-specific training may offer a more individualized approach to rehabilitation, for instance by training patients that often freeze while turning to curve-walk on a turning-based treadmill [80][III−1]. Furthermore, aquatic obstacle training outperformed regular aquatic training on subjective FOG severity and performance of a timed up and go test [81][III−1]. Supervised static body posture slack-lining (for postural instability training) in combination with physical therapy also led to a significant, albeit small (average one point difference on the freezing of gait questionnaire) decrease in FOG compared to physical therapy alone, although no retention effects were found after 4 weeks [82][III−2]. Finally, bicycling is remarkably resistant against FOG in PD [83][IV], possibly due to the suppression of pathological beta synchrony in the basal ganglia [84]. Bicycling therefore offers possibilities to increase physical activity levels in PD patients with FOG [83] and could perhaps be used by patients as a non-external cueing condition. Indeed, mimicking bicycling improved FOG during gait initiation and promoted gait rhythmicity in a case report of two PD patients [85][IV].

Interestingly, benefits from cognitive training can translate beyond cognition, improving several gait characteristics [86]. Recent insights into the pathophysiology underlying FOG indicate that freezing involves impairments in the frontal cortices involved in executive functioning, specifically in the domains of attention, conflict resolution and inhibitory control [5,55,61,87]. Targeted cognitive training to improve a patient's ability in these cognitive areas might therefore translate into a reduction in FOG severity [86][V]. Cognitive training may also prove to have preventive properties for FOG when applied before freezing occurs. For instance, cognitive therapy strategies could help reduce anxiety [6,88][II], which can contribute to FOG [4]. However, to date only one RCT is in progress but has yet to report (Trial ID: ACTRN12613000359730).

4.5. Real-time neurofeedback

During real-time neurofeedback, subjects are asked to make introspective efforts to modulate specific brain responses that can mediate behavioural outcomes [89]. Faster analysis has allowed

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fMRI-based neurofeedback to emerge as a spatially specific technique to improve motor function in Parkinson's disease [90]. Indeed, preliminary results showed that feedback improved motor scores in five patients with PD who learned to increase their activity in the supplementary motor area (SMA) over two fMRI sessions using motor imagery [90][III−2]. SMA neurofeedback also changed activation in other regions that play a crucial role in the pathophysiology of FOG, such as motor cortex and basal ganglia [90]. We envision that future studies might use the emerging knowledge of FOG to combine fMRI-based neurofeedback with a functional task, such as motor imagery [90] or virtual reality gait paradigms [91], to safely improve FOG (e.g. through expert guided training)[V]. Furthermore, cheaper and portable techniques, such as fNIRS and EEG, could be implemented for neurofeedback rehabilitation in clinics and the patient's home setting [92]. Combining two devices also enables 'hyperscanning', where the coherence between two simultaneously measured and interacting brains can be compared [92–94]. Interactive programs could then be developed where patients train to match the brain responses of a healthy spouse [92]. For example, it would be compelling to evaluate whether such neurofeedback training could prevent maladaptive motor learning in Parkinson patients and avert their need for cognitive resources to operate gait, thus reducing FOG during complex situations [61][V]. However, the cost-effectiveness and practicality of neurofeedback systems as a large scaled treatment for FOG remains to be determined and are distant from clinical implementation.

4.6. Non-invasive transcranial stimulation

Non-invasive brain stimulation techniques can modulate neuronal excitability at the site of stimulation and influence brain regions that are anatomically connected to the target site without the need for surgery or anaesthesia [95]. Repetitive TMS shows a medium effect size to reduce motor symptoms in Parkinson's disease [95–97][I]. High-frequency repetitive Transcranial Magnetic Stimulation (rTMS) over the lower leg primary motor cortex significantly reduced subjective FOG and improved gait performance during a 180° turning task [98][III−1]. However, no beneficial effects were found in another study using low-frequency rTMS over the primary motor cortex (M1) and/or dorsolateral prefrontal cortex in six Parkinson patients with dopamine-responsive FOG [99][III−2]. Unfortunately, that study could not be completed as several patients withdrew consent [99]. Similarly, although promising improvements in FOG were recently seen following deep rTMS over the prefrontal cortex, that study also had to be halted after two out of nine patients dropped out due to discomfort and pain during treatment [100][III−1]. A single session of intermittent Theta Burst Stimulation (iTBS) - a specific type of excitatory rTMS - targeted to the unilateral cerebellum showed no benefits for FOG, although it did improve gait speed [101][III−2]. In that study more than 10% of participants also dropped out due to adverse events experienced during the stimulation [101]. Taken together, the evidence to date raises significant concerns as to whether rTMS techniques in their current form will be tolerated in everyday clinical practice for FOG in PD.

Transcranial Direct Current Stimulation (tDCS) is another non-invasive and portable stimulation technique that uses weak constant electric currents through the scalp to modulate excitability in cortical and connected subcortical tissues without inducing action potentials [102,103]. Compared to rTMS, tDCS has the potential to become a safer, more cost efficient and user-friendly technique that allows for easier translation into clinical practice [102]. Importantly, a double-blind, cross-over, randomised sham-controlled study showed that applying 20 min long anodal tDCS sessions of 2 mA on M1 during rest over five consecutive days significantly reduced dopamine-resistant FOG in a small sample of 10 Parkinson patients, even after a month follow-up [103][III−1]. Simultaneous tDCS over the M1 and left DLPFC to modulate consecutive motor and cognitive performance was shown to further improved objective FOG in 20 freezers as compared to sham or tDCS of either target alone [104][III−1]. Similarly, a recent report has proposed a potential role for non-invasive electrical stimulation of the vagus nerve to alleviate FOG (possibly as a way to reduce heightened sympathetic activity associated with FOG [4]). The outcomes of such studies await peer-review publication [105][V]. The limited number of studies performed necessitate further investigation to replicate findings using larger samples, optimized tDCS protocols and enhanced individualized treatment schemes [102].

5. Conclusions

This review provides an overview of upcoming treatment options that aim to improve management of FOG in PD in the near future. The outcomes of this review suggest a clear common theme, namely that the successful future treatment of freezing in Parkinson's disease will require personalized approaches to translational pharmacological, surgical and behavioural treatments that can operate in an on-demand manner. Further enhancement of our understanding of the pathophysiology underlying FOG remains imperative for adequate development of such future treatments.

Conflicts of interest

The authors have no competing interests to declare.

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