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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.

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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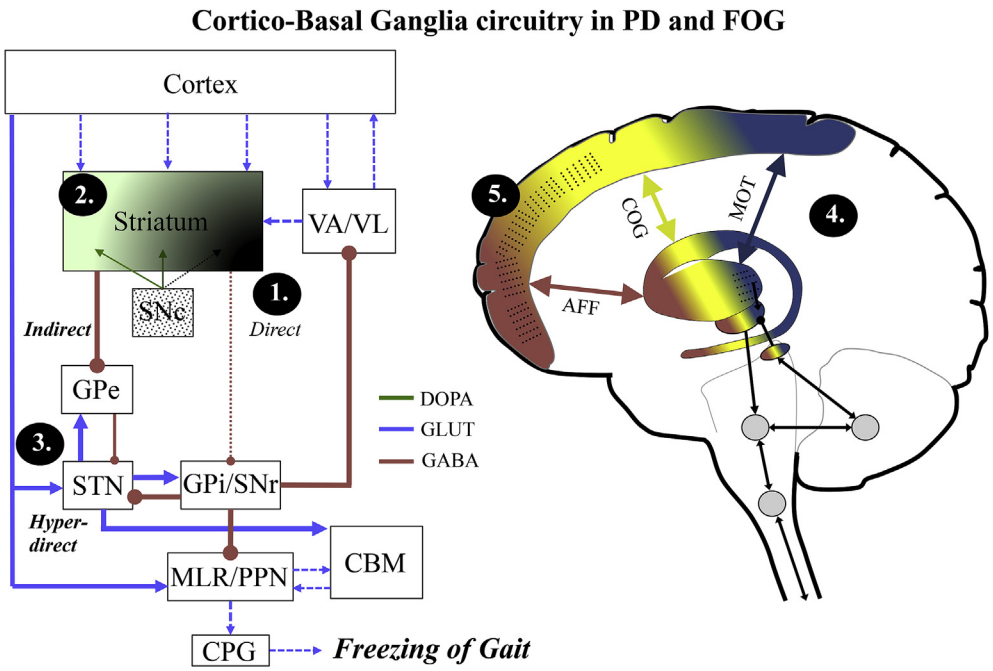

Fig. 1. Schematic representation of the complex pathophysiology underlying FOG.
FOG has a complex pathophysiology that remains poorly understood (for reviews please see Refs. [9] and [10]). Figure 1 depicts five non-exclusive pathophysiological mechanisms that are hypothesized to underlie the manifestation 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