doi:10.1093/brain/awz314 BRAIN 2020: 143; 14–30 | 14

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Freezing of gait: understanding the complexity of an enigmatic phenomenon

Daniel Weiss,[1] Anna Schoellmann,[1] Michael D. Fox,[2,3,4] Nicolaas I. Bohnen,[5] Stewart A. Factor,[6] Alice Nieuwboer,[7] Mark Hallett[8] and Simon J.G. Lewis[9]

Diverse but complementary methodologies are required to uncover the complex determinants and pathophysiology of freezing of gait. To develop future therapeutic avenues, we need a deeper understanding of the disseminated functional-anatomic network and its temporally associated dynamic processes. In this targeted review, we will summarize the latest advances across multiple methodological domains including clinical phenomenology, neurogenetics, multimodal neuroimaging, neurophysiology, and neuromodulation. We found that (i) locomotor network vulnerability is established by structural damage, e.g. from neurodegeneration possibly as result from genetic variability, or to variable degree from brain lesions. This leads to an enhanced network susceptibility, where (ii) modulators can both increase or decrease the threshold to express freezing of gait. Consequent to a threshold decrease, (iii) neuronal integration failure of a multilevel brain network will occur and affect one or numerous nodes and projections of the multilevel network. Finally, (iv) an ultimate pathway might encounter failure of effective motor output and give rise to freezing of gait as clinical endpoint. In conclusion, we derive key questions from this review that challenge this pathophysiological view. We suggest that future research on these questions should lead to improved pathophysiological insight and enhanced therapeutic strategies.

1 Centre for Neurology, Department for Neurodegenerative Diseases, and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
2 Berenson-Allen Center, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical Center, Boston, MA, USA
3 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
4 Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA
5 Departments of Radiology and Neurology, University of Michigan, Ann Arbor, MI, USA; Veterans Administration Ann Arbor Healthcare System, Ann Arbor, MI, USA; Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI, USA
6 Department of Neurology, Emory School of Medicine, Atlanta, GA, USA
7 Neuromotor Rehabilitation Research Group, Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
8 National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-1428, USA
9 Parkinson's Disease Research Clinic, Brain and Mind Centre, University of Sydney, Australia

Correspondence to: Daniel Weiss
MD, Centre for Neurology Department for Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
Email: daniel.weiss@uni-tuebingen.de

Keywords: freezing of gait (FoG); Parkinson's disease; stimulation; neurophysiology; genetics

Abbreviations: DBS = deep brain stimulation; FoG = freezing of gait; (r)TMS = (repetitive) transcranial magnetic stimulation; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus

Received June 26, 2019. Revised August 7, 2019. Accepted August 16, 2019. Advance Access publication October 24, 2019

This targeted review article was inspired by the Second International Workshop on Freezing of Gait in Leuven, Belgium from 6–8 June 2018 (https://kuleuvencongres.be/FOG2018). We selected topics for this manuscript that reflect diverse pathophysiological perspectives in freezing of gait (FoG) research, offering an interdisciplinary approach to identify the well-recognized complexity and variability of FoG. First, we will consider the heterogeneity of FoG based on clinical and genetic observations. Second, we highlight the pathophysiology of FoG and non-gait freezing by reviewing findings from multimodal MRI neuroimaging, PET neurotransmitter studies, neuropathology, and neurophysiological research including neurostimulation. Finally, we develop an overarching perspective on FoG pathophysiology across methodological domains. In this review, we do not strive for completeness in each of the domains. Instead, we aim to catalyse future research and therapeutic avenues by presenting the latest information across these diverse methodological disciplines.

Introduction

Freezing of gait (FoG) in Parkinson's disease has been gaining increased clinical and scientific interest given its impact on patient quality of life and disease-related burden, deterioration of self-dependence and the risk of nursing home placement (Moore *et al.*, 2007; Muslimovic *et al.*, 2008; Kerr *et al.*, 2010; Walton *et al.*, 2015). This mirrors the fact that FoG is difficult to treat (Castrioto *et al.*, 2011; Nutt *et al.*, 2011; Vercruysse *et al.*, 2014). A consensus statement defined FoG as the 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' (Nutt *et al.*, 2011). This broad definition embraces several clinico-phenomenological facets of FoG including the onset of a freezing episode (e.g. gait initiation, walking, or turning) and freezing characteristics such as trembling-in-place, akinetic freezing, or shuffling forward in small steps. Recent work has proposed the existence of subgroups among patients with FoG that can be stratified by predominant freezing triggers; i.e. a motor type (freezing when turning), a cognitive type (freezing when dual-tasking), or a limbic type (freezing when anxious) (Ehgoetz Martens *et al.*, 2018*c*).

Furthermore, freezing episodes have been associated with relatively consistent kinematic abnormalities and cognitive modulators, such as (i) the foot or toe does not leave the ground or only barely clears the supporting surface; (ii) an alternating trembling of the legs may occur at a frequency of 3–8 Hz; (iii) kinematic abnormalities may precede a freeze (e.g. hastening, increase in cadence accompanied by decrease in step length); (iv) asymmetric mobility of the legs with one turning more easily in one direction compared to the other; and (v) non-motor modulators both improving (e.g. cueing) or worsening FoG (e.g. narrow doorways, increased anxiety, dual tasking) (Nutt *et al.*, 2011). In addition, non-gait freezing (e.g. of upper limb movement or speech) has been recognized (Giladi *et al.*, 1992; Naismith and Lewis, 2010) and shows features in common with the phenomenon disrupting gait, although distinctions have been drawn (Barbe *et al.*, 2014; Vercruysse *et al.*, 2014).

Clinically, FoG presents with substantial phenomenological variability within and between individual patients. A rich spectrum of non-Parkinson's disease entities display FoG (Ebersbach *et al.*, 2013; Fasano *et al.*, 2017). Vascular parkinsonism from disseminated subcortical arteriosclerotic encephalopathy may show FoG ranging from 18% to 88% across studies (Bhatia and Marsden, 1994; Giladi *et al.*, 1997; Winikates and Jankovic, 1999; Huang *et al.*, 2002; Factor, 2008). In addition, it should be kept in mind that neurodegenerative and vascular parkinsonism may co-exist, which makes it difficult to draw conclusions on FoG in 'pure' vascular parkinsonism (Rektor *et al.*, 2018). Alternatively, FoG appears to occur rarely in large vessel ischaemic stroke (Fasano *et al.*, 2017) or neuroinflammatory disease (Fietzek *et al.*, 2018). Within Parkinson's disease, FoG varies across phenotypes (e.g. more pronounced in non-tremor dominant) and occurs in up to 63% of the patients with idiopathic Parkinson's disease, with increasing frequency as disease progresses (Perez-Lloret *et al.*, 2014; Forsaa *et al.*, 2015). It is also a common feature of atypical Parkinson's disease including progressive supranuclear palsy and multiple system atrophy (Xie *et al.*, 2015) with FoG often presenting early in the disease course.

Some patients with Parkinson's disease will manifest FoG much earlier along the disease course than others (Hall *et al.*, 2015). The basis for this heterogeneity in FoG is not well understood but there is limited evidence that monogenic determinants or susceptibility genes may account at least for some of the variability (Mirelman *et al.*, 2011; Wang *et al.*, 2014; da Silva *et al.*, 2017). Moreover, recent prospective studies have identified a range of risk factors associated with the development of FoG in Parkinson's disease. These include left-sided disease onset, early lower limb or gait symptom onset, more axial symptoms including speech, bradykinesia and rigidity, higher daily dose of levodopa, an akinetic rigid subtype, lower education, more cognitive and sleep disturbances, poorer balance, the early presence of falls, gait festination, hallucinations, depression and anxiety (Forsaa *et al.*, 2015; Zhang *et al.*, 2016; Ehgoetz Martens *et al.*, 2018*d*; Ou *et al.*, 2018; Banks *et al.*, 2019; Herman *et al.*, 2019).

In this review, we will distil information derived from methodologically diverse approaches and converge these findings in a meaningful way to help identify the network substrates and mechanisms underpinning the phenomenon. We know that a rich set of neuronal integrators and systems contribute to healthy gait referred to as the locomotor network (Bohnen and Jahn, 2013) including spinal central pattern generators, mesencephalic locomotor area, cerebellar locomotor area, subthalamic locomotor region and distributed cortical areas (e.g. fronto-parietal, supplementary

motor area, and primary motor area). However, the challenge is to verify if and how distributed malfunctions of these processors could converge towards a common neural pathway or mechanism (Lewis and Shine, 2016). Such a common pathway might incorporate the mesencephalic locomotor area, the subthalamic nucleus (STN), globus pallidus internus (GPi), and substantia nigra pars reticulata (SNr) in order to regulate the pedunculopontine nucleus (Lewis and Shine, 2016; Snijders *et al.*, 2016; Garcia-Rill *et al.*, 2019). However, this is not to ignore the possibility that meaningful higher level cortical modulators exist from both a broadly motor perspective (e.g. prefrontal cortex, supplementary motor area, premotor cortex, motor cortex), as well as non-motor drivers (e.g. deterioration of cortical movement planning with dual tasking, deterioration of automaticity, fear/anxiety, salience, deficits in visuomotor integration, and failure of sensory processing) (Hallett, 2008; Lewis and Barker, 2009; Heremans *et al.*, 2013; Wu *et al.*, 2015; Gilat *et al.*, 2017; Ehgoetz Martens *et al.*, 2018*a*, *b*, *c*).

In this targeted review, we highlight the existing findings and data in different domains and integrate them into a novel pathophysiological perspective of FoG. Finally, we pose critical questions for future research to scrutinize this perspective.

The contribution of clinical observations and genetic studies to our understanding of freezing of gait

Whilst FoG is common in Parkinson's disease, it is well recognized across other neurodegenerative diseases (Ebersbach *et al.*, 2013). Compared to idiopathic Parkinson's disease, the freezing phenomenon is typically more severe in other parkinsonian conditions such as progressive supranuclear palsy (e.g. Richardson syndrome, pure akinesia with gait freezing) and multiple system atrophy (Ebersbach *et al.*, 2013). The frequency of FoG seems to be similar in both types of atypical parkinsonism (Xie *et al.*, 2015), albeit large prevalence studies are not available. Despite this clinical distinction, it has been emphasized that there is no specific FoG-related feature that separates the gait abnormality in idiopathic Parkinson's disease from these conditions (Ebersbach *et al.*, 2013).

In the absence of any recognized neurodegenerative condition, a wide variety of brain lesions have been reported to result in FoG including ischaemic stroke, intracerebral haemorrhage, tumour and inflammatory disease (Fasano *et al.*, 2017; Fox, 2018). As the aetiologies of lesions driving FoG are diverse, it is likely that it is not necessarily the aetiology but rather the strategic localization of an insult that is critical to the paroxysmal failure of gait that manifests as the freezing phenomenon. These observations would indicate that there is a vulnerability of critical nodes across a distributed functional network that represents a key feature underpinning the pathophysiology of FoG.

Parkinson's disease patients with idiopathic or familial disease show pronounced interindividual variability with respect to their dominant motor and non-motor symptoms, disease progression and response to therapy (Lewis *et al.*, 2005; Ferreira and Massano, 2017). Long-term prospective cohorts, deep-phenotyping approaches and genetic characterization have provided the first insights into those patients with the more severe and progressive 'postural instability and gait disorder' (PIGD) subtype. In familial Parkinson's disease, carriers of the *LRRK2 G2019S* mutation display a PIGD subtype three times more commonly and have more difficulty walking while fewer patients exhibit a tremor dominant subtype compared to non-mutation carriers. Indeed, gait disturbance was the initial presenting symptom in 22% of these mutation carriers compared to just 4% of the non-mutation carriers (Mirelman *et al.*, 2013). A higher risk of falling 'in the year before diagnosis' was mentioned in 35% of the mutation carriers as opposed to 20% of the non-mutation carriers. Furthermore, mutation carriers differed in kinematic aspects, such as greater stride time variability across different walking conditions (normal and fast gait, dual tasking during gait) (Mirelman *et al.*, 2013). Gait kinematic abnormalities have even been observed in non-symptomatic mutation carriers of the *LRRK2* G2019S mutation in Ashkenazi Jewish cohorts (Mirelman *et al.*, 2011). This included increased stride time variability in fast gait or dual-tasking gait conditions. In addition, there was higher gait variability and higher stride-to-stride fluctuations in the mutation carriers (Mirelman *et al.*, 2011).

More specifically, some studies investigated the genetic associations to FoG. Heterozygous mutation carriers in the glucocerebrosidase gene (*GBA*) show increased susceptibility for developing Parkinson's disease and a higher incidence in gait impairment, FoG, and postural instability when compared to *LRRK2* patients or non-mutation carriers with sporadic disease (Wang *et al.*, 2014; da Silva *et al.*, 2017). Moreover, *GBA* mutation carriers with FoG showed more pronounced motor symptoms (Wang *et al.*, 2014) and more rapid progression of cognitive dysfunction, and this may correlate with more severe gait impairment (Brockmann *et al.*, 2011; Alcalay *et al.*, 2012; Weiss *et al.*, 2012). Additional candidate genes and polymorphisms may be associated with the development of FoG. They mostly relate to dopamine metabolism and function. As such, Parkinson's disease patients homozygous for the *V81M* polymorphism in the tyrosine hydroxylase gene had more severe FoG scores compared to V81M heterozygous/wild-type, although the V81M polymorphism did not contribute to a higher rate of Parkinson's disease itself or FoG risk (Tekin *et al.*, 2016). The authors indicated that this might be associated with lower catecholamine synthetic capacity. In another study, the *DRD2* T allele, but not *COMT* or *BDNF* polymorphisms, was associated with higher

medication responsiveness but overall worse gait measures including shorter steps and slower pace (Miller *et al.*, 2018). There are also genetic variations that may reflect a more benign phenotype as FoG has previously been inversely associated with the presence of the CYP2D6*4 allele [odds ratio (OR) 0.41, 95% confidence interval (CI) 0.21–0.80; $P = 0.009$] suggesting a protective effect. Similarly, *APOE* ε4 was associated with less pronounced postural instability and falling (OR 0.21; CI 0.05–0.91; $P = 0.03$) (Factor *et al.*, 2011).

The contribution of network dysfunction to our understanding of freezing of gait

Cognitive processes are integrated across large-scale brain networks (Steriade *et al.*, 1996; Singer, 1999; Fries, 2009; Engel and Fries, 2010; Siegel *et al.*, 2012; Hallett *et al.*, 2017; Shine *et al.*, 2019). In this context, neuropsychiatric diseases, including Parkinson's disease, are increasingly being understood as complex network disorders (Uhlhaas and Singer, 2006, 2010; Gerloff and Hallett, 2010; Engel *et al.*, 2013; Hallett *et al.*, 2017). Strikingly, various nodes contribute to such functional networks where dysregulation of one or several of these key nodes may produce critical network imbalance, ultimately resulting in clinical signs (Kuhn *et al.*, 2006; Weiss *et al.*, 2015; Fasano *et al.*, 2017), including the freezing phenomena (Nieuwboer and Giladi, 2013; Shine *et al.*, 2013, 2014; Scholten *et al.*, 2016; Ehgoetz Martens *et al.*, 2018*a*; Handojoseno *et al.*, 2018). In the following section, we focus on different methodologies that have been used to illuminate the diverse network components and network processes contributing to freezing.

Insights from neuroimaging

Whilst structural MRI studies have revealed associations between FoG and patterns of both grey matter loss and white matter tract involvement, these studies have shown little consensus (Tessitore *et al.*, 2012; Hall *et al.*, 2018; Pietracupa *et al.*, 2018). Such an observation would be consistent with the concept that FoG represents the breakdown of an underlying neural network rather than arising from discrete lesions. Another perspective would be to assume that different pathophysiology and circuits exist, and that critical alteration or damage of individual circuits would imbalance the entire system whereby a 'weak link' could give rise to FoG (Fasano *et al.*, 2015; Lewis and Shine, 2016). A series of functional MRI studies utilizing mental imagery and virtual reality approaches have highlighted that frontostriatal projections and the basal ganglia hyperdirect pathway may contribute to freezing (Snijders *et al.*, 2011; Shine *et al.*, 2013*a*, *b*, *c*; Gilat *et al.*, 2017). In line with proposed trigger-dependent subtypes of FoG, one recent functional connectivity analysis has suggested distinct network signatures and abnormalities along 'motor', 'cognitive', and 'limbic' subtypes (Ehgoetz Martens *et al.*, 2018*a*). In this study, coupling between the cognitive and limbic networks was associated with 'worse freezing severity', whereas anti-coupling between the putamen and the cognitive and limbic networks related to reduced freezing severity. Additionally, anti-coupling between cognitive cortical regions and the caudate nucleus was 'independent of freezing severity' and thus may represent common neural underpinnings of freezing. Furthermore, these connectivity patterns could be related to each of the individual components (e.g. motor, cognitive and affective in turn), thus exposing latent heterogeneity in the freezing phenotype, whilst also identifying critical functional network signatures that may represent 'weak links' or nodes, as well as serving as potential targets for novel therapeutic intervention. These findings provide confirmatory evidence for systems-level impairments in the pathophysiology underpinning FoG, and suggest that whole-brain deficits may mediate symptom expression in Parkinson's disease. In addition, the findings demonstrate that patients in neuroimaging cohorts need to be characterized carefully for their clinical characteristics including freezing severity, as well as for cognitive and psychiatric traits as these variables may account for distinct subtypes of network pathology—or heterogeneity in the findings, if studies do not control for these variables.

In addition to those neuroimaging findings that have described the network characteristics of those patients with FoG, other more dynamic event-related studies have been able to highlight the ultimate failure of the network processes closely before or during freezing itself. For example, studies using a functional MRI virtual reality paradigm have highlighted the network correlates of FoG associated with dual-tasking, turning and approaching narrow doorways (Shine *et al.*, 2013; Gilat *et al.*, 2015; Matar *et al.*, 2019).

In addition to studies using MRI, further support for the role of disseminated networks in FoG comes from neurometabolic studies using glucose PET and *N*-isopropyl-p-[I-123] iodoamphetamine (^{123}I-IMP) SPECT. These studies pointed to changes in the frontal and parietal cortical areas of Parkinson's disease patients with FoG (Matsui *et al.*, 2005; Imamura *et al.*, 2012). Further research highlighting the divergence and convergence across imaging studies and modalities have been summarized elsewhere (Fasano *et al.*, 2015). However, in brief, whilst there is some heterogeneity across studies, structural and neurometabolic network abnormalities have been commonly reported. This included the fronto-parietal executive attention network, but also the sensorimotor and visual networks including 'regional tissue loss of the inferior frontal gyrus, parietal lobe, the precuneus, cuneus and angular gyrus, premotor and primary motor areas, and visuospatial area' (Fasano *et al.*, 2015).

To summarize, different imaging modalities have implicated a variety of brain regions, supporting the view that

FoG reflects network alterations. Yet, it remains unclear which region or network shows the most reproducible neuroimaging abnormalities and whether any of these neuroimaging abnormalities is causally related to generating FoG symptoms.

Insights from lesion-network mapping

Lesion analysis is a valuable complement to functional neuroimaging as it identifies causal neuronal links between the locations of brain injury, their position in a proposed functional network and their relation to symptom expression (Stanley and Adolphs, 2013; Fox, 2018). Lesions in several different brain locations have been reported to cause FoG, including parasagittal frontal areas, the left postcentral gyrus, cerebellum, midbrain tegmentum, brainstem, and basal ganglia including external globus pallidus (GPe)/GPi (Fasano *et al.*, 2017). The fact that these lesions occur in multiple different brain locations supports results from functional neuroimaging in suggesting that locomotion and FoG involve a network of connected brain regions.

Recently, it has been tested whether lesions in different brain locations are part of a common network, referred to as 'lesion-network mapping' (Boes *et al.*, 2015; Fasano *et al.*, 2017; Fox, 2018; Joutsa *et al.*, 2018*a*, *b*). The technique first maps lesion locations from different patients to a common brain atlas (e.g. in MNI space) then identifies the network of regions functionally connected to each lesion location using a database of normative brain connectivity before testing whether different lesions are part of a common brain network. When applied to lesions causing FoG, the identified anatomical site fell within a common brain network that was functionally connected to the dorsal medial cerebellum, referred to as cerebellar locomotor region (Fasano *et al.*, 2017). Connectivity to this region was specific to lesions causing FoG as opposed to lesions causing hemichorea or asterixis. Further, lesions causing parkinsonism mapped to a different brain network, which involved the midbrain, basal ganglia, cingulate cortex, cerebellum, and claustrum (Joutsa *et al.*, 2018). Furthermore, the FoG lesion within the cerebellar locomotor region was aligned with previous functional neuroimaging studies in Parkinson's disease patients with FoG that reported abnormalities of both anatomical and functional connectivity with this cerebellar region (Schweder *et al.*, 2010; Fling *et al.*, 2013, 2014). Relevant limitations of the lesion-network mapping approach include the fact that the neural substrate of lesion-associated freezing may be different from the FoG associated with neurodegenerative diseases including Parkinson's disease. Similarly, it remains unclear whether therapeutic targets identified with lesion-network mapping would prove effective in neurodegenerative disease, although accumulating data are promising (Fasano *et al.*, 2017; Joutsa *et al.*, 2018*a*, *b*) and a recent activation of likelihood estimation (ALE) meta-analysis of neuroimaging studies identified the cerebellar locomotor region as the most consistent gait-related activation region in Parkinson's disease (Gilat *et al.*, 2019).

Insights from extra-nigral system findings

Striatal dopaminergic denervation is critical in the pathophysiology of FoG in Parkinson's disease given that it occurs most frequently when patients are in the OFF state (Snijders *et al.*, 2016). However, nigrostriatal losses alone cannot explain ON state freezing, which has been reported in 38.2% of Parkinson's disease patients in a large study (Perez-Lloret *et al.*, 2014). It has been proposed that if dopaminergic loss is complicated by the impairment of another neurotransmitter system, such as cholinergic or glutamatergic changes, then the motor control system may break down, which would manifest as ON freezing (Snijders *et al.*, 2016).

Previously, falls and slow gait speed in Parkinson's disease have been associated with degeneration of the pedunculopontine nucleus-thalamic and forebrain cortical cholinergic projection systems, respectively (Bohnen *et al.*, 2009; Bohnen and Jahn, 2013). More severe loss of striatal dopaminergic and cortical cholinergic binding, and the presence of cortical amyloidopathy have been shown to be more common in Parkinson's disease freezers compared to non-freezers (Bohnen *et al.*, 2014). Therefore, striatal dopaminergic losses combined with extra-nigral pathological conditions may contribute to FoG. Mechanistically, extra-nigral pathologies may impair cerebellar, thalamic and cortical information flow across sensorimotor, cognitive and affective pathways to the striatal motor network. In this conceptual framework, attenuating the transfer of important information to the basal ganglia could result in the failure to detect relevant sensory or movement cues (Sarter *et al.*, 2014). Such disruption of information flow would further exacerbate impaired movement selection and sequencing in a dopamine-depleted striatum and thereby increase the risk of FoG.

Experimental studies in striatal dopaminergic and cortical cholinergic lesioned rats have shown that dual system-lesioned rats have more prominent attentional deficits and a substantially greater number of slips and falls whilst traversing a complex balance beam compared to single-system or sham lesioned animals (Kucinski *et al.*, 2013). Interestingly, behavioural risk factors for these slips and falls include more micropauses, slower traversal speed and less effective rebalancing after slips in the dual-lesioned rats. These observations suggest that cholinergic-attentional loss superimposed on striatal dopaminergic loss greatly impairs effective motor control for gait and postural functions. In these animal experiments, treatment with combined cholinesterase inhibitor (donepezil) and 5HT-6 receptor antagonist (idalopirdine) resulted in significantly fewer freezing-like episodes in dopaminergic and

cholinergic dual-lesioned rats when the freezes remained relatively short (<2 s) but had no effect on the fall risk during longer freezing episodes (Kucinski *et al.*, 2017). This treatment may potentially reduce fall propensity in Parkinson's disease patients by maintaining planned movement sequences in working memory and improving the vigour of executing such movements following brief periods of FoG. It is possible that longer durations of freezing are a function of more severe striatal dopaminergic rather than cholinergic losses *per se*. For example, doorframe-induced falls in rats with large striatal lesions were preceded by relatively longer freezing episodes compared to those in rats with small striatal dopaminergic lesions combined with cortical cholinergic loss. Alternatively, it is possible that cholinergic augmentation of working memory capacity to maintain planned movement sequences may have a limited temporal therapeutic window. Although cholinesterase inhibitor monotherapy failed to significantly reduce FoG episodes in Parkinson's disease patients (Henderson *et al.*, 2016), clinical observations of an association between more frequent exposure to anti-muscarinic anticholinergic drugs and the presence of FoG in Parkinson's disease caution against the use of anticholinergic drugs in patients at risk of FoG (Perez-Lloret *et al.*, 2014).

Insights from neurophysiology

Neurophysiological studies offer high temporal resolution to study the pathophysiology of FoG. Kinematic abnormalities of the gait cycle have been reported in Parkinson's disease gait freezers and these motor abnormalities accumulate in the transition period between effective forward stepping and the cessation of forward progression (Vercruysse *et al.*, 2012). A closer look at these transition periods indicates the occurrence of both temporal and spatial abnormalities of gait integration and pathological frequency activation of the kinematic traces (Vercruysse *et al.*, 2012). For example, an increase in frequency of the repetition cycle and the consecutive decline in amplitude of a movement appear to be prominent features in both upper limb freezing and FoG (Vercruysse *et al.*, 2012). This suggests a failure of neuromuscular integration and this view is substantiated by neurophysiological studies (Nieuwboer *et al.*, 2004; Scholten *et al.*, 2016).

Kinematic spatiotemporal abnormalities of both upper limb movement and gait have been described prior to a freezing episode, which may mirror defective spinal motor neuron activation (Nieuwboer *et al.*, 2004). Work on upper limb freezing has demonstrated a pathological frequency content of antagonistic muscles during repetitive finger tapping (i) in contrast to healthy controls; and (ii) when comparing preserved tapping and upper limb freezing within Parkinson's disease freezers (Scholten *et al.*, 2016). Given the defective frequency activation of the EMG (mirroring spinal motor neuron activity), it is plausible to consider that supra-spinal circuits could mediate such disengagement of spinal motor neurons and thus induce abnormal patterns of frequency activation. Recent evidence coming from STN recordings in acute perioperative or chronic postoperative settings has revealed that in akinetic-rigid Parkinson's disease patients (as opposed to tremor dominant cases) there is an enhanced beta band oscillatory activity during standing that was suppressed during postural transitions, e.g. when changing body positions to sitting, lying or walking (Quinn *et al.*, 2015). Additionally, Parkinson's disease freezers showed enhanced event-related beta band activity in the STN during gait initiation, which was not observed in non-freezers (Storzer *et al.*, 2017). Pathological frequency activation at the level of the STN may therefore play a role in start hesitation, although this will need to be confirmed in future studies.

It would be of substantial interest for future adaptive neuromodulation concepts to know if beta band activity is co-modulated during the normal gait cycle, and if so, if a breakdown in this co-modulation would indicate the emergence of FoG. Two recent studies have started to explore this aspect by providing evidence that beta band activity at the level of STN is modulated with stepping (Fischer *et al.*, 2018) and throughout the gait cycle (Hell *et al.*, 2018). In addition, deep brain stimulation (DBS) sensing technology enabled Anidi *et al.* (2018) to demonstrate that STN beta band bursts were prolonged and enhanced in Parkinson's disease freezers. One important methodological issue to resolve in these studies is to gain reassurance that the observed spectral modulations do not simply reflect mechanical gait-related perturbations (Kline *et al.*, 2015). Interestingly, mechanical perturbations and their artefacts generally increase with the speed and amplitude of stepping. Therefore, some reassurance can be drawn from one recent study that showed these perturbations were similarly present both when stepping in place (causing relatively few mechanical perturbations) and during walking (Fischer *et al.*, 2018). A further approach to address this concern would be for future studies to confirm that the observed beta band co-modulation is lateralized to the STN contralateral to the swing leg.

Little is known about the neurophysiology associated with the transition phase between regular repetitive movement (in gait or during upper limb movement) and the emergence of freezing. However, insights are accumulating from ambulatory EEG recordings. In this framework, cortico-cortical phase synchronization of the beta frequency range indicated enhanced susceptibility to the occurrence of upper limb freezing (Scholten *et al.*, 2016). Moreover, in this study, individual freezing episodes presented with enhanced alpha oscillatory activity, which was most pronounced in left prefrontal and centroparietal areas during right finger movements (Scholten *et al.*, 2016). To apply and interpret surface EEG during overground walking is challenging but accumulating evidence exists that meaningful conclusions can be drawn when adequate artefact suppression methods are used (Seeber *et al.*, 2014, 2015; Arad *et al.*, 2018). Nevertheless, these findings must be interpreted with caution given that gait cycle-related artefacts

arise from multiple mechanisms that may finally confound the interpretation (e.g. from mechanical perturbations, micro-shivering of the electrode, sweating, breathing, cardiac signals and intracranial conductivity change time-locked to cardiac beat, and muscle artefacts from neck muscles). Component analysis and source level reconstructions may help suppress such artefacts and focus on genuine cortical activity. These studies have shown that oscillatory band activity (alpha, beta, gamma) seems to co-modulate with the gait cycle, similar to what has been found in the STN of patients with Parkinson's disease (Seeber *et al.*, 2014, 2015). This co-modulation is of particular interest for future Parkinson's disease gait research, as it provides a valuable entry point to study the cortical network pathology in relation to the gait cycle in real time. More precisely, such oscillatory features might exhibit a critical imbalance and deterioration as patients enter the transition period on the way from walking to a freezing episode. Early studies in this field have used machine learning techniques to classify this transition phase (Handojoseno *et al.*, 2012) or have reported a transient increase in cortical midline theta and beta activity (Shine *et al.*, 2014). In addition, cortical connectivity of the frontal area in terms of the directed transfer function has also shown promise in separating regular gait from the transition period and FoG (Handojoseno *et al.*, 2014, 2018). More recent work has also used ambulatory EEG to identify specific neurophysiological signatures (Ly *et al.*, 2016) including gait initiation failure (Quynh Tran *et al.*, 2016; Ly *et al.*, 2017) and turn freezing (Handojoseno *et al.*, 2015; Quynh Tran *et al.*, 2016). A recent study identified derangement of neuronal synchronization between the STN and cortex in the disease-dominant hemisphere with less striatal dopaminergic innervation from 4 Hz to 13 Hz in the transition phase and during FoG (Pozzi *et al.* 2019, https://doi.org/10.1093/brain/awz141).

Insights from neuromodulation studies

Cortical stimulation

Various studies have highlighted that the freezing phenomenon is paralleled by cortical dysfunction (Scholten *et al.*, 2016*a*, *b*) and thus cortical 'non-invasive' brain stimulation offers a potential method to modulate FoG and to learn about the role of the cortex. Although stepping and gait rhythms are primarily represented in the spinal central pattern generators, complex supra-spinal modulation likely modifies these oscillators. Noting the well-known cognitive (Nieuwboer and Giladi, 2013) and executive aspects of FoG (Hallett, 2008), it is not surprising that distributed cortical areas are directly involved in modulating FoG.

There is evidence that stimulation to the primary motor cortex (M1) can modulate FoG (Lee *et al.*, 2014; Kim *et al.*, 2015; Chang *et al.*, 2017; Dagan *et al.*, 2018) and in particular, the M1 primary leg area has been implicated (Lee *et al.*, 2014; Valentino *et al.*, 2014; Kim *et al.*, 2015; Chang *et al.*, 2017). In more detail, a single session of 10 Hz repetitive transcranial magnetic stimulation (rTMS) over the M1 lower leg area in 20 Parkinson's disease gait freezers improved the timed up-and-go test, turn steps and turn times compared to sham stimulation (Lee *et al.*, 2014). A similar study with multiple sessions of rTMS over M1 lower leg area delivered at 90% resting motor threshold (10 Hz rTMS, 1000 pulses) reported an improvement in turning and a slight improvement in the FoG Questionnaire (Kim *et al.*, 2015). Furthermore, anodal transcranial direct current stimulation (tDCS) delivered over M1 in a group of 10 Parkinson's disease patients also resulted in improvements in the number and duration of FoG events in the Stand-Walk-Sit Test (Valentino *et al.*, 2014).

There is also evidence that stimulation to the dorsolateral prefrontal cortex (dlPFC) may impact FoG (Lee *et al.*, 2014; Dagan *et al.*, 2018), whereas there is no convincing evidence that cortical stimulation targeting the supplementary motor area has a modulatory role (Lee *et al.*, 2014; Lu *et al.*, 2018). In terms of the dlPFC, rTMS improved the number of turn steps and turn time in 20 Parkinson's disease patients (Lee *et al.*, 2014). Furthermore, high-frequency rTMS of the medial PFC (4 weeks with three sessions of rTMS per week, followed by 4 weeks with one session per week) led to an improvement of a FoG provocation test but not subjective FoG scores in nine Parkinson's disease patients, although it should be noted that this study was exploratory (Dagan *et al.*, 2017).

Using another modality, simultaneous tDCS over both M1 and dlPFC has reportedly improved clinical symptoms of FoG, whereas stimulation of M1 alone was not beneficial (Dagan *et al.*, 2018). Furthermore, dual mode stimulation [high frequency (HF)-rTMS over the M1 lower leg area plus anodal tDCS over the left dlPFC] has been compared to single mode (HF-rTMS over the M1 lower leg area plus sham anodal tDCS over the left dlPFC). The FoG outcome (measured by the FoG Questionnaire and turning steps) improved over time in both groups but did not yield a statistically significant difference (Chang *et al.*, 2017). The dual mode group did show improved executive function. These findings could point to combined involvement of both M1 and the PFC, underlining the motor as well as the cognitive/executive aspects of FoG.

Subcortical stimulation

Several lines of evidence indicate that DBS may modulate FoG with the broad potential to both improve and worsen the phenomenon in Parkinson's disease. Albeit being rather helpful or neutral in most cases, DBS may induce or aggravate FoG, in particular when a subthalamic electrode is misplaced in the medio-anterio-cranial direction. Stimulation at this location induces an anti-kinetic effect, presumably through the activation of pallido-thalamic fibre tracts (Fleury *et al.*, 2016), when there is excessive energy delivery (Moreau *et al.*, 2008), or through pallidal

stimulation, which has been seen as an adverse outcome in patients treated for dystonia (Schrader *et al.*, 2011; Mahlknecht *et al.*, 2018).

STN stimulation may reduce FoG in the early period following DBS (Fasano *et al.*, 2012) and remains effective for at least 3–5 years (Schupbach *et al.*, 2005; Vercruysse *et al.*, 2014; Schlenstedt *et al.*, 2017; Barbe *et al.*, 2018). One study reported sustained FoG improvement in ~50% of patients 1 year from DBS compared to preoperative FoG (Vercruysse *et al.*, 2014), and a more recent study reported improvements in FoG and falls in around one-third of patients (Karachi *et al.*, 2019). A beneficial effect on FoG can be predicted from the preoperative levodopa response of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS III), as well as from the gait-specific items of the MDS-UPDRS III based on a meta-analysis (Schlenstedt *et al.*, 2017). It has been shown that STN stimulation modulates stride length as well as amplitude scaling of gait, thus treating hypokinetic features of the parkinsonian gait disorder (Potter-Nerger and Volkmann, 2013; Scholten *et al.*, 2017). Treatment with levodopa further increases the beneficial effect on postural instability and gait difficulty (Fasano *et al.*, 2012). Interestingly, STN-DBS mainly seems to improve levodopa-responsive OFF freezing (Maurer *et al.*, 2003; Ferraye *et al.*, 2008; Fasano *et al.*, 2012). However, some patients showed zero, partial or only short-term transient improvements in their FoG and it has been suggested that this therapy resistance arises from the accumulation of non-dopaminergic pathology as the disease progresses (Ferraye *et al.*, 2008; Castrioto *et al.*, 2011; Weiss *et al.*, 2012; Vercruysse *et al.*, 2014; Collomb-Clerc and Welter, 2015; Schlenstedt *et al.*, 2017). Ongoing reprogramming of STN stimulation is critical for management as an excess of energy delivered, as well as the unwanted spread of current to neighbouring structures (especially antero-medial to STN) may provoke adverse effects on gait (Moreau *et al.*, 2008; Fleury *et al.*, 2016).

The limited response of FoG to subthalamic stimulation has previously prompted interest for alternative management strategies and DBS target sites. One such promising approach was to lower the stimulation frequency to 60–80 Hz compared to the more typically used 130 Hz stimulation, while keeping the total electric energy delivery constant. This approach can produce a relevant improvement in FoG (Moreau *et al.*, 2008; Xie *et al.*, 2012, 2015) but the attenuation of an initially good effect over several weeks has been reported repeatedly (Ricchi *et al.*, 2012; Zibetti *et al.*, 2016). However, it has been suggested that low frequency DBS can be maintained in ~60% of patients with PIGD symptoms remaining stable over a period of up to 3 years (Zibetti *et al.*, 2016). From the available literature, it is still not entirely clear if this observation represents a 'true' frequency effect, or whether lowering of frequencies prevents 'excess stimulation' by lowering the 'total electric energy delivered'. More studies controlling for energy delivery and axon models of fibre activation when studying different stimulation frequencies are needed in order to learn about the true effect of frequency modulation approaches (Weiss *et al.*, 2018). Moreover, studying the network effect of such frequency modulation approaches would help to gain deeper understanding, if different pathways and networks could be accessed with different frequencies.

Alternative DBS targets have been proposed and it has been argued that stimulation of the GPi may result in better effects on gait and postural control compared to STN procedures. However, higher levodopa dosages in GPi-stimulated patients may confound such interpretations (St George *et al.*, 2010). Better outcomes of gait were observed in the GPi group only in the ON but not in the OFF state and this supports the view that levodopa dosage plays perhaps a more critical role than the mere choice of the stimulation target (St George *et al.*, 2010).

There is considerable interest in neuromodulation of the midbrain and brainstem locomotor centres for treating FoG. As such, neurostimulation of the pedunculopontine (PPN) area has been evaluated (Ferraye *et al.*, 2010; Thevathasan *et al.*, 2011). This approach has not been widely adopted for a variety of clinical, technical, and methodological reasons and the recent evidence for PPN DBS has been reviewed in detail elsewhere (Snijders *et al.*, 2016; Albin *et al.*, 2018; Thevathasan *et al.*, 2018; Garcia-Rill *et al.*, 2019). In brief, the first challenge is to define the exact neuroanatomical correlate. Not only the cholinergic PPN but also the area 1–2 mm medial and inferior to the PPN's cholinergic portion, which receives direct pallidal input, may be relevant to mediate the effects on gait (Garcia-Rill *et al.*, 2019). A second challenge is that studies of PPN stimulation to date have incorporated a range of divergent clinical endpoints in small case series with inconsistent stimulation parameter adjustments. Nevertheless, the PPN target has shown substantial promise in animal research and it is probably too early to draw a conclusion on whether it will become established as a treatment for a subset of well-selected patients with FoG.

More recently, the SNr is under ongoing exploration as another candidate hub to access the mesencephalic locomotor integration through its known GABAergic connectivity with the PPN. In the routine clinical setting, SNr stimulation may be delivered in combination with the STN if a caudal electrode contact of a subthalamic lead reaches the SNr area (Chastan *et al.*, 2009; Weiss *et al.*, 2011). From a pathophysiological perspective, the SNr is overactive in Parkinson's disease (Breit *et al.*, 2006; Lafreniere-Roula *et al.*, 2010; Milosevic *et al.*, 2018) and therefore, has an inhibitory net effect on motor output. Neurostimulation of this target aims to suppress this overactivity and may induce inhibitory synaptic plasticity (Lafreniere-Roula *et al.*, 2010; Milosevic *et al.*, 2018). Indeed, there are accumulating case series (Chastan *et al.*, 2009; Weiss *et al.*, 2011; Brosius *et al.*, 2015) and one small randomized controlled trial (Weiss *et al.*, 2013) suggesting that SNr stimulation may modulate axial motor symptoms and in particular, FoG, when delivered at high

frequencies of ~125–130 Hz. A similar effect was suggested with SNr stimulation using lower frequencies at 63 Hz in a series of six patients (Valldeoriola *et al.*, 2018). Based on current neurophysiological and clinical findings, stimulation frequencies of 125 or 63 Hz seem to exert concordant effects on nigral single cell activity and inhibitory plasticity measures (Milosevic *et al.*, 2018; Weiss *et al.*, 2018).

In conclusion, neuromodulation of cortical and subcortical targets has suggested that the network correlates of FoG can be accessed and modulated in a meaningful way. However, further carefully designed clinical trials are needed to learn about the true effect of these targets, as well as about how to best deliver neuromodulation in terms of a rich set of possible stimulation parameters.

Cerebellar stimulation

The field of cerebellar stimulation is worthy of further study given the reproducible pathophysiological findings that point to the involvement of the cerebellar locomotor region in the pathophysiology of FoG. Whilst it is recognized that cerebellar activity is increased in Parkinson's disease, there is an ongoing debate on whether this reflects 'compensation' or a 'pathophysiological change' from overactive basal ganglia (in particular increased glutamatergic drive from STN efferent projections to the cerebellum) (Wu and Hallett, 2013). Supporting the latter assumption, STN-DBS has been shown to normalize cerebellar activity (Hilker *et al.*, 2004; Asanuma *et al.*, 2006). Moreover, it has been reported that the cerebellum of Parkinson's disease patients with FoG shows a distinct increase in activation and altered connectivity profiles with other brain regions when compared to non-freezers (Bharti *et al.*, 2019). This led to the concept that cerebellar stimulation might help to regulate the locomotor network in order to reduce FoG. One recent study using a unilateral stimulation protocol (applying both an inhibitory and excitatory theta burst stimulation, respectively) (Janssen *et al.*, 2017) demonstrated no change in FoG or M1 cortical excitability. One critical aspect in the delivery of cerebellar TMS to achieve cerebellar locomotor region modulation is that the stimulation field needs to reach deep enough, which could represent a significant limitation (Hardwick *et al.*, 2014).

Discussion

Here, we reviewed the diverse features of FoG. In the following section, we would like to suggest that these seemingly diverse research directions may be integrated into a common overarching pathophysiological perspective on FoG that could be validated through specific hypotheses in future studies.

We argue that FoG depends on (i) vulnerability of the locomotor network, as established by a diverse set of neurodegenerative diseases and other disorders, lesions or genetic determinants. This structural damage may set critical network susceptibility such that (ii) modulators may both decrease or increase the threshold for expressing FoG. Such bidirectional modulators may include cognitive processes such as interference triggering events (e.g. cognitive load or dual tasking) as well as increased attention-promoting events (e.g. cueing). As highlighted above, both pharmacological and neuromodulation interventions have the capacity to potentially induce or relieve the expression of FoG. Such modulation might then act as the next step to induce (iii) neuronal integration failure that may affect one or more nodes and connections in the locomotor network. Input from those disseminated nodes may possibly converge to a common (iv) ultimate pathway (Lewis and Shine, 2016) acting as a bottleneck that may unify diverse network components and freezing subtypes and finally determine whether a FoG episode is expressed or not. In this context, it was emphasized that overinhibitory basal ganglia nuclei like the GPi or the SNr may attenuate effective locomotor output from the mesencephalic locomotor region and thereby deregulate the spinal central pattern generator (Lewis and Shine, 2016; Snijders *et al.*, 2016). Ultimately, such a common tract will have to be challenged in future studies through goal-directed hypotheses. Other pathways exist that might also modulate such a common tract or directly modulate spinal motor neurons. In particular, this is true for the corticospinal tract. As such, corticomuscular coherence was been shown to be defective in upper limb freezing, but is yet uncharacterized in FoG (Scholten *et al.*, 2016). In addition, the role of proprioceptive afferences as well as the vestibulo-cerebellar system are less well understood in FoG but may contribute to FoG (Seemungal, 2014; Huh *et al.*, 2016; Lewis and Shine, 2016). Finally, network inputs to such a common tract would determine whether a FoG episode is expressed or eventually rescued, given that (v) FoG will occur as the final clinical consequence of a converging network failure.

In the following, we discuss future urgent research questions that will be needed to challenge our pathophysiological perspective and to illuminate our understanding of the FoG phenomenon.

What clinical studies should we be conducting next?

Much of the available research focuses on idiopathic Parkinson's disease in its advanced stage. However, a more complete understanding should consider the wide aetiological spectrum and genetic determinants behind FoG in a more comprehensive way. To this end, we encourage international registers that address the freezing phenomenon across the full spectrum of disease treatment states, severities and entities where FoG is observed using identical methods and diagnostic work-up. This includes more detailed prevalence data on FoG across other degenerative and non-degenerative disease entities. This might

provide important clues with respect to the pathology, neural systems, and transmitters involved.

To achieve high data quality in such overarching initiatives, several aspects are considered key when harmonizing assessment protocols across centres: (i) harmonization of diagnostic criteria, i.e. FoG diagnosis should be confirmed from clinical observation (Snijders *et al.*, 2012); (ii) use of quantitative objective FoG assessments (Ziegler *et al.*, 2010), in addition to self-reporting instruments such as the New Freezing of Gait Questionnaire (NFOG-Q) (Nieuwboer *et al.*, 2009); (iii) assessment of quality of life; (iv) meticulous dissection of freezing subtypes, triggers, and modulators; (v) cognitive assessments including cognitive set shifting, working memory, attention, and visuospatial abilities; (vi) assessments of limbic domains, in particular mood including depressive symptoms, and anxiety; (vii) genetic characterization including control for potential confounders such as motor severity and others. The genetic data thus far are from small studies without clear replication and therefore are in their infancy. Nevertheless, one can see how genetic characterization could provide clues to pathophysiology and potential therapeutic targets as well as prediction of FoG and its subtypes. With such well characterized subjects as described above we could aim for larger sample sizes and perform hypothesis-free genome-wide association studies to investigate as yet unknown causative or susceptibility genes for FoG in Parkinson's disease and other disorders; and (viii) harmonization of imaging protocols.

This would allow investigators, for example, to determine whether FoG is truly operating via the same pathways across conditions. In particular, studying the genetics of FoG will require large and well-characterized cohorts where findings can be reproduced independently. A closer phenotyping of Parkinson's disease patients with respect to gait, motor phenotype, cognitive and mood measures may also be important in these studies.

In addition, it may be promising to predict the individual disease courses and whether or not a Parkinson's disease patient 'non-freezer' will stay a 'non-freezer' or convert to a 'freezer' in the future, which can be predicted with accuracies ranging from 70–90% (Ehgoetz Martens *et al.*, 2018*b*). The FoG Questionnaire and the anxiety scores were the strongest predictors to this end. Here, we would like to propose that the prediction of phenotype conversion may allow for the design of intervention studies. This means that interventions could take advantage of such at-risk populations that will likely develop FoG in the near future. Physiotherapy, cognitive training (Walton *et al.*, 2015; Ehgoetz Martens *et al.*, 2018*d*), or neuromodulation/neuropharmacology (e.g. with cholinergic drugs) (Bohnen and Albin, 2011; Bohnen *et al.*, 2014; Lieberman *et al.*, 2019) should be studied for their capacity to prevent, delay, or attenuate the expression of FoG.

Finally, it is unclear that FoG has identical characteristics across therapeutic conditions (e.g. when comparing levodopa OFF versus ON) (Factor *et al.*, 2014), or if freezing triggers lead to identical or different types of freezing (e.g. turning, doorways) with potentially different pathophysiological mechanisms. Therefore, more work is required to confirm the breakdown point in the locomotor networks across these conditions.

What is the clinico-pathology of freezing of gait?

One obvious area where very little work has been conducted to date is in relation to the neuropathological changes that underlie FoG. This would require detailed prospective case characterization *in vivo* and a constrained pathophysiological hypothesis. It should be highlighted that FoG is, at its core, a paroxysmal event akin to other intermittent phenomena such as tremor, visual hallucinations and rapid eye movement sleep behaviour disorder. For example, it has been relatively easy to map certain clinico-pathological features, such as the loss of nigrostriatal projection with striatal dopamine deficiency, which in turn can be correlated to *in vivo* measures such as dopaminergic PET changes and clinical scores for bradykinesia (Kish *et al.*, 1988; Rinne *et al.*, 1999). The intermittent nature of FoG and its disseminated neural network not only in Parkinson's disease but across all the neurodegenerative and non-neurodegenerative disorders will require a multimodal approach. At this stage, the field is limited by the lack of prospectively and phenotypically described cases and by the lack of *in vivo* data that can be used at post-mortem. Given the contributions of dopaminergic and cholinergic imaging to our current level of understanding, it is likely that insights from studying other neurotransmitter systems (e.g. serotonergic and noradrenergic) would be especially useful. Beyond transmitter imaging, a consequent work-up of pharmacological intervention on cholinergic, serotonergic and noradrenergic pathways (e.g. via locus coeruleus) (Masilamoni *et al.*, 2017) may add to improve therapy and enhance our understanding of transmitters involved in FoG.

What imaging studies should we be doing next?

Important shortcomings of the neuroimaging studies conducted in FoG to date are the small number of patients and clinical diversity of subjects that have been included. Therefore, future imaging studies need to examine large and 'well phenotypically described' patients, ideally harmonizing protocols and pooling data across international centres. Combining in-depth characterization with imaging methods (e.g. in virtual reality paradigms or in combination with ambulatory neurophysiology) would shed novel light on a critical question, i.e. if FoG subtypes are reflected by distinct network substrates and failures or whether there may be various network patterns that will finally converge to a common pathway. There is a growing anticipation that

'big data' approaches may help to find the meaningful and reproducible key anatomical structures involved in the pathophysiology of FoG. In this sense, building large imaging cohorts (characterized with similar clinical assessments and testing paradigms) should help separate out the meaningful network nodes. This should ultimately help to find signals that (i) may not be seen in small cohorts owing to a lack of statistical power); (ii) are so central and consistent to FoG pathophysiology (across subtypes and heterogeneity) that they may show up as a common neuronal link; and (iii) define the imaging methods that lead to robust and replicable results.

Other insights may come from imaging studies focusing on causal sources of information rather than correlates of a clinical phenomenon. Lesion studies represent one such approach, including advances such as lesion network mapping that help address why some patients with brain lesions will display FoG symptoms. However, not all patients with similar lesions show FoG, and it will also be of interest to learn if there are unrecognized sources of vulnerability that make a lesion symptomatic or not. This will probably need large and well-characterized cohorts and deep metadata. Another causal source of information that remains to be fully leveraged for investigating FoG is symptom change following brain stimulation to specific neuroanatomical locations.

How can we harness neuromodulation for freezing of gait treatment?

Whilst the research techniques outlined above will help to dissect the vulnerability as well as the spatial and temporal network processes modulating FoG expression, our therapeutic approaches may ultimately be restricted to where in the brain neuromodulation therapy may effectively be applied. Therapeutic neuromodulation depends upon how targeted stimulation of a neuroanatomical substrate will provide meaningful access and the potential to modulate the functional network in the desired direction. To this end, neuroimaging and neurophysiological techniques such as EEG oscillations, DBS, TMS and tDCS may help to identify meaningful access points to the locomotor network, which may include a variety of cortical and subcortical hubs, as well as the cerebellum. All of these candidates should undergo rigorous clinical trials with a well-defined primary endpoint of specific FoG outcome.

Possibly, the locomotor network can be accessed at different points, and stimulating at different spots might mean accessing the same network at different (yet connected) anatomical positions. This is particularly true when analysing 'volumes of tissue activated' from DBS pulses across individuals in order to model (i) the tissue interactions; (ii) network connectivity; and (iii) correlated clinical effects (Horn *et al.*, 2017). This may help to generate heat maps or functional intervention maps with approaches similar to those derived by the lesion-network imaging techniques. By treating the volumes of tissue activated as 'surrogate lesions' it may be possible to determine how such stimulation may converge or diverge between clinical responders and non-responders. Such effects are likely to be mediated via the differential stimulation of nodes affecting common functional fibre tracts. This approach may help to discover 'sweet spots' for favourable access to the functional network as well as to identify 'no go areas', where stimulation (e.g. by DBS pulses) should be avoided to prevent a paradoxical worsening of gait. Such insights would inform both future implantation strategies, as well as DBS reprogramming approaches through conventional and innovative technology (Kuhn and Volkmann, 2017; Weiss and Massano, 2018).

One key aspect of these innovative strategies to treat FoG, which is known to be episodic, will be the need for on-demand systems. Thus, and in contrast to more stable clinical signs such as bradykinesia and rigidity, patients may benefit from a more efficient and temporally patterned intervention in FoG. Initial approaches may use individual strategies to intervene at meaningful transition points in the daily profile, when a freeze is most likely to occur or needs compensation. In this sense, a meaningful therapy would ideally prevent a freeze before it occurs, avoiding its potential clinical complications like falling. In this framework, therapy could be triggered by premonitory abnormal biosignatures when the network is in a stage of enhanced freezing susceptibility but still stable enough to enable effective forward progression of repetitive movement or gait (Scholten *et al.*, 2016; Fischer *et al.*, 2018; Handojoseno *et al.*, 2018; Hell *et al.*, 2018). We detailed above that meaningful neurophysiological signatures might become available from different parts of a multilevel system including basal ganglia, cortex and muscle, not withstanding kinematic time series from sensors that also have substantial potential as reviewed elsewhere (Mancini *et al.*, 2019). There is a rich potential armamentarium to prevent a freezing episode during a state of increased freezing susceptibility. As such, closed-loop therapy may embrace DBS techniques on several candidate levels of the 'freezing network' including STN, SNr or PPN, but also cortical areas of interest, e.g. with TMS or through subdural electrode. As neuromodulation technology becomes more and more differentiated from a technological standpoint, the time is ripe to customize closed-loop applications to intervene with such susceptibility states in order to 'reset' a functional network before symptoms emerge (Little *et al.*, 2013; Arlotti *et al.*, 2018; Weiss and Massano, 2018; Velisar *et al.*, 2019). Similarly, temporally adaptive cognitive interventions would also be feasible, i.e. in setting acoustic or visual cues when a gait pattern is becoming increasingly irregular before transitioning into a FoG event (Gilat *et al.*, 2018; Ginis *et al.*, 2018). Such 'cognitive' interventions would help to stabilize motor integration preventing a freeze. Moreover, they will need to be amenable for daily living and operate in an on-demand fashion rather than

relying on strategies that are likely to habituate, such as a constant metronome or visual cue.

Conclusion

This review has highlighted the major challenges for our understanding of FoG, and thus improving its treatment. We assert that the multimodal approach to this review provides valuable clues to identify meaningful signatures of FoG that may benefit from specific treatment strategies. Importantly, the methodological domains in this review begin to complement each other in fruitful ways. This may pave the way to a comprehensive model and towards personalized novel therapeutic avenues to better tackle the deteriorating and seemingly enigmatic clinical challenge of FoG.

Acknowledgement

With special thanks to Professor Martin Sarter for providing slides for the presentation at the Leuven Freezing of Gait Conference.

Funding

We would like to thank 'The International Parkinson and Movement Disorder Society' and the 'Research Foundation Flanders' for financial support of the *Second International Workshop on Freezing of Gait* in Leuven, Belgium from June 6–8, 2018 (https://kuleuvencongres.be/FOG2018). D.W. received research support from the Michael J Fox Foundation and the German Research Council (DFG; WE5375/1-1; WE5375/1-3). M.D.F. is supported by funding from the NIH (R01MH113929), the Nancy Lurie Marks Foundation and the Dystonia Medical Research Foundation. N.I.B. reports research support from NIH grants P01 NS015655, RO1 NS070856, P50 NS091856, the Department of Veterans Affairs grant I01 RX001631, and the Michael J. Fox Foundation. S.A.F. was supported by the Curtis Family Foundation and Sartain Lanier Family Foundation. A.N. received research support by the European Commission, the Research Foundation Flanders, the King Baudouin Funds, KU Leuven Internal Funds, Jacques and Gloria Gossweiler Foundation, Michael J Fox Foundation. M.H. is supported by the NINDS Intramural Program. S.J.G.L. is supported by an Australian NHMRC-ARC Dementia Fellowship #1110414.

Competing interests

D.W. received research support, speakers honoraria from Medtronic, Abott (formerly St Jude), Boston Scientific, Abbvie; received consultant fees from STADA. M.D.F has submitted intellectual property on using brain connectivity to guide brain stimulation. S.A.F. has received honoraria from Lundbeck, Teva, Sunovion, Biogen, Acadia, Neuroderm, Acorda, CereSpir. Grants support from Ipsen, Medtronic, Boston Scientific, Teva, US World Meds, Sunovion Therapeutics, Vaccinex, Voyager, Jazz Pharmaceuticals, Lilly, CHDI Foundation, Michael J. Fox Foundation, NIH- U10-NS077366-01, Royalties: Demos, Blackwell Futura, Springer for textbooks, Uptodate, Other Bracket Global LLC, CNS Ratings LLC. M.H. may accrue revenue on US Patent #6,780,413 B2 (Issued: August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He is on the Medical Advisory Boards of CALA Health and Brainsway. He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, and Elsevier. M.H's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by Merz for treatment studies of focal hand dystonia, Allergan for studies of methods to inject botulinum toxins, Medtronic, Inc. for a study of DBS for dystonia, and CALA Health for studies of a device to suppress tremor. S.J.G.L. has received personal grant support from an NHMRC-ARC Dementia Fellowship (1110414) and funding to Fore-Front, a collaborative research group at the Brain and Mind Centre University of Sydney, from the National Health and Medical Research Council Program (1132524), Dementia Research Team (1095127) and Centre of Research Excellence (1060992, 1152945) grants.

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