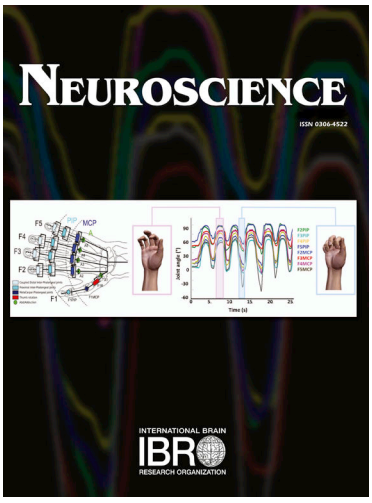
Journal Pre-proofs



Review

Potential non-invasive brain stimulation targets to alleviate freezing of gait in Parkinson's disease

Alexandra Potvin-Desrochers, Caroline Paquette

PII: S0306-4522(21)00284-0
DOI: https://doi.org/10.1016/j.neuroscience.2021.05.037
Reference: NSC 20221

To appear in: *Neuroscience*

Received Date: 20 March 2021
Revised Date: 14 May 2021
Accepted Date: 31 May 2021

Please cite this article as: A. Potvin-Desrochers, C. Paquette, Potential non-invasive brain stimulation targets to alleviate freezing of gait in Parkinson's disease, *Neuroscience* (2021), doi: https://doi.org/10.1016/j.neuroscience.2021.05.037

Potential non-invasive brain stimulation targets to alleviate freezing of gait in Parkinson's disease

Alexandra Potvin-Desrochers, MSc [a,b,c] & Caroline Paquette*, PhD [a,b,c]

[a] Department of Kinesiology and Physical Education, Currie Gymnasium, 475 Pine Avenue West, McGill University, Montréal, Québec, H2W 1S4, Canada
[b] Integrated Program in Neuroscience, Montreal Neurological Institute, 3801 University Street, McGill University, Montréal, Québec, H3A 2B4, Canada
[c] Centre for Interdisciplinary Research in Rehabilitation (Jewish Rehabilitation Hospital Research Site), 3205 Place Alton-Goldbloom, Laval, Québec, H7V 1R2, Canada

Corresponding author: Caroline Paquette, Department of Kinesiology and Physical Education, Currie Gymnasium, 475 Pine Avenue West, McGill University, Montréal, Québec, H2W 1S4, Canada
Email: caroline.paquette@mcgill.ca, Phone: 514-398-4184 x00890.

Word count: 4,904
Running Title: NIBS targets for freezing of gait
Keywords: freezing of gait, Parkinson's disease, non-invasive brain stimulation, repetitive transcranial magnetic stimulation, transcranial direct-current stimulation

Funding: This work was supported by Parkinson Canada (#2016-987). Alexandra Potvin-Desrochers is supported by Parkinson Canada and Healthy Brain Healthy Lives.

Conflict of interest: none

Abstract

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease (PD). Although FOG reduces quality of life, affects mobility and increases the risk of falls, there are little to no effective treatments to alleviate FOG. Non-invasive brain stimulation (NIBS) has recently yielded attention as a potential treatment to reduce FOG symptoms however, stimulation parameters and protocols remain inconsistent and require further research. Specifically, targets for stimulation require careful review. Thus, with current neuroimaging and neuro-electrophysiological evidence, we consider potential cortical targets thought to be involved in the pathophysiology of FOG according to the Interference model, and within reach of NIBS. We note that the primary motor cortex, the supplementary motor area and the dorsolateral prefrontal cortex have already drawn attention as NIBS targets for FOG, but based on neuroimaging evidence the premotor cortex, the medial prefrontal cortex, the cerebellum, and more particularly, the posterior parietal cortex should be considered as potential regions for stimulation. We also discuss different methodological considerations, such as stimulation type, medication state, and hemisphere to target, and future perspectives for NIBS protocols in FOG.

Introduction

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease (PD) that affects 38% of adults with early PD and up to 79% of individuals with advanced PD (Tan et al., 2011). Characterized by a brief and sudden inability to take a step despite the intention to walk (Nutt et al., 2011), FOG is considered an episodic phenomenon associated with specific triggers generally requiring a quick change in motor programs, solving problems, selecting a response under pressure or inhibiting inappropriate responses (Snijders et al., 2007; Nutt et al., 2011).

Although FOG reduces quality of life by affecting mobility and increasing the risk of falls (Bloem et al., 2004), current evidence is not sufficient to identify effective and reliable treatments to alleviate FOG (Fasano and Lang, 2015; Nonnekes et al., 2015). While L-DOPA therapy (Bloem et al., 2015), deep brain stimulation (Gilat et al., 2018) and exercises-based interventions (Tomlinson et al., 2012; Schlenstedt et al., 2018; Clerici et al., 2019; Silva-Batista et al., 2020) seem to have beneficial effects on posture and gait, they have variable effects on FOG itself. Cueing strategies have been shown to have transient positive effects on FOG but they do not reliably prevent FOG episodes (Delgado-alvarado et al., 2019). Current therapeutic interventions for FOG lack efficacy likely because they do not specifically target neural mechanisms associated with FOG. There is thus a pressing need to develop more focus and evidence-based interventions to better manage and further reduce FOG.

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are two common types of non-invasive brain stimulation (NIBS) that have the ability to either reduce or increase excitability of the cortical region stimulated, with beneficial effects on motor symptoms outlasting the stimulation period (Paquette et al., 2011; Lewis et al., 2016; Chen and Chen, 2019). Such beneficial effects can be achieved with NIBS by training the brain to use favorable or alternative circuits to those affected (Paquette and Thiel, 2012). A recent meta-analysis (Kim et al., 2019) and a systematic review (Nardone et al., 2020) concluded that NIBS show beneficial effect on FOG, but the optimal protocol is yet to be determined. Indeed, not only does stimulation type, duration, frequency, and intensity need be determined, but targets for stimulation also need careful review. Thus, in the perspective of addressing one of these issues, the purpose of this conceptual literature review is, for the first time, consider potential cortical targets accessible for NIBS intervention specifically for FOG, based on existing neuroimaging and neuro-electrophysiological literature. Previous work (Benninger and Hallett, 2015; Madrid and Benninger, 2021) has already reviewed NIBS for PD (motor and non-motor symptoms), but minimally addressing FOG. Even though reporting on multiple FOG NIBS studies, they only discussed the effectiveness of existing NIBS studies for FOG without including any potential targets for FOG beyond what had been already done in existing studies. We believe that we offer a more comprehensive and deep understanding of the potential of NIBS for FOG, as we do not simply review current NIBS studies for FOG, but also review neuroimaging and neurophysiological studies to guide the development of evidence-based NIBS interventions for FOG. Therefore, the hypothesized neural mechanisms of FOG will first be introduced, followed by a discussion of potential cortical targets for FOG, considerations and futures perspectives for NIBS protocols in FOG.

Neural mechanisms of FOG

Although the precise causes of FOG remain unknown, many hypotheses arose to explain its pathophysiology (for review (Nutt et al., 2011; Nieuwboer and Giladi, 2013)) with most based around a specific trigger, or category of triggers. An hypothesis suggests that FOG would be associated with less automatic processes so that when normally automated movements, such as gait (Nutt et al., 2011) are performed, more stress is directed toward voluntary mechanisms rather than automatic pathways (Vandenbossche et al., 2013). Impaired visuospatial skills and poor perceptual judgement are also thought to contribute to the occurrence of FOG, especially in narrow passages (Almeida and Lebold, 2010; Cowie et al., 2012; Nantel et al., 2012). FOG is also seen as the result of executive dysfunction occurring during increased demands on problem solving, attention division, attention shift and response inhibition (Snijders et al., 2007; Nutt et al., 2011).

However, the most accepted hypothesis for FOG remains the Interference model initially proposed by Lewis and Shine's group (Lewis and Barker, 2009; Shine et al., 2013b; Lewis and Shine, 2016; Ehgoetz Martens et al., 2018), and later named by Nieuwboer and Giladi (Nieuwboer and Giladi, 2013). This hypothesis provides a model that explains most FOG triggers together, and thus, the network failure nature of FOG. Based on the Interference model, FOG would be the paroxysmal result of a set-shifting problem between cognitive, limbic and motor cortico-basal ganglia pathways (Figure 1A) all functionally converging to the globus pallidus internal (GPi; Figure 1B). Specifically, because of the dopamine depletion in the basal ganglia circuity, the overwhelming increase in neural inputs (i.e. cognitive, limbic and motor) arising from different FOG triggers leads to an overload at the striatum. This causes a transient overactivity of the GPi, and thus, a temporary oscillatory overinhibition of the thalamus and brainstem leading to FOG. Furthermore, when a conflicting response arises due to a FOG trigger, the hyperdirect pathway is solicited, increasing subthalamic nucleus (STN) activity. The latter is believed to exacerbate the oscillatory output from the GPi and affects cerebellar output, contributing to the emergence of the trembling knees associated with FOG (Lewis and Shine, 2016). The Interference model has recently been identified as the probable common and ultimate pathway of FOG in individuals with vulnerable locomotor network (i.e. PD, other disorders, lesions, genes, etc.; Weiss et al., 2019).

NIBS effects on FOG mechanisms

Potential mechanisms for the beneficial effects of NIBS on FOG are abundant. Although no evidence currently exists for NIBS acting on compensatory circuits in FOG, it is conceivable that NIBS uses alternative intact circuits to favor locomotion with less FOG. Modulating the excitability of dysfunctional brain regions in FOG could normalize their activity, favoring more effective neural processing for gait and in turn, reduce FOG. Alternatively, NIBS could modify cortical excitability at the stimulation site, but also modulate the activity and the neurotransmitter function of the network of structures linked to that site, including deeper structures not accessible by NIBS (Tremblay et al., 2020). This is especially interesting for FOG as it likely emerges from a network dysfunction (Potvin-Desrochers et al., 2019), whereas cortical

stimulation could potentially reinstated an equilibrium in the activity of the basal ganglia to avoid FOG (Figure 1C). It has also been shown that high-frequency rTMS has the capacity to induce a significant release of endogenous dopamine in the striatum of healthy and mild PD individuals (Strafella et al., 2001, 2003, 2005). This may hold potential to increase depleted neural reserves thought to be involved in the striatum overload occurring prior to FOG episodes (Lewis and Barker, 2009; Shine et al., 2013b; Lewis and Shine, 2016). The following sections will review neuroimaging and neuro-electrophysiological evidence of potential areas hypothesized to be involved in the pathophysiology of FOG according to the Interference model, as potential targets for NIBS.

Potential cortical targets for NIBS

The potential targets for FOG presented below are the cortical and NIBS-accessible regions of the Interference model (Figure 1C).

Motor targets

Areas part of the motor loop of the Interference model include the primary motor cortex (M1), the premotor cortex (PMC), and the supplementary motor area (SMA). Targeting these regions with NIBS could potentially rebalance the connectivity of the motor cortical areas with the motor striatum and the STN.

Primary motor cortex

M1 is the main motor output, releasing motor commands through the corticospinal tract and playing a central role in executing locomotion (Takakusaki, 2013). In FOG, M1 is atrophied (Vastik et al., 2017), has reduced metabolism at rest (Gallardo et al., 2018) and reduced activity during motor arrests in a virtual reality pedalling paradigm (Shine et al., 2013a). Excitatory NIBS applied on M1 could thus potentially improve FOG. Targeting M1 could also increase neural reserve by increasing availability of dopamine in the putamen, contributing to reduced striatal processing overload thought to occur before a FOG episode (Strafella et al., 2001, 2003, 2005). Increasing the excitability of M1 could also contribute to a better recruitment of this area when needed, and thus, strengthen reliability of the motor output to minimize FOG. Consistent with this idea, the majority of NIBS studies applying on M1 in FOG found significant immediate and long-term positive effects on multiple outcomes such as gait parameters, FOG severity and UPDRS, following one or multiple sessions of excitatory rTMS or tDCS applied on M1 representation of the leg area (Lee et al., 2014; Valentino et al., 2014; Kim et al., 2015; Chang et al., 2017b). We noticed that one study that did not use the leg area of M1 as the target of NIBS did not find any improvement in FOG or gait (Kim et al., 2018). Thus, when stimulating M1 to improve FOG, the leg representation is likely the ideal area to target.

Supplementary motor area

The SMA is a motor region that plays a critical role in gait preparation, especially during gait initiation through anticipatory postural adjustments (Takakusaki, 2013). Along with the STN, it is also part of the hyperdirect pathway, a fast-acting inhibitory motor network, that has been hypothesized to be overly

active in FOG (Lewis and Shine, 2016). The SMA has been extensively studied in FOG, with numerous changes found in its structure (Fling et al., 2013; Vastik et al., 2017; Hall et al., 2018) and function (Snijders et al., 2011; Fling et al., 2014; Shine et al., 2014; Gilat et al., 2015; Butler et al., 2017; Mitchell et al., 2018). Overall, neuroimaging studies demonstrate that during tasks mimicking walking, SMA activity is reduced in individuals with FOG (Snijders et al., 2011; Gilat et al., 2015). However, during real walking tasks, SMA recruitment is increased and even further during a FOG episode (Shine et al., 2014; Mitchell et al., 2018). Its functional connectivity with the mesencephalic and cerebellar locomotor regions as well as the STN is increased (Fling et al., 2014). Recordings of lateralized readiness potentials from the SMA also suggest that motor preparation occurs earlier and to a greater extent in FOG (Butler et al., 2017). All this evidence demonstrates that a substantial increase in SMA and hyperdirect pathway recruitment may be associated with FOG. By decreasing excitability of the SMA, we could potentially reduce the likelihood of recruiting the hyperdirect pathway and ultimately avoid FOG. Interestingly, studies using SMA NIBS to reduce FOG have only investigated the potential of excitatory stimulation. Unsurprisingly, three studies using excitatory protocols did not find any effect of the NIBS on FOG and gait after one session of high-frequency rTMS (Lee et al., 2014), excitatory theta-burst rTMS (Brugger et al., 2020) or anodal tDCS (Lu et al., 2018). Other studies did however demonstrate short- and long-term improvements in FOG severity, gait parameters and UPDRS, but only following multiple sessions of excitatory SMA rTMS (Kim et al., 2018; Ma et al., 2019; Mi et al., 2019), although assessing FOG subjectively through questionnaire or objectively with a very small sample size (n=6) (Kim et al., 2018). Thus, future studies should explore the potential of inhibitory NIBS on FOG.

Premotor cortex

The PMC is an area known to use visuomotor information to generate motor programs, and thus, is essential for sensory-guided gait initiation (Takakusaki, 2013). Reduced activity and glucose metabolism of the PMC has been noted when individuals with FOG perform turns in a virtual reality pedalling paradigm (Gilat et al., 2015) and during real walking (Tard et al., 2015). In contrast, another study found increased metabolism of the PMC after participants completed a real complex steering walking task including several turns (Mitchell et al., 2018). As functional changes in PMC have been observed in FOG during real walking tasks (Tard et al., 2015; Mitchell et al., 2018), PMC could be a target for NIBS. However, because of the incongruency in the results of the neuroimaging studies, both inhibitory and excitatory protocols should be compared when targeting PMC. Only one study increased the excitability of the left PMC in individuals with FOG during a single session of rTMS, by applying theta-burst stimulation, a type of patterned rTMS, without any changes in the objective assessment of FOG or the kinematic parameters of gait (Tard et al., 2016). It is unclear whether the lack of significant improvement in FOG results from the stimulation site, an insufficient dose consisting of a single session of stimulation, the excitatory nature of the protocol, or the theta-burst stimulation itself which effects are still not well characterized in PD (for a review (Suppa et al., 2016)). Thus, more studies should explore PMC as a potential target to reduce FOG through NIBS.

Cognitive targets

The dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC) are the two cognitive cortical regions of the Interference model involved in the pathophysiology of FOG. Increasing their excitability could upregulate their functions, dysfunctional in FOG.

Posterior parietal cortex

The PPC is a key area integrating sensorimotor information to guide motor programs, and thus is fundamental to visuospatial processing and planning of locomotion (Culham et al., 2006; Drew and Marigold, 2015; Marigold and Drew, 2017; Hinton et al., 2019). Impaired visuospatial skills and poor perceptual judgement have been hypothesized to contribute to the occurrence of FOG (Almeida and Lebold, 2010; Cowie et al., 2012; Nantel et al., 2012), and thus, the PPC could play a role in these altered functions. Despite multiple evidence of altered volume (Kostić et al., 2012; Rubino et al., 2014; Pietracupa et al., 2018), connectivity (Hall et al., 2018), activity (Shine et al., 2013a, 2014; Gilat et al., 2015; Mi et al., 2017; Piramide et al., 2020) and metabolism (Bartels et al., 2006; Tard et al., 2015; Mitchell et al., 2018) of the PPC in FOG, no studies attempted to apply NIBS on this area. Because of this substantial alteration in PPC function and structure in FOG, more attention should be directed to the PPC as a target for NIBS to improve FOG. Evidence from neuroimaging studies generally support decreased parietal control in individuals with FOG, especially when performing a task mimicking walking, when producing effective walking and at rest (Bartels et al., 2006; Gilat et al., 2015; Mitchell et al., 2018; Piramide et al., 2020). However, how PPC is altered during real FOG episodes remains to be determined. Motor arrests that occurred during a foot pedalling task are associated with increased activity in the PPC (Shine et al., 2013a), but when transitioning from effective walking to real FOG episodes, PPC oscillatory activity is substantially decreased (Shine et al., 2014). Thus, both inhibitory and excitatory NIBS protocols should be assessed, although it seems more likely that facilitating recruitment of the PPC would enhance visuospatial processing, a compensatory mechanism to avoid FOG.

Dorsolateral prefrontal cortex

The DLPFC plays a central role in executive functions, dysfunctional in FOG (Amboni et al., 2008; Naismith et al., 2010; Nutt et al., 2011; Vandenbossche et al., 2011). Indeed, in PD individuals with FOG, DLPFC activity is significantly increased during turns and motor arrests of a pedaling task in a virtual reality walking paradigm (Shine et al., 2013a; Gilat et al., 2015), and its glucose metabolism is increased during a real complex walking task (Mitchell et al., 2018). Currently, it is difficult to determine whether this increased recruitment of DLPFC contributes to FOG or whether it is part of a compensatory mechanism. Neuroimaging studies confirm that the DLPFC is a potential target to improve FOG (Shine et al., 2013a; Gilat et al., 2015; Mitchell et al., 2018), and results of the few studies that applied NIBS on the DLPFC in FOG demonstrate the potential of excitatory stimulation on this area. While one small and interrupted study did not find any effect on gait (Rektorova et al., 2007), two studies did find positive and immediate effects on various gait parameters following one session of high-frequency rTMS (Lee et al., 2014) or anodal tDCS (Putzolu et al., 2018) over the DLPFC. These protocols however, had no effect on FOG severity. Another study compared the application of a dual-

site and dual-modality excitatory protocol (tDCS on DLPFC and rTMS on M1) with a standard rTMS M1 protocol in PD individuals with FOG (Chang et al., 2017a). Both protocols yield equivalent improvement in FOG, gait and UPDRS, but executive function was improved only when stimulating M1 simultaneously with the DLPFC (Chang et al., 2017a). Thus, increasing excitability of the DLPFC could potentiate executive functions and reduce FOG when triggers are encountered. Finally, high-frequency stimulation of the DLPFC could also induce dopamine release in the ipsilateral caudate nucleus (Strafella et al., 2001; Cho and Strafella, 2009) thus increasing neural reserve in the cortico-striatal-thalamic circuity to hopefully reduce FOG.

Limbic target

Limbic cortical regions of the Interference model include the medial prefrontal cortex (mPFC) and the anterior insula. The latter is unreachable with NIBS thus, not discussed here. NIBS of mPFC has the potential of better regulating its function and reinstating a balanced connection with the striatum to reduce FOG.

Medial prefrontal cortex

The mPFC is a key brain region for the regulation and the coordination of emotions, including stress (Etkin et al., 2011; McKlveen et al., 2015), a well-known trigger of FOG. Neuroimaging studies suggest that the mPFC of FOG individuals is underactive during walking (Tard et al., 2015), but is increased during FOG episodes (Shine et al., 2013a) or when there is a risk for freezing to occur (Maidan et al., 2015; Belluscio et al., 2019). However, it is unclear whether this increased activity of the mPFC is a compensatory mechanism or if it leads to the emergence of FOG. Therefore, we propose that mPFC is an appropriate target for NIBS in FOG, but insufficient evidence from neuroimaging studies exist to determine if increasing or decreasing excitability should be prioritized. A small sample size NIBS study demonstrated that multiple sessions of high-frequency rTMS over the mPFC improved FOG, UPDRS and gait variability (Dagan et al., 2017). Although these results should be considered carefully because the study had to be discontinued due to participants drop-out, they could indicate that increasing the excitability of the mPFC might help reduce FOG. Inhibitory protocol should also be investigated, as the role of the mPFC in FOG is still unclear.

Other possible target

The Interference model comprises multiple brain regions thought to be involved in FOG, but only a few are accessible by NIBS. Although not part of the original Interference model (Lewis and Barker, 2009; Shine et al., 2013b), the cerebellum was recently added due to its central role in the control muscle activity and coordination of posture and gait (Lewis and Shine, 2016). NIBS has thus the potential of enhancing cerebellum control of locomotion to reduce FOG.

Cerebellum

The cerebellar locomotor region (CLR), an area located in the mid-part of the cerebellar white matter and corresponding to the fastigial nucleus, has been shown to modulate locomotor rhythms and postural

muscle activity in cats (Mori et al., 1999). In humans, the cerebellum is thought to be involved in the coupling between gait preparation and execution (Richard et al., 2017). Neuroimaging studies demonstrate that individuals with FOG have multiple lesions in areas of the cerebellum all connected to the CLR (Fasano et al., 2017). To our knowledge, no studies reported changes in cerebellum or CLR activity and/or metabolism in FOG when performing a real or virtual walking task compared to PD individuals without FOG, or during FOG episodes. However, spontaneous activity at rest in the cerebellum is reduced in FOG (Mi et al., 2017) and its structural and functional connectivity is decreased with many cortical and subcortical regions (Schweder et al., 2010; Fling et al., 2014; Lenka et al., 2016; Wang et al., 2016; Bharti et al., 2018). Thus, upregulating the cerebellum, and more particularly the CLR, with excitatory NIBS could help ensure uninterrupted walking, as increased activity of the cerebellum has been identified in PD without FOG as a beneficial compensatory mechanism for defective functioning of the basal ganglia, especially for locomotion (Gilat et al., 2019). This hypothesis was partially confirmed by the only study that applied NIBS on the cerebellar hemisphere ipsilateral to the most affected side of individuals with FOG (Janssen et al., 2017). It was found that excitatory theta-burst rTMS improved gait speed, but neither excitatory nor inhibitory stimulation altered the duration of FOG episodes (Janssen et al., 2017). It is still unclear whether targeting CLR would lead to better outcomes.

NIBS considerations

This review focused on the specific candidate regions for NIBS treatment of FOG. Several factors other than site need significant research efforts to validate the effects of NIBS, and their duration, on FOG. As noted in previous reviews (Kim et al., 2019; Nardone et al., 2020), key considerations for an effective treatment of FOG include *medication state*, *stimulation type*, and *targeted hemisphere*.

Medication state of FOG participants during NIBS studies is heterogeneous. Most were performed ON-medication (Valentino et al., 2014; Lee et al., 2014; Kim et al., 2015, 2018; Tard et al., 2016; Dagan et al., 2017, 2018a; Putzolu et al., 2018, 2019; Ma et al., 2019; Mi et al., 2019) and a few OFF-medication (Rektorova et al., 2007; Janssen et al., 2017; Lu et al., 2018). Improved gait or FOG was observed during both ON- (Valentino et al., 2014; Kim et al., 2015, 2018; Ma et al., 2019; Mi et al., 2019; Putzolu et al., 2019) and OFF-medication (Janssen et al., 2017) state protocols. A recent meta-analytic review addressing the effects of NIBS on freezing of gait (Kim et al., 2019), suggests that the effects of medication state on NIBS in FOG should be explored as well to determine the overall best protocol. While an ON-state study seems more feasible, it is possible that the effects of NIBS are more important in the OFF-state and could outstand the difficulty of participants to be OFF-medication. Since dopaminergic medication effect on FOG is variable, it may be also necessary to consider freezing responsiveness to medication of each participant while selecting the medications-state of a study (Fasano and Lang, 2015).

Multiple types of NIBS exist. While tDCS remains easier and more practical to apply, rTMS offers a more focal and precise stimulation of the targeted region. Among rTMS protocols, the traditional high-

frequency and low-frequency stimulations protocols remains the most widely used, but patterned stimulation, such as theta-burst stimulation is attracting more attention considering its numerous advantages over traditional protocols (e.g., shorter stimulation time, longer after-effects; for a review: (Suppa et al., 2016)). Recently, studies introduced dual-mode stimulation combining two NIBS modalities. For example, protocols simultaneously stimulating bilateral M1s with tDCS and rTMS (one on each side), or preconditioning the rTMS stimulation of M1 with tDCS, improved motor performance in upper limb tasks and M1 excitability in healthy individuals (Park et al., 2014a, 2014b). Similar results were obtained in PD, where preconditioning M1 with anodal tDCS, followed by high-frequency rTMS further improved bilateral gait kinematics (Von Papen et al., 2014). Future studies should further investigate the potential of preconditioning rTMS with tDCS as these protocols seem to yield better effects.

The hemisphere to target can be hard to choose. Some consider FOG as a bilateral symptom usually appearing in later stages of PD, when other motor symptoms are already bilateral, and because it consists of a bilateral cessation of movement (Plotnik et al., 2005). Others have associated FOG to changes predominantly in the right (Bartels and Leenders, 2008) or in the left (Pieruccini-Faria et al., 2015) brain circuity. We thus suggest that the choice of the hemisphere to target should be based on the particularities of each cortical region. For example, the leg area of M1, the SMA and the mPFC are all regions located on the borders of the interhemispheric fissure. It may be more appropriate and feasible to stimulate both sides by targeting those regions at the midline. The selection of the hemisphere to target should also ponder the brain function lateralization. For example, considering the central role of the PPC in sensorimotor integration and the widely agreed right lateralization of spatial cognition to the right hemisphere (Cai et al., 2013; Corballis, 2014), studies should first focus on stimulating the right PPC to improve FOG. Nevertheless, left PPC stimulation could also be investigated as the left PPC seems to play a dominant role in motor attention (Rushworth et al., 2001b, 2001a). Another example is the DLPFC, for which most studies have targeted the left hemisphere in FOG (Rektorova et al., 2007; Chang et al., 2017b; Dagan et al., 2018b; Putzolu et al., 2018), likely because it is the main target for treatment refractory depression (Perera et al., 2016). However, bilateral activation of the DLPFC is associated with attention and task planning, with each side being specific to a subset of these functions (Vanderhasselt et al., 2009; Kaller et al., 2011). Furthermore, behavioral inhibition and visual change awareness have been located in the right DLPFC (Turatto et al., 2004; Shackman et al., 2009). Thus, the hemisphere to target should be based on the specific function desired to up or down regulate.

Future perspectives

Dual-site protocols

Although combining two stimulation sites in a NIBS session is still very recent, it seems to result in more important changes in cortical excitability or motor function compared to single-site (Chang et al., 2017b; Dagan et al., 2018b). As FOG likely emerges from more than one dysfunctional brain region, multi-target NIBS would likely yield more efficient results in reprogramming the brain to avoid FOG. In FOG, two studies applied dual-site protocols. First, simultaneous application of excitatory tDCS on left

DLPFC and excitatory rTMS on the dominant M1 resulted in similar improvements in gait and FOG than the excitatory M1 rTMS alone, but yielded better improvement of executive functions (Chang et al., 2017b). Similarly, excitatory tDCS applied simultaneously on M1 and DLPFC resulted in greater improvement on FOG and gait compared to tDCS of M1 alone (Dagan et al., 2018b). Therefore, dual-site stimulation could help prevent FOG by acting on the different regions proposed in the Interference model to play a critical role in the pathophysiology of FOG, and by potentially facilitating communication within its pathways.

NIBS to enhance physical training

In recent years, the potential therapeutic effect of combining NIBS with rehabilitation therapy to produce more robust and durable effects has been investigated (Paquette and Thiel, 2012). Improvements are seen on cognitive and motor functions in multiple clinical populations (Lim et al., 2010; Kakuda et al., 2013; Yamada et al., 2013; Barros Galvão et al., 2014; Gillick et al., 2014; Koganemaru et al., 2015; Zheng et al., 2015; Zumbansen et al., 2020; Edwards et al., 2021), including PD (Yang et al., 2013; Kaski et al., 2014b, 2014a; Moisello et al., 2015; Lawrence et al., 2018). In terms of gait improvement, beneficial effects of combining NIBS with a treadmill training or a balance and gait program have been shown in stroke (Wang et al., 2019) and PD (Yang et al., 2013; Kaski et al., 2014b, 2014a) to be beyond the effects of the rehabilitation training alone. Through the promotion of motor cortical plasticity, NIBS has the potential to prime the brain to use specific brain regions and reinforce beneficial circuits during the rehabilitative training to potentialize its after-effects on FOG (Tsagaris et al., 2016). Furthermore, training programs and NIBS have separately shown beneficial effects on FOG and gait of individuals with FOG (Tomlinson et al., 2012). We thus believe that studies should investigate the potential of combining NIBS and rehabilitation programs in FOG, as their effects could be potentialized when united (Tsagaris et al., 2016).

Targeting the appropriate cortical area based on the selected training (i.e. sensory cueing, balance & gait program, action observation training, etc.) could enhance the benefits observed on FOG. For example, stimulation of the SMA could be combined with a balance and gait training, due to the critical role of the SMA in balance control during gait. The choice of cortical stimulation site and the type of rehabilitative training could also be individualized to the type of FOG triggers patients mostly experienced. For example, if FOG is elicited mostly when a patient performs turns or walks through doorways, NIBS could target the PPC and be combined with a sensorimotor gait training. We thus suggest that future studies investigate the effects of NIBS and a physical training based on triggers and explore the effectiveness and the feasibility of individualization of such rehabilitative NIBS protocols.

In conclusion, FOG is a complex symptom of PD that still has no effective management therapy. By modulating the excitability of brain regions involved in the neural mechanisms of FOG, NIBS may have the potential to improve FOG. This review has identified cortical regions part of the Interference model that should be considered for NIBS intervention in FOG. While M1, SMA and DLPFC have already drawn the most attention as NIBS targets for FOG, PMC, mPFC, cerebellum, and more particularly

PPC, should now be considered. Evidence from neuroimaging studies should guide us on the type of excitability change to induce in these cortical areas to improve FOG. Finally, future studies should consider dual-site protocols, and combine NIBS with rehabilitation interventions, as all of these procedures have been shown to better improve motor function compared to traditional NIBS interventions.

Authors' roles

Alexandra Potvin-Desrochers

- Conception, Organization and Execution of the Research Project (1A,B,C)
- Writing and Review of the manuscript (3A,B)

Caroline Paquette

- Conception, Organization and Critique of the Research Project (1A,B)
- Review and Critique of the manuscript (3A,B)

Financial Disclosures

Alexandra Potvin-Desrochers

- Scholarships from Parkinson Canada, Healthy Brain Healthy Lives and Centre de recherche interdisciplinaire en réadaptation.
- Part-time consultant contract with Parkinson Québec

Caroline Paquette

- Employment by McGill University
- Grants from NSERC and CFI

References

Almeida QJ, Lebold CA (2010) Freezing of gait in Parkinson's disease: a perceptual cause for a motor impairment? J Neurol Neurosurg Psychiatry 81:513–518 Available at: https://www.ncbi.nlm.nih.gov/pubmed/19758982.

Amboni M, Cozzolino A, Longo K, Picillo M, Barone P (2008) Freezing of gait and executive functions in patients with Parkinson's disease. Mov Disord 23:395–400 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.21850.

Barros Galvão SC, Borba Costa Dos Santos R, Borba Dos Santos P, Cabral ME, Monte-Silva K (2014) Efficacy of coupling repetitive transcranial magnetic stimulation and physical therapy to reduce upper-limb spasticity in patients with stroke: A randomized controlled trial. Arch Phys Med Rehabil 95:222–229.

Bartels AL, de Jong BM, Giladi N, Schaahsma JD., P. MR, Veenma L, Pruim J, Balash Y, Youdim MBH, Leenders KL (2006) Striatal dopa and glucose metabolism in PD patients with freezing of gait. Mov Disord 21:1326–1332 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.20952.

Bartels AL, Leenders KL (2008) Brain imaging in patients with freezing of gait. Mov Disord 23:S461–S467 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.21912.

Belluscio V, Stuart S, Bergamini E, Vannozzi G, Mancini M (2019) The Association between Prefrontal Cortex Activity and Turning Behavior in People with and without Freezing of Gait. Neuroscience 416:168–176 Available at: https://doi.org/10.1016/j.neuroscience.2019.07.024.

Benninger DH, Hallett M (2015) Non-invasive brain stimulation for Parkinson's disease: Current concepts and outlook 2015. NeuroRehabilitation 37:11–24.

Bharti K, Suppa A, Pietracupa S, Upadhyay N, Giannì C, Leodori G, Di Biasio F, Modugno N, Petsas

N, Grillea G, Zampogna A, Berardelli A, Pantano P (2018) Abnormal Cerebellar Connectivity Patterns in Patients with Parkinson's Disease and Freezing of Gait. The Cerebellum 18:1–11 Available at: http://link.springer.com/10.1007/s12311-018-0988-4 [Accessed January 25, 2019].

Bloem BR, Hausdorff JM, Visser JE, Giladi N (2004) Falls and freezing of gait in Parkinson's disease: A review of two interconnected, episodic phenomena. Mov Disord 19:871–884 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.20115.

Bloem BR, Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N (2015) Freezing of gait: a practical approach to management. Pers View Lancet Neurol 14:768–778 Available at: http://dx.doi.org/10.1016/ [Accessed January 24, 2019].

Brugger F, Wegener R, Walch J, Galovic M, Hägele-Link S, Bohlhalter S, Kägi G (2020) Altered activation and connectivity of the supplementary motor cortex at motor initiation in Parkinson's disease patients with freezing. Clin Neurophysiol 131:2171–2180 Available at: https://doi.org/10.1016/j.clinph.2020.05.023.

Butler JS, Fearon C, Killane I, Waechter SM, Reilly RB, Lynch T (2017) Motor preparation rather than decision-making differentiates Parkinson's disease patients with and without freezing of gait. Clin Neurophysiol 128:463–471 Available at: https://www.sciencedirect.com/science/article/pii/S1388245716310318?via%3Dihub [Accessed April 8, 2019].

Cai Q, Van Der Haegen L, Brysbaert M (2013) Complementary hemispheric specialization for language production and visuospatial attention. Proc Natl Acad Sci U S A 110.

Chang WH, Kim MS, Park E, Cho JW, Youn J, Kim YK, Kim Y-H (2017a) Effect of Dual-Mode and Dual-Site Noninvasive Brain Stimulation on Freezing of Gait in Patients With Parkinson Disease. Arch Phys Med Rehabil 98:1283–1290 Available at:

https://www.sciencedirect.com/science/article/pii/S0003999317300722 [Accessed January 22, 2019].

Chang WH, Kim MS, Park E, Cho JW, Youn J, Kim YK, Kim YH (2017b) Effect of Dual-Mode and Dual-Site Noninvasive Brain Stimulation on Freezing of Gait in Patients With Parkinson Disease. Arch Phys Med Rehabil 98:1283–1290 Available at: http://dx.doi.org/10.1016/j.apmr.2017.01.011.

Chen KHS, Chen R (2019) Invasive and Noninvasive Brain Stimulation in Parkinson's Disease: Clinical Effects and Future Perspectives. Clin Pharmacol Ther 106:763–775.

Cho SS, Strafella AP (2009) rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. PLoS One 4:2–9.

Clerici I, Maestri R, Bonetti F, Ortelli P, Volpe D, Ferrazzoli D, Frazzitta G (2019) Land Plus Aquatic Therapy Versus Land-Based Rehabilitation Alone for the Treatment of Freezing of Gait in Parkinson Disease: A Randomized, Controlled Study. Phys Ther Available at: https://academic.oup.com/ptj/advance-article/doi/10.1093/ptj/pzz003/5290327 [Accessed January 22, 2019].

Corballis MC (2014) Left Brain, Right Brain: Facts and Fantasies. PLoS Biol 12.

Cowie D, Limousin P, Peters A, Hariz M, Day BL (2012) Doorway-provoked freezing of gait in Parkinson's disease. Mov Disord 27:492–499.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: What have we learned from neuroimaging? Neuropsychologia 44:2668–2684 Available at: https://www.sciencedirect.com/science/article/pii/S0028393205003568 [Accessed March 17, 2019].

Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, Manor B, Hausdorff JM (2018a) Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov

Disord 33:642–646.

Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, Manor B, Hausdorff JM (2018b) Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov Disord 33:642–646 Available at: http://doi.wiley.com/10.1002/mds.27300 [Accessed January 24, 2019].

Dagan M, Herman T, Mirelman A, Giladi N, Hausdorff JM (2017) The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. Exp Brain Res 235:2463–2472 Available at: http://link.springer.com/10.1007/s00221-017-4981-9 [Accessed January 24, 2019].

Delgado-alvarado M, Marano M, Santurtún A (2019) Nonpharmacological , Nonsurgical Treatments for Freezing of Gait in Parkinson ' s Disease : A Systematic Review Results Methods Identi fi cation and Selection of Studies. :1–11.

Drew T, Marigold DS (2015) Taking the next step: Cortical contributions to the control of locomotion. Curr Opin Neurobiol 33:25–33 Available at: http://dx.doi.org/10.1016/j.conb.2015.01.011.

Edwards JD, Black SE, Boe S, Boyd L, Chaves A, Chen R, Dukelow S, Fung J, Kirton A, Meltzer J, Moussavi Z, Neva J, Paquette C, Ploughman M, Pooyania S, Rajji TK, Roig M, Tremblay F, Thiel A (2021) Canadian Platform for Trials in Noninvasive Brain Stimulation (CanStim) Consensus Recommendations for Repetitive Transcranial Magnetic Stimulation in Upper Extremity Motor Stroke Rehabilitation Trials. Neurorehabil Neural Repair 35:103–116.

Ehgoetz Martens KA, Hall JM, Georgiades MJ, Gilat M, Walton CC, Matar E, Lewis SJG, Shine JM (2018) The functional network signature of heterogeneity in freezing of gait. Brain Available at: https://www.ncbi.nlm.nih.gov/pubmed/29444207.

Etkin A, Egner T, Kalisch R (2011) Emotional processing in anterior cingulate and medial prefrontal

cortex. Trends Cogn Sci 15:85–93 Available at: http://dx.doi.org/10.1016/j.tics.2010.11.004.

Fasano A, Laganiere SE, Lam S, Fox MD (2017) Lesions causing freezing of gait localize to a cerebellar functional network. Ann Neurol 81:129–141 Available at: https://www.ncbi.nlm.nih.gov/pubmed/28009063 [Accessed January 22, 2019].

Fasano A, Lang AE (2015) Unfreezing of gait in patients with Parkinson's disease. Lancet Neurol 14:675–677.

Fling BW, Cohen RG, Mancini M, Carpenter SD, Fair DA, Nutt JG, Horak FB (2014) Functional reorganization of the locomotor network in Parkinson patients with freezing of gait. PLoS One 9:e100291 Available at: https://www.ncbi.nlm.nih.gov/pubmed/24937008.

Fling BW, Cohen RG, Mancini M, Nutt JG, Fair DA, Horak FB (2013) Asymmetric pedunculopontine network connectivity in parkinsonian patients with freezing of gait. Brain 136:2405–2418 Available at: https://www.ncbi.nlm.nih.gov/pubmed/23824487 [Accessed December 5, 2018].

Gallardo MJ, Cabello JP, Corrales MJ, Torres-Donaire J, Bravo JJ, Talavera MP, León A, Vaamonde-Gamo J, Corrales J, Torres-Donaire J, Bravo JJ, Prado Talavera M, León A, Vaamonde-Gamo J (2018) Freezing of gait in Parkinson's disease: functional neuroimaging studies of the frontal lobe. Neurol Res 40:900–905 Available at: https://www.tandfonline.com/action/journalInformation?journalCode=yner20 [Accessed January 23, 2019].

Gilat M, Dijkstra BW, D'Cruz N, Nieuwboer A, Lewis SJG (2019) Functional MRI to Study Gait Impairment in Parkinson's Disease: a Systematic Review and Exploratory ALE Meta-Analysis. Curr Neurol Neurosci Rep 19.

Gilat M, Lígia Silva de Lima A, Bloem BR, Shine JM, Nonnekes J, Lewis SJG (2018) Freezing of gait: Promising avenues for future treatment. Parkinsonism Relat Disord 52:7–16 Available at:

https://www.sciencedirect.com/science/article/pii/S1353802018301238 [Accessed January 22, 2019].

Gilat M, Shine JM, Walton CC, O'Callaghan C, Hall JM, Lewis SJG (2015) Brain activation underlying turning in Parkinson's disease patients with and without freezing of gait: a virtual reality fMRI study. npj Park Dis 1:15020 Available at: https://www.nature.com/articles/npjparkd201520?__tw_private=1405483513.

Gillick BT, Krach LE, Feyma T, Rich TL, Moberg K, Thomas W, Cassidy JM, Menk J, Carey JR (2014) Primed low-frequency repetitive transcranial magnetic stimulation and constraint-induced movement therapy in pediatric hemiparesis: A randomized controlled trial. Dev Med Child Neurol 56:44–52.

Hall JM, Shine JM, Ehgoetz Martens KA, Gilat M, Broadhouse KM, Szeto JYY, Walton CC, Moustafa AA, Lewis SJG (2018) Alterations in white matter network topology contribute to freezing of gait in Parkinson's disease. J Neurol 265:1353–1364 Available at: http://link.springer.com/10.1007/s00415-018-8846-3 [Accessed April 8, 2019].

Hinton DC, Thiel A, Soucy JP, Bouyer L, Paquette C (2019) Adjusting gait step-by-step: Brain activation during split-belt treadmill walking. Neuroimage 202:116095 Available at: https://doi.org/10.1016/j.neuroimage.2019.116095.

Janssen AM, Munneke MAM, Nonnekes J, van der Kraan T, Nieuwboer A, Toni I, Snijders AH, Bloem BR, Stegeman DF (2017) Cerebellar theta burst stimulation does not improve freezing of gait in patients with Parkinson's disease. J Neurol 264:963–972 Available at: http://link.springer.com/10.1007/s00415-017-8479-y [Accessed January 22, 2019].

Kakuda W, Abo M, Nakayama Y, Kiyama A, Yoshida H (2013) High-frequency rTMS using a double cone coil for gait disturbance. Acta Neurol Scand 128:100–106 Available at:

http://doi.wiley.com/10.1111/ane.12085 [Accessed January 29, 2019].

Kaller CP, Rahm B, Spreer J, Weiller C, Unterrainer JM (2011) Dissociable Contributions of Left and Right Dorsolateral Prefrontal Cortex in Planning. Cereb Cortex 21:307–317 Available at: https://academic.oup.com/cercor/article-lookup/doi/10.1093/cercor/bhq096 [Accessed March 11, 2019].

Kaski D, Allum JH, Bronstein AM, Dominguez RO (2014a) Applying anodal tDCS during tango dancing in a patient with Parkinson's disease. Neurosci Lett 568:39–43 Available at: http://dx.doi.org/10.1016/j.neulet.2014.03.043.

Kaski D, Dominguez RO, Allum JH, Islam AF, Bronstein AM (2014b) Combining physical training with transcranial direct current stimulation to improve gait in Parkinson's disease: A pilot randomized controlled study. Clin Rehabil 28:1115–1124.

Kim MS, Chang WH, Cho JW, Youn J, Kim YK, Kim SW, Kim Y-H (2015) Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. Restor Neurol Neurosci 33:521–530 Available at: http://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/RNN-140489 [Accessed January 22, 2019].

Kim SJ, Paeng SH, Kang SY (2018) Stimulation in supplementary motor area versus motor cortex for freezing of gait in Parkinson's disease. J Clin Neurol 14:320–326.

Kim YW, Shin I-SS, Moon HI, Lee S-CC, Yoon SY (2019) Effects of non-invasive brain stimulation on freezing of gait in parkinsonism: A systematic review with meta-analysis. Park Relat Disord 64:82–89 Available at: https://www.sciencedirect.com/science/article/pii/S1353802019300756?via%3Dihub [Accessed March 13, 2019].

Koganemaru S, Sawamoto N, Aso T, Sagara A, Ikkaku T, Shimada K, Kanematsu M, Takahashi R,

Domen K, Fukuyama H, Mima T (2015) Task-specific brain reorganization in motor recovery induced by a hybrid-rehabilitation combining training with brain stimulation after stroke. Neurosci Res 92:29–38 Available at: http://dx.doi.org/10.1016/j.neures.2014.10.004.

Kostić VS, Agosta F, Pievani M, Stefanova E, Ječmenica-Lukić M, Scarale A, Špica V, Filippi M (2012) Pattern of brain tissue loss associated with freezing of gait in Parkinson disease. Neurology 78:409–416.

Lawrence BJ, Gasson N, Johnson AR, Booth L, Loftus AM (2018) Cognitive training and transcranial direct current stimulation in mild cognitive impairment: A randomized pilot trial. Parkinsons Dis 2018.

Lee SY, Kim M-SS, Chang H, Cho J-WW, Youn J-YY, Kim Y-HH, Chang WH, Cho J-WW, Youn J-YY, Kim Y-HH (2014) Effects of repetitive transcranial magnetic stimulation on freezing of gait in patients with Parkinsonism. Restor Neurol Neurosci 32:743–753 Available at: https://content.iospress.com/articles/restorative-neurology-and-neuroscience/rnn140397 [Accessed January 22, 2019].

Lenka A, Naduthota RM, Jha M, Panda R, Prajapati A, Jhunjhunwala K, Saini J, Yadav R, Dawn Bharath E, Pal PK (2016) Freezing of gait in Parkinson's disease is associated with altered functional brain connectivity. Parkinsonism Relat Disord 24:100–106.

Lewis PM, Thomson RH, Rosenfeld J V., Fitzgerald PB (2016) Brain Neuromodulation Techniques: A Review. Neuroscientist 22:406–421 Available at: http://journals.sagepub.com/doi/10.1177/1073858416646707 [Accessed January 29, 2019].

Lewis SJ, Barker RA (2009) A pathophysiological model of freezing of gait in Parkinson's disease. Park Relat Disord 15:333–338 Available at: https://www.ncbi.nlm.nih.gov/pubmed/18930430.

Lewis SJ, Shine JM (2016) The Next Step: A Common Neural Mechanism for Freezing of Gait.

Neurosci 22:72–82.

Lim JY, Kang EK, Paik NJ (2010) Repetitive transcranial magnetic stimulation for hemispatial neglect in patients after stroke: An open-label pilot study. J Rehabil Med 42:447–452.

Lu C, Amundsen Huffmaster SL, Tuite PJ, MacKinnon CD (2018) The effects of anodal tDCS over the supplementary motor area on gait initiation in Parkinson's disease with freezing of gait: a pilot study. J Neurol 265:2023–2032 Available at: http://link.springer.com/10.1007/s00415-018-8953-1 [Accessed January 22, 2019].

Ma J, Gao L, Mi T, Sun J, Chan P, Wu T (2019) Repetitive Transcranial Magnetic Stimulation Does Not Improve the Sequence Effect in Freezing of Gait. Parkinsons Dis 2019:1–8 Available at: https://www.hindawi.com/journals/pd/2019/2196195/.

Madrid J, Benninger DH (2021) Non-invasive brain stimulation for Parkinson's disease: Clinical evidence, latest concepts and future goals: A systematic review. J Neurosci Methods 347:108957 Available at: https://doi.org/10.1016/j.jneumeth.2020.108957.

Maidan I, Bernad-Elazari H, Gazit E, Giladi N, Hausdorff JM, Mirelman A (2015) Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures. J Neurol 262:899–908 Available at: http://link.springer.com/10.1007/s00415-015-7650-6 [Accessed January 23, 2019].

Marigold DS, Drew T (2017) Posterior parietal cortex estimates the relationship between object and body location during locomotion. Elife 6:1–24.

McKlveen JM, Myers B, Herman JP (2015) The Medial Prefrontal Cortex: Coordinator of Autonomic, Neuroendocrine and Behavioural Responses to Stress. J Neuroendocrinol 27:446–456.

Mi TM, Garg S, Ba F, Liu AP, Wu T, Gao LL, Chan P, McKeown MJ, Dan XJ, Chan P, McKeown MJ (2019) High-frequency rTMS over the supplementary motor area improves freezing of gait in

Parkinson's disease: a randomized controlled trial. Park Relat Disord 68:85–90 Available at: https://doi.org/10.1016/j.parkreldis.2019.10.009.

Mi TM, Mei SS, Liang PP, Gao LL, Li KC, Wu T, Chan P (2017) Altered resting-state brain activity in Parkinson's disease patients with freezing of gait. Sci Rep 7 Available at: https://www.ncbi.nlm.nih.gov/pubmed/29196699.

Mitchell T, Potvin-Desrochers A, Lafontaine A-L, Monchi O, Thiel A, Paquette C (2018) Cerebral Metabolic Changes Related to Freezing of Gait in Parkinson Disease. J Nucl Med 60:671–676 Available at: http://www.ncbi.nlm.nih.gov/pubmed/30315142%0Ahttp://jnm.snmjournals.org/lookup/doi/10.2967/jnumed.118.218248.

Moisello C, Blanco D, Fontanesi C, Lin J, Biagioni M, Kumar P, Brys M, Loggini A, Marinelli L, Abbruzzese G, Quartarone A, Tononi G, Di Rocco A, Ghilardi MF (2015) TMS Enhances Retention of a Motor Skill in Parkinson's Disease. Brain Stimul 8:224–230 Available at: https://www.sciencedirect.com/science/article/pii/S1935861X14003611 [Accessed February 1, 2019].

Mori S, Matsui T, Kuze B, Asanome M, Nakajima K, Matsuyama K (1999) Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J Neurophysiol 82:290–300.

Naismith SL, Shine JM, Lewis SJG (2010) The specific contributions of set-shifting to freezing of gait in Parkinson's disease. Mov Disord 25:1000–1004 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.23005.

Nantel J, McDonald JC, Tan S, Bronte-Stewart H (2012) Deficits in visuospatial processing contribute to quantitative measures of freezing of gait in Parkinson's disease. Neuroscience 221:151–156

Available at: https://www.ncbi.nlm.nih.gov/pubmed/22796080.

Nardone R, Versace V, Brigo F, Golaszewski S, Carnicelli L, Saltuari L, Trinka E, Sebastianelli L (2020) Transcranial magnetic stimulation and gait disturbances in Parkinson's disease: A systematic review. Neurophysiol Clin 50:213–225 Available at: https://doi.org/10.1016/j.neucli.2020.05.002.

Nieuwboer A, Giladi N (2013) Characterizing freezing of gait in Parkinson's disease: Models of an episodic phenomenon. Mov Disord 28:1509–1519 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.25683.

Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR (2015) Freezing of gait: a practical approach to management. Lancet Neurol 14:768–778 Available at: https://www-sciencedirect-com.proxy3.library.mcgill.ca/science/article/pii/S1474442215000411 [Accessed January 24, 2019].

Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A (2011) Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 10:734–744 Available at: http://www.sciencedirect.com/science/article/pii/S1474442211701430.

Paquette C, Sidel M, Radinska BA, Soucy JP, Thiel A (2011) Bilateral transcranial direct current stimulation modulates activation-induced regional blood flow changes during voluntary movement. J Cereb Blood Flow Metab 31:2086–2095.

Paquette C, Thiel A (2012) Rehabilitation interventions for chronic motor deficits with repetitive transcranial magnetic stimulation. J Neurosurg Sci 56:299–306.

Park E, Kim YH, Chang WH, Kwon TG, Shin Y Il (2014a) Effects of dual-mode non-invasive brain stimulation on motor function. Neurosci Lett 567:24–29 Available at: http://dx.doi.org/10.1016/j.neulet.2014.03.022.

Park E, Kim YH, Chang WH, Kwon TG, Shin Y Il (2014b) Interhemispheric Modulation of Dual-Mode,

Noninvasive Brain Stimulation on Motor Function. Neurosci Lett 567:24–29.

Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS (2016) The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. Brain Stimul 9:336–346 Available at: https://www.sciencedirect.com/science/article/pii/S1935861X16300389 [Accessed January 29, 2019].

Pieruccini-Faria F, Ehgoetz Martens KA, Silveira CRA, Jones JA, Almeida QJ (2015) Side of basal ganglia degeneration influences freezing of gait in parkinson's disease. Behav Neurosci 129:214–218.

Pietracupa S, Suppa A, Upadhyay N, Giannì C, Grillea G, Leodori G, Modugno N, Di Biasio F, Zampogna A, Colonnese C, Berardelli A, Pantano P (2018) Freezing of gait in Parkinson's disease: gray and white matter abnormalities. J Neurol 265:52–62 Available at: http://link.springer.com/10.1007/s00415-017-8654-1 [Accessed January 22, 2019].

Piramide N, Agosta F, Sarasso E, Canu E, Volontè MA, Filippi M (2020) Brain activity during lower limb movements in Parkinson's disease patients with and without freezing of gait. J Neurol Available at: https://doi.org/10.1007/s00415-019-09687-1.

Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM (2005) Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann Neurol 57:656–663 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/ana.20452.

Potvin-Desrochers A, Mitchell T, Gisiger T, Paquette C (2019) Changes in Resting-State Functional Connectivity Related to Freezing of Gait in Parkinson's Disease. Neuroscience 418:311–317 Available at: https://doi.org/10.1016/j.neuroscience.2019.08.042.

Putzolu M, Ogliastro C, Lagravinese G, Bonassi G, Trompetto C, Marchese R, Avanzino L, Pelosin E

(2019) Investigating the effects of transcranial direct current stimulation on obstacle negotiation performance in Parkinson disease with freezing of gait: A pilot study. Brain Stimul:6–8 Available at: https://linkinghub.elsevier.com/retrieve/pii/S1935861X19302906.

Putzolu M, Pelosin E, Ogliastro C, Lagravinese G, Bonassi G, Ravaschio A, Abbruzzese G, Avanzino L (2018) Anodal tDCS over prefrontal cortex improves dual-task walking in Parkinsonian patients with freezing. Mov Disord 33:1972–1973.

Rektorova I, Sedlackova S, Telecka S, Hlubocky A, Rektor I (2007) Repetitive transcranial stimulation for freezing of gait in Parkinson's disease. Mov Disord 22:1518–1519 Available at: http://doi.wiley.com/10.1002/mds.21289 [Accessed January 22, 2019].

Richard A, Van Hamme A, Drevelle X, Golmard JL, Meunier S, Welter ML (2017) Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. Neuroscience 358:181–189.

Rubino A, Assogna F, Piras F, Di Battista ME, Imperiale F, Chiapponi C, Spalletta G, Meco G (2014) Does a volume reduction of the parietal lobe contribute to freezing of gait in Parkinson's disease? Parkinsonism Relat Disord 20:1101–1103 Available at: https://www.sciencedirect.com/science/article/pii/S1353802014002612?via%3Dihub [Accessed April 8, 2019].

Rushworth MFS, Ellison A, Walsh V (2001a) Complementary localization and lateralization of orienting and motor attention. Nat Neurosci 4:656–661.

Rushworth MFS, Krams M, Passingham RE (2001b) The attentional role of the left parietal cortex: The distinct lateralization and localization of motor attention in the human brain. J Cogn Neurosci 13:698–710.

Schlenstedt C, Paschen S, Seuthe J, Raethjen J, Berg D, Maetzler W, Deuschl G (2018) Moderate

Frequency Resistance and Balance Training Do Not Improve Freezing of Gait in Parkinson's Disease: A Pilot Study. Front Neurol 9:1084 Available at: http://www.ncbi.nlm.nih.gov/pubmed/30619044 [Accessed April 8, 2019].

Schweder PM, Hansen PC, Green AL, Quaghebeur G, Stein J, Aziz TZ (2010) Connectivity of the pedunculopontine nucleus in parkinsonian freezing of gait. Neuroreport 21:914–916.

Shackman AJ, Mcmenamin BW, Maxwell JS, Greischar LL, Davidson RJ (2009) Right Dorsolateral Prefrontal Cortical Activity and Behavioral Inhibition. Available at: www.unizh.ch/ [Accessed March 11, 2019].

Shine JM, Handojoseno AMA, Nguyen TN, Tran Y, Naismith SL, Nguyen H, Lewis SJG (2014) Abnormal patterns of theta frequency oscillations during the temporal evolution of freezing of gait in Parkinson's disease. Clin Neurophysiol 125:569–576 Available at: https://www.sciencedirect.com/science/article/pii/S1388245713010420 [Accessed January 23, 2019].

Shine JM, Matar E, Ward PB, Bolitho SJ, Gilat M, Pearson M, Naismith SL, Lewis SJ (2013a) Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease. Brain 136:1204–1215 Available at: https://www.ncbi.nlm.nih.gov/pubmed/23485851.

Shine JM, Naismith SL, Lewis SJG (2013b) The differential yet concurrent contributions of motor, cognitive and affective disturbance to freezing of gait in Parkinson's disease. Clin Neurol Neurosurg 115:542–545 Available at: http://www.sciencedirect.com/science/article/pii/S0303846712003460.

Silva-Batista C, de Lima-Pardini AC, Nucci MP, Coelho DB, Batista A, Piemonte MEP, Barbosa ER, Teixeira LA, Corcos DM, Amaro E, Horak FB, Ugrinowitsch C (2020) A Randomized, Controlled

Trial of Exercise for Parkinsonian Individuals With Freezing of Gait. Mov Disord 35:1–12.

Snijders AH, Leunissen I, Bakker M, Overeem S, Helmich RC, Bloem BR, Toni I (2011) Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. Brain 134:59–72 Available at: https://www.ncbi.nlm.nih.gov/pubmed/21126990.

Snijders AH, Verstappen CC, Munneke M, Bloem BR (2007) Assessing the interplay between cognition and gait in the clinical setting. J Neural Transm 114:1315–1321 Available at: https://link.springer.com/article/10.1007/s00702-007-0781-x.

Strafella AP, Ko JH, Grant J, Fraraccio M, Monchi O (2005) Corticostriatal functional interactions in Parkinson's disease: A rTMS/[11C]raclopride PET study. Eur J Neurosci 22:2946–2952.

Strafella AP, Paus T, Barrett J, Dagher A (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 21:RC157 Available at: http://www.ncbi.nlm.nih.gov/pubmed/11459878.

Strafella AP, Paus T, Fraraccio M, Dagher A (2003) Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126:2609–2615.

Suppa A, Huang Y-Z, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, Ziemann U, Rothwell JC (2016) Ten Years of Theta Burst Stimulation in Humans: Established Knowledge, Unknowns and Prospects. Brain Stimul 9:323–335 Available at: https://www.sciencedirect.com/science/article/pii/S1935861X16300018 [Accessed January 29, 2019].

Takakusaki K (2013) Neurophysiology of gait: From the spinal cord to the frontal lobe. Mov Disord 28:1483–1491 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/mds.25669.

Tan DM, McGinley JL, Danoudis ME, Iansek R, Morris ME (2011) Freezing of gait and activity limitations in people with Parkinson's disease. Arch Phys Med Rehabil 92:1159–1165 Available at:

https://www.ncbi.nlm.nih.gov/pubmed/21704798.

Tard C, Delval A, Devos D, Lopes R, Lenfant P, Dujardin K, Hossein-Foucher C, Semah F, Duhamel A, Defebvre L, Le Jeune F, Moreau C (2015) Brain metabolic abnormalities during gait with freezing in Parkinson's disease. Neuroscience 307:281–301 Available at: https://www.ncbi.nlm.nih.gov/pubmed/26341909.

Tard C, Devanne H, Defebvre L, Delval A (2016) Single session intermittent theta-burst stimulation on the left premotor cortex does not alleviate freezing of gait in Parkinson's disease. Neurosci Lett 628:1–9 Available at: https://www.sciencedirect.com/science/article/pii/S0304394016303913 [Accessed January 22, 2019].

Tomlinson CL, Patel S, Meek C, Clarke CE, Stowe R, Shah L, Sackley CM, Deane KH, Herd CP, Wheatley K, Ives N (2012) Physiotherapy versus placebo or no intervention in Parkinson's disease. In: Cochrane Database of Systematic Reviews (Tomlinson CL, ed), pp CD002817. Chichester, UK: John Wiley & Sons, Ltd. Available at: http://doi.wiley.com/10.1002/14651858.CD002817.pub3 [Accessed January 24, 2019].

Tremblay S, Tuominen L, Zayed V, Pascual-Leone A, Joutsa J (2020) The study of noninvasive brain stimulation using molecular brain imaging: A systematic review. Neuroimage 219:117023 Available at: https://doi.org/10.1016/j.neuroimage.2020.117023.

Tsagaris KZ, Labar DR, Edwards DJ (2016) A Framework for Combining rTMS with Behavioral Therapy. Front Syst Neurosci 10:82 Available at: http://journal.frontiersin.org/article/10.3389/fnsys.2016.00082/full [Accessed February 1, 2019].

Turatto M, Sandrini M, Miniussi C (2004) The role of the right dorsolateral prefrontal cortex in visual change awareness. Neuroreport 15:2549–2552.

Valentino F, Cosentino G, Brighina F, Pozzi NG, Sandrini G, Fierro B, Savettieri G, D'Amelio M,

Pacchetti C (2014) Transcranial direct current stimulation for treatment of freezing of gait: A cross-over study. Mov Disord 29:1064–1069.

Vandenbossche J, Deroost N, Soetens E, Coomans D, Spildooren J, Vercruysse S, Nieuwboer A, Kerckhofs E (2013) Freezing of gait in Parkinson's disease: disturbances in automaticity and control. Front Hum Neurosci 6 Available at: https://www.frontiersin.org/articles/10.3389/fnhum.2012.00356/pdf.

Vandenbossche J, Deroost N, Soetens E, Spildooren J, Vercruysse S, Nieuwboer A, Kerckhofs E (2011) Freezing of Gait in Parkinson Disease Is Associated With Impaired Conflict Resolution. Neurorehabil Neural Repair 25:765–773 Available at: http://journals.sagepub.com/doi/abs/10.1177/1545968311403493.

Vanderhasselt MA, de Raedt R, Baeken C (2009) Dorsolateral prefrontal cortex and Stroop performance: Tackling the lateralization. Psychon Bull Rev 16:609–612.

Vastik M, Hok P, Valosek J, Hlustik P, Mensikova K, Kanovsky P (2017) Freezing of gait is associated with cortical thinning in mesial frontal cortex. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 161:389–396 Available at: https://doi.org/10.5507/bp.2017.035 [Accessed December 5, 2018].

Von Papen M, Fisse M, Sarfeld AS, Fink GR, Nowak DA (2014) The effects of 1 Hz rTMS preconditioned by tDCS on gait kinematics in Parkinson's disease. J Neural Transm 121:743–754.

Wang M, Jiang S, Yuan Y, Zhang L, Ding J, Wang J, Zhang J, Zhang K, Wang J (2016) Alterations of functional and structural connectivity of freezing of gait in Parkinson's disease. J Neurol 263:1583–1592 Available at: https://www.ncbi.nlm.nih.gov/pubmed/27230857.

Wang RY, Wang FY, Huang SF, Yang YR (2019) High-frequency repetitive transcranial magnetic stimulation enhanced treadmill training effects on gait performance in individuals with chronic

stroke: A double-blinded randomized controlled pilot trial. Gait Posture 68:382–387 Available at: https://doi.org/10.1016/j.gaitpost.2018.12.023.

Weiss D, Schoellmann A, Fox MD, Bohnen NI, Factor SA, Nieuwboer A, Hallett M, Lewis SJG (2019) Freezing of gait : understanding the complexity of an enigmatic phenomenon. Brain 143:14–30.

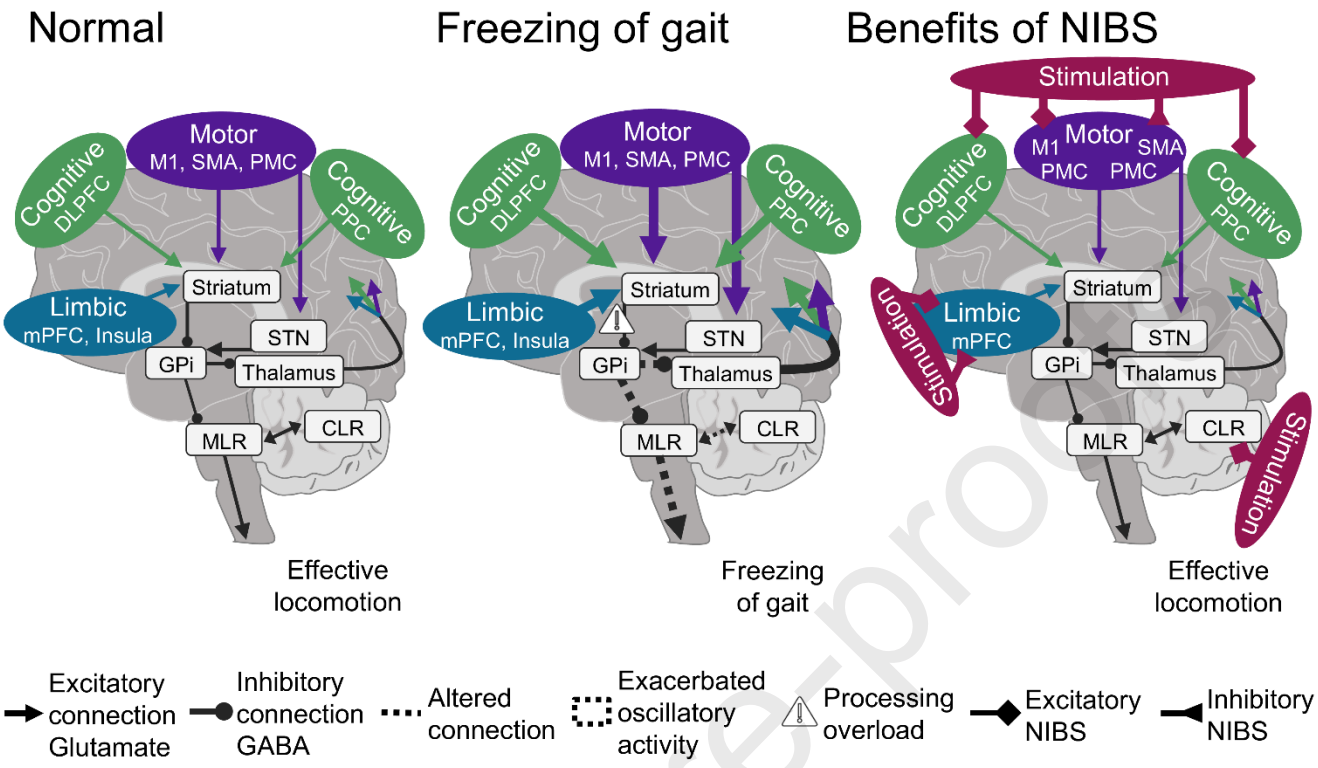
Yamada N, Kakuda W, Kondo T, Shimizu M, Mitani S, Abo M (2013) Bihemispheric repetitive transcranial magnetic stimulation combined with intensive occupational therapy for upper limb hemiparesis after stroke: A preliminary study. Int J Rehabil Res 36:323–329.

Yang YR, Tseng CY, Chiou SY, Liao KK, Cheng SJ, Lai KL, Wang RY (2013) Combination of rTMS and treadmill training modulates corticomotor inhibition and improves walking in parkinson disease: A randomized trial. Neurorehabil Neural Repair 27:79–86.

Zheng CJ, Liao WJ, Xia WG (2015) Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: A double-blind randomized controlled trail. J Huazhong Univ Sci Technol - Med Sci 35:248–254.

Zumbansen A, Black SE, Chen JL, J Edwards D, Hartmann A, Heiss WD, Lanthier S, Lesperance P, Mochizuki G, Paquette C, Rochon EA, Rubi-Fessen I, Valles J, Kneifel H, Wortman-Jutt S, Thiel A (2020) Non-invasive brain stimulation as add-on therapy for subacute post-stroke aphasia: a randomized trial (NORTHSTAR). Eur Stroke J 5:402–413.

Figure 1. Left panel. General representation of the cortico-striatal-thalamic circuity for locomotion in healthy individuals. Thalamus sends processed information from the basal ganglia towards motor, cognitive and limbic cortical areas, which is sent back to the basal ganglia to ultimately reach brainstem nuclei for locomotion. To note, STN – CLR connectivity is not represented here. **Centre panel.** Locomotor control in FOG as suggested by the Interference model. Increased motor, cognitive and/or limbic inputs cause an overload at the striatal level, altering its control over the GPi. Inhibitory GPi output is then increased and follows an oscillatory pattern, which can be exacerbated by STN activity, thus transiently altering the activity of the thalamus, the CLR, the MLR, and ultimately the spinal pattern generators, causing FOG. Bold lines and arrows represent increased activity. Dashed lines and boxes represent activity following a transient and oscillatory pattern. The caution sign represents the striatal overload leading to an irregular control of GPi. **Right panel.** Non-invasive brain stimulation in FOG. Modulation of cortical areas involved in FOG (mPFC, DLPFC, M1, PMC, SMA, PPC and cerebellum) with rTMS or tDCS (areas in magenta) potentially induces changes in excitability that may modulate cortico-striatal-thalamic circuity, ultimately improving FOG. M1: primary motor area; SMA: supplementary motor area; PMC: premotor cortex; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; mPFC: medial prefrontal cortex; GPi: globus pallidus internal; STN: subthalamic nucleus; CLR: cerebellar locomotor region; MLR: mesencephalic locomotor region. *Adapted from Lewis & Shine (2016) and Mitchell et al. (2019).*



- FOG is a complex symptom of PD that still has no effective management therapy.
- Non-invasive brain stimulation may have the potential to improve FOG.
- A review of neuroimaging has identified several potential cortical regions to target for FOG.
- Empirical data shows positive effects of NIBS over M1, SMA and DLPFC on FOG.
- PMC, mPFC and PPC are theory-driven candidate regions to consider for NIBS.