Neural mechanisms of freezing of gait in Parkinson's Disease: A quantification- and modulation-based investigation

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Abstract

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease (PD) that is characterized by a brief and sudden inability to take a step despite the intention to walk. Even though FOG has debilitating consequences, including falls and a poor quality of life, therapeutical options are still limited. Patients usually rely on their dopaminergic medication, which has been shown to reduce the severity of FOG, without completely eliminating the occurrence of FOG episodes. Such lack of reliable therapeutic options for FOG is mainly the result of its pathophysiology that is insufficiently understood. There are hypothetical models that attempt to define the neural mechanisms of FOG with the most inclusive and accepted being the Interference Model. According to this model, FOG episodes occur as the result of a paroxysmal over-inhibition of the basal ganglia output nuclei due to an input overload at the striatum level during walking. However, this model has never been tested in terms of its altered baseline connectivity in FOG nor its modulation by dopaminergic medication. Furthermore, although key cortical brain areas of the Interference Model were previously associated to FOG, their specific role in the occurrence of FOG remains to be confirmed. Therefore, my doctoral work aims to assess the neural mechanisms of FOG in PD through quantification and modulation using respectively brain functional connectivity at rest and non-invasive brain stimulation. This thesis includes a review paper and three experimental studies.

Manuscript 1: This first study aimed at identifying the changes in brain functional connectivity at rest in individuals with FOG. Although no significant changes were observed within regions of the Interference model per se, an increased connectivity between subcortical nuclei and visual-related areas was observed in freezers. This research study provides further evidence for the contribution of altered visuospatial-related neural correlates in FOG.

Manuscript 2: The effect of dopaminergic medication on the neural mechanisms of FOG was studied with brain functional connectivity at rest. A freezer-specific improvement in brain functional organization was found mainly within regions of the Interference Model after dopaminergic medication intake. Interestingly, the posterior parietal cortex (PPC) was the cortical region with the connectivity the most modulated by medication. Our findings suggest that dopaminergic medication modulation was achieved either through a normalization of the connectivity or by a compensatory mechanism that could contribute to FOG.

Manuscript 3: A full review of the current neuroimaging and neuro-electrophysiological literature was undertaken to identify key cortical brain regions part of the Interference Model that are associated with FOG to inform interventions modulating brain excitability to improve FOG. Brain regions have been identified as new promising targets for non-invasive brain stimulation, with the PPC being a region of high interest due to substantial neuroimaging and neuro-electrophysiological evidence supporting its involvement in FOG.

Manuscript 4: This final study was the first to apply non-invasive brain stimulation, and more specifically theta burst stimulation, to increase and decrease the excitability of the PPC in freezers. Results demonstrate that increasing the excitability of this region led to a significant reduction in the number of FOG episodes and in the percent time frozen during a standardized FOG-provoking task. Increasing PPC excitability also had a tendency to induce an inhibitory connection between the PPC and the lower leg primary motor cortex, hypothetically releasing the burden of the cortical inputs on the striatum and thus explaining the observed changes in FOG. This provides evidence for the beneficial role of recruiting PPC for preventing FOG.

My doctoral work uncovered the importance of visuospatial and sensorimotor neural mechanisms in FOG and present evidence for the beneficial involvement of the PPC in preventing FOG. Understanding the neural correlates of FOG is critical for the development of effective therapeutical options, and results of my doctoral work set the scene for future interventions to avoid FOG.

Résumé

Le *freezing* de la marche est un symptôme commun dans la maladie de Parkinson et est caractérisé par une incapacité brève et soudaine d'avancer d'un pas malgré l'intention de le faire. Bien que le *freezing* engendre des conséquences débilitantes comme des chutes et une faible qualité de vie, les options thérapeutiques sont limitées. Les patients se fient à leur médication dopaminergique laquelle diminue la sévérité du *freezing* sans toutefois éliminer complètement les épisodes. Un tel manque d'options thérapeutiques provient principalement du fait que la pathophysiologie du *freezing* est encore mal comprise. Certaines hypothèses tentent d'expliquer les mécanismes neuronaux de ce symptôme. Le Modèle d'interférence est le plus inclusif et accepté d'entre elles et explique que les épisodes de *freezing* surviendraient à la suite d'une surinhibition des noyaux efférents des ganglions de la base, elle-même causée par une surcharge d'afférences au niveau du striatum. Ce modèle n'a toutefois pas été testé en termes d'altération de la connectivité fonctionnelle cérébrale, ni par comment la médication dopaminergique la module. De plus, bien que certaines régions corticales de ce modèle aient été associées au *freezing*, leur rôle dans l'occurrence du *freezing* reste à confirmer. Ainsi, mes travaux doctoraux ont comme objectif d'étudier les mécanismes neuronaux du *freezing* de la marche dans la maladie de Parkinson en quantifiant et modulant ceux-ci à l'aide de la connectivité fonctionnelle au repos et de la stimulation non-invasive. Cette thèse inclut un article de revue de littérature et trois études expérimentales.

Manuscrit 1: Cette étude avait pour but d'identifier les changements de connectivité fonctionnelle au repos du cerveau d'individus ayant du *freezing*. Bien qu'aucun changement n'ait été observé entre les régions du Modèle d'interférence, une augmentation de la connectivité entre des noyaux

sous-corticaux et des régions liées à la vision a caractérisée les individus ayant du *freezing.* Cette étude fournit des preuves pour le rôle d'une altération des circuits neuronaux liés au traitement visuospatial dans le *freezing.*

Manuscrit 2: La connectivité fonctionnelle cérébrale au repos a été utilisée pour étudier les effets de la médication dopaminergique sur les mécanismes neuronaux du *freezing* de la marche. Une amélioration de l'organisation fonctionnelle spécifique aux personnes ayant du *freezing* a été trouvée principalement entre les régions impliquées dans le Modèle d'interférence, et ce, après la prise de la médication dopaminergique. De plus, le cortex pariétal postérieur (CPP) était la région corticale dont la connectivité était la plus modulée par la médication. Nos résultats suggèrent que la modulation causée par la médication dopaminergique s'est produite soit par une normalisation de la connectivité, soit par un mécanisme compensatoire pouvant contribuer au *freezing.*

Manuscrit 3: Une revue complète de la littérature actuelle en neuroimagerie et neuro-électrophysiologie a été effectuée pour identifier les régions corticales clé faisant partie du Modèle d'interférence et qui sont associées au *freezing* de la marche, et ce, dans le but de guider des interventions conçues pour moduler l'excitabilité du cerveau afin d'améliorer le *freezing.* Des régions cérébrales corticales ont été identifiées comme cibles potentielles et prometteuses pour la stimulation cérébrale non-invasive, avec le CPP comme région de grand intérêt en raison de son implication évidente dans le *freezing* de la marche.

Manuscrit 4: Cette dernière étude fût la première à stimuler de façon non-invasive le CPP de personnes ayant du *freezing*, soit pour augmenter ou diminuer son excitabilité. Les résultats démontrent qu'augmenter l'excitabilité de cette région a résulté en une réduction significative de *freezing* observée lors d'une tâche de marche standardisée conçue pour provoquer du *freezing*. Augmenter l'excitabilité du CPP a aussi eu tendance à induire une connexion inhibitrice entre le CPP et la représentation de la jambe sur le cortex moteur, libérant possiblement la charge mise sur le striatum par les afférences et expliquant potentiellement l'amélioration observée dans le *freezing*. Ces résultats fournissent des preuves pour le rôle bénéfique du CPP dans la prévention du *freezing* de la marche.

En somme, cette thèse de doctorat révèle l'importance des mécanismes neuronaux visuospatiaux et sensorimoteurs dans le *freezing* de la marche et présente des preuves de l'implication bénéfique du CPP dans la prévention du *freezing.* Bien comprendre les corrélats neuronaux du *freezing* de la marche est essentiel pour le développement d'options thérapeutiques efficaces. Les résultats de ce travail doctoral pourront ainsi agir comme un tremplin vers de futures interventions visant à prévenir le *freezing* de la marche.

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr. Caroline Paquette, for her mentorship. During my time in the Human Brain Control of Locomotion lab, you allowed me to gain confidence in my abilities and become a better researcher. Thank you for transmitting me your passion, rigor and critical thinking. I am also grateful for countless hours discussing research and all the opportunities you provided me. Merci pour ta patience, tes conseils et ta confiance.

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Contribution to Original Knowledge

This doctoral thesis makes original contribution to the fields of Parkinson's disease and locomotion using neuroimaging and non-invasive brain stimulation methods. Specifically, this work expands current knowledge about the causes of freezing of gait (FOG), a debilitating symptom of Parkinson's disease. Neural circuity involved in FOG was quantified and modulated, which allowed to uncover the involvement of sensorimotor and visuospatial neural mechanisms in this symptom.

Chapter 1 consists of an introduction of the research problem and presents the thesis purpose and objectives.

Chapter 2 provides an in-depth review of the current literature on FOG. Specifically, FOG epidemiology, assessment, consequences, and management are summarized, and the hypotheses on its neural mechanisms, and ways to assess them via quantification and modulation, are described.

Chapters 3 to 6 include the original manuscripts of my thesis studies. Manuscripts of Chapters 3 and 5 are published in Neuroscience, the manuscript of Chapter 4 is published in the European Journal of Neuroscience, and the manuscript of Chapter 6 will be submitted to Neurorehabilitation and Neural Repair.

Chapter 3 consists of the manuscript ***Changes in Resting-State Functional Connectivity Related to Freezing of Gait in Parkinson's Disease*** (*Neuroscience:* Potvin-Desrochers, Mitchell, et al., 2019). This is the first study to assess the resting functional connectivity of the most widely

accepted model of FOG neural mechanisms. Results highlight the contribution in FOG of brain regions involved in visuospatial processing.

Chapter 4 consists of the manuscript ***Freezer-Specific Medication-Induced Changes in Resting-State Functional Connectivity*** (*European Journal of Neuroscience*: Potvin-Desrochers, Atri et al., 2022). This neuroimaging study was the first to assess the effect of dopaminergic medication, taken to control Parkinson's Disease symptoms, on the functional organization of FOG neural mechanisms. This study was critical in better understanding the inconsistent effectiveness of this medication on FOG. Results demonstrate that dopaminergic medication modifies the functional connectivity of key brain regions selectively in freezers either via a normalization or a compensation mechanism with the latter potentially contributing to FOG.

Chapter 5 consists of the manuscript ***Potential Non-Invasive Brain Stimulation Targets to Alleviate Freezing of Gait in Parkinson's Disease*** (*Neuroscience*, Potvin-Desrochers & Paquette, 2021). This conceptual literature review is the first that reviewed all neuroimaging and neuro-electrophysiological evidence to inform interventions modulating brain excitability to reduce FOG. Brain regions have been identified to act as new promising targets for non-invasive brain stimulation, and novel multimodal interventions have been proposed.

Chapter 6 consists of the manuscript ***Upregulation of the Parietal Cortex Improves Freezing of Gait in Parkinson's Disease*** (Potvin-Desrochers, Martinez Moreno, et al. In preparation for submission to *Neurorehabilitation and Neural Repair*). This study expands on the findings of Chapter 5 by being the first to apply non-invasive brain stimulation on the posterior parietal cortex (PPC) in freezers. This is also the first study that used a novel dual coil protocol allowing to quantify PPC functional connection with the lower limb motor cortex in a clinical population. Results show the potential of modulating PPC excitability to help reduce FOG.

Chapter 7 provides an overall discussion of the thesis results and expands on the contribution and on the impact of the findings.

Contribution of Authors

As the lead author of the manuscripts included in this thesis, I, Alexandra Potvin-Desrochers, was responsible for the overall conception, execution, and dissemination of each study under the supervision of Dr. Caroline Paquette. Co-authors provided essential support as detailed below.

Manuscript 1

Changes in Resting-State Functional Connectivity Related to Freezing of Gait in Parkinson's Disease - doi.org/10.1016/j.neuroscience.2019.08.042

Alexandra Potvin-Desrochers: design, objectives and hypotheses formulation, recruitment, data collection, data analysis, results interpretation, manuscript writing, and dissemination.

Trina Mitchell: recruitment, data collection, guidance on analysis, assistance in results interpretation, and manuscript editing.

Thomas Gisiger: pipeline development, technical assistance and, feedback on manuscript.

Caroline Paquette: overall supervision.

Manuscript 2

Freezer-Specific Medication-Induced Changes in Resting-State Functional Connectivity - doi.org/10.1111/ejn.15849

Alexandra Potvin-Desrochers: design, objectives and hypotheses formulation, recruitment, data collection, data analysis, results interpretation, manuscript writing, and dissemination.

Alisha Atri: assistance in data collection and analysis, and feedback on manuscript.

Alejandra Martinez Moreno: assistance in data collection, and feedback on manuscript.

Caroline Paquette: overall supervision.

Manuscript 3

Potential Non-invasive Brain Stimulation Targets to Alleviate Freezing of Gait in Parkinson's Disease - doi.org/10.1016/j.neuroscience.2021.05.037

Alexandra Potvin-Desrochers: conceptualization, review of the literature, manuscript writing, and dissemination.

Caroline Paquette: overall supervision.

Manuscript 4

Upregulation of the Parietal Cortex Improves Freezing of Gait in Parkinson's Disease – In preparation for submission in *Neurorehabilitation and Neural Repair*

Alexandra Potvin-Desrochers: design, objectives and hypotheses formulation, piloting, recruitment, data collection, data analysis, results interpretation, manuscript writing, and dissemination.

Alejandra Martinez Moreno and **Julien Clouette:** piloting, data collection, and feedback on manuscript.

Frédérike Parent-L'Ecuyer, Henri Lajeunesse and **Freddie Seo:** assistance in data collection and manuscript revision.

Caroline Paquette: overall supervision.

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List of Abbreviations

AMT: Active motor threshold

BOLD: Blood-oxygen-level-dependent

C-FOG: Characterizing freezing of gait questionnaire

CLR: Cerebellar locomotor region

CSF: Cerebrospinal fluid

cTBS: Continuous TBS

DLPFC: Dorsolateral prefrontal cortex

FEF: Frontal eye field

fMRI: Functional MRI

FOG: Freezing of gait

FOG+: People living with PD and FOG

FOG-: People living with PD without FOG

GPe: Globus pallidus external

GPi: Globus pallidus internal

HADS: Hospital anxiety and depression scale

ICA: Independent component analysis

ID: Identification

IFG: Inferior frontal gyrus

iTBS: Intermittent TBS

L-DOPA: Levodopa

LGN: Lateral geniculate nucleus

M1: Primary motor cortex

MEP: Motor evoked potential

MGN: Medial geniculate nucleus

MNI: Montreal neurological institute

MoCA: Montreal cognitive assessment

mPFC: Medial prefrontal cortex

MRI: Magnetic resonance imaging

PD: Parkinson's disease

PPC: Posterior parietal cortex

PMC: Premotor cortex

PPN: Pedunculopontine nucleus

SEF: Supplementary eye field

MD: Medial dorsal nucleus

MDS: Movement Disorder Society

MLR: Mesencephalic locomotor region

NFOGQ: New freezing of gait questionnaire

NIBS: Non-invasive brain stimulation

rs-FC: Resting-state functional connectivity

RMT: Resting motor threshold

RSN: Resting-state networks

rTMS: Repetitive TMS

tSMS: Transcranial static magnetic stimulation

SMA: Supplementary motor area

SNr: Substantia nigra pars reticula

SNc: Substantia nigra pars compacta

STN: Subthalamic nucleus

TBS: Theta burst stimulation

tDCS: Transcranial direct current stimulation

TMS: Transcranial magnetic stimulation

TMT: Trail Making Test

UPDRS-III: Unified Parkinson's disease rating scale Part II

VA: Ventral anterior nucleus

VL: Ventral lateral nucleus

VPL: Ventral posteriolateral nucleus

VPM: Ventral posteriomedial nucleus

WM: Whiter matter

Chapter 1

Introduction

1.1 Thesis Rationale

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease (PD) that is characterized by a brief and sudden inability to take a step despite the intention to walk (Nutt et al. 2011). FOG affects 27% of adults with early PD, a number that rises to 79% in the advanced stages of the disease (Tan et al. 2011). Because FOG has debilitating consequences for patients, including falls (Okuma et al. 2018) and a poor quality of life (Moore, Peretz, and Giladi 2007), it is paramount to understand how the neural control of locomotion is altered by FOG. This is especially important to develop evidence-based therapies to alleviate FOG that would be more efficient and longer lasting than what currently exists. Indeed, dopaminergic medication is commonly taken for the control PD symptoms and has been shown to reduce FOG severity without eliminating episodes completely (Schaafsma et al. 2003). Furthermore, beneficial effects of exercise-based interventions for FOG are typically not retained after the intervention (Gilat et al. 2021), requiring a long-haul commitment from the patients. Alternatively, techniques such as sensory cueing can be used to overcome FOG episodes (Nieuwboer 2008), but such strategies does not reliably prevent FOG (Delgado-alvarado et al. 2020) and can evolve into a cue dependency (Spildooren et al. 2012).

Such lack of reliable therapeutic options for FOG mainly results from an insufficient understanding of its pathophysiology. Currently, some hypotheses attempt to define the neural mechanisms of FOG. The most inclusive and accepted of them proposes that FOG episodes occur as the result of

a paroxysmal over-inhibition of the cortico-basal ganglia output nuclei due to an input (i.e., cognitive, motor and limbic inputs) overload at the striatum level during walking (Snijders et al. 2016; Lewis and Barker 2009; Lewis and Shine 2016). This model was later named the Interference Model (Nieuwboer and Giladi 2013) and is currently considered the probable common and ultimate pathway of FOG in individuals with a vulnerable locomotor network (Weiss et al. 2020). However, little is known about how the baseline connectivity of the brain regions composing this model is altered in FOG, and its modulation by dopaminergic medication has never been assessed. Furthermore, although key cortical brain areas of the Interference model were previously associated with FOG (Gilat et al. 2015; Shine, Matar, Ward, Bolitho, et al. 2013; Shine, Matar, Ward, Frank, et al. 2013; Matar et al. 2019; Mitchell et al. 2018), their specific role in the occurrence of FOG episodes remains to be confirmed. Therefore, the purpose of my doctoral thesis was to assess, through quantification and modulation, the neural mechanisms of FOG in PD to better understand its pathophysiology and better guide future therapeutical interventions.

1.2 Thesis Objectives and Hypotheses

The specific objectives of this thesis are to:

1. Identify FOG-associated changes in brain functional connectivity at rest within the Interference model framework.
2. Determine how PD dopaminergic medication in FOG influences brain functional connectivity at rest within the Interference model framework.
3. Review neuroimaging and neuro-electrophysiological literature of FOG to identify key cortical brain regions part of the Interference model that could be potential targets for non-invasive brain stimulation to improve FOG.
4. Modulate the excitability of the posterior parietal cortex (PPC) using non-invasive brain stimulation to infer its role in FOG.

In line with the objectives (1, 2, and 4), the following corresponding hypotheses were tested:

1. Changes in brain functional connectivity at rest will occur within the cortico-basal ganglia-thalamic circuity in individuals experiencing FOG and will represent an increase in inhibitory drive as described by the Interference Model (Lewis and Barker 2009).

2. Altered brain resting state functional connectivity of regions part of the Interference Model will be normalized by dopaminergic medication in individuals with FOG, similarly to the medication-induced normalization effect observed in the cortico-striato-thalamic network in PD (Tahmasian et al. 2015).
4. Increasing PPC excitability with non-invasive brain stimulation will result in less FOG, probably through an enhancement of its sensorimotor integration (Culham, Cavina-Pratesi, and Singhal 2006), visuospatial processing and planning of locomotion (Drew and Marigold 2015; Marigold and Drew 2017) functions, thus confirming the beneficial involvement of the PPC to prevent FOG.

Chapter 2

Review of the Literature

2.1 Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disease that affects 0.4% of the Canadian population with a prevalence of 2% in people aged 80 years and older (Bray et al. 2014). PD causes a variety of symptoms including motor, sensory, cognitive and emotional deficits, and disturbances in autonomic function (Poewe 2008). Although PD is characterized by four cardinal signs (i.e., tremor, bradykinesia, rigidity and postural instability), patients usually experience a much broader variety of motor symptoms including speech disturbances, swallowing difficulties and freezing of the arms, eyelids and legs (i.e., freezing of gait; Poewe et al. 2017).

PD symptoms are caused by a depletion of dopamine in the striatum due to a loss of nigrostriatal neurons (Kish, Shannak, and Hornykiewicz 1988). This leads to reduced dopaminergic transmission in the basal ganglia circuity, more precisely in the cortico-basal ganglia loops modulating motor, oculomotor, cognitive and limbic processing (Figure 2.1) (Nambu et al. 2005). In the healthy state, the hyperdirect motor pathways inhibit all possible motor programs (e.g. before movement or during response conflicts) and the indirect motor pathway stops the movement. The direct motor pathway activates the appropriate motor program, allowing the execution of the movement (Figure 2.2A; Nambu 2005). In PD, dopamine depletion downregulates the direct pathway and upregulates the indirect pathway, leading to an overactivation of the output nuclei, and thus an increased movement inhibition (Figure 2.2 B) (Nambu 2005). While there is currently no cure to PD, the vast majority of individuals living with PD are treated with levodopa

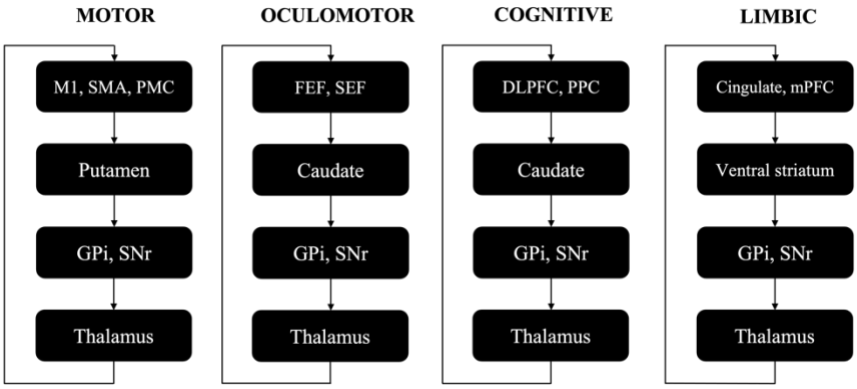

Figure 2.1 *Parallel cortico-basal ganglia loops*
DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye field; GPi: globus pallidus internal; M1: primary motor area; mPFC: medial prefrontal cortex; PMC: premotor cortex; PPC: posterior parietal cortex; SEF: supplementary eye field; SMA: supplementary motor area; SNr: substantia nigra reticula.

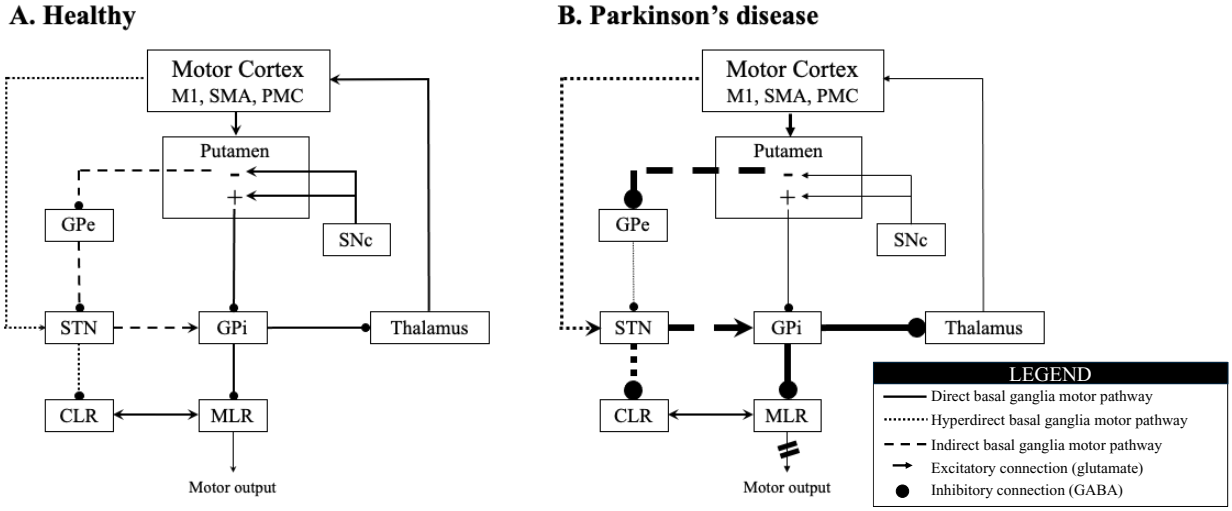

Figure 2.2 *Motor cortico-basal ganglia loops in (A) healthy and (B) parkinsonian movement.*
Thick lines represent higher activity and thin lines represent lower activity. CLR: cerebellar locomotor region; GPe: globus pallidus external; GPi: globus pallidus internal; M1: primary motor area; MLR: mesencephalic locomotor region; PMC: premotor cortex; SMA: supplementary motor area; SNc: substantia nigra pars compacta.

(L-DOPA), the gold standard drug therapy to reduce and manage PD motor symptoms (LeWitt and Fahn 2016). L-DOPA is the precursor of dopamine and is used to increase the brain concentrations of this neurotransmitter with the goal of restoring a normal activity within the cortico-basal ganglia-thalamic circuity and thus, reducing PD symptoms (LeWitt and Fahn 2016).

L-DOPA has also been shown to normalize atypical brain functional organization in PD, which could account for L-DOPA-related improvements in PD symptoms (Tahmasian et al. 2015). While L-DOPA remains the best option to alleviate PD, it also has little to no effect on some symptoms, with gait impairments, postural instability and FOG usually seen as L-DOPA unresponsive motor features of PD (Sethi 2008). Furthermore, L-DOPA becomes less effective at reducing PD symptoms over time, probably because it induces a profound reorganization of patients' neural circuity (Poewe et al. 2017).

2.2 Freezing of Gait in Parkinson's Disease

2.2.1 Clinical Presentation: FOG a Heterogeneous Symptom

FOG, a common motor symptom in PD, is defined as a brief and sudden inability to take a step despite the intention to walk (Nutt et al. 2011), and is often recognized by either a sudden akinesia, trembling in place or shuffling forward with small steps (Schaafsma et al. 2003). Most FOG episodes are short, lasting less than ten seconds, but in severe cases, episodes can go over thirty seconds (Schaafsma et al. 2003). Several situations are known to trigger FOG episodes including stressful situations, crowds, a time constraint, narrow passages, directional changes, turning movements, gait initiation, doorways, changes in floor covering, talking, etc. (Bloem et al. 2004; Nutt et al. 2011; Snijders et al. 2008). The most commonly encountered triggers in a patient can help identify FOG subtype as sensory-attentional (e.g. dual-tasking, distractions), anxious (e.g. time constraint, emotional circumstances) or asymmetric-motor (e.g. turns, doorway, elevator) (Ehgoetz Martens et al. 2018). Up to 27% of individuals with PD that are in a very early stage of the disease experience FOG, a number rising to 79% in advanced stages (Tan et al. 2011). The higher prevalence of FOG in advanced PD and the usual longer disease duration of freezers compared to non-freezers may indicate that FOG is a late symptom of PD (Zhang et al. 2021). FOG is also the most frequent cause and one of the main risk factor of falls in PD (Okuma et al. 2018). Impaired weight-shifting (Dijkstra et al. 2021) and dynamic postural stability (Hasegawa et al. 2021) in freezers contribute considerably to inadequate postural responses, making patients more susceptible to fall (for a review: Bekkers et al. 2018). FOG is also a significant independent contributor to poor quality of life (Walton et al. 2015; Moore, Peretz, and Giladi 2007) and is associated with less functional independence (Santos-García et al. 2020), making this symptom one of high interest in the treatment of PD.

2.2.2 Assessment

Due to the episodic and unpredictable nature of FOG and to the misunderstanding of this symptom by patients, the assessment of FOG is challenging. For a brief evaluation, FOG can be assessed using the item 3.11 of the Motor examination of the Movement Disorder Society (MDS) Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) (Goetz et al. 2008). However, only one score is used to evaluate multiple dimensions of FOG (e.g. trigger, duration, frequency), thus lacking specificity. The New Freezing of Gait Questionnaire (NFOGQ) is a commonly used questionnaire to determine the subjective severity of FOG (Nieuwboer et al. 2009). A video demonstrating FOG occurring in different situations is presented before asking a series of questions on FOG occurrence, duration and repercussion. This ensures the patients' understanding of the symptom, not previously accounted for in the FOGQ, an earlier version of this test still widely used today (Giladi et al. 2000). The NFOGQ has been validated in large cohorts (Nieuwboer et al. 2009) and its score correlates with objective measures of FOG (Ribeiro De Souza et al. 2022). Recently, a new FOG-related questionnaire, the Characterizing Freezing of Gait (C-FOG) questionnaire, has been developed to assess FOG and more particularly to characterize situations that trigger FOG and strategies that help overcome episodes (Ehgoetz Martens et al. 2018). To provide a more complete evaluation of FOG, one should thus consider using CFOGQ to inform FOG based on each patient's freezing phenotypes in conjunction with NFGOQ to, in turn, characterize FOG severity.

Despite the difficulty to elicit FOG episodes in clinical settings, turning in place (e.g. 360 turns) has been shown to be the best way to provoke and objectively assess FOG (Mancini et al. 2017; Snijders et al. 2008; Bertoli et al. 2019; Son et al. 2022). However, this type of assessment tackles only one known trigger of FOG. Common gait and balance tests, such as the Time up and Go (Podsiadlo and Richardson 1991) or the 6-meter walk tests have been used to assess FOG (Shine et al. 2012), but results of these tests only weakly correlate with FOG severity (Tan et al. 2011). Thus, a gait trajectory test specifically designed for FOG should be used. Ziegler and colleagues (2010) developed a specific FOG-provoking test composed of several situations known to trigger FOG. As shown in Figure 2.3, the trajectory consists of sitting-to-standing, walking, performing two full turns, one in each direction, opening a door, walking thru its frame, and turning back to walk towards the chair and sit back on it. This is performed as is, while carrying a tray holding a

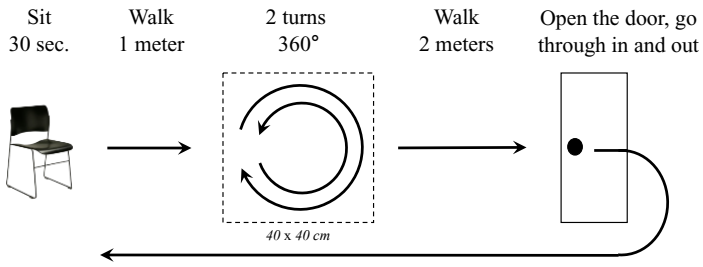

Figure 2.3 *FOG-provoking test by Ziegler et al. (2010). Arrows represent the trajectory followed by patients. This is performed three times: as is, while carrying a tray, and while carrying the tray and performing a backward counting task.*

cup full of water and while carrying the same tray and performing a backward counting to gradually increase the cognitive and motor demand, thus increasing the chances of provoking FOG, especially the sensory-attentional FOG subtype. The score obtained on this FOG-provoking test represents FOG occurrence and severity, and a change of 3 points has been shown to be clinically significant (Fietzek et al. 2020). As previously suggested (Bloem et al. 2004; Herman et al. 2020), videotaping and timing patients while performing such test is crucial as it allows the quantification of other outcomes derived from the test, including the number of FOG episodes, their duration, and their frequency, as well as the percent time frozen, with high degree of measurement accuracy, even between evaluators (Kondo et al. 2022). The percent time frozen has been shown to be the most reliable metric of FOG severity (Morris et al. 2012).

2.2.3 Therapies and Interventions

There is currently no standardized approach to manage FOG. The vast majority of individuals with PD, including freezers, are under L-DOPA therapy (PD MED Collaborative Group 2014). The frequency and the duration of FOG has been shown to be significantly reduced following L-DOPA intake compared to OFF-medication state where patients tend to freeze more (Schaafsma et al. 2003). Such beneficial effects may be explained by a L-DOPA-induced restoration in motor, thalamic and cerebellar activations, and by a suppression of accessory neural circuits (i.e., premotor-parietal, brainstem) (Maillet et al. 2015). However, FOG episodes still occur in the ON-medication state in about a third of patients (Amboni et al. 2015). L-DOPA is thus not effective to control FOG for all patients (Landes et al. 2022), and could even worsen FOG episodes in some cases (Moreira, Rebelo Gomes, and Januário 2019; Espay et al. 2012). One hypothesis is that L-

DOPA could overflow to the prefrontal cortex (PFC), negatively impacting its function during complex walking (Dagan et al. 2020) and possibly leading to FOG.

Just like for treating cardinal symptoms of PD, deep brain stimulation can also be used in patients with FOG to regulate abnormal electrical signaling in the basal ganglia circuity (Poewe et al. 2017), and thus, to alleviate FOG (Ferraye et al. 2008; Yokoyama et al. 1999; Kim et al. 2019; Mestre and Sidiropoulos 2016; Moro et al. 2010; Thevathasan et al. 2012; Yu et al. 2022). However, results of this technique are inconsistent (Bourilhon et al. 2022; Kim et al. 2019; Mei et al. 2019; Meoni et al. 2019; Mestre and Sidiropoulos 2016) and efficacy generally seems to decreased after two years (Razmkon et al. 2022). Even though this procedure is performed only in very selective cases (Nonnekes, Snijders, Nutt, Deuschl, and Giladi 2015), a bilateral low frequency stimulation seems to be associated with better responses for FOG and could be a good therapeutical option for severe freezers (Razmkon et al. 2022).

Several exercise-based interventions have been tested in FOG. Gilat et al. (2021) recently categorized the purpose of such interventions into three levels: 1) avoiding or overcoming FOG episodes via compensatory strategies, 2) reducing the risk of triggering situations to result in FOG by teaching patients how to deal with those situations, and 3) targeting neural correlates of FOG to train compensatory gait control. Improvement in FOG severity has been found following water-based obstacle training (Zhu et al. 2018), action observation training (Pelosin et al. 2018; Mezzarobba et al. 2018), conventional physiotherapy (Cosentino et al. 2020) and general exercise (Silva-Batista et al. 2020; Wroblewska et al. 2019). However, recent systematic reviews concluded that beneficial effects of exercise-based interventions for FOG are not retained after the intervention (Kwok et al. 2022; Gilat et al. 2021), requiring accessibility and long-term commitment from the patients.

Unsurprisingly, compensatory strategies are the most-used by patients in their daily-life to deal with FOG. Sensory cueing is the best-known of these strategies, an approach shown to improve FOG (Nieuwboer 2008; Ginis et al. 2017, 2018; Sweeney et al. 2020). PD-related dopamine depletion is greater in the posterior putamen, the striatal region associated with the production of automatized behavior such as locomotion, than in the rostro medial striatum, which is mainly

associated with the control of goal-directed movements, that seems to be relatively spared (Kish, Shannak, and Hornykiewicz 1988; Redgrave et al. 2010). Thus, the use of sensory cues to induce a goal-directed control of gait would allow processing to be shift from more to less affected neural circuits (Ginis et al. 2018). However, there still a debate about the use of sensory cueing in the long run as benefits tend to decline overtime (Rochester et al. 2007; Morris et al. 1996), and, in some cases, could even create a cue-dependency (Spildooren et al. 2012). A more successful alternative seems to combine gait and balance training with the use of auditory cueing, an approach that has shown FOG improvements retained for up to 4 weeks after the intervention (Plotnik et al. 2014; Brichetto et al. 2006; Allen et al. 2010). To overcome the difficulty of cueing strategies being used in any type of environment, technologies have been developed to detect FOG episodes and provide immediate cueing support. Examples of such apparatus are laser-shoes (Barthel et al. 2018), body-worn sensors combining a device emitting acoustic cues (Mazilu et al. 2014; Bachlin et al. 2010), and smart glasses projecting 3D visual cues (Janssen et al. 2017; Geerse et al. 2022). Even though these technologies still need to be refined (i.e., detection of triggers, faded feedback, etc.) they offer a great opportunity for patients to efficiently overcome FOG episodes.

Finally, although still not easily accessible in clinical settings, non-invasive brain stimulation (NIBS) shows promising results for improving FOG. Compared to the other aforementioned therapeutical options, NIBS can directly act on the neural correlates of FOG (Kim et al. 2019). By altering the excitability of the stimulated region, NIBS could improve FOG by : 1) normalizing abnormal activity of a dysfunctional region (Matsuda et al. 2017); 2) promoting cortical plasticity for the use of beneficial circuits (Paquette and Thiel 2012); 3) modulating neurotransmitter function (Tremblay et al. 2020); and 4) inducing a release of endogenous dopamine in the striatum (Strafella et al. 2001, 2003, 2005). To date, improvement in FOG have been observed after NIBS was applied on the primary motor cortex (M1) (Kim et al. 2015; Sun et al. 2021; Valentino et al. 2014), the supplementary motor area (Ma et al. 2019; Kim, Paeng, and Kang 2018; Mi et al. 2019) and the medial prefrontal cortex (Dagan et al. 2017). However, before finding the optimal protocol to induce long-term benefits on FOG, more studies are needed to determine ideal stimulation type, duration, frequency, intensity, target, and schedule (Nardone et al. 2020; Kim et al. 2019).

2.2.4 Hypotheses and Models

The heterogeneous nature of FOG cannot be adequately explained by the traditional dopamine depletion model of PD. Therefore, many hypotheses were brought forward attempting to better describe its pathophysiology. First, impaired visuospatial skills and poor perceptual judgement are thought to contribute to the occurrence of FOG, especially in narrow passages (Almeida and Lebold 2010; Cowie et al. 2012; Nantel et al. 2012). The Threshold model also proposes that FOG is the result of a motor breakdown reached following an accumulation in multiple gait deficits that characterize freezers such as increased stepping frequency and poor bilateral coordination and symmetry (Plotnik, Giladi, and Hausdorff 2012; Nieuwboer and Giladi 2013). Executive dysfunction that could occur following increased demands on problem solving, attention division, attention shift and response inhibition could also lead to FOG (Snijders et al. 2007; Nutt et al. 2011). Another hypothesis suggests that FOG would be the result of a de-automatization process, so that when normally automatized movements, such as gait, are performed, more stress would be put on voluntary mechanisms (e.g. cerebellum-dorsal premotor cortex pathways), rather than on automatic pathways (e.g. frontostriatal circuity; Vandenbossche et al. 2013). According to this hypothesis, in a situation where FOG patients are walking in a complex or ambiguous environment, automatic pathways would be forsaken for more cognitive pathways, but cognitive resources would be insufficient to handle the situation. Executive malfunction would be exacerbated, leading to a cognitive overload and ultimately, to the occurrence of FOG (Nutt et al. 2011; Vandenbossche et al. 2013).

Although these hypotheses do contribute to a better understanding of FOG, most arise from a category of triggers and explain only a few aspects of FOG heterogeneity. Alternatively, the Interference model, initially proposed by Lewis and Shine's group (Lewis and Shine 2016; Lewis and Barker 2009; Shine, Naismith, and Lewis 2013) and later named by Nieuwboer and Giladi (2013), is the only hypothesis that provides a unified explanation for most FOG triggers altogether and that attempts to model the altered neural circuity involved in FOG. Details of the Interference model are presented in the following section.

2.3 Interference Model of Freezing of Gait

According to this model, when a trigger of FOG is encountered while walking, a cross-talk, or interference, in concurrent upstream processing of cognitive, motor and limbic information would overwhelm a common downstream circuitry, leading to FOG (Lewis and Shine 2016; Lewis and Barker 2009; Shine, Naismith, and Lewis 2013). Specifically, because of decreased neural reserve (i.e., dopamine depletion) in the basal ganglia circuity, an overwhelming increase in neural inputs (i.e., cognitive, limbic and motor), leads to an overload in the processing capacity of the striatum (Figure 2.4). This causes a transient overactivity of the globus pallidus internal (GPi), and thus, a temporary oscillatory over inhibition of the thalamus and brainstem, leading to FOG. The hyperdirect pathway also gets solicited when a response conflict arises, thus increasing subthalamic nucleus (STN) activity. This increased STN activity in FOG is believed to exacerbate the oscillatory output from the GPi, to affect cerebellar output, and to contribute to the emergence of the trembling knees associated with FOG (Lewis and Shine 2016).

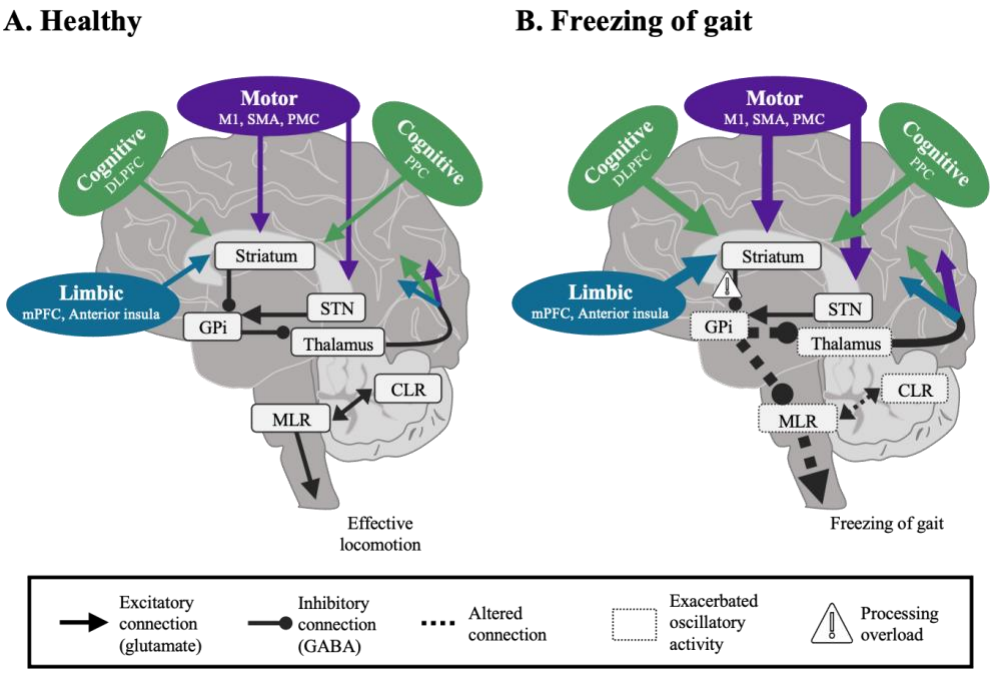

Figure 2.4 *Neural circuity involved in FOG as proposed by the Interference model.*
A) cortico-striatal-thalamic circuity in healthy individuals. B) A substantial increase in motor, cognitive and limbic inputs would cause a processing overload at the striatal level, ultimately increasing the output inhibitory drive from the basal ganglia, leading to FOG. CLR: cerebellar locomotor region; DLPFC: dorsolateral prefrontal cortex; GPi: globus pallidus internal; M1: primary motor area; mPFC: medial prefrontal cortex; MLR: mesencephalic locomotor region; PMC: premotor cortex; PPC: posterior parietal cortex; SMA: supplementary motor area; STN: subthalamic nucleus; Adapted from Potvin-Desrochers & Paquette 2021.

The overwhelming increase in cortico-basal ganglia processing is thought to occur when there is an increase in cognitive, limbic and/or motor stimuli, such as when a trigger of FOG is encountered. For example, FOG episodes could be triggered by anxiety associated with crowds. According to the Interference model, such situation would provoke a substantial increase in the processing load of the limbic system, thus competing for neural reserve with other ongoing processing, then causing an overload in the basal ganglia processing capacity, and ultimately leading to FOG. A similar process is thought to occur when patients encounter a situation requiring a high level of cognitive and/or motor demand.

Multiple brain imaging studies support the Interference model by showing changes in activity or metabolism of brain regions involved in cognitive, limbic and motor circuity in freezers during or between motor arrests associated with foot pedaling in a virtual reality paradigm (Gilat et al. 2015; Matar et al. 2013; Shine, Matar, Ward, Bolitho, et al. 2013) or during real walking (Mitchell et al. 201; Shine et al. 2014; Handojoseno et al. 2015; Maidan et al. 2015). The Interference model has also been recently identified as the probable common ultimate pathway to FOG in individuals with vulnerable locomotor network following integration failure within or between different networks (Weiss et al. 2020). However, considering that cognitive and limbic circuity can influence brainstem nuclei on their own, it cannot be ignored that FOG could occur without the involvement of the described common final pathway that includes the striatum (Ehgoetz Martens et al. 2020). Nevertheless, the Interference model remains, to date, the most complete model of FOG, explaining the neural basis of its heterogeneity and providing a plausible framework to study its neural mechanisms.

2.4 Assessing the Neural Mechanisms of Freezing of Gait

Many different techniques can be used to study the neural mechanisms of FOG. While functional magnetic resonance imaging (fMRI) combined with a foot pedalling virtual-reality paradigm can provide good insights on the neural correlates of FOG-like episodes, electroencephalography, functional near-infrared spectroscopy, and positron emission tomography can be used to study the brain when real FOG episodes occur. In this thesis, neural mechanisms of FOG were quantified using resting-state functional connectivity (rs-FC), a neuroimaging method that characterizes

baseline brain functional organization. Transcranial magnetic stimulation (TMS), a neuromodulation method, was also used to assess the role of a key cortical brain region for FOG. These two techniques, used to assess neural mechanisms of FOG, are further presented in the following sections.

2.4.1 Neuroimaging: Resting-State Functional Connectivity

rs-FC is a measure of how spontaneous activity between different brain regions correlates in the absence of any task. Specifically, low frequency fluctuations of the blood-oxygenated-level-dependent (BOLD) signal, acquired through fMRI at rest, are correlated across different brain regions to assess their functional affinity (Biswal et al. 1995). Brain regions structurally connected are generally highly functionally connected at rest, but high rs-FC is also probable between regions not anatomically connected together; in that case, it represents indirect structural links and functional relationships (Rubinov and Sporns 2010; Adachi et al. 2012). rs-FC is also suggested to demonstrate the maintenance of the different neural systems in an active competent state, so that they are ready to efficiently process information when a behavior is needed (Varela et al. 2001). This is supported by the observation that brain activity evoked by an external stimulus accounts for less than 5% of the total brain energy expenditure; thus the majority of brain energy consumption comes from its resting activity (Raichle and Mintun 2006; Fox and Greicius 2010). Therefore, quantifying baseline (i.e., resting) functional connectivity is of high interest when studying the neural mechanisms of FOG, as observed changes in the resting state can predispose to FOG in an active state (i.e., while walking). Furthermore, unlike task-based studies, fMRI at rest allows to study brain networks without the performance of any task that could be influenced by PD's or FOG's cognitive or motor symptoms (Fox and Greicius 2010) and can be used to investigate various neural systems at the same time (Daliri and Behroozi 2013). When combined with other brain imaging modalities (e.g., activation, metabolism, anatomical connectivity, etc.), rs-FC has the potential to provide a picture of the brain global architecture and functioning, and to compare it between healthy and disease states at the whole-brain level. This is particularly interesting for FOG as it is thought to arise from a multi-system network failure.

Different methods can be used to assess and quantify rs-FC. Briefly, Graph Theory analysis is used to assess topological organization of brain networks by quantifying the global and local properties

of network nodes (Sporns 2018). Another common network-based analysis is independent component analysis (ICA). With this method, data is decomposed into independent components, each representing one of the resting-state networks (RSNs) (Beckmann et al. 2005; Bartels and Zeki 2004), which are large-scale spatial patterns of rs-FC consistently observed in human brains (Damoiseaux et al. 2006; Lv et al. 2018; Raichle et al. 2001). Traditionally, there are ten RSNs usually emerging from network-based analysis, including the well-known default mode network considered the baseline brain mode, the executive control network, the salient network, the attentional network, the sensorimotor network and the visual networks (Damoiseaux et al. 2006; Lv et al. 2018; Raichle et al. 2001; Robinson et al. 2009). Although ICA provides a complete portrait of brain rs-FC, it is a data-driven approach that does not allow to assess specific hypotheses like the Interference model. Instead, seed-based analyses is widely used to directly test a priori hypotheses (Lv et al. 2018) by determining rs-FC between a region of interest and all other brain voxels (i.e., seed-to-voxel) or between two specific regions (i.e., seed-to-seed). BOLD signal is generally averaged for each region of interest and inputted in a general linear model to determine functional affinity with another region of interest or with all brain voxels (Cole, Smith, and Beckmann 2010). Although results from seed-based approaches are more dependent of the preprocessing steps and the correct placement of the seeds (Power, Schlaggar, and Petersen 2015), this type of analysis offers a unique opportunity to quantify the relationship between specific regions involved in the same functional processing network (Lv et al. 2018).

In the past decade, multiple studies have investigated rs-FC in FOG. Lower rs-FC within the attentional (Maidan et al. 2019; Tessitore, Amboni, Esposito, et al. 2012; Li et al. 2020), the default mode (Canu et al. 2015; Li et al. 2020), the sensorimotor (Canu et al. 2015) and the visual (Tessitore et al. 2012; Canu et al. 2015) networks have been shown, supporting cognitive, visuospatial and sensorimotor integration dysfunctions as part of FOG. Studies using Graph Theory approaches to characterize brain networks in FOG found altered degree of centrality of the inferior (Ruan et al. 2020; Liu et al. 2019; Li et al. 2021) and middle (Guo et al. 2020; Jin et al. 2021) frontal gyri and within limbic (Li et al. 2021; Ruan et al. 2020), sensorimotor (Li et al. 2021) and subcortical (Li et al. 2021) networks. Other studies used a seed-based analysis to investigate rs-FC within either the limbic or the motor circuity. Lower rs-FC between the putamen and the amygdala (Gilat, Ehgoetz Martens, et al. 2018), and greater rs-FC of the putamen and the insula

with fronto-parietal regions (Gilat, Ehgoetz Martens, et al. 2018; Mi et al. 2020) have been shown in freezers, providing evidence for a disorganization of the limbic circuity in the Interference model. Altered locomotor networks has also been demonstrated, with the SMA being more connected to the mesencephalic locomotor region (MLR) and the cerebellar locomotor region (CLR) in FOG at rest (Fling et al. 2014; Mccalley et al. 2021). Freezers also have higher rs-FC between the MLR and the pallidum (Mi et al. 2020), as well as of the MLR (Lench et al. 2020) and the pallidum (Miranda-Domínguez et al. 2020) with sensorimotor regions, all supporting the idea of an increased cortical control of gait in this population.

Altogether, these results generally support the Interference model by demonstrating altered rs-FC within different networks or between areas involved in the cortico-basal ganglia circuity. However, the Interference model has never served as the a priori hypothesis in functional connectivity studies at rest in FOG. To my knowledge, two studies investigated functional connectivity of the Interference model as a whole, but this was carried out in an active state where participants were performing foot pedaling in a virtual reality paradigm while being in a MRI scanner (Ehgoetz Martens et al. 2018; Shine, Matar, Ward, Frank, et al. 2013). During motor blockages, decreased connectivity was observed between the basal ganglia and cognitive (Shine, Matar, Ward, Frank, et al. 2013; Ehgoetz Martens et al. 2018) and motor (Ehgoetz Martens et al. 2018) cortical regions, while increased coupling was observed between limbic regions and the striatum (Ehgoetz Martens et al. 2018), overall supporting the Interference model. While linking motor blockages occurring in a virtual reality foot pedaling paradigm to FOG offers important insight into the neural correlates of FOG, fMRI study of real FOG remains impossible. It is thus also paramount to characterize functional connectivity of the Interference model at rest as alterations in the resting state could indicate network disruption predisposing to FOG in an active state.

The study of levodopa-related neural changes is also precarious. As presented in section 2.2.3, only two studies explored changes in neural correlates of gait in FOG after L-DOPA intake, finding levodopa-specific changes during an imagery task (Maillet et al. 2015) and real walking (Dagan et al. 2020). However, no studies have investigated how L-DOPA modifies neural networks of FOG nor how these modulations differ from non-freezers. Therefore, quantifying brain functional

organization in freezers within the Interference model is important as it could provide the first step towards a better explanation for FOG heterogenous response to L-DOPA.

2.4.2 Neuromodulation: Transcranial Magnetic Stimulation

TMS is a NIBS technique used to modulate the excitability of the superficial cortical brain regions (Barker, Jalinous, and Freeston 1985). Using a coil, TMS discharges a magnetic field to the stimulated brain area, crossing high resistance tissues (i.e., skull, meninges) painlessly and inducing an electrical field that depolarizes neurons into the brain tissue underneath the stimulation site (Barker, Jalinous, and Freeston 1985). TMS is a multi-purpose tool that can be used to explore or modulate excitability of brain regions in healthy and clinical populations. When TMS is applied on M1, the activation of the corticospinal tract (Di Lazzaro, Ziemann, and Lemon 2008) results in twitches in the corresponding muscle (Barker, Jalinous, and Freeston 1985). When recorded with electromyography, those muscle twitches are called motor-evoked potentials (MEPs) and are usually represented by their peak-to-peak amplitude. MEPs obtained at different stimulation intensities are used to determine excitability thresholds such as the resting and the active motor thresholds (RMT and AMT, respectively; Rossini et al. 1994). These thresholds represent the minimal stimulation intensity necessary to depolarize the corticospinal tract, and thus, motor cortical excitability.

Changes in cortical excitability can also be assessed by applying single TMS pulses to M1 at a specific intensity and at different timepoints. When acquired before and after an intervention, it can act as an outcome measure to indicate how the intervention modulated the excitability of a specific region (Groppa et al. 2012). In turn, dual coil paradigms can be used to determine changes in excitability of non-motor regions that do not have a direct quantifiable output (Hallett et al. 2017). The connections of such regions with the M1 are assessed using two coils, each sending a pulse at a very short interval (i.e., a few milliseconds). Specifically, a conditioning stimulus is applied on the non-motor region to activate intracortical circuits to the M1, quickly followed by a stimulus applied on M1. To detect changes in the excitability of M1 due to the non-motor region, MEPs that resulted from the dual coil protocol are compared with those acquired when only the M1 is stimulated. If paired-coil MEPs are smaller than M1 only MEPs, then an inhibitory connection from the non-motor region to the M1 can be concluded. In turns, when paired-coil

MEPs are bigger than M1 only MEPs, a facilitatory connection exists. Finally, if the MEPs are similar in dual and single coil MEPs, then there is no effect of the non-motor region on the M1. Such dual coil protocols have been established for the PPC (Koch et al. 2007, 2008), the premotor cortex (PMC) (O'Shea et al. 2007; Mochizuki, Huang, and Rothwell 2004), the SMA (Arai et al. 2012), the pre-SMA (Civardi et al. 2001; Mars et al. 2009) and the cerebellum (Ugawa et al. 1995; Pinto and Chen 2001).

Repetitive TMS (rTMS) is another type of TMS that consists in a rapid succession of pulses over a certain period of time, resulting in a sustained change in cortical excitability of the stimulation site outlasting the stimulation period (Ziemann 2004; Pascual-Leone et al. 1994; Jennum, Winkel, and Fuglsang-Frederiksen 1995). rTMS modifies cortical excitability to either facilitate (i.e., pulses at > 5 Hz) or inhibit (i.e., pulses at 0.2-1 Hz) cortical activity (Chen et al. 1997; Pascual-Leone et al. 1994). rTMS effects are thought to arise from a change in synaptic efficacy (Fitzgerald, Fountain, and Daskalakis 2006). rTMS-induced cortical facilitation would cause an increased efficacy of excitatory synapses, leading to a process similar to long-term potentiation (Pascual-Leone et al. 1994; Esser et al. 2006; Brown et al. 2020), while cortical inhibition would resemble long-term depression, where rTMS reduces the activity in synapses (Chen et al. 1997).

rTMS can be applied following different protocols. Theta burst stimulation (TBS) is a form of patterned rTMS consisting of very short pulses delivered at a very high frequency (i.e., 50Hz – frequency causing powerful effects on neural plasticity in animal and human experiments (Huang and Rothwell 2004)) in bursts of 5Hz (i.e., theta frequency – frequency of brain oscillations associated with learning and memory in rodents and humans (Suppa et al. 2016))(Huang et al. 2005). There are two common patterns of TBS, the continuous (cTBS) and the intermittent (iTBS) (Figure 2.5). cTBS causes a decrease in cortical excitability of M1, and iTBS an increase, both thought to last at least 50 minutes after the stimulation period (Chung et al. 2016). Similar effects are found when applied to temporal, parietal, occipital and cerebellar regions (Kirkovski et al. 2020). Even though mechanisms of action of TBS are still not fully understood (Rounis and Huang 2020) and high inter-individual variability in TBS response has been described, but is still not well understood, in the healthy population (Hamada et al. 2013; Suppa et al. 2016; Corp et al. 2020), TBS has some considerable advantages over traditional rTMS protocols, including lower

stimulation intensity, shorter stimulation period, higher acceptability from patients and more prolonged after-effects (Suppa et al. 2016; Rossi et al. 2009; Huang et al. 2005). In a meta-analysis exploring the safety of TBS, the risks associated with this type of rTMS (i.e., transient headache, neck pain, seizures) were determined to be comparable and even less considerable than other high frequency rTMS protocols (Oberman et al. 2011).

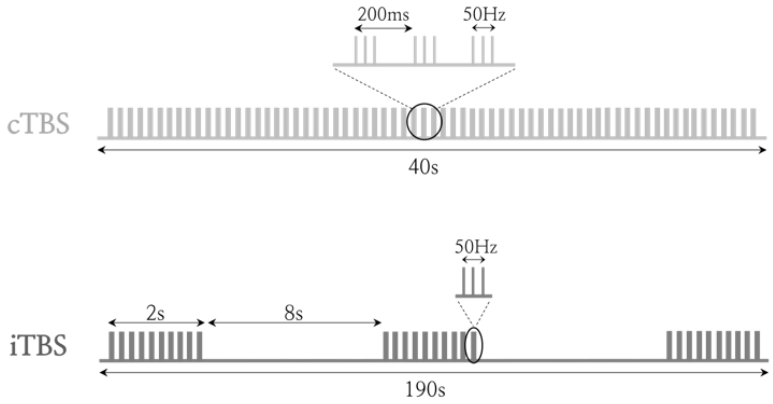

Figure 2.5 *Pulses firing pattern in TBS.*
cTBS: continuous theta burst stimulation, iTBS: intermittent theta burst stimulation, s: seconds, ms: milliseconds: Hz: hertz.

In its repetitive form, TMS utility can be used for two different purposes, as a therapeutical tool or to map brain functions. First, rTMS is used in different clinical conditions, with evidence of definite or probable beneficial effects of rTMS described for depression, post-traumatic stress disorder, pain, fibromyalgia, motor recovery after stroke, lower leg spasticity in multiple sclerosis and motor symptoms and depression in PD (Lefaucheur et al. 2020). In PD, rTMS is of particular interest as it has the capacity of regulating cortical excitability at the stimulation site, but also of modulating the neurotransmitter function, such as dopamine's, of the network of structures linked to that site including deeper structures not accessible by NIBS (Strafella et al. 2001, 2003, 2005; Tremblay et al. 2020). In FOG, studies looking at the potential of rTMS as a therapy yield incongruent results. Some found less freezing or improved gait following high-frequency rTMS applied on the SMA, mPFC, DLPFC or lower leg M1 (Kim et al. 2015; Dagan et al. 2017; Kim, Paeng, and Kang 2018; Mi et al. 2019; Ma et al. 2019; Lee et al. 2014) or after iTBS of the cerebellum or lower leg M1 (Janssen et al. 2017; Sun et al. 2021). In turns, other studies found no beneficial effect of facilitatory rTMS when applied on the SMA, PMC or M1 (Brugger et al. 2020,

2021; Kim, Paeng, and Kang 2018; Tard et al. 2016; Lee et al. 2014; Rektorova et al. 2007). Such incongruent results may be explained by differences in the stimulation protocol, region targeted, assessment of FOG and sample size. Therefore, while rTMS holds potential to reduce FOG severity, the optimal stimulation type, target, duration, frequency, intensity and schedule still need further investigation (Nardone et al. 2020; Kim et al. 2019).

rTMS can also be used to map brain functions by identifying a causal effect between a brain area (i.e., stimulation site) and a specific function, cognitive process or behavior (Hallett 2007). By using rTMS, excitatory or inhibitory effects can be induced in a specific cortical region, and when combined with the performance of a task simultaneously or after rTMS, it is possible to determine the contribution of the area in the task performance. For example, the role of the SMA in the organization of motor sequences was confirmed in a study where high-frequency rTMS over the SMA caused accuracy errors in complex finger tapping (Gerloff et al. 1997). Similarly, SMA involvement in gait initiation timing and preparation was shown by a reduced duration of the automatic postural adjustments phase following SMA downregulation by cTBS (Richard et al. 2017). Such rTMS protocols can also provide evidence that a brain area is not part of a particular function. For example, cTBS applied over the PPC does not influence the capacity to detect changes in the tempo of a beat-based perception task, demonstrating that this brain area does not have an active role in beat perception (Ross, Iversen, and Balasubramaniam 2018). Similar rTMS protocols can be conducted in disease states to identify the involvement of a brain area in a symptom. Using this approach, the cerebellum was found to play a role in essential tremor (Filip et al. 2016), the ipsilateral M1 to contribute to chronic stroke recovery (Werhahn et al. 2003) and the SMA to be involved in hypokinetic symptoms of PD (Hamada et al. 2009). Such studies offer a unique opportunity to study the neural correlates of real FOG episodes. Indeed, when combined with the performance of a FOG-provoking test, modulating the hypothesized neural mechanisms of FOG can give insight on the contribution of certain brain areas in real FOG. To date, only two studies of this type were conducted in FOG. First, despite being interrupted because of too many participants' drop-outs (i.e., discomfort/pain), results of a study demonstrated that high-frequency rTMS over the mPFC reduces FOG occurrence during a FOG-provoking task, supporting the cause-and-effect link between this area and FOG (Dagan et al. 2017). Secondly, iTBS applied on the cerebellum did not improve FOG during a gait protocol known to elicit FOG, but impacted

gait speed, providing evidence for the involvement of the cerebellum in gait disturbances caused by PD (Janssen et al. 2017). Although these studies have some important pitfalls, including the absence of a sham condition in both studies and discomfort experienced by participants during a traditional rTMS protocol, they demonstrate that assessing the role of a brain area in real FOG is feasible.

Chapter 3

Changes in Resting-State Functional Connectivity Related to Freezing of Gait in Parkinson's Disease

PREFACE

As proposed by the Interference model, FOG is the clinical consequence of an inability to concurrently process information from motor, cognitive and limbic cortico-striatal-thalamic circuits. Specifically, when patients encounter a known trigger of FOG while walking, a burst in neural inputs would create a processing overload at the striatum, affecting numerous subsequent projections within the basal ganglia and ultimately leading to an unsuccessful motor output causing FOG (Lewis and Barker 2009). Several brain imaging studies, mainly fMRI conducted while performing a task mimicking walking, support this model (Shine, Matar, Ward, Bolitho, et al. 2013; Gilat et al. 2015; Matar et al. 2013). However, despite FOG being associated to a multi-system network failure and inferring on connectivity changes leading to FOG, no studies attempted to test the Interference model in terms of baseline brain functional connectivity. In this next chapter, we thus quantified changes in brain rs-FC associated with FOG within the Interference model framework. A seed-to-voxel analysis was used to determine how subcortical regions of the Interference model were functionally connected to the whole brain and subsequently compared between freezers and non-freezers. Although no significant changes were observed within regions of the Interference model, an increased connectivity between subcortical nuclei and visual-related areas was observed in freezers. Results highlight the contribution of baseline alterations in brain regions involved in visuospatial processing in FOG.

MANUSCRIPT 1

Changes in resting-state functional connectivity related to freezing of gait in Parkinson's disease

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3.1 Abstract

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease (PD) thought to arise from the dysfunctional cortico-basal ganglia-thalamic circuity. The purpose of this study was to assess the changes in brain resting-state functional connectivity (rs-FC) of subcortical structures comprising the cortico-basal ganglia-thalamic circuity in individuals with PD with and without FOG. Resting-state functional magnetic resonance imaging was acquired in 27 individuals with idiopathic PD (14 with FOG and 13 without FOG). A seed-to-voxel analysis was performed with the seeds in the bilateral basal ganglia nuclei, thalamus, and pedunculopontine nucleus. Between-group differences in rs-FC revealed that the bilateral thalamus and globus pallidus external were significantly more connected with visual areas in PD with FOG compared to PD without FOG. In addition, PD with FOG had increased connectivity between the left putamen and retrosplenial cortex as well as with the cerebellum. Our findings suggest an increased connectivity at rest of subcortical and cortical regions involved in sensory and visuospatial processing that may be compensating for sensorimotor deficits in FOG. This increased connectivity may contribute to the hypothesized overload in the cortico-basal ganglia-thalamic circuity processing capacity, which may ultimately result in FOG occurrence.

3.2 Introduction

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease (PD) defined as a brief and sudden inability to take a step despite the intention to walk (Nutt et al. 2011). FOG is a debilitating symptom that reduces mobility and quality of life and significantly increases the risk of falls (Bloem et al. 2004). Despite the possible devastating consequences of FOG, there are currently no effective treatments and PD dopaminergic medication has variable effects on FOG (Bloem et al. 2004).

Such lack of therapeutic options for FOG is mainly due to our poor understanding of its pathophysiology. The most accepted hypothesis has been proposed by Lewis and Barker (2009) (and later named the Interference model by Nieuwboer and Giladi (2013)). Based on this model, FOG is proposed to emerge from an inability to concurrently process information from motor, cognitive and limbic cortico-striatal-thalamic circuits. When patients encounter challenging situations, an overwhelming increase in neural inputs (i.e., cognitive, limbic and motor) is thought

to provoke a transient overload at the striatum, leading to a disinhibition of the globus pallidus internal (GPi), the output nuclei of the basal ganglia, and thus, to its excessive activity. This would ultimately result in a temporary over inhibition of the thalamus and the brainstem, leading to the paroxysmal phenomenon of FOG (Lewis and Barker 2009). The Interference model has been supported by brain imaging studies showing alterations in cortico-basal ganglia-thalamic systems (Shine, Matar, Ward, Bolitho, et al. 2013; Mitchell et al. 2018). Specifically, FOG-like episodes during foot peddling in a magnetic resonance imaging (MRI) scanner have been associated with increased activation of cognitive and limbic areas, and decreased activation of sensorimotor cortices and subcortical regions (e.g. anterior thalamus, GPi, mesencephalic locomotor region, subthalamic nucleus and caudate head) (Shine, Matar, Ward, Bolitho, et al. 2013). Recently, we used a novel paradigm to measure cerebral metabolism of PD patients with and without FOG during a real complex walking task (i.e., turning) that is known to elicit FOG episodes, using positron emission tomography (Mitchell et al. 2018). These results demonstrate that individuals with FOG have increased activation of the thalamus, motor areas and frontal cognitive regions (i.e., dorsolateral prefrontal cortex), and decreased activation of parietal cognitive areas (e.g. posterior parietal cortex) during challenging gait. Furthermore, it is clear that FOG does not originate from a single isolated brain region, but instead results from impaired communication within the cortico-basal ganglia-thalamic circuity, making it important to adopt a network perspective when studying neural mechanisms of FOG. A novel way to do this is by measuring resting-state functional connectivity (rs-FC), a non-invasive MRI method that quantifies the tendency for functionally linked brain regions to be active simultaneously in the absence of an experimental task. Compared to task-based functional MRI analyses, rs-FC MRI can be used to study multiple neural systems simultaneously, making this type of analysis particularly suitable for studying FOG.

Surprisingly, few studies have examined the neural circuity underlying FOG using rs-FC. FOG has been associated with reduced FC within the visual, the sensorimotor, the attentional, the fronto-parietal and the default mode networks (Tessitore et al. 2012; Canu et al. 2015; Maidan et al. 2019). Furthermore, reduced rs-FC of the mesencephalic locomotor region and the cerebellum locomotor region with the supplementary motor area have been suggested to reflect a less automatic control of movement, while reduced rs-FC between the subthalamic nuclei and the supplementary motor

area has been proposed to reflect a reduced capacity to inhibit competing motor programs in FOG (Fling et al. 2014). rs-FC of the pedunculopontine nuclei, a major nuclei of the mesencephalic locomotor region, was also assessed, reporting an altered FC with visual temporal areas, as well as within the corticopontine-cerebellar pathways (Wang et al. 2016). These results generally support the Interference model by demonstrating altered rs-FC within different networks or between areas involved in the cortico-basal ganglia-thalamic circuity thought to be altered in FOG. However, only one study has directly assessed changes in rs-FC between areas involved in the model, but this study only focused on changes in the limbic circuity (Gilat, Ehgoetz Martens, et al. 2018).

Thus, the purpose of this study was to quantify changes in brain rs-FC associated with FOG within the cortico-basal ganglia-thalamic circuity hypothesized to be involved in FOG. rs-FC of subcortical regions of the cortico-basal ganglia-thalamic circuity was analyzed in patients with (FOG+) and without FOG (FOG-). Based on the Interference model, we hypothesized that FOG+ would have an altered rs-FC within the cortico-basal ganglia-thalamic circuity, favoring an increase in inhibitory drive (Lewis and Barker 2009).

3.3 Experimental Procedures

3.3.1 Participants

Twenty-eight right-handed participants with a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria (Hughes et al. 1992) and Hoehn and Yahr Stage 2 or 3, were recruited through the Quebec Parkinson Network (Table 3.1). Inclusion criteria were a diagnosis of idiopathic PD, no cognitive impairment as assessed by the Montreal Cognitive Assessment (MoCA) (score ≥ 26), and no diagnosis of any other neurological disorders. Patients were classified as exhibiting FOG if they had a score of >1 in Part I of the New Freezing of Gait Questionnaire (NFOGQ) and were further assessed for severity of FOG using Parts II and III of the NFOGQ (Nieuwboer et al. 2009). As shown in Table 3.1, both groups were matched for age, sex, disease duration, motor symptoms severity, medication dosage, anxiety, depression and cognitive function. All participants signed an informed consent form in accordance with the Declaration of Helsinki and the McGill Faculty of Medicine Institutional Review Board

regulations for human subjects' studies. The study was part of a project assessing neural mechanisms of FOG and took place in the ON-medication state (Mitchell et al. 2018).

Table 3.1 *Participants characteristics*

Variables	**FOG+ (n=14)**	**FOG- (n=13)**	**P**
Sex (male/female)	10/4	8/5	0.603
Age (years)	67.7 (7.6)	65.8 (3.4)	0.401
Time since disease onset (years)	7.9 (5.0)	6.0 (4.8)	0.317
Dopa equivalent dose (mg)	874 (514)	677 (394)	0.278
MoCA	27 (2)	27 (2)	0.574
MDS-UPDRS-III	39 (10)	33 (9)	0.122
Hoehn & Yahr scale	**2.5 (0.5)**	**2.1 (0.3)**	**0.015**
NFOGQ score	**14 (7)**	**0 (0)**	**< 0.001**
HADS Anxiety	7 (4)	6 (3)	0.369
HADS Depression	7 (3)	5 (2)	0.059

Mean (standard deviation) presented for all variables except sex which is presented as a proportion. Significant group differences indicated in bold type, *p<0.05.*
MoCA: Montreal Cognitive Assessment
MDS-UPDRSIII: Movement Disorder Society Unified Parkinson's Disease Rating scale (Part III)
NFOGQ: New Freezing of Gait Questionnaire
HADS: Hospital Anxiety and Depression Scale

3.3.2 Image Acquisition

MRI images were acquired on a Siemens 3T Prisma Scanner (Siemens, Knoxville, TN) at the Montreal Neurological Institute (MNI). The acquisition of the T1-weighted anatomical images (echo time = 2.96ms; repetition time=2,300ms, flip angle=9°, 192 slices, voxel size=1mm^3 isotropic) was followed by a 5-minute sequence for BOLD echoplanar (MOSAIC) images at rest (echo time=30ms; repetition time=2,300ms; 38 slices; voxel size=3.5mm^3 isotropic). During resting-state image acquisition, participants were asked to stay awake, clear their mind and fixate a cross placed in front of them.

3.3.3 Image Preprocessing

A resting-state pipeline developed by the Center for Research on Brain, Language and Music (www.crblm.ca) relying on FSL 5.0.8 (FMRIB Software Library, Oxford, UK) and MATLAB 2018b software (http://www.mathworks.com) was used to analyze data. Individual image preprocessing consisted of: (1) discarding the first 5 volumes of each scan to allow the stabilization of the signal, (2) calculating the linear registration transformations connecting the resting-state, anatomical and MNI spaces (3) slice-timing correction using Fourier-space time-series phase shifting, (4) brain extraction using FSL's Brain Extraction Tool (BET), (5) motion correction using rigid-body transformations (3 rotations and 3 translations) as implemented in FSL's Linear Image Registration Tool (FLIRT), (6) global intensity normalization, (7) spatial smoothing using a Gaussian kernel of FWHM 6mm, (8) band-pass filtering performed by MATLAB using a butterworth filter preserving frequencies in the 0.01-0.1Hz range (function filtfilt in Matlab's signal processing toolbox), and (9) removal of motion outlier volumes (Power et al. 2012). Exclusion criteria for head motion was an absolute mean displacement of > 0.70mm. One participant was excluded due to excessive head motion (2.76mm) contrasting significantly with average motion for the remaining participants (0.25 mm ± 0.14). The data presented are thus from 14 FOG+ and 13 FOG-. The absolute mean displacement of the head was calculated for each group and did not reveal any difference ($p = 0.56$).

3.3.4 Seeds

A seed-based FC analysis was performed to identify voxels temporally correlated with the mean time series of eight bilateral subcortical regions that are part of the Interference model. Specifically, seeds included bilateral caudate nuclei, globus pallidus external (GPe), GPi, STN, putamen, ventral striatum, thalamus and pedunculopontine nuclei. Basal ganglia seeds were anatomical masks from the Basal Ganglia Human Area Template atlas (Prodoehl et al. 2008). The ventral striatum seed consisted of a 6mm diameter sphere placed at $x = \pm 9$, $y = 10$, $z = -5$ (Shine, Matar, Ward, Bolitho, et al. 2013). The thalamus masks were created with the WFU PickAtlas tool (Maldjian et al. 2003) using Statistical Parametric Mapping software version 12 (SPM12, Wellcome Centre for Human Imaging, London, UK). Pedunculopontine nucleus masks were taken from the Harvard Ascending Arousal Networks Atlas (Edlow et al. 2012). All seeds were in MNI

standard space and linearly transformed to native space using FLIRT within FSL (FMRIB Software Library, Oxford, UK).

3.3.5 Functional Connectivity Analysis

A rs-FC regression analysis was performed in native space, to produce individual FC maps. To do so, seed regions time series obtained from the preprocessing steps and the nuisance variables time series were entered in a general linear model as predictors, with FMRIB Expert Analysis Tool (FEAT). For each seed, the mean time series was calculated by averaging the BOLD signal from all voxels within the seed region. The following nuisance predictors were included in the analysis: cerebrospinal fluid (CSF), white matter (WM), global signal, motion outlier volume masks, and six motion parameters obtained from the motion correction step (x, y and z translations and rotations). Physiological noise from CSF and WM were computed as follows: masks for CSF and WM were extracted from the T1 image through image segmentation and thresholded at 80% tissue type probability, and then transformed into functional space. The BOLD signal was then averaged over each of these masks, yielding a time series that can be used as nuisance variable.

For the group analysis, resulting rs-FC individual maps were linearly transformed to MNI standard space using FLIRT. First, functional images were aligned to native T1-weighted anatomical images using a 7-degrees of freedom transformation. Then, T1-weighted images were aligned to MNI $2mm^3$ standard space using a 12-degrees of freedom linear affine transformation. Resulting transformation matrices were applied to the native rs-FC maps to obtain the rs-FC map in MNI standard space.

3.3.6 Statistical Analyses

For group-level analyses, Z-statistic rs-FC individual maps were entered into a mixed-effect model using a Bayesian modelling scheme that takes both inter-session and inter-subject random-effect components in the data, as implemented in FLAME, FSL (Woolrich et al. 2004). Correction for multiple comparisons was carried out using a Gaussian random field theory, with a cluster thresholding of $Z > 2.3$ and a cluster significance of $p < 0.05$, corrected (Worsley 2001). Resulting clusters were identified using the Anatomy toolbox implemented in SPM 12. Mean rs-FC from each resulting cluster was also compared between the groups using independent samples t-tests.

Relationships between the severity of PD and FOG with rs-FC were explored with correlations. Pearson's coefficient was used to correlate mean FC measures from clusters showing significant differences between groups, with clinical severity measures in the FOG+ group.

3.4 Results

Between-group differences are presented in Table 3.2 and Figure 3.1. Globally, FOG+ had increased functional connectivity compared to FOG-. No significant decrease in rs-FC was observed in FOG+. FOG+ had significantly higher rs-FC between bilateral thalamus and a large cluster comprising bilateral calcarine, cuneus and middle occipital gyri compared to FOG-. rs-FC between bilateral GPe and visual areas was also significantly higher in FOG+. Finally, rs-FC was significantly higher for FOG+ between the left putamen and a cluster comprising the anterior lobule V of the cerebellum and Brodmann area 29 and 30, both areas forming the retrosplenial cortex. No group differences were observed for the following seeds: bilateral caudate nuclei, bilateral GPi, right putamen, bilateral STN, bilateral ventral striatum and bilateral PPN.

Table 3.2 *Differences in rs-FC between FOG+ and FOG-*

Contrasts	Clusters								
	Seeds	Regions	Brodmann areas	Size (voxels)	MNI Coordinates			Max Z-value	P
					X	Y	Z		
FOG+ > FOG-	Right thalamus	Right calcarine and cuneus gyri	17,18,19	1501	10	-84	10	3.41	< 0.001
	Left thalamus	Right middle occipital and calcarine gyri	17.18	1682	24	-104	22	3.75	< 0.001
	Left putamen	Left lingual gyrus, cerebellum (anterior lobule V)	29, 30	710	-10	-56	2	3.70	0.036
	Right GPe	Right calcarine, right cuneus gyri	18	881	2	-100	2	3.34	0.012
	Left GPe	Right and left calcarine gyri	18.19	1026	20	-86	14	3.33	0.004

GPe: globus pallidus external
MNI: Montreal Neurological Institute standard space
FOG+: PD with freezing of gait
FOG-: PD without freezing of gait

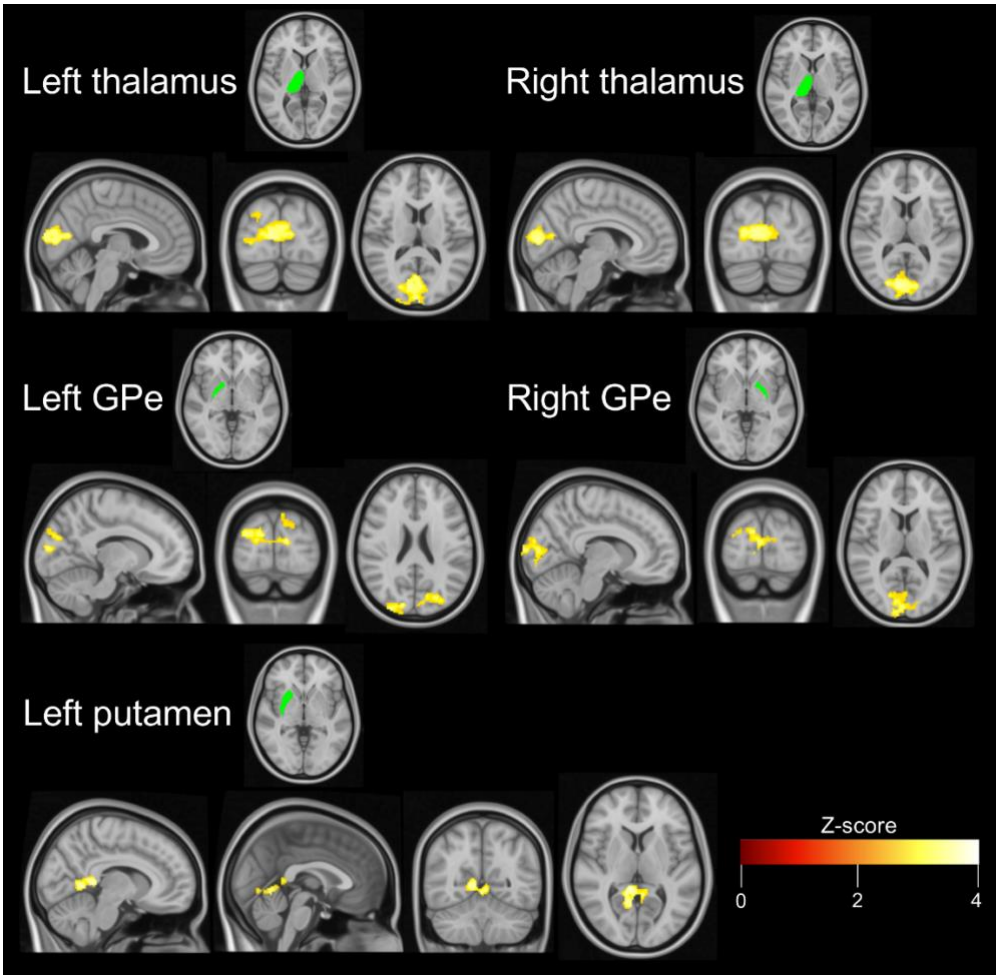

Figure 3.1 *Statistical maps (Z-score) for each seed showing significant between-group differences. rs-FC of the seeds is greater for FOG+ versus FOG- (FOG+ > FOG-). Mask of the seeds are presented in green and axial slices show largest mask area. $p < 0.05$ corrected. GPe: globus pallidus external.*

Mean rs-FC between the resulting clusters and their seed for both groups are presented in Figure 3.2. In FOG+, positive rs-FC was found between all the seeds and their corresponding cluster. In comparison, in FOG-, rs-FC between all the seeds and their corresponding cluster was negative, representing an anti-coupling (i.e., anti-correlation). For the left putamen in FOG-, mean rs-FC with its cluster (i.e., retrosplenial cortex and cerebellum) was near 0, representing no relationship between those two areas.

Mean rs-FC between the resulting clusters and their seeds did not correlate with any of FOG or PD severity measures.

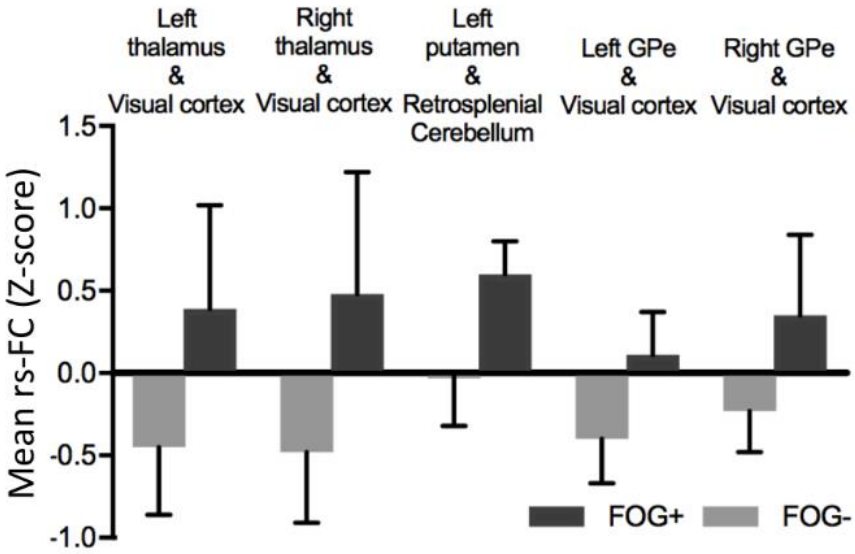

Figure 3.2 *Mean rs-FC strength (Z-score) between the seeds showing significant between-group differences and their cluster for each group. Mean rs-FC is significantly different between the groups for each seed ($p < 0.001$). Positive values represent a positive connectivity, while negative values represent a negative connectivity (i.e., anti-coupling). GPe: globus pallidus external; rs-FC: resting-state functional connectivity.*

3.5 Discussion

This is the first study to assess rs-FC changes in the motor, cognitive and limbic cortico-basal ganglia-thalamic circuits thought be dysfunctional in PD with FOG. Our findings show that in FOG+, the bilateral thalamus and GPe are more connected with visual areas, and that the left putamen has higher connectivity with the retrosplenial cortex and the cerebellum. These results provide evidence for altered functional connectivity within subcortical and cortical sensory and visuospatial processing regions that may contribute to the striatal overload suggested by the Interference model.

The increased rs-FC observed in this study between the bilateral thalamus and visual areas may represent a compensatory mechanism to counteract the atrophy and reduced metabolism of these areas in FOG+. Specifically, the thalamus has been shown to have reduced spontaneous activity at rest (Mi et al. 2017), metabolism during motor arrests (Shine, Matar, Ward, Bolitho, et al. 2013) and volume (Sunwoo et al. 2013). The visual cortex is also atrophied (Tessitore et al. 2012), and has reduced metabolism compared to FOG- (Tard et al. 2015), and white matter damages have

been observed in the posterior thalamic projections connecting the thalamus with the visual cortex of FOG+ (Wang et al. 2016). Furthermore, rs-FC between the thalamus and visual areas is negative in healthy individuals (Zou et al. 2009), a similar pattern we observed in FOG-. Therefore, the thalamus and visual areas are anti-coupled, meaning that when spontaneous activity increases in one, the other one synchronously decreases its spontaneous activity. This is thought to arise from the differential task-related responses of these areas, whereas at rest, the thalamus maintains the standby state of the brain, and the visual areas are not particularly solicited due to minimal visual input (Zou et al. 2009).

In the current study, we observed a switch from negative to positive connectivity in FOG+, meaning that the thalamus and visual areas are spontaneously active at the same time. We propose that this compensatory mechanism could be maladaptive and might predispose to an excessive increase in cortical inputs, and thus to a striatal overload when patients are actually walking. The increased connectivity observed in this study between the bilateral GPe and the visual cortex could be similarly associated with FOG. It is also supported by a study showing that in non-human primates, GPe contain visual specialized neurons that are thought to be involved in the rejection of valueless visual elements (Kim, Amita, and Hikosaka 2017).

Increased connectivity between the left putamen and the retrosplenial cortex was also observed in FOG+. The retrosplenial cortex has been associated with spatial cognition, more specifically with the ability to set up and retrieve spatial schemas for orientation (Mitchell et al. 2018). Recently, Brodmann area 30, which composes the retrosplenial cortex, has been shown to be anatomically, but not functionally, connected to the putamen in healthy individuals (Li et al. 2018). Similarly and consistent with previous literature in PD (Simioni, Dagher, and Fellows 2016), we found negative, but almost null, connectivity between these two areas in FOG-. In patients with FOG, metabolism of Brodmann area 30 has been shown to be significantly higher (Tard et al. 2015), demonstrating that they do recruit the retrosplenial cortex compared to patients without FOG. In accordance, we found that in FOG+, the putamen and the retrosplenial cortex are more functionally connected. This may be a compensatory mechanism for poor visuospatial skills of patients with FOG (Nantel et al. 2012), whereas the putamen and the retrosplenial cortex start to communicate to retrieve spatial schemas to perform appropriate motor processing for locomotion. However, in

support of the Interference model, we suggest that this compensatory mechanism possibly increases the total amount of processing, and thus, may contribute to a striatal overload leading to FOG.

The left putamen was also significantly more connected to the culmen of the cerebellum in FOG+. This is consistent with a previous study showing that the rs-FC between the putamen and motor regions of the cerebellum was higher in PD patients compared to healthy individuals, and that this connectivity was back to healthy individuals' values when L-DOPA was administered (Simioni, Dagher, and Fellows 2016). The authors have suggested that the increased putamen-cerebellar connectivity was a compensatory mechanism indirectly resulting from the loss of dopamine innervation to the putamen in order to optimize the motor performance. Our findings demonstrate that putamen-cerebellar connectivity is even more enhanced in FOG+, even though patients were on their PD medication. We propose that it might represent an effort to compensate for dysfunctional cortico-basal ganglia-thalamic circuity in FOG+.

We did not find any significant correlations between clinical measures and changes in rs-FC, meaning that changes in rs-FC were not more substantial with increased or decreasing FOG severity. However, FOG was self-reported rather than objectively measured, and thus, severity of FOG measure might have been biased. This may partially explain the absence of correlation between FOG severity and changes in rs-FC. Another consideration is the relatively small sample size, reducing the statistical power, increasing false negatives and diminishing the possibility to generalize the results to all patients with FOG. Thus, to ensure reliability of our findings, especially in rs-FC, future studies should include a greater sample size. Future work could also compare changes in rs-FC between FOG+, FOG- and healthy individuals.

In conclusion, the main finding of this study suggests that in PD with FOG there is increased connectivity between subcortical and cortical brain regions involved in sensory and visuospatial processing. This may represent a compensatory neural mechanism for sensorimotor deficits in PD with FOG. Importantly, this increased connectivity may interfere with the processing capacity of the cortico-basal ganglia thalamic circuity suggested by the Interference model, which may ultimately result in FOG.

3.6 Acknowledgements

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Chapter 4

Levodopa alters resting-state functional connectivity more selectively in Parkinson's Disease with freezing of gait.

PREFACE

In Chapter 3, we identified significant changes in brain rs-FC that characterize FOG. While no changes were found within the Interference model per se, results indicate that a shift from anti-coupling to positive connectivity between subcortical and cortical regions involved in sensory and visuospatial processing could predispose to FOG in an active state. However, this data was acquired when participants were on their dopaminergic medication (i.e., L-DOPA). Although commonly taken by patients for their overall PD symptoms, the control of FOG by L-DOPA is far from optimal. Indeed, FOG episodes nevertheless occur in the ON-medication state (Amboni et al. 2015) and are, in some cases, worsened by levodopa (Espay et al. 2012). Previous studies explored levodopa-modulation of gait neural correlates during an imagery task (Maillet et al. 2015) and of the prefrontal cortex during real walking (Dagan et al. 2020), both only in freezers without a PD control group. Furthermore, no studies have yet focused on the baseline state of the neural networks associated specifically with FOG in ON- and OFF-medication states. Chapter 4 demonstrates for the first time how L-DOPA intake increases brain functional organization selectively in freezers within the Interference model. Findings suggest that L-DOPA could contribute to better sensorimotor, cognitive, and limbic processing to prevent FOG, but could also contribute to FOG by interfering with the processing capacity of the striatum. These results are crucial for a better understanding of the inconsistent effectiveness of L-DOPA on FOG.

MANUSCRIPT 2

Levodopa alters resting-state functional connectivity more selectively in Parkinson's Disease with freezing of gait

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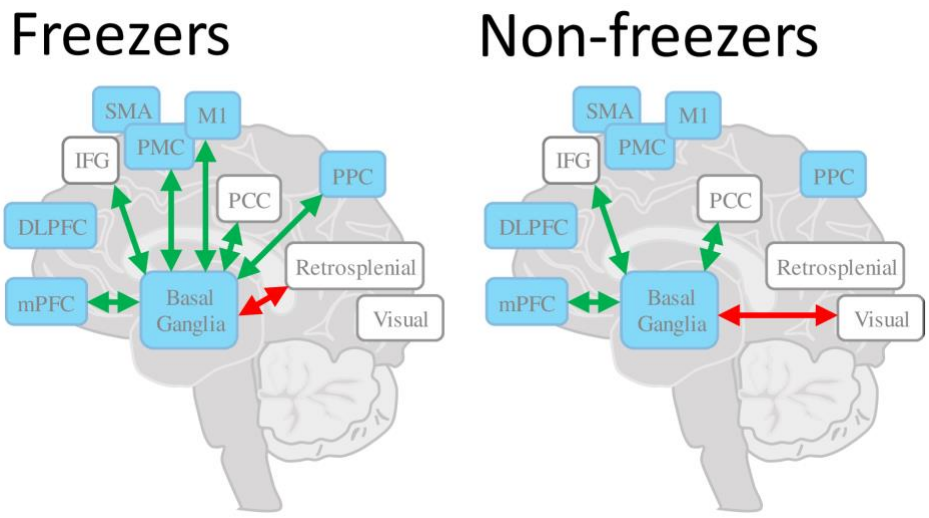

Figure 4.1 *Graphical abstract. This study shows that Levodopa taken to control Parkinson's disease symptoms, induces changes in functional connectivity at rest, in freezers only. Increases (green) in functional connectivity of GPe, GPi, putamen, and thalamus with cognitive, sensorimotor, and limbic cortical regions of the Interference model (blue) was observed. Our results suggest that levodopa can normalize connections similar to non-freezers or increases connectivity to compensate for dysfunctional networks.*

4.1 Abstract

Freezing of gait (FOG) is a debilitating motor symptom of Parkinson's disease (PD). Although PD dopaminergic medication (L-DOPA) seems to generally reduce FOG severity, its effect on neural mechanisms of FOG remains to be determined. The purpose of this study was to quantify the effect of L-DOPA on brain resting-state functional connectivity in individuals with FOG. Functional magnetic resonance imaging was acquired at rest in 30 individuals living with PD (15 freezers) in the ON- and OFF- medication state. A seed-to-voxel analysis was performed with seeds in the bilateral basal ganglia nuclei, the thalamus and the mesencephalic locomotor region. In freezers, medication-state contrasts revealed numerous changes in resting-state functional connectivity, not modulated by L-DOPA in non-freezers. In freezers, L-DOPA increased the functional connectivity between the seeds and regions including the posterior parietal, the posterior cingulate, the motor and the medial prefrontal cortices. Comparisons with non-freezers revealed that L-DOPA generally normalizes brain functional connectivity to non-freezers levels but can also increase functional connectivity, possibly compensating for dysfunctional networks in freezers. Our findings suggest that L-DOPA could contribute to a better sensorimotor, attentional, response

inhibition and limbic processing to prevent FOG when triggers are encountered but could also contribute to FOG by interfering with the processing capacity of the striatum.

4.2 Introduction

Freezing of gait (FOG) is a motor symptom of Parkinson's disease (PD) characterized by a brief and sudden inability to take a step despite the intention to walk (Nutt et al. 2011) that affects up to 79% of individuals with advanced PD (Tan et al. 2011). Although FOG leads to debilitating consequences such as reduced quality of life and increased risks of falls (Bloem et al. 2004), no reliable treatments currently exist to alleviate this symptom (Zach et al. 2015). People with PD thus rely on their dopaminergic medication to better control FOG. However, the effects of levodopa (L-DOPA) on FOG are variable. Overall, L-DOPA seems to reduce the frequency and the duration of FOG (Koehler, Nonnekes, and Bloem 2019), but FOG episodes are still observed after its intake (Schaafsma et al. 2003) and it is not effective in preventing falls (Bloem et al. 2004). Although less common, in some cases, L-DOPA can induce FOG (Moreira, Rebelo Gomes, and Januário 2019) and in L-DOPA supra-state, even increase its severity (Espay et al. 2012). Responsiveness of FOG to L-DOPA has also been used to categorize FOG (Mckay et al. 2019; Amboni et al. 2015; Schaafsma et al. 2003). Based on a patient questionnaire, 62% of FOG patients declared having FOG only in the OFF-state, 36% in both ON- and OFF-state and 2% only in the ON-state (Amboni et al. 2015). This type of classification is however still controversial. Some argue that FOG occurring in both states could result from inadequate treatment, while others demonstrated that FOG is still present despite controlling L-DOPA serum levels (Mckay et al. 2019). It is thus clear that more studies are needed to elucidate the relationship between FOG and L-DOPA.

Several hypotheses attempt to explain the neural causes of FOG (Nieuwboer and Giladi 2013), but the most inclusive and accepted of them is the Interference model (Lewis and Barker 2009). According to this model, FOG would be the paroxysmal result of an overload in the processing capacity at the striatum level following a substantial increase in motor, cognitive and/or limbic inputs. This would in turn alter striatal control over the globus pallidus internal (GPi) and increase inhibitory and oscillatory output from the GPi. The activity of the thalamus, the cerebellar locomotor region (CLR), the mesencephalic locomotor regions (MLR), and ultimately the spinal

pattern generators, would thus be transiently altered, ultimately causing FOG. The very few studies that explored L-DOPA modulation of neural correlates of gait in FOG did find dopa-specific changes during an imagery task (Maillet et al. 2015) and during real walking (Dagan et al. 2020). Interestingly, no studies have investigated how L-DOPA modifies neural networks of FOG nor how these modulations differ from participants with PD who do not freeze. To better characterize the effects of L-DOPA on the neural mechanisms of FOG, the purpose of this study was to determine the effect of PD dopaminergic medication on brain resting-state functional connectivity (rs-FC) in individuals with FOG within the Interference model framework. rs-FC is a measure quantifying the tendency of functionally linked brain regions, simultaneously active, during rest, in the absence of an experimental task. Our previous study demonstrated that rs-FC can detect FOG-specific changes in connectivity (Potvin-Desrochers et al. 2019). In PD, studies suggest that L-DOPA therapy normalizes atypical rs-FC in the cortico-striato-thalamic network which could account for the improvement in PD symptoms when in the ON-state (Tahmasian et al. 2015). Thus, we hypothesized that L-DOPA would normalize the abnormal rs-FC of brain regions proposed by the Interference model specifically for PD with FOG to functional connectivity levels similar to non-freezers PD.

4.3 Methods

4.3.1 Participants

Sixteen freezers (FOG+) and sixteen non-freezers (FOG-), all right-handed participants, took part in this study. Fifteen participants (9 FOG+) were recruited as part of a previous study (Potvin-Desrochers et al. 2019), and the remaining participants were recruited from the Quebec Parkinson Network. Inclusion criteria were a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria (Hughes et al. 1992), no change in dopaminergic therapy for 6 months, no medication-induced FOG, and no diagnosis of any other neurological disorder. Participants were classified as FOG+ if they had a score of >1 in Part I of the New Freezing of Gait Questionnaire (NFOGQ) (Nieuwboer et al. 2009), as typical for FOG studies (Maidan et al. 2019; Lench et al. 2021). One FOG+ and 1 FOG- were excluded due to abnormal findings (i.e., ventriculomegaly and T1-hypointense temporal lobe lesion) on anatomical magnetic resonance images (MRI). The data presented is thus for 15 FOG+ (8 females, mean age 69±8) and 15 FOG- (6 females, mean age 64±6), with demographic details provided in Table 4.1.

Dopaminergic medication taken by each participant is listed in Supplementary Table S4.1. All participants provided written informed consent in accordance with the Declaration of Helsinki and the McGill Faculty of Medicine Institutional Review Board regulations for studies on human participants.

Table 4.1 *Participants characteristics*

Variables	FOG+		FOG-		*P (FOG+ vs FOG-)*	*P (ON vs OFF)*	
	Mean (SD)	Range	Mean (SD)	Range		*FOG+*	*FOG-*
Sex (male/female)	7/8	n.a.	9/6	n.a.	.464		
Age (years)	**69 (8)**	56-85	**64 (6)**	54-75	**.049**		
Disease duration (years)	**8 (4)**	1-17	**4 (3)**	1-11	**.008**		
L-DOPA equivalent dose (mg)	882 (442)	100-1,700	572 (394)	225-13,00	.052		
NFOGQ score	**12 (5)**	4-22	**0 (0)**	N/A	**<.001**	n.a.	
Hoehn & Yarh scale	2.5 (0.5)	2-3	2 (0)	2-2.5	.840		
MoCA	27 (2)	21-30	28 (1)	26-30	.098		
TMT A	37 (20)	15-100	28 (9)	17-48	.113		
TMT B	66 (19)	33-232	71 (38)	39-190	.691		
MDS-UPDRS III - ON	**37 (9)**	23-51	**26 (9)**	16-43	**.004**	**<.001**	**<.001**
MDS-UPDRS III - OFF	**54 (12)**	40-77	**43 (13)**	27-73	**.015**		
HADS anxiety ON	8 (5)	0-18	**6 (4)**	1-14	.073	0.411	**0.047**
HADS anxiety OFF	7 (4)	1-16	**5 (3)**	1-17	.507		
HADS depression ON	8 (4)	1-13	7 (5)	0-9	.096	0.160	0.373
HADS depression OFF	**7 (4)**	1-12	**5 (3)**	1-9	**.040**		

Sex is presented as a proportion.
Significant group and medication-state differences are indicated in bold type, $P < .05$.
FOG+: Participants with freezing of gait
FOG- : Participants without freezing of gait
SD: Standard deviation
L-DOPA: levodopa
NFOGQ: New Freezing of Gait Questionnaire.
MDS-UPDRSIII: Movement Disorder Society Unified Parkinson's Disease Rating scale (Part III).
HADS: Hospital Anxiety and Depression Scale.
MoCA: Montreal Cognitive Assessment.
TMT A & B: Trail Making Test Part A & Part B
n.a.: not applicable

4.3.2 Experimental Design

In 25 participants, both rs-MRI scans were acquired on the same day with OFF-medication-state scan acquired first. Participants arrived in the morning at our facilities in the OFF-state after ~12h withdrawal from all dopaminergic medication by skipping their usual morning dose of medication.

The OFF rs-MRI scan was followed by clinical assessments as described in 4.3.3. Participants then took their usual morning dose of dopaminergic medication and waited ~1h (mean 60 [SD 12] minutes) to be in the ON-state before undergoing a second series of rs-fMRI and clinical assessments. ON-state rs-fMRI was used from a recent study (Potvin-Desrochers et al. 2019) for the five remaining participants. These participants had no change in their medication and no clinically nor statistically significant differences in their clinical assessment since their participation in that previous study (p=0.621, maximum difference in UPDRS = 2 points), as seen in Supplementary Table S4.2. They were thus included in the study and therefore only performed the OFF-medication rs-fMRI assessment followed by clinical assessments. The average time between the ON- and OFF-state scans for these five participants was 42 (SD 8) weeks.

4.3.3 Clinical Assessment

Motor symptoms and PD severity were assessed using the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS-III)(Goetz et al. 2008), and the NFOGQ and the Characterizing FOG questionnaire (CFOG)(Ehgoetz Martens et al. 2018) assessed the severity and the multidimensional complexity of FOG, respectively. The MoCA (Nasreddine et al. 2005) and the Trail Making Test (Reitan 1958) were administered to assess cognitive function, and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) to evaluate general mood. Clinical assessments were performed in the ON- and OFF-state, except for the MoCA and the TMT, performed only following medication intake.

4.3.4 Image Acquisition

MRI images were acquired on a Siemens 3T Prisma Scanner (Siemens, Knoxville, TN) at the Montreal Neurological Institute (MNI) in Montreal, Canada. In addition to the 5-min sequence for BOLD echoplanar (MOSAIC) images obtained at rest (echo time=30ms; repetition time=2300ms; 38 slices; voxel size=3.5mm^3 isotropic), a T1-weighted anatomical images (echo time=2.96 ms; repetition time=2300ms, flip angle=9°, 192 slices, voxel size=1mm^3 isotropic) was acquired in the ON-state. During resting-state image acquisition, participants were asked to stay awake, clear their mind, keep their eyes open while fixating a cross placed in front of them.

4.3.5 Image Analysis

A resting-state pipeline developed by the Center for Research on Brain, Language and Music relying on FSL 5.0.8 (FMRIB Software Library, Oxford, UK) and MATLAB R2019b (MathWorks Inc., Natick, MA, USA) was used to preprocess the data and perform the analysis. Details of the analysis can be found in Figure 4.1 and in Potvin-Desrochers et al. (2019). Briefly, a seed-based FC analysis was performed for each participant in their native space to identify voxels temporally correlated with the mean BOLD signal of 9 seeds bilaterally, for a total of 18 seeds. The seeds consisted of the subcortical regions involved in the Interference model, namely, the caudate nuclei, putamen, ventral striatum, globus pallidus external (GPe), GPi, subthalamic nucleus (STN), thalamus, the pedunculopontine nucleus (PPN) and the CLR. The basal ganglia seeds were anatomical masks from the Basal Ganglia Human Area Template atlas (Prodoehl et al. 2008). The ventral striatum and the CLR each consisted of a 6 mm sphere placed at, respectively, x=±9, y=10, z=-5 (Shine, Matar, Ward, Bolitho, et al. 2013) and x=±6, y= -48, z=-14 (Fasano et al. 2017). PPN masks were taken from the Harvard Ascending Arousal Networks Atlas (Edlow et al. 2012).

Absolute mean head displacement in the scanner did not differ between the medication-states but was higher in FOG+ (OFF: 0.35[SD 0.23]mm, ON: 0.33[SD 0.19]mm) compared to FOG- (OFF: 0.21[SD 0.06]mm, ON: 0.18[SD 0.09]mm; $p<0.0001$). No participant was excluded due to excessive head motion.

4.3.6 Statistical Analyses

To determine the effect of medication on rs-FC in FOG+, medication-state contrasts were performed. Z-statistic rs-FC individual maps of FOG+ were entered into a mixed-effect model using a Bayesian modeling scheme implemented in FLAME, FSL, with time between scans as a confounder (Woolrich et al. 2004), as shown in Figure 4.1. Correction for multiple comparisons was carried out using a Gaussian random field theory, with cluster and significance thresholds set at $Z>2.6$ and $p<0.05$, respectively (Worsley 2001). Given the sample size, we used more liberal thresholds (Bharti et al. 2018; Lench et al. 2020, 2021). As a supplementary analysis, medication-state contrasts were also performed in FOG-, but only for the seeds that resulted in significant clusters for FOG+. Resulting clusters were identified using the Anatomy toolbox implemented in

Statistical Parametric Mapping software version 12 (SPM12, Wellcome Centre for Human Imaging, London, UK).

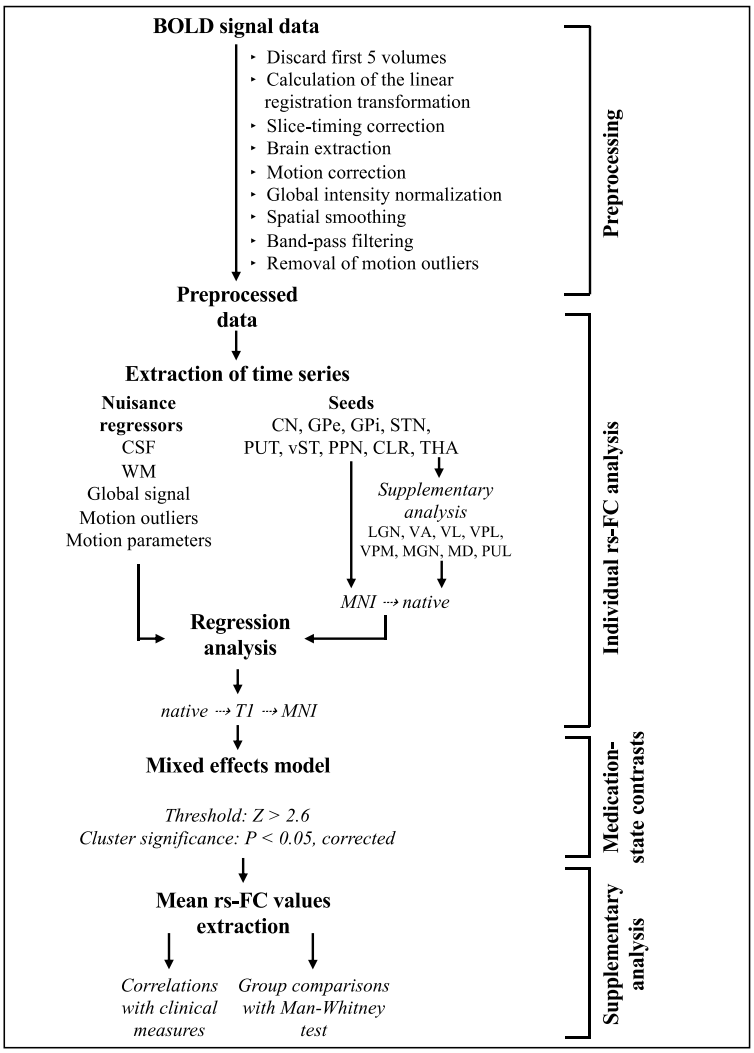

Figure 4.2 *Schema of the resting-state pipeline's analysis steps. BOLD: blood-oxygen-level-dependent, CSF: cerebrospinal fluid, WM: white matter, CN: caudate nucleus, GPe: globus pallidus external, GPi: globus pallidus internal, STN: subthalamic nucleus, PUT: putamen, vST: ventral striatum, PPN: pedunculopontine nucleus, CLR: cerebellar locomotor region, THA: thalamus, LGN: lateral geniculate nucleus, VA: ventral anterior nucleus, VL: ventral lateral nucleus, VPL: ventral posterior lateral nuclei, VPM: ventral posterior medial nuclei, MGN: medial geniculate nuclei, PUL: pulvinar, MNI: Montreal Neurological Institute, rs-FC: resting-state functional connectivity.*

Because medication-state contrast revealed numerous results for the thalamus seeds in FOG+, a supplementary analysis was conducted. The resting-state analysis was repeated with 8 bilateral thalamic nuclei seeds for a total of 16 seeds (lateral geniculate nuclei, ventral anterior nuclei, ventral lateral nuclei, ventral posterior lateral nuclei, ventral posterior medial nuclei, medial geniculate nuclei, medial dorsal nuclei and pulvinar) and medication-state contrasts were performed. Thalamus masks were created with the WFU PickAtlas tool (Maldjian et al. 2003) using SPM12.

For all significant clusters, their mean rs-FC was extracted and compared to identify differences between groups and medication-states. Mean values were not normally distributed as assessed with the Shapiro-Wilk test of normality. Mann-WhitneyU tests were therefore used to locate significant differences. Relationships between clinical measures and the medication-induced changes in mean rs-FC of all the significant clusters in FOG+ were assessed using Spearman's rho correlation with a $p<0.01$.

4.4 Results

4.4.1 Participants Characteristics

Participant characteristics are presented in Table 4.1. All freezers reported an improvement in their FOG with L-DOPA, based on item 4 of the CFOG questionnaire. Among those, 10 reported having no FOG in the ON-state. FOG phenotypes were defined for each FOG+ participant according to the CFOG questionnaire and can be found in Table S4.3. Both groups had similar L-DOPA equivalent dose, Hoehn & Yarh, MoCA, TMT A & B, HADS Anxiety & Depression ON and HADS Anxiety OFF. FOG+ were on average 5 years older, with a longer disease duration (mean of 4 years), a higher score on the MDS-UPDRS III (mean increase of 11 in OFF versus ON), and an increase of 2 points in the HADS Depression OFF.

4.4.2 L-DOPA Alters Functional Connectivity Differently in FOG+

In the FOG+ group, medication altered the connectivity of the seeds with many more regions than in FOG-, as observed in Table 4.2. None of the functionally connected regions altered by L-DOPA in FOG+ were modulated by L-DOPA in FOG-.

Medication-state contrasts for FOG+ only are presented in Figure 4.2 and Table 4.2. There was

increased functional connectivity ON medication (Figure 4.2A, ON>OFF contrast) between the seeds and multiple common regions. The bilateral seeds for the thalamus, putamen and GPe, as well as the left GPi, were all significantly connected to clusters of functional regions identified as the right posterior parietal cortex (PPC, blue in Figure 4.2A). rs-FC between the bilateral GPe and the right putamen seeds and the posterior cingulate cortex (green in Figure 4.2A) was also significantly increased in the ON-state for FOG+. L-DOPA significantly increased rs-FC between the left GPe, left GPi, bilateral thalamus and bilateral putamen with clusters comprising the right inferior frontal gyrus (IFG, red in Figure 4.2A) and the right motor cortices including the premotor and the primary motor cortices (pink in Figure 4.2A). Finally, in the ON-state, the right thalamus had increased functional connectivity with a cluster located in the anterior cingulate gyrus, identified as the medial prefrontal cortex (mPFC, yellow in Figure 4.2A). The rs-FC decreased in the ON-state (ON<OFF contrast) only between the left thalamus seed and a cluster comprising the left thalamus and a region of the left calcarine gyrus identified as the retrosplenial cortex (teal in Figure 4.2B).

Medication-state contrasts for FOG- are presented in Table 4.2. The functional connectivity of regions shown to be changed by L-DOPA in FOG+ is not altered by L-DOPA in FOG-. Instead, rs-FC increased after L-DOPA intake between the right GPe and right IFG, left GPi and left dorsolateral prefrontal cortex, as well as with the right thalamus and bilateral cingulate cortex. L-DOPA also decreased rs-FC between the left GPi and visual areas.

4.4.3 L-DOPA Alters the Magnitude of Functional Connectivity Differently in FOG+ and FOG-

Mean rs-FC between the seeds showing significant medication-state differences in FOG+ and their clusters are shown in Figure 4.3 for both groups. The magnitude of rs-FC was not altered by L-DOPA in FOG-.

After L-DOPA intake, mean ON-state rs-FC of the PPC clusters with their seed regions was generally significantly higher in FOG+ compared to FOG- (Figure 4.3AB). The change in rs-FC with L-DOPA between the right putamen and the right PPC was negatively correlated to the disease duration (r_s=-0.65, p=0.008). The rs-FC between the left GPi and the right PPC was also increased after L-DOPA intake in FOG+, but was still significantly lower than FOG- (Figure 4.3A)

Table 4.2 *Differences in rs-FC between ON-medication and OFF-medication states in FOG+ and FOG-.*

Groups	Contrasts	Clusters									
		Seeds	Regions	Functional ID	Brodmann areas	Size (voxels)	MNI Coordinates			Max Z-value	P
							X	Y	Z		
FOG+	ON > OFF	Left GPe	Right posterior cingulate cortex	Cingulate	23, 31	3685	11	-38	41	4.42	0.007
			Right inferior frontal & precentral gyri	Motor & IFG	6, 9, 45	4553	57	27	19	2.73	0.002
			Right superior temporal gyrus, inferior parietal lobule	PPC	39, 40	8811	39	-46	41	4.3	<0.001
		Right GPe	Bilateral posterior cingulate cortices	Cingulate	23, 31	5530	0	-12	28	4.43	<0.001
			Right superior temporal gyrus, inferior parietal lobule	PPC	39, 40	7641	69	-50	16	4.36	<0.001
		Left GPi	Right inferior frontal & precentral gyri	Motor & IFG	4, 6, 44	3399	34	12	27	4.43	0.014
			Right supramarginal gyrus	PPC	39 ,40	3713	38	-43	41	4.32	0.008
		Left Putamen	Right inferior frontal & precentral gyri	Motor & IFG	6, 44	2517	44	14	28	4.22	0.047
			Right angular & supramarginal gyri	PPC	39, 40	5463	62	-52	32	3.94	<0.001
		Right Putamen	Bilateral posterior cingulate cortices	Cingulate	23	4092	-2	-14	27	4.42	0.003
			Right angular & supramarginal gyrus	PPC	39, 40	4259	60	-56	38	4.47	0.002
			Right precentral & inferior frontal gyri	Motor & IFG	4, 6, 44	5387	46	-9	31	3.72	<0.001
		Left Thalamus	Right inferior parietal lobule	PPC	39	6083	61	-63	25	4.06	<0.001
			Right precentral & inferior frontal gyri	Motor & IFG	44	6591	61	16	9	4.91	<0.001
			Left supramarginal gyrus	PPC	39, 40	8132	-64	-47	23	4.65	<0.001
		Right Thalamus	Right supramarginal gyrus	PPC	39, 40	2852	70	-30	34	3.79	0.019
			Left supramarginal gyrus	PPC	39, 40	3781	-71	-40	29	4.39	0.004
			Left superior medial gyrus, right anterior cingulate gyrus	mPFC	9, 10, 33	6811	-7	55	17	4.9	<0.001
			Right inferior frontal & precentral gyri	Motor & IFG	44	6869	59	16	7	5.65	<0.001
	ON < OFF	Left Thalamus	Right thalamus, calcarine gyrus	Thalamus & retrosplenial	29, 30	2567	8	-33	11	4.81	0.003
FOG-	ON > OFF	Right GPe	Right inferior frontal gyrus opercularis, orbitalis & triangularis	IFG	44, 45, 47	3695	46	17	20	4.42	0.005
		Left GPi	Left middle frontal gyrus	DLPFC	10, 46	3365	-35	49	19	3.88	0.009
		Right Thalamus	Bilateral medial cingulate cortices	Cingulate	24, 32	2623	6	27	32	3.70	0.030
	ON < OFF	Left GPi	Right inferior occipital & temporal gyri	Visual	19, 37	2662	42	-78	-2	3.90	0.031

FOG+: Participant with freezing of gait
FOG-: Participant without freezing of gait
ON: On dopaminergic medication
OFF: Off dopaminergic medication
ID: Identification
MNI: Montreal Neurological Institute
GPe: Globus Pallidus external
GPi: Globus Pallidus internal
IFG: Inferior Frontal Gyrus
PPC: Posterior Parietal Cortex
mPFC: Medial Prefrontal Cortex
DLPFC: Dorsolateral Prefronta

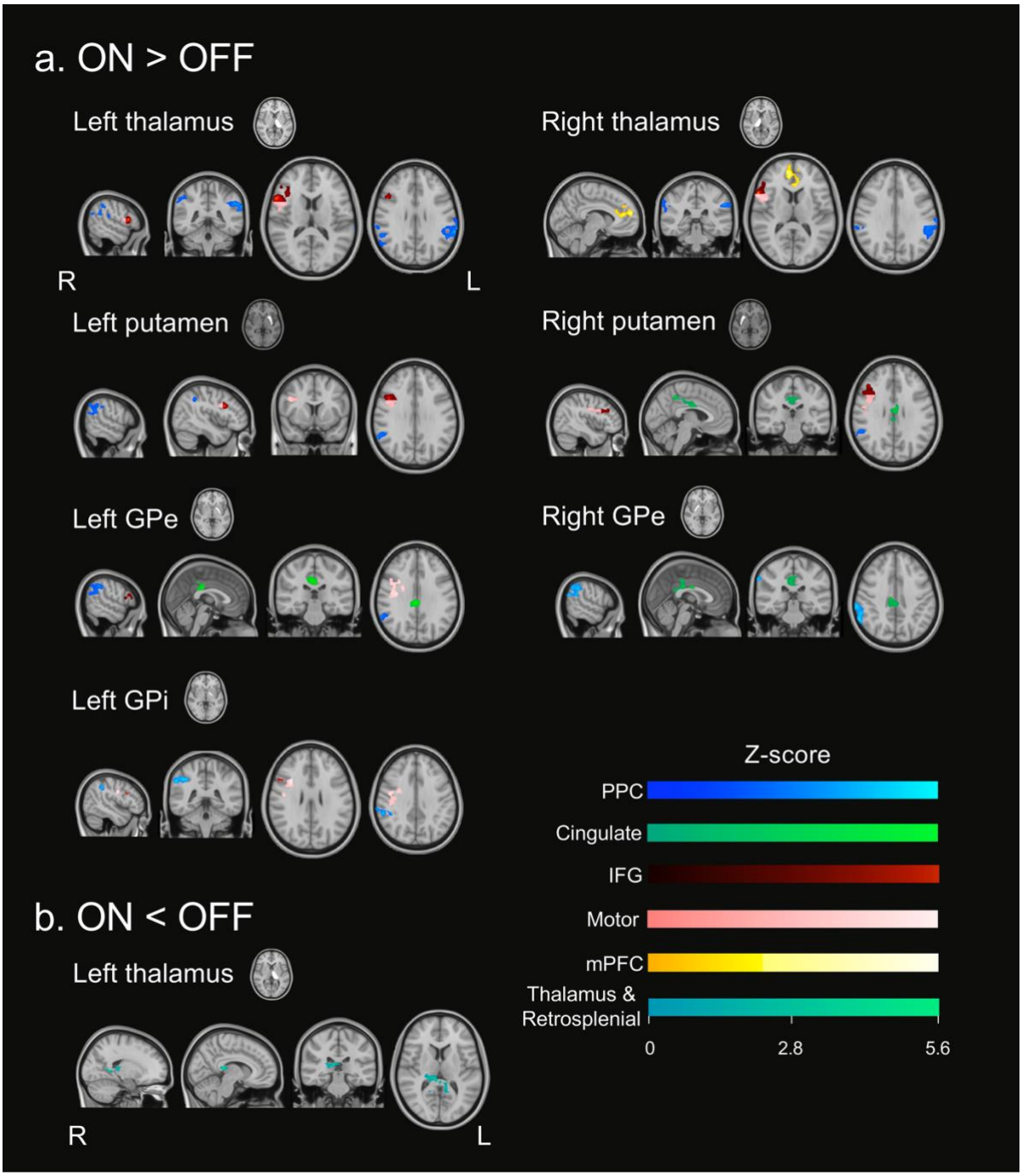

Figure 4.3 *Statistical maps (Z-score) for each seed showing significant medication-state differences in FOG+. The color of the Z-score scale identifies each cluster region. Masks of each seed are presented in white to the right of each seed label.* ***A*** *shows rs-FC greater when FOG+ are ON versus OFF, and* ***B*** *shows rs-FC greater when FOG+ are OFF versus ON. P < .05, corrected. R: right, L: left, GPe: globus pallidus external, GPi: globus pallidus internal, PPC: posterior parietal cortex, IFG: inferior frontal gyrus, mPFC: medial prefrontal cortex, ON: On dopaminergic medication, OFF: Off dopaminergic medication.*

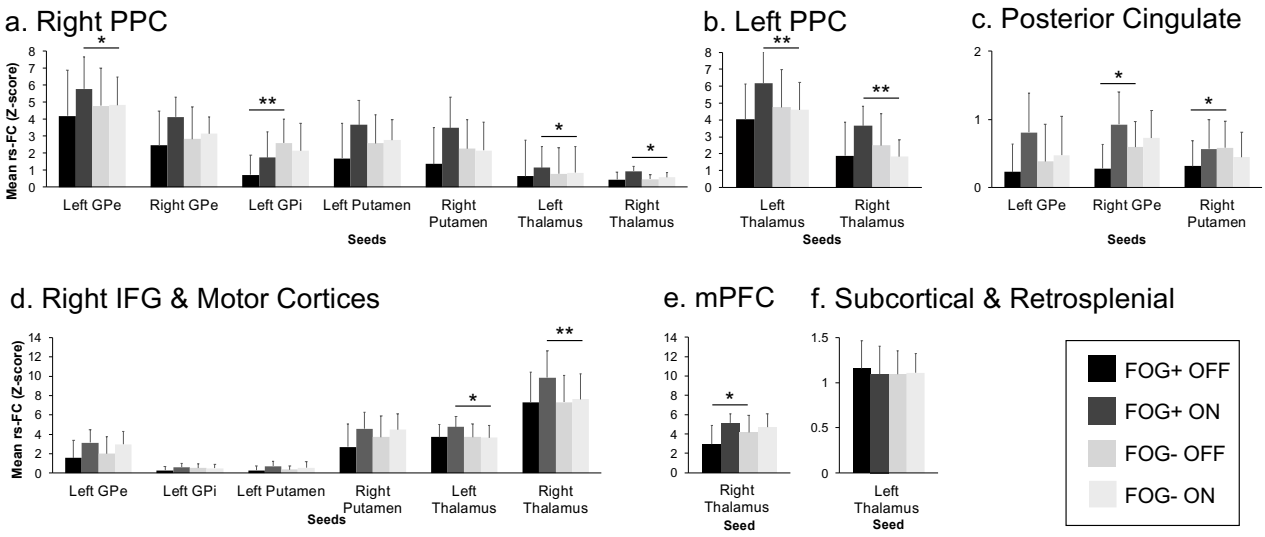

Figure 4.4 *Mean rs-FC strength (Z-score) between the seeds showing significant medication-state differences in FOG+ and their clusters for both groups. Mean rs-FC presented is significantly different between medication-state in FOG+, but not in FOG-, as confirmed by higher-level analysis. Thus, only between group differences in medication-state are highlighted. * P < .05, ** P < .001, GPe: globus pallidus external, GPi: globus pallidus internal, PPC: posterior parietal cortex, IFG: inferior frontal gyrus, mPFC: medial prefrontal cortex, FOG+: Participant with freezing of gait, FOG-: Participant without freezing of gait, ON: On dopaminergic medication, OFF: Off dopaminergic medication*

and this change in rs-FC negatively correlated to the Posture Impairments and Gait Disorders Item of the MDS-UPDRS III (r_s=-0.67, p=0.006 for ON and OFF scores) and correlated to the HADS-D score (r_s=0.65, p=0.008). The change in rs-FC between the right thalamus and the right PPC following L-DOPA intake was negatively correlated with the score on the MoCA (r_s=-0.66, p=0.007).

Mean OFF rs-FC of the posterior cingulate cortex clusters with their seeds was generally significantly lower for FOG+ than FOG- (Figure 4.3C). The L-DOPA-induced change in mean rs-FC between the cingulate cortex and the left GPe correlated with HADS-D score (r_s=0.67, p=0.006). Specifically, the higher the depression score, the more change in rs-FC was observed.

The mean ON-state rs-FC of the right IFG with the premotor and primary motor cortices clusters with the thalamus seeds was significantly higher in FOG+ than in FOG- (Figure 4.3D). Larger changes in mean rs-FC of that cluster with the left GPi and GPe were associated with shorter disease duration (GPi: r_s=-0.66, p=0.007; GPe r_s=-0.74, p=0.0001).

The OFF-state rs-FC between the bilateral mPFC and the right thalamus was significantly lower in FOG+ than in FOG- (Figure 4.3E). Finally, the rs-FC between the left thalamus and the cluster comprising a subcortical area and the retrosplenial cortex was not significantly different between FOG+ and FOG- (Figure 4.3F).

4.4.4 L-DOPA Alters the Functional Connectivity of Thalamic Nuclei in FOG+ and FOG-

Resulting clusters of medication-state contrasts for the thalamus nuclei supplementary analysis are presented in Supplementary Table S4.4. In the FOG+ group, medication altered the rs-FC of the thalamic nuclei seeds with many more regions than in FOG-. Results confirm the functional connectivity changes observed with the general thalamus seeds in FOG+ and assign them to specific thalamic nuclei.

4.5 Discussion

This is, to our knowledge, the first study assessing how dopaminergic medication can influence baseline brain networks specific to FOG. L-DOPA-induced changes in functional connectivity at rest between regions involved in the Interference model selectively in freezers. Specifically, results demonstrate that in the FOG+ group, L-DOPA increases the connectivity at rest of the GPe, GPi, putamen, and thalamus with key cognitive, sensorimotor and limbic cortical regions of the Interference model. Since all our FOG+ participants reported an improvement or an absence of freezing in the ON-state, changes in rs-FC due to L-DOPA observed in this study may be considered favorable by contributing to less freezing. We discuss how our results indicate that L-DOPA can normalize some connections to be similar to those of non-freezers or to increase functional connectivity as a compensation for dysfunctional networks.

Following L-DOPA intake, freezers had increased rs-FC between several seeds (pallidum, putamen, and thalamus) and the PPC, a region known to be at the core of sensorimotor integration to program gait (Takakusaki 2013), and part of the cognitive loop of the Interference model (Lewis and Barker 2009). It has been shown that freezers have atrophy (Pietracupa et al., 2018) and hypometabolism (Bartels et al., 2006) of the PPC. We propose that the effects of L-DOPA on this functional connectivity compensates for these PPC alterations since the mean rs-FC of the PPC with the pallidum, the putamen and the thalamus is significantly higher in freezers than in non-

freezers. Considering that all our participants freeze less or not at all when on L-DOPA, this increased in rs-FC could represent the facilitating effect of L-DOPA in relaying information between the thalamus and the motor striatum to the PPC to ensure effective sensorimotor integration, and to improve visuospatial skills known to be impaired in freezers and to contribute to FOG episodes [38]. Significant correlations between rs-FC and clinical outcomes suggest that participants with more severe posture and gait symptoms and those who score better on the MoCA are less efficient at using this compensatory mechanism. However, we cannot ignore that such a compensatory mechanism could be maladaptive, possibly increasing the total neural processing load, and thus, may further contribute to a striatal overload leading to FOG. More studies are needed to determine if this compensation could, with time, contribute to the process leading to ON-FOG.

The only seed that did not follow this compensatory pattern with the PPC is the left GPi. Indeed, L-DOPA increased this functional connectivity in freezers to values not significantly different from non-freezers in the ON-state. Thus, a different mechanism may be in place, where L-DOPA normalizes left GPi and right PPC rs-FC to values similar to non-freezers. A recent study demonstrated that patients with PD who have speech impairments have higher rs-FC between the left GPi and the right and the left angular gyrus than those without speech impairments (Manes et al., 2018). Thus, considering our results, lower rs-FC between GPi and PPC could indicate fewer secondary symptoms of PD.

The functional connectivity between the left thalamus and a cluster comprising the right thalamus and retrosplenial area was found to be reduced in freezers to similar levels as non-freezers. The retrosplenial cortex is another area involved in spatial cognition, and more specifically to its working memory aspect (Mitchell et al. 2018), and has been shown to be anatomically and functionally connected to the thalamus (Li et al. 2018). This result is consistent with our previous work, showing that the retrosplenial cortex is more functionnaly connected to the motor striatum in freezers in the ON-state, which could potentially be a compensatory mechanism contributing to the striatal overload leading to FOG (Potvin-Desrochers et al. 2019). In the current study, we propose that L-DOPA normalizes rs-FC between the thalamus and the retrosplenial cortex in

freezers to levels similar to non-freezers to optimize the processing capacity of the cortico-basal ganglia thalamic circuity, and ultimately reducing FOG occurrence.

rs-FC of the bilateral GPe and right putamen seeds with the posterior cingulate cortex was found to be higher in the ON-state in freezers. In the ON-state, their functional connectivity did not differ from non-freezers but was significantly lower in the OFF-state, suggesting that L-DOPA normalizes the rs-FC of the posterior cingulate cortex with the GPe and the putamen in freezers, to levels similar to non-freezers. Although the posterior cingulate cortex is not part of the cognitive loop of the Interference model (Lewis and Barker 2009), it is involved in cognitive functions and could potentially contribute to FOG. Indeed, it is known to be involved in the control of the balance between internal and external focus of attention and in the maintenance of a vigilant attentional state (Leech and Sharp 2014). An external focus of attention has been shown to improve postural control and gait in PD, even in fallers (Landers et al. 2005). Thus, our results may indicate that the increased posterior cingulate rs-FC with basal ganglia nuclei from L-DOPA could lead to an improvement in the tuning of the focus of attention to avoid FOG when triggers are encountered. Interestingly, we found positive correlations between the change in rs-FC between the left GPe and the posterior cingulate cortex and depression levels, indicating that more depressed participants seem to benefit more from this L-DOPA effect on rs-FC. Although anxiety is a known trigger of FOG, the relationship between depression, anxiety and dopaminergic medication in FOG still needs further investigation.

In freezers, the pallidum, putamen, and thalamus were more functionally connected to a cluster comprising the right IFG and motor cortices in the ON-state. L-DOPA seems to normalize this rs-FC with the pallidum and the putamen. Correlations revealed that freezers that have a longer disease duration have smaller changes in the connectivity between the pallidum and motor cortices and IFG due to L-DOPA, suggesting that the normalization effect is stronger in earlier stages of PD. On the other hand, the increase in functional connectivity of the IFG and motor cortices cluster with the thalamus in freezers exceeded the functional connectivity observed in non-freezers, which could imply a compensatory mechanism for FOG+. The IFG, atrophied in freezers (Kostić et al. 2012), is involved in inhibitory control (Hampshire et al. 2010), an altered executive function contributing to FOG (Cohen et al. 2014). We propose that L-DOPA improves functional

organization to favor more efficient response inhibition. Thus, freezers could be better able to inhibit responses to inappropriate stimuli (i.e., FOG triggers) and avoid freezing. The clusters also included the primary and the premotor cortices, the main cortical regions of the motor loop of the Interference model (Lewis and Barker 2009). Canu and colleagues (2015) proposed that lower rs-FC within the sensorimotor network may contribute to FOG. Our results demonstrate that L-DOPA improves functional organization of the motor cortico-basal ganglia thalamic circuity, contributing to more efficient motor processing. However, we need to emphasize that the rs-FC between these areas and the thalamus is significantly higher than in non-freezers. Thus, as discussed with the PPC results, this compensatory mechanism could be maladaptive and in more severe cases contribute to FOG.

The right thalamus also had a significantly higher functional connectivity with the mPFC in the ON-state compared to the OFF-state in freezers. The mPFC is one of the cortical region of the limbic loop of the Interference model (Lewis and Barker 2009), and is known to be involved in behavioral responses to stress and fear (McKlveen, Myers, and Herman 2015). The thalamus and the mPFC have been shown to be anatomically connected through the thalamus' medial dorsal nuclei (Amaral 2013), and functionally connected (D. Zhang et al. 2008), as supported by our results (Supplementary Table S4.4). We demonstrate here that L-DOPA normalizes rs-FC between the right thalamus and the mPFC to be similar to non-freezers, as its magnitude is significantly lower in freezers than in non-freezers in the OFF-state but does not change between the groups in the ON-state. We propose that L-DOPA facilitates the relay of information between the thalamus and the mPFC in freezers, improving limbic processing, especially when emotional triggers of FOG are encountered. Our results are in opposition with a recent study suggesting that L-DOPA negatively impacts the functioning of prefrontal areas during real walking due to excessive dopamine in this area (Dagan et al. 2020). Differences in active and resting states could account for this discrepancy.

Among the twenty resulting clusters in freezers, fifteen were located in the right hemisphere, two were bilateral and three in the left hemisphere. This is consistent with previous studies demonstrating altered functional connectivity of many regions and networks in the right hemisphere for freezers (Wang et al. 2016; Tessitore, Amboni, Esposito, et al. 2012; Maidan et al.

2019; Bharti et al. 2019). This could be explained by the lateralization of visuospatial skills (Noggle and Hall 2011) and inhibitory function (Liakakis, Nickel, and Seitz 2011) in the right hemisphere. Considering that visuospatial and perceptuomotor deficits are contributing to FOG (Nantel et al. 2012), the right-hemispheric lateralization of our clusters also support the hypothesis that the right circuity is more affected in freezers.

We did not find any significant correlations between FOG severity (score on NFGOQ) and levodopa-induced changes in rs-FC. This may be partially explained by the fact that we did not objectively assess FOG and its response to L-DOPA. FOG is known to be challenging to elicit in a laboratory setting. Participants with severe freezing would be needed to reliably determine the magnitude of FOG improvement after L-DOPA intake. Other limitations should also be taken into consideration when interpreting our results. We present data acquired in the resting state and under the Interference model framework, which is a hypothesis of what leads to FOG in an active state. Thus, L-DOPA could have different effects on brain dynamics in an active state, making important to study brain functional organization during real FOG episodes, such as when performing a walking task provoking FOG. Another consideration is the small sample size included in this study, which may have reduced statistical power and the capacity of generalizing the results to all freezers. Four participants (1 FOG- and 3 FOG+) were on dopaminergic agonists, generally requiring >12h of withdrawal to be considered in the OFF-state. These participants were nevertheless included in the study as they did have a highly clinically significant (Horváth et al. 2015) change in their UPDRS-III score between OFF and ON (range: 17 to 26 points), suggesting an important tampering effect of medication. Lastly, ON-fMRI was taken from a previous study for five participants. The time between the scans was inputted in the analysis as a confounder, and we ensured that clinical measures of PD and of FOG were not clinically significant between the two time points, thus limiting this possible bias.

4.6 Conclusion

This is the first study characterizing the effects of L-DOPA on neural mechanisms specific to FOG using rs-FC. In freezers, L-DOPA increases the functional connectivity between key regions of the Interference model, and more particularly between regions involved in cognitive processing. Comparisons with non-freezers revealed that L-DOPA generally normalizes brain functional

connectivity to be similar to non-freezers but can also increase rs-FC connectivity to compensate for dysfunctional networks in freezers. While in both cases L-DOPA could contribute to a better sensorimotor, attentional, response inhibition and limbic processing to prevent FOG when triggers are encountered, the latter could interfere with the processing capacity of the striatum, and eventually contribute to FOG.

4.7 Acknowledgements

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4.9 Supplementary Material

Table S4.1 *Dopaminergic medication taken by each participant*

	Participants	Dopaminergic medication
FOG+	1	Carbidopa/Levodopa, Pramipexole
	2	Stalevo 125, Azilect
	3	Carbidopa/Levodopa, Azilect
	4	Carbidopa/Levodopa, Levodopa/carbidopa CR
	5	Levodopa/Carbidopa CR
	6	Levodopa/Benserazide, Levodopa/carbidopa CR, Pramipexole
	7	Levodopa/carbidopa CR, Amantadine, Azilect, Pramipexole
	8	Carbidopa/Levodopa, Levodopa/carbidopa CR
	9	Carbidopa/Levodopa, Levodopa/carbidopa CR, Azilect
	10	Carbidopa/Levodopa, Levodopa/carbidopa CR, Selegiline, Stalevo 125
	11	Carbidopa/Levodopa
	12	Carbidopa/Levodopa
	13	Carbidopa/Levodopa
	14	Carbidopa/Levodopa, Levodopa/Benserazide, Levodopa/carbidopa CR, Amantadine
	15	Carbidopa/Levodopa, Amantadine, Stalevo 150
FOG-	1	Carbidopa/Levodopa, Entacapone, Tasmar, Pramipexole
	2	Levodopa/carbidopa CR
	3	Levodopa/carbidopa CR
	4	Levodopa/carbidopa CR
	5	Carbidopa/Levodopa, Levodopa/carbidopa CR, Azilect
	6	Levodopa/carbidopa CR
	7	Levodopa/carbidopa CR
	8	Carbidopa/Levodopa, Amantadine, Azilect, Stalevo 150
	9	Carbidopa/Levodopa, Levodopa/carbidopa CR, Entacapone
	10	Carbidopa/Levodopa, Amantadine, Stalevo 150
	11	Carbidopa/Levodopa, Levodopa/carbidopa CR
	12	Levodopa/Benserazide
	13	Carbidopa/Levodopa
	14	Carbidopa/Levodopa
	15	Carbidopa/Levodopa

Table S4.2 *Individual clinical scores for participants from which their ON-state fMRI was acquired on averaged 42 (SD 8) weeks before their OFF-state scan. Change in UPDRS ON between the two visits was not clinically (< 3 point[1]) nor statistically significantly different (p=0.621). Medication (dose and type) remained unchanged.*

Group	Participants	UPDRS ON		UPDRS OFF		NFOGQ	
		Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
FOG +	1	24	23	38	40	15	17
	5	25	24	m.d.	m.d.	10	8
FOG -	2	28	28	39	37	n.a.	n.a.
	4	38	38	m.d.	m.d.	n.a.	n.a.
	5	23	22	40	41	n.a.	n.a.

NFOGQ: New Freezing of Gait Questionnaire.

MDS-UPDRSIII: Movement Disorder Society Unified Parkinson's Disease Rating scale (Part III).

m.d.: missing data

n.a.: not applicable

[1] Horváth, K., Aschermann, Z., Ács, P., Deli, G., Janszky, J., Komoly, S., ... & Kovács, N. (2015). Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. Parkinsonism & related disorders, 21(12), 1421-1426.

Table S4.3 *Score obtained for each FOG phenotype and for each FOG+ based on the CFOG questionnaire*

Participants	Anxious (/16)	Asymmetric-Motor (/20)	Sensory-Attentional (/12)	Main phenotype
1	8	8	2	Anxious & Asymmetric-Motor
2	4	5	1	Asymmetric-Motor
3	3	3	0	Anxious & Asymmetric-Motor
4	1	5	1	Asymmetric-Motor
5	0	2	0	Asymmetric-Motor
6	10	2	4	Anxious
7	4	9	2	Asymmetric-Motor
8	0	4	0	Asymmetric-Motor
9	0	5	0	Asymmetric-Motor
10	0	4	0	Asymmetric-Motor
11	0	3	0	Asymmetric-Motor
12	4	8	0	Asymmetric-Motor
13	4	12	2	Asymmetric-Motor
14	6	9	2	Asymmetric-Motor
15	5	6	0	Asymmetric-Motor

Table S4.4 *Differences in rs-FC between ON-medication and OFF-medication states in FOG+ and FOG- for the thalamus nuclei seeds.*

FOG+	ON > OFF	Left LGN	Right cuneus, left middle occipital gyrus	Visual	18, 19	18322	14	-89	16	5.2	<0.001
		Left VA	Left inferior parietal lobule	PPC	40	2833	-55	-65	39	4.76	0.023
		Left VL	Left supramarginal gyrus	PPC	40	8477	-59	-44	31	5.22	<0.001
		Right VL	Left supramarginal gyrus	PPC	40	4208	-71	-41	29	4.67	0.003
		Left VPL	Right superior temporal & supramarginal gyri	PPC	50	3353	60	-46	23	4.14	0.007
			Right medial cingulate gyrus	Cingulate	23, 24	4434	6	-20	29	4.53	0.001
			Right inferior frontal gyrus, Rolandic operculum	IFG	44, 45	5110	61	16	7	5.32	<0.001
			Left postcentral & supramarginal gyri	PPC	40	5239	-71	-25	26	4.58	<0.001
		Right VPL	Right anterior & medial cingulate cortices	Cingulate	23	2364	7	22	29	4.25	0.048
			Right inferior frontal gyrus	IFG	44, 45	2441	54	21	12	4.99	0.041
		Left VPM	Right superior temporal & supramarginal gyri	PPC	40	2789	57	-46	22	3.72	0.021
			Right inferior frontal gyrus	IFG	44, 45	3207	60	16	7	5.26	0.010
			Left supramarginal gyrus	PPC	40	3467	-71	-25	26	4.50	0.006
			Bilateral cingulate cortex	Cingulate	23	4737	3	-9	25	4.51	<0.001
		Right VPM	Bilateral cingulate cortex	Cingulate	23	2478	4	-10	26	4.24	0.042
		Left MGN	Left middle occipital & superior occipital gyri	Visual	17, 18, 19	12226	-20	-101	8	4.45	<0.001
		Left MD	Right inferior frontal gyrus	IFG	44, 45	3550	59	15	12	4.76	0.006
			Left supramarginal gyrus	PPC	40	5562	-62	-43	29	4.84	<0.001
			Left superior medial gyrus, right anterior cingulate cortex	mPFC	24, 32	8035	-2	30	10	4.87	<0.001
		Right MD	Left supramarginal gyrus	PPC	40	3379	-71	-38	32	4.28	0.011
			Right Rolandic operculum, inferior frontal gyrus	IFG	44, 45	5096	46	7	13	4.81	<0.001
			Left superior medial gyrus, right anterior cingulate cortex	mPFC	32	7302	-7	54	17	4.40	<0.001
		Left Pulvinar	Right supramarginal gyrus	PPC	40	2954	70	-34	31	3.48	0.014
			Left supramarginal gyrus	PPC	40	3707	-71	-36	28	4.35	0.004
			Left superior medial gyrus, left anterior cingulate cortex	mPFC	10, 32	4517	-9	51	14	4.37	<0.001
			Right inferior frontal gyrus	IFG	44	7070	59	15	8	5.49	<0.001
		Right Pulvinar	Left supramarginal gyrus	PPC	40	3391	-71	-35	27	4.32	0.008
			Right supramarginal gyrus	PPC	40	3792	56	-34	29	3.79	0.004
			Right inferior frontal gyrus	IFG	44, 45	8848	59	16	8	5.58	<0.001
			Left anterior cingulate cortex	mPFC	10, 24, 32	10152	-3	27	22	4.82	<0.001
FOG-	ON > OFF	Right VPL	Right thalamus, globus pallidus, putamen	Subcortical	N/A	3308	14	-5	-11	4.26	0.008
		Left MD	Bilateral medial & anterior cingulate cortices	Cingulate	32	3033	5	28	33	3.87	0.017
		Right MD	Right putamen, subthalamic nucleus, thalamus	Subcortical	N/A	2402	26	6	-15	4.84	0.047
			Bilateral medial & anterior cingulate cortices	Cingulate	32, 33	3655	5	28	32	4.34	0.005
		Right Pulvinar	Right insula, inferior frontal gyrus	Insula	47	3888	37	25	1	4.70	0.003
	ON < OFF	Right VPL	Left middle temporal & angular gyri	PPC	39	2454	-57	-64	21	4.75	0.038
		Right VPM	Left middle temporal gyrus	PPC	39	2712	-57	-64	21	4.43	0.025
		Right Pulvinar	Left middle temporal & angular gyri	PPC	39	2562	-56	-64	17	4.55	0.029

Colors represent the functional identification of each cluster region as presented in Figure 4.2.

FOG+: Participants with freezing of gait
FOG-: Participants without freezing of gait
ON: On dopaminergic medication
OFF: Off dopaminergic medication
ID: Identification
MNI: Montreal Neurological Institute
LGN: Lateral Geniculate Nucleus
VA : Ventral Anterior Nucleus
VL: Ventral Lateral Nucleus
VPL: Ventral Posteriolateral Nucleus
VPM: Ventral Posteromedial Nucleus
MGN: Medial Geniculate Nucleus
MD : Medial Dorsal Nucleus
IFG: Inferior Frontal Gyrus
PPC: Posterior Parietal Cortex
mPFC: Medial Prefrontal Cortex

Chapter 5

Potential Non-Invasive Brain Stimulation Targets to Alleviate Freezing of Gait in Parkinson's Disease

PREFACE

In Chapters 3 and 4, brain-wide changes in functional organization were identified in FOG using rs-FC. Alterations in baseline organization of brain regions involved in visuospatial, sensorimotor, cognitive, and limbic processing were observed specifically in freezers. However, like any other brain imaging modality, rs-FC alone is not sufficient to provide a complete understanding of FOG neural mechanisms. In Chapter 5, we thus review all existing neuroimaging and electrophysiological evidence of FOG to determine if cortical regions part of the Interference model are in agreement with the literature. Having this more global perspective on the neural causes of FOG could guide interventions aimed at acting directly on its neural mechanisms. Current interventions for FOG are limited, and there is a pressing need for more efficient options. Thus, in Chapter 5, we also sought to identify the cortical brain regions of the Interference model that could act as potential targets for future evidence-based NIBS interventions specifically aimed at reducing FOG. New promising brain targets were identified, with the PPC being a region of high interest due to its evident involvement in FOG. Key considerations for such interventions, including medication-state, stimulation type and hemisphere to target, are also reviewed, and the novel and never tested idea of combining NIBS with a physical training for FOG is also introduced, keeping the same motivation to set the stage for evidence-based interventions aimed at reducing FOG.

MANUSCRIPT 3

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

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5.1 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.

5.2 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, Snijders, Nutt, Deuschl, Giladi, et al. 2015). While L-DOPA therapy (Nonnekes, Snijders, Nutt, Deuschl, and Giladi 2015), deep brain stimulation (Gilat, Silva de Lima, 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. 2020). 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, to 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.

5.3 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, Naismith, and Lewis 2013; Lewis and Shine 2016; Ehgoetz Martens et al. 2018) and later named by 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 5.1 left) all functionally converging to the globus pallidus internal (GPi; Figure 5.1 center). 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).

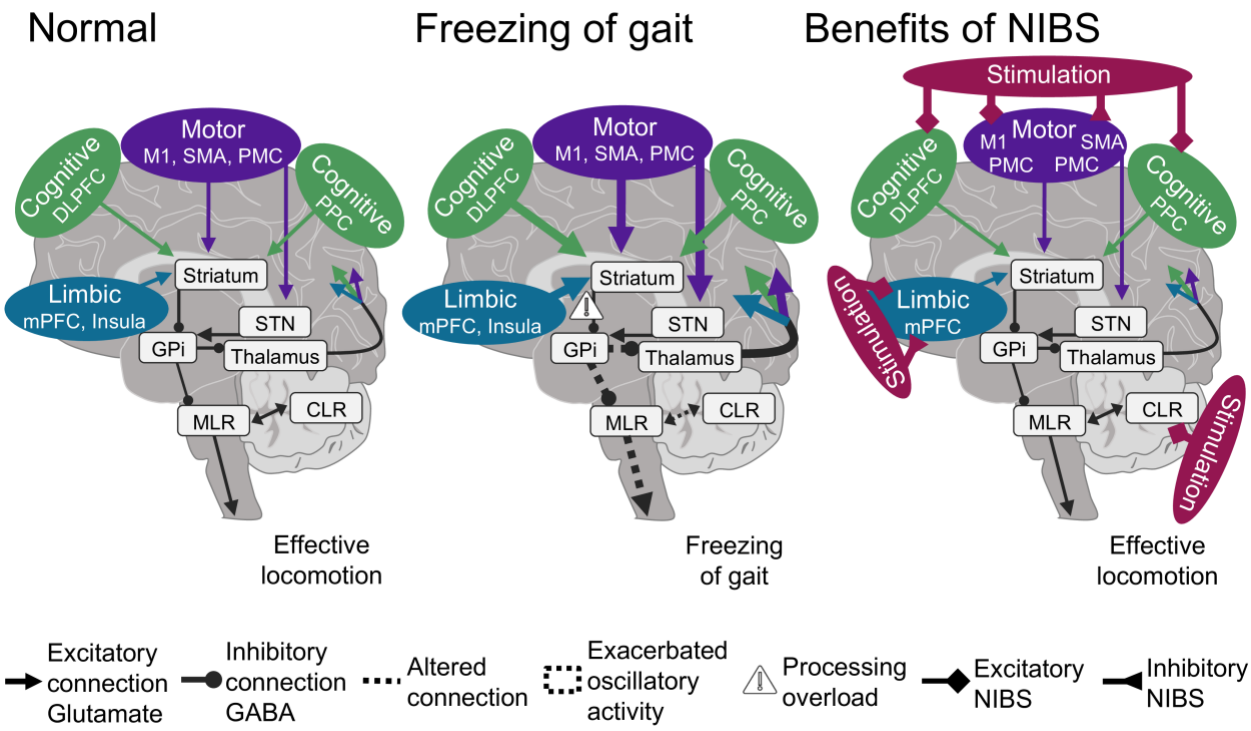

Figure 5.1. ***Left panel.*** *General representation of the cortico-striatal-thalamic circuity for locomotion in healthy individuals. Thalamus sends processed information from the basal ganglia towards motor, cognitive and limbic cortical areas, which is sent back to the basal ganglia to ultimately 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. (2018).*

5.4 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 reinstate an equilibrium in the activity of the basal ganglia to avoid FOG (Figure 5.1 right). 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, Naismith, and Lewis 2013; 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.

5.5 Potential Cortical Targets for NIBS

The potential targets for FOG presented below are the cortical and NIBS-accessible regions of the Interference model (Figure 5.1 right).

5.5.1 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, Matar, Ward, Bolitho, et al. 2013). 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. 2017). 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, Paeng, and Kang 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, Paeng, and Kang 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, Paeng, and Kang 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.

5.5.2 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, Cavina-Pratesi, and Singhal 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, Matar, Ward, Bolitho, et al. 2013; Shine et al. 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, Matar, Ward, Bolitho, et al. 2013), 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, Shine, and Lewis 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, Matar, Ward, Bolitho, et al. 2013; 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, Matar, Ward, Bolitho, et al. 2013; 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. 2017). 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. 2017). 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.

5.5.3 Limbic Targets

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, Egner, and Kalisch 2011; McKlveen, Myers, and Herman 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, Matar, Ward, Bolitho, et al. 2013) 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.

5.5.4 Other Possible Targets

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, Matar, Ward, Bolitho, et al. 2013), 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.

5.6 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; Kim, Paeng, and Kang 2018; Tard et al. 2016; Dagan et al. 2017, 2018; 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; Kim, Paeng, and Kang 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. 2014, 2014). 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, Van Der Haegen, and Brysbaert 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, Ellison, and Walsh 2001; Rushworth, Krams, and Passingham 2001). Another example is the DLPFC, for which most studies have targeted the left hemisphere in FOG (Rektorova et al. 2007; Chang et al. 2017; Dagan et al. 2018; 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, de Raedt, and Baeken 2009;

Kaller et al. 2011). Furthermore, behavioral inhibition and visual change awareness have been located in the right DLPFC (Turatto, Sandrini, and Miniussi 2004; Shackman et al. 2009). Thus, the hemisphere to target should be based on the specific function desired to up or down regulate.

5.7 Future Perspectives

5.7.1 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. 2017; Dagan et al. 2018). 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. 2017). 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. 2018). 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.

5.7.2 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, Kang, and Paik 2010; Yamada et al. 2013; Galvão et al. 2014; Gillick et al. 2014; Koganemaru et al. 2015; Zheng, Liao, and Xia 2015; Zumbansen et al. 2020; Edwards et al. 2021), including PD (Yang et al. 2013; Kaski, Allum, et al. 2014; Kaski, Dominguez, et al. 2014; 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, Allum, et al. 2014; Kaski, Dominguez, et al. 2014) 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, Labar, and Edwards 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, Labar, and Edwards 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 interventions 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.

5.8 Manuscript References

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Chapter 6

Upregulation of the Parietal Cortex Improves Freezing of Gait in Parkinson's Disease

PREFACE

The results presented in the previous three chapters indicate: 1) an increased coupling between the subcortical nuclei and visual- and sensorimotor-related regions in freezers, 2) a levodopa-induced modulation of the functional organization of the PPC specific to freezers, and 3) substantial evidence for PPC alteration in FOG. My thesis work thus supports the involvement of sensorimotor and visuospatial neural mechanisms in FOG, and more specifically, of the PPC, a key region involved in those aforementioned functions. The PPC is therefore a target of choice for NIBS aimed at reducing FOG, as suggested in Chapter 5. However, before testing such an intervention, the role of PPC in real FOG must be determined as it could impact the type of modulation (i.e., excitatory or inhibitory) to cause improvements in FOG. In this next chapter, we used excitatory and inhibitory rTMS to alter PPC excitability and determine how these stimulation protocols may impact objective behavioral outcomes of FOG and brain excitability. This study is the first to use a paired-coil TMS protocol to assess the modulation-induced changes in the connectivity between the PPC and the lower leg representation of M1 to directly quantify the magnitude of excitability change induced by the rTMS interventions. This chapter provides the first evidence for the beneficial role of the PPC in real FOG, as increasing PPC excitability resulted in less FOG, and set the scene for potential NIBS interventions targeting the PPC to reduce FOG episodes.

MANUSCRIPT 4

Upregulation of the Parietal Cortex Improves Freezing of Gait in Parkinson's Disease

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6.1 Abstract

BACKGROUND The posterior parietal cortex (PPC) is a key brain area for visuospatial processing and locomotion. It has been repetitively shown to be involved in the neural correlates of freezing of gait (FOG), a common symptom of Parkinson's disease (PD). However, current neuroimaging modalities do not allow to precisely determine the role of the PPC during real FOG episodes. OBJECTIVES The purpose of this study was to modulate the PPC cortical excitability using repetitive transcranial magnetic stimulation (rTMS) to determine whether the PPC contributes to FOG or compensates for dysfunctional neural networks to reduce FOG. METHODS Fourteen participants with PD who experience freezing took part in three experimental sessions targeting the PPC with inhibitory, excitatory and, sham rTMS. Objective FOG outcomes and cortical excitability measurements were acquired before and after each stimulation protocol. RESULTS Increasing PPC excitability resulted in significantly fewer occurrence of freezing episodes and percent time frozen during a FOG-provoking task. This reduction in FOG most likely emerged from the trend in PPC excitability inhibition of the lower leg motor cortex. CONCLUSION Our results suggest that the recruitment of the PPC is linked to less FOG, providing support for the beneficial role of the PPC in preventing FOG. This could potentially be achieved by a reduction of the cortical input burden on the basal ganglia prior to FOG. Therefore, excitatory rTMS interventions targeting the PPC has the potential to reduce FOG.

6.2 Introduction

Freezing of gait (FOG) is a common motor symptom of Parkinson's disease (PD) that consists of brief and sudden episodes of gait cessation despite the intention to walk (Nutt et al. 2011). FOG is a debilitating symptom that reduces quality of life by affecting mobility and increasing the risk of falls (Bloem et al. 2004). The literature currently supports the hypothesis that FOG occurs as the result of a converging network failure in individuals with vulnerable locomotor networks (Weiss et al. 2020). Specifically, the integration failure of multiple cortical inputs would lead to an overload in the processing capacity of the basal ganglia, affecting numerous subsequent projections and ultimately producing an unsuccessful motor output causing FOG (Lewis and Shine 2016; Weiss et al. 2020). For example, deficits in visuospatial function could play a role in the upper level of this common pathway of FOG. Indeed, individuals with FOG have variety of conditions associated with visuospatial processing, including a greater loss in stereopsis (Alhassan,

Hovis, and Almeida 2019), cognitive deficits in visuospatial domains that correlate with FOG duration (Nantel et al. 2012), gait parameters alteration while approaching a narrow doorway (Almeida and Lebold 2010), and altered cortical visuomotor integration (Strigaro et al. 2020), providing further evidence for visuospatial and perceptual deficits in the occurrence of FOG.

A key region for visuospatial processing is the posterior parietal cortex (PPC), an associative region that integrates sensory information to guide action (Culham, Cavina-Pratesi, and Singhal 2006). Body schema is thought to be shaped by the PPC (Takakusaki 2013) ensuring error monitoring of movements in relation to the environment (Gwin et al. 2011). The PPC is thus critical in updating the locomotor plan for ongoing gait adjustments during visually guided locomotion (Hinton et al. 2019; Drew and Marigold 2015). Several studies have demonstrated PPC alterations associated with FOG, including changes related to its volume (Kostić et al. 2012; Rubino et al. 2014; Pietracupa et al. 2018), connectivity (Hall et al. 2018), activity (Shine, Naismith, and Lewis 2013; Shine et al. 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). However, as highlighted in our previous literature review (Potvin-Desrochers and Paquette 2021), the role of the PPC in FOG remains unclear. Decreased parietal control has been observed when transitioning from effective walking to FOG episodes (Shine et al. 2014), but motor arrests during a foot pedaling task were linked to increased PPC activity (Shine, Matar, Ward, Bolitho, et al. 2013). Current research provides undeniable evidence that the PPC is involved in FOG, but whether its recruitment is beneficial or contributing to FOG remains to be determined.

Repetitive transcranial magnetic stimulation (rTMS) is a tool that can be used to assess brain functions by identifying a causal effect between a brain area (i.e., stimulation site) and a specific function, cognitive process or behavior (Hallett 2007). rTMS can transiently increase or decrease cortical excitability of a specific brain region depending on the type of stimulation parameters (Lewis et al. 2016). When combining rTMS with the performance of a task, simultaneously or after rTMS, the effects of changing cortical excitability can then be assessed on behavioral outcomes. In FOG, Dagan et al. (2017) demonstrated that increasing the excitability of the medial prefrontal cortex with rTMS reduces FOG occurrence, supporting the cause-and-effect link between this area and FOG. To our knowledge, no studies have yet attempted to characterize

behavioral effects of PPC excitability modulation with rTMS on FOG. In this current study, we applied theta burst stimulation (TBS)(Huang et al. 2005), a form of patterned rTMS, to determine the role of the PPC in real FOG. To do so, the effects of increasing and decreasing the excitability of the right PPC with, respectively, intermittent TBS (iTBS) and continuous TBS (cTBS), were studied on FOG behavioral outcomes and brain excitability quantification and compared to a sham protocol. The right PPC was targeted because of the right lateralization of spatial cognition to the that hemisphere (Cai, Van Der Haegen, and Brysbaert 2013). It was hypothesized that increasing PPC excitability would results in less FOG as it would potentially enhance visuospatial processing.

6.3 Methods

6.3.1 Participants

Fourteen TMS-naive individuals (6 women, mean age of 66 ± 13 years) diagnosed with idiopathic PD according to the UK PD Society Brain Bank Diagnostic Criteria (Hughes et al. 1992), at an Hoehn and Yahr Stage of 2 or 3, experiencing FOG (New Freezing of Gait Questionnaire > 1 (Nieuwboer et al. 2009)), on a stable dose of dopaminergic medication for 2 months, right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971) and with normal vision were recruited. Participant demographics can be found in Table 6.1. Exclusion criteria were any neurological disorders or conditions interfering with mobility other than PD, FOG worsened by the intake of dopaminergic medication and any contraindications to TMS (Rossi et al. 2009). All participants provided an informed consent in accordance with the McGill Faculty of Medicine Institutional Review Board regulations for human subjects' studies and the Declaration of Helsinki.

6.3.2 Study Design

This double-blind counterbalanced study consisted of four sessions during which participants followed their usual medication schedule. The participants and the researcher analyzing the outcomes measures were blinded to the nature of the different stimulation protocols and to the acquisition timepoint of the outcome measures. During the first session, a clinical assessment was conducted, and participants were familiarized with TMS and with the FOG-provoking task. A T1-weighted magnetic resonance image (MRI, Siemens 3T Prisma, echo time=2.96 ms; repetition time=2300ms, flip angle=9°, 192 slices, voxel size=1mm^3 isotropic) of their brain was also

obtained at the initial session and TMS parameters were acquired thereafter. Participants received iTBS, cTBS or sham stimulation targeting the right PPC on three separate experimental sessions, in a randomized order and separated by at least 72 hours to avoid carry-over effect of the stimulation (Figure 6.1A). Outcome measures were acquired before and after each TBS protocol (Figure 6.1B).

Table 6.1 *Participants demographics*

	Mean (SD)	Range
Sex (male/female)	8/6	n.a.
Age (years)	66 (13)	50-79
Disease duration (years)	10 (5)	3-20
L-DOPA equivalent dose (mg)	1118 (480)	400-2296
NFOGQ score	17 (4)	9-24
Hoehn & Yahr scale	2.5 (0.5)	2-3
MoCA	28 (2)	25-30
MDS-UPDRS III	42 (9)	28-64
HADS anxiety	8 (3)	4-15
HADS depression	6 (4)	1-17
Mean TA RMT (%)	49 (15)	27-85
Mean FDI RMT (%)	46 (10)	32-70
Mean FDI AMT (%)	39 (7)	27-48
%MSO 1mV TA (resting, n=10)	55 (14)	32-70
%MSO 1mV TA (active, n=4)	67 (6)	60-73

L-DOPA: levodopa, NFOGQ: New Freezing of Gait Questionnaire, MoCA: Montreal Cognitive Assessment, MDS-UPDRSIII: Movement Disorder Society Unified Parkinson's Disease Rating scale (Part III), HADS: Hospital Anxiety and Depression Scale, TA: Tibialis anterior, RMT: Resting motor threshold, FDI: First dorsal interosseous, MSO: Maximal stimulator output, mV: millivolt, SD: Standard deviation

6.3.3 TMS Parameters

Participants received TMS while comfortably seated in an armchair. Disposable surface Ag-AgCL electrodes of 2.5cm x 2.5cm (Biopac Systems, Inc.) were used to record the electromyographic activity of the left first dorsal interosseous (FDI) following a belly-tendon mount and of the left tibialis anterior (TA) in a bipolar array. Signals were recorded via a Biopac EMG100C EMB amplifier connected to a Biopac MP150 acquisition system, sampled at 5kHz on a 16-bit analog-to-digital board, amplified and bandpass filtered (10-2000Hz). The protocol required the use of four different coils and three TMS machines. Coils used included two 50 mm figure-of-eight coated

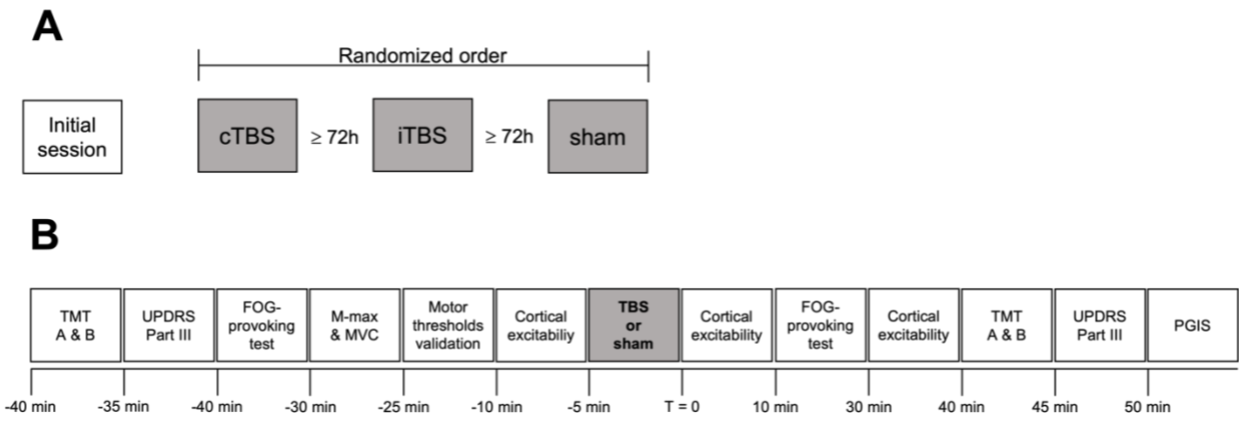

Figure 6.1 *Schematic representation of (A) the counterbalanced study design and (B) the course of each session. Acquisition of outcomes are in white and stimulation protocols in grey. cTBS: continuous theta burst stimulation, iTBS: intermittent theta burst stimulation, TMT A & B: Trail making test Part A & B, UPDRS Part III: Unified Parkinson's Disease Rating Scale Part 3, FOG: freezing of gait, MVC: maximal voluntary contraction, PGIS: patient global impression scale.*

coils (Magstim Company, UK) connected to a Super Rapid^2 machine (Magstim Company UK), a 25 mm figure-of-eight (Jaltron Lcc) and a 60 mm domed coil (Jaltron Lcc) each connected to one of the two Magstim 200^2 (Magstim Company UK). A Brainsight frameless stereotaxic neuronavigation system (Rogue Research Inc, Montreal, Canada) was used to register the coils with the participants' T1 to ensure the precise location, orientation and repositioning of the coils.

6.3.3.1 Optimal Stimulation Points

The PPC stimulation targeted the right PPC corresponding to MNI coordinates x=60 y=-52 z=43. This region was selected based on a foot pedaling MRI paradigm study in freezers (Shine, Matar, Ward, Bolitho, et al. 2013) in which activity in that specific area was significantly higher during motor arrests compared to effective walking. The right PPC was targeted because of the right lateralization of spatial cognition to the that hemisphere (Cai, Van Der Haegen, and Brysbaert 2013) and because FOG has been associated with changes predominantly in the right brain circuity (Bartels, de Jong, Giladi, Schaahsma, et al. 2006; Maidan et al. 2019; Bharti et al. 2019). Hotspots of the FDI and of the TA were located using a Magstim 200^2 system. For the FDI, a 50 mm figure-of-eight coil placed tangentially to the scalp at a 45° angle from the midline was used to map the hand area of the motor cortex with the FDI muscle relaxed. Once a potential hotspot location was located, a fine grid personalized to each participant (average of 16 points ± 7 and mean spacing of 3.5mm ± 1) was positioned over this area. Two pulses were applied at each point of the grid and

the point that elicited 2 consecutives motor evoked potentials (MEPs) with the greatest mean amplitude was deemed to be the hotspot. The same procedure was followed to find the TA hotspot location. For the TA, pulses were delivered with the 60 mm domed coil while the TA muscle slightly contracted at ± 0.3mV to facilitate the search of the hotspot. The TA grids had on average 13 points ± 3 and a mean spacing of 3.0mm ± 1. The neuronavigation system was used to mark and monitor the position of the FDI, TA and PPC target regions and ensured that the same locations were targeted across timepoints and sessions.

6.3.3.2 Motor Thresholds

Resting and active motor thresholds (RMT and AMT) were acquired during the initial session and validated at each following session. RMT was defined as the lowest intensity required to induce 10 MEPs of at least 0.05mV in the targeted relaxed muscle out of 20 TMS pulses (Rossini et al. 2015). RMT was acquired in the FDI with the 25 mm figure-of-eight coil using a Magstim 200^2 system to set the stimulation intensity of the PPC during the measurement of cortical excitability outcomes (see 6.5.2). To determine TBS stimulation intensity (Huang et al. 2005), AMT was acquired following the same protocol as RMT, but using a 50 mm figure-of-eight coil connected to a Super Rapid 2 system and with the participants maintaining their FDI at 20% of their maximal voluntary contraction (MVC) using visual biofeedback. MVC was determined as the maximal EMG amplitude of three maximal contractions each held for three seconds. The stimulator intensity required to elicit an average of 1mV MEP response in the relaxed TA over 10 trials was acquired using the domed coil and a Magstim 200^2 system to set the stimulation intensity of the TA M1 during the measurement of cortical excitability outcomes. In 4 participants, obtaining a 1mV MEPs in the relaxed TA was not possible. Thus, in these participants, the stimulator intensity for 1mV MEPs was determined with the TA active at 10% of its MVC. During the experimental sessions to minimize the time taken to find multiple motor thresholds, the latter were validated starting with the stimulator intensity set at the intensity determined at the previous session. The stimulator intensity was subsequently adjusted by increasing or decreasing it by 1% MSO increments, increasing the intensity if <10/20 pulses of at least 0.05mV were obtained or otherwise decreasing the intensity. AMT was determined before RMTs to reduce any potential impact of muscle contraction on TBS effect (Gentner et al. 2008).

6.3.3.3 M-max

To compare TA MEPs across sessions and minimize the effect of any day-to-day peripheral changes, M-wave recordings were obtained at each experimental session prior to motor threshold validation. A stimulating electrode (MFI Medical Bar Electrode) connected to a peripheral nerve stimulator (DS7AH, Digitimer Ltd, UK) was used to stimulate the peroneal nerve that innervates the TA muscle. The electrical stimulation intensity was slowly increased (i.e., one stimulus per intensity) until no further increase in MEP amplitude was observed for 3 consecutive stimuli. The highest peak-to-peak M-wave was defined as the M-max.

6.3.4 Theta Burst Stimulation

Patterned rTMS in the form of iTBS and cTBS, delivered in bursts of high frequency (i.e., 50Hz) at an interval of 0.2 second, were administered to the PPC using a Super Rapid 2 system and a 50 mm figure-of-eight coil oriented tangentially to the scalp and 10° from the midline at an intensity of 80% of the FDI AMT (Huang et al. 2005). The FDI AMT was used to set TBS intensity because PPC is located at a similar cortical depth as the FDI. For sham stimulation, a second 50 mm figure-of-eight coil was placed between the scalp and the stimulating coil. The latter was upside-down and delivered the stimulation (80% of FDI AMT) away from the PPC. With this set-up, stimulation to the cortical region was minimized to none, while preserving the sound and some of the sensation of vibration on the head.

6.3.5 Outcome Measures

6.3.5.1 FOG-Provoking Task

To quantify the effect of modulating the PPC on FOG, the participants performed the FOG-provoking test designed by Ziegler and colleagues (2010) before and 10 minutes after each stimulation condition. Briefly, this test includes a series of common FOG triggers: sit-to-stand, walk, perform two full turns, one in each direction, open a door and walk through the doorway, and turn back walking towards the chair and sit back on it. The task is performed 3 times in the following order: as described, while carrying a tray with a cup full of water, and while carrying the same tray with water and performing a cognitive task (i.e., backward counting). The primary outcome measure was the score obtained on this FOG-provoking test. Secondary outcomes included the time to complete the task, the number of freezing episodes, the percentage time frozen,

the step count for each foot during the turn and the total time for turning for each side. Each FOG-provoking test related outcome was calculated based on video recordings and represent the sum of the three difficulty levels of the FOG-provoking task. Turns and FOG episodes were identified following previously established criteria (D'Cruz et al. 2021). The percent time frozen was calculated as the summation of the duration of all FOG episodes divided by the total duration of the FOG-provoking task.

6.3.5.2 Cortical Excitability

Twenty-five TMS pulses were applied over the TA cortical motor representation with a domed coil before, immediately after and thirty minutes after TBS and sham. The stimulation intensity used was the same at all time points and corresponded to what was required to elicit 1mV MEPs at baseline. In twenty-five other trials, TA stimulation was preceded by the stimulation of the PPC in a dual coil set-up (PPC+TA). PPC pulses were applied 4 milliseconds before the TA pulses with a 25 mm figure-of-eight coil and at 90% of the FDI RMT (Koch et al. 2007). The TA alone trials and the PPC+TA trials were randomly intermixed and delivered using two high-power Magtstim 200^2.

6.3.5.3 Clinical Outcomes

Because of the PPC's involvement in visuospatial integration (Culham, Cavina-Pratesi, and Singhal 2006), changes in motor symptoms and in executive function were assessed using the UPDRS III and the TMT A & B, respectively, before and after TBS and sham. The Patient Global Impression Scale (PGIS) was also administered at the end of the experimental sessions to assess how participants perceived changes in their walking and FOG after TBS and sham.

6.3.6 Preprocessing of Cortical Excitability Data

To ensure that data was representative of the sample and not influenced by extreme values, while keeping the variable nature of cortical excitability, the minimum and maximum MEP were removed from the block of 25 trials for each of the TA alone and PPC+TA. Then, MEPs with a peak-to-peak amplitude < 0.05mV (n=39, corresponding to 0.67% of all MEPs acquired in the study) were replaced by 0mv. MEPs preceded by background TA activity 2SD above its average (n=410, corresponding to 7.03% of all MEPs acquired in the study) were discarded. For each

participant, MEPs above 3xIQR were considered outliers and were discarded (n=5, corresponding to 0.09% of all MEPs acquired in the study).

For comparison across sessions, TA MEPs were normalized by M-max. Specifically, for each participant, M-max obtained at each session was divided by the averaged M-max of the three sessions. The resulting three coefficients were then used to divide the mean TA MEPs of each session and for each participant.

All cortical excitability outcomes are presented as group mean peak-to-peak amplitudes ± SD.

6.3.4 Statistical Analyses

Statistical analyses were carried out using SPSS v25 (IBM, NY, USA). Because all outcome measures did not pass the normality Shapiro-Wilk test, non-parametric analyses were carried out. Significance was set at $p \leq 0.05$. Outcomes that resulted in a significant change were correlated with NFOGQ score and the other outcome measures using Spearman's rank correlation. All results are presented as mean ± SD.

6.3.4.1 FOG-Provoking Task

For each outcome measure, Wilcoxon-Ranked tests were performed to identify changes between PRE and POST each stimulation condition. To test for any placebo effect, changes in each outcome measure following iTBS and cTBS was compared with sham using Friedman tests.

6.3.4.2 Cortical Excitability

To determine if iTBS, cTBS or sham influenced TA cortical excitability, mean TA MEPs were compared across the three time points with Friedman tests for each stimulation condition separately. Mean TA MEPs normalized by M-max were used to compare iTBS and cTBS with sham using two separate Friedman tests at all timepoints.

To determine the baseline effect of PPC on TA excitability, the grand average of the PPC+TA and TA alone MEPs of all sessions were compared at PRE compared using Wilcoxon Signed-Rank tests. The conditioning effect of the PPC on TA cortical excitability, i.e., the PPC+TA ratio, was

expressed as (PPC+TA)/TA alone and compared across time for each stimulation protocol using Friedman tests. The PPC+TA ratio obtained during iTBS and cTBS sessions was compared to sham at all timepoints using two Friedman tests. When needed, post hoc of all Friedman tests was carried out using Nemenyi tests and the false discovery rate method to correct for multiple tests.

6.3.4.3 Clinical Outcomes

Wilcoxon-Ranked tests were performed to detect any effect of iTBS, cTBS or sham on clinical outcomes. Post-Pre changes in each clinical outcome measure following both TBS protocol was compared with sham using Friedman tests.

6.4 Results

6.4.1 FOG-Provoking Task

As shown in Figure 6.2 and Table 6.2, iTBS led to a significant reduction in the number of freezing episodes (z=-2.195, p=0.028, r=0.587) and in the percent time frozen (z=-1.957, p=0.050, r=0.523). This effect was not observed in cTBS or sham. POST-PRE changes in FOG score (z=-2.053, p=0.040, r=0.549), number of freezing episodes (z=-2.464, p=0.014, r=0.659) and percent time frozen (z=-2.395, p=0.017, r=0.640) were significantly larger after iTBS than sham. None of the other measures derived from the FOG-provoking test (i.e., time to complete the task, step count during the turns and total time for turning) were altered by any of the stimulation condition (Table 6.2), and none of the outcome measures correlated with NFOGQ score or other clinical outcomes.

6.4.2 Cortical Excitability

At baseline, PPC preconditioning had no effect on TA cortical excitability (mean TA alone = 1.20mV±0.71, mean PPC+TA=1.18±0.54, z=0.635, p=0.525). The PPC+TA ratio was similar across sessions (p=0.525) and as reflected by the low inter-session variability (mean SD=0.097). When looking into the effect of the three different stimulation conditions, only iTBS tended to alter measures of cortical excitability. Indeed, as shown in Table 6.2 and Figure 6.3, there was a trend for a lower PPC+TA ratio after iTBS ($\chi^2(2)=5.143$, p=0.058, W=0.184), specifically at POST0 compared to POST30 (z=3.207 , p=0.060, r=0.229). Furthermore, at POST 0, iTBS PPC+TA ratio was significantly lower than cTBS (z=-2.139, p=0.032, r=-0.404) and sham (z=2.381, p=0.017, r=0.372). Among the fourteen participants, iTBS reduced PPC+TA ratio in 9

participants, to increase it in 4 participants, and did not change it in 1 participant. The PPC+TA ratio did not change following sham and cTBS, and TA cortical excitability did not change following all TBS protocols.

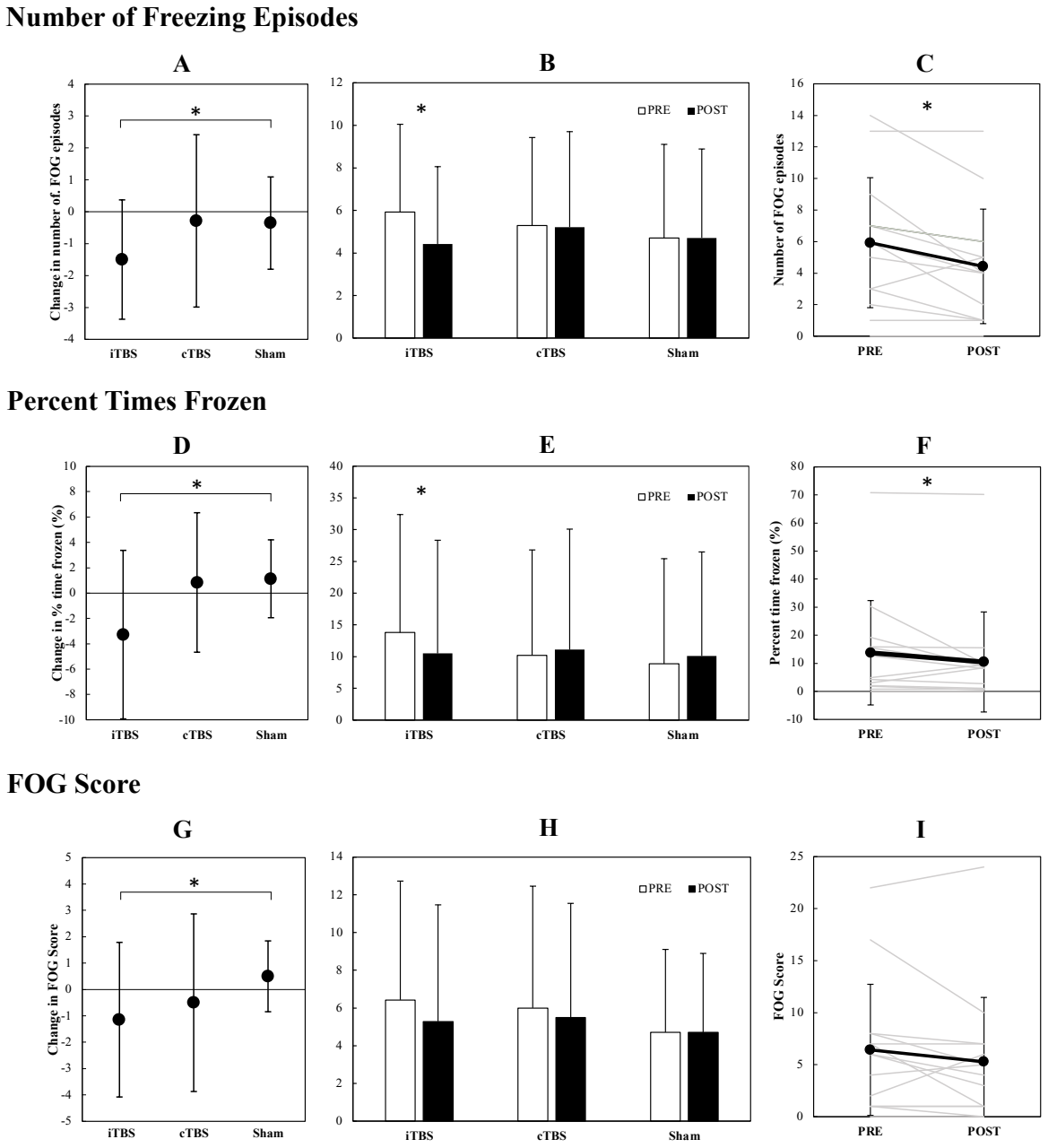

Figure 6.2 *Changes in the number of FOG episodes (upper panel), percent time frozen (middle panel) and FOG score (lower panel) from the freezing-provoking test after each TBS protocol. A, D & G represent group changes in each outcome for each stimulation protocol. B, E & H represent group average for each outcome PRE and POST each stimulation protocol. C, F & I represent individuals changes in each outcome in grey and the group mean in black for iTBS only. * denotes a significant change p<0.05.*

Table 6.2 *Behavioral, clinical, and cortical excitability outcomes*

	iTBS			cTBS			Sham			iTBS vs sham	cTBS vs sham
FOG-Provoking Test	**PRE**	**POST 10**	***P***	**PRE**	**POST 10**	***P***	**PRE**	**POST 10**	***P***	***P***	***P***
Score	6(6)	5(6)	0.20	6(6)	6(6)	0.67	5(5)	5(5)	0.21	**0.04**	0.28
Time to complete (s)	132(36)	124(32)	0.26	130(32)	132(45)	0.75	121(31)	125(37)	0.86	0.29	0.97
Number of FOG episodes	**6(4)**	**4(4)**	**0.03**	5(4)	5(4)	0.98	5(4)	5(4)	0.88	**0.01**	0.69
% time frozen	**14(19)**	**10(18)**	**0.05**	10(16)	11(19)	0.95	9(17)	10(16)	0.76	**0.02**	0.67
Step count turn most affected side	19(10	19(10)	0.25	18(9)	18(12)	0.93	18(11)	18(12)	0.51	0.39	0.93
Step count turn less affected side	19(10	19(11)	0.75	17(13)	19(12)	0.24	18(14)	18(11)	0.61	0.45	0.16
Time turning most affected side (s)	23(30)	26(37)	0.90	21(23)	23(36)	0.86	21(24)	22(26)	0.29	0.85	0.47
Time turning less affected side (s)	22(25)	23(29)	0.78	20(25)	20(24)	0.60	20(21)	19(18)	0.55	0.53	0.62
Clinical Outcomes											
MDS-UPDRSIII	**43(11)**	**41(10)**	**0.05**	44(12)	43(12)	0.14	**45(12)**	**42(11)**	**0.02**	0.76	0.19
TMT A (s)	32(14)	31(12)	0.78	32(10)	31(19)	0.15	30(13)	26(10)	0.06	0.31	0.44
TMT B (s)	78(42)	72(39)	0.35	82(51)	73(44)	0.57	79(47)	81(60)	0.47	0.38	0.55
PGIS	n.a.	3(2)	n.a.	n.a.	3(2)	n.a.	n.a.	3(1)	n.a.	0.85	0.10
Cortical excitability Outcomes	**PRE**	**POST 0**	**POST 30**	***P***	**PRE**	**POST 0**	**POST 30**	***P***	**PRE**	**POST 0**	**POST 30**	***P***	***P***	***P***
TA MEPs normalized by M-max	1.14(0.56)	1.23(0.44)	1.21(0.52)	0.40	1.23(0.77)	1.20(0.75)	1.38(0.86)	0.07	1.11(0.42)	1.21(0.49)	1.51(1.12)	0.08	0.64	0.46
PPC+TA ratio	1.03(0.20)	0.94(0.17)$^{+}$	1.08(0.15)$^{+}$	0.06^{+}	0.98(0.13)	1.00(0.31)	0.98(0.10)	0.74	1.07 (0.18)	1.03(0.16)	1.06(0.10)	0.61	0.67	0.50

Bold represent significant changes at p≤0.05

$^{+}$ denotes a tendency for a post hoc difference for iTBS POST30 > POST0 at p=0.06.

n.a.: non-applicable

FOG: Freezing of gait

s: seconds

MDS-UPDRSIII: Movement Disorder Society Unified Parkinson's Disease Rating scale (Part III).

TMT A: Trail Making Test item A

TMT B: Trail Making Test item B

PGIS: Patient General Impression Scale

TA: tibialis anterior

PPC: posterior parietal cortex

MEPs: motor-evoked potentials

iTBS: intermittent theta burst stimulation

cTBS: continuous theta burst stimulation

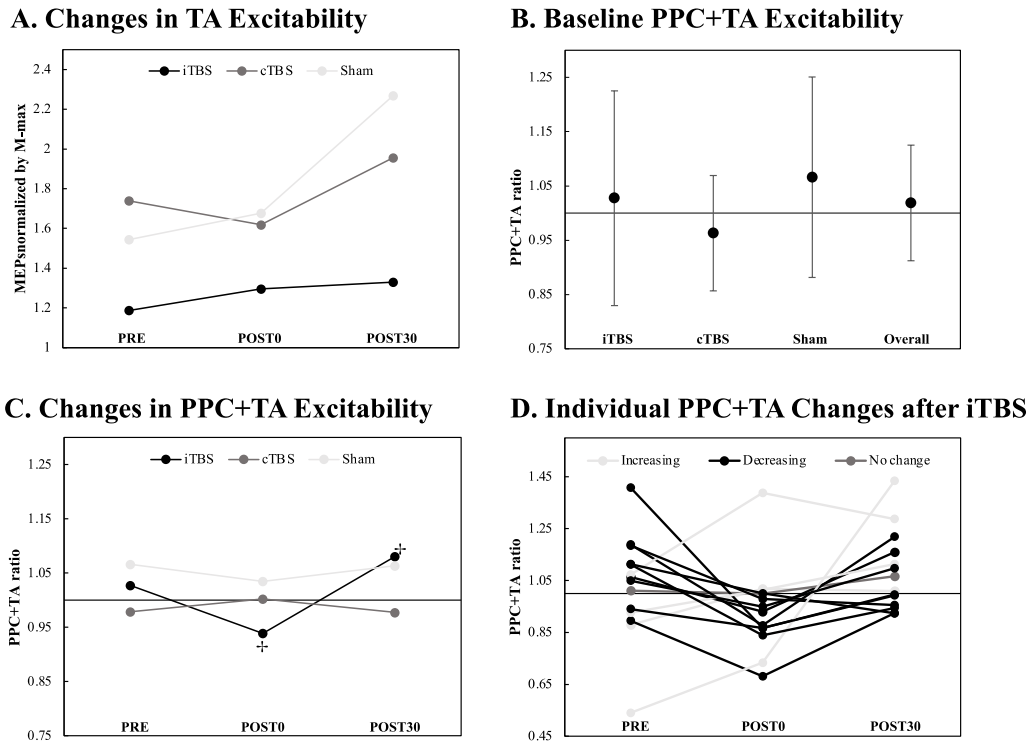

Figure 6.3 *Cortical excitability outcomes. (A) Changes in mean TA cortical excitability for each stimulation protocol. (B) Baseline mean PPC+TA excitability for all sessions. (C) Changes in mean PPC+TA excitability for each stimulation protocol. (D) Changes PPC+TA excitability for each participant following iTBS, with nine showing a decreased excitability, four an increase and one with no change. PPC+TA excitability is quantified by the PPC+TA ratio which corresponds to (PPC+TA MEPs)/TA alone MEPs. ✛ denotes a trend for iTBS POST30 > POST0 at p=0.060. TA: tibialis anterior, PPC: posterior parietal cortex, MEPs: motor evoked potentials, iTBS: intermittent theta burst stimulation, cTBS: continuous theta burst stimulation, PRE: before stimulation protocol, POST0: immediately after stimulation protocol, POST30: 30 minutes after stimulation protocol.*

6.4.3 Clinical Outcomes

TMT scores did not significantly change after each PPC modulation protocol as shown in Table 6.2. MDS-UPDRSIII score was significantly reduced after sham (z=-2.243, p=0.025, r=0.599) and iTBS (z=1.889, p=0.050, r=0.505) with a moderate effect size, but not after cTBS. PGIS scores demonstrate that participants had the impression that their gait and FOG were a little better following all stimulation protocols, but were not significantly different between iTBS, cTBS and sham (p=0.247). As shown in Figure 6.4, the change in MDS-UPDRSIII score significantly and strongly correlated with the PGIS score but only in the iTBS condition (r_s=-0.606, p=0.022).

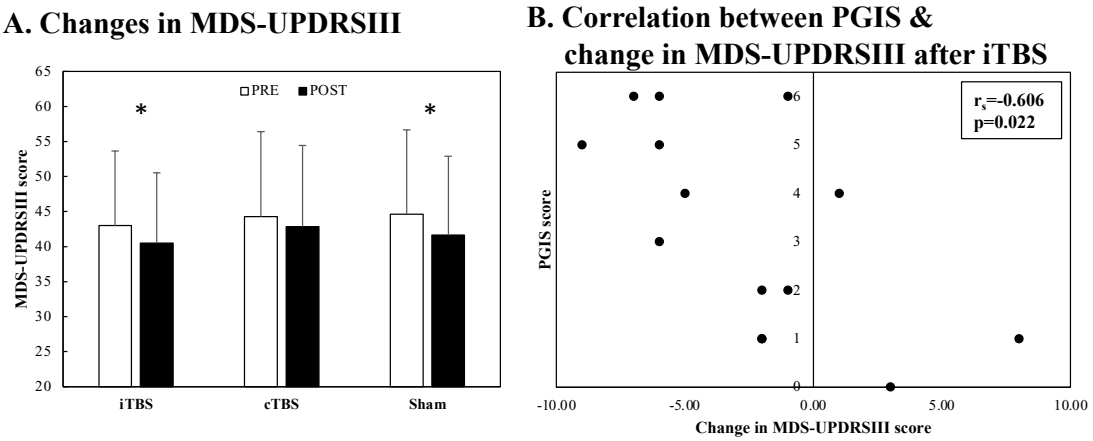

Figure 6.4 *(A) Mean and SD of MDS-UPDRSIII score before and after each stimulation protocol and (B) correlation between the PGIS score and the change in MDS-UPDRSIII after iTBS (r_s=-0.606, p=0.022). * denotes a significant change p<0.05. MDS-UPDRSIII: Movement Disorder Society Unified Parkinson's Disease Rating scale (Part III), PGIS: Patient global impression scale, iTBS: intermittent theta burst stimulation, cTBS: continuous theta burst stimulation, r_s: Pearson correlation*

6.5 Discussion

To the best of our knowledge, this is the first study to apply non-invasive brain stimulation to the PPC in FOG. We showed that upregulating PPC excitability led to quantifiable changes in its excitability and to beneficial changes in FOG. Specifically, PPC iTBS resulted in reduced FOG severity, number of FOG episodes and percent time frozen, as well as in the tendency to the induce an inhibitory functional connectivity from the PPC towards the lower limb motor cortex. These results provide, for the first time, evidence for the beneficial involvement of the PPC in preventing FOG, as increasing the likelihood of the PPC being recruited while walking resulted in less FOG.

Previous studies associated FOG with a downregulation of the PPC. First, decreased resting metabolism of parietal regions have been shown in freezers compared to PD non-freezers (Bartels, de Jong, Giladi, Schaafsma, et al. 2006). fMRI studies have demonstrated decreased recruitment of superior parietal areas in freezers compared to healthy individuals during foot-pedaling (Piramide et al. 2020) and during turns in a virtual reality foot-pedaling paradigm (Gilat et al. 2015). In our previous study (Mitchell et al. 2018), PPC metabolism was also significantly decreased during a steering of gait task that resulted in multiple FOG episodes, supporting less parietal control of gait in individuals experiencing FOG. In the current study, in agreement with our hypothesis, fewer FOG episodes and a reduced percent time frozen and FOG severity were

observed shortly after applying an excitatory TBS protocol on the PPC. Altogether, these findings could indicate an inability for freezers to efficiently recruit PPC while walking in a potentially complex environment. Upregulating the PPC seems to have beneficial effects on FOG, thus supporting a potential beneficial role of PPC recruitment in preventing the occurrence of FOG episodes. This is, however, in contradiction with results showing increased PPC activity during motor arrests (i.e.,, a proxy for FOG episodes) that occurred in a virtual reality foot-pedaling paradigm (Shine, Matar, Ward, Bolitho, et al. 2013). This could be explained by the differences in visuospatial and sensorimotor requirements in such paradigm compared to those of real complex walking, which could explain why PPC activity seems to behave differently in a virtual reality environment.

In our study, we show that facilitating recruitment of the PPC results in less FOG. While we hypothesized that this could be achieved through an enhancement of visuospatial functions, we did not observe any significant change in the TMT performance. The exact PPC area that we stimulated might not have been related to the domains tested by the TMT, namely visual attention, processing speed and mental flexibility (Tombaugh 2004; Bowie and Harvey 2006). However, this does not mean that an enhancement of visuospatial function or sensorimotor integration did not occur following our excitatory stimulation protocol on the PPC. In healthy young adults, iTBS applied on the right PPC did not impact visuospatial function (i.e., line bisection task) or temporal attention (i.e., attentional blink task and saccade task)(Whybird et al. 2021; Moretti et al. 2022), but faster reactions to a visual N-back task were observed (Whybird et al. 2021). Thus, beneficial effects of upregulating PPC for FOG could also be achieved through other mechanisms than visuospatial function enhancement. A more thorough cognitive assessment could potentially help determine if FOG improvement following PPC modulation is mediated by better visuospatial, sensorimotor, or other type of processing.

In this study, we attempted to quantify the effects of TBS on the excitability of a non-motor region (i.e., the PPC), something rarely done in rTMS studies. Because PPC has no direct quantifiable output but has strong reciprocal connections with motor areas (Hyvärinen 1982; Cattaneo et al. 2020), PPC excitability quantification is achieved by combining its stimulation with the primary motor cortex in a dual coil set-up (Koch and Rothwell 2009). Previous studies have shown a

facilitatory functional connection of the PPC with the hand motor cortex in healthy young (Koch et al. 2007, 2008) and older adults (Palomar et al. 2013) that is lost in PD (Palomar et al. 2013). However, such protocol targeting the hand representation of the motor cortex has little value for the study of gait impairments. Thus, in this study, we conducted for the first time a dual coil protocol in which the stimulation of the TA cortical area was preconditioned by PPC stimulation. At baseline, we found no functional connection between the PPC and the cortical TA which is in agreement with previous literature in the hand motor cortex of individuals with PD (Palomar et al. 2013). A tendency for changes in parieto-motor connectivity were observed only after iTBS, the excitatory protocol. Specifically, upregulating PPC excitability induced an inhibitory connection from the PPC towards the cortical TA immediately after iTBS in nine of our fourteen participants, and this connectivity was brought back to baseline level thirty minutes after. We believe that this inhibitory connection could possibly be involved, at least partly, in the improvement in FOG observed also after PPC upregulation. A substantial increase in cortical input prior to a FOG episode is thought to contribute to an overload in the processing capacity of the basal ganglia, and ultimately to FOG (Shine, Naismith, and Lewis 2013). The tendency for an inhibitory drive we observed in this study from the PPC toward the cortical TA could contribute to reducing the cortical burden put on the basal ganglia. Indeed, direct PPC connection with primary motor cortex could be depressed to prioritize the connections with premotor areas for better sensorimotor integration. However, this explanation remains speculative as PPC connectivity with premotor areas was not assessed, and only a statistical tendency was observed. While this study did not establish the existence of such inhibitory drive from the PPC to the cortical lower leg, it does not mean that it does not exist; the variable nature of brain excitability and the lack of power due to our small sample size could explain the lack of statistical significance. Furthermore, it cannot be ignored that other neurophysiological processes could also explain the beneficial effect of PPC iTBS on FOG. For example, it has 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). Even though this has yet to be studied with TBS, it remains a plausible explanation for the observed FOG improvement.

Interestingly, we found significantly decreased PD motor symptoms severity as depicted by the MDS-UPDRSIII score after both iTBS and sham protocols. PGIS scores also indicate that

participants perceived their gait and FOG as a little better following all stimulation protocols. This is not surprising as placebo effect is common in PD. It is thought to be caused by a dopamine release induced by participant's expectancy of improvement (Quattrone et al. 2018) and has the capacity to reduce MDS-UPDRSIII score during a sham protocol to the same extent as real rTMS (Okabe, Ugawa, and Kanazawa 2003). We found a significant correlation between the PGIS score and the change in MDS-UPDRSIII following iTBS. This could mean that participants perception of improvement corresponds to MDS-UPDRSIII score only when there is a real objective change in motor symptoms (i.e., in FOG). While the changes in MDS-UPDRSIII score were statistically significant, clinical significance was not met after iTBS and only a minimal clinical significant change was reached for sham (Shulman et al. 2010). Thus, this result should be interpreted with caution.

Overall, we demonstrated that increasing the likelihood of the PPC being recruited while walking using TBS resulted in less FOG. Despite our randomized counterbalanced design, FOG score was higher and more FOG episodes occurred at baseline during the iTBS condition compared to the baseline of the other conditions (i.e., cTBS and sham). We cannot ignore that this could explain why improvements in FOG were observed. This highlights the highly variable nature of FOG and may illustrates that more severe freezers could benefit more from iTBS. However, we did not find correlations to support this idea, possibly because our samples size did not allow for enough variability in FOG severity and in response to iTBS, but previous studies have shown that more severe freezers recruit less parietal areas than milder freezers (Piramide et al. 2020). Furthermore, in 4 participants, 1mV MEPs were not obtainable at rest, thus cortical excitability outcomes were acquired while they were maintaining their TA muscle contracted. However, the behavior of their TA alone MEPS and PPC+TA ratio after all stimulation protocols was similar to the rest of the sample. For example, after iTBS, three followed the tendency for a decreased PPC+TA ratio and one exhibited increased PPC+TA ratio; thus they were not different from the resting participants. Nevertheless, the current study sets the stage for promising research on PPC modulation for improving FOG. Future studies should include larger sample size so that participants can be classified based on their FOG phenotypes to determine who benefits the most from such PPC modulation. Interventions should also be tested on a longitudinal design, and the combination with a physical training (i.e., gait and balance, sensory cueing, action observation, etc.) should also be

explored. Finally, as improvement in FOG following iTBS was accompanied by a tendency for an inhibitory PPC functional connection with the cortical TA, cortico-cortical paired associative stimulation on the PPC and the motor cortex (Chao et al. 2015) could be of high interest in FOG to modulate and restore this connection specifically.

6.6 Manuscript References

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Chapter 7

Discussion

7.1 Summary of Results

The overall goal of this thesis was to assess the neural mechanisms of FOG in PD to gain a better understanding of its pathophysiology and guide future therapeutical interventions. This was achieved using four different methodologies. Hypothesized neural mechanisms of FOG were quantified using rs-FC and dual coil TMS, and modulated with TBS. A conceptual literature review was also conducted to discuss neural correlates of FOG and their potential as targets of NIBS interventions aimed at reducing FOG. Results corresponding to each specific thesis objectives and hypotheses are summarized below.

The first two objectives of this thesis aimed to identify FOG-related changes in brain functional connectivity at rest within the Interference model. This was achieved using seed-to-voxel rs-FC, a type of analysis that allows to test specific a priori hypothesis such as the Interference model. Results of the first experimental study (Chapter 3) did not allow to directly corroborate our hypothesis which stated that changes in rs-FC would occur within the cortico-basal ganglia-thalamic circuity and would represent an increase inhibitory drive as described by the Interference model. Indeed, changes between subcortical nuclei were not observed, possibly because of a lack of power due to our sample size (see section 7.4.1) and to the resting nature of our study (see section 7.4.3). Instead, we demonstrated that in freezers, the bilateral thalamus and GPe are more connected with visual areas, and that the left putamen has higher connectivity with the retrosplenial cortex and the cerebellum. Even though these cortical regions are not included in the Interference

model per se, they accomplish visual and sensorimotor processing that could compensate for altered visuospatial processing in FOG (see section 7.3) or could contribute to overwhelming the processing capacity of the basal ganglia and potentially lead to FOG (see section 7.2).

To test the second hypothesis (Chapter 4), a functional connectivity analysis was carried out on resting fMRI data acquired ON- and OFF-medication. The hypothesis, which stated that changes in rs-FC would represent a medication-induced normalization of the cortico-striato-thalamic circuity, was partly corroborated. Indeed, L-DOPA intake mainly changed rs-FC to bring the connectivity to levels similar to those of non-freezers. However, L-DOPA also increased connectivity between several subcortical nuclei and cortical regions including the PPC, the motor cortices and the inferior frontal gyrus, to levels higher than non-freezers, thus representing a compensatory mechanism with the potential of contributing to FOG (see section 7.2). Interestingly, changes induced by L-DOPA between regions involved in the Interference model were specific to freezers, providing support for this model explaining the neural correlates of FOG. Furthermore, the PPC was the brain region with the functional organization the most modulated by medication. This could be explained by the fact that asymmetrical-motor FOG was the only type of FOG triggers experienced by all the participants included in this study (see section 7.4.2).

As part of the third objective of this thesis (Chapter 5), reviewing FOG neuroimaging and neuro-electrophysiological literature led: (1) to the confirmation that cortical regions of the Interference model are involved in FOG, and (2) to the identification of potential NIBS cortical targets to improve FOG. The M1, the SMA and the DLPFC are targets that have already drawn attention, generally resulting in improved gait or FOG. This literature review also identified promising brain targets, including the PMC, the mPFC, the cerebellum and the PPC. The latter is considered a region of high interest due to its evident involvement in FOG. Different methodological considerations were discussed in Chapter 5 and will be further explored in sections 7.5.3-4.

Before considering NIBS interventions for FOG, the role in FOG of the region wished to stimulate must be assessed as it may impact the type of stimulation to deliver. For example, suppressing a brain region found to be detrimental to FOG is probably more desired than up-regulating it. Thus, in Chapter 6, the objective was to modulate the excitability of the PPC to deduce its role in FOG

and better guide future PPC NIBS interventions. As hypothesized, increasing PPC excitability with TBS resulted in significantly less FOG, whereas the sham and inhibitory stimulation did not change any FOG outcomes. Upregulating the PPC also had the tendency to induce an inhibitory functional connection from the PPC towards the lower limb M1. Overall, it was demonstrated in Chapter 6 that increasing the likelihood of the PPC being recruited while walking with TBS results in less FOG, thus providing evidence for the beneficial role of the PPC in preventing FOG.

Altogether, results of Chapters 3 to 6 uncover the importance of visuospatial and sensorimotor neural correlates in FOG and support the role of PPC recruitment in preventing FOG episodes. In the next sections, the implication of the results for research and clinical purposes will be discussed. Specifically, in section 7.2, insights from rs-FC and TBS will help determine if compensatory neural mechanisms are beneficial or detrimental to FOG, and, in section 7.3, how visuospatial and sensorimotor neural correlates fit in the Interference model will be examined. In section 7.4, methodological considerations will be discussed, and, in section 7.5, results will be considered in terms of their potential to set the stage for future promising research and clinical opportunities.

7.2 Are Compensatory Neural Mechanisms Beneficial or Detrimental to FOG?

FOG has been previously shown to be associated with reduced volume, activity, and metabolism of several brain areas (Rubino et al. 2014; Vastik et al. 2017; Gilat et al. 2015; Shine, Matar, Ward, Bolitho, et al. 2013; Mi et al. 2017; Mitchell et al. 2018; Gallardo et al. 2018). Many results of this thesis have been interpreted as a compensation for these neural changes. However, whether such compensatory mechanisms have beneficial or detrimental effects on FOG is still unclear. Thus, insights from the Interference model, rs-FC and TBS will be discussed in that perspective.

7.2.1 Insights from the Interference Model

According to the Interference model, FOG would be the consequence of an inability to concurrently process information from motor, cognitive and limbic circuity (Lewis and Shine 2016; Lewis and Barker 2009; Shine, Naismith, and Lewis 2013). Specifically, when a trigger of FOG is encountered while walking, a crosstalk in upstream processing would overwhelm the

striatum processing capacity, leading to FOG. Therefore, we can wonder if compensatory neural mechanisms could also compete for the neural resources and contribute to such crosstalk and ultimately cause FOG. A recent study conducted with a foot pedalling virtual reality paradigm found an association between worse FOG and greater cortical crosstalk (i.e., Ehgoetz Martens et al. 2018). This provides evidence for compensatory mechanisms being detrimental to FOG as they could increase interference with concurrent processing and compete for neural reserves.

7.2.2 Insights from Quantification by rs-FC

In Chapter 3, increases in rs-FC were observed between subcortical nuclei and cortical areas in freezers compared to non-freezers and such differences were attributed to an effort to compensate for poor visuospatial skills that characterize freezers (Nantel et al., 2012). However, with the data collected it is not possible to determine if such compensation is beneficial for FOG or if it is contributing to FOG. In Chapter 4, a levodopa-induced normalization in brain functional organization was observed when increases in rs-FC following levodopa intake was similar to levels observed in non-freezers. However, when L-DOPA increased rs-FC significantly more in freezers than in non-freezers, this change was attributed to a possible levodopa-modulated compensatory mechanism. Considering that all the participants reported freezing less or not at all when taking levodopa, this compensatory mechanism could be favorable by contributing to the reduced occurrence of FOG. Indeed, L-DOPA could have a facilitation effect in relaying information between the thalamus and the basal ganglia to the PPC and M1 to ensure effective sensorimotor integration. However, it is well established that a third of freezers still experience FOG in the ON-state (Amboni et al. 2015). Thus, we cannot ignore that such compensatory mechanism could be maladaptive and account for the remaining FOG episodes in the ON-state. Significant correlations between connectivity and clinical outcomes suggest that participants with more severe posture and gait symptoms and those who score better on the MoCA are less efficient at using this mechanism. While a better MoCA score could represent a better capacity to use this compensation, worst observed posture and gait seems contradictory. The lack of correlation between rs-FC changes and FOG severity in this study also makes difficult the interpretation of such compensation.

Previous rs-FC studies did show a positive correlation between freezers-specific increase in connectivity of locomotors hubs and markers of FOG severity (Fling et al. 2014; Lench et al. 2020). The reorganization of the locomotor network was thus considered as serving a maladaptive and ineffective compensatory role that may contribute to FOG. Interestingly, Fling and colleagues (2014) noted that the longer disease duration usually observed in freezers compared to non-freezers, as it is the case in Chapter 4, might allow more time for the nervous system to compensate for disease-related changes in brain functional organization. Thus, it would be interesting to determine wether non-freezers with a disease duration similar to freezers have the same compensatory connectivity changes or if they are freezers specific. Furthermore, if such compensatory neural mechanisms are deemed beneficial to optimize neural processing and avoid FOG, longitudinal studies could help determine whether they become detrimental after some time, with PD progression for example.

It is also important to note that results of Chapters 3 and 4 are specific to the resting state. As it will be discussed in section 7.4.3, changes in rs-FC may predispose to what occurs in an active state, but the resting nature of the results hinders our capacity to assume that the compensatory mechanisms are persistent in other states. The increased rs-FC that characterized these compensations could solely represent an effort to improve baseline communication between brain regions, so that they are ready to efficiently process information when needed, without increasing the total amount of processing in an active state. In this case, increased rs-FC could be a beneficial resting compensation to maintain relevant cortical functional connection in a competent state.

7.2.3 Insights from Modulation by TBS

In Chapter 6, PPC excitability was increased to compensate for the hypometabolic and hypoactive PPC typically observed in freezers (Bartels et al. 2006; Gilat et al. 2015; Mitchell et al. 2018; Piramide et al. 2020). As it resulted in significantly smaller number of FOG episodes and percent time frozen, such compensatory mechanism could be considered beneficial, similarly to other studies demonstrating that increasing the excitability of the mPFC or the SMA improves gait and FOG, possibly representing the use of compensatory mechanisms to reduce predisposition to FOG (Dagan et al. 2017; Mi et al. 2019). In our study, this compensatory increase in PPC excitability could have been mediated by beneficial TBS-induced network effects, through a possible

inhibitory drive to the M1, reducing crosstalk between the motor and cognitive loops. Furthermore, it cannot be ignored that such beneficial compensation occurred because participants were not cognitively impaired, neither in a severe stage of PD. It is thus possible that they had enough neural resources to manage additional neural processing that could have resulted from this compensation.

Altogether, results of this thesis suggest that freezers undergo brain functional reorganization in an effort to compensate for altered brain structure and function and to optimize visuospatial and sensorimotor processing. L-DOPA itself could be considered a compensatory mechanism, sometimes normalizing brain functional connectivity, sometimes in a way that could lead to FOG. Based on the Interference model, such compensation could be detrimental because it enhances competition in the allocation of neural resources between different concurrent processing, leading to an overload in the basal ganglia processing capacity. Even though evidence from stimulating the PPC suggests beneficial effects for FOG of a possible compensatory increase in PPC excitability, several unanswered questions were raised in this section, and must be addressed before determining if compensatory mechanisms can really be beneficial to efficiently compensate for dysfunctional networks and sensorimotor deficits in FOG.

7.3 Where do Sensorimotor and Visuospatial Neural Correlates fit in the Interference Model?

This thesis was initially set up to assess the neural mechanisms of FOG within the Interference model framework, not to the test the neural correlates of sensorimotor and visuospatial processing. Considering that most results however pointed back to them, it is interesting to discuss how sensorimotor and visuospatial neural correlates fit in this model. The component of the Interference model the most closely linked to those functions is the PPC. Initially excluded from the model, the PPC is now considered part of its cognitive loop. Based on results from fMRI studies showing parietal activation during increase cognitive load in a virtual reality walking paradigm, the PPC was included in the cognitive loop of the Interference model, but interpretated as part of the cognitive control network, mediating executive functions and goal-directed behavior (Shine, Matar, Ward, Frank, et al. 2013; Shine, Matar, Ward, Bolitho, et al. 2013; Ehgoetz Martens et al. 2018). Since then, only a very few studies have discussed the PPC in the Interference model in

terms of visuospatial deficits and integration of sensorimotor information (Lewis and Shine 2016; Mitchell et al. 2018; Gilat et al. 2015).

As mentioned in previous chapters, beyond its involvement in executive functions, the PPC plays a key role in locomotion by receiving sensory information and integrating it to guide action (Culham, Cavina-Pratesi, and Singhal 2006; Takakusaki 2013) and by ensuring error monitoring of movements in relation to the environment (Gwin et al. 2011; Hinton et al. 2019; Drew and Marigold 2015; Marigold and Drew 2017). Considering its critical role in locomotion, the PPC should be seen in the Interference model as a critical hub for sensorimotor integration, and not solely as a contributor to processing speed and set-shifting deficits. Perhaps the PPC should be included in the motor loop of the model, which could even be seen more as a sensorimotor loop. The cognitive and motor loops are currently seen as competing for neural reserves, which is most likely true, but part of the cognitive loop (i.e., PPC) is also feeding the cortical areas of the motor loop for locomotion planning and programming (Takakusaki et al. 2022). Furthermore, in Chapter 6, we showed that upregulating the PPC had the tendency to induce an inhibitory drive from the PPC towards the lower leg M1 and reduced FOG occurrence. This could possibly mean that the PPC is not competing with motor processing, but instead working along with the motor loop. In Chapter 4, we also demonstrated that levodopa-induced changes in rs-FC occurred between the PPC and the motor striatum (i.e., putamen), whereas no significant changes were observed between the PPC and the cognitive striatum (i.e., caudate). Altogether, these results indicate an important contribution of sensorimotor neural correlates in FOG and could support the addition of the PPC in a sensorimotor loop of the Interference model.

A subfunction of the PPC in sensorimotor integration is visuospatial processing (Drew and Marigold 2015; Marigold and Drew 2017). Interestingly, freezers have: (1) deficits in visuospatial domains that correlate with FOG duration (Nantel et al. 2012), (2) altered gait parameters and increased FOG while approaching a narrow doorway (Almeida and Lebold 2010; Ehgoetz Martens, Pieruccini-Faria, and Almeida 2013), (3) greater loss in stereopsis which measures the perception of depth and three-dimensional structure (Alhassan, Hovis, and Almeida 2019), and (4) increased dependency on visual feedback from nearby areas in the environment (Vanegas-Arroyave et al. 2022). The retrosplenial cortex is another area that has been associated with spatial

cognition (Mitchell et al. 2018) and that could be contributing to the aforementioned visuospatial deficits in freezers. In Chapters 3 and 4, the connectivity of the retrosplenial cortex was shown to be higher in freezers with the putamen and normalized by levodopa with the thalamus. Again, such evidence demonstrates the important role of visuospatial neural correlates in FOG and support the idea of including visuospatial areas in a hypothetical sensorimotor loop in the Interference model.

Evidence also exists for a contribution of vision neural correlates in FOG and for a potential relevance of considering the visual cortex in the Interference model. A recent study used a dual coil TMS protocol to demonstrate altered cortical visuomotor integration in freezers, showing that they have an excessive inhibitory drive from the visual cortex towards the M1 compared to non-freezers (Strigaro et al. 2020). In Chapter 3, we have shown alterations in the functional connections of the visual cortex in freezers, similarly to results of another study denoting increased rs-FC between the visual cortex and the striatum in freezers (Steidel et al. 2021). As the visual cortex and its connectivity with subcortical nuclei seem to be linked to FOG, visual neural correlates could be competing with other concurrent processing for neural resources and thus could be relevant to add in the Interference model along other visuospatial-related regions.

Finally, locomotion is more complex than only the three broad types of processing (i.e., motor, cognitive and limbic) covered by the Interference model. Instead, several different types, and subtypes, of neural processes occur concurrently in the upper level of the Interference model (Takakusaki et al. 2022). That is in part why this model has recently been identified as the probable common ultimate pathway to FOG (Weiss et al. 2020). Integration failure of multiple and diverse upstream networks could lead to this final pathway to FOG (Ehgoetz Martens et al. 2020). Results of this thesis support such idea and provide evidence for the neural correlates of visuospatial function and sensorimotor integration playing an important role in FOG.

7.4 Methodological Considerations

The three experimental studies included in this thesis have methodological factors and limitations that must be considered when interpreting the results. They will be developed in this section.

7.4.1 Sample Size

The sample size of the studies included in this thesis is relatively small, but comparable to most studies found in the literature. Despite the typical challenges of MRI and rTMS studies, the biggest challenge remained the COVID situation. Sample size of Chapter 4 study was planned to be twice as large, but the project had to be interrupted due to the first wave of COVID. Study of Chapter 6 was conducted during milder times of COVID pandemic, but the situation still dampened the participation enthusiasm. Combined with our stringent exclusion/inclusion criteria, these factors contributed to smaller samples size, which has a probable impact on our results. Small samples size has possibly reduced statistical power, increased false negatives, and certainly diminished the possibility of generalizing results to all individuals experiencing FOG. In the rs-FC studies, small sample size probably translated in more subtle connectivity changes not being detected. In the PPC modulation study (Chapter 6), small sample size could have resulted in a difficulty to obtain statistically significant changes in parieto-motor connectivity following iTBS due to the highly variable nature of brain excitability. Nevertheless, small sample size studies allow to the shed the light on probable neural mechanisms of FOG, and thus set the stage for larger studies that have more power to account for FOG variability, to establish clear links between FOG neural mechanisms and FOG assessment, and to stratify results based on FOG phenotype. This aspect will be discussed in the following section.

7.4.2 FOG Phenotypes

As previously mentioned, FOG is a highly heterogenous symptom. In the literature, three aspects have been used to classify FOG: motor presentation, most common triggers, and medication response. In terms of motor presentation, individuals can experience FOG as shuffling, trembling in place or total akinesia (Schaafsma et al. 2003). Because this is observable during an objective assessment of FOG, motor presentation was only recorded in the study of Chapter 6. However, results were not compared based on motor presentation as it may be linked to FOG severity (Ziegler et al. 2010) and thus be represented by the other FOG outcomes included in the study.

FOG classification based on the most common triggers of FOG is mainly assessed with the C-FOG. Since its publication in 2018 by Ehgoetz Martens et al., we have used this questionnaire to determine if our participants' FOG was characterized as anxious, asymmetrical-motor or sensory-

attentional. This is still not commonly done in the literature and remains a strength of our studies. Since all the results included in this thesis demonstrate that visuospatial and sensorimotor neural correlates are involved in FOG pathophysiology, one can question if asymmetrical-motor phenotype was common among the participants. The first study of this thesis (Chapter 3) was conducted before the publication of the C-FOG questionnaire; thus, such FOG classification is not available. In the study of Chapter 4, all the freezers reported experiencing asymmetrical-motor triggers and it was the most common type of FOG for twelve of them (Table S4.3). For two of the remaining freezers, this type of triggers was equally common as anxious triggers. A similar portrait can be drawn for the study of Chapter 6, whereas twelve participants matched the asymmetrical-motor phenotype, one equally experienced FOG from the three categories of triggers and one did not report specific triggers for their FOG. Thus, it is possible that if more diverse FOG phenotypes were included in our studies, other neural correlates of FOG could have been found and response to PPC TBS could have been different. It is thus essential that future studies characterize their participants based on FOG phenotype, as further discussed in section 7.5.1.

Finally, FOG can be classified based on its response to L-DOPA (Mckay et al. 2019; Amboni et al. 2015; Schaafsma et al. 2003; Espay et al. 2012). In our studies, we only included individuals with FOG not occurring when taking L-DOPA (OFF-FOG) and with FOG improved by L-DOPA but still occurring in the ON-state (ONOFF-FOG). Individuals with FOG occurring only when L-DOPA is taken or with FOG unresponsive to L-DOPA were not included because these types are still not well understood and most likely have different causes (Moreira, Rebelo Gomes, and Januário 2019; Espay et al. 2012). In Chapter 4, all participants reported an improvement in their FOG with L-DOPA, and ten out of fifteen reported having no FOG in the ON-state. That is why we are able to consider that observed changes in rs-FC following L-DOPA intake may be favorable by contributing to less FOG. In Chapter 6, even though six participants reported having no freezing when taking levodopa, a FOG-provoking test carried out in the ON-state was able to elicit FOG in all the participants, highlighting the importance of an objective assessment of FOG.

7.4.3 Neuroimaging at Rest for an Active Symptom

In Chapters 3 and 4, rs-FC was used to quantify neural mechanisms of FOG. This type of neuroimaging analysis is a valuable method to provide a picture of the baseline functional

organization of the brain representing the maintenance of neural networks in a competent state to readily process information when required (Varela et al. 2001). Quantifying rs-FC, as accomplished in Chapters 3 and 4, allows to determine important baseline changes in brain functional organization that could influence the occurrence of FOG in an active state. Alterations in brain function and organization are unlikely to be present only when individuals are walking; baseline differences must exist and help understand the pathophysiology of FOG. However, FOG remains a symptom of an active state and occurs when individuals are walking. Thus, results of Chapters 3 and 4 do not directly translate in the causes of FOG but should be instead interpreted as possible predispositions to FOG. Like any brain imaging technique, rs-FC alone is not sufficient to provide a full picture of neural correlates of FOG; its potential lies in its combination with different brain imaging modalities. This was carried out in Chapter 5 and contributed to a broader picture of the brain global architecture and functioning in freezers.

7.4.4 Objective Assessment of FOG

People living with PD are sometimes not aware that they experience FOG, while, in other cases, freezers could overestimate their FOG. Some individuals do not realize that they freeze in certain situations as this has been part of their daily life and do not pay much attention to it anymore. Those are all examples of why subjective reports of FOG through questionnaires might not reliably evaluate its severity and highlight the importance of an objective assessment. Unfortunately, in Chapters 3 and 4, FOG severity assessment was achieved only through subjective questionnaires. This is mainly because some resting scans were taken from a previous study and such objective assessment was not available. This limits the interpretation of the results and could possibly explain why no correlations were found between the rs-FC changes and FOG severity. However, it is important to note that the latter was determined with the NFOGQ (Nieuwboer et al. 2009), a questionnaire that inquire on FOG occurrence, duration, and repercussion after showing a video demonstrating different types of FOG, thus ensuring participants understanding of FOG.

In Chapter 6, the goal was to determine if there was any effect of PPC modulation on FOG; thus, it was paramount that FOG assessment was carried out objectively. Ziegler's FOG-provoking test (Ziegler et al. 2010) was selected as it includes multiple common triggers of FOG, is easily

administrable and results in a score representing FOG occurrence and severity. As previously suggested (Bloem et al. 2004; Herman et al. 2020), participants were videotaped and timed while performing this test and this allowed to quantify multiple temporal characteristics of FOG. Such detailed objective assessment of FOG permitted to pinpoint what aspect of FOG could be modulated by TBS. Quantifying gait parameters could also offer more insight on subtle effects on gait that cannot be detected with standard FOG assessment. Even though not included in this thesis, gait kinematics data is available for the study of Chapter 6 and will eventually be analyzed.

7.4.5 Thorough Cognitive and Visuospatial Evaluation

Because the thesis was not initially set out to assess visuospatial and sensorimotor processing specifically, an in-depth cognitive and visuospatial assessment was not conducted in the experimental studies. This certainly limits the interpretation of the results as possible links between visuospatial function and our outcome measures could have provided more insight into visuospatial impairments and their neural correlates in FOG. Nevertheless, general cognitive abilities were assessed in all experimental studies using the MoCA. The Trail Making Test was included in Chapter 3 to characterize the sample, but also as an outcome measure in Chapter 6. However, this test assesses visual attention, processing speed and mental flexibility (Tombaugh 2004; Bowie and Harvey 2006) and does not directly address domains of visuospatial function more pertinent to FOG (i.e., visual perception, integration of spatial relations, working memory, etc.). Thus, it is not possible to comment on how our results relate to the visuospatial capacity of our participants, neither on which visuospatial domain may be most affected.

7.5 Future Directions

7.5.1 Addressing the Challenge of FOG Heterogeneity

Results of this thesis highlight the importance of characterizing FOG heterogeneity when studying this symptom. *One size does not fit all* is an appropriate statement for FOG research. At first, identifying common neural mechanisms of FOG regardless of FOG phenotype is important and necessary for a broad understanding of the symptom. However, FOG is more complex and probably cannot realistically be reduced to only a few common neural correlates. Therefore, studies should put effort on well stratifying their samples in terms of each FOG phenotype (i.e.,

medication-, trigger-, and manifestation-based) or start focussing on specific ones. The latter seems to be currently done for anxiety driven FOG, whereas several recent studies attempted to describe the neural correlates of anxious triggers (Gilat, Ehgoetz Martens, et al. 2018; Pimenta et al. 2018; Quek et al. 2021; Sarasso et al. 2021; Taylor et al. 2022). Thesis support the involvement of visuospatial and sensorimotor correlates in FOG and efforts should be put on an in-depth investigation of asymmetrical-motor FOG. Studying the impact of L-DOPA on FOG manifestation and neural mechanisms also seems critical, especially to confirm the accuracy of medication-based FOG subtypes and their implication for an effective management of FOG. In terms of interventional studies, FOG heterogeneity could underline the need for more personalized approaches, an idea that will be further discussed in section 7.5.4.

A promising way to tackle the challenge of FOG heterogeneity could be to turn to technological advances. Computational modelling, artificial intelligence and machine learning are methods getting more and more refined that could help address this matter. Such technology could be used for a better detection of FOG (Ren et al. 2022; Shalin et al. 2021). It could also serve for a better identification of FOG neural correlates, whereas different neuroimaging modalities including rs-FC could be combined to characterize neural mechanisms of each FOG phenotype, with the potential of using them as biomarkers. Other important FOG-related measures such as genetic determinants and gait kinematics could also be integrated in the models to provide a more global, but yet phenotype-specific, understanding of FOG onset, pathophysiology and manifestation. But to achieve that, larger cohorts are needed. It will probably require the research community to work more collaboratively, emphasizing on multi-center studies. Even though this brings important challenges, like a harmonization of research methods (i.e., diagnostic criteria, FOG assessment, imaging protocol, etc.)(Weiss et al. 2020), such progress would be beneficial not only for researchers, but also for the patients themselves as it will likely considerably enhance and precise our understanding of FOG and thus open doors for better ways to manage this symptom.

7.5.2 rs-FC as a Biomarker of FOG and a Predictor of its Improvement

rs-FC abnormalities have been used to detect differences between patients and healthy controls in different clinical populations with highly consistent findings for cognitive impairments, multiple

sclerosis and amyotrophic lateral sclerosis (Rosazza and Minati 2011). Consistent disruptions have been seen mainly in the default mode network in Alzheimer's disease (Greicius et al. 2004), and a disruption in interhemispheric rs-FC of the sensorimotor network has been able to discriminate PD from healthy controls with high accuracy and sensitivity (Rubbert et al. 2019). Such rs-FC biomarker would be of high interest for FOG to differentiate freezers from non-freezers early on. A recent study found that changes in cerebral structural morphology of the parietal cortex in drug-naïve PD was able to predict future FOG at a 5-year follow up (Wei et al. 2022). In this thesis, results of Chapters 3 and 4 indicate changes in resting functional organization of visuospatial and sensorimotor neural correlates in freezers experiencing predominantly asymmetrical-motor FOG. Thus, the potential of functional biomarkers such as rs-FC to predict FOG phenotypes is of interest. With such early detection of FOG, interventions to train the implicated networks and to preserve function could be put in place to possibly delay FOG onset.

rs-FC could also be used to guide NIBS studies and predict their effectiveness. In older adults, lower baseline interhemispheric rs-FC between the sensorimotor cortices and the SMAs was strongly associated with responsiveness to iTBS applied on M1, and these connections were shown to be enhanced after iTBS (Liu et al. 2022). In clinical populations, this has mainly been studied in treatment-resistant depression. Baseline functional connectivity was shown to predict beneficial response to a DLPFC-rTMS depression treatment (Avissar et al. 2017; Salomons et al. 2014; Ge et al. 2020). The content of this thesis, in which rs-FC and TBS were separately studied, leads to the idea of combining both modalities to possibly potentiate the effectiveness of NIBS interventions for FOG. For example, in Chapter 6 of this thesis, characterizing baseline resting connectivity of the PPC and the lower leg M1 could have potentially guided TBS response. Future work could thus try to determine biomarkers of NIBS effectiveness in freezers.

7.5.3 Optimization of rTMS Protocols for FOG

As discussed in Chapter 5 and in other reviews (Benninger and Hallett 2015; Madrid and Benninger 2021; Caulfield and Brown 2022) a wide variety of parameters can be studied to optimize rTMS protocols for FOG, but only a few ones will be presented here. First, as it was discussed in-depth in Chapter 5, selecting relevant *targets* for FOG is essential when studying

rTMS, and this should be achieved based on existing evidence for FOG neural correlates. As done in Chapter 6, the role of the selected targeted region should also be a priori determined, before engaging into interventional studies. It could also be interesting to determine cortical areas or neural mechanisms not enhanced by L-DOPA and target them to determine if FOG can be ameliorated by their compensatory recruitment.

Stimulation intensity is another parameter that could be optimized for effective rTMS in FOG. Currently, stimulation intensity is based on motor thresholds, but it is still unknown if this is adequate for rTMS of cortical regions other than M1. Clinical benefits will likely not be observed if the targeted region is not sufficiently engaged by the stimulation. In Chapter 6, the motor threshold used to determine TBS intensity was taken from the FDI M1 as the PPC is located at a similar cortical depth. However, there is no evidence confirming that the stimulation intensity was in fact optimal for the PPC. Therefore, future work could investigate if interleaved TMS-fMRI can guide the optimization of stimulation intensity. This technique consists of applying a single pulse TMS while recording changes in BOLD signal and therefore directly measure brain response to TMS (Bergmann et al. 2021). Such technique may be useful in determining the stimulation intensity required to modulate non-motor regions adequately and efficiently. This could be especially interesting in freezers as it could account for known alterations in cortical structure and function that may impact differently motor and non-motor regions, and thus, response to rTMS.

Another element to optimize for interventional rTMS for FOG is the *scheduling of the doses,* but this is still a matter for investigation. There are currently no guidelines regarding the number of sessions or the duration of NIBS interventions in FOG, nor in PD. In Chapter 6, participants took part in one session of each type of stimulation. Even though effects on FOG were seen shortly after PPC upregulation, more sessions would likely be required to see improvements sustained in the long term. NIBS studies that included at least five sessions in their protocol resulted in improved FOG or gait maintained for at least one week and up to four weeks (Valentino et al. 2014; Kim et al. 2015; Dagan et al. 2017; Mi et al. 2019; Ma et al. 2019), but it is possible that less sessions could result in the same long-term effect. Therefore, some studies should focus on determining how many sessions are required to observe long-term beneficial effects on FOG, while others could try determining the duration of such effect following a single rTMS session.

Despite all these suggestions for optimizing rTMS, I strongly believe that the potential of rTMS for FOG lies in its combination with physical training or rehabilitative interventions. While rTMS alone can have beneficial effects on FOG, these could be magnified if combined with a training program. Considering that freezers have been shown to exhibit less motor learning than their counterparts non-freezers (Peterson and Horak 2016), priming the brain with rTMS could potentially enhance training-induced neural plasticity leading to stronger behavioral benefits. This has been shown in several conditions, including pediatric hemiparesis, hemispatial neglect and stroke motor impairments (Gillick et al. 2014; Lim, Kang, and Paik 2010; Kakuda et al. 2013). In FOG, this was investigated in only one study, which combined an inhibitory stimulation of the SMA with a daily gait training (Lench et al. 2021). While FOG severity ameliorated, the change was not different than from a sham stimulation combined with the same training, but changes in SMA functional connectivity were observed only after the real stimulation. Results from such studies in PD are even more promising, showing beneficial gait improvements beyond the effects of a rehabilitation training alone (Agarwal et al. 2019; Cucca et al. 2017; Migdadi et al. 2018; Yang et al. 2013; Kaski, Dominguez, et al. 2014; Kaski, Allum, et al. 2014). A recent study also showed that excitatory rTMS applied on the right PPC after training for a visuo-motor task led to better skill retention than the placebo stimulation in PD (Moisello et al. 2015). Therefore, considering the benefits of upregulating the PPC for FOG as shown in Chapter 6, future work should attempt to combine PPC modulation with a rehabilitation training that includes visuospatial demands. This also bring the idea of personalized neuromodulation and training interventions, a point that will be discussed in section 7.5.4.

Finally, all these different ways of optimizing rTMS for FOG should be accompanied by an electrophysiological quantification of the modulation applied. Indeed, it is important to know if and how any behavioral changes are linked to a real change in excitability of the targeted brain area; it can provide a mechanistical explanation to possible FOG improvement. This is usually achieved by recording MEPs before and after the stimulation. If a non-motor region is targeted, then it implies the use of dual coil protocol as done in Chapter 6. Furthermore, in doing so, it would be important to stay away from FDI M1, the most commonly used motor hotspot, and instead use the leg M1 as an output, which is the most relevant to study gait impairments such as FOG.

7.5.4 Personalized Rehabilitative Approaches

Recent systematic reviews revealed that exercise-based interventions have beneficial effects for FOG, but that these effects are not retained after the intervention (Kwok et al. 2022; Gilat et al. 2021). One way to optimize such interventions could thus be to move towards a more personalized approach. Considering FOG heterogeneity and the diversity of predominant triggers, patient-oriented interventions where specific functions related to each individual FOG phenotype would be targeted could yield better and possibly longer-lasting effects on FOG. For example, individuals with predominant asymmetrical-motor triggers could particularly benefit from a computerized working memory training shown to enhance visuospatial working memory in PD (Giehl et al. 2020). A recent study tested three different types of interventions, namely cognitive training, cognitive behavioral therapy and proprioceptive training, to address, respectively, cognitive, limbic and sensorimotor mechanisms of FOG (Chow et al. 2021). The cognitive training and the proprioceptive training resulted in reduced FOG severity, but information about participants' FOG phenotype was not provided. Thus, it is impossible to know if the cognitive behavioral therapy did not result in FOG improvement because participants were not experiencing much anxious trigger, and if the improved FOG severity occurred because asymmetrical-motor and attentional triggers were common among the participants. Thus, future work could select participants based on their FOG phenotype and test interventions relevant to their most commonly encountered triggers.

In Chapter 6, we observed less FOG after upregulating the PPC with iTBS. Considering that most of our participants experienced asymmetrical-motor triggers, such beneficial effects could come from the stimulation targeting a brain region specifically involved in participants' FOG phenotype. Building on this idea, the brain region to target with NIBS could be selected based on the neural correlates of the FOG phenotype. Such personalized NIBS could also be combined with a training, as discussed in section 7.5.3, to offer a way to efficiently improve FOG. Selecting the stimulation site and the type of rehabilitative training based on FOG phenotype seems to be an even more promising patient-oriented intervention. For example, modulation of the PPC could be combined with an action-observation balance and gait training (Pelosin et al. 2018; Mezzarobba et al. 2018; Pelosin et al. 2010; Agosta et al. 2017), as the PPC is involved in the mirror-neuron system (Cattaneo and Rizzolatti 2009) and the latter has been shown to be mediating FOG improvement

linked to this type of training (Pelosin et al. 2018). Future studies could therefore investigate the effectiveness and feasibility of such individualized rehabilitative NIBS protocols.

Finally, personalization of NIBS interventions could be pushed even further by using individual brain imaging and neuro-electrophysiology data to guide NIBS parameters (Caulfield and Brown 2022). For example, changes in brain structure or connectivity could guide the selection of the brain regions to target. In terms of electrophysiology, it has been recently shown that the best treatment depression-related outcome occurred when the frequency of the stimulation was the same as the inherent resonant frequency of the stimulated area for each individual (Leuchter et al. 2021). FOG has been associated with increases in alpha frequency in M1 and in the pre-SMA, and in decreased alpha, delta and theta frequency in parietal areas (Shine et al. 2014). Future work could thus attempt to personalize stimulation frequency to individual alterations in brain frequency, with a focus on regions related to the FOG phenotype. While all these NIBS individualizations need further investigation as they are currently emerging ideas, they offer promising patient-oriented therapeutical options for individuals experiencing FOG.

7.5.5 Providing Accessible NIBS

One may argue that interventional rTMS research for FOG is vain as it is an expensive and inaccessible research-oriented tool. However, considering the growing interest for neuromodulation and that it is FDA- and Health Canada-approved for major depressive disorders, it is not wrong to believe that rTMS may become more accessible and could eventually be offered for motor disorders. Furthermore, the current use of rTMS in research allows to determine with more options and higher precision potential effective protocols for FOG that could then be disseminated using more accessible types of neuromodulation, such as tDCS or transcranial static magnetic stimulation (tSMS). Although less focal and precise, tDCS delivers a stimulation that is able to alter membrane potential outlasting the period of stimulation, similarly to rTMS (Lefaucheur et al. 2017). tDCS is easier to apply than rTMS, and it can even be done remotely. Indeed, recent studies showed the feasibility and the effectiveness of home-based and self-administered tDCS in PD for fatigue, mood and sleep (Agarwal et al. 2018). Future work could thus try to determine if rTMS protocols effective for FOG could be delivered using home-based tDCS, which is of particular interest for freezers whose difficulty with mobility can restrain their

capacity to go regularly in clinics. New devices under the form of a headband or headphone (i.e., LIFTiD© and Halo Sport©) have recently been designed to deliver tDCS-like stimulation (Getliftid.com 2022; Huang et al. 2019; Park et al. 2019) with the goal of enhancing focus and sports performance. There is certainly a strong need for rigorous research on these devices, but they could potentially offer a good home-based neuromodulation alternative for freezers.

tSMS could also be a good accessible neuromodulation option as it has been shown to be a safe, inexpensive and portable tool (Oliviero et al. 2015). It consists in the application of a strong compact magnet on a specific brain region, delivering a static magnetic field to this area. tSMS is able to induce inhibitory effects to the ipsilateral M1 excitability in healthy (Oliviero et al. 2011; Silbert et al. 2013; Takamatsu et al. 2021) and PD (Dileone et al. 2017). The feasibility of at-home repeated tSMS sessions have also been established in PD (Dileone et al. 2022). Future studies could investigate the potential of such tool for stimulating non-motor regions and for motor symptoms improvement such as FOG. Even though more studies are needed to bring the potential of rTMS in the home of individuals experiencing FOG, creativity of the research community will certainly give rise to a panoply of options for providing accessible NIBS to who may need it.

7.6 Conclusion

The content of this thesis contributes significantly to advancing our understanding of FOG, a symptom of PD that affects considerably the quality of life of individuals experiencing it. In this work, neural correlates of FOG were assessed using quantification and modulation methods. Results demonstrate that: 1) subcortical nuclei and vision- and sensorimotor-related regions are more coupled in freezers, 2) L-DOPA selectively modulates brain functional organization in freezers, especially for PPC connectivity, 3) substantial evidence exists for PPC alteration in FOG and for its use as a target for NIBS to improve FOG, and 4) upregulating PPC ameliorates FOG, supporting its beneficial role in preventing FOG. Altogether, findings reveal that specific visuospatial- and sensorimotor-related neural mechanisms may predispose individuals to experience asymmetrical-motor FOG, and that targeting these mechanisms with NIBS could help avoid FOG. By better understanding neural correlates of this symptom, more targeted and evidence-based interventions can be designed and tested for FOG. As proposed in this thesis,

optimizing NIBS protocols may hold potential to improve FOG, especially if cortical modulation is combined with personalized training and guided by biomarkers. This doctoral work thus provides a launching point for future therapeutical studies aimed at that reducing FOG and hopefully contributes to improving quality of life of people living with this debilitating symptom.

Chapter 8. Thesis References

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