Freezing of gait after Deep brain Stimulation: predictors and low frequency stimulation as an effective therapeutic option

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"The difficulty lies, not in the new ideas, but in escaping from the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds. »

Oliver Sacks, in Awakenings

« Parecia que tínhamos chegado ao fim da estrada e afinal era apenas uma curva a abrir para outra paisagem e novas curiosidades”

Jose Saramago

Para a Avó Mercês, que ouviu a minha primeira história

To Paulo, the first person to hear this one

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Resumo

Sintomas axiais, incluindo comprometimento da marcha, *freezing* (FOG) e instabilidade postural, são sintomas comuns em pacientes com doença de Parkinson (PD). Eles são encontrados nos estágios iniciais da doença, e sua frequência e gravidade aumentam com a progressão da doença, levando à perda de mobilidade, independência, um aumento no risco de quedas e uma diminuição na qualidade de vida. Embora nos estagios inicias o FOG seja tipicamente responsivo à terapia com levodopa (LD) os sintomas axiais geralmente são menos sensíveis à LD quando comparados com os sintomas apendiculares, como rigidez, bradicinesia e tremor.

A Estimulação Cerebral Profunda do Núcleo Subtalâmico (STN-DBS) é um tratamento bem estabelecido para pacientes com PD com complicações motoras (MC). Embora o STN-DBS tenha mostrado benefícios a longo prazo para sinais apendiculares, flutuações motoras, discinesias e qualidade de vida, sua eficácia em abordar sinais axiais, incluindo FOG, é mais controversa. Alguns estudos indicaram que a estimulação pode melhorar a marcha e o FOG, especialmente a curto prazo, mas com uma diminuiçao do benefício a longo prazo. Outros estudos mostraram que os sintomas axiais permaneceram inalterados ou pioraram após a cirurgia de STN-DBS. Além disso, os fatores preditivos, clínicos e demográficos, dos resultados da marcha e do FOG após o STN-DBS não estão bem estabelecidos.

A optimizaça terapeutica dos doentes que apresentam FOG apos cirurgia de estimulacao cerebral profunda constitui um desafio terapeutico. Paradigmas alternativos de estimulação, como a estimulação de baixa frequência (LFS), foram tentados para melhorar o FOG pós-cirúrgico, contud, nem todos os estudos foram capazes de reproduzir os mesmos resultados.

Nesta tese, o nosso primeiro objectivo foi estabelecer a frequência e identificar os fatores de risco para o desenvolvimento de FOG e alteracoes da marhca pós-cirúrgicas.

Dados de 109 pacientes com PD submetidos a STN-DBS com um acompanhamento de 8 anos foram coletados retrospectivamente. A sobrevida a 8 anos e a frequência de marcos de incapacidade foram avaliadas. Mostramos que quedas (73% dos pacientes) e *freezing* (47% dos pacientes) foram os marcos mais precoces e frequentemente observados, ocorrendo em 40,4 ± 25,4 e 39,6 ± 28,4 meses, respectivamente. Demência, alucinações e institucionalização surgiram mais tarde e foram menos frequentes, com uma relação temporal entre a presença de marcos de incapacidade e morte sendo constatada. Pontuaçoe mais altas na MDS-UPDRS parte II na condiçao medicaçao-OFF e idade mais avançada a data da cirurgia estavam associados a um maior risco de quedas e FOG.

Dezoito pacientes com PD submetidos a STN-DBS foram avaliados pré-cirúrgicamente e acompanhados durante 18 meses apos a cirurgia. Marcha e FOG foram avaliados sob diferentes condições. A estimulação mostrou uma melhora não significativa na severidade da marcha em condições de OFF-medicação, mas uma piora não significativa na condição de ON-medicação. A estimulação reduziu a gravidade do FOG em condições de OFF-medicação, mas não teve impacto na gravidade em ON-medicaçao. Um aumento na frequência tanto de alteracoes da marcha quanto do FOG na melhor condição funcional também foi observado. A gravidade do FOG após 18 meses da cirurgia foi melhor correlacionada com a resposta pré-operatória à LD de métricas cinemáticas do que com a resposta do MDS-UDRS-III. Em relação aos efeitos da estimulação e LD na biomecânica da marcha, a avaliação pós-cirúrgica revelou que a estimulação foi associada a uma redução na velocidade, comprimento de passo e passada, e um aumento na variabilidade da marcha.

Diante das limitações da avaliação clínica em pacientes com PD, estudamos a resposta motora à LD usando análise cinemática 3D baseada em inércia. Dezessete pacientes com PD no estágio de complicações motoras foram estudados no pré-cirúrgico. A cinemática 3D assistida por IMU detectou alterações motoras tão cedo quanto 20 minutos após a administração de levodopa, mais cedo do que a avaliação clínica padrão usando o MDS-UPDRS parte III, sugerindo que a análise cinemática usando dispositivos vestíveis

pode detectar alterações motoras relacionadas ao tratamento de forma mais abrangente do que o MDS-UPDRS III.

Após estabelecer a frequência e os fatores de risco para o FOG, selecionamos pacientes com PD submetidos a STN-DBS que apresentavam FOG na melhor condição funcional (score de item 3.11 ≥2 na condição de MedicaçãoON/EstimulaçãoON) para avaliar a resposta do FOG ao LD e diferentes frequências de estimulação (130 Hz e 60 Hz). Dezessete pacientes foram incluídos neste estudo transversal e avaliados em cinco condições terapêuticas diferentes: MedicaçãoOFF/EstimulaçãoOFF; MedicaçãoOFF/EstimulaçãoON; MedicaçãoON/EstimulaçãoOFF e MedicaçãoON/EstimulaçãoON . Além da avaliação clínica e cinemática da marcha, um modelo de detecção automática de FOG foi aplicado a esses pacientes. A nível de grupo, comparado a MedicaçãoOFF/EstimulaçãoOFF, o número de episódios de FOG foi significativamente reduzido na condição MedicaçãoON/EstimulaçãoON 130 Hz. Observamos uma alta variabilidade nas respostas individuais à LD ou estimulação. Enquanto aproximadamente 29% dos pacientes pioraram do FOG com LD e foram resgatados pelo STN-DBS, cerca de 18% apresentaram o padrão reverso. Não foram observadas diferenças significativas no número de episódios de FOG entre diferentes frequências de estimulação, mas a variabilidade da marcha emergiu como a dimensão cinemática mais forte associada ao FOG. A detecção automática de FOG mostrou uma boa correlação com métricas clínicas de FOG em todas as condições testadas.

O presente trabalho fornece evidências de que FOG é um sintoma comum após STN-DBS, com sua prevalência aumentando ao longo do tempo. Pacientes com maior gravidade da doença e idade mais avançada no momento da cirurgia parecem ter um risco maior de desenvolver resultados axiais negativos. Com o papel do teste de desafio com levodopa (LCT) recentemente questionado como preditor de resultados axiais, mostramos que a resposta ao LD de métricas cinemáticas específicas da marcha pode estar melhor correlacionada com os resultados do FOG do que a resposta motora global. Também demonstramos que a estimulação e o LD podem impactar de forma diferente a biomecânica da marcha.

Em pacientes com FOG pós-cirúrgico na condição funcional melhor, mostramos que o FOG é em sua maioria resistente à terapia, mas parcialmente melhorado por estimulação e medicação. No entanto, essa resposta é inferior à resposta ao LD pré-cirúrgico, sugerindo que a progressão da doença pode ter um papel no surgimento desse FOG pós-cirúrgico. A heterogeneidade clínica e cinemática nas respostas ao FOG ao LD e estimulação (incluindo frequência) devem ser consideradas clinicamente, e uma avaliação extensiva com LD e testes de estimulação deve ser oferecida a pacientes com FOG pós-cirúrgico. A análise cinemática 3D da marcha pode ser um instrumento poderoso para identificar episódios de FOG, estudar fenótipos da marcha e esclarecer os mecanismos do circuito do FOG.

Abstract

Axial motor features, including gait impairment, freezing of gait (FOG), and postural instability, are common symptoms in Parkinson's disease (PD) patients. They are found in the early stages of the disease, and their frequency and severity increase with disease progression, leading to loss of mobility, independence, an increased risk of falls, and a decrease in quality of life. Although FOG is typically responsive to levodopa (LD) therapy in the early stages, axial symptoms are generally less sensitive to LD compared to appendicular symptoms such as rigidity, bradykinesia, and tremor.

Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) is a well-established treatment for PD patients with motor complications (MC). While STN-DBS has shown long-term benefits for appendicular signs, motor fluctuations, dyskinesias, and quality of life, its efficacy in addressing axial signs, including FOG, is more controversial. Some studies have indicated that stimulation can improve gait and FOG, especially in the short-term follow-up, but these benefits may diminish in the long term. Other studies have shown that axial symptoms either remained unchanged or worsened after STN-DBS surgery. Additionally, the pre-surgery clinical and demographic factors predictive of gait and FOG outcomes after STN-DBS are not well established.

Managing patients who present FOG in the postoperative phases of DBS remains challenging. Alternative stimulation paradigms such as low-frequency stimulation (LFS) have been attempted to improve post-surgery FOG, but consistent results have not been found across different studies.

In this thesis, we aimed to establish the frequency and identify risk factors for the development of post-surgery FOG and gait impairment. Data from 109 PD STN-DBS patients with an 8-year follow-up were retrospectively collected. Survival at 8 years and the frequency of disability milestones were assessed. We found that falls (73% of patients) and freezing (47% of patients) were the earliest and most frequently observed milestones,

occurring at 40.4 ± 25.4 and 39.6 ± 28.4 months, respectively. Dementia, hallucinations, and institutionalization emerged later and were less frequent, with a temporal relationship between the presence of disability milestones and death being ascertained. Higher Activities of Daily Living (ADL) scores in the OFF state and older age at surgery were associated with a higher risk of falls and freezing.

Eighteen STN-DBS PD patients were evaluated at baseline (pre-surgery) and followed up at 18 months post-surgery. Gait impairment and FOG were assessed under different conditions. Stimulation showed a non-significant improvement in the severity of gait impairment in medication-off conditions but a non-significant worsening in the medication-on condition. Stimulation reduced the severity of medication-OFF FOG, but it had no impact on severity. An increase in the frequency of both gait impairment and FOG in the best functional condition was also observed. FOG severity at 18 months post-surgery was better correlated with the pre-operative response to LD of specific kinematic metrics than with the MDS-UDRS-III response. Regarding the effects of stimulation and LD on gait biomechanics, post-surgical assessment revealed that stimulation was associated with a reduction in speed, step and stride length, and an increase in gait variability.

Given the limitations of clinical assessment in PD patients, we studied the motor response to LD using inertial-based 3D kinematic analysis. Seventeen PD patients at the stage of motor complications undergoing pre-surgery evaluation were studied. IMU-assisted 3D kinematics detected motor alterations as early as 20 minutes after levodopa administration, earlier than the gold-standard clinical evaluation using the MDS-UPDRS part III, suggesting that kinematic analysis using wearable devices can detect motor alterations related to treatment more comprehensively than the MDS-UPDRS III.

After establishing the frequency and risk factors for FOG, we selected PD STN-DBS patients presenting FOG in the best functional (score item 3.11 ≥2 on MedicationON/Stimulation ON condition) to assess the response of FOG LD and different stimulation frequencies (130 Hz and 60 Hz). 17 patients were included in this cross-sectional study, and evaluated in five different therapeutic conditions: MedicationOFF/StimulationOFF; MedicationOFF/StimulationON;

MedicationON/StimulationOFF and MedicationON/StimulationON. Besides the clinical and kinematic evaluation of gait a model for automatic FOG detection was applied to these patients. At a cohort level, compared to MedOFF/StimOFF, the number of FOG episodes was significantly reduced in the MedONStimON 130Hz condition. A high variability in individual responses to LD or stimulation was observed. While approximately 29% of patients worsened their FOG with LD and were rescued by STN-DBS, about 18% presented the reverse pattern. No significant differences were observed in the number of FOG episodes between different stimulation frequencies, but gait variability emerged as the strongest kinematic dimension associated with FOG. Automatic FOG detection showed a good correlation with clinical FOG metrics across all conditions tested.

The present work provides evidence that FOG is a common symptom after STN-DBS, with its prevalence increasing over time. Patients with higher disease severity and older age at the time of surgery appear to have a higher risk of developing negative axial outcomes. With the role of a levodopa challenge test (LCT) being recently questioned as a predictor of axial outcomes, we show that the response to LD of specific kinematic gait metrics may be better correlated with FOG outcomes than the overall motor response. We also demonstrated that stimulation and LD may impact gait biomechanics differently.

In patients with post-surgery FOG in the best-functional condition, we have shown that FOG is mostly therapy-resistant but partially improved by stimulation and medication. Nonetheless, this response is inferior to the pre-surgery response to LD, suggesting that disease progression may play a role in the emergence of this post-surgery FOG. The clinical and kinematic heterogeneity in FOG responses to LD and stimulation (including frequency) should be clinically considered, and an extensive evaluation with LD and stimulation testing should be offered to patients with post-surgery FOG. 3D-kinematic gait analysis can be a powerful instrument to identify FOG episodes, study gait phenotypes, and clarify the circuit mechanisms of FOG.

Table of Contents

List of Abbreviations and Acronyms

α-sync: alfa-synuclein
AE: Adverse Effects
APA- Anticipatory Postural Adjustment
BMT: Best-medical treatment
COMT-I: Catechol-O-methyltransferase inhibitor
CSAI: Continuous subcutaneous apomorphine infusion
DA: Dopamine agonist
DBS: Deep Brain Stimulation
FOG: Freezing of gait
FOG-Q: Freezing of gait Questionnaire
GBA: Glucocerebrosidase
GPi: Globus Pallidus Internus
HC: Healthy control
HR: Harmonic Ratio
IMAO: Monoamine Oxidase Inhibitors
IL-IL: interleaved-interlink
LB: Lewy Body
LD: Levodopa
LCIG: Levodopa-carbidopa intestinal gel
LFS: Low frequency stimulation
LRKK2: Leucine-rich repeat kinase 2
MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale
MC: Motor complication
MF: Motor fluctuation
NFOG-Q: New Freezing of gait Questionnaire
NMS: Non motor symptom
PD: Parkinson’s Disease
PD: Pharmacodynamics
PIGD/AR: Postural instability gait difficulty / akineto-rigid
PINK1: PTEN-induced putative kinase 1
PK: Pharmacokinetics
PRKN: parkin RBR E3 ubiquitin protein ligase
QoL: Quality-of-life
RBD: REM sleep behavior disorder

RCT: Randomized controlled trial

SCNA: Synuclein Alpha

SN: Substancia Nigra

SNpr: Substancia Nigra pars reticulata

STN: Subthalamic nucleus

TD: Tremor dominant

UPDRS: Unified Parkinson's Disease Rating Scale

VIM: Thalamic ventralis intermedius nucleus

VTA: volume of tissue activated

Chapter I. Introduction

IA- Introducing Parkinson's Disease

a) Epidemiology

Described for the first time by James Parkinson in 1817, Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. PD affects approximately 2-3% of the population aged over 65 year, with approximately 6.1 million people being affected worldwide in 2016.[1–5]

With an aging population these number are estimated to increase, and by 2040 it is estimated that more than 12 million people worldwide will suffer for PD. The "Parkinson pandemic" is believed to stem not only from an aging population but also from increasing longevity. Furthermore, decreasing smoking rates, along with rising levels of pesticides, solvents, and heavy metals, are also thought to contribute to the growing number of PD diagnoses.[1,6–8]

Despite being an age-related disease, it should be noticed that around ¼ of PD patients have less than 65 years at disease onset and 5-10% have less than 50 years old at the time of the first symptoms (young-onset PD).[1,2,4,9,10]

PD is more prevalent in men than in women, and age of onset is also lower in the former ones, with consequently more years lived with disability. A protective effect of estrogen has been put forward to explain both the low risk of PD in women and the increased prevalence after menopause years.[1,2,11–13]

In 90% of the cases PD is an idiopathic disease, with only 10% of the cases being a monogenic form of the disease. The likelihood of a monogenic form of PD is higher in patients with a positive family history of PD and/or patients with a younger age of disease onset, with proportion of genetically defined cases rising to more than 40% in those with disease onset before 30 years.[1,2]

In sporadic PD patients; environmental factors probably interact with genetic factors to cause PD **(Table 1.1).**[1–3,5,14–17] In monogenic forms of PD, autossomic dominant and recessive forms have been identified with the list of mutations causing monogenic

types of Parkinson comprising genes as SCNA, LRKK2, PRKN and PINK1.[18–21] In addition, heterozygotic mutations in the GBA gene have been associated to an increased risk for the sporadic form of the disease.[22–24]

Table 1.1 Risk factors for the development of Parkinson's disease

Risk Factors	Protective factors
Exposure to pesticides	Smoking
Head injury	Coffee drinking
Rural Living	Physical exercise
Beta-blocker use	High plasma urate levels
Agricultural occupation	Non-steroidal Anti-inflamatory drugs (NSAID)
Well-water drinking	

Despite the increasing knowledge gathered in the last years about genetic and environmental factors associated with PD, the precise molecular mechanisms that cause dopaminergic cell loss are still not fully understand. [1,2,25–28]

The neuropathologic hallmark of PD includes neuronal loss in specific areas of the *substantia nigra* (SN) and widespread intracellular accumulation of α-synuclein (α-sync) e presence of this two neuropathologic changes are specific for a diagnosis of idiopathic PD.[2,27,28]

Generalized brain atrophy, reflecting widespread neuronal loss is not typical of PD, where neuronal loss appears to be restrained to specific brain regions. In early-stage disease, loss of dopaminergic neurons is restricted to the ventrolateral SN with relative

sparing of other midbrain dopaminergic neurons but becomes more widespread with disease progression.[29]

The other main neuropathologic alteration is the presence of intracellular Lewy Body (LB), largely made up of aggregated α-sync.

Several mechanisms are probably involved on the accumulation and aggregation of α-sync[2]: (1) a relative overproduction of the protein, (2) the presence of mutations that increase the likelihood for its misfolding and oligomerization or (3) impairments in the molecular pathways that are charged with degrading native or misfolded α-sync. Here, a progressive, age-related decline in proteolytic defense mechanisms in the ageing brain might play an important part in the accumulation of α-sync. Lysosomal autophagy system (LAS) and ubiquitin-proteasome system are normally responsible for the maintenance of intracelular α-sync homeostasis. Increasing age – a major risk factor for PD - is associated with reduced activity of these systems, potentiating intracellular α-sync deposition. [30–32] The initial deposition of misfolded α-sync in a small number of cells would subsequently spread to neighboring structures due to a Prion-like propagation mechanism. Consequently, initial α-sync misfolding and aggregation in a small number of cells could progressively lead to the spread of LB to multiple brain regions.[33] This is consistent with the Braak's hypothesis, where a specific pattern for α-sync spreading is proposed.[34] According to the Braak's staging system, the pathology is hypothesized to spread according to a specific pattern, starting on the olfactory bulb and gut and spreading via the olfactory tract and the vagal nerve, respectively, toward and within the central nervous system (CNS). [2,34,35]

Mitochondrial dysfunction has been also intimately linked to the pathogenesis of PD, possible by potentiating dysfunction on axonal transport, increasing vulnerability of nigral dopaminergic neurons and increasing oxidative stress. It has also been postulated that a α-sync aggregation and mitochondrial dysfunction would perpetuate each other in a vicious cycle.[36–38] Neuroinflamation also appears to promote α-sync misfolding, and although the exact relationship between neuroinflammation and neurodegeneration is complex and not fully understood, there is growing evidence to suggest that inflammatory

processes contribute to the progression of the disease. α-sync appears to have a role role in triggering neuroinflammation, that, in its turn, will increase and promote α-sync misfolding and aggregation. In addition, recent evidence suggests that systemic inflammation may contribute to neuroinflammation in Parkinson's disease contributing to disease progression at the central nervous system. [26,33,39–41]

Overall, pathophysiologic alterations in PD appear to result from this complex interaction of aberrant α-synuclein aggregation, dysfunction of mitochondria, lysosomes, synaptic transport issues, and neuroinflammation. Altogether, this will result in neuronal death of primarily dopaminergic neurons, with a consequent decrease in dopaminergic transmission at the motor region of the striatum. This will translate into an imbalance between direct (facilitatory) and indirect (inhibitory) pathways explaining the emergence of bradykinesia, one of the cardinal motor symptoms of PD. [2]

b) Clinical Presentation

A triad of motor signs described initial by James Parkinson persists up to our days as the foundation for the diagnosis of PD.[42,43] More than 200 years after its initial description, the diagnosis remains fundamentally clinical and requires the presence of bradykinesia, rest tremor and/or rigidity.[44] Gait and postural impairment, even if not required for the clinical diagnosis of PD, are also classically recognized as cardinal disease signs. Additional motor features, that can appear throughout disease progression at different rates, includes micrography, hypomimia, hypophonia, dysarthria, dysphagia, freezing and festination. [1,44,45]

A high variability of motor phenotypes exists between subjects, with some patients presenting predominantly with a 4-6 Hz asymmetric rest tremor while in others gait impairment and postural instability will be the motor symptoms dominating the clinical presentation. According to the predominantly motor presentation, two major motor subtypes of PD have been defined: Tremor-dominant subtype (TD) and Postural Instability-Gait difficulty/ Akinetic-rigid (PIGD/AR) subtype.[46,47] Prognostic implications have been

attributed to each phenotype, with PIGD/AR patients classically presented faster rates of disease progression and higher degrees of functional disability (faster cognitive decline, higher risk of depression and apathy and higher prevalence of non-motor symptoms). [48–52]

More recently, limitations in the currently used algorithms have been highlighted as patients seem to transition between phenotypes both due to disease progression and treatment, lacking phenotypic stability over time. .[51,53] Accordingly it has been proposed that PIGD and TD should not be considered distinct biological entities but reflect the progression of parkinsonian motor symptoms throughout several stages.

Despite these limitations, differentiating between appendicular (tremor, bradykinesia and axial symptoms (gait, freezing, dysarthria, posture) has probably prognostic and therapeutically implications. [48–52]

Classically described as a motor disorder, the clinical spectrum of PD symptoms also comprehends several non-motor symptoms (NMS) touching several domains from cognition, autonomic dysfunction and affective disorders. **(Table 1.2)** It is of paramount importance recognizing (and treating) the existence of these non-motor symptoms since they contribute substantially to quality of life and disability. [1,2,54–57]

In addition, these non-motor symptoms may predate the emergence of motor complains, with constipation, REM-Sleep Behavior Disorder (RBD), hyposmia and depression appearing up to ten years before the emergence of the first motor symptoms. [58,59]

Table 1.2 Non-motor symptoms in PD

	Hyposmia	Decreased or absent sense of smell
Sleep dysfunction	REM- sleep behavior disorder (RBD)	Loss of REM sleep muscle atonia. It is associated with jerking and sometimes very violent limb and body movements

		which seem to be related to dream content (dream-enactment).
	Daytime sleepiness	Affects around 50% PD patients. It exists a significant correlation between the dose of dopaminergic medication and the severity of daytime sleepiness.
	Sleep-maintenance insomnia	May be associated with the presence of nocturnal cramping, painful dystonia, or difficulties turning in bed
Autonomic dysfunction	Constipation	Dysfunction occurs along the entire length of the gastrointestinal tract in PD. Constipation may occur in in 28% to 61% od PD patients
	Delayed gastric emptying	
	Urinary urgency and frequency	Urinary symptoms are associated with detrusor hyperreflexia
	Erectile dysfunction	
	Blood pressure variability	Includes orthostatic hypotension and labile hypertension, especially supine hypertension.
	Diaphoresis	
Psychiatric disturbances	Depression	Occurs in 35% of the PD population. Is generally milder, associated with apathy and anhedonia.
	Anxiety	Anxiety affects up to 60% of patients with PD and encompasses generalized anxiety, panic attacks and social phobias
	Apathy	Affects 60% of PD patients. May coexist with depression and dementia but can also occur independently.
	Psychosis	Common symptoms include visual hallucinations and delusions, and affects up to 40% of PD patients
	Mild cognitive impairment or Dementia	Often initially affects attention, executive, and visuospatial functions
	Pain	Affects 30–85% of the patient population. Pain may fluctuate with the motor state of the patient, often worsening during the off state.
	Fatigue	Affects around 50% of the patients. Is characterized by a lack of energy, exhaustion and tiredness.
Visual Disturbances	Diplopia	Visual disturbances in general are relatively common in PD with prevalence from 22-72%
	Loss of visual acuity	

c) Staging

Disease staging is a "classification system that produces clusters of patients requiring similar treatments and with expected similar outcomes. Staging can serve as the basis for clustering clinically homogeneous patients and help clinicians to define treatments and define prognosis. [60,61] In PD, many classification systems have been proposed based in age of onset, clinical phenotypes (brain-first vs body-first), disease progression (motor and non-motor milestones) and more recently based on biologic biomarkers[60,61].

An accepted definition of PD staging is still lacking,[61,62] but the natural history of PD can be divided into an Early-stage, Mid-stage and a Late-stage, according to the presence and severity of motor symptoms, presence and severity of motor complications (MC) and the level of physical independence of the patients.[2,63]

Neurodegeneration in PD likely begins years or decades before full PD diagnosis can be made and the existence of a prodromal PD phase is now universally recognized.[58,59,64,65] This prodromal phase is marked by the emergence of non-motor symptoms as constipation, REM-Sleep Behavior Disorder (RBD), hyposmia and depression, that may predate the emergence of motor symptoms on average by 10 years. Despite the relatively lack of specificity of these symptoms for PD, an algorithm that combines the presence of several non-motor features in addition to risk factors has been proposed to calculate the individual risk of PD.[58,59,65–67]

The emergence of clinical motor symptoms, normally after a phase of non-motor prodromal symptoms, correspond to the early-disease stage. At this stage the diagnosis of PD is normally made, upon the presence of bradykinesia, in combination with at least one of rest tremor or rigidity.[44] Supportive criteria , absolute exclusion criteria and red flags, should be also considered in order to identify possible atypical parkinsonism syndromes. This early stage is marked by an excellent motor response to levodopa (LD), with motor symptoms improving substantially with the introduction of dopaminergic therapy (honeymoon phase). At this stage axial signs are not relevant and cognitive status is relatively well preserved. [1,2,44]

The advanced-stage is mostly characterized by the emergence of MC, with motor fluctuations (MF) and dyskinesia leading to increasing disability and worsening of quality of live.[2,68,69] MF are thought to occur at a rate of 10% per year, with 50% of patients experiencing them within 5 years after disease onset. .[70–72] However, it has been reported that up to 50% of patients may have MF within 2 years of starting LD therapy[73] and, in the ELLDOPA trial, by the end of the 9-month trial period, almost a third (29.7%) of patients receiving the highest daily dose of levodopa (600 mg/day) experienced wearing-off phenomenon.[74] This stage is also marked by the emergence of motor axial signs (postural instability, freezing, dysarthria) that may not be totally responsive to LD, and by the emergence of non-motor signs as mild dementia and mild hallucinations. [2,62,68,75]

The late-stage is characterized by a decrease in motor complications with disability being mainly determined by the emergence of LD-resistant axial signs and NMS.[63,76,77] In the long-term follow up of the Sydney cohort, 80% of the patients will develop falls, > 50% will present hallucinations/dementia and 40% will be institutionalized after 15-20 years of disease duration.[78] The emergence of this set of disability milestones will mark the late-stage of PD, with this disability milestones preceding death in around 3-5 years a process that seems to be "biological-age" dependent.[63,79,80]

Mortality ratios appear to be 1.5 times higher in PD patients than in healthy controls, with long term cohorts showing a survival rate of around 26% after 20 years of disease. Pneumonia is the most common cause of death in PD patients, with PD itself being considered as relevant contributor in around 50% of the patients. [78,81–83]

The introduction of Deep Brain Stimulation (DBS) and other advanced therapies has enabled a significative improvement in QoL, due to their capacity of reducing MC, improving QoL and overall motor function.[84–88] However, up to this day there is no evidence of a neuroprotective or disease-modifying role of DBS, even it can exert beneficial effect on the progression of incapacity and QoL.[89–96]

a) Pharmacologic management of Parkinson's Disease

Introduced in 1967 by C. Cotzias, levodopa remains de most effective treatment for PD-related motor symptoms.[97] The notion that an earlier introduction of LD would potentially accelerate neuronal degeneration and disease progression, triggering an earlier emergence of motor complications, had led many physicians to avoid LD specially in young PD patients.[98–103] However, recent trials have changed this view, showing a substantial improvement in motor symptoms and QoL in patients treated with LD (when compared with patients where LD treatment was delayed), with this improvement not being paralleled by an increased risk of MC or faster disease progression.[104,105] In line with this, at the time being, no evidence exists to postpone dopaminergic treatment in PD patients whose motor symptoms are associated with disability or impairment on QoL.[106]

In addition to LD, dopamine agonists (DA), Monoamine Oxidase Inhibitors (IMAO) can be used alone (in the early disease stages) or as an add-on to LD. Catechol-O-methyltransferase inhibitors (COMT-I) are usually added to the therapeutic regime once motor fluctuations emerge.[107–111]

Despite the excellent initial response to dopaminergic replacement, disease progression brings the emergence of MC, with MF and dyskinesia.[73,112] The emergence of MC is largely related to the abnormal PK and PD of LD. Despite the fact that the pathophysiological mechanism is not yet fully understood it's probably related with the intermittent oral delivery of levodopa, as opposed to continuous physiological dopaminergic stimulation that associated with the relentless loss of nigrostriatal nerve terminals and reduced endogenous dopamine storage/release capacity, contributes to a pulsatile stimulation of dopaminergic terminals.[113,114]

When they appear, an adaptation of prescription patterns is mandatory, mostly aiming to provide a more continuous dopaminergic stimulation.[71,115] A common initial strategy consists in adjust the time and dose of oral LD, with a increasing number of intakes per day and a decreasing dose of LD per intake. Additionally, a COMT-I can be added as a strategy to increase the half-life of LD.[71]Nonetheless, in some of the patients these strategies will be insufficient to provide a good control of the off periods and at the same time preclude the emergence of bothersome peak-dose dyskinesia. In these cases, the

introduction of a device-aided therapy should be considered. An expert consensus has identified several indicators that, when present, should signal the presence of a inadequately controlled MF and the need to transition to a device-aided therapy. [68] According to this consensus, the presence of OFF symptoms for more than two hours/ per day, the presence of dyskinesia for more than one hour/ per day and a prescription regime with 5 or more intakes of LD per day, should led to the consideration of a device-aided therapy.[68]

Nowadays, three types device-aided therapies are available for patients in advance-disease stages: Deep Brain Stimulation (DBS), Continuous subcutaneous apomorphine infusion (CSAI) and levodopa-carbidopa intestinal gel (LCIG) infusion. All of them are able to provide a continuous dopaminergic stimulation and being able to improve motor fluctuations, decrease dyskinesia, improve motor function and QoL. [116–118]

Since each one of them present a specific profile regarding side effects, effects in non-motor symptoms, and individualized approach should be undertaken when choosing a device-aided therapy for a specific patient (**Figure 1.1**). [116–119]

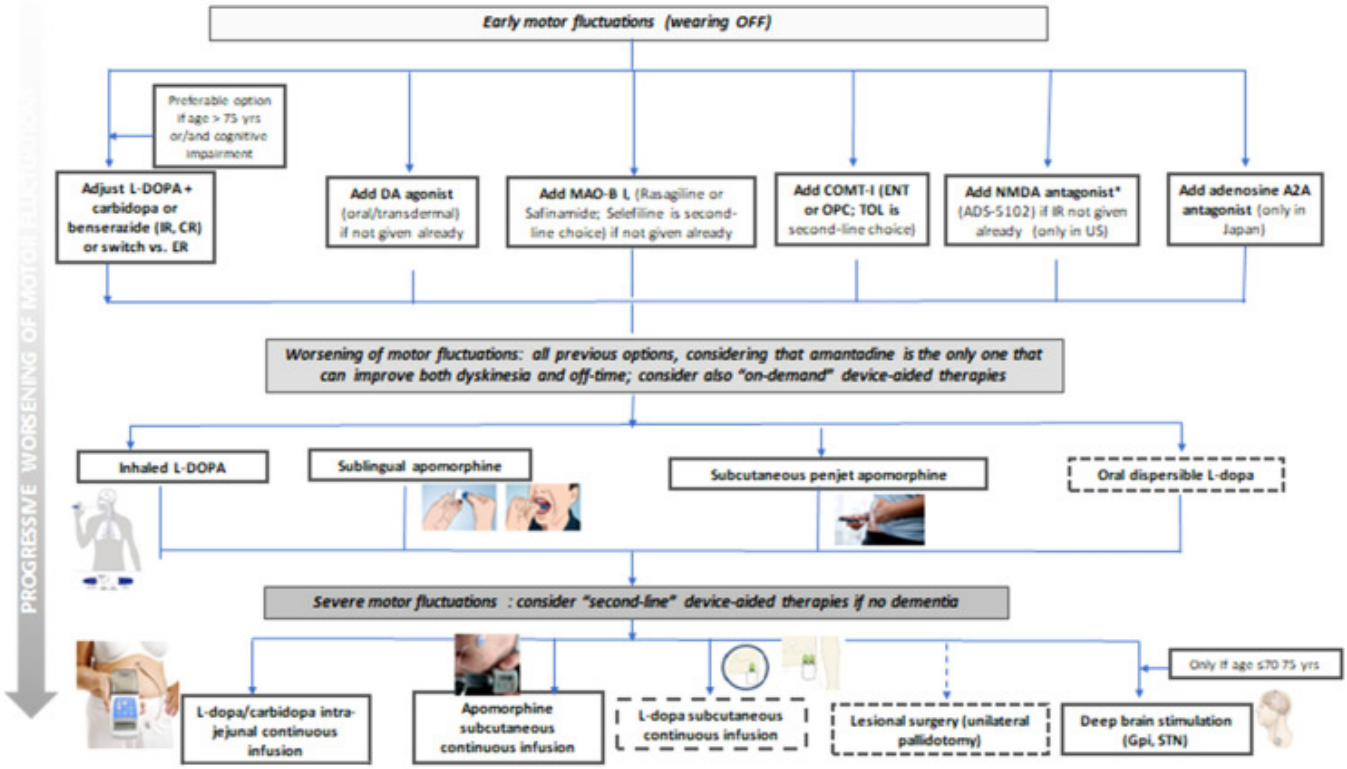


Figure 1.1 – Treatment options for the management of MF, from the early advanced stage to the appearance of troublesome MF in the severe advanced stage. Dotted lines indicate treatments with lower levels of evidence (to be considered with limitations or with few data available and still not marketed) *Adapted from Fabbri M, Barbosa R, Rascol O, Neurol Ther. 2023*

IB – Axial Symptoms in Parkinson's Disease

The emergence of axial signs, with gait impairment, freezing of gait (FOG), falls and postural instability, marks the entrance on an advance disease stage, characterized by a reduction on [63,79,80,120–122] mobility[123,124], increased injuries,[125] increased levels of dependence[124] and reduced quality of live . [124,126–129] In addition, some studies have shown that the emerge of axial signs was temporally related to the appearance of some non-motor symptoms as cognitive impairment and psychosis.[78–80,121]

These symptoms appear to progress together, signaling disease progression and death. In fact, a chronological pattern on the apparition of these disability milestones has been previously described. [63,79,80]

Despite the significant impact on quality of life, level of independence, and overall mobility, there is currently no effective treatment available for axial signs. Regardless of the initial good response to LD observed for mild gait difficulties, progression of axial signs is marked by a loss of LD responsiveness as well as an unsatisfactory response to surgical therapies. [123,124,127,128,130,131]

These treatment refractory conditions have a high socio-economic impact associated and constitute one of the major unmet needs of PD.[132,133]

a) Gait disorders

Gait disturbance is one of the key features of Parkinson's disease, as remarked by James Parkinson in his "An Essay on the Shaking Palsy".[42] On this very first description of PD patients, the notion of a slowly progressive gait impairment is pointed out, with James Parkinson describing a progressive evolution of gait difficulties, starting from the time where the patient feels that

"one of the legs is discovered slightly to tremble, and is also found to suffer fatigue sooner than the leg of the other side" to the state were: "Walking becomes a task which cannot be performed without considerable attention. The legs are not raised to that height,

or with that promptitude which the will directs, so that the utmost care is necessary to prevent frequent falls".[42]

The final disease stages are marked by. "The patient walks now with great difficulty, and unable any longer to support himself with his stick, he dares not venture on this exercise, unless assisted by an attendant, who walking backwards before him, prevents his falling forwards, by the pressure of his hands against the fore part of his shoulders".[42]

This increasingly perception of severity of gait ultimately leading to falls, reflects well the progressive course of axial signs and its importance on signaling disease progression.[134]

It was also on his seminal paper that James Parkinson introduced de notion of festination as a gait phenomenon where "patients, whilst wishing to walk in the ordinary mode, are forced to run".[42,135]

More than two centuries after the initial description of James Parkinson, the current understanding of gait impairments in PD patients is still limited.[133,134] Gait alterations are present throughout the disease course, with a progressive worsening being observed from the early prodromal stages to the late-stages of disease. At this stage, gait becomes ultimately impossible with patients becoming dependent of walking-aids. [134,136–140]

At a biomechanical level, PD gait is characterized by a reduction in walking speed, shorter steps and reduced cadence. The association of an decrease step length and reduced foot clearance leads to the emergence of a shuffling gait a distinctive and recognizable feature of PD. [134,138,140] The decrease on speed, step length and reduced foot clearance are the reflection of the overall bradykinesia and hypokinesia observed in PD patients, with this hypokinetic features also being observed at the upper limbs.[134,141] An asymmetric reduction of arm swing is a hallmark feature of PD patients, and recently, it has been shown that decreased arm swing is already present at the prodromal phases of PD, reflect the underlying asymmetrical basal ganglia neuropathology. [142]

PD patients can still increase walking speed, sometimes even to the same range as healthy controls (HC) but, and contrarily to HC, they do it so by increasing cadence instead of step length.[143,144]

Despite the fact that gait speed is significantly reduced in PD patients when compared to HC, and commonly used as an evaluation metrics, is important to note that reduced gait speed it's not specific of PD patients and can be seen on a myriad of other neurologic and non-neurologic pathologies.[134]

In PD patients, gait becomes less automatic with patients relying on their attentional resources to achieve optimal walking.[134,138] Consequently, attentional processes have a main influence on gait, with a decrease on walking speed and step length, and an increase in the number of steps during dual tasking. A relationship between the complexity of the dual task and the associated gait worsening have been hinted by some authors but needs further validation.[145–149] This dependence of attentional processes is often reported by the patients as an increase in gait difficulties while using mobile phones or searching for house keys in their pockets while walking. In the early-disease stages, the realization of a dual task during gait evaluation, may be put in evidence gait alterations that were otherwise too subtle to be noticed.[134]

Spatiotemporal gait metrics as speed, step length, step time are classically used to described PD gait. More recently other metrics have been explored, thought to better reflect the overall organization and control of gait. [150–152] Gait variability[153–156], asymmetry[150,157], and metrics as Harmonic ration (HR)[158–161] and entropy[162–164] are thought to provide a more nuanced understanding of the irregularities and complexity in the walking patterns of individuals with Parkinson's disease. (see chapter **IB-cGait and Freezing assessment**)

Disease progression is accompanied by an inexorable gait deterioration. To compensate the progressive slower gait, patients try to increase speed by increasing cadence, which translates in smaller and smaller steps sometimes triggering an episode of festination. [134,135,138] Festination is characterized by a progressive increase in speed and a shortening of step length, leading to a forward-leaning posture which contributes to an increased risk of falls.[135]

Advanced disease is also marked by an increase on FOG severity and frequency[122,128,165], loss of postural reflexes and increase postural instability,[166,167] postural changes with a consequent increase on risk of falling.[123,131,137]

The progression towards more severe gait dysfunction, specially the emergence of FOG and postural instability, is also associated to a decline on response to LD.[134,168] Involvement of nondopaminergic pathways, as cholinergic and nor-adrenergic ones, are thought to be responsible to the emergence of gait disturbances not responsive to dopaminergic medication.[134,168] In line with these, therapeutic trials with anticholinesterase inhibitors[169] and blockers of noradrenaline reuptake[170,171] have been pursuit but a clear amelioration of gait or FOG was not found.

Throughout all the disease stages, the presence of non-motor symptoms as depression, anxiety or cognitive impairment can increase the already present gait problems, augmenting gait slowness, gait variability and triggering freezing episodes.[134] The presence of orthostatic hypotension has also been associated to a augmentation of gait and postural impairments. Understanding the extent to which gait problems are truly a motor symptom potentially amenable to improvement upon augmentation of dopaminergic therapy or the consequence of non-motor features (and in this case worsened by dopaminergic therapy) is of paramount importance, as it will influence therapeutic decisions, particularly given the exacerbation of orthostatic hypotension by dopaminergic medication.

b) Freezing of gait

FOG is a distinctive gait disorder in which patients are unable to initiate or continue locomotion. FOG is classically defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk." Patients classically described FOG as "having the feet glued to the floor" or "being stuck in place".[122,172,173]

In 1987 James Parkinson remarked that PD patients had a "propensity to bend the trunk forwards, and to pass from a walking to a running pace".[42] This phenomenon is now recognized as festination a paroxystic gait disturbance closely related to FOG.

However, a precise description of a freezing of gait (FOG) episode is not found in James Parkinson's essay. In 1887, Charcot wrote what is likely the first mention FOG in the literature : "*elle ne part pas; il semble, qu'auparavant, elle ait besoin de s'equilibrer: elle est quelque sorte incertaine, ayant le tronc incline en avant; enfin elle se decide. Lente tout d'abord, la marche progressivement s'accélere*." [174]

In 1921 the notion of a "glued feet" is introduced in this description of Souques: "*Un parkinsonian que j'ai observé, malade depuis dix ans, ne pouvait marcher que très péniblement, les pieds collés au sol. Or parfois, il pouvait courir et même soulever les pieds assez haut pour sauter un obstacle* ». [174]

In 1948 Raymond Garcin, professor of neurology in Paris, France, and his assistant, Professor Roberto Melaragno described a phenomenon defined by a "*bégaiement de la mise en route du mouvement*" in patients with Parkinson's disease. This translates literally by ""stuttering to start the movement".[175] However, it was only in 1972 that Barbeau introduced the term "freezing." [174]

Since its initial description, several terms have been used to refer to FOG. (**Table 1.3**)

Table 1.3: Terms used to refer to FOG

Frozen gait
Akinesia paradoxica
Start hesitation
Marche a petit pas
Piétinement
Magnetic gait
Ignition failure
Gait apraxia
Arrythmokinesia

Despite being more common in the later disease's stages, with 80% of the patients presenting FOG, 21 to 27% present FOG on the early stages of PD. [165] Besides disease duration, FOG is correlated with disease severity (presence of motor fluctuations and dyskinesias), dysarthria, dementia and severity of overall axial involvement.[172,176–178] More contradictory is the suggestion that a relationship between FOG and chronic long-term LD may exists.[172,179–183] Gender, sporadic or familial nature, and the age of onset of the disease don't appear to be associated with the presence of FOG. FOG is also not exclusive from PD, being present in other synucleinopathies like Multiple System Atrophy as also other atypical parkinsonism as Progressive supranuclear palsy and vascular parkinsonism.[185–187] In addition, and despite most commonly affecting gait, freezing can also manifests during alternated movement of the upper limbs and during speech. [173,188–191]

FOG is one of the most frequent causes of falls in PD, contributing to high fall rates ranging from 35% up to 90%. Consequently, FOG seriously impacts normal daily life functioning and overall quality of life.[172,173,192,193]

Phenomenologically, different subtypes of FOG have been described according to the associated leg movement during the episode of freezing: (1) trembling in place, with alternating tremor of the legs but no effective forward motion ; (2) shuffling forward, with very short, shuffling steps with minimal forward movement; and (3) complete akinesia, where no movement of the limbs or trunk, can be observed. [194,195]

FOG is considered an episodic gait phenomenon, emerging under different triggering factors. The factors that may trigger a FOG episode are not the same across individuals, with situations that may triggered a FOG episode being variable and normally organized in three big categories: motor, cognitive and affective (**Table 1.4**).

Table 1.4: Main FOG triggers	
Motor	Gait initiation
	Narrow spaces
	Turning
	Destination arrival
Cognitive	Cognitive load (e.g dual tasking)
Affective	Stress
	Anxiety
	Depression

In 1995, Fahn distinguished five types of FOG, that were all related to motor triggers: (i) start hesitation, when freezing was detected as the patient initiated walking; (ii) turn hesitation, when freezing emerge whilst making a turn; (iii) tight quarters hesitation, if FOG was noted when the patient passed through a narrow space; (iv) destination-hesitation, when a FOG episode appear as the patient approached a target (the final 2 m of the task), and (v) open space hesitation, when patients experienced a spontaneous freezing episode whilst walking in an open space. [196] (**Figure 1.2**)

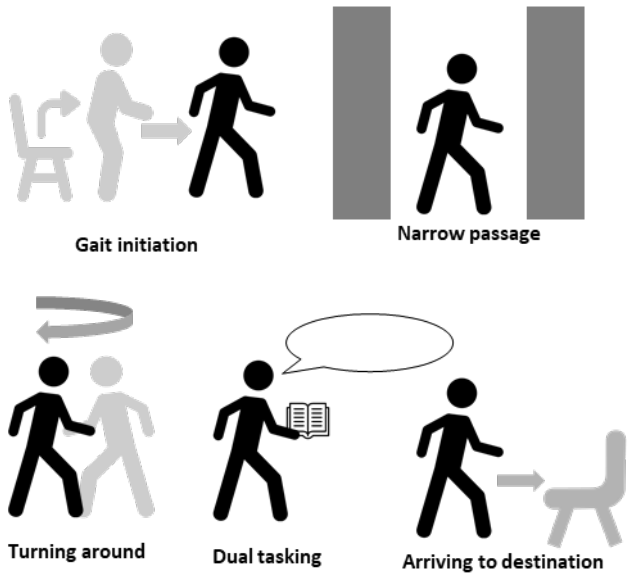


Figure 1.2: Triggers of FOG episodes

The strongest provocative factor of FOG is turning, followed by start hesitation, tight quarters hesitation or destination-hesitation.

Anxiety, depression and stressful situations that limit time or space are known FOG triggers of FOG.[122] Gait in FOG-patients is more attention-dependent, which explains the worsening on FOG when cognitive load increase, such as verbal fluency task and "serial 7 calculation" task. Dual tasking and cognitive challenging situations, such as carrying a tray or bags, or talking on the phone while walking also aggravates FOG.[148,172,197–199] On the reverse, the use of visual or auditory cues to help focus attention on gait, may lead to an improvement on FOG.[200–203]

FOG is most commonly observed in the OFF-medication state, with some studies showing that 95% of the patients experienced freezing on the OFF state whilst only 32% experience it on the ON-medication state.[194] Consequently, FOG can also classified according to its response to LD. Most of the FOG episodes occur during the OFF-medication period, being totally, or almost totally, relieved by it (OFF-FOG).[194] This is classically the type of FOG that will improve with surgery and that when present during pre-surgery evaluation doesn't contra-indicate DBS surgery. On the other end of the spectrum are FOG episodes triggered or induced by LD, that will progressively increase in severity with increasing LD doses (ON-FOG).[183,199,204] This is different from LD unresponsive-FOG whereas FOG is already present in the OFF-mediation state and persists despite dopaminergic treatment. More recently, a fourth type of FOG has been described – biphasic FOG - whereas, akin to biphasic dyskinesias, freezing is not present in the OFF state, emerges with intermediate doses of LD and disappears when LD doses are increased.[205] Distinguishing between all these subtypes of FOG has therapeutic value. [183]Patients with OFF-FOG, ON-FOG or biphasic-FOG may be good surgical candidates whilst patients with unresponsive-FOG will not likely improve with DBS surgery.[206]

Classically, gait has been divided in continuous and episodic gait disturbances, with FOG being classified as an episodic phenomenon due to its paroxystic nature.[122] However this dichotomy has proved to be too simplistic not being able to capture the complexity of freezing. Objective gait analysis using wearable devices or instrumented gait labs have enabled a better understanding of the biomechanical changes occurring during gait in PD patients with freezing. [207,208]

In freezers, step length is shorter than non-freezers, both during treadmill and steady-state gait.[209,210] Freezers have also higher gait variability, lower vertical, antero-posterior and medio-lateral. Harmonic-ratio translating a less smother gait than their non-freezers counterparts, with this alterations occurring even outside a clinical identifiable FOG episode.[211–213] A higher asymmetry and loss of bilateral coordination of gait have also been identified.[157,214,215]

Immediately before a freezing episode, step length and speed progressively decreases as the number of steps increases, with a consequent increased in cadence. The double limb support phase increases and premature onset of tibialis anterior and gastrocnemius muscle activities occurs. [209,216,217] Anticipatory postural adjustments (APA) have also been found to be different in PD patients with freezing when compared with their non-freezers counterparts. During a FOG episode, multiple APAs have been described, which can delay and even preclude the compensatory steps with consequent loss of balance. A relationship between this multiple APAs and the trembling of the knees commonly observed during a FOG episode has also been suggested.[218,219]

This works has highlighted the fact that even outside FOG events, gait in PD-FOG patients is substantially different than in non-FOG patients. Accordingly, transient FOG episodes appear to emergence from a background of continuous gait alterations, that may predispose and set the stage for the emergence of this episodic gait disturbances.[122,192]

c) Gait and Freezing assessment

Gait assessment has traditionally reposed on clinical observation. The MDS-UPDRS scale (and the former UPDRS scale) is the most widely used clinical rating scale for Parkinson's disease (PD), consistently considered the gold standard for motor assessment in PD patients. It is subdivided in 4 sections: the first two (MDS-UPDRS part I and part II) report to the subjective non-motor and motor experiences as reported by the patients; MDS-UPDRS Part III comprises the motor examination; and MDS-UPDRS part IV explores the presence of MC**. (Figure 1.3)**

Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping– Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

Figure 1.3: MDS UPDRS Score Sheet. Source : Goetz C et al., 2008.[220]

Gait is assessed by the item 2.12 from the MDS-UPDRS part II and by the item 3.10 from the MDS-UPDRS part III. Accordingly, to the MDS-UPDRS scale, gait assessment requires the patient to walk approximately 10 meters away from and toward an examiner. The overall score of gait should reflect the stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and the degree of arm swing. ranging from a score of 0 indicating no motor impairments to a score of 4 for patients unable to move

independently. Using a single item with a limited range of scores available, presents a clear limitation in utilizing the MDS-UPDRS III item 3.10 to assess gait.The Postural Instability and Gait Difficulty Score (PIGD) is constructed based on 5 MDS-UPDRS items (items 2.12-2.13 and 3.10-3.12) reporting gait and postural instability with higher scores reflecting greater PIGD severity. The PIGD score of the UPDRS is more commonly used for the classification of subtypes and less frequently as outcome. Despite the expanded range of possible scores, which facilitates improved classification and stratification of patients, some of the items used rely on patient self-report rather than objective gait assessment, which may pose a limitation in clarity and accuracy. Additional clinical scales have been used to evaluate gait in PD patients, even if they are not specific or specially constructed to the PD population: Tinetti Balance Scale, Berg Scale, the Mini-BESTest, and the Dynamic Gait Index/Functional Gait Assessment.

Gait is also assessed by questionnaires, as the Generic Walking Scale [Walk-12G], Activities-specific Balance Confidence scale [ABC], Falls Efficacy Scale [FES], Fear of Falling Measure [FFM]. Here, gait assessment relies on the subjective patient self-report of gait difficulties and complains pertaining for a determinate period of time (e.g. last month). Its subjective nature linked to the recall bias constitutes the main limitation of these questionnaires.

Trying to increase objectivity in gait evaluation, gait tests that assess either the time or distance walked by the patient are also used in clinical practice: 6- minute walk, 10-m walk, functional reach, and Timed Up-and-Go. Overall these tests provide information regarding general gait characteristics as gait speed, but they lack the granularity needed to understand the biomechanical properties of parkinsonian gait since they only assess simple gait metrics. In addition, these tests present a high inter and intra-rater variability, being influenced by instruction and tester bias, and by the overall patient's status and compliance.

Instrumented walkways equipped with pressure sensors or motion-capture systems allow for detailed kinematic and kinetic analysis of gait. These systems provide a comprehensive understanding of gait parameters such as step length, stride length, and

gait variability, increasing objectivity in gait assessment whilst minimizing the level of inter and intra-rater variability. However instrumented walkways are typically located in controlled laboratory settings limiting the ecological validity of the assessment, as it may not fully capture the natural gait patterns of individuals with PD in real-world environments. Additionally, the high cost of these systems and the requirement for a high level of expertise to interpret the data have limited their accessibility and broader utilization.

More recently, technological advances have produced relatively low-cost tools, that enable a better and more objective characterization of gait. Wearable devices such as smartphones, inertial sensors (eg, accelerometers and gyroscopes) and pressure-sensitive carpets suitable for quantifying gait, are rapidly replacing the complex camera-based motion-capture systems, allowing a more widespread use of this devices by clinicians and enabling them to get a more accurate, qualitative gait description.

Wearable devices are portable and movable accessories that can be worn on the body or embedded in clothes. These devices include smart glasses, smart watches, smart clothes, or pressure shoes, among others. They contain both special hardware and software technology, with unique functions of collecting kinematic gait parameters, data processing, storage, and transmission. Currently, most of the wearable devices used in the field of PD are gyroscopes, accelerometers, or magnetometers. In addition to an objective and quantitative gait characterization, wearable devices may enable gait evaluation during long periods of time and in ambulatory settings, which enable clinicians to more accurately analyze the patients' motion state in real time.[221–223]

This has allowed a better understand of the biomechanical alterations observed in PD gait, enabling the decomposition of gait into several gait subcomponents with increases the granularity of gait evaluation**. (Figure 1.4)** In addition to the detection of subclinical gait changes, their progression could also be tracked. Even if the importance of this early detection it's not totally yet understood, detecting some specific gait changes may be useful to identify patients who are in a higher risk to developed more severe gait changes.

This more detailed and fine-tuned approach to gait has enable to go beyond the analysis of the classical spatiotemporal variables as speed, step length and step time, to

asses gait domains that may provide important insights regarding motor control of gait and pathologic age-related locomotor dysfunction. Here, gait metrics as gait variability, and metrics reflecting stability and smoothness of gait (eg, HR and Entropy).

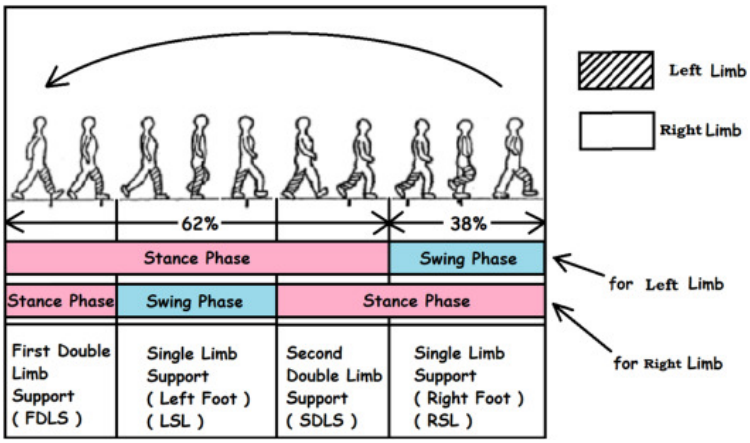


Figure 1.4 : A gait cycle can be broadly divided into two phases: stance and swing. The definitions of these phases are relative to a particular lower limb. During stance phase, the foot of the corresponding limb is on the ground, whereas in swing, the foot is no longer in contact with the ground, i.e., it is swinging through to move the body forward.

Gait variability refers to fluctuations in step length, step time, and other gait parameters from one stride to the next, translating the capacity to maintain a rhythmic and regular gait pattern.[153,154,211] In PD, increased gait variability is often observed, reflecting difficulties in motor control and coordination. PD patients present higher step-to-step variability when compared to age-matched HC.[155,156,224] This hold true even in the prodromal disease stages, with prodromal PD patients presenting significantly higher levels of gait asymmetry and variability than age-matched HC.[225] In addition, gait variability appears to be higher in PD patients who fall and have FOG, when compared with non-fallers and non-freezers ones.[211,212,226,227] Also in non-PD elderly populations, higher gait variability is associated to an increase risk of negative gait outcomes, mainly falls.[156,228,229] This suggests that gait variability metrics may provide clinicians and researchers with quantitative insights into the intricate motor control challenges that individuals with Parkinson's disease face during walking.[153]

While both spatiotemporal and variability metrics are important and describe much of the observable gait changes in PD, they fail to account for and explain more subtle alterations. In particular, they do not examine the dynamics of gait, failing to ascertain how gait changes over time, from one stride to the next within a given walk.[153]

Harmonic ratio (HR) is a gait metric that has been increasingly explored in PD population. HR provides information about the smoothness and regularity of movement during walking, translating the overall rhythmicity and regularity of gait cycles.[230] Previous studies have shown that PD patients have lower HR than HC translating into a greater gait arrhythmicity and irregularity[160,161,230], with lower HR being observed in fallers vs non-fallers.[160,231]

Entropy quantify the regularity and predictability of walking patterns reflecting to the amount of disorder or randomness in a time series of gait data. [162] In PD, in increased gait entropy is often associated with gait impairment and disease progression, signaling a less regular and more variable walking patterns. The rationale is that as the disease advances, there is a breakdown in the regularity of gait patterns, leading to higher entropy values.[162–164]

Akin to HR, Entropy provides a more nuanced understanding of the irregularities and complexity in the walking patterns of individuals with Parkinson's disease.

In addition, the use of wearable devices may provide important insights regarding the capacity of different treatment strategies to modulate individual gait metrics.

In line with this, it has already been shown that not all gait subcomponents have the same profile regarding their response to LD. For instance, spatiotemporal features such as speed, stride and step length or lower-body angular features such as hip flexion have all been shown to significantly improve with LD. In contrast, cadence, stride/step and double support time seem to be LD-resistant. For certain gait features that may help monitor the severity of gait dysfunction and predict the emergence of negative gait outcomes (e.g., gait variability and metrics reflecting stability and smoothness of gait), the degree of modulation by LD is less well understood.

STN-DBS has been shown to improve most of the spatiotemporal gait and angular metrics, mimicking the results obtained with LD. [232–236] Regarding postural control and gait metrics related with variability, rhythmicity and regularity, the effects of STN-DBS have been more contradictory. [237–241]

FOG assessment

The assessment of FOG is even more challenging. The episodic and paroxystic nature of FOG, associated to the fact that patients often get better during medical assessments (*kinesia paroxistica*) makes FOG a symptom difficult to capture in the outside clinical evaluation. The improvement of FOG during medical visits has been explained by an increase attention on gait during medical examination, which can temporarily suppress FOG, by the fact that hospital corridors are typically less narrow or crowded than furniture-crammed house divisions or by the fact that during medical appointments patients are ON medication and FOG is typically more severe in the OFF state. [208,242] In addition to the fact that FOG is commonly not reproduced in the presence of a clinician, the identification of FOG by patients is also not optimal, since they may not recognize what an actual freezing episode looks like. Mimicking what a FOG episode may look may help the patients to recognize its presence in its daily live and increase the likelihood of capturing its presence.

Despite all these limitations, FOG assessment is still mostly based on the patient's retrospective self-assessment over a specific time period. Several questionnaires are commonly use to evaluate the presence of FOG. The old Unified Parkinson's Disease Rating Scale (UPDRS)[243] had a single item (item 14) to specifically assess FOG as well the more recent and currently Movement Disorders Society (MDS)-UPDRS questionnaire (item 2.13)[220]. The Freezing of Gait Questionnaire (FOG-Q) pulls together 6 questions that specifically assessed the presence and severity of FOG.[244] FOG-Q question 3 "Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking?" has proven to be as good as item 14 of UPDRS part 2 for distinguishing between freezers and non-freezers. The original FOG-Q, was later revised by Nieuwboer and

colleagues into the New FOG-Q (NFOG-Q).[245] NFOG-Q comes with an accompanying video showing the different types of FOG episodes making easier to the patients to to identify freezing behavior. Both the FOG-Q and the NFOG-Q show both high internal consistency and high reliability scores between people with PD and their caregivers. Consequently, they have been considered as "recommended" and "suggested", respectively, instruments to assess posture, gait and balance, by the MDS Task Force. [244–246] However, a recent study has highlighted the NFOG-Q's insufficient capacity to detect small effect sizes, arguing against its use as the primary outcome for intervention studies. This underscores the necessity for more robust and objective freezing of gait (FOG) outcome measures..[247]

Despite the lowest incidence of FOG observed in medical visits when compared to the ambulatory setting, physical examination, and specially gait examination should be undertaken to assess the presence of FOG. The item 3.11 from the MDS-UPDRS part III allows clinicians to score the severity of FOG observed during a clinical visit. Here, the severity of FOG is assessed on a 0 to 4 scale, with FOG during straight walking considered to be more severe than FOG occurring during turning, starting or walking in a narrow space.[220]

The FOG score proposes an evaluation during a trajectory comprising four possible triggering circumstances (start hesitation, clockwise and counter clockwise turns, narrow space). This score considers also the different clinical subtypes of (shuffling vs leg trembling vs akinetic FOG) attributing to each one different degrees of severity.[215,248] However, it doesn't account neither for all the possible triggers, nor to the frequency or the duration of FOG episodes.[249]

What is clear, is that patients should be tested on a standardized gait trajectory featuring all the possible circumstances that may provoke FOG: gait initiation, crossing doors or narrow spaces, doing a half turn, walking while dual-tasking and also during normal, undisturbed walk in an open space. A full turn (360° turn) on top of the most common 180° turn should be performed, since it may most easily trigger a FOG episode, and may be especially useful in cases of asymmetric FOG. [208,249,250]

Gait can also be timed, number of FOG episodes counted in addition to the circumstances in which FOG appeared. This may help to assess FOG severity, monitor FOG progression, make patients more familiar to their FOG triggers and consequently enable to put in place strategies to prevent FOG.

A composite score based not only on the number of FOG episodes but also in their duration has also been used: short episodes (less than 10 seconds) are given a score of 1, medium-length episodes (lasting between 10 and 30 seconds) are given a score of 2 and episodes lasting for more than 30 seconds are scored as a 3. FOG has also been quantified regarding the percent of time frozen (total duration of freezing episodes/total gait duration). A recent study comparing FOG evaluation using number of FOG episodes or percent time frozen, found the last one to be more reliable**.** [251] However, all these evaluations remain observer-dependent, and it has been, shown on a recent study, that eve- across expert raters, despite a high reliability found for the percent of time frozen, only a moderate reliability was achieved when assessing the number of FOG episodes.

A biomechanical characterization of FOG, based on data collected by wearable devices, has enable a more objective assessment of FOG episodes. Different algorithms and strategies have been proposed in order to the detect the occurrence and characterize the severity of freezing episodes, with two major different approaches being described in the literature: i) gait assessment outside the actual FOG episode, and ii) description of the FOG episodes themselves. [208]

In FOG patients, the overall gait structure has shown to be altered even outside the FOG episodes. When comparing with non-freezers, PD patients with FOG have higher levels of gait variability and asymmetry and lower synchronization between upper and lower limbs, translating a loss of stability and rhythmicity on the background gait. These continuous gait abnormalities have been also evaluated in ambulatory settings, during extended periods of time (3-days) enabling a more ecologic assessing of FOG. [252] These continuous assessment of gait outside the clinic corroborate previous findings that freezers had increased gait variability altered gait consistency during s community ambulation, even during optimal performance and outside FOG episodes. More important, it has also been

shown that kinematic metrics correlated well with the impact of FOG in daily-life function assessed by the NFOG-Q.[252]

The assessment of the FOG episode itself has been performed using spectral analysis, where an abnormal peak in the 3-8 Hz band was found to occur concomitantly to a FOG episode. At the same time, a decrease in the physiologic 0.5-3Hz band corresponding to the normal gait was found. Consequently a "freezing band" situated within the frequency spectrum between the 3-8Hz, has found to reflect the high frequency trembling movement of legs during a FOG episode. A freezing index was also defined, based on a ration of the mean power on the 3-8Hz band/ mean power on the 0.5-3Hz band; the higher the ratio more likely a FOG episode will occur. However, this approach was only able to detect the "trembling in place" subtype of FOG, missing the akinetic subtype

Using wearable sensors both in laboratory as in ambulatory settings, machine learning approaches (neural networks, decision trees, random forests, naïve Bayes, nearest neighbor, and support vector machines) have been increasing used in order to identify the best set of features that identify a FOG episode. Here the percentage of time frozen and the number of FOG episodes have been used as the main outputs. This approach has proved to have a higher sensitivity than the previous ones, at the expenses, however, of a higher computation cost. [253]

Reviewing all the studies using wearable devices to identify FOG, an overall sensitivity of 73-100%, specificity of 67-100% and accuracy of 68-96% was found, when looking to FOG detection in both controlled and uncontrolled conditions.

d) Treatment of axial symptoms

Effects of medical therapy on axial signs

The response of gait to levodopa is not uniform throughout the disease course. In early disease stages, LD commonly improves speed and step length, reducing the overall gait slowness. At this stage gait alterations are mainly thought to be the reflection of the overall bradykinesia, which improves upon dopaminergic replenishment.

Despite being classically considered a dopamine-resistant symptom, especially in the early stages of the disease, FOG predominantly occurs in the off-state, often improved by levodopa (LD) and other dopaminergic medications.[128,183]

Besides LD, it has been shown that dopamine agonists can improve some aspects of gait, including gait initiation and turning. [254,255] However, dopamine agonists might lead to sedation, increased fall risk and increase axial postural alterations. It has been suggested that IMAOS may have a role on improving FOG.[255–257] However it's possible that the improvement is due to an overall increase in dopaminergic stimulation and not from a specific effect of the IMAO.

Disease progression is marked by a progressive worsening of gait and a loss of response to LD. The involvement of non-dopaminergic pathways, as cholinergic and nor-adrenergic ones, is thought to be responsible for the emergence of gait features not amenable to modulation by dopaminergic treatment.

In line with these, therapeutic trials with anticholinesterase inhibitors have been pursuit but despite a possible reducing in falls, a clear amelioration of gait or FOG was not found.[169,258]

Trying to tackle the nor-adrenergic system, methylphenidate, an amphetamine-like psychomotor stimulant with inhibitory action on the striatal and cortical presynaptic transporter for dopamine and norepinephrine, has also been studied. In a first trial on PD patients with moderate gait disturbance, no significative improvement on gait, freezing or kinematic variables was found.[170] However, a posterior trial addressing PD STN-DBS patients with refractory FOG had shown a beneficial effect of methylphenidate on freezing episodes.[171] Amantadine (oral and intravenous) has also been essayed in FOG patients, and despite the presence of an uniform response across studies, it appears to may have a small benefit in freezing episodes, including in STN-DBS patients. [259–262] A single study has demonstrated the positive effect of caffeine, an adenosine A2A antagonist, in improving FOG.[255,263] However, this result was not reproduced on further studies and further validations is needed. The effect of botulinum toxin injections into the calf muscles has also been studied in an open-label study, yielding positive results on FOG. .[264] Subsequent

double-blind placebo-controlled studies have failed to confirm this, and instead, have suggested a potential increase in the risk of falls following the treatment.. [265,266]

Non-pharmacologic treatments

The role of conventional physiotherapy in managing gait and other axial problems is well known and recognized. [267,268]Additionally, in the recent years, a growing body of works has also highlighted the role of specific exercise programs in improving gait and FOG.[269,270] Exercise programs including resistance training, aquatic therapy, dance, Nordic walking, balance and gait training and martial arts (Tai Chi and Qigong) have been proved to improve gait, freezing and falls at different level, with most forms of exercise showing clinical benefits on both spatial and temporal measures (ie, velocity, stride length, and cadence). [269,270] More recently, other alternative training methods have also been explored. Here, boxing has been shown to improve balance and gait[271,272] and a trial about the use of trampoline beds as a possible therapeutic stagey is ongoing. [273]

Auditory, visual and attentional cues have also been used to improve gait in PD patients, with overall gait variability and rhythmicity being improved with the use of external cues. [200,201]

In FOG patients the utilization of cues is also associated to a reduction on the number and duration of FOG episodes. The most common types of cues used are visual and auditory external cues that may prevent a FOG episode by increasing stride length and regulating cadence.[274] Overall, they improve overall rhythmicity and variability of gait, decrease the likelihood of a freezing episode. Spatial cues, were classically delivered using lines on the floor or encouraging patients to focus on a specific target point in the distance More recently, more sophisticated system to deliver visual cues have been developed as laser shoes[275] or laser beam associated to a rolling walker.[276] Auditory rhythmic cues can be delivered by a metronome with patients being instructed to match step frequency to the auditory rhythm. Walking to the beat of music or other rhythmic auditory sound can also serve as an auditory cue. Besides external cues, internal cueing can also be used to improve FOG. Here an attentional strategy ("think about taking larger steps") is used to

focus attention in specific components of gait and shift from automatic to goal-directed motor control. Internal cues may be more practical (not dependent on external devices) and has been shown to be equally effective as external spatial cues for improving step size and gait velocity. [277] Some patients found that when marching, skipping, running, walking backwards or sideways have an improvement on freezing. The adoption of a new walking pattern will use an alternate motor program that is likely overlearned and less dependent on the automatic mode of motor control. A summary of compensation strategies that can be used to improve gait and FOG in PD patients is provided in **Table 1.5**.

Table 1.5 Compensatory gait strategies for gait impairment in Parkinson's disease

Compensatory strategy	Principal mechanism	Examples
External cueing	Introduction of a goal-directed behavior by introducing a movement reference or target	Walking to the rhythm of music Stepping over lines on the floor
Internal cueing	Focused attention towards specific components of gait, to shift from automatic to goal-directed control	Mental singing or counting
Adopt a new walking pattern	Use walking patterns that may be less overlearned and less dependent on the automatic mode of motor control	Skipping Walking backwards or sideways Running Making skate movements
Alternatives to walking	Walking difficulty may be a task-specific problem	Riding a bycicle Skateboarding Riding a scooter Roller skating

Adapted from Tosserams A et all; *Mov Disord Clin Pract*. 2022 [136]

Non-invasive neuromodulation has been increasingly explored as a possible therapeutic strategy to improve gait and FOG in PD patients.[278] Repetitive Transcranial Magnetic Stimulation (rTMS) alone[279–281] or associated to transcranial direct current stimulation (tDCS)[282] has proven to be able to improve FOG, with Supplementary Motor Area (SMA) being the localization of choice.[280]

The efficacity of thoracic spinal cord stimulation on gait and freezing has been assessed on a pilot study in five patients with advanced Parkinson's disease. Improvement in gait metrics as step length and velocity, as well in the severity of FOG were observed. suggests that this procedure might improve gait and even freezing of gait.[283] However, the mechanism of spinal cord stimulation is unclear and further research is needed to assess the long-term benefits of both this technique.

Despite the increasing arsenal of therapies to manage gait disturbance and freezing, we are still far from being optimal in treating this debilitating motor symptoms.[132]

IC. Deep Brain Stimulation

The quest for a surgical treatment for PD started long before the introduction of LD. Between 1940 and 1960, the ablation of different basal ganglia structures (initially the pallidum and later the thalamus) was pursued in an attempt to mitigate parkinsonian motor symptoms. [284,285] Led sometimes by solid neuroanatomical and pathophysiological rationales, sometimes by surgical misadventures turned out strokes of serendipity, the surgical impetus would come to a halt in 1967 with the introduction of LD.[284,285]

With the subsequent emergence of motor complications secondary to long-term levodopa treatments, and the difficult to manage them only with oral medication, the 90's were marked by a renewed interest in PD surgery.[286] Due to the improvement in tremor upon lesioning the *thalamic ventralis intermedius nucleus* (VIM), this nucleus was chosen as the first target for neuromodulation in patients with PD. [287]However, and despite the dramatic benefit in tremor, the benefit of VIM-DBS on other parkinsonian motor symptoms was far satisfactory.[287] After the discovery of the pathophysiologic role of the Subthalamic Nucleus (STN) in PD, DBS electrodes started to be implanted in this nucleus.[288,289] In 1993, the first STN-DBS surgery for PD was performed in Grenoble by Benabid and Pollack's team. Since then, over 150,000 patients have been treated with DBS, averaging more than 10,000 per year..[290,291]

Later, Globus Pallidus Internus (GPI) was also introduced as a target for DBS, upon observations of motor improvement in PD patients after unilateral pallidotomy.[292]

Despite its widespread use, being performed in more than 700 centers across the world, the mechanism of action of DBS is still not totally understood.

A division between excitatory or inhibitory effects of DBS is probably too simplistic and its possible that the mechanism is not merely inhibitory or excitatory. A combination of both, with excitation of axonal projections and simultaneous inhibition of the neuronal cell bodies is probably a best explanation for the mechanism of action of DBS. Modulation

of the pathologically increased beta-band activity observed on the basal ganglia of PD patients has also been appointed as a mechanism of action.[293–295]

In DBS surgery, electrodes are implanted into the deep structures of the brain in order to electrically stimulate specific structures, thereby modulating the dysfunctional neural circuits. **(Figure 1.5)** DBS enables a continuous electric stimulation, where three main parameters – voltage/amplitude, frequency and pulse width - can be adjusted in order to obtain the maximal benefit with the least adverse effects (AE) (larger therapeutic window). Therapeutic amplitudes for DBS (across all targets) normally range between 1 and 3.6 V. Above that, minimal clinical improvements are observed and there is a significant increase of energetic cost. Frequency is normally set at 130 Hz. Except for tremor, little additional benefit is seen above that, and no additional benefit is seen on frequencies above 200 Hz. Lower frequencies (<10 Hz) may aggravate parkinsonian signs, but stimulations above 50 Hz can improve some axial symptoms. Pulse width seems to have the least important role in improving clinical signs in DBS patients. It is recommended to start stimulating with the lowest possible pulse width of 60 us. [296,297]

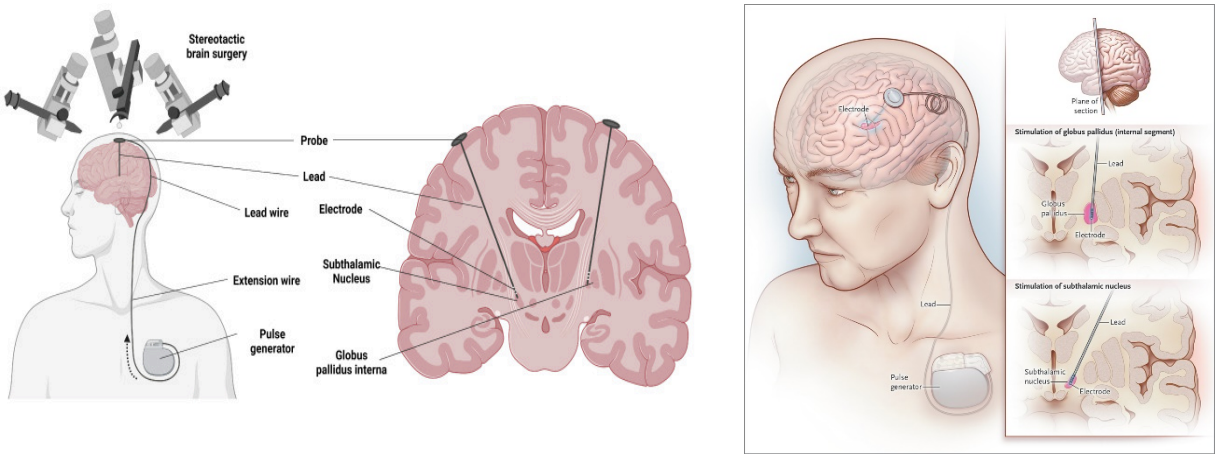


Figure 1.5 – Deep Brain Stimulation System with representation of DBS electrodes placed either at the level of the STN or the level of GPI *Adapted from Senevirathne DKL et al, Cells. 2023*[298] and *Okun MS, N Engl J Med. 2012*[299]

The superiority of STN-DBS and GPI-DBS over Best-Medical treatment (BMT) in advanced-stage PD patients, has been shown in several short-term follow-up studies.[84,85,87,300,301] Here, a reduction of around 2.5 hours on OFF-time and a gain of around 4 hours of "ON" time without troublesome dyskinesias was shown. Additionally, (QoL) was significantly improved in the surgery group and a 50% reduction on the total medication doses was also observed on the patients submitted to DBS. [84,85,87,300,301]

Medium and long-term follow up studies have confirmed the persisted benefits of DBS surgery, with a persist benefit over motor complications, quality of live and medication reduction. Moreover, when looking to the overall motor scores in the OFF-medication state, a significantly improvement with stimulation was observed up to 15 years after surgery.[302–305] The benefit of DBS on the ON-medication state motor scores is nonetheless lost on the medium to long-term follow-up, with this being especially true for axial symptoms. [303,306]

There is an ongoing debate about the best target for DBS in PD. Both STN and GPI-DBS appear to be equally effective in reducing UPDRS OFF-medication scores, with perhaps a slight advantage for STN. Additionally, quality of life (QoL) is equally improved with both targets.[300] STN enables a highest reduction in medication requirements whilst GPI appear to have a slight better cognitive profile, less psychiatric side effects and better effect on the axial symptoms. Both are able to improve dyskinesia but whilst STN does it so by significantly reducing LD, GPI has a direct effect on dyskinesia suppression.[307,308]

In addition to the GPI and STN, the *Pedunculopontine Nucleus* (PPN)[309] and the *Substantia Nigra pars reticulata* (SNpr)[310,311] have been studied as possible targets mostly for gait and FOG improvement. Both for PPN and SNpr, programming approaches and outcomes have been highly variable across studies which limit further conclusions and a more widespread use of this targets on clinical practice.

STN- DBS has also been studied in patients with less advanced PD. In the EARLYSTIM trial, PD patients with relatively short disease duration (mean 7.5 years) and recent onset of levodopa-induced motor complications (less than 3 years) were randomized to either receive bilateral STN-DBS or best medical treatment. [87,312] At the end

of a two-years follow-up, patients in the surgery group presented better QOL, less motor disability and less levodopa-induced MC than the ones in the BMT group.[87] In addition, freezing and axial symptoms were also significantly improved on the surgery group (vs the BMT group).[312]

The discussion about the best timing for surgery is still ongoing. "If some advocate for surgery to be performed as early as the first MC arises, citing the potential for greater improvement in QoL compared BMT, consideration should also be given to the surgical AE to which the patient will be exposed, as well as the patient's own expectations Adding to this, there is the ongoing debate about the potential neuroprotective and disease modifying role of DBS.[89,92,94,96] Up to now, only animal studies have shown a potential role of DBS on delaying disease progression, with studies in PD patients not being able to provid the same straightforward results. [91,94] In fact, proving a disease modifying effect in DBS cohorts poses several methodological and ethical difficulties that may preclude adequate conclusions. [89,96]

The real therapeutic value of DBS needs to consider the possible adverse effect of this procedure. The prevalence of AEs has been evaluated in several reviews and multicentric retrospective studies, adding to the data included in the RCT. AEs occur in less than half of patients, but the coexistence of more than one AE per patient is not uncommon. Intracerebral hemorrhage is one of the most feared complications with a risk of 1-5%. Infection of the hardware is a severe hardware-related complication with an incidence ranging for 1.5–22%. Postprocedural seizures have also been reported, with an estimated incidence of 2.4%. Less life-threatening AE includes weight gain, mood/behavioral disorders, apathy, increased suicide risk, dysarthria, gait disorders, dyskinesia, dystonia and decreased verbal fluency.[313–316] Some of this side effects may be the result of stimulation spread to areas outside the STN or GPI, while others are possible due to a combination of events, from disease progression, lesional effect during electrode insertion and medication side effects. The utilization of new imaging techniques as functional MRI or functional and structural connectivity studies may help not only to understand the brain

networks involved in the emergence of a specific side effect but also to guide deep brain stimulation reprogramming.[317–320]

According to current recommendations, a levodopa challenge test (LCT) using a suprathreshold dose of LD should be performed before surgery in order to access the degree of motor response to LD, since motor response to LD is considered to be the best predictor of the STN-DBS outcomes at least on short follow up studies.[321,322] Nonetheless, more recent studies have shown that the correlation between LD responsiveness and stimulation response is far from perfect, with the LCT posing important limitation on the prediction of individual responses to stimulation.[206,323–325]This appears to be particularly true for the PIGD score, were axial-motor scores in the pre-surgery Medication-OFF condition, appear to alone, better predict surgery outcomes than the response to the LCT.[326,327] Nonetheless, a decreased on the motor scores of more than 33% upon a LCT is still required to LD responsiveness is still used as a selection criteria.[206,321,328]

In the recent years, and partially sparked by the appearance of multiple manufacturers of DBS technology on the global market, advances in DBS technology have been made, that will certainly extend the scope of its application and are expected to yield additional benefits, both clinically and scientifically. [317] Contrary to the traditional open-loop traditional DBS systems, closed-loop or adaptive DBS systems aim to adjust stimulation based on real-time feedback from the patient's brain activity or other physiological indicators. This has the potential to optimize therapy and reduce side effects.[329,330] The recent years have also seen the appearance of directional leads, enabling to sculpt the volume of tissue activated, allowing a more precise targeting of specific brain areas and better customization of therapy, potentially leading to improved symptom control and reduced side effects. [331,332]

New devices with remote monitoring and programming capabilities have been developed, enabling healthcare providers to adjust DBS settings without patients needing to physically visit the clinic. This advancement can enhance patient convenience, reduce the necessity for frequent in-person appointments, and democratize access to specialized healthcare.

Altogether, these developments will further enhance the management of patients with DBS-PD, resulting in safer and less invasive procedures that are more accurate and efficacious. Moreover, this technology holds the potential to be applied to a greater proportion of patients.. [317,332,333]

Effects of DBS on Axial Symptoms

The benefits of STN-DBS on gait impairments and FOG remain conflicting, with symptoms improving in some patients, remaining unaltered in others and worsening in another subgroup.[127,232,326]

In a cohort of 331 PD patients, falls and FOG were assessed at baseline and after one year of STN-DBS surgery.[326] Whilst 42% of the patients who presented FOG at baseline became FOG free after surgery, 50% of the patients who didn't had FOG before surgery developed FOG. ON-FOG and Resistant-FOG were the only subtypes of FOG whose prevalence increased after STN-DBS. Regarding severity, a trimodal distribution can be observed with FOG severity improving in 37%, remaining unchanged in 34.5% and increasing in 28.5%. Similar numbers were found for falls, with falls severity decreasing in 28%, remaining unchanged in 52.6% and increasing in 22.5%. [326]

LD responsiveness before surgery has been deemed as a principal predictor of symptom improve after surgery.[321] In this sense patients with LD-resistant axial signs would not be amenable to improvement and have been excluded from surgical programs. On the other hand, patients who have a LD-responsive axial signs would be expected to improve after surgery, with simulation mimicking the effect of LD. However, some DBS-STN will develop treatment-resistant axial symptoms despite an initial pre-surgery response to LD.

More recent works have questioned the role of LCT in predicting axial outcomes after STN-DBS sugery[206,324] with, on the reverse, and association between baseline OFF-state severity of gait and freezing, but not with the acute response to LD, and posterior worsening of these axial features have been reported.[326,327] Nonetheless, patients with LD-

resistant axial signs are classically excluded from surgical protocols [206,321] even if some isolated finding have suggested that axial non-LD responsive signs may improve with STN-DBS. [334] The use of a objective gait metrics on gait assessment at the pre-surgery evaluation may help to identify the patients which will more likely benefit from surgery. Here, a previous work has shown that among kinematic measures, preoperative LD response of stride length and range of motion showed the highest correlation with favorable FOG outcomes. [335] These findings still need be reproduced in larger and independent cohorts, but with the increasing use of wearable devices for gait evaluation, they may become important tools for patient's assessment and counseling.

When looking to both medium and long-term follow-up cohorts, despite the persistent significative benefit of stimulation observed on bradykinesia and tremor scores, the same benefit is not reproduced on gait, postural instability, posture and speech disorders. In the Toronto cohort PD STN-DBS patients were followed up for 10 years after surgery. At the end of the 10 years follow-up, axial symptoms presented a progressive loss of stimulation benefit that was accompanied by a similar loss of a response to LD.[303] This suggest that disease progression, with loss of dopamine sensitivity, probably due to involvement of non-dopaminergic pathways, would be the reason for the emergence of axial symptoms non-responsive to stimulation.

In a recent meta-analysis aiming to assess the short- and long-term effect of stimulation on gait and FOG, a persistent beneficial effect was observed for both outcomes on the Medication-OFF condition with, nonetheless, the magnitude of improvement progressively decreasing throughout the follow-up. On reverse, on the Medication-ON condition, no addition improvement on gait or FOG was observed with stimulation. [336]

From all the axial features, gait appears to be the one most likely to respond to LD. Using quantitative gait analysis to evaluate gait changes up stimulation and LD, both stimulation and LD appear to improve spatiotemporal gait metrics as speed and step and stride length, with stimulation appearing to have a higher magnitude of effect than LD. Regarding metrics related with gait rhythmicity, disagreement has been shown between studies, with some showing an improvement of gait-variability metrics by stimulation

whereas others shown no impact of stimulation on these variables. One explanation for the differences encountered can be the different ways used to measure variability. Nonetheless, gait variability is a parameter classically non-responsive to LD.

Cavallieri and collaborators have assessed the effect of stimulation and LD on gait using an instrument TUG test.[233] Both stimulation and medication were found to improve speed but dopaminergic therapy presented a more marked effect. The same study also shows an improvement in the duration of turns, approaching it to the physiological levels. This may be important since slower and wider turns have been associated to higher risk of falls and freezing. As the authors highlight, despite the improvement in gait provided by both stimulation and medication, the improvement in axial symptoms was less relevant than the improvement in other cardinal symptoms as tremor, rigidity and bradykinesia.[233]

Suboptimal targeting, a stimulation-induced effect, induction of structural brain lesion by the stimulation electrodes and disease progression have all been appointed as putative causes for the deterioration and emergence of axial signs after surgery.[104]

The experience accumulated throughout the years have shown that both levodopa and DBS are effective in controlling and significative improving akinesia, rigidity and tremor which are the clinical correlates of dopaminergic neuronal loss at the level of SNpc. Axial signs, on the other hand, are thought to result also from the involvement of non-dopaminergic pathways and the with the reduced responsiveness to levodopa of axial motor signs being a well-recognized feature of advanced Parkinson's disease. Accordingly, the observed reduction in the beneficial effect of DBS, and progressively emergence of axial signs non-responsive to therapy probably reflects disease progression and extension of the pathological process beyond the nigro-striatal dopaminergic system.

Nonetheless, in some patients acute/subacute worsening of gait akinesia and FOG occurring in the immediate post-operative period has been related to current spread beyond the subthalamic region. The mechanisms have not been totally clear but one study, evaluating 12 patients, has shown that gait deterioration was associated to electrode misplacement with stimulation of more dorsal and anterior parts of the STN. On the other hand, other studies have found that increasing gait akinesia could be observed on distal

stimulation, due to current diffusion to the pallidothalamic fibers running into the Ansa lenticularis.

To improve FOG and gait refractory to DBS therapy, different approaches have been tried, mainly focused in alternative stimulation paradigms. Low-frequency stimulation (LFS) (80-60 Hz)[i], stimulation on the PPN[309], co-stimulation of the STN and the SNr [310,311], asymmetric STN stimulation[344,345] and interleaved-interlink (IL-IL) stimulation[346,347], have all been tried in small cohorts. LFS have proved to be useful in improving FOG both in the short and long-term but a worsening in appendicular signs poses some limitations to its use.[339,340,343] The results of PPN and SN stimulation are more contradictory, with small cohorts, different methodologies limiting further conclusions. Two studies have used an asymmetric STN stimulation in patients with refractory FOG. In both of them, voltage was decreased on the least affected side on 30-50%. Contradictory results steamed from both studies and no other further studies have been conducted to explore this therapeutic strategy.[344,348] A first study using IL-IL stimulation has shown subjective improvements in several axial metrics as gait, balance and speech prompting the realization of a RCT who confirmed the initial results.[346,347] However, and despite all these possible therapeutic strategies, STN-DBS patients who evolve to present severe gait and FOG symptoms refractory to stimulation and treatment, remain a therapeutic challenge.

Chapter II. Aims and methodological approach

The present thesis aimed to establish the frequency, identify risk factors, and understand the mechanisms of gait impairment and FOG that emerge after STN-DBS surgery. The ultimate goal is to contribute to improvements in selection and prognosis establishment of PD patients submitted to STN-DBS surgery by predicting their individual risk for developing axial signs after the procedure. Leveraged by inertial sensor-based 3D kinematics, gait and FOG will be studied under various therapeutic conditions to elucidate the impact of stimulation and levodopa (LD) on gait impairments. At last, based on our data, we want to contribute to improve therapeutic management of post-surgery FOG and gait impairment.

Complementary methodological approaches were adopted to successfully achieve the different aims of the research work.

Aim 1: To identify the frequency and risk factors for post-surgery gait impairment and FOG in PD STN-DBS patients

To address the first aim of this thesis two studies with distinct designs were implemented. In a retrospective study, data from a cohort of PD patients who underwent STN-DBS surgery and were followed up for 8 years was analyzed. It was hypothesized that in this group of PD patients with a long disease duration, the development of FOG and gait impairment would mirror the behavior observed in non-surgical PD cohorts.

The development and risk factors of FOG and gait impairment were then validated in a second prospective study in a different population. In this study, 18 PD patients were

followed for 18 months after surgery. In addition to clinical evaluation, gait analysis was performed both pre- and post-surgery using wearable devices.

Aim 2: To explore the role of objective gait analysis using inertial-sensor based 3D-kinematics in STN-DBS PD patients and surgical candidates

To address the second aim of the study, three studies employing two different methodological designs were conducted. Initially, a prospective study was undertaken involving a group of 18 PD patients who underwent STN-DBS surgery. Gait analysis using 3D-kinematics was performed at baseline and 18 months post-surgery, assessing the distinct effects of stimulation and LD on various kinematic gait metrics.

A cross-sectional study was conducted in advanced PD patients subjected to an LD challenge test. The study aimed to evaluate the role of 3D-kinematics in detecting motor changes induced by LD administration and compare it with the gold-standard clinical assessment.

Finally, a third study involved 17 PD STN-DBS patients experiencing severe freezing of gait (FOG). Kinematic analysis and an automatic FOG detection model were employed to achieve a more standardidzed objective quantification of FOG.

Aim 3: To identify the role of stimulation and LD in freezing of gait in PD STN-DBS patients: is FOG after STN-DBS, stimulation induced?

To address this question, we conducted a cross-sectional study in a cohort of 17 PD STN-DBS patients who exhibited severe FOG in their best-functional condition. We assessed the individual effects of LD and STN-DBS on FOG outcomes. Our hypothesis posited that therapy-refractory FOG in PD-STN DBS patients is predominantly associated with disease progression and a reduced sensitivity to LD.

Chapter III. Long-term follow-up of subthalamic nucleus deep brain stimulation in patients with Parkinson's disease: an analysis of survival and disability milestones

In this chapter, the research work was developed under Aim 1. To determine the frequency and risk factors for post-surgery gait impairment and FOG in STN-DBS patients

Background

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-recognized and effective treatment for patients with advanced Parkinson's Disease (PD).[133,208,221,291,349] Prior studies have shown that STN-DBS significantly improves levodopa-induced motor complications (MC), motor symptoms and quality-of-life (QoL) in the short-to-medium term (6 to 12 months and up to 5 years) [84,350–352]with a sustained benefit being observed in long-term follow-up studies (up to 15 years).[302–304,327,353] However, data on the long-term survival and disability milestones is more limited.[89,354]

Despite improvements in MC and appendicular signs upon STN-DBS, axial signs such as gait, freezing-of-gait (FOG), postural instability and dysarthria fail to experience comparable benefit in both medium- and long-term follow-ups,[303,305,327,353] probably reflecting disease progression and the involvement of non-dopaminergic pathways unresponsive to stimulation.[304,305,327] Indeed, studies on non-DBS patients have found that the emergence of these axial signs tend to cluster with the development of certain non-motor symptoms (e.g. psychosis, cognitive impairment, and autonomic dysfunction), and that such association is strongly correlated with disease progression.[63,78,79] Accordingly, the development of dementia and hallucinations, occurrence of falls and nursing home placement represent important PD milestones that mirror disease progression, reflect disease severity and offer valuable insights into its prognosis. Additionally, gathering knowledge of the development of these disability milestones is important for assessing long-term safety of DBS. Of particular note, the concept of "late-stage disease" can be translated into this DBS population, whereby despite no longer disabled by tremor, rigidity or severe MC, patients still suffer from axial, dysautonomic, cognitive and behavioral symptoms non-responsive to stimulation (and dopaminergic) therapy that predominate the clinical picture.[63,355]

Taking this into consideration, the aim of this study was to characterize the long-term survival of PD patients submitted to STN-DBS surgery and to identify the emergence

of and the delay until the occurrence of disability milestones: falls, FOG, hallucinations, dementia, and institutionalization.

Material & Methods

Design: a longitudinal retrospective study

Primary objective: to assess mortality of PD patients submitted to bilateral STN-DBS after a follow-up of 8 years.

Secondary objective: to determine the frequency and the determinants of disability milestones (falls, FOG, hallucinations, dementia, and institutionalization) in the same population of patients.

Patients: All PD patients undergoing bilateral STN-DBS from 2006 to 2012 at Hospital Santa Maria were included in the study. Patients implanted in the globus pallidus internus were excluded (n=2). PD was diagnosed according to the UK Brain Bank criteria[356] and the criteria for DBS were: i) presence of clinically significant levodopa-induced MC not optimally controlled with medication, ii) ≤ 70 years-old, iii) a ≥ 33% reduction in the Unified Parkinson's Disease Rating Scale (UPDRS)[243] motor score after a supra-threshold levodopa dose, iv) no dementia, v) no major/refractory psychiatric illness, and vi) no postural instability or FOG in the best ON state. Patients who had the leads or the implanted pulse generator definitively removed during the follow-up were identified and censored at the time of DBS system removal.

Study Outcomes:

Primary outcome - mortality during the 8 years after DBS.

Secondary outcomes - occurrence of any of the following disability milestones: falls; FOG; hallucinations; dementia; and institutionalization.

All patient data was retrospectively retrieved and analyzed from baseline and up to 8 years post-surgery. Data was extracted from every single hospital visit of patients.

Patients were followed-up until the time of death or the end of the follow-up period (8 years), whichever occurred first.

Assessment tools

Falls: defined as a fall report by the patient or caregivers on two consecutive visits.

FOG: defined by the presence of FOG observed by the clinician on two consecutive visits. Both falls and FOG were considered only after 6 months into the post-surgical period, as we considered 6 months the time required for treatment stabilization.

Dementia: defined according to the diagnostic criteria of the DSM-V.

Institutionalization: the date of placement in a nursing home was either the specific date recorded in files or the date of the visit when institutionalization was first mentioned.

Additional baseline pre-surgery data was collected: age and duration of disease at surgery, gender, scores of parts II (activities of daily living) and III (motor) of the UPDRS in both OFF and ON states, scores of part I (mental) and IV (motor complications) of UPDRS, Hoehn and Yahr (H&Y) stage and Schwab and England score in both ON and OFF state, percentage of response to a supra-threshold dose of levodopa. The percentage of patients with a significant gait impairment (score ≥2 on item 29 of the UPDRS-III) or postural instability (score ≥2 on item 30 of the UPDRS-III) in the OFF state were calculate. Clinical phenotype, i.e. postural instability/gait disorder (PIGD) and tremor dominant (TD),[47] and levodopa-equivalent daily doses (LEDD) (mg/day) were calculated as previously described.[357] Data from formal neuropsychological evaluation including the MMSE score were collected. As our institution started using the MDS-UPDRS[220] only from 2012 onwards, the MDS-UPDRS II and III scores were converted from the corresponding UPDRS ones using the available conversion formula,allowing for the standardization of the entire cohort.[358]

Data Analysis

Clinical and demographic characteristics were described as mean ± standard deviation or percentages, as appropriated. Two group comparisons were performed using Mann-Whitney U-test for continuous variables or Chi-square tests for categorical variables. Multicollinearity was tested using Spearman coefficients between all possible pairs of variables (Supplementary **Figure S3.1**).

For the primary outcome, Cox proportional hazards regression analysis was performed to allow handling multiple quantitative and categorical variables simultaneously. The time-dependent survival was fit using each individual variable, and variables of interest were subsequently selected for statistical variable adjustment and multivariable regression. The log-rank (Mantel-Cox) test was used for comparison of the survival curves between groups and estimation of the respective hazard ratios (Mantel-Haenszel). For secondary outcomes, the primary outcome (i.e., death) hindered the occurrence of the secondary outcome in a time-dependent way. Thus, competing risk analysis were performed and cumulative incidence calculated for all secondary outcomes, as previously reported.[359] Then, multivariable regression analysis in the presence of competing risks was performed using the semiparametric proportional hazards model (i.e. sub-distribution hazards of cumulative incidence functions) based on the Gray's test, in order to assess the contributions of different variables (adjusted and non-adjusted) to the development of secondary outcomes.[360] For all models, a backwards stepwise regression model was used, removing independent variables until all contributing variables had a p-value < 0.2. Analysis and graphical representations as cumulative incidence, survival or forest plots was performed using R 4.0.4 and the analysis pipeline can be found at [https://github.com/Le-bruit-de-nos-pas/PD_Milestones_STN-DBS]. Exact p-values, hazard ratios and 95% confident intervals are reported.

Data availability statement: Anonymized data of this study will be available from the corresponding author on reasonable request from any qualified researcher, following the

EU General Data Protection Regulation. analysis pipeline can be found at [https://github.com/Le-bruit-de-nos-pas/PD_Milestones_STN-DBS].

Results

a) Clinical and demographic baseline characteristics

109 patients underwent STN-DBS during the study period. Clinical and demographic data are presented in **Table 3.1**. During follow-up, 8 patients were censored: 7 due to system removal because of infection (at months 5, 35, 45, 57, 61, and 2x 95) and 1 was referred to another institution and lost to follow up (at month 72). 84 patients reached the end of the 8-year follow-up: mean age of 68.6 ± 7.6, mean disease duration of 21.38 ± 4.38 years, mean H&Y 2.8 ± 1.1, mean LEDD of 600.90 ± 370.14 mg (vs 1252.66 ± 521.17 mg at baseline; average reduction of 49.64 ± 29.52 %, $p < 0.001$). Stimulation parameters at the end of follow-up in **Table 3.2**.

Table 3.1 – Demographic and clinic characteristics of study participants

Variable under study	
Gender: male, n=109	55 (54.1%)
Age at disease onset ($\bar{x}$ ± SD, n = 104)	47.9 ± 7.9
Age at surgery ($\bar{x}$ ± SD), n=109	61.3 ± 7.5
Disease duration at surgery (y ± SD), n=104	13.8 ± 5.5
UPDRS II OFF-MED ($\bar{x}$ ± SD), n=98	25.7 ± 32.7
UPDRS II ON-MED ($\bar{x}$ ± SD), n=98	8.9 ± 5.9
UPDRS III OFF-MED ($\bar{x}$ ± SD), n=105	44.5 ± 13.4
UPDRS III ON-MED ($\bar{x}$ ± SD), n=105	18.8 ± 17.6
UPDRS IV ($\bar{x}$ ± SD), n=98	9.5 ± 4.9
MDS-UPDRS IV ($\bar{x}$ ± SD), n= 9	9.1 ± 5.3
H&Y OFF MED ($\bar{x}$ ± SD), n=105	2.8 ± 0.2
H&Y ON MED ($\bar{x}$ ± SD), n=105	2.0 ± 1.0
SE OFF ($\bar{x}$ ± SD), n=100	51.9 ± 20.2
SE ON ($\bar{x}$ ± SD), n=100	86.6 ± 14.9
Levodopa % response ($\bar{x}$ ± SD) n=106	57.6 ± 13.5
LEDD mg ($\bar{x}$ ± SD), n=107	1252.6 ± 521.2
Item 29 UPDRS III OFF ≥2, n=105	65 (61.9%)
Item 30 UPDRS III OFF ≥2, n=105	43 (41.0%)
Phenotype, n=95	
Tremor-dominant	45 (47.4%)
PIGD	39 (41.1%)
Indeterminate	11 (11.6%)
MMSE score ($\bar{x}$ ± SD), n=100	27.8 ± 2.1
Neuropsychological diagnosis, n=90	
Normal	71 (78.9%)
Mild Cognitive impairment	19 (21.1%)

Values are presented as mean ± SD. SE: Schwab and England ADL; LEDD: levodopa equivalent daily dose; PIGD: postural instability gait disorder; MMSE: mini mental state examination. UPDRS: Unified Parkinson Disease Rating Scale; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale

Table 3.2 – Stimulation parameters at the end of follow-up

	Right STN (n=83)	Left STN (n=83)
Monopolar (%)	**81.9% (68)**	**85.5% (71)**
Voltage (mV)	3.91 ± 0.46	3.06 ± 0.47
Pulse width (μs)	63.1 ± 10.3	62.5 ± 9.67
Frequency (Hz)	123 ± 17.1	124 ± 17.1
Bipolar (%)	**14.5% (12)**	**12.0% (10)**
Voltage (mV)	3.78 ± 0.64	3.87 ± 0.69
Pulse width (μs)	64.2 ± 9.96	62 ± 6.32
Frequency (Hz)	131 ± 6.69	130 ±1.58
Interleaving	**3.6% (3)**	**1.2% (1)**
Voltage (mV)	3.6 ± 1.25	5.0 ± 0
Pulse width (μs)	60.0 ± 0	60 ± 0
Frequency (Hz)	125 ± 0	125 ± 0
Double monopolar	**0%**	**1.2% (1)**
Voltage (mV)		2.6 ± 0
Pulse width (μs)		60 ± 0
Frequency (Hz)		130 ± 0

Values are presented as mean ± SD and pertain to those recorded at the end of follow-up. Patients are stratified by stimulation mode: monopolar, bipolar, interleaving, double monopolar. Some patients on Monopolar stimulation have low frequency, which explains a higher value for voltage.

b) Mortality

Seventeen patients died during the study, accounting for a mortality rate at the end of follow-up of 16%. On average, patients died 62.1 ± 21.3 months after surgery (**Figure 3.1**), at a mean age of 69.9 ± 6.0 years. The presence of disability milestones in the follow-up did not significantly alter the mortality rate (**Figure 3.1**). In the patients who died during follow-up, falls preceded death by 34.6 ± 13.7 months, FOG by 35.8 ± 21.4, dementia and hallucinations by 18.5 ± 14.5 and 18.7 ± 14.4, respectively. None of the patients who died were institutionalized.

Non-adjusted, univariate analysis showed that a preoperative higher UPDRS part II score in OFF (HR 1.012, C.I. 1.005-1.020, p = 0.001) and older age at surgery (HR 1.108, C.I. 1.008-1.218, p = 0.034) significantly increased mortality rates (**Figure 3.1**). On multivariate analysis, age at surgery (HR 1.121, C.I. 1.035-1.463, p = 0.019) and the preoperative UPDRS part III score in OFF (HR 0.942, C.I. 0.890 - 0.996, p = 0.037) were significant drivers of overall mortality **(Figure 3.1**).

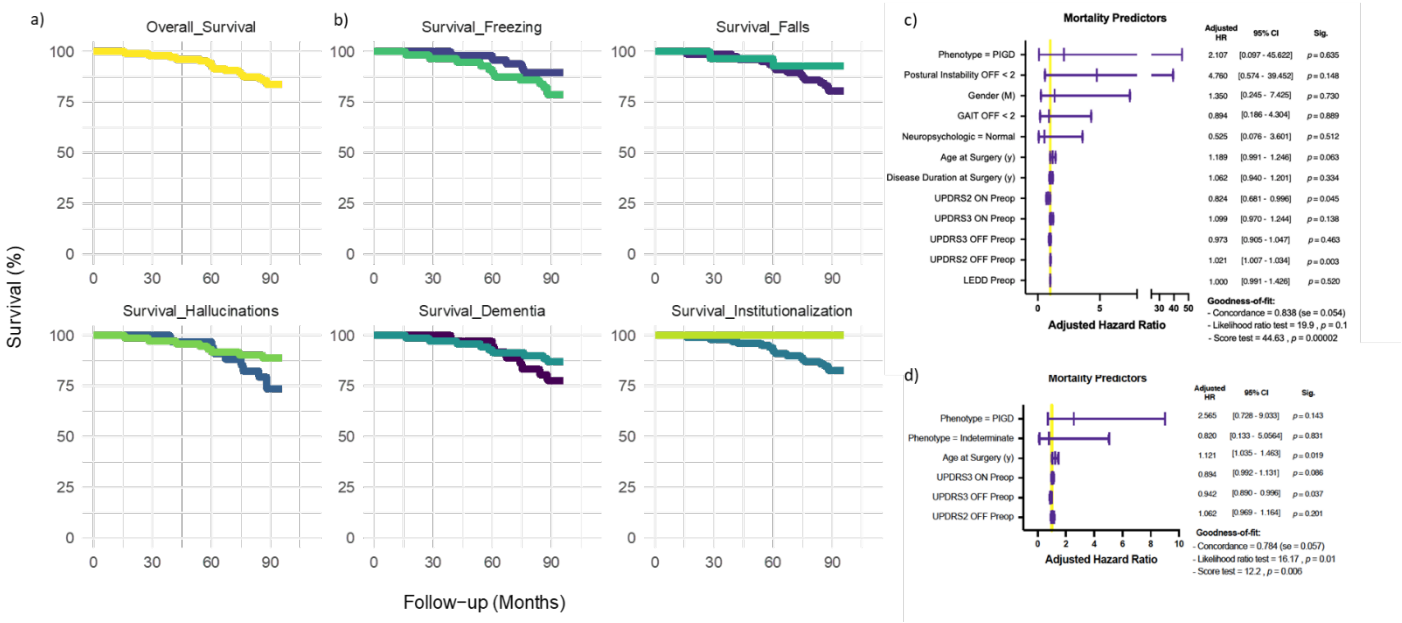


Figure 3.1: Survival plots for the entire cohort (a) and for the same cohort split between patients developing a given milestone and those failing to do so. Comparisons performed using Log-rank (Mantel-Cox) tests (b) Unadjusted univariate analysis (c) and multivariate analysis of predictors for mortality (d). Each and every single variable is adjusted for all other variables in the respective plot. Multivariable regression analysis in the presence of competing risks was performed using the (semiparametric proportional hazards model) sub-distribution hazards of cumulative incidence functions based on the Gray's test. A backward elimination method for selection of variables was using a cut-off of 0.2. Variables including in the initial model were the same for all the outcomes studies: Gender, age at surgery, disease duration at surgery, UPDRS II OFF-MED, UPDRS II ON-MED, UPDRS III OFF-MED, UPDRS III ON-MED, H&Y OFF MED >2, LEDD, Item 29 UPDRS III OFF ≥2, Item 30 UPDRS III OFF ≥2, Phenotype (Tremor/ PIGD/ Indeterminate, Neuropsychological diagnosis (Normal/ Mild Cognitive impairment).

c) Disability Milestones

Falls were the most likely event during follow-up (**Figure 3.2 and 3.3**), with a competing risk-adjusted probability of 73% at 8 years post-DBS (95% C.I., 63.6 - 89.7%). The average time from surgery to first fall was 40.4 ± 25.4 months. FOG was observed in 47% (95% C.I., 37.7 - 56.6%) of the cohort (**Figure 3.2 and 3.4**). The average time from surgery to FOG was 39.6 ± 28.4 months. In turn, the competing risk-adjusted probability of developing hallucinations was 32% (95% C.I., 23.1- 40.9%) (**Figure 3.2 and 3.5**), with an average time from surgery to hallucinations of 60.0 ± 20.7 months. 34% of patients developed dementia (95%C.I., 25.4 - 43.6%) (**Figure 3.2 and 3.6**), with an average time from surgery to dementia diagnosis of 56.2 ± 21.2 months. Only 6% of the cases were institutionalized (95% C.I., 2.4 - 11.7%) (**Figure 3.2 and 3.7**), after 62.3 ± 22.0 months of surgery.

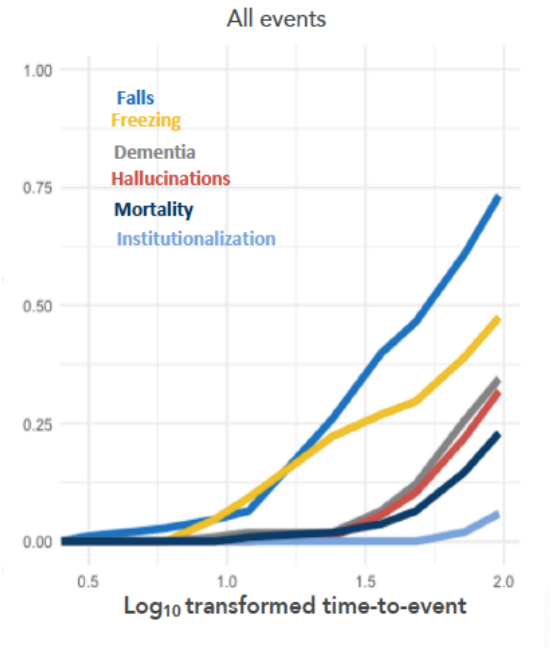


Figure 3.2- Summary incidence plot across all events under study adjusted for competing risks (falls, freezing, hallucinations, dementia, mortality, and institutionalization). For the sake of visibility, values on the X-axis correspond to the base 10 logarithmic of the number of elapsed months to event (1 -> 10 months, 1.5 -> 32 months, 2 -> 100 months)

d) Determinants of axial milestones

Fallers had worse baseline scores in UPDRS II (28.0 ± 38.3 vs 19.9 ± 6.7, p=0.015) and UPDRS III item 30 (postural instability) (1.6 ± 1.0 vs 1.0 ± 1.1, p= 0.022) in OFF than non-fallers (**Table 3.3**). The baseline variables that in univariate analysis were significantly associated with falls are show in **Figure 3.3**. When adjusting for confounders, older age at surgery (HR 1.184, 95% C.I., 0.779 - 1.086, p = 0.004) remained significant associated with falls (**Figure 3.3**). The cumulative incidence of falls was significantly higher among patients who also developed FOG during follow-up (86%, 95% C.I., 71.8 – 93.2%) compared to those who did not (62%, 95% C.I., 47.8 – 73.5%, p = 0.010) and in those who developed hallucinations (85% %, 95% C.I., 67-94% vs 67%, 95% C.I., 55-77%, p = 0.039) (**Figure 3.3**).

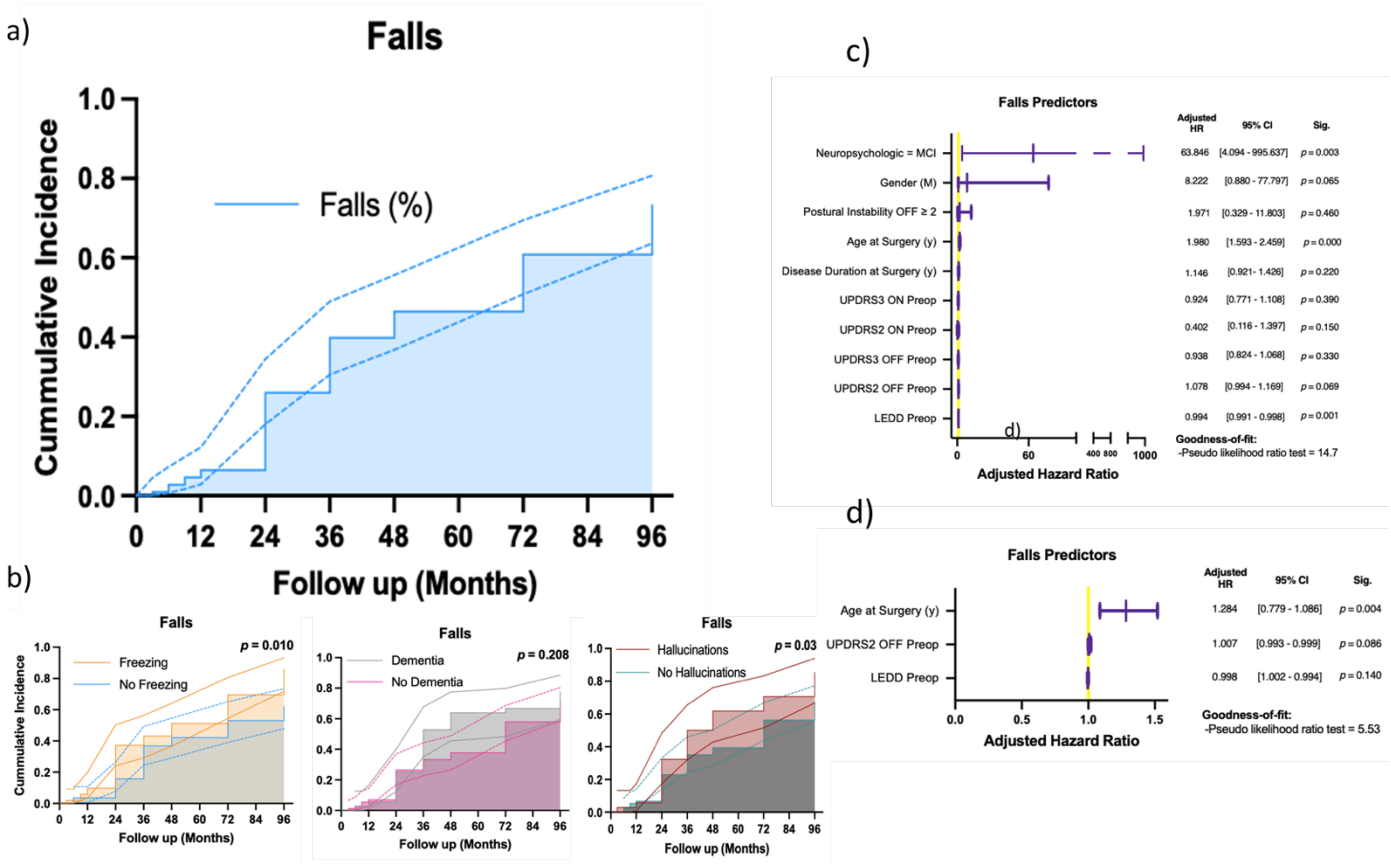


Figure 3.3- Estimated cumulative incidence curves for Falls, with mortality treated as competing risk. Shaded lines represent (upper and lower) 95% confidence intervals (a) Estimated cumulative incidence plots of falls, with equality between plots based on the Gray's test (i.e. comparison of the weighted averages for the sub-distribution

hazards of each event of interest) (b) Unadjusted univariate analysis (c) and multivariate analysis of predictors for falls (d). Each and every single variable is adjusted for all other variables in the respective plot. Multivariable regression analysis in the presence of competing risks was performed using the (semiparametric proportional hazards model) sub-distribution hazards of cumulative incidence functions based on the Gray's test. A backward elimination method for selection of variables was using a cut-off of 0.2. Variables including in the initial model were the same for all the outcomes studies: Gender, age at surgery, disease duration at surgery, UPDRS II OFF-MED, UPDRS II ON-MED, UPDRS III OFF-MED, UPDRS III ON-MED, H&Y OFF MED >2, LEDD, Item 29 UPDRS III OFF ≥2, Item 30 UPDRS III OFF ≥2, Phenotype (Tremor/ PIGD/ Indeterminate, Neuropsychological diagnosis (Normal/ Mild Cognitive impairment).

Table 3.3 – Demographic and clinic characteristics of fallers vs non-fallers at baseline evaluation

	Fallers (n = 79)	Non-Fallers (n=30)	*p*-value
Gender: male, n=109	39	20	0.105
Age at surgery ($\bar{x}$ ± SD), n=109	61.4 ± 7.0	60.8 ± 8.7	0.905
Disease duration at surgery (y ± SD), n=104	13.9 ± 5.4	13.5 ± 5.9	0.694
UPDRS I ($\bar{x}$ ± SD), n=98	2.6 ± 1.5	2.6 ± 1.9	0.564
UPDRS II OFF-MED ($\bar{x}$ ± SD), n=98	28.0 ± 38.3	19.9 ± 6.7	**0.015**
UPDRS II ON-MED ($\bar{x}$ ± SD), n=98	9.3 ± 6.5	8.3 ± 4.1	0.928
UPDRS III OFF-MED ($\bar{x}$ ± SD), n=105	44.7 ± 13.5	43.9 ± 13.3	0.886
UPDRS III ON-MED ($\bar{x}$ ± SD), n=105	19.1 ± 7.8	18.2 ± 7.2	1.00
H&Y OFF MED ($\bar{x}$ ± SD), n=105	2.8 ± 1.1	2.6 ± 0.9	0.182
H&Y ON MED ($\bar{x}$ ± SD), n=105	2.0 ± 0.2	1.9 ± 0.3	0.066
Levodopa % response ($\bar{x}$ ± SD)n=106	57.5 ± 13.2	58.0 ± 14.5	0.686
LEDD mg ($\bar{x}$ ± SD) , n=107	1238.8 ± 507.7	1288.3 ± 561.6	0.687
Item 29 UPDRS III OFF MED ($\bar{x}$ ± SD) , n=105	1.9 ± 1.6	1.6 ± 1.2	0.473
Item 30 UPDRS III OFF MED ($\bar{x}$ ± SD), n=105	1.6 ± 1.0	1.0 ± 1.1	**0.022**
Item 29 UPDRS III ON MED ($\bar{x}$ ± SD), n=105	0.4 ± 0.6	0.2 ± 0.5	0.112
Item 30 UPDRS III ON MED ($\bar{x}$ ± SD), n=105	0.5 ± 0.6	0.3 ± 0.5	0.384
Phenotype, n=95			
Tremor	30	15	0.442
PIGD	30	9	
Indeterminate	9	2	
MMSE score ($\bar{x}$ ± SD), n=100	27.9 ± 1.8	27.7 ± 2.7	0.763
Neuropsychological diagnosis, n=90			
Normal	51	20	0.272
Mild Cognitive impairment	16	3	

Values are presented as mean ± SD. LEDD: levodopa equivalent daily dose; PIGD: postural instability gait disorder; MMSE: mini mental state examination; UPDRS: Unified Parkinson Disease Rating Scale; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale

Freezers had significantly higher baseline scores in UPDRS III item 29 (gait) in OFF than non-freezers (2.0 ± 0.9 vs 1.6 ± 1.5, p = 0.029) (**Table 3.4**). Univariate analysis showed that longer disease duration at surgery (HR 1.070, 95% C.I., 1.010 - 1.140, p = 0.021), higher preoperative UPDRS part III score in ON (HR 1.080, 95% C.I. 1.020 - 1.140, p = 0.012) and higher preoperative UPDRS part II score in OFF (HR 1.010, 95% C.I. 1.010 - 1.020, p = 0.000) significantly modulated the rate FOG (**Figure 3.4**). When adjusting for confounders, older age at surgery (HR 1.186, 95% C.I. 1.050 – 1.340, p = 0.006) and higher UPDRS part II score in OFF (HR 1.024, 95% C.I., 1.012 - 1.040, p = 0.000) were significantly associated with freezing. (**Figure 3.4)** The cumulative incidence of freezing was significantly higher in the fallers (56%, 95% C.I., 44.0 – 65.9%) when compared to the non-fallers (25%, 95% C.I., 10.6 – 41.6%, p = 0.007) (**Figure 3.4)**

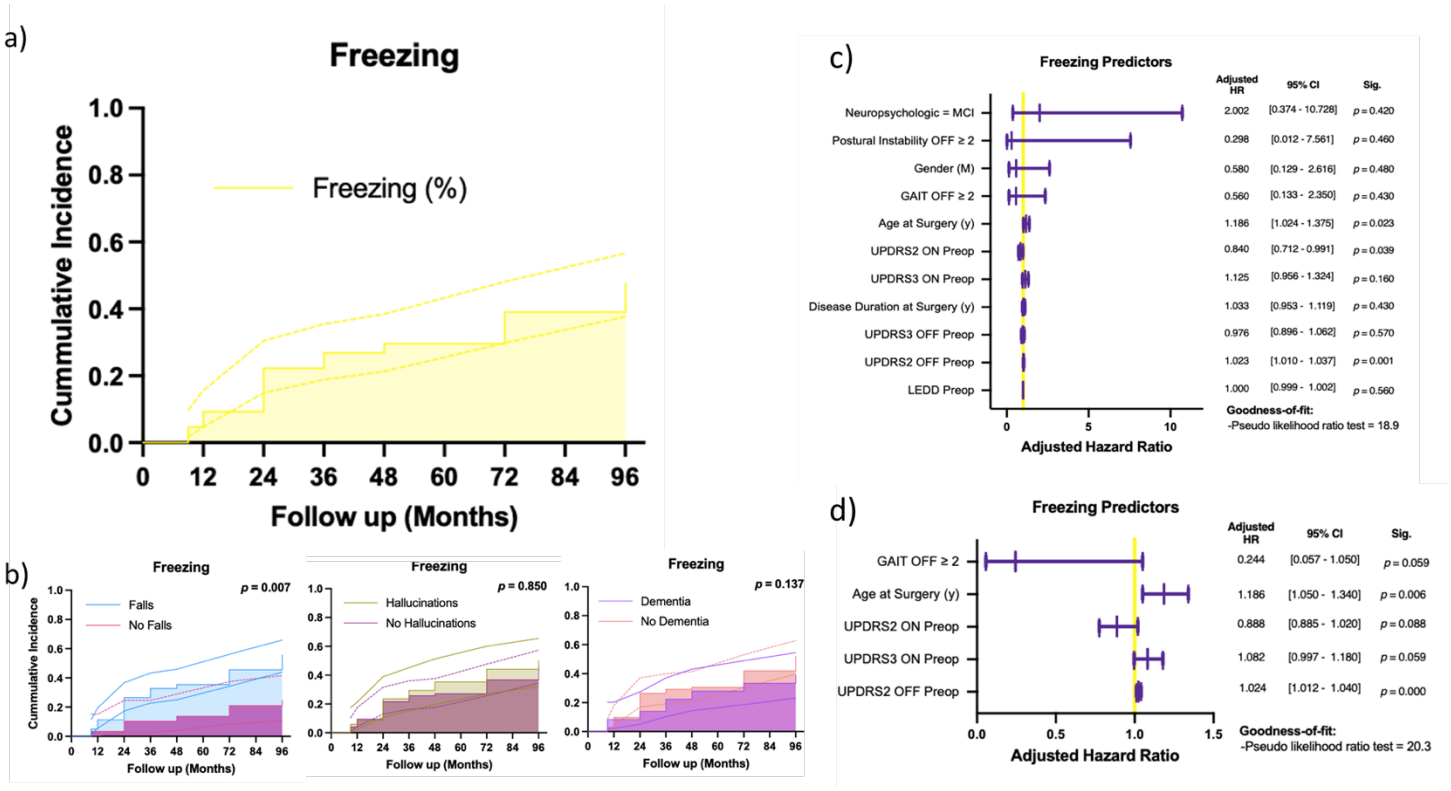


Figure 3.4- Estimated cumulative incidence curves for FOG, with mortality treated as competing risk. Shaded lines represent (upper and lower) 95% confidence intervals (a) Estimated cumulative incidence plots of falls, with equality between plots based on the Gray's test (i.e. comparison of the weighted averages for the sub-distribution hazards of each event of interest) (b) Unadjusted univariate analysis (c) and multivariate analysis of predictors

for FOG (d). Each and every single variable is adjusted for all other variables in the respective plot. Multivariable regression analysis in the presence of competing risks was performed using the (semiparametric proportional hazards model) sub-distribution hazards of cumulative incidence functions based on the Gray's test. A backward elimination method for selection of variables was using a cut-off of 0.2. Variables including in the initial model were the same for all the outcomes studies: Gender, age at surgery, disease duration at surgery, UPDRS II OFF-MED, UPDRS II ON-MED, UPDRS III OFF-MED, UPDRS III ON-MED, H&Y OFF MED >2, LEDD, Item 29 UPDRS III OFF ≥2, Item 30 UPDRS III OFF ≥2, Phenotype (Tremor/ PIGD/ Indeterminate, Neuropsychological diagnosis (Normal/ Mild Cognitive impairment).

Table 3.4 – Clinical and demographic characteristics of *freezers* vs non-*freezers* at baseline evaluation

	FOG Patients (n = 51)	No-FOG patients (n=58)	p-value
Gender: male, n=109	30 (58.8%)	29 (50%)	0.356
Age at surgery ($\bar{x}$ ± SD), n=109	62.2 ± 6.6	60.4 ± 8.1	0.224
Disease duration at surgery (y ± SD), n=104	13.88 ± 4.1	13.7 ± 6.7	0.358
UPDRS I ($\bar{x}$ ± SD), n=98	2.7± 1.6	2.4 ± 1.7	0.115
UPDRS II OFF-MED ($\bar{x}$ ± SD), n=98	23.0 ± 6.3	28.3± 45.4	0.324
UPDRS II ON-MED ($\bar{x}$ ± SD), n=98	8.2 ± 6.2	9.7±5.7	0.127
UPDRS III OFF-MED ($\bar{x}$ ± SD), n=105	44.9 ± 12.2	44.0 ± 14.5	0.486
UPDRS III ON-MED ($\bar{x}$ ± SD), n=105	17.9 ± 7.2	19.7 ± 7.9	0.217
H&Y OFF MED ($\bar{x}$ ± SD), n=105	2.9 ± 1.0	2.7 ± 1.0	0.241
H&Y ON MED ($\bar{x}$ ± SD), n=105	2.0 ± 0.3	2.0 ± 0.2	0.104
Levodopa % response ($\bar{x}$ ± SD)n=106	59.6 ± 13.3	56.3 ± 13.3	0.133
LEDD mg ($\bar{x}$ ± SD) , n=107	1320.6±524.1	1190.8±515.4	0.204
Item 29 UPDRS III OFF MED ($\bar{x}$ ± SD) , n=105	2.0 ± 0.9	1.6 ± 1.5	**0.029**
Item 30 UPDRS III OFF MED ($\bar{x}$ ± SD), n=105	1.3 ± 1.0	1.5 ± 1.1	0.268
Item 29 UPDRS III ON MED ($\bar{x}$ ± SD), n=105	0.3 ± 0.6	0.3 ± 0.6	0.414
Item 30 UPDRS III ON MED ($\bar{x}$ ± SD), n=105	0.5 ± 0.7	0.4 ± 0.5	0.624
Phenotype, n=95			0.680
Tremor	22	23	
PIGD	20	19	
Indeterminate	4	7	
MMSE score ($\bar{x}$ ± SD), n=100	27.9 ± 1.5	27.7 ± 2.5	0.610
Neuropsychological diagnosis, n=90			0.334
Normal	35	36	
Mild Cognitive impairment	7	12	

Values are presented as mean ± SD. LEDD: levodopa equivalent daily dose; PIGD: postural instability gait disorder; MMSE: mini mental state examination; UPDRS: Unified Parkinson Disease Rating Scale; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale

e) Determinants of hallucinations, dementia and institutionalization

The preoperative UPDRS part II score in OFF (HR 1.010, C.I. 1.010 - 1.020, p < 0.001) significantly modulate the rate of hallucinations **(Figure 3.5)**, dementia **(Figure 3.6)** and institutionalization **(Figure 3.7)** in univariate, non-adjusted analysis. After adjustment for confounders, no variable remained significantly associated with hallucinations **(Figure 3.5)**. As for dementia, both older age at surgery (HR 1.029, C.I. 1.000 - 1.374, p = 0.05) and preoperatory UPDRS part II score in OFF (HR 1.026, C.I. 1.014 - 1.037, p < 0.001) and ON (HR 0.996, C.I. 0.711 - 0.962, p = 0.014) significantly modulated the rate of event development **(Figure 3.6)**. In the case of institutionalization, multivariate analysis showed that both preoperatory higher UPDRS part II score in OFF (HR 1.010, 95% C.I., 1.010 - 1.020, p < 0.001) and older age at surgery (HR 1.190, C.I. 1.070 - 1.320, p = 0.001) were significant drivers of institutionalisation **(Figure 3.7).**

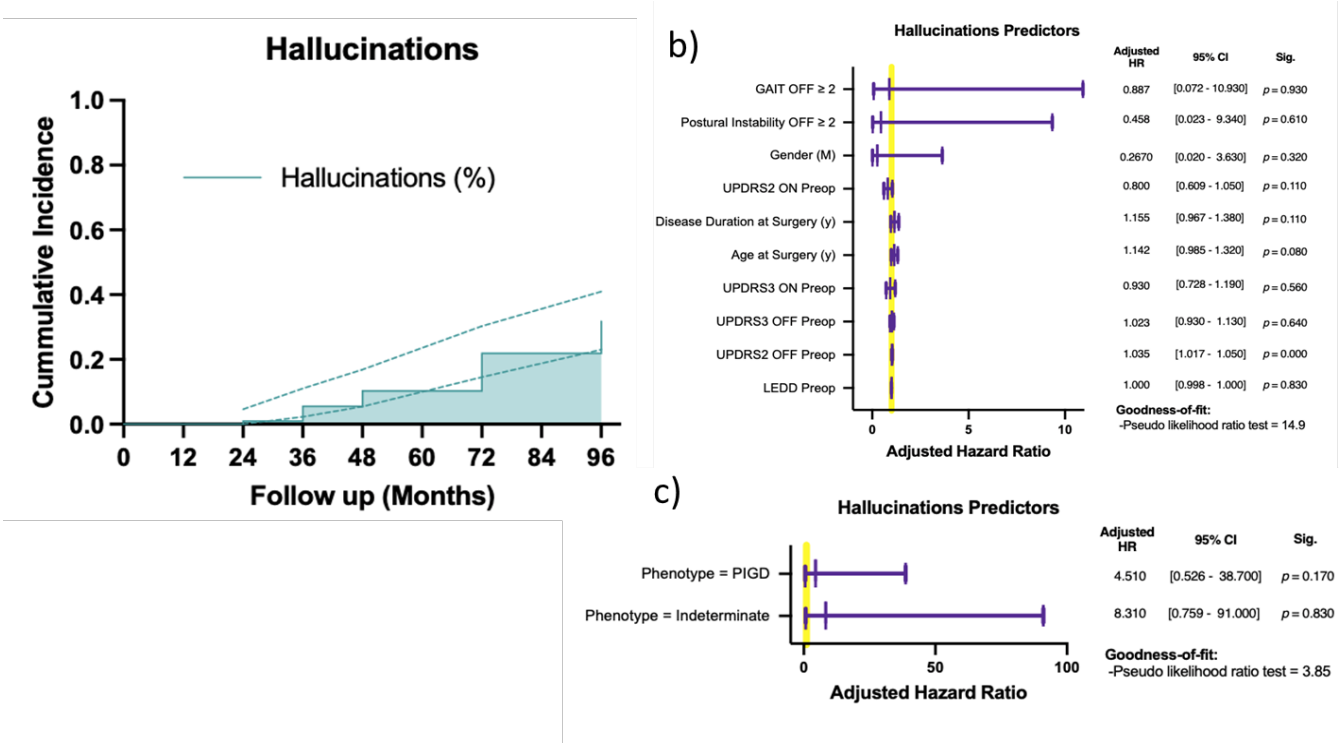


Figure 3.5- Estimated cumulative incidence curves for hallucinations, with mortality treated as competing risk. Shaded lines represent (upper and lower) 95% confidence intervals (a) Unadjusted univariate analysis (b) and multivariate analysis of predictors for hallucinations (c). Each and every single variable is adjusted for all other variables in the respective plot. Multivariable regression analysis in the presence of competing risks was performed using the (semiparametric proportional hazards model) sub-distribution hazards of cumulative

incidence functions based on the Gray's test. A backward elimination method for selection of variables was using a cut-off of 0.2. Variables including in the initial model were the same for all the outcomes studies: Gender, age at surgery, disease duration at surgery, UPDRS II OFF-MED, UPDRS II ON-MED, UPDRS III OFF-MED, UPDRS III ON-MED, H&Y OFF MED >2, LEDD, Item 29 UPDRS III OFF ≥2, Item 30 UPDRS III OFF ≥2, Phenotype (Tremor/ PIGD/ Indeterminate, Neuropsychological diagnosis (Normal/ Mild Cognitive impairment).

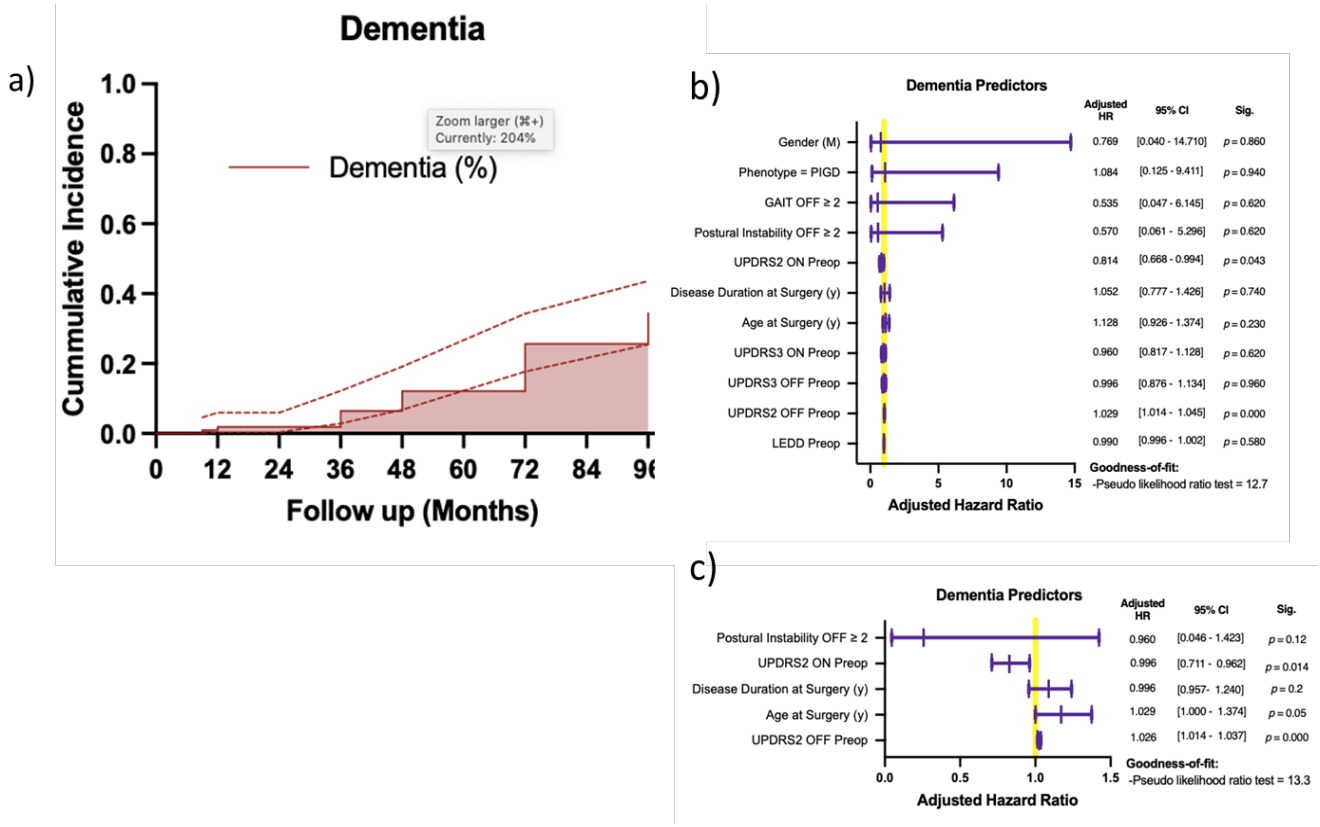


Figure 3.6- Estimated cumulative incidence curves for dementia, with mortality treated as competing risk. Shaded lines represent (upper and lower) 95% confidence intervals (a) Unadjusted univariate analysis (b) and multivariate analysis of predictors for dementia (c). Each and every single variable is adjusted for all other variables in the respective plot. Multivariable regression analysis in the presence of competing risks was performed using the (semiparametric proportional hazards model) sub-distribution hazards of cumulative incidence functions based on the Gray's test. A backward elimination method for selection of variables was using a cut-off of 0.2. Variables including in the initial model were the same for all the outcomes studies: Gender, age at surgery, disease duration at surgery, UPDRS II OFF-MED, UPDRS II ON-MED, UPDRS III OFF-MED, UPDRS III ON-MED, H&Y OFF MED >2, LEDD, Item 29 UPDRS III OFF ≥2, Item 30 UPDRS III OFF ≥2, Phenotype (Tremor/ PIGD/ Indeterminate, Neuropsychological diagnosis (Normal/ Mild Cognitive impairment).

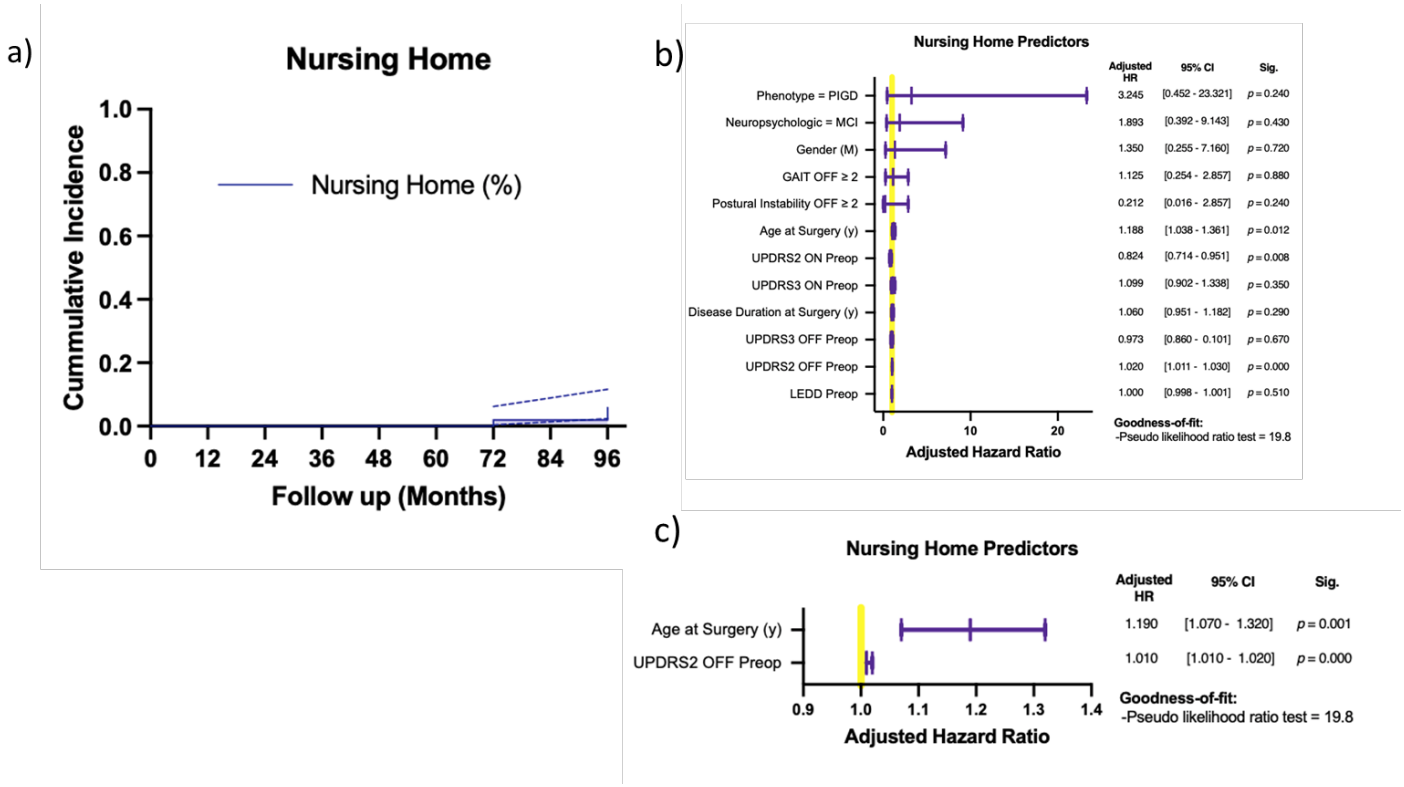


Figure 3.7- Estimated cumulative incidence curves for institutionalisation, with mortality treated as competing risk. Shaded lines represent (upper and lower) 95% confidence intervals (a) Unadjusted univariate analysis (b) and multivariate analysis of predictors for institutionalisation (c). Each and every single variable is adjusted for all other variables in the respective plot. Multivariable regression analysis in the presence of competing risks was performed using the (semiparametric proportional hazards model) sub-distribution hazards of cumulative incidence functions based on the Gray's test. A backward elimination method for selection of variables was using a cut-off of 0.2. Variables including in the initial model were the same for all the outcomes studies: Gender, age at surgery, disease duration at surgery, UPDRS II OFF-MED, UPDRS II ON-MED, UPDRS III OFF-MED, UPDRS III ON-MED, H&Y OFF MED >2, LEDD, Item 29 UPDRS III OFF ≥2, Item 30 UPDRS III OFF ≥2, Phenotype (Tremor/ PIGD/ Indeterminate, Neuropsychological diagnosis (Normal/ Mild Cognitive impairment).

Discussion

The mortality and incidence of major disability milestones of 109 PD patients followed-up for 8 years after STN-DBS have been studied using a competitive risk analysis. This cohort had an excellent benefit from DBS, with a 50% reduction in the LEDD at the end of follow-up. Mortality rate was low (overall 16%), with survivors presenting a mean age of 69 and mean disease duration of 22. For those who died, the mean time to death was about 5 years after surgery. Falls developed in three-quarters of patients, whereas FOG afflicted nearly half. Mean time to falls and FOG after surgery was about 3 years. About one-third of the patients developed hallucinations and dementia, on average 5 years after STN-DBS. Nursing home institutionalization occur in a small percentage of patients and took place on average 5 years after DBS

Mortality

Across different studies, highly variable mortality rates have been reported (from 17 to 61%) in long-term DBS cohorts[303,304,361–364], probably reflecting high heterogeneity of study populations regarding disease and follow-up duration. We have herein observed figures for cumulative mortality and cumulative incidence of falls, dementia, and hallucinations similar to those recently reported by Mahlknecht et al.[364] for STN-DBS, who found a mortality rate of 17% after 7 years of follow-up. Age and disease duration at surgery were similar in both studies.[364] Likewise, a similar survival was found after 7 years of follow-up in a cohort with a similar age at surgery.[363] The importance of comparing cohorts with similar demographic characteristics is reinforced by the increase in mortality rates with older age at surgery.[363,365] Older age at PD onset has been associated with increased mortality[366,367] however, findings from Kempster et al. have instead suggested that death (and disability milestones) occurs at around the same age regardless of the age at PD onset.[79,80] In our cohort, the mean age of death is around 70 years old, similar to what has been previously observed despite the longer disease duration.[79,80] Thus,

mortality would be related to biological age more than to disease duration, or age of disease-onset.

Interestingly, regarding the milestone-to-death interval, we have found a similar temporal relationship as previous studies,[79] reinforcing the idea that the late phase of PD (independently of age-of-onset, disease duration and DBS) follow a stereotyped pattern, with the appearance of milestones preceding death.

Falls and FOG

Falls and FOG were both the earliest and the most frequent disability milestones and tended to occur at around the same time after surgery. The incidence of falls surpassed that of freezing in the long run. In previous studies, falls were present in 61% of a DBS cohort followed-up during > 8 years[364] and in 64% of patients 7 years after surgery.[365] In the same study, 64% of the patients also developed FOG.[365] Different sample sizes and methods used to assess FOG and falls could explain the different rates between studies. A time-depended deterioration of axials signs after surgery[303,305,327,365,368] has been suggested and can explain the lower incidence of falls (32% of 260 patients) in a study with shorter disease duration at surgery (6 ± 3.8 years) and shorter follow-up time (median 3.1 years).

Older age at STN-DBS was a strong driver of increase rates of both falls and freezing. Several studies have shown an association between age and the occurrence of falls and freezing[361,362]. Besides age at DBS, only a worse baseline UPDRS II OFF score was an independent predictor of freezing, but not falls. Our results reinforce the previously highlighted importance of baseline disease severity, namely in OFF, for future incidence of axial disability milestones, irrespectively of levodopa responsiveness.[327,351] Interesting, though, is the finding that the impairment on ADL in the OFF state is a predictor of axial disability milestones. When selecting patients for DBS, special attention should be given to the performance of patients in ADL in the OFF state, besides their objective motor

disability, since it can help to identify patients with a higher risk of developing disability milestones.

Even though FOG is not often assessed when studying disability milestones in advanced disease[63,79,80] we have decided to evaluate freezing because it is a symptom associated with significant disability and deterioration in QoL, and most often unresponsive to levodopa. The response of FOG to DBS-STN has been controversial and as such, there is a need for future studies to accurately characterize its response to DBS.

Hallucinations and Dementia

Cognitive/behavioral milestones had a lower incidence than axial symptoms in our study. The rates of hallucinations and dementia after STN-DBS have been highly variable across studies, ranging from 18 to 61% for hallucinations [89,361,362,364,365,369] and from 5 to 61% for dementia.[304,305,361,364,369] An association between hallucinations and dementia (i.e., similar incidence and close temporal relationship) has been previously reported[63,79], pointing to a common pathophysiology. On the one hand, a higher cortical burden of Lewy body pathology as well as a higher load of Alzheimer's disease neuropathological changes have been associated with both dementia and hallucinations.[79,80] On the other hand, the presence of cortical Lewy bodies appears not to be correlated with motor milestones, indicating that cortical pathology is specifically implicated in the development of cognitive milestones.[369]

Likewise, older age is a risk factor for dementia in PD[361,362] which might explain the higher risk of dementia in those patients older at STN-DBS.

Nursing home placement

We found a much lower rate of admission to nursing home facilities compared to other post-DBS[305,362,364,365] and non-DBS studies. [76]Nonetheless, a previous study of Portuguese late-stage non-DBS patients also found a lower frequency of nursing home admissions than that reported in the Swedish and Dutch counterparts.[76] Sociocultural

stigma together with inadequate social support systems are likely to explain such lower institutionalization rates. [364,370]

The present study lacks a control group, but comparing the observed numbers with comparable size historical cohorts[77,78], one is lead to conclude that STN-DBS patients still developed the same disability milestones than non-DBS PD patients, but at a lower rate despite similar disease duration.[77,78,370] One possible explanation is the difference in age at PD onset, with DBS patients being relatively younger at disease onset (47 vs 54, 56, and 61 years old at disease onset) and at the end of follow-up.[77,78,370] Accordingly, a negative correlation between age at disease onset and time-to-development of the first disease milestone has been previously reported.[63,79] When compared to the Sydney cohort, a delay of 10 to 15 years in achieving the same level of disability milestones was found in the Toronto study.[365] A younger age of onset in the Toronto study was the explanation for the difference in findings, suggesting that the disease progresses relatively slowly in younger patients but disability milestones are reached at similar ages independently of age at disease onset.[63,80,365] Our data supports this hypothesis.
Interestingly, even though STN-DBS patients are a particular sample of PD patients, considering that more frequently includes patients with younger age at onset, highly responsive to levodopa and no dopaminergic resistant axial symptoms before surgery, they still end up developing the same disability milestones **(Figure 3.2).** Additionally, MC have been well-controlled with STN-DBS, this study shows that surgery does not prevent the development of such milestones.

In contrast to the usual sequence of events reported in late-stage non-DBS PD patients[63,79], we have observed the development of falls antedating that of hallucinations. The decrease in dopaminergic medication after surgery and the lack of cognitive impairment before DBS may explain such a difference.[364]

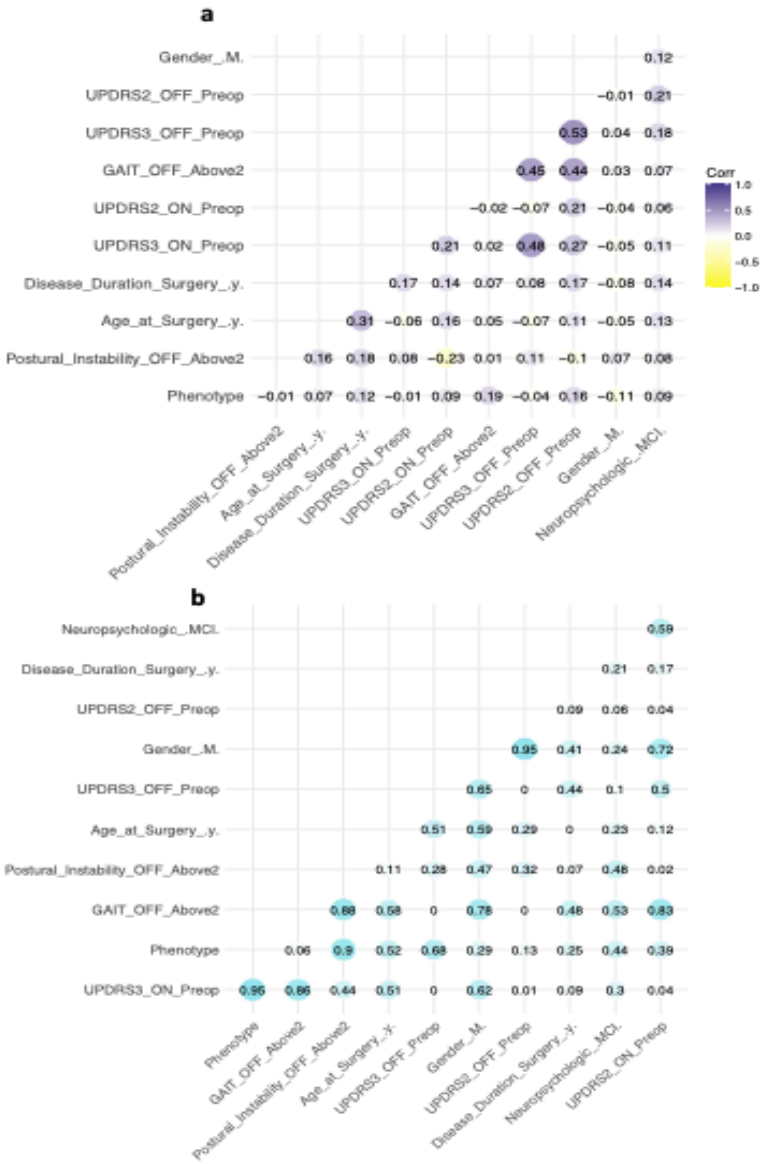
Strength and limitations

The present study is, to the best of our knowledge, the largest long-term cohort of STN-DBS PD patients comprising incidence rates and predictors of PD disability milestones. The relatively comprehensive baseline characterization has allowed for the dissection of pre-surgical clinical and demographic variables of relevance for the development of disability milestones after STN-DBS surgery. However, the retrospective nature of the study precludes a systematic evaluation of the patients regarding assessment time and instruments used. To minimize errors inherent to this type of design, we chose very clear and objective definitions for the identification of disability milestones. Like most long-term DBS follow-up studies, our study lacks a control group. To minimize this limitation, we tried to discuss our finding using historical DBS and non-DBS cohorts previously reported in the literature.

Conclusions

Long-term mortality rate is low after STN-DBS, with older age at surgery and baseline motor impairment being the best predictors. Disability milestones follow a consistent progression (mostly at very late disease stages) suggesting the same neurodegenerative process dictating disease progression in non-DBS patients to also be the predominant one among DBS patients. With biological age as the most important driver, there is a case to be made in support of STN-DBS surgery being performed earlier rather than later.

Supplementary Material Chapter III



Supplementary Figure S3.1. Graphical Spearman correlation matrix of clinical variables of interest with r score (a) and p-values (b).

Chapter IV. Gait impairment and Freezing of gait after 18 months of subthalamic nucleus deep brain stimulation: a prospective study

In this chapter, the research work was developed under **Aim 1** with the objective of determining the frequency and identifying risk factors associated with post-surgery gait impairment and FOG in patients who underwent STN-DBS surgery. Additionally, this research delved into **Aim 2,** aiming to investigate the significance of objective gait analysis through inertial sensor-based 3D-kinematics in motor assessment of patients with Parkinson's disease who underwent STN-DBS. More specifically, the study sought to assess the distinct roles of stimulation and medication in relation to various gait metrics.

Background

Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) is an effective treatment for Parkinson's disease (PD), significantly reducing motor fluctuations, dyskinesias and increasing quality of life.[84,85,87,371] In addition, motor signs such as rigidity, bradykinesia and tremor appear to be particularly improved. However, the effect of STN-DBS on axial signs such as freezing of gait (FOG) and gait impairment is still under debate.[127]

Because gait and FOG outcomes were not considered primary endpoints in previous large-scale, randomized controlled trials, evidence regarding the effect of STN-DBS in these symptoms is still scarce. [127,312] Some studies report an improvement, whilst in others a worsening, or a lack of effect is observed. [127]

FOG increases in severity and frequency with disease duration,[372] significantly affecting quality of life,[373] increasing the risk of falls[374] and reducing independence. In most of the cases, FOG improves with LD (OFF-FOG) but in rare cases can be induced by dopaminergic medication.[375] Regarding the effect of STN-DBS, some studies report an improvement, whilst in others a worsening, or a lack of effect is observed. [127]Alternative DBS approaches to diminish FOG has also been investigated, yielding somewhat contradictory results.[310,337,344,376]

In addition, the factors that may contribute to the aggravation of FOG after surgery or the predictive factors for the postoperative outcome of FOG have not been clearly identified. Higher axial scores at baseline[326], longer disease duration[312] and small levodopa equivalent daily dose (LEED) reduction post-surgery[377], have all been associated to a higher risk of FOG worsening. On the reverse, improvement of axial signs during the LD challenge test doesn't appear to predict the response to STN-DBS surgery.[326,327]

Recently, sensor based kinematic features have been used to assess the effect of STN-DBS on gait outcomes. Kinematic analysis provides a quantitative and more standardized analysis, with higher temporal and spatial resolution which allows for the detection of subtle changes in gait patterns. Previous studies have highlighted the role of stimulation in improving stride length and velocity and range of motion (ROM) at the lower

limbs [236,335,378,379], with more contradictory effects on gait variability metrics.[379,380] The role of these individual gait metrics to predict gait and FOG outcomes after STN-DBS surgery has not been clearly identified but a previous work have suggested that they may be useful.[335]

Our main goal was to prospectively assess the effect of STN-DBS on the frequency and severity of FOG and gait impairment after surgery. In addition, we tried to uncover baseline clinical and kinematic dimensions that could be used to identify patients at higher risk of developing or aggravating axial signs after STN-DBS. Since our previous study failed to show a role on motor response to LD in predicting FOG outcomes (**Chapter III**), we specifically look to the role of LD-induced changed in individual kinematic metrics as predictors of FOG response. The individual effects of LD and stimulation on kinematic gait metrics were further investigated.

Methods

Objectives: Assess the effect of STN-DBS on FOG and gait impairment in comparison to the preoperative state (off and on-medication)

Study Population

We included 18 consecutive PD patients submitted to STN-DBS surgery between 2020 and 2021. All of them were selected for STN-DBS for surgery according to the CAPSIT-PD protocol.[321] DBS surgery followed standard stereotactic techniques, and postoperative neuroimaging confirmed lead position. The DBS programming parameters and medication were optimized in post-surgery by a movement disorders specialist. Patients submitted to DBS of the Globus pallidus internus (GPi) were excluded.

Study Design:A prospective study with an 18-months follow-up, using clinical evaluation and inertial sensor-based 3D-kinematics

Patient's assessment:

All patients were assessed at baseline, before surgery, and at 18 months after STN-DBS surgery.

At the baseline all patients were evaluated in two conditions: (i) clinical off-state after overnight withdrawal of dopaminergic medication (MedOFF) and (ii) clinical on-state (MedON) assessed 1-hour after administration of a suprathreshold dose of levodopa corresponding to 150% of the usual morning dose of antiparkinsonian medication converted to levodopa equivalents doses. In both conditions motor impairment was assessed using MDS-UPDRS part III, axial sub-score (items 3.9-3.12 from the MDS-UPDRS part III), akinesia sub-score (items 3.4-3.8 and item 3.14), tremor sub-score (items 3.15 to 3.18), Hoehn and Yahr scale and the Stand-Walk and Sit test (SWS-test). The SWS test is a standardized, timed test where subjects walk a 14-meter distance between sitting and standing. The overall duration of the test (time to walk 14 meters, SWS time) and the number of FOG episodes (#FOG episodes) were recorded. FOG was defined as a transient incapacity to move forward, despite the intention to walk, including both akinetic and "trembling in place" forms.[173,192] Patients performed the SWS test three times, and individual patient data was averaged to report results.

At 18-months, clinical evaluations were conducted under four different conditions, by the following order: i) Medication OFF/Stimulation ON (MedOFF/StimON), ii) Medication OFF/Stimulation OFF (MedOFF/StimOFF), iii) Medication ON/Stimulation OFF (MedON/StimOFF), iv) Medication ON/Stimulation ON (MedON/StimON). The "OFF-drug" condition was assessed after 12 hours of medication withdrawal. A levodopa challenge test (LCT) was performed with the same dose of LD used on the pre-surgery LCT. Patients were evaluated with the stimulation settings that had shown the best clinical results over the previous 6 months (MedOFF/StimON and MedON/StimON conditions). A 30 minutes

interval was kept between evaluations when stimulation was changed(MedOFF/StimON to MedOFF/StimOFF and MedONStimOFF to MedON/StimON) .

In all conditions, both at baseline and at follow-up post-surgery evaluation, the same clinical assessment was conducted.

The presence of a gait disorder was defined by a score ≥2 in the item 3.10 of the MDS-UPDRS III. The presence of FOG was defined by a score ≥1 in the item 3.11 of the MDS-UPDRS III. Gait and FOG were further classified into: 1) OFF Gait/FOG (present only in the OFF medication/stimulation condition); 2) OFF+ON Gait/FOG (present in the OFF-treatment condition and persisting in the ON-treatment condition – unresponsive Gait/FOG); 3) ON Gait/FOG (present exclusively in the ON-treatment condition).[204,326] The percentage of each type of FOG/Gait impairment was calculated at baseline and at 18-months.

Data pertaining to MDS-UPDRS part I, II and IV scores, modified AIMS score, Freezing of Gait Questionnaire (FOG-Q), were collected both at baseline and post-surgery visit. Medication (baseline and post-surgery) and stimulation parameters (post-surgery) were also collected at each visit.

Wearable sensor-based gait analysis:

During the SWS test, both at baseline (12 patients) and post-surgery (18 patients) evaluations, patients wore seven wearable sensors. Each IMU consisted of a tri-axial accelerometer, a gyroscope and a magnetometer (Xsens Technologies, Enschede, The Netherlands), that was fixed to a patient's body using a Velcro elastic band. The inertial sensors were positioned in pelvis, right and left thighs, legs and feet**.** (**Figure 4.1**)

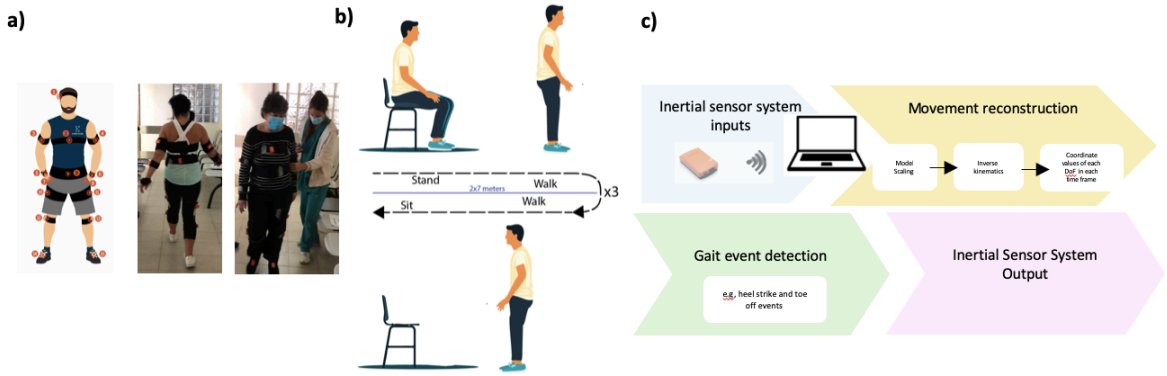


Figure 4.1 – Body sensor placement (a, head, arms, wrists, back, legs, and feet), data collection pipeline (b) and step-by-step representation of the SWS test (c)

The data collected from the IMUs were processed using the KINETIKOS cloud-based platform to reconstruct each subject's body motion using a 3D kinematic biomechanical model. Each trial out of the 3 SWS trials were individually computed and final results were averaged. A final dataset consisted of 25 variables organized into 4 domains (spatio-temporal, asymmetry, variability, and non-linear metrics) selected based on their relevance in the literature.[150,151,381] **(Table 4.1)** For spatiotemporal variables, coefficients of variation (e.g. standard deviation of variable X score / mean of variable X score) and asymmetries [(variable X score on the right side – variable X score on the left side) / (variable X score on the right side + variable X score on the left side)] were calculated.

Table 4.1: Kinematics variables under study across the different gait domains

Domain	Metric	Unit	Descriptizon
Spatio-temporal	Speed	Meters per second	The forward speed of the subject, measured as the forward distance traveled during the gait cycle divided by the gait cycle duration
	Step Length	meters	Distance between the heel contact point of one foot and that of the other foot (left/right)
	Stride Length	meters	Distance between the successive heel contact points of the same foot
	Cadence	steps per minute	Number of steps per minute, counting steps made by both feet
	Step Time	seconds	Time period between the heel contact point of one foot and that of the other foot (left/right)
	Stride Time	seconds	Time period between successive foot contacts of the same limbs (= cycle time)
	Stance Time	seconds	Time period of the cycle during which part of the foot touches the ground (left/right)
	Swing Time	seconds	Time period of the cycle during which the foot is in the air and does not touch the ground (left/right)
	Double Support Time	seconds	Time period of the cycle when both feet touch the ground (left/right)
	Single Support Time	seconds	Time period of the cycle when the foot touches the ground (left/right)
Variability	Speed Variability Step Time Variability Step Width Variability Stride Time Variability Stride Length Variability Double Support Time Variability Stance Fraction Variability	-	Fluctuation in spatiotemporal characteristics from one stride to the next
Non-linear	Entropy : measures the probability that a similar pattern in sign is repeated and followed by additional similar patterns, thus indicating regularity of a time series	AP	.Quantification of a system antero-posterior regularity
		Vert	Quantification of a system vertical regularity
		ML	Quantification of a system medio-latera regularity
	Harmonic Ratio	AP	smoothness of antero-posterior walking acceleration
	Harmonic Ratio	Vert	smoothness of vertical walking acceleration
	Harmonic Ratio	ML	smoothness of medio-lateral walking acceleration

	Center-of-Mass	AP	Antero-posterior center of mass displacement
	Center-of-Mass	Vert	Vertical center of mass displacement
	Center-of-Mass	ML	Medio-lateral center of mass displacement
Asymmetry	Step Time Asymmetry, Step Length Asymmetry, Stance Time Asymmetry, Swing Time Asymmetry Step Length asymmetry	-	differences in the bilateral behavior of lower limbs during walking

AP, antero-posterior; ML, medio-lateral, Vert, Vertical;

Statistical Analysis

Our main outcome measures were the changes in the percentage of patients and severity in FOG and gait impairment between baseline and end of FUP, relative to the same preoperative treatment condition.

Summary statistics were presented as mean ± SD, median ± IQR, or proportion [n]. The Mann-Whitney U test or the Wilcoxon Signed Rank Test were performed whenever comparing to independent or dependent (paired data) groups, respectively. Whenever stratifying the patients across multiple groups, the Kruskal-Wallis Rank Sum Test with post hoc Dunn's test for multiple comparison adjustment or the Friedman Test with Bonferroni correction were employed in the case of non-paired or paired data, respectively. Proportions across multiple groups were compared using the Fisher's exact test followed by multiplicity adjusted pairwise comparisons. For all analyses based on inferential statistics, a multiplicity-adjusted 2-tailed p-value of <0.05 will be set as the threshold for statistical significance. Visualizations depicting standardized mean responses were based on the average response divided by the respective standard deviation and may be positive or negative, depending on the direction of change. Correlations between the delta in items 3.11 or 3.10 from the Pre-OP OFF to the Post-OP MedON/StimON states were made with the delta in kinematic or clinical variables the Pre-OP MedOFF to the Pre-OP MedON states. A positive correlation implies that these variables moved in tandem, while a negative correlation suggests they moved in opposite directions. For instance, the delta in speed

exhibited a negative correlation with the delta in item 3.11. This observation indicates that the more speed increased during the levodopa challenge in the Pre-OP phase (i.e., the more responsive it was), the more the 3.11 item experience a reduction (opposite duration) in the Post-OP evaluation. Raw accelerometer/gyroscope/magnetometer data was processed using the Python programming language. Statistical analysis and figure rendering was carried out using the R programming language, except for the Sankey plots which were rendered in JavaScript.

Results

18 PD patients (78% male), age at disease onset 50.11 ± 9.46 years and age at surgery 60.72 ± 8.35 years, respectively (**Table 4.2**) were included. A 51% reduction on LEDD was observed from baseline to the end of FUP. MDS-UPDRS motor score and akinesia subscores presented a significant reduction from baseline MedOFF condition to post-surgery MedON/StimON condition (49.9 ± 2.6 vs 30.7 ± 2.4, $p<0.01$; 20.4 ± 1.1 vs 13.3 ± 1.3, $p<0.05$, respectively), whilst a non-significant reduction in axial subscore was observed (5.5 ± 0.7 vs 2.9 ± 0.6, $p>0.05$). When comparing the baseline MedON condition to the post-surgery MedONStimON condition, a significantworsening on the axial subscore was observed (1.1 ± 0.3 vs 2.9 ± 0.6, $p<0.05$). A significant improvement in the MDS-UPDRS IV score was observed at the end of FUP.

Full demographic, clinical data and stimulation parameters presented at end of FUP are depicted in **Table 4.2, 4.3, S4.1, S4.2 and Figure 4.2.**

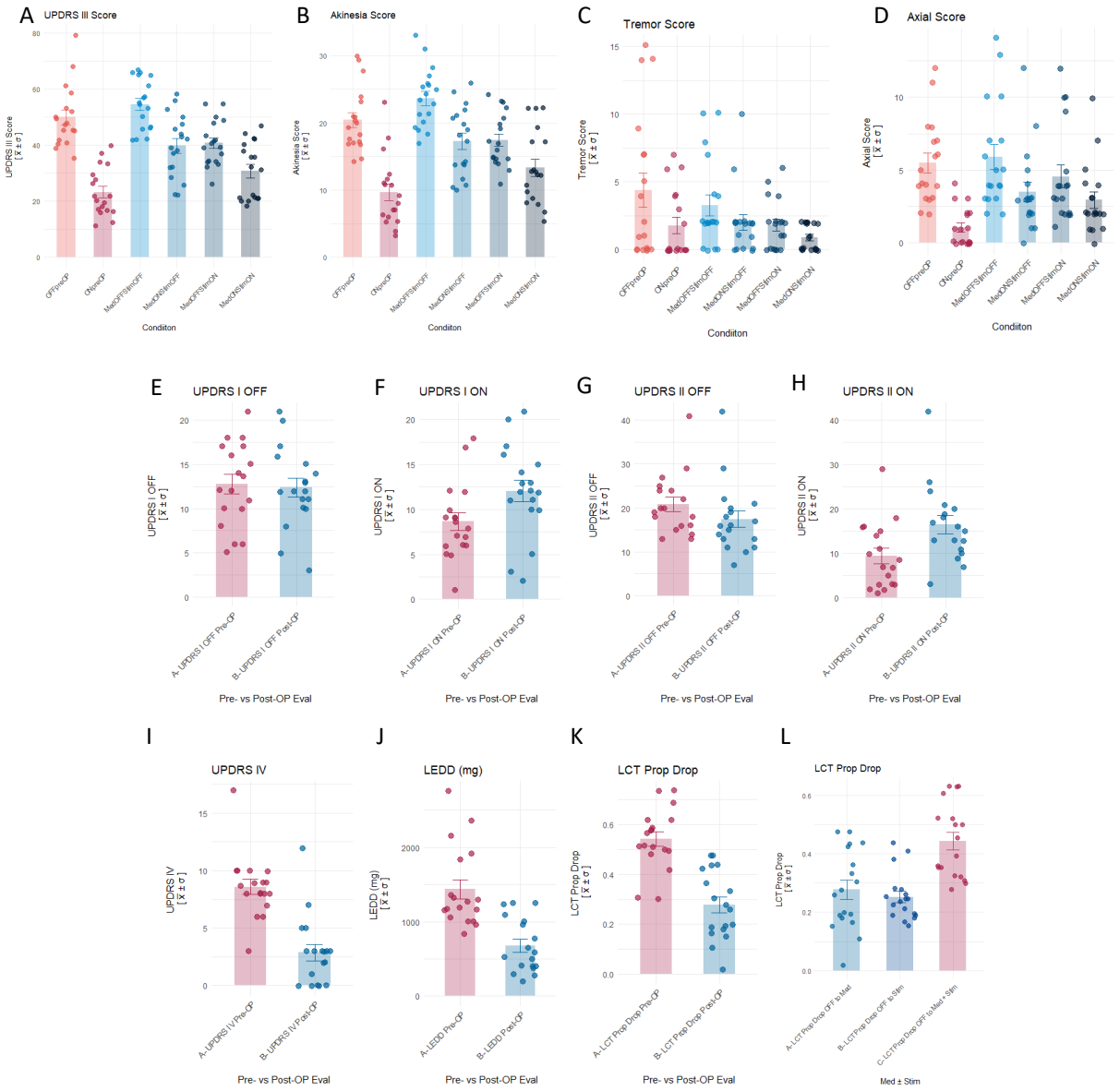


Figure 4.2 - (A) MDS-UPDRS III score; (B) Akinesia sub-score, (C) Tremor score, (D) axial score, (E) MDS-UPDRS I (F) MDS-UPDRS II score (G) MDS-UPDRS IV score assessed at baseline and at 18-moths after STN-DBS surgery across different medication and stimulation conditions, with higher scores indicate higher severity of motor symptoms; (H) LEDD at baseline, pre-surgery assessment and at 18-months post-surgery assessment; (I) Response in the LCT at baseline and post-surgery assessment (left side image)) and post-op assessment of response to LD (A), stimulation (B) and combined effects of stimulation and medication (C) when compared with the OFF-treatment condition (right side image). Akinesia score: sum of items 3-4 to 3.8 and 3.14; Tremor Score: sum of items 3.15 to 3.18; Axial score, sum of items 3,9-3,12; OFFPreOP, Medication OFF at baseline; ONpreOP: Medication ON at baseline; MedONStimON: MedicationON/stimulation ON; MEDOFF/StimOFF:medicationOFF/stimulation OFF; MedONStimOFF: Medication ON/Stimultion OFF; MedOFFSTIMON: MedicationOFF/StimulationON; LEDD: levodopa equivalent daily dose; LCT: levodopa challenge test

Table 4.2- Summary clinicodemographic statistics	
Feature	**Mean ± SD** *(or n [%])*
Gender (Male)	14 [78%]
Age at disease onset (years)	50.11 ± 9.46
Age at DBS surgery (years)	60.72 ± 8.35
Age at evaluation (years)	58.89 ± 13.52
Disease duration at STN-DBS surgery (years)	13.61 ± 14.43
Disease duration at evaluation (years)	17.72 ± 3.36
Elapsed time since STN-DBS surgery (months)	19.22 ± 7.60
LEDD Pre-OP (mg)	1436 ± 540
LEDD Post-OP (mg)	678 ± 364
MDS-UPDRS I OFF Pre-OP	12.76 ± 4.67
MDS-UPDRS I ON Pre-OP	8.65 ± 4.16
MDS-UPDRS II OFF Pre-OP	20.78 ± 6.95
MDS-UPDRS II ON Pre-OP	9.48 ± 7.42
MDS-UPDRS IV Pre-OP	8.59 ± 2.74
MDS- UPDRS IV Post-OP	2.89 ± 3.03
LCT dose Pre-OP (mg)	471 ± 153
LCT dose Post-OP (mg)	469 ± 154
MDS-UPDRS I OFF Post-OP	12.39 ± 4.57
MDS-UPDRS I ON Post-OP	12.06 ± 5.09
MDS-UPDRS II OFF Post-OP	17.44 ± 8.00
MDS-UPDRS II ON Post-OP	16.50 ± 8.67
MMSE Pre-OP	27.15 ± 1.87

Data is presented as average and standard deviation; STN-DBS: subthalamic nucleus deep brain stimulation; LEDD: levodopa equivalent daily dose; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale; LCT: Levodopa challenge test; Pre-Op: pre-operative assessment; Post-op: post-operative assessment; MMSE: Mini mental state evaluation

Table 4.3 - Stimulation parameters at the end of follow-up (n=18)

Parameter	STN-Right	STN-Left
Stimulation mode Monopolar: Bipolar: Interleaving Directional	12[67%] 2[11%] 1[6%] 3[17%]	13[72%] 2[11%] 1[6%] 2[11%]
Voltage (mV)	2.8 ± 0.8	2.9 ± 0.8
Frequency (Hz)	112 ± 29	113 ± 29
Pulse width	63.89 ± 16.50	64.44 ± 18.86

Data is presented as mean and standard deviation

1– Evaluation of Gait impairment after STN-DBS surgery

a) OFF medication Condition

At baseline OFF-medication state, gait impairment was present in 15 (83%) patients with an average gait score of 1.9 ± 0.2. In the post-surgery evaluation, stimulation did not significantly change the severity of gait impairment (MedOFF baseline: 1.9 ± 0.2 vs MedOFFStimON post-surgery: 1.8 ± 0.2, $p>0.05$) whilst it was associated to a non-significant increase on the percentage of patients presenting gait impairment (MedOFF baseline: 83% vs MedOFFStimON:94% post-surgery, $p>0.05$).

Regarding the MedOFF/StimOFF condition, a mild non-significant improvement in both the percentage of patients (100% vs 94%) and the severity of gait impairment (2.3 ± 0.1 vs 2.2 ± 0.1, $p> 0.05$) was observed with stimulation (MedOFF/StimON). **(Figure 4.3)**

Full data is presented in **Supplementary Table S4.1**, **S4.2**, **S4.3**, **S4.4**.

b) ON medication Conditi

At baseline, pre-surgery assessment, medication-ON state average gait score was 0.5 ± 0.1 with only 1 patient presenting gait impairment. In the post-surgery evaluation, stimulation was associated to an increase on both severity (MedON baseline: 0.5 ± 0.1 vs MedONStimON post-surgery: 1.8 ± 0.2, $p<0.05$) and percentage of gait impairment (MedON baseline: 6% vs MedONStimON post-surgery:78% , $p<0.05$). **(Figure 4.4)**

When compared with the MedONStimOFF condition, stimulation (MedONStimON) didn't change neither the severity (1.8 ± 0.2 vs 1.8 ± 0.2, p>0.05) neither the percentage of patients with gait impairment (78% vs 78%, p>0.05) (**Figure 4.4)**

Full data is presented in **Supplementary Table S4.1**, **S4.2**, **S4.3**, **S4.4**.

c) Gait impairment subtypes:

Accompanying this post-surgery shift towards more unfavorable gait outcomes, at baseline 78% of the patients presented gait impairment exclusively in OFF-treatment condition, with 17% of the patients being free of gait alterations. At the end of FUP all patients developed some type of gait impairment, with an exclusively OFF-treatment gait changes present in 22% of the patients and a unresponsive- gait impairment in 78% of the patients. **(Figure 4.4, Supplementary Table S4.3, S4.4)**

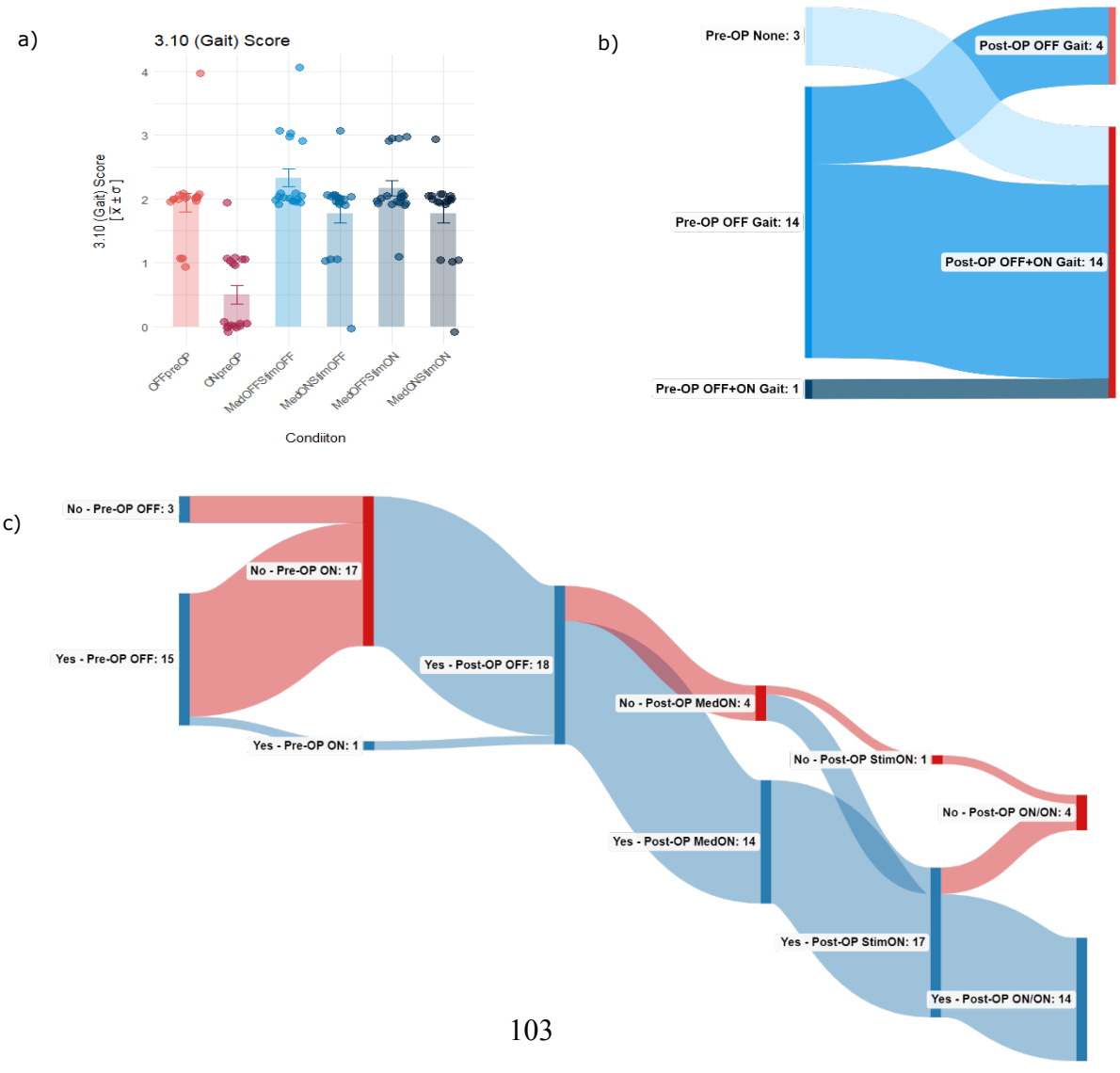


Figure 4.3: **Effect of stimulation in Gait impairment from baseline to 18-months FUP**: (A) Gait score assessed at baseline and at 18-moths after STN-DBS surgery across different medication and stimulation conditions, with higher scores indicating higher severity of motor symptoms; (B) Sankey charts depicting the sub-type of gait impairment from the baseline, pre-surgery assessment to the 18-months post-surgery assessment; (C) Sankey charts depicting the percentage of gait impairment at baseline, pre-surgery assessment,, and at the 18-months post-surgery assessment, in the different treatment conditions. OFFPreOP, Medication OFF at baseline; ONpreOP: Medication ON at baseline; MedONStimON: MedicationON/stimulation ON; MEDOFF/StimOFF:medicationOFF/stimulation OFF; MedONStimOFF: Medication ON/Stimultion OFF; MedOFFSTIMON: MedicationOFF/StimulationON; Pre-OP None: no gait impairment at baseline evaluation; Pre-OP OFF Gait: Gait impairment presented exclusively at the OFF state at baseline evaluation; Pre-op OFF+ON Gait/FOG: Gait impairment present at the OFF and ON state at baseline evaluation – unresponsive gait impairment ; Post-OP None: no gait impairment post-surgery; Post-op OFF Gait: Gait impairment presented exclusively at the OFF state post-surgery; Post-op OFF+ON Gait: Gait impairment presenting at the OFF and ON state at baseline evaluation – unresponsive Gait impairment. Gait impairment was defined as a presence of a score ≥ 2 on item 3.10 of MDS-UPDRS part III and FOG as presence of a a score ≥ 1 on item 3.11 of MDS-UPDRS part III.

2 – Evolution of FOG after STN-DBS surgery

a) OFF-medication state

At baseline, OFF-medication FOG was present 13 (72%) patients, with an average FOG score of 1.6 ± 0.3. At 18-months post-surgery, stimulation was able to reduce the % of FOG (MedOFF baseline: 72% vs MedOFFStimON post-surgery: 39%), as well the severity of FOG (1.6 ± 0.3 vs 0.9 ± 0.3, p> 0.05).

When comparing with the MedOFF/StimOFF condition, stimulation (MedOFF/StimON) non significantly decreased severity (1.4 ± 0.3 vs 0.9 ± 0.3, p>0.05) and percentage of patients presenting FOG (72% vs 39%, p>0.05). **(Figure 4.4, Supplementary Table S4.1, S4.2, S4.3, S4.5)**

b) ON-medication state

On the medication-ON condition at baseline, the average FOG score was of 0.2 ± 0.1 with only 2 (11%) patients presenting FOG. At the post-surgery evaluation, stimulation had no impact neither on the percentage nor severity of on-medication FOG, with a trend for slight worsening on both percentage (MedON baseline:11% vs MedONStimON post-

surgery: 28 %) and severity (MedON baseline: 0.2 ± 0.1 vs MedONStimON post-surgery: 0.4 ± 0.2, $p<0.05$) of FOG being observed

When repeating the LCT at 18 months after surgery, a higher percentage of patients presented FOG with an also higher severity, when compared to the same state before surgery (MedON baseline: 11% vs MedONStimOFF post-surgery: 39%; (MedON baseline: 0.2 ± 0.1 vs MedONStimOFF post-surgery: 0.7 ± 0.3, $p>0.05$, respectively) (Figure 1, Table 2 and 3)

On the post-surgery ON-medication state (MedON/StimOFF), stimulation (MedON/StimON) was associated to a non-significant improvement on FOG percentage (39% vs 28%) and severity (0.7 ± 0.3 vs 0.4 ± 0.2, $p> 0.05$ **(Figure 4.5, Supplementary Table S4.1, S4.2, S4.3, S4.5)**

c) FOG subtypes

From baseline to the end of follow up, the proportion of each subtype of FOG was also altered: at baseline 22% of the patients were free of FOG, with 67% of the cohort presenting FOG exclusively on the OFF-treatment condition. At the end of the FUP, the percentage of OFF-treatment FOG decreased (44%), at the expense of an increase on the percentage of treatment-resistant FOG (28% vs 6% at baseline). The only patient presenting a LD-induced FOG at baseline, become non-freezer at the end of FUP. **(Figure 4.5, Supplementary Table S4.3, S4.5)**

According to the FOGQ, 72% of patients were classified as freezers at the end of FUP, with a mean FOGQ score of 9.4 ± 5.9. .4(Figure 4, Table 4.6 and 4.7) **(Figure 4.5)**

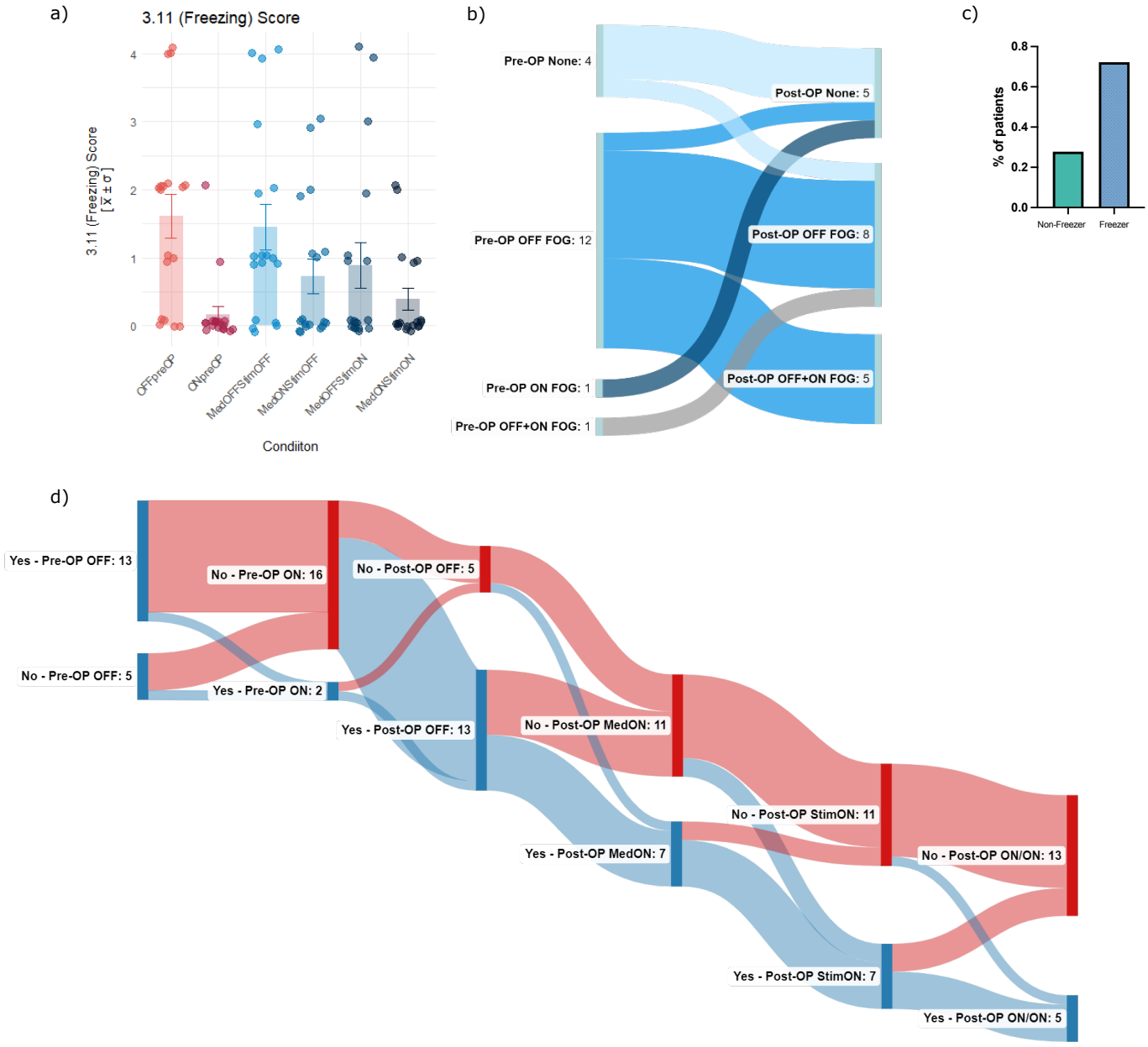


Figure 4.4: **Effect of stimulation in FOG from baseline to 18-months FUP**: **Figure 4.4**: (A) Freezing score assessed at baseline and at 18-months after STN-DBS surgery across different medication and stimulation conditions, with higher scores indicating higher severity of motor symptoms; (B) Sankey charts depicting the sub-type FOG from the baseline, pre-surgery assessment to the 18-months post-surgery assessment; (C) percentage of patients classified as Freezers or non-freezers at 18-months post-surgery assessment according to the FOG-Questionnaire. Patients were classified as "freezers if they scores more than 1 point in the FOG-Q question 3; (D) Sankey charts depicting the percentage of and FOG at baseline, pre-surgery assessment,, and at the 18-months post-surgery assessment, in the different treatment conditions. OFFPreOP, Medication OFF at baseline; ONpreOP: Medication ON at baseline; MedONStimON: MedicationON/stimulation ON; MEDOFF/StimOFF:medicationOFF/stimulation OFF; MedONStimOFF: Medication ON/Stimultion OFF;

MedOFFSTIMON: MedicationOFF/StimulationON; Pre-OP None: no FOG at baseline evaluation; Pre-OP OFF FOG: FOG presented exclusively at the OFF state at baseline evaluation; Pre-op OFF+ON GFOG: FOG presenting at the OFF and ON state at baseline evaluation – unresponsive FOG; Pre-OP ON FOG: FOG presenting exclusively at the ON condition at the baseline evaluation; Post-OP None: no FOG post-surgery; Post-op OFF Gait/FOG: Gait impairment/FOG presented exclusively at the OFF state post-surgery; Post-op OFF+ON FOG: FOG presenting at the OFF and ON state at baseline evaluation – unresponsive FOG; Post-OP ON FOG: FOG presenting exclusively at the ON condition at the baseline evaluation. FOG was defined by the presence of a score ≥ 1 on item 3.11 of MDS-UPDRS part III.

3 – The role of medication and stimulation on modulating kinematic-driven metrics

a) Baseline MedOFF vs MedON

Spatiotemporal gait metrics as speed 0.64 ± 0.14 vs 0.88 ± 0.18, $p<0.05$), step length (0.33 ± 0.05 vs 0.46 ± 0.06, $p< 0.05$) and stride length (0.71 ± 0.10 vs 0.96 ± 0.13) were significantly improved by medication as was the step time variability (0.16 ± 0.13 vs 0.05 ± 0.02, $p<0.01$). A significant increase on vertical Entropy was also observed (1.15 ± 0.49 vs 1.69 ± 0.49, $p<0.05$). **(Table 4.4 and 4.5)**

b) Post-surgery MedOFF/StimOFF vs MedONStimOFF vs MedOFFStimON

Regarding kinematic gait metrics, no significant differences were observed from the MedOFF/StimOFF condition to either stimulation alone (MedOFF/StimON) or LD alone (MedON/StimOFF) condition. **(Table 4.4)**

However, some particular gait metrics were distinctly modulated by LD and stimulation (MedONStimOFF vs MedOFFStimON). When compared with the MedOFFStimOFF condition, an increase on speed, step length and stride length was observed under LD (MedONStimOFF) whilst stimulation (MedOFFStimON) decreased this metrics. Step width variability was increased by stimulation (MedOFFStimON) but decreased by LD (MedONStimOFF). **(Table 4.4 and Figure 4.6)**

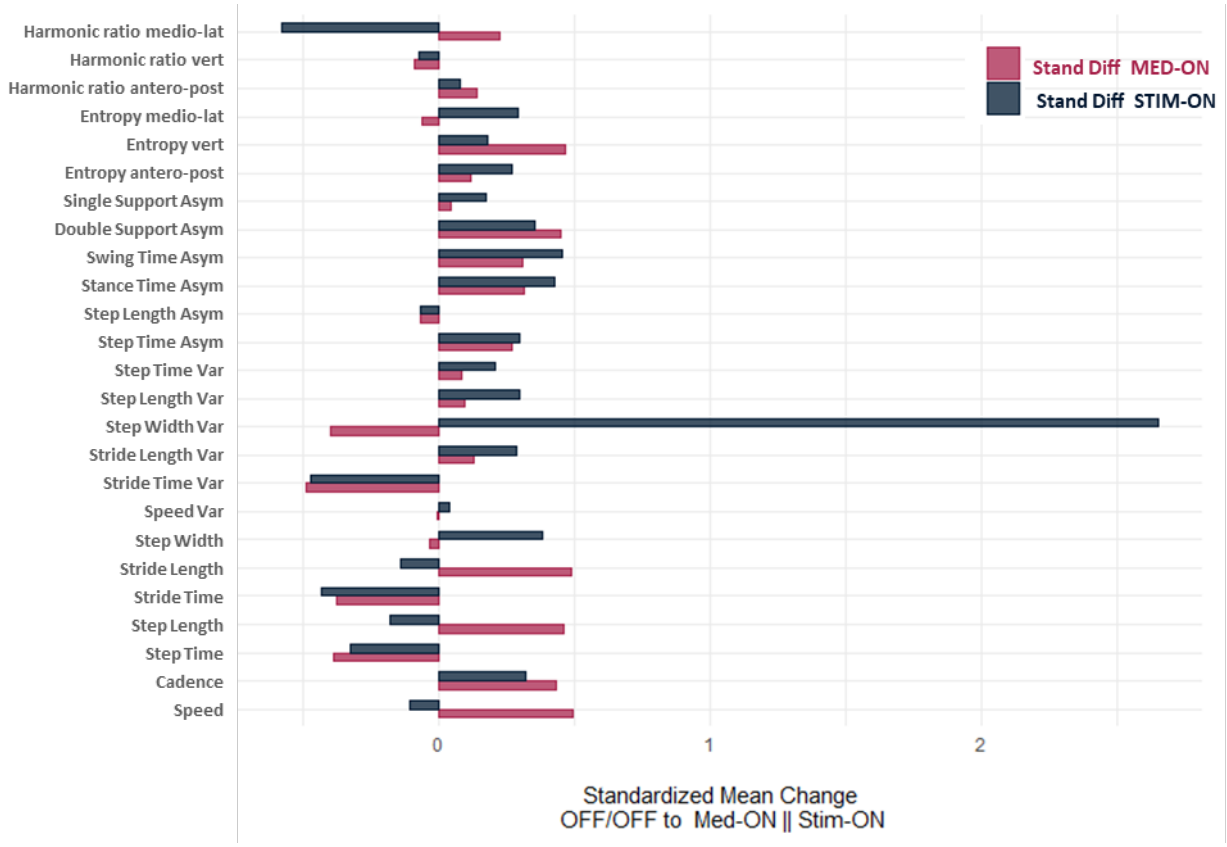


Figure 4.6: The delta of each kinematic variable representing the change from the Post-OP MedOFF/StimOFF to the Post-OP MedOFF/StimON (dark blue) and Post-OP MedON/StimOFF (red) condition. A positive value means that there was an increase in that specific metrics from the OFF/OFF to the medication-only or stimulation-only condition, whilst a negative value represents a decrease on that specific value from the OFF/OFF to the medication-only or stimulation-only condition.

c) Stimulation effects: Baseline Med-OFF vs Post-surgery MedOFF/StimON and Baseline Med-ON vs Post-surgery MedON/StimON

When comparing with the baseline OFF-medication condition, at the post-surgery assessment, stimulation significantly increased step width variability (0.41 ± 0.18 vs 1.54 ± 0.36, $p<0.01$) and medio-lateral entropy (1.55 ± 0.41 vs 1.91 ± 0.13, $p<0.05$), whilst reducing step length variability (0.60 ± 0.17 vs 0.29 ± 0.08, $p<0.05$).

In the medication-ON condition, stimulation was associated with a significantly decreased speed (0.88 ± 0.18 vs 0.69 ± 0.11), step (0.46 ± 0.06 vs 0.37 ± 0.06) and stride length (0.96 ± 0.13 vs 0.77 ± 0.12) and a significant increase in step width variability (0.32 ± 0.08 vs 1.45 ± 0.52), step time variability (0.05 ± 0.02 vs 0.11 ± 0.11) and antero-posterior entropy (0.54 ± 0.49 vs 1.56 ± 0.35).

Overall, in both medication conditions, stimulation was associated to a slower, more arrhythmic and irregular gait when compared with baseline evaluation. **(Table 4.4 and 4.5)**

Table 4.4- Summary kinematic statistics

Kinematic Variable	Mean ± SD					
	[Pre-OP] OFF/OFF	[Pre-OP] ON	[Post-OP] OFF/OFF	[Post-OP] Med-OFF/Stim-ON	[Post-OP] Med-ON/Stim-OFF	[Post-OP] ON/ON
Speed (m/s)	0.64 ± 0.14	0.88 ± 0.18	0.58 ± 0.15	0.56 ± 0.17	0.68 ± 0.15	0.69 ± 0.11
Cadence (steps/min)	116. ± 10.4	114. ± 13.0	107. ± 15.7	115. ± 28.1	115. ± 12.8	112. ± 9.89
Step Time (s)	0.54 ± 0.06	0.53 ± 0.05	0.58 ± 0.11	0.57 ± 0.10	0.54 ± 0.04	0.55 ± 0.04
Step Lenght (m)	0.33 ± 0.05	0.46 ± 0.06	0.32 ± 0.06	0.30 ± 0.09	0.36 ± 0.08	0.37 ± 0.06
Stride Time (s)	1.07 ± 0.12	1.06 ± 0.10	1.19 ± 0.28	1.14 ± 0.21	1.07 ± 0.08	1.11 ± 0.09
Stride Length (m)	0.71 ± 0.10	0.96 ± 0.13	0.66 ± 0.14	0.64 ± 0.18	0.75 ± 0.15	0.77 ± 0.12
Step Width (m)	0.16 ± 0.00	0.16 ± 0.00	0.15 ± 0.00	0.16 ± 0.00	0.15 ± 0.00	0.15 ± 0.00
Speed Variability	0.35 ± 0.15	0.30 ± 0.10	0.38 ± 0.14	0.39 ± 0.13	0.38 ± 0.13	0.36 ± 0.20
Stride Time Variability	0.49 ± 0.81	0.04 ± 0.02	0.61 ± 1.14	0.10 ± 0.10	0.08 ± 0.08	0.29± 0.26
Stride Lenght Variability	0.19 ± 0.09	0.11 ± 0.06	0.16 ± 0.06	0.18 ± 0.06	0.17 ± 0.06	0.14 ± 0.04
Step Width Variability	0.41 ± 0.18	0.32 ± 0.08	0.47 ± 0.25	1.54 ± 0.36	0.37 ± 0.08	1.45 ± 0.52
Step Length Variability	0.60 ± 0.17	0.22 ± 0.05	0.26 ± 0.07	0.29 ± 0.08	0.27 ± 0.08	0.25 ± 0.06
Step Time Variability	0.16 ± 0.13	0.05 ± 0.02	0.10 ± 0.05	0.14 ± 0.17	0.11 ± 0.10	0.11 ± 0.11
Step Time Asymmetry	0.04 ± 0.05	0.02 ± 0.01	0.03 ± 0.02	0.05 ± 0.08	0.04 ± 0.05	0.04 ± 0.06
Step Lenght Asymmetry	0.09 ± 0.11	0.13 ± 0.13	0.22 ± 0.14	0.20 ± 0.13	0.20 ± 0.13	0.17 ± 0.19
Stance Time Asymmetry	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02	0.02 ± 0.02	0.02 ± 0.02
Swing Time Asymmetry	0.05 ± 0.04	0.03 ± 0.02	0.03 ± 0.02	0.05 ± 0.05	0.05 ± 0.04	0.04 ± 0.04
Doubble Support Asymmetry	0.05 ± 0.05	0.06 ± 0.03	0.05 ± 0.04	0.10 ± 0.13	0.08 ± 0.06	0.10 ± 0.08
Single Support Asymmetry	0.05 ± 0.05	0.03 ± 0.02	0.05 ± 0.04	0.06 ± 0.05	0.05 ± 0.05	0.04 ± 0.06
Entropy Antero-posterior	0.66 ± 0.41	0.54 ± 0.49	1.25 ± 0.51	1.46 ± 0.57	1.32 ± 0.57	1.56 ± 0.35
Entropy Vertical	1.15 ± 0.49	1.69 ± 0.49	1.69 ± 0.41	1.79 ± 0.34	1.88 ± 0.20	1.79 ± 0.39
Entropy Medio-lateral	1.55 ± 0.41	1.68 ± 0.53	1.84 ± 0.23	1.91 ± 0.13	1.81 ± 0.37	1.85 ± 0.24
Harmonic ratio Antero-posteior	0.98 ± 1.11	1.32 ± 0.72	0.92 ± 0.55	0.96 ± 0.66	1.03 ± 0.62	0.71 ± 0.30
Harmonic ratio Vertical	0.82 ± 0.67	1.54 ± 0.93	0.86 ± 0.42	0.80 ± 0.56	0.79 ± 0.61	0.83 ± 0.82
Harmonic ratio Medio-lateral	3.77 ± 2.46	3.32 ± 1.90	3.77 ± 2.04	2.73 ± 1.59	4.42 ± 2.74	4.30 ± 1.90

Data is presented as mean and standart deviation and median and IQR**.** OFFP preOP, Medication OFF at baseline; ON preOP: Medication ON at baseline; MedON/StimON post-op: MedicationON/stimulation ON at 18 months post-surgery evaluation; MedOFF/StimOFF post-op:medicationOFF/stimulationOFF at 18 months post-surgery evaluation; MedONStimOFF post-op: MedicationON/StimultionOFF at 18 months post-surgery evaluation; MedOFF/StimON post-op: MedicationOFF/StimulationON at 18 months post-surgery evaluation

Table 4.5 - Pairwise comparisons for kinematic variables between Pre-OP OFF, Pre-OP Med-ON and Post-OP Med-ON/Stim-ON
[Friedman rank sum test followed by bonferroni-adjusted pairwise comparisons using Wilcoxon signed rank test]

Kinematic Variable	Group comparison		
	[Pre-OP] OFF vs [Pre-OP] ON	**[Pre-OP]OFF vs [Post-OP]OFF/ON**	**[Pre-OP]ON vs [Post-OP] ON/ON**
Speed (m/s)	*		*
Cadence (steps/min)			
Step Time (s)			
Step Lenght (m)	*		**
Stride Time (s)			
Stride Length (m)	*		**
Step Width (m)			
Speed Variability			
Stride Time Variability			
Stride Lenght Variability			
Step Width Variability		**	**
Step Length Variability	**	*	
Step Time Variability			*
Step Time Asymmetry			
Step Lenght Asymmetry			
Stance Time Asymmetry			
Swing Time Asymmetry			
Doubble Support Asymmetry			
Single Support Asymmetry			
Entropy Antero-posterior			**
Entropy Vertical	*	*	
Entropy Medio-lateral			
Harmonic ratio Antero-posteior			
Harmonic ratio Vertical			
Harmonic ratio Medio-lateral			

preOP OFF, Medication OFF at baseline; preOP ON: Medication ON at baseline; Post-OP OFF/ON: MedicationOFF/StimultionONat 18 months post-surgery evaluation; post-op ON/ON: MedicationON/StimulationON at 18 months post-surgery evaluation

4 - Predictors of FOG and Gait impairment

A reduction in FOG severity at 18 months post-surgery (calculated as the difference in FOG scores from the baseline OFF-medication condition to the post-surgery MedON/StimON condition) was correlated with the pre-operative response to LD of several gait metrics. A LD-induced decreased in Entropy on the medio-lateral plan (r=0.63) correlated better with the FOG outcomes, than the pre-operative LD-response of axial score (r= 0.57). Additionally, pre-operative LD response of HR AP (r = -0.46), HR ML (r = -0.46), Entropy AP (r = 0.46), Stride time (r = 0.39), stride time variability (r= 0.38), were all better associated to FOG improvement than the baseline LD-response of MDS-UPDRS III (r = 0.34) **(Figure 4.7, Supplementary Table S4.6)**

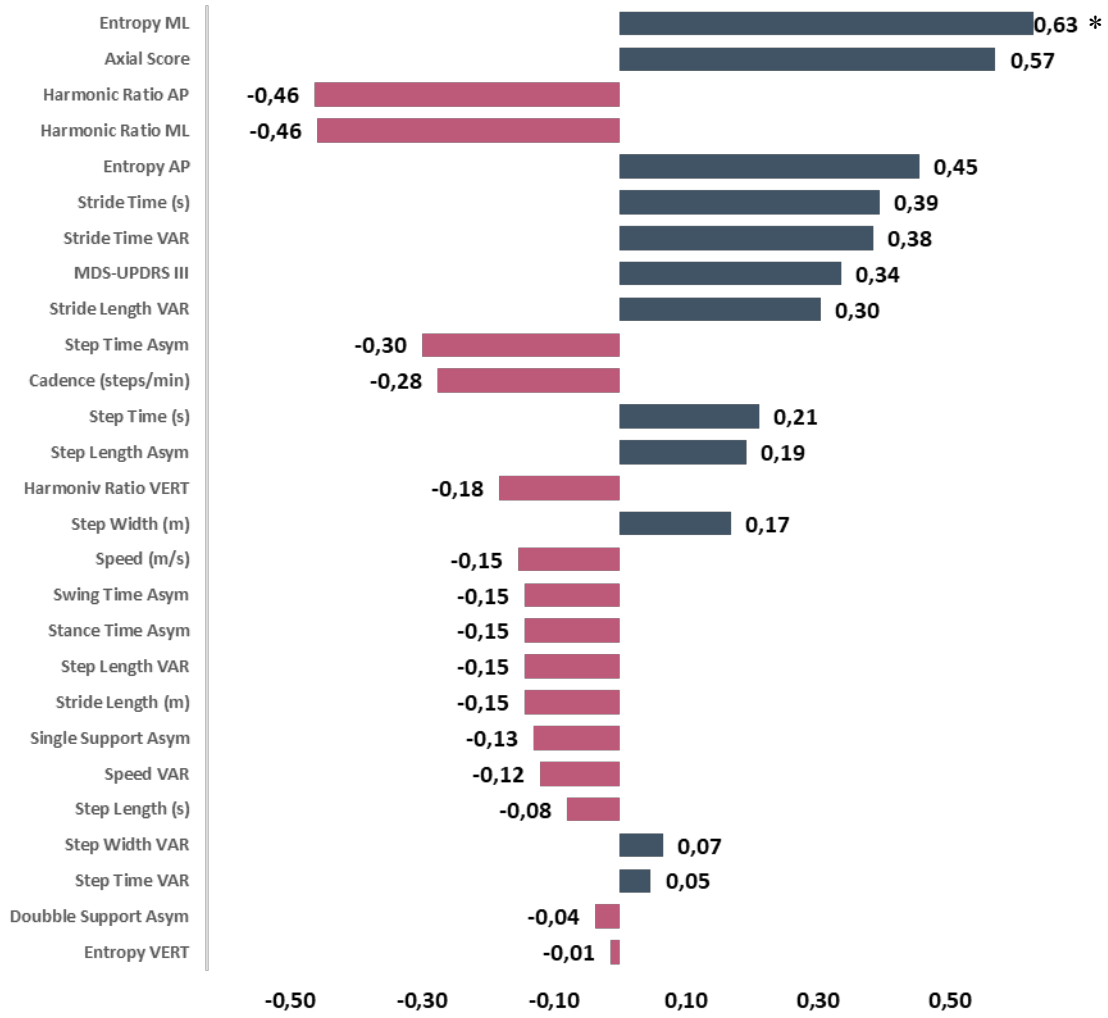


Figure 4.7 – Correlation between post-surgery FOG outcomes (delta 3.11) and LD response of individual kinematic metrics, MDS-UPDRS III and axial score at baseline. The delta 3.11 represents the change from the OFF Pre-OP to the ON Post-OP state (3.11 MedONStimON – 3.11 Pre-op MedOFF). A higher value indicates they got worst. A more negative (lower) value, indicates they got better. This metric was subjected to a Spearman correlation analysis with the Kinematics/UPDRS/Axial Score from the OFF to the ON state. A positive correlation implies that these variables move in tandem, while a negative correlation suggests they move in opposite directions. For example, the speed exhibits a negative correlation. This means that as the speed increased during the levodopa challenge in the Pre-OP phase, the more the 3.11 showed a reduction in the Post-OP evaluation. *, p-value <0.05

Regarding gait impairment, a reduction on gait severity at the end of FUP (calculated as the difference in Gait scores (item 3.10 MDS-UPDRS part III) from baseline OFF-medication condition to the post-surgery MedON/StimON condition) was mostly correlated with a baseline LD-reduction in Axial and MDS-UPDRS III scores (r=0.60, r= 0.58, respectively) **(Figure 4.8, Supplementary Table S4.7)**

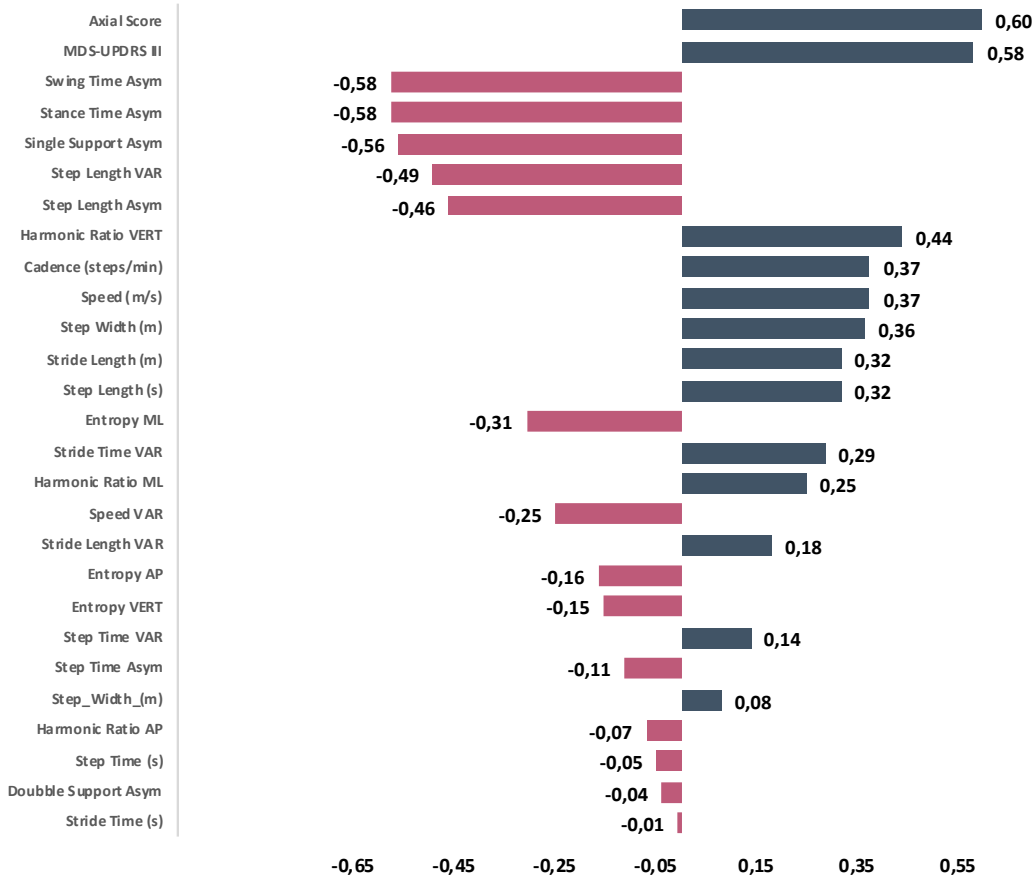


Figure 4.8: Correlation between post-surgery Gait impairment outcomes and LD response of individual kinematic metrics, MDS-UPDRS III and axial score at baseline. The delta 3.10 represents the change from the OFF Pre-OP to the MedON/StimON Post-OP state (3.10 MedONStimON – 3.10 Pre-op MedOFF). A higher value indicates they got worst. A more negative (lower) value, indicates they got better. This metric was subjected to a Spearman

correlation analysis with the Kinematics/MDS-UPDRS/Axial Score from the OFF to the ON state in the baseline evaluation. A positive correlation implies that these variables move in tandem, while a negative correlation suggests they move in opposite directions.

The same analysis was performed for the MDS-UPDRS part III. Here, a LD-induced decreased in Entropy in the medio-lateral plan (r=0.63) was better correlated with motor outcomes than the LD-response of the MDS-UPDRS III score (r=0.55). HR in the medio-lateral and antero-posterior plane were also well correlated with the post-surgery change on MDS-UPDRS part III. **(Figure 4.9, Supplementary Table S4.8)**

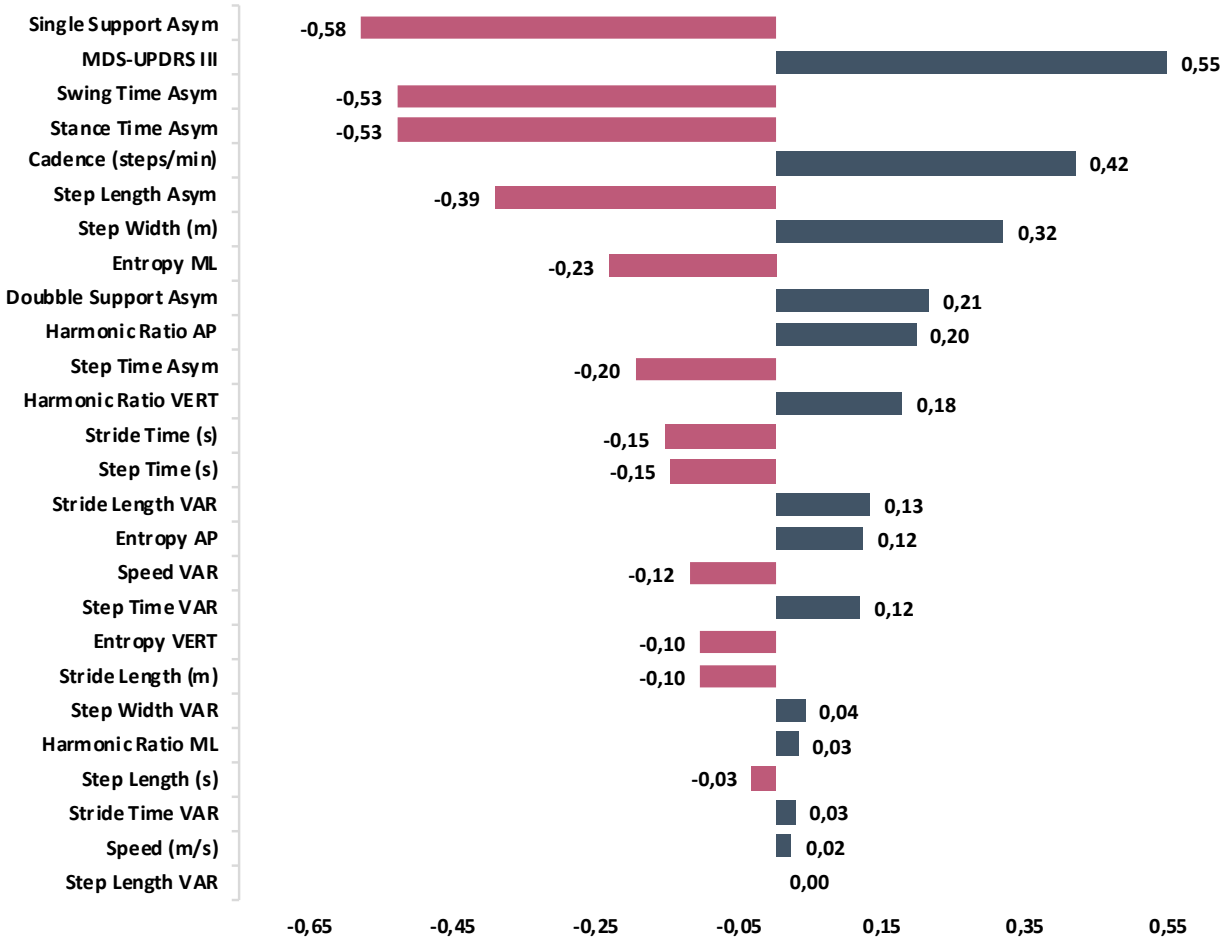


Figure 4.9: Correlation between post-surgery MDS-UPDRS III outcomes and LD response of individual kinematic metrics, MDS-UPDRS III and axial score at baseline. The delta MDS-UPDRS III represents the change from the OFF Pre-OP to the MedON/StimON Post-OP state (MDS-UPDRS III MedONStimON – MDS-UPDRS III Pre-op MedOFF). A higher value indicates they got worst. A more negative (lower) value, indicates they got better. This metric was subjected to a Spearman correlation analysis with the Kinematics/MDS-UPDRS/Axial Score from the

OFF to the ON state in the baseline evaluation. A positive correlation implies that these variables move in tandem, while a negative correlation suggests they move in opposite directions.

Discussion

In this study, we assessed the frequency of FOG and gait impairment in both medication-OFF and medication-ON states, comparing values from baseline to the 18-month post-surgery evaluation. Our aim was to enhance the understanding of FOG and gait impairment evolution post-surgery and to evaluate the role of stimulation on improving FOG and gait disturbances.

Our findings reveal an increase in the percentage of patients experiencing FOG and gait impairment following STN-DBS, particularly in the on-medication states. This increase is likely linked to a rise in the proportion of patients exhibiting unreponsive- gait alterations. Stimulation was not associated to an additional benefit on medication-ON FOG, whilst a non-significative improvement in medication-OFF FOG was observed with stimulation. The impact of stimulation on gait impairment is, however, less clear.

Therapy-resistant FOG and gait impairment increases 18 months after STN-DBS

The effect of STN-DBS on FOG and other axial signs is still under debate. A positive effect of STN-DBS on FOG and gait outcomes specially on the OFF-medication condition has been suggested, mostly from data provided by uncontrolled, retrospective studies.[326,336,368,382] One small prospective, non-randomized study comparing STN-DBS patents with Best medical treatment (BMT) showed that STN-DBS was associated to a reduction on FOG occurrence and severity. [377] A subsequent prospective trial, randomized 251 patients with PD to either STN-DBS surgery or BMT. Within the first 2 years after surgery, FOG and other axial signs improved in the medication-off condition compared to best medical treatment. [312] Another small, prospective non-controlled study, showed an improvement on freezing severity from the baseline OFF-medication condition to the 6-months MedON/StimON state.[335] The first two studies assessed FOG based on the patients-self reported FOG, using either the New Freezing of Gait Questionnaire or the item 2.14 of UPDRS part II. No objective assessment of FOG was made in these previous studies, and the estimation of both the frequency and severity of FOG in the different stimulation and medication

conditions is consequently limited. Trying to overcome these limitations, a more recent study assessed theseverity of FOG in 52 STN-DBS patients using video-based FOG analysis. Similar to previous results, a positive effect on off-medication FOG was observed, whilst a the benefit on on-medication FOG was less consistent. [382]

In the present study, and according to previous results, both the severity and the percentage of OFF-medication FOG was improved by stimulation, both when compared with baseline (medication-OFF state) and with the off-medication condition after-surgery. Consequently, a reduction on the percentage of patients presenting with OFF-Freezing was found at 18 months after surgery.

These results show that stimulation effectively reduces the severity of off-medication FOG, albeit to a lesser extent than the reduction observed with a suprathreshold LD dose during the pre-surgery evaluation. A lower magnitude of motor improvement in the post-surgery LCT (when compared with the tone performed at baseline) suggest some loss of dopamine sensitivity, a common marker of disease progression.[127,351,382]

A previous work have also hypothesized that the apparent decrease on LD response after STN-DBS surgery could be due to a reduced sensitization of the post-synaptic dopaminergic receptor.[351] Even if the reduction in dopaminergic receptor sensitivity can play a role, disease progression also exists, as shown by an increase in off-medication motor scores.

In the on-medication state, stimulation did not yield further improvement, and a slight deterioration in both severity and the percentage of individuals experiencing FOG was observed by the end of the follow-up period. Here, we believe that the worsening of FOG outcomes on the best-functional state is again the result of disease progression. [127,383] The same pattern was observed for the axial sub-score but not for the tremor sub-score, which reinforces the idea that disease progression with involvement of non-dopaminergic structures will determinate the emergence of LD and stimulation non-responsive axial signs. This phenotype, with mild rigidity and bradykinesia but increasing burden of axial

symptom, has been previously described in long-term DBS cohorts as representing new phenotype of PD patient, - 'long-term DBS syndrome'.[127]

In contrast to previous studies[312,336] which predominantly FOG using item 2.14 of the UPDRS II scale, we opted for a more objective assessment of FOG. Although FOG is a paroxysmal event that may be overlooked in a single evaluation, the MDS-UPDRS Part II captures symptoms present over the last week[220], making it unsuitable for assessing transitions between treatment states occurring within a shorter timeframe.

Similar to findings regarding FOG, prior studies on gait impairments have reported a sustained and statistically significant improvement in post-operative gait scores, reaching a peak at 6–15 months and persisting up to 48 months.[336] In our work, even if different assessment tools have been used, a worsening on both the percentage and severity of Gait scores were observed on the OFF-medication condition. Similar results were observed on the on-medication condition, where a worsening on both gait impairment severity and presence was observed from the baseline evaluation to the end of FUP. Even if one can envisage that some degree of disease progression may justify the lack of responsivity to stimulation (in patients previously LD responsive) one is led to question the existence of a deleterious effect of STN-DBS on gait.

To address this question effectively, a randomized controlled trial comparing STN-DBS patients with BMT- patients (but suitable for STN-DBS) is necessary. Prioritizing gait outcomes, this trial should incorporate gait evaluations using wearable devices and explore various kinematic variables.

Whist most studies have shown an improvement on spatiotemporal gait metrics with STN-DBS, mimicking the results obtained with LD, [232,234,235,384,385] deleterious effects of STN-DBS on postural control and gait have been found regarding several kinematic gait parameters, mostly related with gait rhythmicity and regularity.[237–240,386,387] If these effects are directly related to DBS or also a reflection of disease progression is still not clear, but it has been shown that a distinct modulation by levodopa and stimulation regarding some gait metrics may exist. [232,237,386] In our study, we have found dissimilar effects of LD and stimulation regarding several gait metrics which may impact the overall

outcomes in gait. Accordingly, stimulation but not LD, is associated to a slower gait, with high asymmetry and variability, and associated to lower levels of rhythmicity and predictability. This was translated clinically in a worsening on gait scores under stimulation (but not medication) when compared with the baseline OFF-treatment condition. We acknowledge that the interpretation of these results should be taken with caution considering our small sample, higher inter-individual variability and the limited statistic power. Bigger, independent studies could help us clarify these findings and elucidate the roles of stimulation and LD in modulation of gait biomechanics.

Kinematic gait analysis in the prediction of post-surgery FOG and gait outcomes

The specific factors responsible for the worsening of FOG or gait following STN-DBS remain unclear. In particular, there is a lack of clearly identified predictive factors for the postoperative outcomes of these debilitating motor symptoms. Previous works have yield contradictory results. Karachi and collaborators have found that the post-surgery FOG severity was strongly correlated with the baseline FOG severity in the OFF-medication state, independently of LD responsiveness. [326] Looking to gait, not specifically to FOG, levodopa responsiveness of the UPDRS III came out as the stronger predictor of gait outcomes. [336] More recently, preoperative levodopa response of FOG has shown a high correlation with favorable post-surgery FOG outcomes. In the same study, modulation of specific gait metrics by LD, as stride length and range of motion also showed strong correlation with good FOG outcome. [335]

Classically, a LCT is performed at baseline to predict magnitude of motor improvement after surgery. [206,321,328,388] However, the role of the LCT has been questioned, as the relationship between pre and post-surgery motor improvements have not been consistently reproduced.[323,324,351,389,390] These observations appear particularly relevant regarding axial outcomes. [324,389–391] Nonetheless, patients with LD-resistant axial signs, including FOG, are classically excluded from surgical protocols [206,321]. In this work, we

used both the classical MDS-UPDRS III assessment and kinematic metrics response to LD to predict the outcomes of FOG and gait impairment.

Interestingly, the response to LD of several kinematic metrics as Entropy, Harmonic ratios and stride time variability presented a stronger correlation with FOG outcomes than the response to LD of the MDS-UPDRS part III score. These metrics have been increasingly appointed as reflecting overall gait rhythmicity, structure and organization [153,159,162,163,392,393] and being important predictors of negative gait outcomes as falls and FOG outcomes[226,227,231,394]. Regarding gait impairment, axial and MDS-UPDRS motor response to LD seem to be the ones with the strongest correlation with gait outcomes. Nonetheless, several kinematic metrics were also strongly correlated with post-surgery gait outcomes. Moreover, Entropy in the medio-lateral plan presented a higher correlation with the overall post-surgery motor response (represented by the delta of UPDRS part III) than the pre-surgery motor response during the LCT. Additionally, variables such as HR also showed high correlation with the post-surgery motor response, thus reinforcing the idea that gait parameters reflecting the overall structure and organization of gait may provide valuable insights for predicting post-surgery motor outcomes.

The integration of mobile health technologies into the routine assessment and care of patients with PD is increasing. The improvements in sophistication, versatility, and wearability of the different wearable devices have enabled motor assessment to leave the clinics and gain the ambulatory settings, enabling a more ecologic and comprehensive view of the motor behavior of PD patients. [395–397]. In line with this, exploring the use of kinematic metrics as possible predictor of post-surgery FOG and gait outcomes is not only, more feasible than ever, but also needed.

Our results are limited by the small sample size, which constitutes a major limitation and precludes generalization of our results, nonetheless, we believe that pave the way for the exploration of the role of kinematic metrics in the prediction of STN-DBS outcomes in bigger cohorts.

Conclusion

Based on the MDS UPDRS III, this study shows that STN-DBS is able to significantly improve overall motor scores on the OFF-medication condition, but with FOG and gait impairment being less amenable to modulation by stimulation. In the ON-medication state, a slight worsening on FOG and gait scores is observed, probably related to disease progression, and emergence of non-dopaminergic features.

Overall, a shift towards less favorable gait and FOG profiles was observed in our cohort of patients 18 months after STN-DBS surgery, where despite a decrease on the percentage of patients presenting FOG/gait impairment on the OFF condition, an increase on the percentage of therapy-resistant gait alterations was observed.

Supplementary Material – Chapter IV

Supplementary Table S4.1 – Summary FOG/Gait Impairment-related statistics across evaluations

Variable	OFF	ON	MEdOFF/StimOFF	MedON/SimOFF	MedOFF/StimON	MEdON/StimON
	Pre-OP (Mean ± SE)		*Post-OP (Mean ± SE)*			
MDS-UPDRS III	49.9 ± 2.6	23.2 ± 2.0	54.4 ± 2.1	39.7 ± 2.6	40.7 ± 1.9	30.7 ± 2.4
Axial	5.5 ± 0.7	1.1 ± 0.3	5.9 ± 0.9	3.5 ± 0.7	4.6 ± 0.8	2.9 ± 0.6
Akinesia	20.4 ± 1.1	9.7 ± 1.2	23.7 ± 1.0	17.3 ± 1.2	17.4 ± 0.9	13.3 ± 1.3
Tremor	4.4 ± 1.3	1.8 ± 0.6	3.3 ± 0.8	2.0 ± 0.6	1.8 ± 0.4	0.9 ± 0.24
Item 3.10	1.9 ± 0.2	0.5 ± 0.1	2.3 ± 0.1	1.8 ± 0.2	2.2 ± 0.1	1.8 ± 0.2
Item 3.11	1.6 ± 0.3	0.2 ± 0.1	1.4 ± 0.3	0.7 ± 0.3	0.9 ± 0.3	0.4 ± 0.2
H&Y score	2.3 ± 0.6	2.0 ± 0.0	2.3 ± 0.7	2.1 ± 0.5	2.2 ± 0.4	2.1 ± 0.2
AIMS score	0.9 ± 2.0	16.1 ± 11.9	0.8 ± 1.3	3.7 ± 4.7	1.7 ± 2.2	4.8 ± 5.9

Data is presented as mean and standard deviation. Akinesia score: sum of items 3.4 to 3.8 and 3.14; Tremor Score: sum of items 3.15 to 3.18; Axial score, sum of items 3,9-3,12; OFFPreOP, Medication OFF at baseline; ONpreOP: Medication ON at baseline; MedON/StimON: MedicationON/stimulationON; MedOFF/StimOFF:medicationOFF/stimulationOFF; MedONStimOFF: Medication ON/Stimultion OFF; MedOFFSTIMON: MedicationOFF/StimulationON; H&Y: Hoehn and Yahr; AIMS: Abnormal Involuntary Movements Scal

Supplementary Table S4.2 – Summary FOG/Gait Impairment-related statistics across evaluations

Variable	OFF Pre-OP vs ON Pre-OP	OFF Pre-OP vs OFF/OFF Post-OP	OFF Pre-OP vs Med-ON/Stim-OFF Post-OP	OFF Pre-OP vs Med-OFF/Stim-ON Post-OP	OFF Pre-OP vs Med-ON/Stim-ON Post-OP	ON Pre-OP OFF/OFF	ON Pre-OP Med-ON/Stim-OFF Post-OP	ON Pre-OP vs Med-OFF/Stim-ON Post-OP	ON Pre-OP vs ON/ON Post-OP	OFF/OFF Post-OP vs Med-ON/Stim-OFF Post-OP	OFF/OFF Post-OP vs Med-OFF/Stim-ON Post-OP	OFF/OFF Post-OP vs ON/ON Post-OP	Med-ON/Stim-OFF Post-OP vs Med-OFF/Stim-ON Post-OP	Med-ON/Stim-OFF Post-OP vs Med-ON/Stim-ON Post-OP	Med-OFF/Stim-ON Post-OP vs ON/ON Post-OP
MDS_UPDRS III	**				**	**	**	**		**	**	**		**	**
Axial	**					**	*	*	*	*		**			*
Akinesia	**				*	**	*	**		**	**	**			*
Tremor															
Item 3.10	**					**	*	**	**						
Item 3.11	*														
H&Y score															
AIMS score	****					****	***	****	*						

Akinesia score: sum of items 3.4 to 3.8 and 3.14; Tremor Score: sum of items 3.15 to 3.18; Axial score, sum of items 3,9-3,12; OFFPreOP, Medication OFF at baseline; ONpreOP: Medication ON at baseline; MedON/StimON: MedicationON/stimulationON; MedOFF/StimOFF:medicationOFF/stimulationOFF; MedONStimOFF: Medication ON/Stimultion OFF; MedOFFSTIMON: MedicationOFF/StimulationON; H&Y: Hoehn and Yahr; AIMS: Abnormal Involuntary Movements Scale

Supplementary Table S4.3 – Proportion of patients with OFG/Gait Impairment across evaluations

Condition	% Gait Impairment		% Freezing-of-Gait	
	No (%)	*Yes (%)*	*No (%)*	*Yes (%)*
OFF Pre-OP	3 (17%)	15 (83%)	5 (28%)	13 (72%)
ON Pre-OP	17 (94%)	1 (6%)	16 (89%)	2 (11%)
OFF/OFF Post-OP	0 (0%)	18 (100%)	5 (28%)	13 (72%)
Med-ON/Stim-OFF Post-OP	4 (22%)	14 (78%)	11 (61%)	7 (39%)
Med-OFF/Stim-ON Post-OP	1 (6%)	17 (94%)	11 (39%)	7 (39%)
ON/ON Post-OP	4 (22%)	14 (78%)	13 (72%)	5 (28%)

Gait impairment was defined as a presence of a score ≥ 2 on item 3.10 of MDS-UPDRS part III and FOG as presence of a score ≥ 1 on item 3.11 of MDS-UPDRS part III. OF FP preOP, Medication OFF at baseline; ON preOP: Medication ON at baseline; MedON/StimON post-op: MedicationON/stimulation ON at 18 months post-surgery evaluation; MedOFF/StimOFF post-op:medicationOFF/stimulationOFF at 18 months post-surgery evaluation; MedONStimOFF post-op: MedicationON/StimultionOFF at 18 months post-surgery evaluation; MedOFF/StimON post-op: MedicationOFF/StimulationON at 18 months post-surgery evaluation

Supplementary Table S4.4: Pairwise comparisons for the proportion of patients with Gait Impairment across evaluations
[Fisher's exact test followed by multiplicity adjusted pairwise comparisons]

	OFF Pre-OP	ON Pre-OP	OFF/OFF Post-OP	Med-ON/Stim-OFF Post-OP	Med-OFF/Stim-ON Post-OP
OFF Pre-OP	-	0.00017	1.00000	1.00000	1.00000
ON Pre-OP	0.00017	-	1.00000	0.00060	0.0000080
OFF/OFF Post-OP	1.00000	0.0000014	-	1.00000	1.00000
Med-ON/Stim-OFF Post-OP	1.00000	0.00060	1.00000	-	1.00000
Med-OFF/Stim-ON Post-OP	1.00000	0.0000080	1.00000	1.00000	-
ON/ON Post-OP	1.00000	0.00060	1.00000	1.00000	1.00000

Gait impairment was defined as a presence of a score ≥ 2 on item 3.10 of MDS-UPDRS part III a. OFFP preOP, Medication OFF at baseline; ON preOP: Medication ON at baseline; MedON/StimON post-op: MedicationON/stimulation ON at 18 months post-surgery evaluation; MedOFF/StimOFF post-op:medicationOFF/stimulationOFF at 18 months post-surgery evaluation; MedONStimOFF post-op: MedicationON/StimultionOFF at 18 months post-surgery evaluation; MedOFF/StimON post-op: MedicationOFF/StimulationON at 18 months post-surgery evaluation

Supplementary Table S4.5: Pairwise comparisons for the proportion of patients with FOG across evaluations
[Fisher's exact test followed by multiplicity adjusted pairwise comparisons]

	OFF Pre-OP	ON Pre-OP	OFF/OFF Post-OP	Med-ON/Stim-OFF Post-OP	Med-OFF/Stim-ON Post-OP
OFF Pre-OP	-	0.011	1.000	1.000	1.0000
ON Pre-OP	0.011	-	0.011	1.0000	1.0000
OFF/OFF Post-OP	1.000	0.011	-	1.0000	1.0000
Med-ON/Stim-OFF Post-OP	1.000	1.0000	1.0000	-	1.0000
Med-OFF/Stim-ON Post-OP	1.0000	1.0000	1.0000	1.0000	-
ON/ON Post-OP	0,255	1.0000	0.255	1.000	1.000

FOGs presence was defined by a score ≥ 1 on item 3.11 of MDS-UPDRS part III. OFFP preOP, Medication OFF at baseline; ON preOP: Medication ON at baseline; MedON/StimON post-op: MedicationON/stimulation ON at 18 months post-surgery evaluation; MedOFF/StimOFF post-op:medicationOFF/stimulationOFF at 18 months post-surgery evaluation; MedONStimOFF post-op: MedicationON/StimultionOFF at 18 months post-surgery evaluation; MedOFF/StimON post-op: MedicationOFF/StimulationON at 18 months post-surgery evaluation

Supplementary Table S4.6: Correlation between change in FOG scores from the baseline medOFF state to the post-surgery MedONStimONstate (Δ 3.11) and baseline change in clinical and kinematic metrics

Δ 3.11 vs	Correlation coefficient (r)	p-value
Entropy ML	0.63	0.0386
Axial subscore	0.57	0.0674
HR AP	-0.46	0.1506
HR ML	-0.46	0.1576
Entropy AP	0.45	0.1601
Stride Time (s)	0.39	0.2310
Stride Time Variability	0.38	0.2433
MDS-UPDRS III score	0.34	0.3127
Stride Length Variability	0.30	0.3624
Step Time Asymmetry	-0.30	0.3702
Cadence (steps/min)	-0.28	0.4105
Step Time (s)	0.21	0.5337
Step Length Asymmetry	0.19	0.5714
HR Vert	-0.18	0.5907
Step Width (m)	0.17	0.6200
Speed (m/s)	-0.15	0.6498
Stride Length (m)	-0.15	0.6699
Step Length Variability	-0.15	0.6699
Stance Time Asymmetry	-0.15	0.6699
Swing Time Asymmetry	-0.15	0.6699
Single Support Asymmetry	-0.13	0.7006
Speed Variability	-0.12	0.7212
Step Length (s)	-0.08	0.8159
Step Width Variability	0.07	0.8480
Step Time Varibility	0.05	0.8912
Doubble support Asymmetry	-0.04	0.9129
Entropy Vert	-0.01	0.9673

The delta 3.11 represents the change from the OFF Pre-OP to the MedON/StimON Post-OP state (3.11 MedONStimON – 3.11 Pre-op MedOFF). A higher value indicates they got worst. A more negative (lower) value, indicates they got better. HR, Harmonic-ratio; AP, antero-posterior; ML, medio-lateral; Vert, vertical

Supplementary Table S4.7: Correlation between change in Gait scores from the baseline medOFF state to the post-surgery MedONStimONstate (Δ 3.10) and baseline change in clinical and kinematic metrics

Δ 3.10 vs	Correlation coefficient (r)	p-value
Axial Sub-score	0.60	0.0526
MDS-UPDRS Part III	0.580	0.0609
Stance Time Asymmetry	-0.58	0.0639
Swing Time Asymmetry	-0.58	0.0639
Single Support Asymmetry	-0.56	0.0733
Step Lenght Variability	-0.49	0.1250
Step Length Asymmetry	-0.46	0.1551
HR Vert 0.17751865	0.44	0.1775
Speed (m/s)	0.37	0.2559
Cadence (steps/min)	0.37	0.2559
Step Width Variability	0.36	0.2706
Step Length (m)	0.32	0.3424
Stride Length (m)	0.32	0.3424
Entropy ML	-0.31	0.3596
Stride Time Variability	0.29	0.3953
Speed Variability	-0.25	0.4618
HR ML	0.25	0.4618
Stride Length Variability	0.18	0.5973
Entropy AP	-0.16	0.6305
Entropy Vert	-0.15	0.6530
Step Time Variability	0.14	0.6873
Step Time Asymmetry	-0.11	0.7454
Step Width (m)	0.08	0.8169
HR AP	-0.07	0.8410
Step Time (s)	-0.05	0.8896
Double support Asymmetry	-0.04	0.9140
Stride Time (s)	-0.01	0.9877

The delta 3.10 represents the change from the OFF Pre-OP to the MedON/StimON Post-OP state (3.10 MedONStimON – 3.10 Pre-op MedOFF). A higher value indicates they got worst. A more negative (lower) value, indicates they got better. HR, Harmonic-ratio; AP, antero-posterior; ML, medio-lateral; Vert, vertical

Supplementary Table S4.9: Correlation between change in MDS-UPDRS III scores from the baseline medOFF state to the post-surgery MedONStimONstate (Δ MDS-UPDRS III) and baseline change in clinical and kinematic metrics

Δ MDS-UPDRS III vs	Correlation coefficient (r)	p-value
Single Support Asymmetry	-0.58	0.0622
MDS UPDRS III	0.55	0.08152
Stance Time Asymmetry	-0.53	0.0947
Swing Time Asymmetry	-0.53	0.0947
Cadence (steps/min)	0.42	0.1994
Step Length Asymmetry	-0.39	0.2334
Step Width (m)	0.32	0.3454
Speed Variability	-0.30	0.3766
Entropy ML	-0.23	0.4918
Double Support Asymmetry	0.21	0.5272
Step Time Asymmetry	-0.20	0.5637
HR AP	0.20	0.5637
HR Vert	0.18	0.6012
Stride Time (s)	-0.15	0.6492
Step Time (s)	-0.15	0.6689
Stride Length Variability	0.13	0.6989
Entropy AP	0.12	0.7186
Step Time Variability	0.12	0.7289
Stride Length (m)	-0.10	0.7591
Entropy Vert	-0.10	0.7591
Step width variability	0.04	0.9047
HR ML	0.03	0.9258
Step Length (s)	-0.03	0.9258
Stride Time Variability	0.03	0.9364
Speed (m/s)	0.02	0.9469
Step Length Variability	0.00	1.000

The delta MDS-UPDRS III represents the change from the OFF Pre-OP to the MedON/StimON Post-OP state (3.10 MedONStimON – 3.10 Pre-op MedOFF). A higher value indicates they got worst. A more negative (lower) value, indicates they got better. HR, Harmonic-ratio; AP, antero-posterior; ML, medio-lateral; Vert, vertical

Chapter V. "3D kinematics quantifies gait responsiveness to levodopa earlier and to a more comprehensive extent than the MDS-UPDRS"

In this chapter, the research work was developed under **Aim 2**, to explore the role of objective gait analysis using 3D-kinematics for gait assessment in STN-DBS PD patients

Background

Gait dysfunction is an important motor sign in Parkinson's Disease (PD). Even if initially recognized as a late disease feature, we now know that it can be present in early PD patients and in prodromal disease states.[2,134,225,398,399] PD gait is classically described as slower than that of age-matched subjects, consisting of shorter and slower steps with more time spent under double support. In addition, reduced range-of-motion (ROM) at the level of the hip and knees, decreased arm swing, increased gait variability and asymmetry have all likewise been previously reported.[134,400,401] Despite not being disease-specific, these gait changes may have prognostic implications, with increased gait variability being associated with a higher risk of falls.

While symptoms such as tremor, rigidity and bradykinesia display dramatic responses to levodopa (LD), the extent to which other features of PD, including gait, speech disturbance, postural instability and freezing-of-gait (FOG) respond to LD is still a matter of debate.[168,402] Remarkably, different gait subcomponents respond differently to LD. For instance, spatiotemporal features such as speed, stride and step length[152,403] or lower-body angular features such as hip flexion have all been shown to significantly improve with LD.[404,405] In contrast, cadence, stride/step and double support time seem to be LD-resistant.[152,406] Certain gait features, such as gait variability and metrics reflecting stability and smoothness of gait have come to be recognized as insightful regarding motor control of gait and pathologic age-related locomotor dysfunction.[231] However, up to now, a limited number of studies has assessed the effect the levodopa on a limited number of gait domains, using different assessment strategies that are hard to conciliate and thus have generated conflicting ideas in regards to dopa sensitivity.[142,152–154,231,241]

Wearable sensors such as inertial measurement units (IMUs) have come to provide useful insights on gait dysfunction in PD, enabling the deconstruction of gait into several subcomponents and reflecting distinct dimensions of disease progression.[134,407–409] To date, studies exploiting 3D kinematics to evaluate gait responsiveness to LD have employed a

limited number of gait features (mostly spatiotemporal) and have compared between two medication states only (OFF vs Best-ON). Unfortunately, such an approach fails to fully ascertain the complete temporal dynamics of locomotor responses to LD (i.e., when, and how different gait subcomponents change from OFF to the Best-ON). A comprehensive analysis of the biomechanical responsiveness to LD with high granularity over time is still lacking.

The aim of the present study was to characterize the responsiveness and temporal evolution of different gait subcomponents in PD patients in OFF and different ON states upon levodopa administration using both wearable sensors and the gold-standard MDS-UPDRS motor part III, thus pinpointing to which extent different motor disturbances may be amenable to levodopa rescuing and modulation.

Material and Methods

Design**:** This study employs a matched cross-sectional design.

Primary Objective**:** The primary objective of this study is to assess gait and motor responses to a levodopa challenge test over time by employing inertial sensor-based 3D movement analysis in conjunction with the gold-standard clinical assessment tool MDS-UPDRS (Part III).

Participants: We recruited patients with Parkinson's disease (PD) who had developed motor complications due to levodopa treatment (advanced-stage PD) and were being assessed for deep brain stimulation (DBS) surgery. PD diagnosis was made according to the UK Brain Bank criteria. Patients with concomitant osteo-articular or neurological disorders significantly affecting their gait were excluded from the study. We also recruited age-matched (±3 years) and gender-matched healthy individuals who did not have PD (referred to as Healthy Controls or HC) in a 1:2 ratio. HC participants were selected from non-consanguineous family members or caregivers attending the outpatient clinic. Exclusion criteria for HC included any diagnosis of osteo-articular or neurological disorders (except for headaches, which were accepted), which could substantially impair their

walking. Healthy participants underwent examinations to rule out the presence of any movement disorders.

Assessment tools:

Clinical evaluation

Parkinson's disease (PD) patients underwent a levodopa challenge test (LCT) as part of the standard selection process for deep brain stimulation (DBS).[321] The LCT was conducted in the morning after a minimum dopaminergic medication withdrawal of 12 hours or more.[328] Patients were initially evaluated in their OFF medication state and subsequently assessed at 20, 40, 60, and 80 minutes following the administration of a suprathreshold levodopa (LD) dose, equivalent to 150% of their usual morning levodopa dose. The transition to the patient's "Best-ON" state was determined collaboratively by both the patient and the researcher, occurring at varying time points for different individuals. Motor assessment was conducted using the full MDS-UPDRS part III scale in both the OFF and "Best ON" states.[220] A shortened version, sMDS-UPDRS-III, was completed at each time point. The sMDS-UPDRS-III sub-score was derived from items 3.1, 3.3, 3.4, 3.8, 3.10, 3.11, 3.12, 3.15, and 3.17. A short version of the MDS-UPDRS was put in place in order to minimize patient fatigue during the evaluations, as the entire procedure consisting of both clinical and kinematic evaluations at each 20 min interval is particularly hard for the cohort in cause. Previous studies have used abbreviated versions of the MDS-UDPRS. This abbreviated score was constructed similarly to previous versions of the UPDRS part III, with the inclusion of additional items related to gait, freezing, and postural instability.[410,411] Having a shortened version of the MDS-UPDRS is likely to impact data granularity and thus its sensitivity. However, under the available circumstances, a short version had to be enforced. Specific sub-scores of the MDS-UDPRS III were also evaluated: Axial Sub-Score: (items 3.1, 3.10, 3.11, and 3.12), tremor sub-score (items 3.15 to 3.18.), rigidity sub-score (item 3.3) and akinesia sub-score (items 3.4 to 3.8).

It's important to note that the tremor, rigidity, and akinesia scores were calculated only for the OFF and Best-ON states for consistency. Disease severity was measured using the H&Y stage.[412] Parkinsonism was considered asymmetric when the right-to-left differences were equal to or greater than 5 on the sum of the MDS-UPDRS items 3.3, 3.4,

3.6, 3.8, and 3.15-3.17. [413].[31] The side with the highest clinical score was designated as the "worst side. The clinical phenotypes, including postural instability and gait disturbance (PIGD) or tremor dominant (TD), were defined according to previously accepted definitions.[47] In addition to evaluating MDS-UPDRS part III items 3.10 and 3.11, gait was also assessed by instructing patients to walk three times along a 7-meter-long corridor (comprising going, turning, and returning) at a self-selected pace while wearing a complete set of 15 IMUs.

Demographic and clinical variables, including age at disease onset, age at assessment, disease duration, gender, response to the levodopa challenge test (LCT) as a percentage, levodopa-equivalent daily dose (LEDD) in milligrams per day, levodopa dose during the LCT, the Abnormal Involuntary Movement (AIMS) scale to dyskinesia assessment and the Freezing of Gait Questionnaire (FOG-Q) were gathered.[244,357] The FOG-Q is a self-reported questionnaire consisting of six items designed to evaluate Freezing of Gait (FOG). The first two items focus on common gait difficulties, while the remaining four items assess the frequency and duration of FOG episodes.[244]

Motor performance in the healthy control group was evaluated using the motor part of the MDS-UPDRS scale. Gait was assessed in a manner similar to that described for PD patients, with participants wearing the same set of IMUs, as detailed above.

Kinematics evaluation

Each Inertial Measurement Unit (IMU), provided by Xsens Technologies in Enschede, The Netherlands, was equipped with a tri-axial accelerometer, gyroscope, and magnetometer. IMUs are small, weightless, cube-shaped sensors affixed to the body using Velcro elastic bands (**Figure 4.1**) The sensor orientation was as follows: X pointing downward, Y pointing to the right of the subject, and Z pointing backward, ensuring comfort and pain-free wear.

These IMUs were positioned on the head, chest, both arms, forearms, hands, pelvis, both thighs, legs, and feet. Data acquisition and processing were conducted using the KINETIKOS cloud-based platform, a Class IIa medical device with a CE mark, developed

by KINETIKOS in Coimbra, Portugal. The platform facilitated the reconstruction of each participant's body motion by employing a 3D kinematic biomechanical model of the skeletal system, covering the head, thorax, upper and lower extremities, and their corresponding joints.

The reconstruction process involved the application of inverse kinematics, utilizing a global optimization procedure that aimed to minimize the weighted sum of squared distances between the orientations of the experimental IMUs and the IMU frames of the model in each frame.[35]

From the reconstructed 3D biomechanical model, a total of 56 kinematic variables were computed. When dealing with spatiotemporal and angular features measured on both sides of the body, the "worst-side" score was selected based on clinical assessment.

For angular metrics, the maximum, minimum, and mean values were calculated for both the range of movement (ROM) and mean velocities. In the analysis, only the mean value was considered. Spatiotemporal variables were assessed using coefficients of variation (e.g., the standard deviation of variable X score divided by the mean of variable X score) and asymmetries, which were computed as (variable X score on the right side - variable X score on the left side) divided by (variable X score on the right side + variable X score on the left side). Non-linear variables were chosen based on clinical relevance, as established in previous studies (see **Table 4.1**). The final dataset comprised 56 variables categorized into 7 domains, including pace, rhythm, asymmetry, postural control, gait dynamics, non-linear features, and angular metrics (**Table 4.1**). It's worth noting that previous publications have typically characterized gait using a five-domain framework, which encompasses pace, rhythm, variability, asymmetry, and postural control.[401,414,415] To such gait modeling, we have added non-linear,[153,231] and angular (ROM, angular velocities) domains. Non-linear features included metrics such as Harmonic ratios (HR), Entropy and Displacement of Center-of-Mass (CoM). Linear features are considered to be indicative of the integrity of the underlying motor control system, as they quantify the variability of a pattern over time.

Statistical analysis

Descriptive statistics for demographic, clinical and kinematic data were done for continuous [mean and standard deviation (SD)] and categorical (count and percentage) variables. Due to its repeated measures nature, kinematic variables and MDS-UPDRS motor part III scores across 5 different time-points (OFF, 20-, 40-, 60- and 80-min post LD) were compared using the Friedman test with Conover post-hoc correction for multiple comparisons. A comparison of PD patients between OFF and Best-ON states as well as with their respective matched HC was done using the Kruskal-Wallis test with Dunn's post-hoc correction. Whenever comparing only 2 individual paired groups, the Wilcoxon test was employed. High-dimensional data in the raw data space was projected onto a two-dimensional reduced map using t-Distributed Stochastic Neighbor with Principal Component Analysis initialization and a perplexity of 30 for visualization purposes. A *p-value* <0.05 (adjusted for multiple comparisons) was considered statistically significant. Data analysis was performed in Python (version 3.9.3).

Results

a) Clinical and demographics

This study included seventeen Parkinson's disease (PD) patients with a mean age of 60.5 ± 8.1 years, of whom 58% were male. The average duration of PD was 12.1 ± 5.1 years. Additionally, thirty-four healthy controls, with a mean age of 60.68 ± 8.9 years and 58% male, were included. In the OFF state, the mean MDS-UPDRS part III score for PD patients was 50.4 ± 11.3 points, which improved to 21.8 ± 8.9 points in the Best ON state, reflecting a mean improvement of 56 ± 15.3%. The mean levodopa dose administered during the Levodopa Challenge Test (LCT) was 552.9 ± 134.0 mg (**Table 5.1**).

Table 5.1: clinical and demographic variables

Demographic variable	PD (n=17)	Healthy Controls (n=34)
Gender: male	10 (58.%)	20 (58.8%)
Age at disease onset ($\bar{x}$ ± SD)	48.6 ± 10.9	-
Age at evaluation ($\bar{x}$ ± SD)	60.5 ± 8.1	60.7 ± 8.8
Disease duration at evaluation (y ± SD)	12.1 ± 5.1	-
LEDD mg ($\bar{x}$ ± SD)	1357.4 ± 602.4	-
Levodopa dose LCT ($\bar{x}$ ± SD, mg)	552.9 ± 134.0	-
LCT % response ($\bar{x}$ ± SD)	55.9 ± 15.3	-
MDS - UPDRS I OFF-MED ($\bar{x}$ ± SD)	11.0 ± 5.9	-
MDS -UPDRS I ON-MED ($\bar{x}$ ± SD)	6.9 ± 2.6	-
MDS -UPDRS II OFF-MED ($\bar{x}$ ± SD)	20.5 ± 9.0	-
MDS -UPDRS II ON-MED ($\bar{x}$ ± SD)	6.2 ± 6.2	-
MDS - UPDRS III OFF-MED ($\bar{x}$ ± SD)	50.4 ± 11.3	0.9 ± 1.3
MDS - UPDRS III BEST-ON ($\bar{x}$ ± SD)	21.8 ± 8.9	-
MDS - UPDRS IV ($\bar{x}$ ± SD)	7.2 ± 4.0	-
H&Y OFF MED ($\bar{x}$ ± SD)	2.6 ± 1.0	-
H&Y ON MED ($\bar{x}$ ± SD)	2.1 ± 0.2	-
SE OFF MED ($\bar{x}$ ± SD)	57.1 ± 21.4	-
SE ON MED ($\bar{x}$ ± SD)	88.2 ± 15.2	-
AIMS score OFF MED ($\bar{x}$ ± SD)	0.6 ± 1.5	-
AIMS score ON MED ($\bar{x}$ ± SD, mg)	15.2 ± 10.5	-
Phenotype	-	
PIGD	14	-
Tremor	3	
FOG-Q total Score	11.1 ± 5.4	-
Question 3 FOG-Q	2.1 ± 1.3	-

Data is expressed as mean ± standard deviation as appropriate. LEDD, levodopa equivalent daily dose; LCT, Levodopa Challenge Test; MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; OFF-MED, OFF Medication; ON-MED, ON Medication; H&Y, Hoehn and Yahr Scale; SE, Schwab and England ADL scale; AIMS, Abnormal Involuntary Movement Scale; PIGD, postural instability/gait difficulty; FOG-Q, Freezing Of Gait Questionnaire

b) Clinical assessment of levodopa responsiveness using the MDS-UPDRS part III

Significant changes in MDS-UPDRS part III scores were observed upon levodopa (LD) administration from 40 minutes onwards. These changes were evident in the total score, individual items, and total axial scores (refer to **Figure 5.1** and **Table 5.2**). On average, the time to reach the "Best ON" state was 63.5 ± 12.3 minutes. Notably, significant changes between the OFF and Best ON states were detected in rigidity, the MDS-UPDRS III total score, axial, tremor, rigidity, and akinesia sub-scores at approximately this time point (**Table 5.3**).

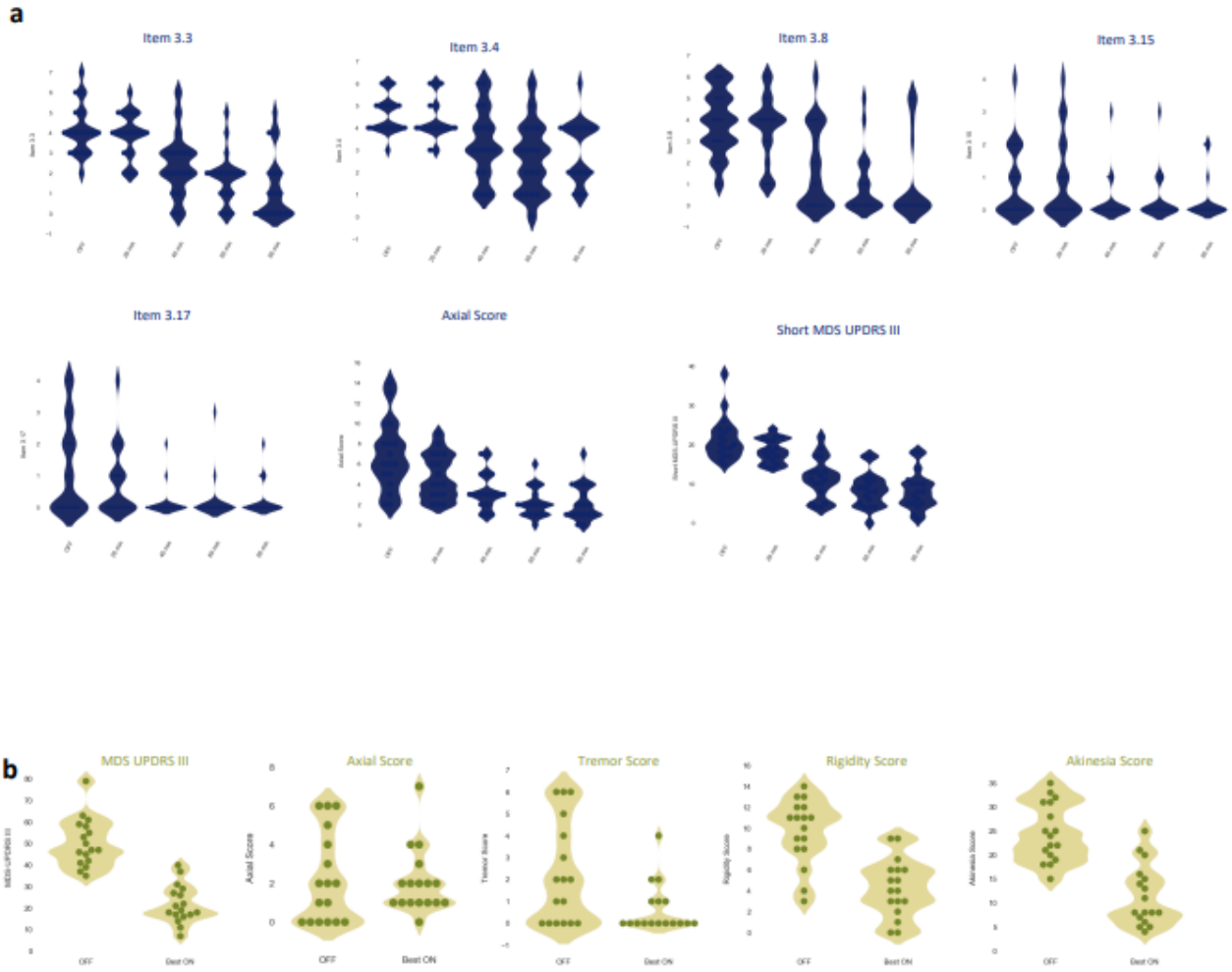


Figure 5.1: Swarm-violin plots of clinical variables under study over time after the administration of levodopa (d-j) and overall sub-scores between the OFF and Best ON states (k-o). Each group depicts a different time-point after the administration of a levodopa dose corresponding to 150% of the usual morning antiparkinsonian medication dose. From baseline up to 80 minutes post-administration. Each clinical variable only significantly differs from baseline from 40 min onwards. For metrics assessed on both sides of the body (d-h) only the scores from the worst side were included in this analysis. Refer to the respective table for the complete statistical analysis thereof using the Friedman test with Conover posthoc correction for multiple comparisons or the Wilcoxon signed-rank test. Axial score (items 3.1, 3.10, 3.11, 3.12). Short MDS-UPDRS III (items 3.1, 3.3, 3.4, 3.8, 3.10, 3.11, 3.12, 3.15, 3.17). Tremor score (items 3.15-3.18). Rigidity Score (item 3.3). Bradykinesia (items 3.4-3.8). *p-value < 0.05 (vs left-most, OFF condition).

Table 5.2: Clinical variables between OFF and Best ON states

Variable	Mean ± SD		Wilcoxon results (*p*-value)
	OFF	Best ON	OFF-Best ON
MDS UPDRS III	50.4 ± 11.3	21.8 ± 8.9	<0.001
Axial Score	6.88 ± 3.46	2.1 ± 1.7	<0.001
Tremor Score	2.3 ± 2.3	0.6 ± 1.1	0.003
Rigidity Score	9.7 ± 3.1	4.3 ± 2.7	<0.001
Akinesia Score	24.6 ± 6.1	11.4 ± 6.3	<0.001

Data are expressed as mean standard deviation, MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale

Table 5.3: Kinematic variables in OFF, Best-ON and Healthy Controls

Variable	Mean ± SD			Kruskal–Wallis test		Posthoc Dunn's Test					
						Z-score			Bonferroni corrected p-value		
	OFF	Best-ON	Healthy-Controls	H statistic	p-value	OFF-Best ON	OFF-Control	Best ON - Control	OFF-Best ON	OFF-Control	Best ON - Control
Speed (m/s)	0.56 ± 0.27	0.93 ± 0.24	0.90 ± 0.18	21.841	<0.001	-3.954	-4.316	0.250	<0.001	<0.001	1.203
Cadence (steps/min)	96.41 ± 40.38	116.38 ± 14.72	108.12±11.19	3.091	0.213	-1.613	-0.360	1.502	0.160	1.077	0.199
Step Time (s)	0.49 ± 0.20	0.53 ± 0.06	0.56 ± 0.06	2.991	0.2241	0.017	-1.402	-1.422	1.479	0.241	0.232
Step Length (m)	0.29 ± 0.15	0.49 ± 0.10	0.49 ± 0.06	29.439	<0.001	-4.249	-5.208	-0.300	<0.001	<0.001	1.146
Stride Time (s)	0.99 ± 0.42	1.05 ± 0.12	1.12 ± 0.12	2.738	0.2543	0.442	-1.046	-1.557	0.987	0.443	0.179
Stride Length (m)	0.60 ± 0.30	0.99 ± 0.15	1.02 ± 0.10	30.848	<0.001	-3.816	-5.498	-1.091	<0.001	<0.001	0.412
Step Width (m)	0.14 ± 0.07	0.18 ± 0.05	0.16 ± 0.01	0.865	0.6487	-0.797	-0.851	0.070	0.637	0.591	1.416
Stance Time (s)	0.66 ± 0.27	0.69 ± 0.08	0.47 ± 0.14	22.538	<0.001	-0.069	3.836	3.916	1.417	<0.001	<0.001
Swing Time (s)	0.33 ± 0.17	0.36 ± 0.05	0.37 ± 0.03	6.314	0.0426	-1.153	-2.489	-1.157	0.373	0.019	0.371
Double Support Time (s)	0.37 ± 0.17	0.34 ± 0.05	0.37 ± 0.06	4.496	0.1056	1.873	0.270	-1.893	0.092	1.180	0.087
Single Support Time (s)	0.30 ± 0.13	0.35 ± 0.04	0.37 ± 0.04	9.222	0.0099	-1.344	-2.999	-1.447	0.268	0.004	0.221
Hip Flexion ROM	24.07±11.66	36.00 ±8.27	38.11 ± 4.47	23.346	<0.001	-3.088	-4.817	-1.252	0.003	<0.001	0.316
Hip Adduction ROM	8.59 ± 5.16	13.01 ±2.39	16.45 ± 4.98	22.143	<0.001	-2.203	-4.667	-2.123	0.041	<0.001	0.050
Hip Rotation ROM	10.00±6.11	16.41 ±3.63	14.82 ± 2.89	19.614	<0.001	-4.146	-3.665	1.122	<0.001	<0.001	0.393
Knee Angle ROM	40.84±24.53	50.33±13.31	57.80 ± 6.47	17.212	<0.001	-2.029	-4.126	-1.783	0.063	<0.001	0.112
Ankle Angle ROM	24.23±15.94	34.33 ±9.35	34.81 ± 6.86	8.018	0.018	-2.029	-2.784	-0.441	0.063	0.008	0.989
Hip Flexion Mean Vel	44.77±21.69	68.76±20.19	68.11 ± 12.76	16.105	<0.001	-3.088	-3.876	-0.311	0.003	<0.001	1.134
Hip Adduction Mean Vel	16.73±10.05	26.81 ± 5.45	29.93 ± 8.82	16.448	<0.001	-2.723	-4.026	-0.881	0.009	<0.001	0.567
Hip Rotation Mean Vel	19.79 ± 9.57	35.82 ± 8.52	31.10 ± 7.15	24.839	<0.001	-4.866	-3.690	1.929	<0.001	<0.001	0.080
Knee Angle Mean Vel	79.29±38.73	111.13±32.87	118.17±18.53	13.676	0.001	-2.376	-3.685	-0.941	0.026	<0.001	0.519
Ankle Angle Mean Vel	48.87±28.43	69.95 ±17.78	73.50 ± 16.19	11.588	0.003	-2.281	-3.383	-0.746	0.033	0.001	0.683
Arm Flexion ROM	6.63 ± 5.37	24.04 ± 13.36	16.37 ± 5.58	26.121	<0.001	-4.831	-4.151	1.427	<0.001	<0.001	0.230
Arm Adduction ROM	4.19 ± 2.33	10.66 ± 5.17	7.50 ± 2.31	22.665	<0.001	-4.666	-3.465	1.923	<0.001	<0.001	0.082
Elbow Flexion ROM	7.00 ± 5.68	19.30 ± 9.64	20.49 ± 8.77	26.476	<0.001	-3.885	-4.997	-0.510	<0.001	<0.001	0.914
Arm Rotation ROM	7.34 ± 6.20	19.28 ± 12.07	18.93 ± 7.20	22.249	<0.001	-3.487	-4.607	-0.580	<0.001	<0.001	0.842
Pronation Supination ROM	6.47 ± 4.34	20.26 ± 11.45	16.56 ± 8.14	27.320	<0.001	-4.787	-4.477	1.051	<0.001	<0.001	0.439
Wrist Flexion ROM	5.59 ± 3.56	29.22 ± 13.24	12.06 ± 5.05	24.098	<0.001	-4.727	-3.811	1.647	<0.001	<0.001	0.149
Wrist Deviation ROM	4.17 ± 3.39	14.05 ± 8.31	11.55 ± 6.90	25.536	<0.001	-4.527	-4.446	0.781	<0.001	<0.001	0.652
Arm Flexion Mean Vel	12.33 ± 9.48	44.46 ± 29.84	29.55 ± 11.17	26.966	<0.001	-4.917	-4.201	1.477	<0.001	<0.001	0.209
Arm Adduction Mean Vel	8.55 ± 4.24	20.88 ± 9.68	16.35 ± 6.77	20.566	<0.001	-4.302	-3.655	1.312	<0.001	<0.001	0.284
Arm Rotation Mean Vel	14.50±10.34	40.59 ± 26.31	36.09 ± 16.16	22.855	<0.001	-3.859	-4.532	-0.075	<0.001	<0.001	1.410
Elbow Flexion Mean Vel	13.63 ± 8.96	42.62 ± 25.67	25.84 ± 16.32	18.511	<0.001	-4.302	-2.532	2.433	<0.001	0.016	0.022
Pronation Supination Mean Vel	17.25±17.32	43.20 ± 30.27	34.45 ± 18.03	17.331	<0.001	-3.824	-3.550	0.866	<0.001	<0.001	0.579
Wrist Flexion Mean Vel	14.69±11.42	43.66 ± 29.76	26.57 ± 12.72	17.162	<0.001	-4.068	-2.989	1.708	<0.001	0.004	0.132
Wrist Deviation Mean Vel	9.85 ± 8.43	29.66 ± 20.89	24.31 ± 14.71	19.956	<0.001	-3.964	-3.971	0.605	<0.001	<0.001	0.817

Data are expressed as mean and standard deviation; post hoc P-values were calculated after applying the Connover correction; ROM,range-of-movement; Vel, velocity; AP, Antero-posterior; Vert, vetical; ML, Medio-lateral; HR, Harmonic-ratio; CoM, Center-of-mass

c) Kinematic Assessment of Levodopa Responsiveness: Various gait metrics exhibit distinct temporal responses to levodopa (LD)

In contrast to the observations made with the MDS-UPDRS, significant changes in angular metrics related to the upper limbs were detected as early as 20 minutes following LD intake through kinematic evaluation. This included metrics such as Arm Adduction, Wrist Flexion, Wrist Deviation Range of Motion (ROM), and Arm Flexion velocity. Furthermore, increases in Entropy in the vertical plane and variability in gait double support were also noted at the 20-minute mark (see **Figure 5.2** and **Table 5.3**).

By the 40-minute mark following LD intake, significant changes were primarily prominent in angular features related to the lower limbs. Notable improvements compared to the OFF state were observed in metrics such as Hip Flexion, Adduction and Rotation Range of Motion (ROM), as well as Hip Rotation velocities. Step and Stride Length also displayed significant improvements at this time point. Additionally, at 40 minutes, incremental improvements in upper-limb performance were observed across a broader spectrum of features.

At the 60-minute mark after LD intake, the observed changes in gait metrics were significant. Notably, Speed was significantly different from the OFF state, primarily due to increased Step/Stride Lengths, without significant changes in cadence or step/stride time. Additionally, significant changes were observed in the center-of-mass in the vertical axis. Angular metrics pertaining to the ankles, elbows, and wrist (including deviation and flexion ROM and mean velocity) also showed significant changes at this time point. Incremental improvements in both lower-limb and upper-limb performance were observed across a broader spectrum of features. Eighty minutes Post LD, swing Time exhibited significant changes only at the 80-minute mark after LD intake (**Figure 5.2** and **Table 5.3**). It's worth noting that inter-individual variability was notably high for all gait metrics at all evaluation moments and conditions, as evidenced by relatively high standard deviations.

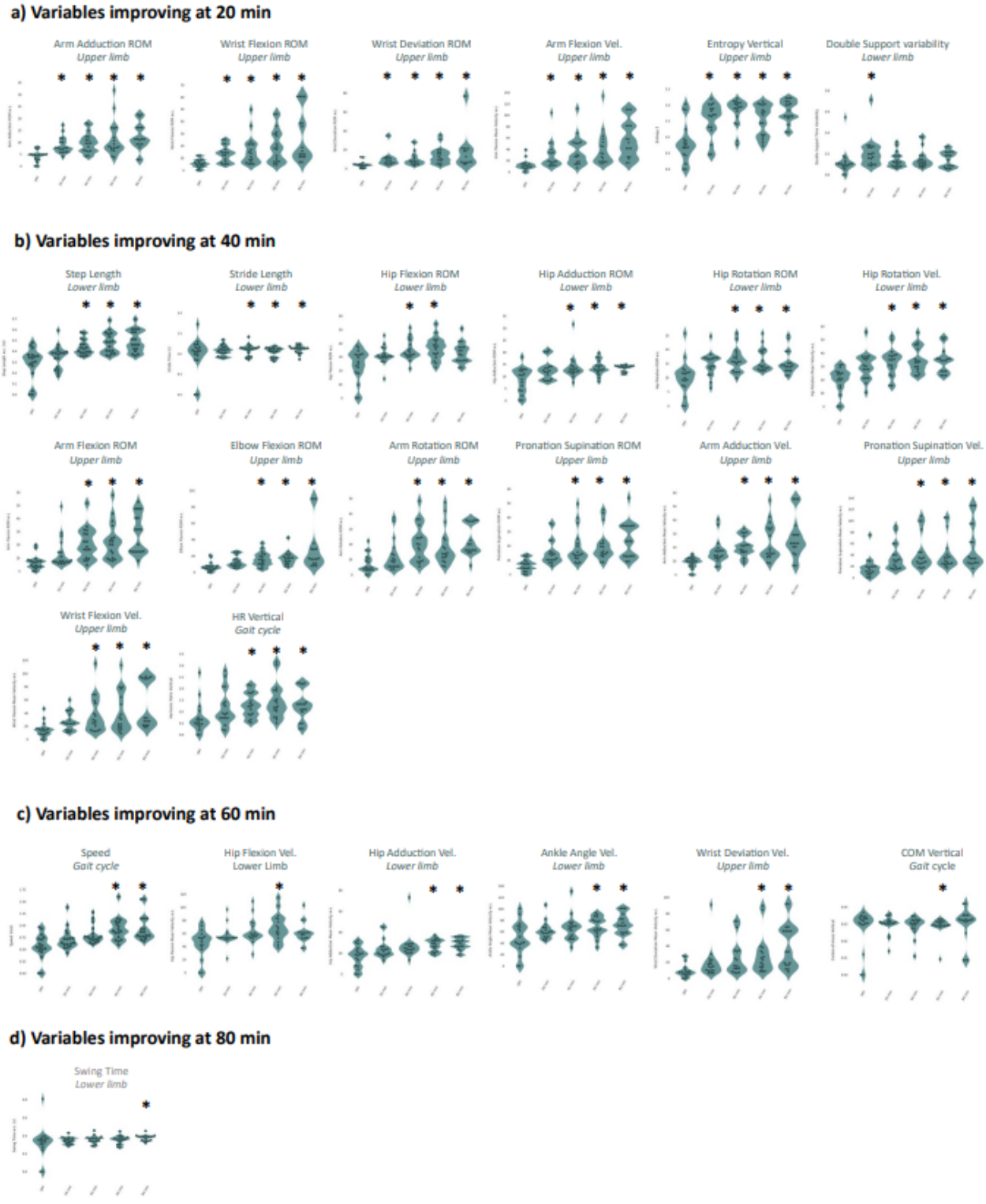


Figure 5.2 - Swarm-violin plots of the kinematic variables under study first presenting significant changes at 20 (a) 40 (b) 60 (c) and 80 (d) minutes post LD administration. Each group depicts a different time-point after the administration of a levodopa dose corresponding to 150% of the usual morning antiparkinsonian medication dose. From baseline up to 80 minutes post-administration. Data collected during free walking with the patients wearing 15 inertial measurement units used consisting of a tri-axial accelerometer, a gyroscope and a magnetometer as

detailed in the methods section. For variables evaluated in both sides of the body, the worst side was considered for analysis. Refer to the respective table for the complete statistical analysis thereof using the Friedman test with Conover posthoc correction for multiple comparisons. COM: Center of mass; ROM: Range of movement; Vel: Velocity. *p-value < 0.05 (vs left-most, OFF condition).

Table 5.3: Repeated measures analysis of MDS-UPDRS III and kinematic variables over time

Variable	Summary statistics (Mean ± SD)					Friedman Test Effect Size			Posthoc Conover (p-value)			
	OFF	20min	40min	60min	80min	Kendall's W Value	χ2	*p*-value	OFF-20min	OFF-40min	OFF-60min	OFF-80min
MDS UPDRS Part III												
Short MDS UPDRS III	21.71 ± 5.71	18.47 ± 3.12	11.41 ± 5.29	8.35 ± 4.51	21.71 ± 5.70	0.839	57.054	<0.001	0.286	<0.001	<0.001	<0.001
Axial Score	6.88 ± 3.46	4.82 ± 2.24	3.35 ± 1.87	2.24 ± 1.52	6.88 ± 3.46	0.657	44.722	<0.001	0.214	0.001	<0.001	<0.001
Item 3.1	1.94 ± 0.75	1.71 ± 0.69	1.53 ± 0.71	1.12 ± 0.86	1.94 ± 0.75	0.386	26.275	<0.001	0.237	0.037	0.001	<0.001
Item 3.3	3.29 ± 0.69	3.12 ± 0.70	2.24 ± 1.20	1.71 ± 1.10	1.12 ± 1.31	0.732	49.799	<0.001	0.416	0.006	<0.001	<0.001
Item 3.4	3.47 ± 0.51	3.29 ± 0.47	2.76 ± 1.03	2.29 ± 1.16	2.41 ± 0.87	0.466	31.731	<0.001	0.563	0.032	<0.001	<0.001
Item 3.8	3.12 ± 0.86	2.82 ± 1.01	1.47 ± 1.46	0.94 ± 1.25	1.06 ± 1.71	0.607	41.283	<0.001	0.519	0.003	<0.001	<0.001
Item 3.10	2.18 ± 0.95	1.53 ± 0.71	1.06 ± 0.66	0.53 ± 0.62	0.35 ± 0.61	0.629	42.816	<0.001	0.166	0.007	<0.001	<0.001
Item 3.11	1.29 ± 1.53	0.94 ± 1.43	0.29 ± 0.47	0.12 ± 0.49	0.24 ± 0.66	0.629	42.816	<0.001	0.182	0.002	0.001	0.002
Item 3.12	1.47 ± 1.62	0.65 ± 1.00	0.47 ± 0.80	0.29 ± 0.77	0.53 ± 1.01	0.181	12.333	0.015	0.099	0.049	0.015	0.049
Item 3.15	0.82 ± 1.01	0.94 ± 1.20	0.29 ± 0.77	0.35 ± 0.79	0.29 ± 0.69	0.349	23.729	<0.001	0.792	0.009	0.017	0.006
Item 3.17	1.18 ± 1.29	0.76 ± 0.97	0.18 ± 0.53	0.24 ± 0.75	0.24 ± 0.56	0.347	23.597	<0.001	0.271	0.002	0.002	0.002
Kinematic variable												
Speed (m/s)	0.56 ± 0.27	0.72 ± 0.22	0.81 ± 0.19	0.93 ± 0.24	0.95 ± 0.27	0.411	28.0	<0.001	0.749	0.211	0.007	0.001
Cadence (steps/min)	96.41 ± 40.38	112.47 ± 13.55	112.19 ± 15.38	116.10 ± 15.107	113.48 ± 12.52	0.035	2.447	0.654	1.000	1.00	0.720	1.000
Step Time (s)	0.49 ± 0.20	0.55 ± 0.06	0.54 ± 0.08	0.53 ± 0.07	0.54 ± 0.05	0.099	6.776	0.148	0.291	0.291	0.660	0.406
Step Length (m)	0.29 ± 0.15	0.35 ± 0.11	0.44 ± 0.07	0.48 ±0.10	0.49 ± 0.10	0.553	37.6	<0.001	0.831	0.016	<0.001	<0.001
Stride Time (s)	0.99 ±0.42	1.08 ± 0.13	1.10 ± 0.14	1.04 ± 0.12	1.11 ± 0.10	0.130	8.847	0.065	0.188	0.182	0.915	0.183
Stride Length (m)	0.60 ± 0.30	0.83 ± 0.16	0.90 ± 0.12	0.98 ± 0.15	0.96 ± 1.16	0.396	26.964	<0.001	0.423	0.013	<0.001	0.003
Step Width (m)	0.14 ± 0.07	0.18 ± 0.06	0.18 ± 0.06	0.17 ± 0.04	0.20 ± 0.07	0.050	3.435	0.488	1.000	0.564	0.564	0.564
Stance Time (s)	0.66 ± 0.27	0.74 ± 0.11	0.74 ± 0.10	0.69 ± 0.08	0.71 ±0.07	0.214	14.541	0.006	0.146	0.226	0.241	0.660
Swing Time (s)	0.32± 0.17	0.35 ± 0.04	0.36 ± 0.04	0.35 ± 0.05	0.38 ± 0.03	0.196	13.317	0.009	0.290	0.183	0.183	0.008
Double Support Time (s)	0.34 ± 0.17	0.40 ± 0.08	0.38 ± 0.09	0.34 ± 0.06	0.34 ± 0.06	0.157	10.682	0.030	0.281	1.000	0.228	0.507
Single Support Time (s)	0.30 ± 0.16	0.34 ± 0.04	0.36 ± 0.03	0.35 ± 0.04	0.36 ± 0.05	0.129	8.752	0.07	0.346	0.082	0.346	0.082
Hip Flexion ROM	24.07 ± 11.66	31.20 ± 6.57	34.94 ± 7.52	36.38 ± 8.21	32.80 ± 7.51	0.296	20.094	<0.001	0.749	0.042	0.004	0.116
Hip Adduction ROM	8.59 ± 5.16	12.76 ± 4.20	13.72 ± 5.14	13.56 ± 3.08	13.38 ± 1.35	0.246	16.705	0.002	0.069	0.041	0.005	0.005
Hip Rotation ROM	10.00 ± 6.11	14.87 ± 4.24	16.21 ± 4.22	16.23 ± 4.08	15.43 ± 4.15	0.266	18.070	0.001	0.089	0.005	0.005	0.007
Knee Angle ROM	40.84 ± 24.53	47.58 ± 10.45	44.92 ± 13.62	50.18 ± 12.97	47.96 ± 10.14	0.107	7.294	0.121	0.405	0.366	0.125	0.405
Ankle Angle ROM	24.23 ± 15. 95	32.26 ± 5.93	33.30 ± 11.45	34.05 ± 9.22	33.41 ± 9.43	0.111	7.5764	0.108	0.153	0.346	0.153	0.153
Hip Flexion Mean Vel	44.77 ± 21.69	56.22 ± 15.05	62.99 ± 18.64	69.11 ± 20.45	60.84 ± 15.74	0.298	20.235	<0.001	0.915018	0.105	0.003	0.114
Hip Adduction Mean Vel	16.73 ± 10.05	24.37 ± 9.17	26.95 ± 12.34	27.71 ± 5.92	28.76 ± 5.72	0.351	23.858	<0.001	0.376189	0.072	0.001	0.004
Hip Rotation Mean Vel	19.79 ± 9.57	30.09 ± 10.36	33.49 ± 10.25	34.83 ± 9.66	34.66 ± 9.56	0.345	23.482	<0.001	0.053742	<0.001	<0.001	0.002
Knee Angle Mean Vel.	79.29 ± 38.73	102.19 ± 25.23	89.76 ± 31.36	111.02 ± 33.30	101.26 ± 27.21	0.119	8.141	0.086	0.915	0.915	0.119	0.912
Ankle Angle Mean Vel	48.87 ± 28.43	62.05 ± 15.16	66.46 ± 21.99	69.09 ± 17.23	71.88 ± 19.97	0.172	11.670	0.019	0.438	0.183	0.047	0.047
Arm Flexion ROM	6.63 ± 5.37	13.83 ± 11.76	20.98 ± 12.15	22.57 ± 14.07	28.71 ± 14.96	0.562	38.211	<0.001	0.3203	0.002	<0.001	<0.001
Arm Adduction ROM	4.19 ± 2.33	8.68 ± 3.51	9.87 ± 4.17	11.57 ± 7.40	12.34 ± 5.75	0.291	19.811	<0.001	0.023	0.023	0.010	<0.001
Elbow Flexion ROM	7.00 ± 5.68	13.21 ± 7.02	16.33 ± 8.77	17.39 ± 8.32	30.49 ± 29.50	0.365	24.847	<0.001	0.226	0.009	0.009	<0.001
Arm Rotation ROM	7.34 ± 6.20	12.56 ± 10.47	20.68 ± 12.20	18.38 ± 12.32	23.01 ± 10.09	0.451	30.682	<0.001	0.161	<0.001	0.003	<0.001

Data are expressed as mean standard deviation; post hoc P-values were calculated after applying the Connover correction; ROM; Range-of-Movement; Vel, Velocity; AP, Antero-Posterior; Vert; Vertical; ML, Medio-lateral; HR, Harmonic-ratio; CoM, Center-of-Mass

d) Selective Motor Response to LD

While LD administration significantly rescued all pace-domain features, it is noteworthy that most rhythmicity features did not exhibit significant modulation; specifically, Cadence and Stride/Step Time remained unchanged with LD. Additionally, the range of motion (ROM) and velocity of most upper- and lower-limb features displayed significant improvements after LD intake, while variables related to asymmetry, variability, and postural control showed no significant changes. Furthermore, most gait dynamics, particularly non-linear features, did not significantly change in response to dopaminergic therapy. An exception to this trend was observed in alterations in features along the vertical axis (**Figure 5.3, Figure 5.4, Table 5.3 and 5.4)**

Table 5.4: Kinematic variables in OFF, Best-ON and Healthy Controls

Variable	Mean ± SD			Kruskal–Wallis test		Posthoc Dunn's Test					
						Z-score			Bonferroni corrected p-value		
	OFF	Best-ON	Healthy-Controls	H statistic	p-value	OFF-Best ON	OFF-Control	Best ON - Control	OFF-Best ON	OFF-Control	Best ON - Control
Speed (m/s)	0.56 ± 0.27	0.93 ± 0.24	0.90 ± 0.18	21.841	<0.001	-3.954	-4.316	0.250	<0.001	<0.001	1.203
Cadence (steps/min)	96.41 ± 40.38	116.38 ± 14.72	108.12±11.19	3.091	0.213	-1.613	-0.360	1.502	0.160	1.077	0.199
Step Time (s)	0.49 ± 0.20	0.53 ± 0.06	0.56 ± 0.06	2.991	0.2241	0.017	-1.402	-1.422	1.479	0.241	0.232
Step Length (m)	0.29 ± 0.15	0.49 ± 0.10	0.49 ± 0.06	29.439	<0.001	-4.249	-5.208	-0.300	<0.001	<0.001	1.146
Stride Time (s)	0.99 ± 0.42	1.05 ± 0.12	1.12 ± 0.12	2.738	0.2543	0.442	-1.046	-1.557	0.987	0.443	0.179
Stride Length (m)	0.60 ± 0.30	0.99 ± 0.15	1.02 ± 0.10	30.848	<0.001	-3.816	-5.498	-1.091	<0.001	<0.001	0.412
Step Width (m)	0.14 ± 0.07	0.18 ± 0.05	0.16 ± 0.01	0.865	0.6487	-0.797	-0.851	0.070	0.637	0.591	1.416
Stance Time (s)	0.66 ± 0.27	0.69 ± 0.08	0.47 ± 0.14	22.538	<0.001	-0.069	3.836	3.916	1.417	<0.001	<0.001
Swing Time (s)	0.33 ± 0.17	0.36 ± 0.05	0.37 ± 0.03	6.314	0.0426	-1.153	-2.489	-1.157	0.373	0.019	0.371
Double Support Time (s)	0.37 ± 0.17	0.34 ± 0.05	0.37 ± 0.06	4.496	0.1056	1.873	0.270	-1.893	0.092	1.180	0.087
Single Support Time (s)	0.30 ± 0.13	0.35 ± 0.04	0.37 ± 0.04	9.222	0.0099	-1.344	-2.999	-1.447	0.268	0.004	0.221
Hip Flexion ROM	24.07±11.66	36.00 ±8.27	38.11 ± 4.47	23.346	<0.001	-3.088	-4.817	-1.252	0.003	<0.001	0.316
Hip Adduction ROM	8.59 ± 5.16	13.01 ±2.39	16.45 ± 4.98	22.143	<0.001	-2.203	-4.667	-2.123	0.041	<0.001	0.050
Hip Rotation ROM	10.00±6.11	16.41 ±3.63	14.82 ± 2.89	19.614	<0.001	-4.146	-3.665	1.122	<0.001	<0.001	0.393
Knee Angle ROM	40.84±24.53	50.33±13.31	57.80 ± 6.47	17.212	<0.001	-2.029	-4.126	-1.783	0.063	<0.001	0.112
Ankle Angle ROM	24.23±15.94	34.33 ±9.35	34.81 ± 6.86	8.018	0.018	-2.029	-2.784	-0.441	0.063	0.008	0.989
Hip Flexion Mean Vel	44.77±21.69	68.76±20.19	68.11 ± 12.76	16.105	<0.001	-3.088	-3.876	-0.311	0.003	<0.001	1.134
Hip Adduction Mean Vel	16.73±10.05	26.81 ± 5.45	29.93 ± 8.82	16.448	<0.001	-2.723	-4.026	-0.881	0.009	<0.001	0.567
Hip Rotation Mean Vel	19.79 ± 9.57	35.82 ± 8.52	31.10 ± 7.15	24.839	<0.001	-4.866	-3.690	1.929	<0.001	<0.001	0.080
Knee Angle Mean Vel	79.29±38.73	111.13±32.87	118.17±18.53	13.676	0.001	-2.376	-3.685	-0.941	0.026	<0.001	0.519
Ankle Angle Mean Vel	48.87±28.43	69.95 ±17.78	73.50 ± 16.19	11.588	0.003	-2.281	-3.383	-0.746	0.033	0.001	0.683
Arm Flexion ROM	6.63 ± 5.37	24.04 ± 13.36	16.37 ± 5.58	26.121	<0.001	-4.831	-4.151	1.427	<0.001	<0.001	0.230
Arm Adduction ROM	4.19 ± 2.33	10.66 ± 5.17	7.50 ± 2.31	22.665	<0.001	-4.666	-3.465	1.923	<0.001	<0.001	0.082
Elbow Flexion ROM	7.00 ± 5.68	19.30 ± 9.64	20.49 ± 8.77	26.476	<0.001	-3.885	-4.997	-0.510	<0.001	<0.001	0.914
Arm Rotation ROM	7.34 ± 6.20	19.28 ± 12.07	18.93 ± 7.20	22.249	<0.001	-3.487	-4.607	-0.580	<0.001	<0.001	0.842
Pronation Supination ROM	6.47 ± 4.34	20.26 ± 11.45	16.56 ± 8.14	27.320	<0.001	-4.787	-4.477	1.051	<0.001	<0.001	0.439
Wrist Flexion ROM	5.59 ± 3.56	29.22 ± 13.24	12.06 ± 5.05	24.098	<0.001	-4.727	-3.811	1.647	<0.001	<0.001	0.149
Wrist Deviation ROM	4.17 ± 3.39	14.05 ± 8.31	11.55 ± 6.90	25.536	<0.001	-4.527	-4.446	0.781	<0.001	<0.001	0.652
Arm Flexion Mean Vel	12.33 ± 9.48	44.46 ± 29.84	29.55 ± 11.17	26.966	<0.001	-4.917	-4.201	1.477	<0.001	<0.001	0.209
Arm Adduction Mean Vel	8.55 ± 4.24	20.88 ± 9.68	16.35 ± 6.77	20.566	<0.001	-4.302	-3.655	1.312	<0.001	<0.001	0.284
Arm Rotation Mean Vel	14.50±10.34	40.59 ± 26.31	36.09 ± 16.16	22.855	<0.001	-3.859	-4.532	-0.075	<0.001	<0.001	1.410
Elbow Flexion Mean Vel	13.63 ± 8.96	42.62 ± 25.67	25.84 ± 16.32	18.511	<0.001	-4.302	-2.532	2.433	<0.001	0.016	0.022
Pronation Supination Mean Vel	17.25±17.32	43.20 ± 30.27	34.45 ± 18.03	17.331	<0.001	-3.824	-3.550	0.866	<0.001	<0.001	0.579
Wrist Flexion Mean Vel	14.69±11.42	43.66 ± 29.76	26.57 ± 12.72	17.162	<0.001	-4.068	-2.989	1.708	<0.001	0.004	0.132
Wrist Deviation Mean Vel	9.85 ± 8.43	29.66 ± 20.89	24.31 ± 14.71	19.956	<0.001	-3.964	-3.971	0.605	<0.001	<0.001	0.817

Data are expressed as mean standard deviation; post hoc P-values were calculated after applying the Bonferroni correction ROM; Range-of-Movement; Vel, Velocity; AP, Antero-Posterior; Vert; Vertical; ML, Medio-lateral; HR, Harmonic-ratio; CoM, Center-of-Mass

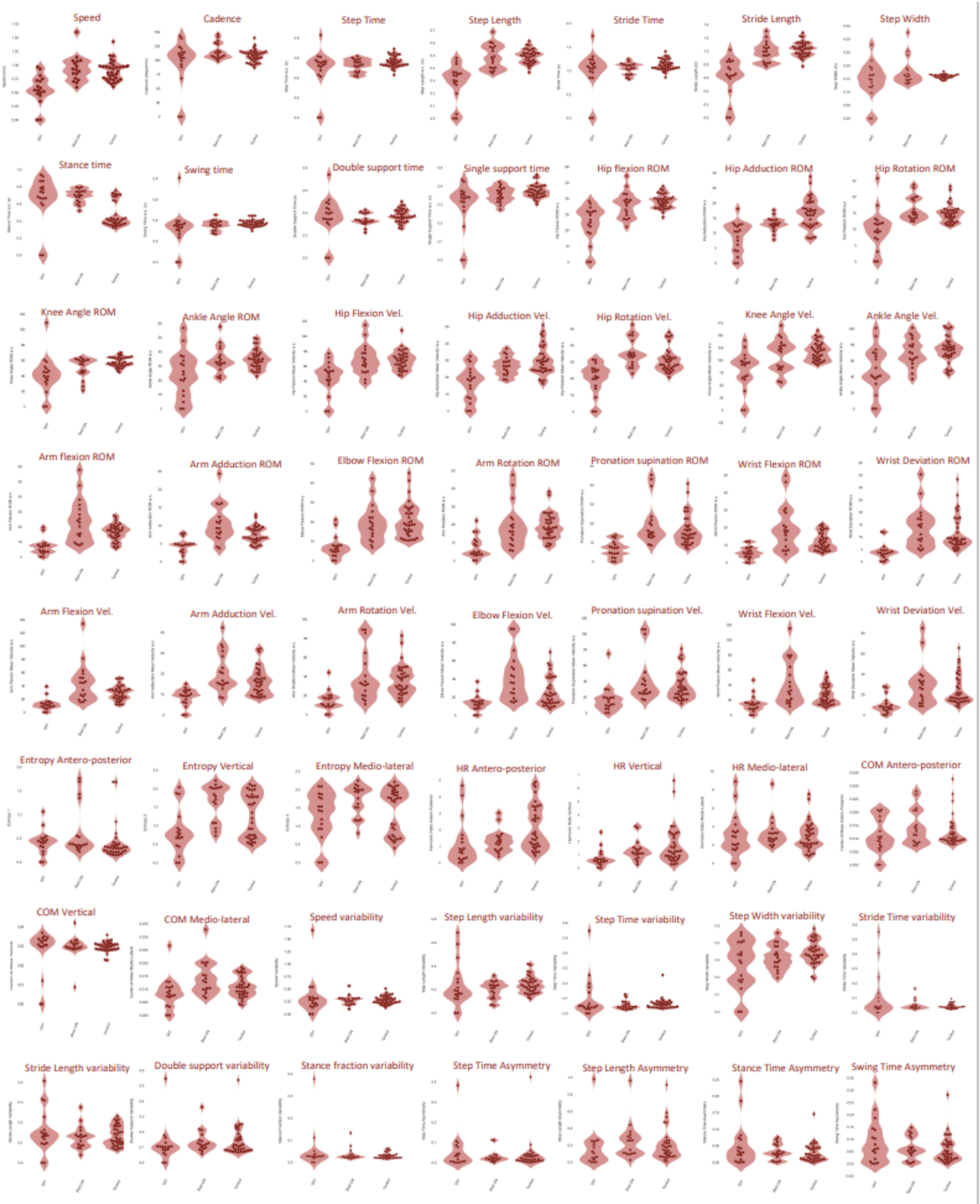


Figure 5.3: Swarm-violin plots of the kinematic variables under study upon levodopa administration for non-PD controls, and PD subjects in their OFF and Best ON states. Data collected during free walking with the patients wearing 15 inertial measurement units used consisting of a tri-axial accelerometer, a gyroscope and a magnetometer as detailed in the methods section. For variables evaluated in both sides of the body, the worst side was considered for analysis. For variables evaluated in both sides of the body, the worst side was considered

for analysis. Refer to the respective table for the complete statistical analysis thereof using the Kruskal–Wallis test with Dunn's posthoc correction for multiple comparisons. COM: Center of mass; ROM: Range of movement; Vel: Velocity. *p-value < 0.05 (vs left-most, OFF condition).

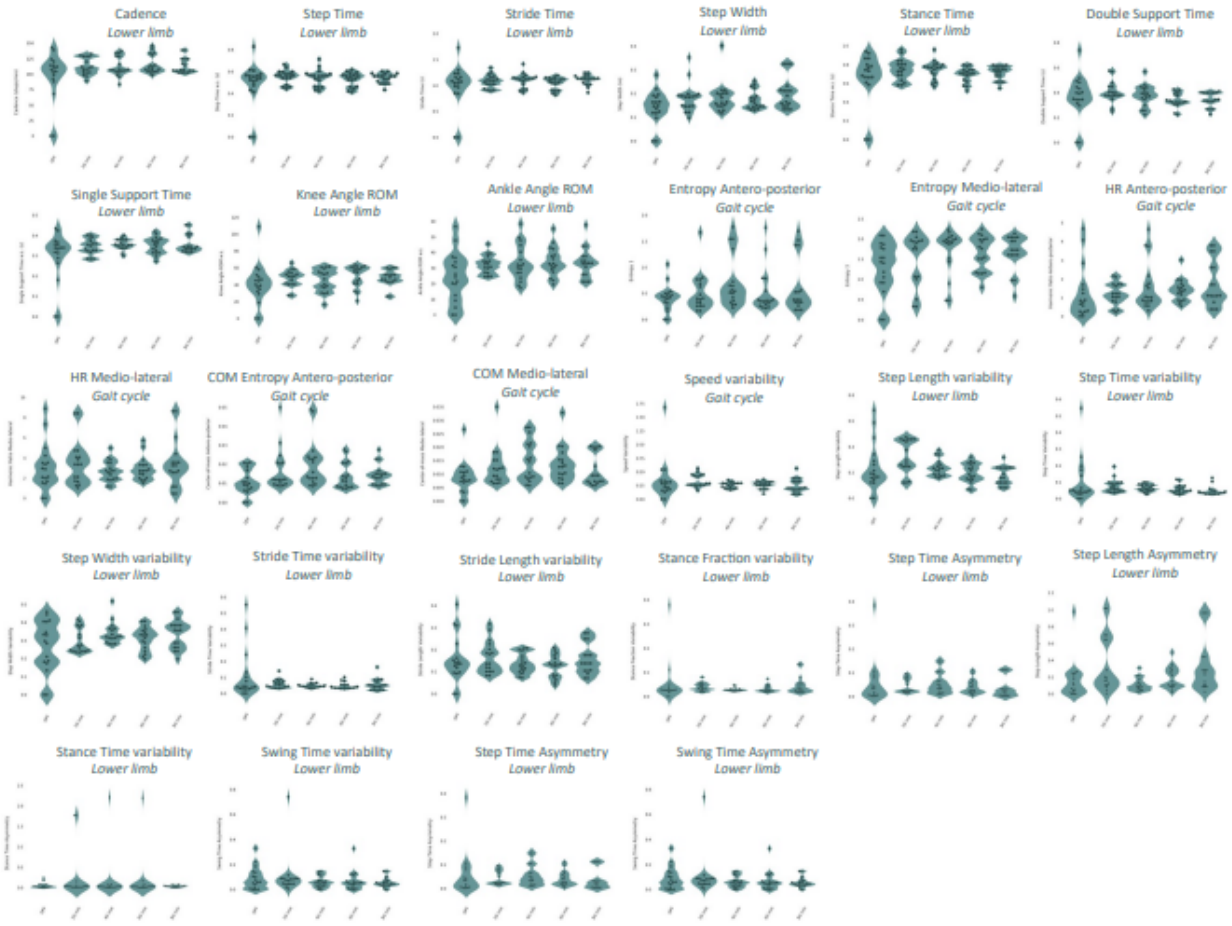


Figure 5.4: Swarm-violin plots of the kinematic variables that failed to significantly change from baseline upon LD administration. Each group depicts a different time-point after the administration of a levodopa dose corresponding to 150% of the usual morning antiparkinsonian medication dose. From baseline up to 80 minutes post-administration. Data collected during free walking with the patients wearing 15 inertial measurement units used consisting of a tri-axial accelerometer, a gyroscope, and a magnetometer as detailed in the methods section. For variables evaluated in both sides of the bodyt, the worst side was considered for analysis. . For variables evaluated in both sides of the body, the worst side was considered for analysis. Refer to the respective table for the complete statistical analysis thereof using the Friedman test with Conover posthoc correction for multiple comparisons. COM: Center of mass; ROM: Range of movement; Vel: Velocity.

e) Most gait features can be rescued with LD to non-PD levels

When compared to matched healthy controls (HC), PD patients in their OFF state exhibited significantly slower gait with shorter steps, reduced range of motion (ROM), and decreased movement velocity for both upper and lower limbs. They also had lower harmonic ratios (**Figure 5.3** and **Table 5.4**).

Following the administration of a supra-threshold LD dose, the gait of PD patients in their "Best-ON" state was not significantly different from that of controls in most spatiotemporal and angular features. However, some differences persisted with stance time and antero-posterior remaining significantly higher among PD patients in the "Best-ON" state compared to those of HC **Figure 5.3** and **Table 5.4**). Additionally, some variables exhibited a supra-physiological response in PD patients. Higher mean velocity on Elbow Flexion and higher values of entropy on the vertical axis were observed in PD Best-ON patients when compared to HC (**Figure 5.3** and **Table 5.4**). Notably, a positive and significant correlation between the AIMS score and most upper limb-related metrics was observed in the Best-ON state (**Table 5.5**).

Table 5.5 – Correlation between AIMS scores and kinematic variables at the Best-On state

	Aims Score Best ON state	p-value
Speed	0,310	0,225
Cadence	0,349	0,170
Step_Time	-0,292	0,256
Step_Length	0,102	0,696
Stride_Time	-0,354	0,163
Stride_Length	0,069	0,789
Step_Width	0,153	0,557
Stance_Fraction	-0,186	0,474
Stance Time	-0,386	0,125
Swing Fraction	0,186	0,474
Swing_Time	-0,261	0,311
Double_Support	0,0586	0,824
Double_Support	-0,167	0,521
Double_Support	-0,324	0,203
Double Support Time	-0,179	0,492
Single Support	-0,219	0,398
Single Support Time	-0,514	0,035
Hip flexion ROM	0,276	0,284
Hip Adduction ROM	0,188	0,470
Hip Rotation ROM	0,634	0,006
Knee Angle ROM	0,046	0,859
Ankle Angle ROM	-0,458	0,064
Hip Flexion Mean Vel	0,304	0,236
Hip Adduction Mean Vel	0,189	0,466
Hip Rotation Mean Vel	0,554	0,021
Knee Angle Mean Vel	0,162	0,535
Ankle angle Mean Vel	-0,147	0,572
Arm Flex ROM	0,445	0,074
Arm Add ROM	0,460	0,063
Elbow Flex ROM	0,367	0,147
Arm Rot ROM	0,421	0,092
Pro Sup ROM	0,7485	<0.001
Wrist Flex ROM	0,667	0,003
Wrist Dev ROM	0,591	0,012
Arm Flex Mean Vel	0,477	0,05
Arm Add Mean Vel	0,558	0,02
Arm Rot Mean Vel	0,566	0,02
Elbow Flex Mean Vel	0,238	0,356
Pro Sup Mean Vel	0,700	0,002
Wrist Flex Mean Vel	0,698	0,002
Wrist Dev Mean Vel	0,612	0,009
Entropy AP	0,017	0,948
Entropy Vert	-0,413	0,099

AIMS, Abnormal Involuntary Movement Scale; AP, antero-posterior; ML, medio-lateral, Vert, Vertical; HR, Harmonic ratio, CoM, Center-of-Mass; ROM, Range-of-Movement; Mean Vel, Mean Velocity; CV, variability

Discussion

This study offers a comprehensive insight into the temporal dynamics of motor responsiveness to LD in a cohort of advanced PD patients, by utilizing both 3D motion analysis and the gold-standard MDS-UPDRS. Notably, the results indicate that the IMUs effectively detected significant motor modulation earlier than the MDS-UPDRS. Additionally, the study highlights a quicker response of the upper limbs to LD.

Both wearable sensors and the MDS-UPDRS successfully detected changes during the LD challenge

IMU-based gait evaluation was capable of detecting significant changes earlier than clinical assessment alone. This approach also illustrated how levodopa (LD) responsiveness evolved across each 20-minute block, as demonstrated in **Figure 5.5**. It's crucial to clarify that this observation is not intended to imply any degree of superiority over clinical assessment. Instead, the data presented here aims to emphasize how clinical data can be significantly complemented by alternative and more objective tools.

Previous research employing various wearable devices has demonstrated their capability to objectively assess motor symptoms, motor fluctuations, and treatment responses, both in controlled laboratory settings and real-world ambulatory environments. [416]For instance, a single wrist-worn sensor, such as the Parkinson's Kinetigraph, has been found to detect bradykinesia and dyskinesias with a high degree of accuracy, enabling the monitoring of motor fluctuations and contributing to therapy management. [417–420] It's worth noting that in this approach, gait and freezing could not be effectively assessed. T

he PD monitor® system overcame this limitation by employing five wearable devices strategically distributed across the trunk and limbs. This innovative system has demonstrated its ability to detect motor symptoms, including gait alterations and freezing of gait (FOG), while also facilitating the monitoring of motor fluctuations.[421] Our study further supports previous findings by illustrating the utility of wearable devices for motor

assessment. It effectively captures the modulation of motor symptoms by medication, reaffirming their value in clinical research and practice.

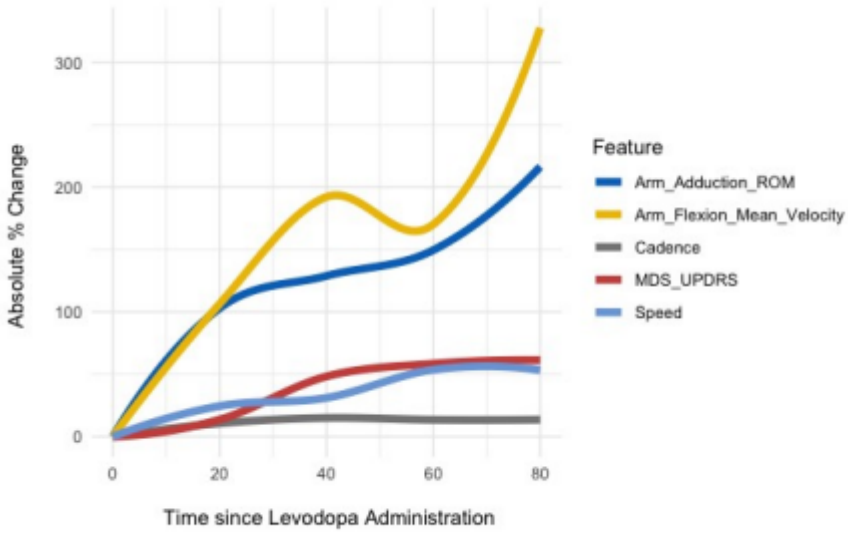


Figure 5.5

Local weighted regression fit of absolute percentage change of over time for the MDS-UPDRS III and example kinematic variables from 20 to 80 min post levodopa administration corresponding to 150% of the usual morning antiparkinsonian medication dose. Data collected during free walking with the patients wearing 15 inertial measurement units used consisting of a tri-axial accelerometer, a gyroscope, and a magnetometer as detailed in the methods section. Summary smoothed fitting, not intended for modeling purposes.

Motor improvement can be detected as early as 20 min using wearable sensors

In this study, motor changes were observed as early as 20 minutes after levodopa (LD) administration when utilizing kinematic-driven metrics. This stands in contrast to previous studies that relied solely on clinical assessment, which typically required a lag period of 30-40 minutes to detect significant motor changes.[422,423] We believe that the delay noted in previous studies may be attributed to the reliance on clinical assessment. In our cohort, a similar lag period of 40 minutes was observed when employing the MDS-UPDRS III.

At the 20-minute mark, the improvement was predominantly observed in proximal upper limb movements, such as amplitude and speed. It's important to note that the MDS-UPDRS items assessing upper limb bradykinesia primarily focus on distal upper limb movements, such as finger tapping and hand movements, which do not fully encompass proximal movements. This discrepancy between kinematic assessment, encompassing both proximal and distal aspects and the exclusive evaluation of distal movements offered by the MDS-UPDRS, may partially account for the differing results observed using clinical and kinematic evaluation.

Given the critical role of the MDS-UPDRS (patient selection for DBS[321], new drug efficacy assessment,[424] disease progression monitoring), its low reliability both within- and inter-subjects is still a limitation where significant room for improvement exists.[425] In this context, the significance of complementary, objective tools that are not reliant on raters becomes evident. Such tools play a crucial role in enhancing both accuracy and broadening access, contributing to democratization in the assessment of medical conditions.

Upper limbs improve first, probably reflecting topographical organization on the striatum

A recent study has shed light on the onset of motor symptoms in Parkinson's disease (PD). It suggests that these symptoms tend to manifest in the upper limbs initially. This may be attributed to either a preferential loss of nigrostriatal dopaminergic terminals in the upper limb area or a lower threshold for the upper limbs to exhibit symptoms in response to dopaminergic depletion.[426] Higher specialization and precision are needed for hand movement,[427,428] which implies not only a larger homunculus representation at the putaminal level, but also a higher dependence for DA.[426,429,430] It is conceivable that the greater degree of neuronal connectivity and dopaminergic activity in the upper limbs could result in heightened levels of glutamatergic transmission or increased neuroinflammation and neurotoxicity. These factors may provide a plausible explanation for the observed "upper-limb first" phenomenon in the onset of motor symptoms.[429–432]

The observed response during a Levodopa Challenge Test (LCT) primarily reflects the Short-Duration Response (SDR) to levodopa. This phenomenon is characterized by its abrupt onset and the substantial magnitude of the response.[113,433,434] It is established that as dopamine levels decline and the severity of degeneration increases, the magnitude of the SDR also increases. This phenomenon becomes a significant marker of disease severity in Parkinson's disease.[433,434] Accordingly, a significant correlation between symptom severity and motor response latency, magnitude, and duration has been reported.[113] Likewise, greater and earlier motor responses occur for the corresponding most affected side.[423] As such, it is possible for the higher degree of denervation in the upper limb area to explain the earlier and potentially supraphysiologic response of upper limbs to LD.

This apparently higher sensitivity of the upper limbs to LD modulation, with high magnitude of change upon treatment (Figure 4), may make them a preferential target to monitor motor response to LD and, consequently, motor fluctuations. Motor fluctuations are typically evaluated based on clinical history and self-reports, both of which are associated with significant and well-known limitations. The use of wearable devices, enabling objective and semi-automated tracking of motor transitions between medication states, presents an opportunity for enhancing the routine assessment of motor fluctuations. [416]

However, it should be noted, that SDR is a function of disease severity, becoming particularly marked in advanced, fluctuating PD-patients, as the ones represented in our cohort. Accordingly, PD patients in early or late-disease stages, where dopamine sensitivity is known to be decreased [413,435],may have a more blunted response to LD with consequently less marked transitions between medication states.

Not all gait metrics change with LD

Gait features related to rhythmicity, variability, asymmetry, smoothness, and dynamic gait stability did not exhibit significant modulation in response to levodopa (LD), as depicted in **Supplementary Figure S1**. This limitation is particularly relevant as it underscores issues that should be addressed, especially considering the increasing

association of these features with a higher risk of falls and freezing events in both the elderly and Parkinson's disease (PD) populations.[152,159,160,436–438] As such, interventions capable of addressing these ought to be invested in. Here, circuits other than the dopaminergic ones have been pinpointed as responsible for axial symptoms,[439] with acetylcholine and norepinephrine likely involved in balance and gait control.[437,439–441] With pace metrics being associated with the classical cardinal LD-responsive signs of PD,[442] such discrepancies are likely to reflect a differential involvement of brain networks across movement dimensions, with some more dopaminergic and responsive to LD and others are non-dopaminergic and non-responsive to LD.[440,441]

Understanding the effect of DBS on these non-responsive domains may contribute to a better understanding of the physiopathology of gait dysfunction.

PD gait can only be partially rescued to a "normal" phenotype

In this study, the gait of PD patients in their OFF state exhibited characteristics such as slower pace, shorter steps and strides, longer stance times, and less time spent in a single support phase when compared to HC. Additionally, shorter range of motion (ROM) and slower movement velocity were noted for most upper and lower limb features in PD patients, aligning with findings from prior studies.[150,151,403,406] PD patients were observed to have lower harmonic ratios in both the vertical and antero-posterior planes. This observation may suggest a loss of gait smoothness, which could potentially increase the risk of falls in this population. [159]

LD was found to bring about improvements in most spatiotemporal and angular features of gait that were significantly different between PD patients in their OFF state and healthy controls HC. This finding contrasts with previous studies, and it is likely attributed to the utilization of a supra-threshold LD dose in this study, which may have been lacking in the later studies.[152,403,406]

In this study, a supra-physiologic response was observed for specific features, particularly those related to the upper arms. This observation leads us to believe that this supra-physiologic response likely reflects the presence of dyskinesia, which further

reinforces the concept of a heightened susceptibility of the upper limbs to dopamine denervation and replenishment.[426]

While most individual gait features were not significantly different between HC and PD patients in their Best-ON state, most gait features of PD patients remained different from what's observed among HC. In general, PD patients in their Best-ON state tended to reach an "intermediate" state between their OFF state and that of the matched HC. Such alterations reflect that the PD gait deficits can indeed be rescued at many different levels (to a variable extent) but that a PD patient, even with a clinical score similar to that of a matched HC still presents detectable deficits at multiple levels. This suggests that PD patients may still face challenges in effectively coordinating various gait domains, possibly indicative of alterations in non-dopaminergic pathways.[440,441]

Study Limitations

The limited size of the described cohort together with the substantial interpatient variability certainly limits the statistical power of the study, leaving ample room for discovery in future with larger studies on similar populations. Future studies should benefit from not only larger cohorts, but also from repeated sampling for the same patient (i.e., repeating the evaluation a multiple point in time). Furthermore, it is important to note that the presented cohort consists of a highly specific subset of PD patients. We deliberately selected this particular group due to their typically more pronounced motor response to LD. Nevertheless, investigating the response to LD in different populations, including early and late-stage PD patients, could yield valuable insights into the progression of dopaminergic sensitivity over the course of the disease.

Conclusion

Gait features exhibit varying degrees of responsiveness to LD, with the upper limbs demonstrating earlier response compared to the lower limbs, as shown in **Figure 5.5**. This discrepancy may arise from differing levels of degeneration within the topographic striatum organization or variations in dopamine depletion. Wearable sensor-based 3D kinematics is adept at detecting responses to LD ahead of the MDS-UPDRS, offering a level of granularity that cannot be attained with the MDS-UPDRS alone. Consequently, IMUs provide a higher level of detail for monitoring disease progression, gauging therapy responsiveness, and identifying potential therapeutic targets.

Chapter VI: The effect of Levodopa and Stimulation on post-surgery Freezing of Gait in STN-DBS Parkinson's Disease patients: a clinical and kinematic analysis

In this chapter, the research work was developed under **Aim 3**, to identify the role of stimulation and LD in freezing of gait in PD STN-DBS patients, and the **Aim 2**, exploring the role of objective gait analysis using 3D-kinematics for gait and FOG assessment in STN-DBS PD patients.

Background

Freezing of gait (FOG) is characterized by a sudden and transient reduction in the forward progression of the feet despite the intention to walk[122,172,192,194,443]. This prevalent and debilitating motor symptom in Parkinson's disease (PD) significantly impairs the quality of life, elevates fall risk, and contributes to increased disability. [444]

While subthalamic nucleus deep brain stimulation (STN-DBS) has demonstrated noteworthy benefits in improving appendicular symptoms, its impact on axial symptoms, including FOG, appears to diminish over the long-term follow-up. [127,303,327,336]Regarding FOG, despite an initial benefit observed in the first years post-surgery, with stimulation effectively mimicking the preoperative effects of dopaminergic medication, this positive effect progressively diminishes. [127,301–303,306,327,336] Consequently, FOG emerges in the best functional state (Medication ON and Stimulation ON), despite the initial pre-surgery good response to dopaminergic medication.[339,445,446]

The etiology of FOG emerging in the best-functional state after surgery remains unclear. It has been hypothesized that this phenomenon reflects disease progression with affection of nondopaminergic pathways, leading to a loss of levodopa (LD) and stimulation responses.[127,447] Alternatively, suboptimal targeting[448–450], stimulation-induced effects[339,341], structural brain lesions due to electrode placement, or inadequate stimulation settings or LD dose, have also been proposed as mechanisms for post-surgery best-functional state FOG.[127]

Other stimulation paradigms, including Low-frequency stimulation (LFS), have been suggested as a potential strategy to ameliorate FOG[339–343,451], but the use of patient-reported questionnaires limit the proper assessment of FOG. [347,452,453] Given the paroxysmal nature and the different phenotypes of FOG, subjective metrics may not be sufficient to capture all phenomenological complexity and particularly differential modulation by therapy.[132,133,208] To address these challenges, integrating unbiased assessment tools (kinematic analysis and wearable sensors) for gait analysis becomes crucial.[208]

In the current study we used clinical and inertial-sensor based tools to study FOG and FOG response to stimulation and medication, in advanced PD patients submitted to STN-DBS. We focused our study on patients that present FOG in the best functional state (Medication ON/Stimulation ON), a major clinical problem in DBS clinics. We expanded our main objective by performing multiple assessments to assess individual responses of FOG to medication, high-frequency (130 Hz) and energy matched low-frequency (60 Hz) stimulation and developing a machine-learning powered classifier of FOG that allowed us to identify kinematic variables related to FOG across conditions, potentially informative in future studies.

Methods

Objective and study design

A cross-sectional and unblinded study assessing the effect of levodopa and stimulation in FOG emerging after STN-DBS, in five different experimental conditions (see below);

Primary Outcome: the difference in the number of FOG episodes between Med OFF/Stim OFF and Med ON/Stim ON 130 Hz conditions.

Study Population

We reviewed the electronical medical records off all PD patients operated at our center since the beginning of the DBS program (2006), to identify those with Med On/Stim ON FOG. The presence of FOG was defined by a score ≥ 2 on item 3.11 (freezing) of the MDS-UPDRS part III on the Med ON/Stim ON state. FOG was considered only after 6 months into the post-surgical period, as we considered 6 months the time required for treatment stabilization. We called into clinic for assessment those still alive and available for evaluation. Patients unable to walk without ambulatory aids in the Med ON/Stim ON state, and those with severe osteo-articular or other non-neurological issues affecting gait, were excluded. All patients had been selected for surgery according to the CAPSIT-PD protocol, and none had levodopa-resistant axial signs before surgery during best ON state. DBS surgery followed standard stereotactic techniques, and postoperative neuroimaging

confirmed lead position. DBS programming parameters were optimized regularly by a movement disorders specialist.

Clinical Evaluation

Clinical evaluations were conducted under five different conditions following a pre-determined order: 1) Medication OFF/Stimulation ON (Med OFF/Stim ON),, 2) Medication OFF/Stimulation OFF (Med OFF/Stim OFF) 3) Medication ON/Stimulation OFF (Med ON/ Stim OFF), 4) Medication ON/Stimulation ON at 130 Hz High-frequency stimulation (Med ON/Stim ON HFS), and 5) Medication ON/Stimulation ON at 60 Hz Low-frequency stimulation (Med ON/Stim ON LFS).

The full assessment lasted approximately 4 hours in a single morning session. Patients were evaluated on the "practical OFF drug" condition after 12 hours of medication withdrawal. A levodopa challenge test (LCT) was performed using the same dose of LD as used on the pre-surgery LCT. The Stim ON condition used the stimulation settings that had shown the best clinical results over the previous 6 months for each patient, while we adjusted the total energy delivered when testing LFS according to the total electrical energy delivered (TEED) formula: TEED (1 second) = voltage^2 X frequency x pulse width/impedance).[309,339]. No patient was on LFS at the time of evaluation. A 30-minute interval was maintained between frequency changes and after stimulation arrest.

Motor evaluations using the MDS-UPDRS part III[220] , gait/axial sub-score (MDS-UPDRS part III items 3.9-3.12)[220], non-gait/axial sub-score (MDS-UPDRS III – gait/axial sub-score), Hoehn and Yahr scale[412] and the Stand-Walk and Sit test (SWS-test)[339] were performed on each of the five conditions. The SWS test is a standardized, timed test where subjects walk a 14-meter distance between sitting and standing. The overall duration of the test (time to walk 14 meters, SWS time) and the number of FOG episodes (#FOG episodes) were recorded. FOG was defined as a transient incapacity to move forward, despite the intention to walk, including both akinetic and "trembling in place" forms.[173,192] Patients performed the SWS test three times, and the data was averaged.

We defined responsiveness to LD and stimulation as any decrease on the number of FOG episodes in the SWS (i.e, a clinical improvement). Accordingly, patients who

worsened or had no change with LD or stimulation were classified as LD-resistant or stimulation-resistant, respectively.

Imaging procedures - Electrode reconstruction and localization

To ensure electrode placement across subjects, we reconstructed the DBS electrodes of all patients whose neuroimaging data was possible to retrospectively retrieve (n=11). This was performed through the advanced processing pipeline in Lead-DBS[454]. For each patient, a post-operative CT scan was linearly coregistered to a pre-operative structural MRI (T1w), and then transformed into the ICBM 2009b NLIN asymmetric MNI space[455] both using Advanced Normalization Tools[456]. A brainshift correction was employed and electrode trajectories were reconstructed automatically using the PaCER algorithm[457], following manual readjustments. Group visualization was performed using Lead Group with the DISTAL Atlas segmentation[458].

Development of an inertial sensor-based classifier for FOG

We used data collected from previous studies [381] to develop a model for automatic detection of FOG. In summary, 20 PD patients (freezers and non-freezers) wearing seven wearable sensors (inertial measurement units, IMUs) fixed to different body parts performed a self-paced gait task. 180° degrees turns were removed from the analysis leaving only straight-line walking. Clinical annotation of FOG episodes (presence and duration) was made by a PD expert clinician (RB) based on video recordings.

Each IMU consisted of a tri-axial accelerometer, a gyroscope and a magnetometer (Xsens Technologies, Enschede, The Netherlands), that was fixed to a patient's body using a Velcro elastic band. The inertial sensors were positioned in pelvis, right and left thighs, legs and feet. We used the raw signal collected by the IMUs and applied a supervised learning methodology on labelled data. This strategy trained a model to distinguish between different labels: FOG and non-FOG.

Continuous IMU data was processed into a one-second dataset, in which all 9 dimensions were splitted into non-overlapping sequential 1-second slices, each of which corresponds to 100 time-points, given the collection rate of 100Hz. Additionally, each resulting slice was then associated with the clinician label of belonging to a FOG episode or not**.** Considering the continuous nature of sensor data, an algorithm for identifying FOG events was envisaged as a time series (TS) classification problem. Deep learning (DL) has been increasingly used in the TS area, especially for multivariate time series problems.[459] Convolutional Neural Network (CNN) based architecture was used to build a FOG detection model, consisting of three sequential convolution modules [460] .The model was built in 13 patients and 7 were used to test the model on unseen data. FOG % was main output of the model, reporting to the percentage of FOG presenting during straight gait.

Wearable sensor-based gait analysis:

During the SWS test, patients wore the same seven sensors as previously described in the same locations (pelvis, right and left thighs, legs and feet), during each of the five stimulation/medication conditions. The data collected from the IMUs were processed using the KINETIKOS (Coimbra, Portugal) cloud-based platform to reconstruct each subject's body motion using a 3D kinematic biomechanical model. Each trial out of the 3 SWS trials were individually computed and results were averaged. A final dataset consisted of 30 variables organized into 4 domains (spaciotemporal, asymmetry, variability, and non-linear metrics) selected based on their relevance in the literature (**Table 4.1**)**.** For spatiotemporal features measured on both sides of the body, the "worst-side" score was selected based on clinical assessment. For spatiotemporal variables, coefficients of variation (e.g. standard deviation of variable X score / mean of variable X score) and asymmetries [(variable X score on the right side – variable X score on the left side) / (variable X score on the right side + variable X score on the left side)] were calculated.

Statistical Analysis

The primary outcome of the study was the difference in the number of FOG episodes between Med OFF/Stim OFF and Med ON/Stim ON 130 Hz conditions. Secondary outcomes

were: a) the change in the number of FOG episodes between the MedOFF/StimOFF and MedON/StimOFF and MedOFF/StimON condition; b) the differences in the number of FOG episodes between 130Hz and 60 HZ conditions c) the association between the automatic detection of FOG and FOG assessed by clinical gait metrics. Exploratory analysis were performed to dissect kinematic dimensions related to FOG.

The statistical analysis was conducted in alignment with the prespecified hypothesis defined in our primary and secondary outcomes. This was done to mitigate the risk of Type II errors. Summary statistics were presented as mean (± SD) and median (IQR). To compare groups, paired non-parametric statistics were used (Wilcoxon signed rank test for comparisons of 2 groups and Friedman test for more than 2 groups with corrections to multiple comparisons performed using Dunn's test). Spearman correlation was used to assess the association between kinematic and clinical variables. A Principal Component Analysis (PCA) used a dimensionality reduction method on the individual gait metrics to facilitate interpretation of data. Significance level was set at 0.05. Data processing was conducted using Matlab R2021a, Python 3.8 and R 4.2.2. Statistical analysis used Graphpad Prism 10.1.1.

Results

A total of 17 PD patients were included in the study: 71% male, disease onset at 51.9 ± 5.9 years and age at bilateral STN-DBS 62.2 ± 5.9 years. Patients were evaluated 7.7 ± 4.6 years after surgery, at a time where mean age and disease duration were 69.9 ± 6.2 and 17.9 ± 5.1 years, respectively. **(Table 6.1)**. FOG emerged on average 24.1 ± 2.11 months after surgery. Before surgery, none of the patients presented severe gait or FOG in their Best ON state (scores 0.6 ± 0.6 of item 3.10 and 0.4 ± 0.4 of item 3.11, during pre-DBS LCT).

Table 6.1: Clinical and demographic characteristics

Sex: male	12 (70%)
Age disease onset, yrs	51.9 ± 5.9
Age at surgery, yrs	62.2 ± 5.9
Disease duration at surgery, yrs	11.59 ± 3.1
Time-to-FoG (months)	24.1± 21.1
Age at evaluation (yrs)	24.1± 21.1
Disease duration at study inclusion (yrs)	17.9 ± 5.1
DBS duration at study inclusion (yrs)	7.7 ± 4.6
MDS UPDRS OFF pre-op*	51.3 ± 14.3
MDS UPDRS ON pre-op*	23.5 ± 11.3
Item 3.10 OFF pre-op*	1.4 ± 1.5
Item 3.11 OFF pre-op**	2.0 ± 2.0
Item 3.10 ON pre-op*	0.6 ± 0.6
Item 3.11 ON pre-op*	0.4 ± 0.4
LEDD pre-op (mg)	1298.8 ± 453.1
LEDD at study inclusion (mg)	838 ± 453.1
LD dose LCT (mg) (pre-op)	433.1 ± 137.5
LD dose LCT (mg) (at study inclusion)	433.1 ± 137.5

Data are expressed as percentage or mean and standard deviation as appropriate. Abbrev: Yrs, years; FoG, freezing of gait; DBS, Deep brain stimulation; MDS UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, Levodopa Equivalent Daily dose; LCT, levodopa challenge test; * n=16 **n=9 ***

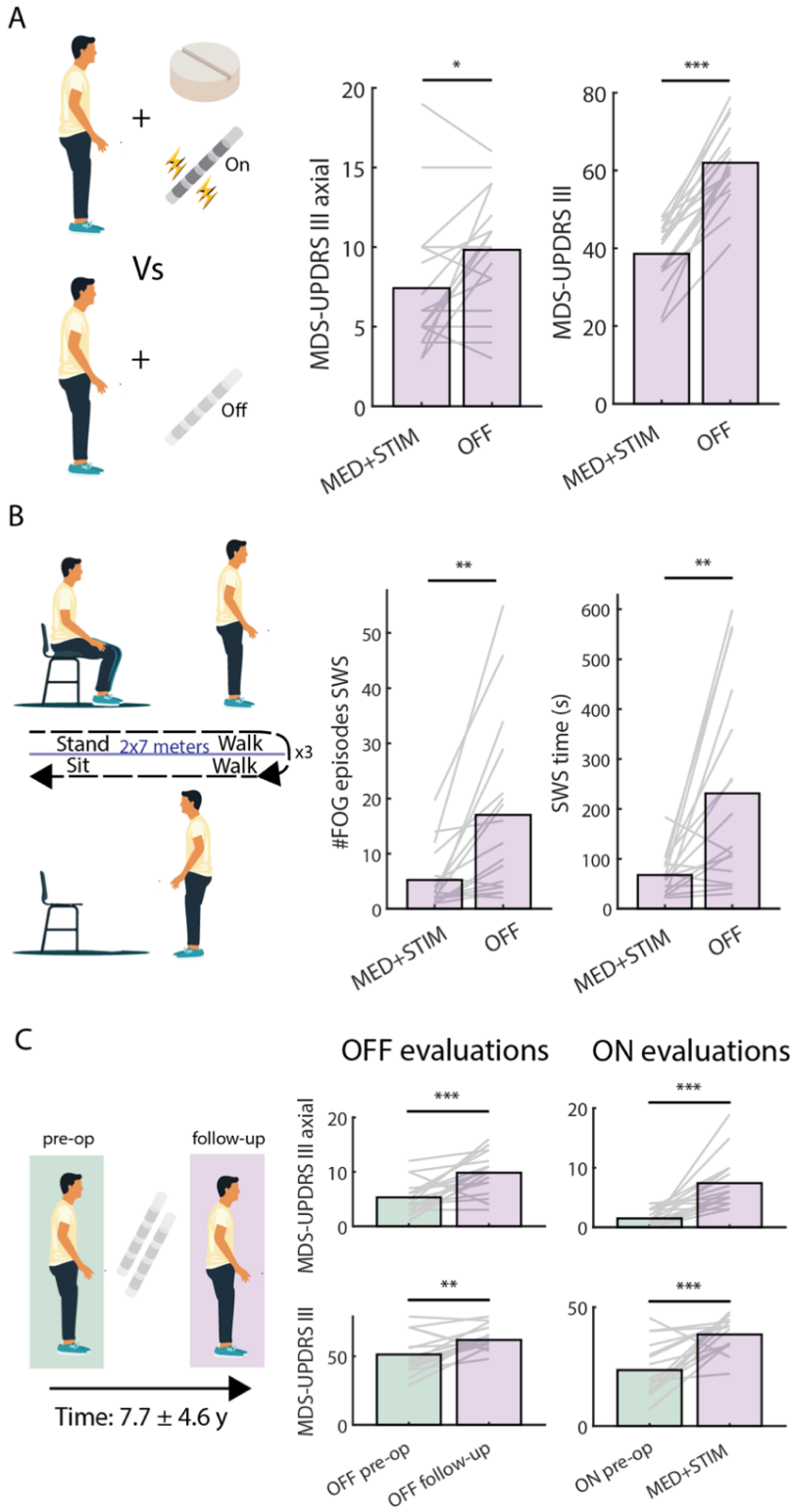


Figure 6.1 – Combined medication and stimulation lead to symptomatic improvement in axial and non-axial motor symptoms in the long term. A) Post surgery evaluation of the MDS-UPDRS III score and axial subscore in Best functional state (Medication On/Stimulation ON) and in the OFF state, higher scores indicate higher severity of motor symptoms B) During the SWS test, patients were asked to stand from a chair, walk 7 meters, do an half turn, walk back 7 meters and sit. Number of FOG episodes and gait time during the test were registered (left); Post surgery evaluation of the #FOG episodes and the SWS time in Best functional state (Medication On/Stimulation ON) and in the OFF state, higher scores indicate higher severity of motor symptoms(right) C) Comparison between the MDS-UPDRS III score and the axial subscore at the pre-surgery evaluation and at the current post-surgery evaluation. A significant progression of motor symptoms in the OFF and Best ON state is observed. Axial subscore, sum of items 3,9-3,12; MED+STIM, medication ON/stimulation ON; OFF, medicationOFF/stimulation OFF; #FOG epsiodes: number of FOG episodes during the Stand-Walk and Sit test; SWS Time: time to complete the Stand-Walk-Sit test; OFF pre-op, OFF medication at the pre-surgery evaluation; OFF follow-up, Medication OFF/stimulation OFF at the current evaluation; ON pre-op, Medication ON state at the pre-surgery evaluation; MED+STIM, medication ON/Stimulation ON state at the current evaluation; *, p<0.05; ***, p≤0,00

Using the same dose of levodopa, the MDS-UPDRS III improvement upon the LCT was significantly lower when compared with the baseline assessment (20.1 ± 13.4% vs 56.1 ± 14.0%, p = 0.001). A similar result was found for the axial sub-score of MDS-UPDRS part III (19 ± 37% vs 78 ± 21% vs, p < 0.001). Total MDS-UPDRS part III score, in both OFF and ON state, were significantly worse compared with pre-surgery evaluation. **(Figure 6.1, Table 6.1).** Stimulation parameters at the time of the study are shown in **Table 6.2** and, in patients whose reconstruction was possible, no electrode was found to be misplaced **(Figure 6.2).**

Table 6.2 - Stimulation parameters at study inclusion (n=17)

	Right STN	Left STN
Stimulation Mode		
Monopolar	94.4% (16)	88.2% (15)
Bipolar	5.9% (1)	11.8% (2)
Contacts		
0	11.8% (2)	0% (0)
1	35.3% (6)*	41.2% (7)*
2	35.3% (6)*	52.9% (9)
3	17.6% (3)	11.8% (2)
Voltage (mV)	3.0 ± 0	2.1 ± 1.3
Pulse width (μs)	61.3 ± 7.8	61.3 ± 7.8
Frequency (Hz)	128.4 ± 17.7	128.4 ± 17.7

Data are expressed as percentage or mean and standard deviation as appropriate. Abbrev: STN, Subthalamic nucleus; mV, millivolts; μs, microseconds; Hz,Hertz

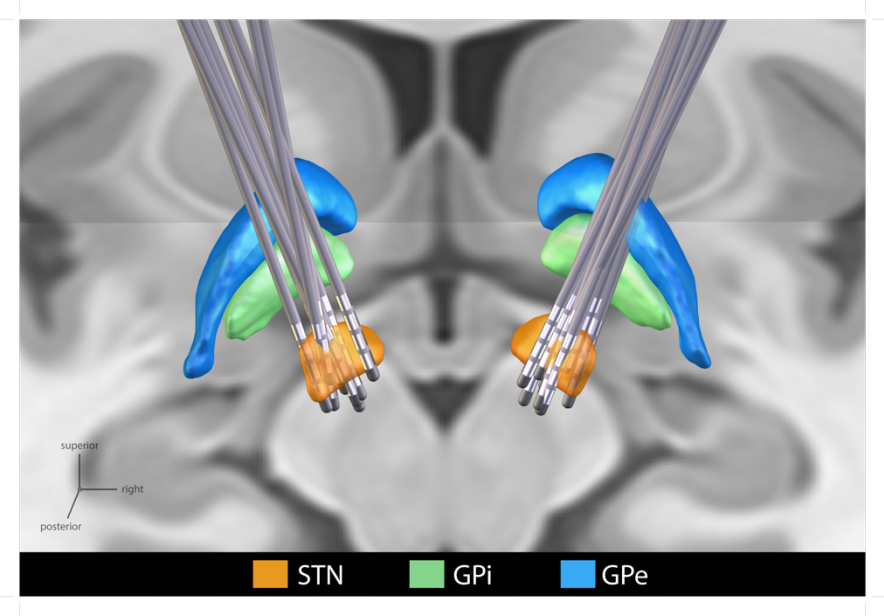


Figure 6.2 : Reconstruction of DBS electrodes (11/17 patients). DBS electrode reconstruction confirmed a similar placement within the subthalamic nucleus (STN) for all eleven patients assessed. Mean MNI coordinate of the right electrode's most ventral/distal contact: x: 10.98 ± 1.40 mm; y: -14.44 ± 1.11 mm; z: -9.26 ± 1.03 mm; Mean MNI coordinate of the left electrode's most ventral/distal contact: x: -11.04 ± 1.63 mm; y: -14.51 ± 1.22 mm; z: -8.85 ± 1.29 mm

1 – FOG assessment in Med OFF/Stim OFF vs Med ON/Stim ON

The number of FOG episodes was significantly reduced in the MedON/StimON condition when compared with the MedOFF/StimOFF (6.3 ± 7.9 vs 17.4 ± 15.7, $p < 0.001$**, Figure 6.1A**) paired with the reduction in the SWS time (76.5 ± 54.0 vs 239.5 ± 198.0 $p = 0.004$, **Figure 6.1B**). A similar finding was observed for the total MDS-UPDRS score (62.0 ± 9.9 vs 38.6 ± 8.5, $p = 0.003$), axial sub-score (9.8 ± 3.8: 7.4 ± 4.4, $p = 0.0247$), FOG (3.4 ± 0.8 vs 2.0 ± 1.4, $p=0.007$) and postural instability (1.9 ± 1.5 vs 0.6 ± 1.1, $p= 0.011$) scores. **(Figure 6.1, Table 6.3, Supplementary Table S6.1)**

Table 6.3– Clinical variables on study (mean & SD)

Variable	MedOFF StimOFF	MedOFF StimON	MedON StimOFF	MedON ON130Hz	MedON ON60Hz
MDS-UPDRS part III	62.0 ± 9.8	45.9 ± 8.6	49.4 ± 10.5	38.6 ± 8.5	40.7 ± 9.6
MDS-UPDRS Axial score	9.8 ± 3.8	7.6 ± 3.5	8.3 ± 3.5	7.4 ± 4.4	5.6 ± 2.6
MDS-UPDRS Non-Axial score	52.2 ± 8.5	38.3 ± 8.7	41.0 ± 8.7	31.2 ±7.3	35.1 ± 8.7
Item 3.10	2.6 ± 0.7	2.4 ± 0.4	2.6 ± 0.7	2.4 ± 0.6	2.0 ± 0.4
Item 3.11	3.4 ± 0.8	2.5 ± 1.5	3.0 ± 1.2	2.4 ± 1.1	2.0 ± 1.4
Item 3.12	1.9 ± 1.5	1.1 ± 1.5	1.2 ± 1.6	1.1 ± 1.6	0.6 ± 1.1
SWS time (s)	239.5 ± 198.0	152.5 ± 151.2	143.5 ± 112.8	76.5 ± 54.0	71.8 ± 54.2
SWS nº FOG events	17.4 ± 15.7	11.2 ± 13.0	9.3 ± 7.5	6.3 ± 7.9	5.1 ± 8.3
H&Y	3.0 ± 1.1	2.6 ± 0.9	2.7 ± 1.1	2.5 ± 0.9	2.2 ± 0.9
AIMS	4.1 ± 7.9	3.6 ± 6.9	9.2 ± 9.4	10.0 ± 12.9	12.2 ± 13.0

Data are expressed as mean and standard deviation. Abbrev: MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SWS, Stand-Walk sit test; FOG, freezing of gait; H&Y, Hoehn and Yahr Scale; AIMS, Abnormal Involuntary Movement Scale; MedOFF-StimOFF, Medication OFF-Stimulation OFF; MedOFF-StimON, Medication OFF-Stimulation ON; MedON-StimOFF, Medication ON-Stimulation OFF; MedON-StimON 130 Hz, Medication ON-Stimulation ON 130 Hz; MedON-StimON 60 Hz, Medication ON-Stimulation ON 60 Hz

2 - Assessing individual effect of stimulation and LD on FOG

2.1 Improvement at the #FOG episodes with both stimulation and medication at a cohort level

We found that either stimulation or LD (Med OFF/Stim ON or Med ON/ Stim OFF) significantly reduced the total MDS-UPDRS part III score (Med OFF/Stim OFF: 62.0 ± 9.9; Med OFF/Stim ON 45.91 ± 8.6; Med ON/Stim OFF: 49.353 ± 10.451, $p<0.0001$, **Figure 6.3A**). This was paired with a significant reduction in the #FOG episodes with any strategy (Med OFF/Stim OFF: 17.395 ± 15.710; Med OFF/Stim ON: 11.235 ± 13.022; Med ON/Stim OFF: 9.279 ± 7.506, **Figure 6.3B**) in line with the observations of SWS time (**Figure 6.3C**). In fact, a strong correlation between the number of FOG episodes and SWS time was observed across all condition (**Figure 6.3D**).

A high heterogeneity of responses on #FOG episodes was observed with either stimulation (maximum worsening of 287% and maximum improvement of 100%) or medication (minimum worsening of -600% and improvement of 94.12%). However, an average improvement of 75.5 ± 16.7 % was obtainable with at least one therapeutic intervention (MED-only or STIM-only) (**Figure 6.3E**). The magnitude of this improvement was not related to the severity of FOG (#FOG episodes) in the Med OFF/Stim OFF condition, excluding a floor or ceiling effect (r=-0.11, p=0.67, **Figure 6.3F**).

Medication or stimulation also significantly improved non-axial MDS-UPDRS subscores (**Figure 6.3H**), whilst reduction in axial subscores only achieved statistical significance on the MedOFF/StimON condition (**Figure 6.3G**). Abnormal involuntary movements were significantly increase with Levodopa, but not with Stimulation (**Figure 6.3I**). Detailed description of clinical metrics can be found in **Table 6.3.**

Although there was always at least one condition where FOG improved (**Figures 6.3B and 6.3E**), an increase in the number of FOG episodes under stimulation was observed in 3 (17.7%) patients whose freezing improved with medication whilst 5 patients (29.4%) worsened their freezing with Levodopa but were rescued by stimulation (**Figure 6.3J-I**). These observations motivated a better description of these groups.

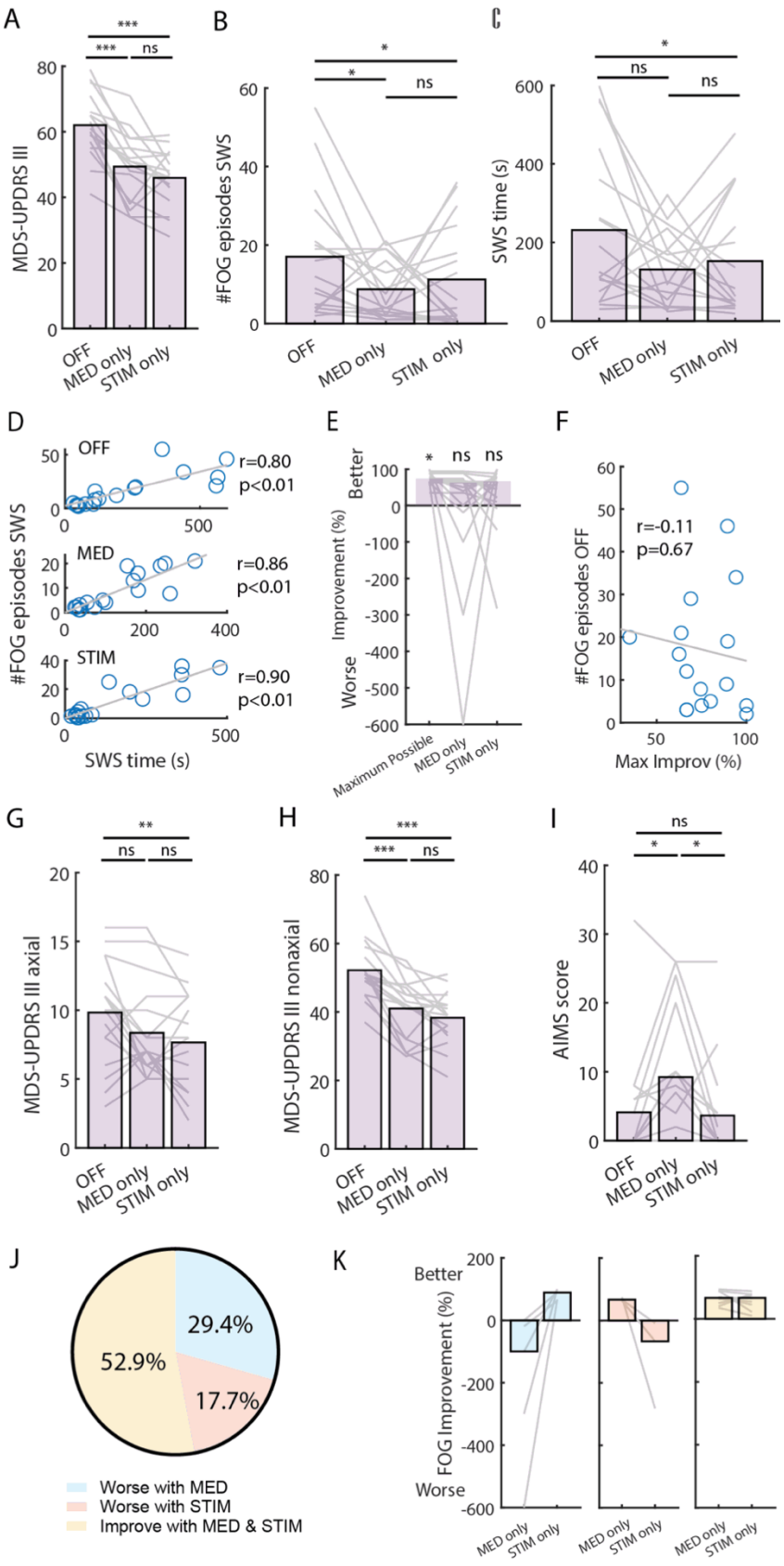


Figure 6.3 – Objective motor assessments reveal intra-individual variability in the FOG responses to Levodopa or DBS. A) MDS-UPDRS III score B) number of FOG episodes C) and SWS time in the OFF, medication only, stimulation only conditions are depicted. While a significant modulation in relation to the OFF state is seen, no difference emerges between medication and stimulation responses. D) SWS times and #FOG epsiodes these variables are significantly correlated across conditions E) Maximal possible improvement from the baseline OFF state regarding the number of FOG episodes. It is possible to significantly reduce the number of FOG episodes considering at least one of the manipulations. Heterogeneity of responses in stimulation or medication are evident. F) There is no association between the number of FOG episodes in the OFF state and the percentage of improvement. these variables are significantly correlated across conditions. G) MDS-UPDRS axial subscore H) non-axial subscore I) and AIMS score in the OFF, medication only, stimulation only conditions. J) Using the number of FOG episodes as outcome, distribution of patients according to their response to LD and stimulation K) Degree of FOG improvement from the baseline OFF conditions in the different subgroups of patients. SWS test, stand walk and sit test; OFF, medicationOFF/stimulationOFF, medication only, medicationON/stimulation OFF; stimulation only, medicationOFF/stimulationON; #FOG, number of FOG episodes; Worse with Med, failure to improve >10% or worsening on the number of FOG episodes from the OFF conditions to the medication only condition; Worse with Stim, failure to improve >10% or worsening on the number of FOG episodes from the OFF conditions to the stimulation only condition; improvement with MED&STIM, decrease on >10% on the number of FOG episodes with both medication and stimulation; *, $p<0.05$; **, $p\leq0,01$; ***, $p\leq0,001$

2.2 Exploring the differential responses of FOG to LD and Stimulation at an individual level

In the five patients presenting a LD-resistant FOG a significant effect of LD on MDS-UPDRS non-axial score was seen (**Figure 6.4A**) excluding ineffective intake as a cause. The #FOG episodes was significantly lower in the MedOFF/StimON that in the MedON/StimOFF condition (1.8 ± 2.4 vs 15.8 ± 6.8, p=0.003) supporting that there was the possibility to recover FOG in these patients (**Figure 6.4A**, left). Interestingly, when these patients were evaluated in the MedON/StimON condition, the addition of medication to the effective stimulation led to a trend in the increase of #FOG episodes (**Figure 6.5A**, Left) reinforcing a possibly deleterious effect of LD in FOG in a subgroup of patients. A similar pattern is observed on MDS-UPDRS III axial score, with stimulation significantly reversing the worsening induced by LD (MedOFF/StimOFF: 7.8 ± 4.8; MedON/StimOFF: 9.6 ± 3.9; MedOFF/StimON : 6.2 ± 4.4, p=0.0278) (**Figure 6.4A**, **Figure 6.5C**, left). The improvement on non-axial MDS-UPDRS III seen with stimulation or medication (**Figure 6.4A**, mid-left) was improved even more in the ON/ON condition (**Figure 6.5B**, Left). This supports a pathophysiological dissociation between FOG and other motor symptoms.

On the STIM-resistant subgroup, stimulation induced an increase on the #FOG episodes, when compared to medication (MedOFF/SimOFF: 13.61 ± 6.73; MedON/StimOFF: 4.55 ± 2.86; MedOFF/StimON : 26.00 ± 11.53, p=0.0278, **Figure 6.4B**, left), supporting again that FOG rescue was possible. In this group, although the comparisons are limited by the low patient number, both LD and stimulation, resulted on a non-significant reduction on non-axial subscore (MedOFF/StimOFF: 55.0 ± 6.1; ON/OFF: 44.00 ± 10.82; OFF/ON: 42.67 ± 8.50, p=0.194 (**Figure 6.4B**), but also a trend for an addictive effect of both therapies in this specific outcome is observed (**Figure 6.5B**, middle). Adding the effects of LD to stimulation completely rescued the lack of FOG response (**Figure 6.5B**, middle).

In the largest group that presented a FOG response with both strategies, this was broadly seen across all motor domains (**Figure 6.4C**).

Importantly, the different responses patterns were not related to the severity of motor symptoms in the baseline (OFF/OFF) state (**Figure 6.4D**). Detailed description of these groups can be found in **Supplementary Table S6.2, S6.3, S6.4.**

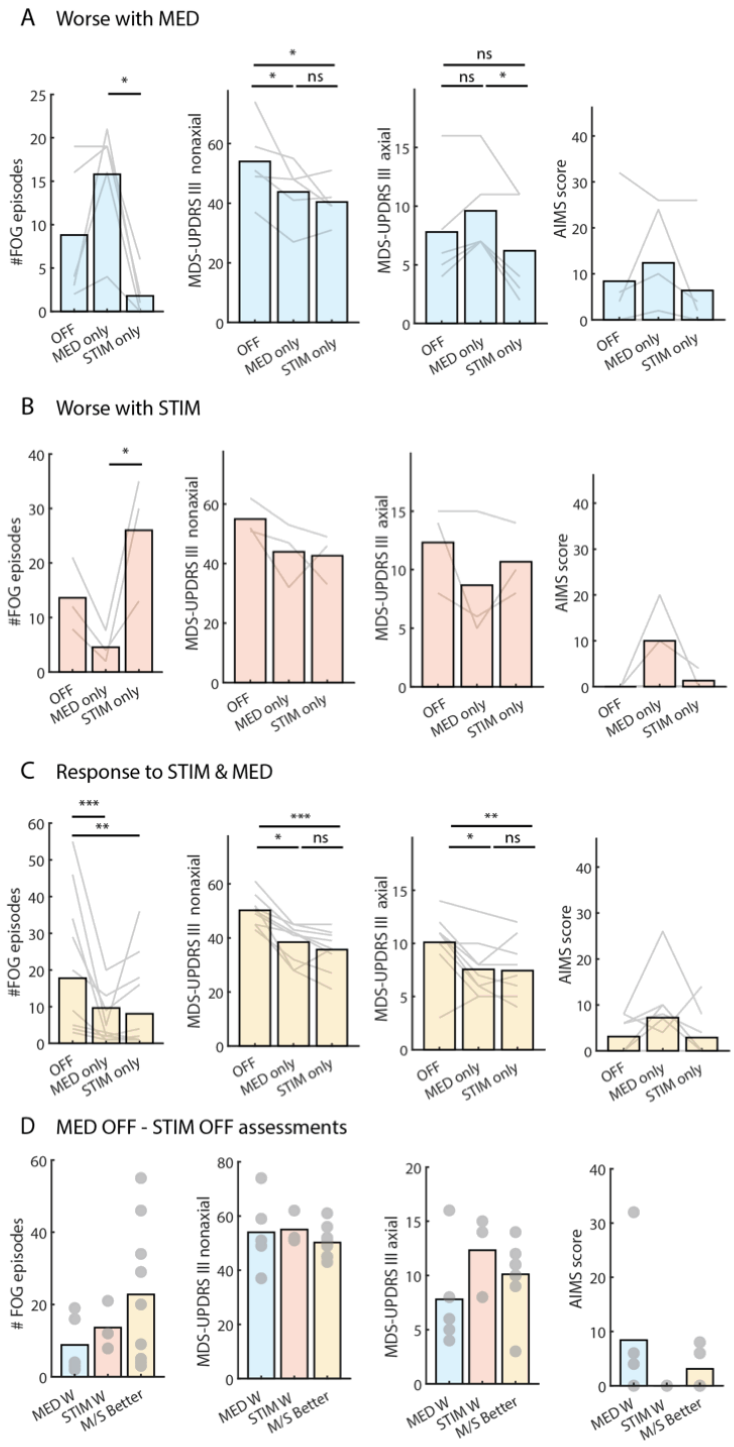


Figure 6.4: Clinical assessment of patients according to the profiles of FOG responses. Number of FOG episodes, MDS-UPDRS non-axial score, MDS-UPDRS axial score and AIMS score in the subgroup of patients A) who worsened with medication and improved with stimulation B) who worsened with stimulation and improved with medication C) who improved with both stimulation and medication. D) Depiction of the number of FOG episodes; MDS-UPDRS III nonaxial subscore, axial subscore and AIMS score in the OFF/OFF condition and their distribution across the different subgroups of patients. No significant differences were identified. OFF/OFF, medicationOFF/stimulationOFF, ON/OFF, medicationON/stimulation OFF; OFF/ON, medicationOFF/stimulationON; #FOG, number of FOG episodes; Worse with Med, failure to improve >10% or worsening on the number of FOG episodes from the OFF conditions to the medication only condition; Worse with Stim, failure to improve >10% or worsening on the number of FOG episodes from the OFF conditions to the stimulation only condition; improvement with MED&STIM, decrease on >10% on the number of FOG episodes with both medication and stimulation; *, p<0.05; **, p≤0,01; ***, p≤0,001

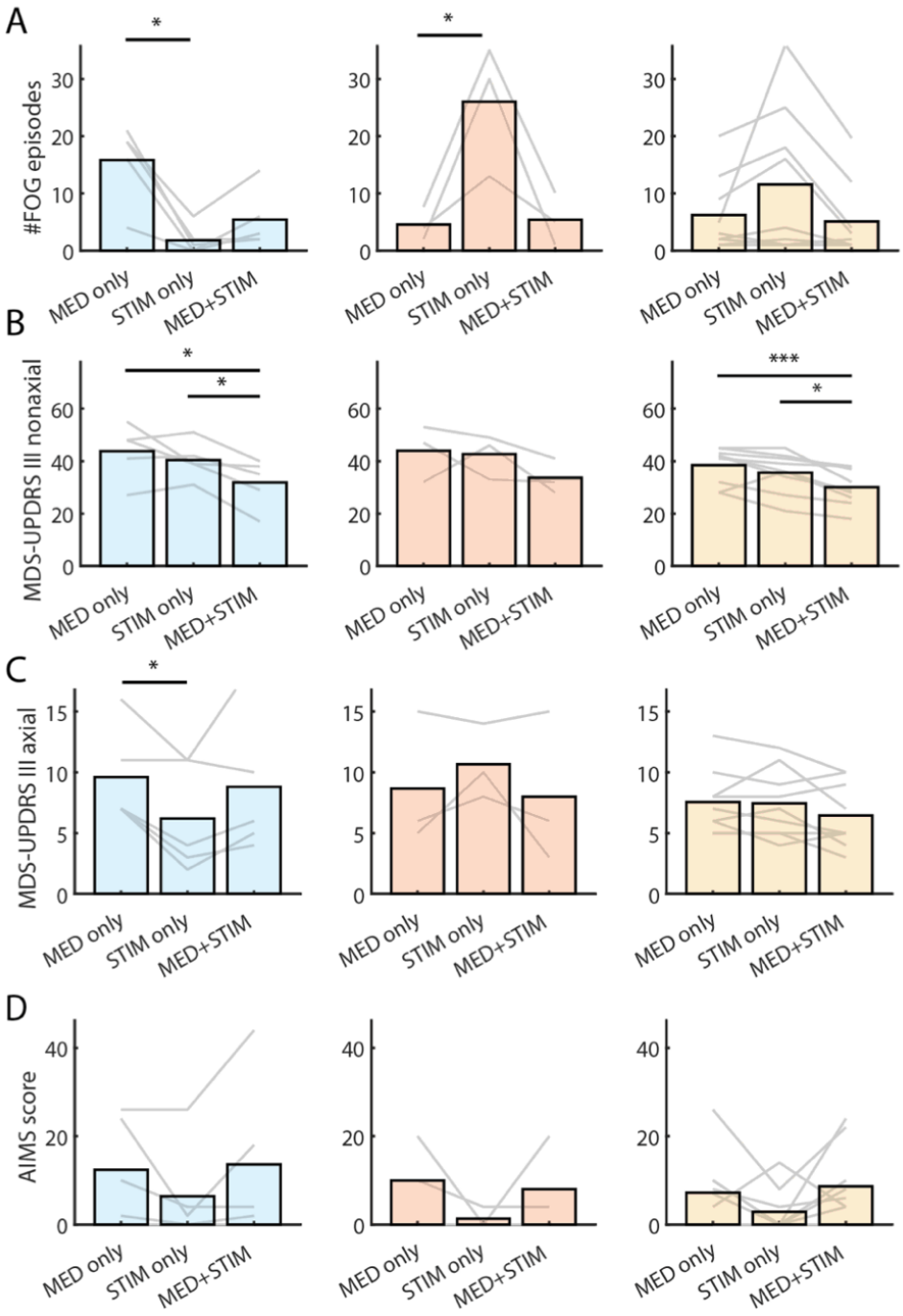


Figure 6.5: #FOG episodes (A) MDS-UPDRS III non axial score (B) MDS-UPDRS III axial score (c) and AIMS scores (D) per condition and per subgroup of patients, where each colour represent a different subgroup of patient: Patients worsening with medication are depicted in blue (left), patients worsening under stimulation are depicted in orange (middle) and patients improving under both stimulation and medication are depicted in yellow (right): #FOG episodes, number of FOG episodes; MED only, Medication ON/Stimulation OFF; STIM only, Medication OFF/Stimulation ON;Med+Stim.MedicationON/StimulationON 130HZ; * p<0.05, ** p<0.01; ***p>0.001

3 - The role of HFS and LFS on FOG

As previously described, combined stimulation and LD resulted in a significant decrease in the number of FOG episodes. Globally, the number of FOG episodes (HFS: 6.32 ± 7.91; LFS: 5.08 ± 8.26, p=0.410) and SWS time (HFS: 76.52 ± 54.03; LFS: 71.84 ± 54.23, p=0.836) were not significantly different between the HFS and LFS conditions (**Figure 6.6A** and **6.6B**). On the contrary, the effects on MDS-UPDRS non-axial and axial sub-scores, were distinct. While HFS was associated to significantly better non-axial scores (HFS: 31.18 ±7.27 ; LFS: 35.12 ±8.75, p= 0.004, **Figure 6.6C**), axial scores were significantly better with LFS (HFS: 7.41 ± 4.36; LFS: 5.59 ± 2.57, p=0.004, **Figure 6.6D**) without any significant change in the AIMS score (**Figure 6.6E**).

Again, an important variability between patients in their response to different frequencies of stimulation was observed (**Figure 6.6F**): in 58.8% of the patients, LFS was superior to HFS in reducing the number of FOG episodes (**Figure 6.6G**), with a decrease in axial MDS-UPDRS sub-score (**Figure 6.6I**) and a trend for an increase in non-axial MDS-UPDRS score (**Figure 6.6J**). By contrast, 25.5% of patients had a better FOG response to HFS condition compared to LFS (**Figure 6.6F-J**). Detailed description of these groups can be found in **Table 6.3** and **Supplementary Table S1**.

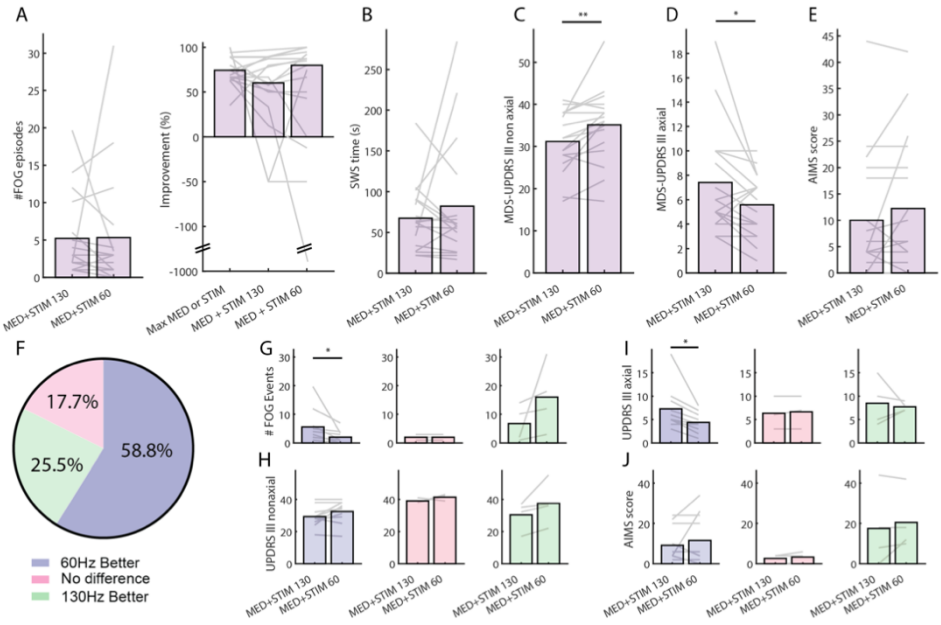


Figure 6.6: Comparison of Clinical responses to High and Low Frequency stimulation (matched for the total energy delivered). A) Left: #FOG episodes observed in the all cohort at ON/ON 130Hz and ON/ON 60 Hz are not significantly different. Right: Maximum possible improvement and observed improvement in these 2 conditions. B) SWS test results in seconds at ON/ON 130Hz and ON/ON 60 Hz C) MDS-UPDRS III non-axial score is lower in HFS and D) MDS-UPDRS III axial score is lower in LFS. E) No difference in the and AIMS scores observed at ON/ON 130Hz and ON/ON 60 Hz. F) Representation of patient distribution regarding their response to the different frequency conditions. G) Distribution of #FOG events H) MDS-UPDRS III non axial score I) MDS-UPDRS III axial score J) and AIMS score across the different subgroups of patients at both 130Hz and 60Hz condition. ON/ON 130 Hz, MedicationON/Stimulation ON 130 Hz; ON/ON 60Hz, MedicationON/StimulationON 60 Hz; #FOG, number of FOG episodes; SWS time, gait time during the SWS test, *, $p<0.05$;**, $p\leq0,01$

4- Using IMU-based approaches to study gait and FOG

4.1 Identification of FOG and kinematic features related with FOG

Using a Convolutional neural network (CNN) in an independent group of 21 PD patients, a model for automatic quantification of the percentage of FOG during straight gait (% FOG) was developed. This detection was not based on specific gait variables, but on the analysis of the inertial sensor signal (**Figure 6.7 A-D**) and had a good specificity and sensitivity for freezing detection compared to clinical assessment (**Figure 6.7-E**).

The % FOG significantly decreased from Med OFF/Stim OFF to Med ON/Stim ON condition (61.51% ± 9.99 vs 24.43% ± 24.43, p=0.0128) (**Figure 6.7F** left). The number of FOG episodes and the SWS time significantly correlated with the %FOG detected by IMUs across conditions (**Figure 6.7F** right, details on correlations can be found in **Table 6.7**). Significant correlation between the %FOG and individual kinematic gait metrics were found across conditions (**Figure 6.7G**, details on correlations can be found in **Table 6.8**) with metrics related to gait variability having the strongest correlations with FOG.

As power was very limited to perform comprehensible analysis, dimension reduction was performed using a Principal Component Analysis (PCA) with the set of 30 pre-specified kinematic variables. The first Principal Component (PC1) was able to explain 75% of the gait variability (**Figure 6.7H**), it was enriched with dimensions of gait variability and asymmetry (**Figure 6.7I**) and was correlated with multiple FOG metrics across conditions (**Figure 6.7J-K,** details on correlations can be found in **Table 6.9**). Another argument suggesting that these dimensions capture relevant FOG-related kinematics emerge from comparison across frequency conditions. In the LFS-better group (n = 10), values of PC1 were lower with 60 Hz (low freezing) compared with 130 Hz (high freezing), whereas in the HFS-better group (n=4), the reverse trend was observed (**Figure 6.8 C-D**).

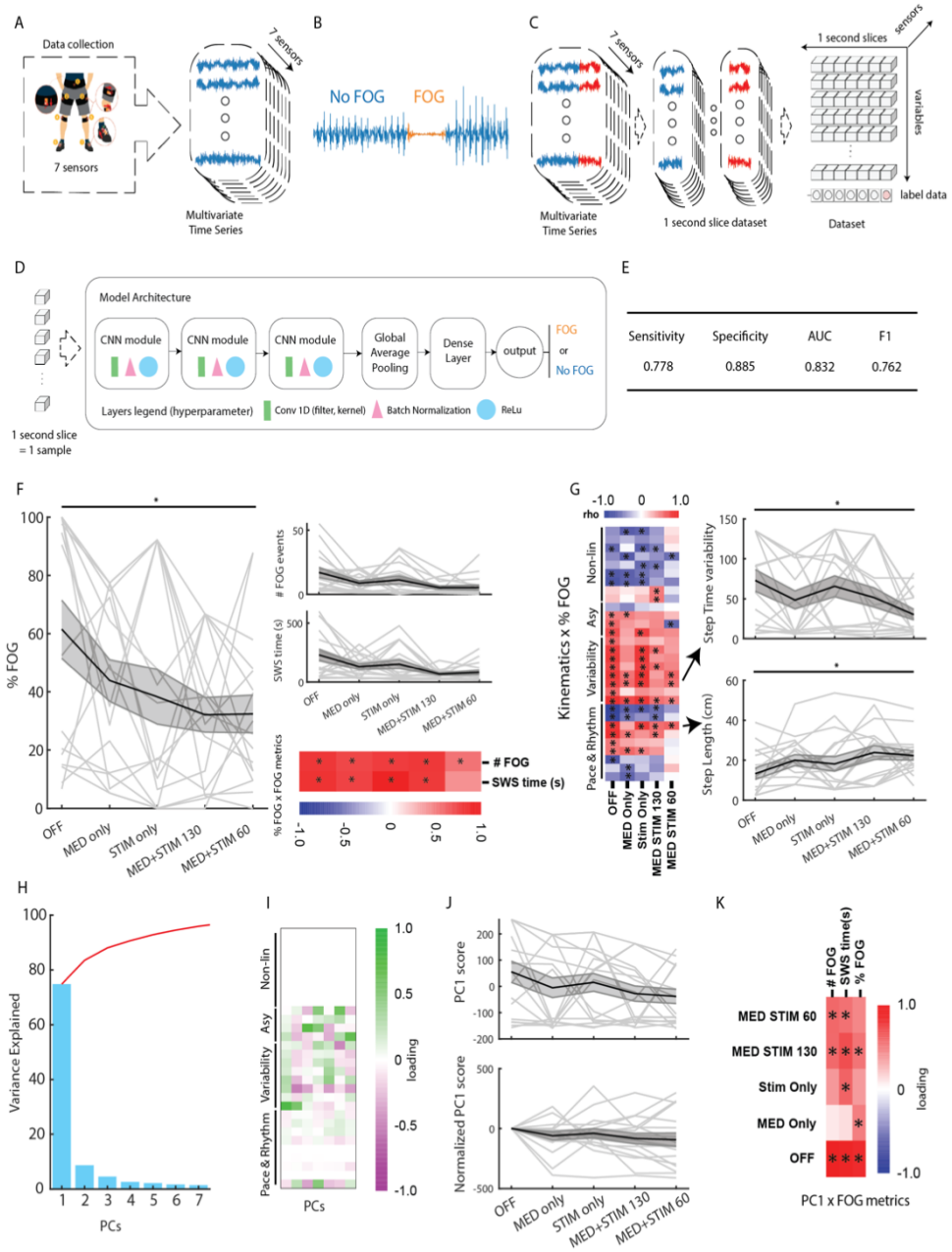


Figure 6.7: For the construction of a model for automatic detection of FOG, data was collecting using a set of 7 wearable device (A) the model was trained to distinguish between two different labels: FOG and non-FOG (B) Continuous IMU data was processed into a one-second dataset and treated as a time series classification problem (C) Convolutional Neural Network (CNN) based architecture was used to build a FOG detection model, consisting of three sequential convolution modules (D) The model was built in 13 patients and 7 were used to test the model on unseen data with, sensitiviy, specificity and overall accuracy of the model in the training dataset being shown (E) %FOG decreased from the OFF condition to the ON/ON condition, with behavior across the different conditions tested being depicted. Individual patients trajectories are also demonstrated ; correlation matrix between the %FOG and clinical metrics (SWS time and #FOG episodes) (F) correlation matrix depicting the relationship between individual kinematic variables and %FOG across the different conditions under study; behavior of two individual variables (step length and step time variability) across stimulation conditions, with a significant decrease from both the MedOFF/StimOFF condition to the ON/ON 130Hz and 60Hz condition being observed (G) Principal component analysis (PCA) was used to reduce the number of kinematic features under study, increasing

data interpretability of data while preserving the maximum amount of information. PC1 explained 75% of the variability found on the dataset (H) Correlation matrix between each one of the 7 PC and individual gait metrics (I) PC1 score in the different conditions tested (J) and correlation of PC1 with FOG%, #FOG episodes, SWS test (K). Dark red and blue red represented higher positive and negative correlations. Correlations with statistical significance are shown on the matrix (CE)

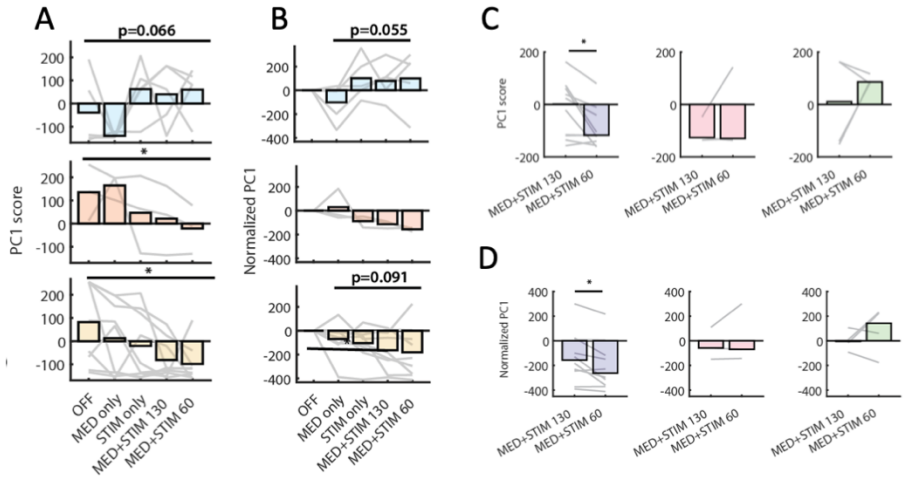


Figure 6.8 - PCI scores (and normalized PC1 scores) per condition and par subgroup of patients are depicted with different subgroups being represented by different colors: Patients worsening with medication are depicted in blue, patients worsening with stimulation are depicted in orange, patient responding to both stimulation and medication are represented in yellow, patients benefiting from LFS are represented in purple, the ones better under HFS are represented in green and rose depicts the subgroup of patients with equal improvements under HFS and LFS (A, B,C, D) PC, principal component; #FOG, number of FOG episodes; SWS time, SWS gait time; %FOG, FOG % detected using a automatic model; OFF, medicationOFF/stimulationOFF, medication only, medicationON/stimulation OFF; stimulation only, medicationOFF/stimulationON; MED+STIM 130, medication ON/Stimulation ON 130 Hz; MED+STIM 60, medication ON/Stimulation ON 60 Hz; *, $p<0.05$

4.2 Using 3D kinematics do describe gait alterations

Kinematic characterization of gait across clinical conditions remains a major need to understand neural circuits dysfunction. On this chapter we provide a detailed description of the selected kinematic variables across the 5 study conditions (**Table 6.4, Supplementary Table S6.1 and S6.8**) . In the current study we found that LFS, when compared to HFS, was related to a global reduction of gait and axial symptoms as assessed by the MDS-UPDRS (**Figure 6.6D**) with no difference in FOG (**Figure 6.6A**).

An exploratory analysis found that gait of patients on LFS tended to be faster with a significantly higher step cadence (p=0.032), but no significant differences on step length (p=0.640) or width (p=0.330) (**Figure 6.9 left**). LFS was also characterized by a lower stance time (p=0.0219), and double support time variability (p=0.022) translating into gait cycles with lower variability (**Figure 6.9** Right). This could not be explained by a difference in the number of FOG episodes (**Figure 6.6A**).

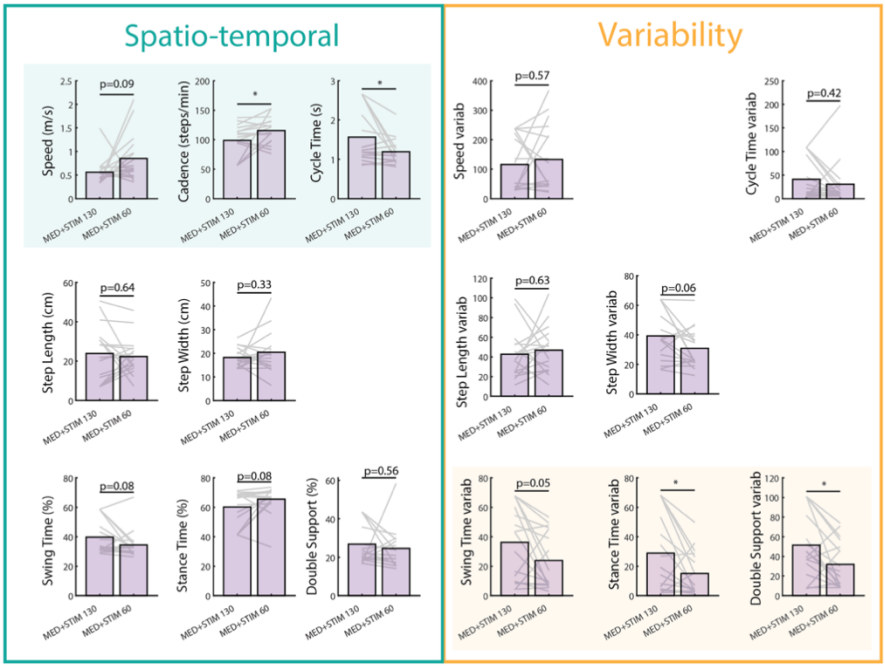


Figure 6.9 - Mean values of spatio-temporal variables and the corresponding variability metric are presented at the Med+Sim 130 Hz condition and at the Med+Stim 60 Hz condition. Med+Stim 130 Hz, Medication ON/Stimulation ON 130 Hz; Med+Stim 60 Hz, Medication ON/Stimulation ON 60 Hz; *, p<0.05

Table 6.4 – Kinematic variables under study

Variable Means	MedOFF-StimOFF	MedOFF-StimON 130Hz	MedON-StimOFF	MedON-ON130Hz	MedON-ON60Hz
Cadence	78.309 ±	90.109 ± 23.078	78.495 ±	98.69 ±	115.226 ±
COM_RMS_AP	0.022 ±	0.017 ± 0.009	0.033 ±	0.031 ±	0.031 ±
COM_RMS_ML	0.009 ±	0.009 ± 0.005	0.011 ±	0.013 ±	0.016 ± 0.01
COM_RMS_Vert	0.013 ±	0.012 ± 0.003	0.013 ±	0.016 ±	0.013 ± 0.01
Cycle_Time	2.799 ±	1.508 ± 0.428	2.118 ± 1.2	1.563 ±	1.191 ±
Cycle_Time_Variability	78.82 ±	36.273 ± 32.484	49.787 ±	40.741 ±	30.426 ±
Double_Support_	11.998 ±	14.486 ± 21.523	23.177 ±	19.543 ±	35.306 ±
Double_Support	47.51 ±	37.026 ± 28.739	49.75 ±	51.518 ±	31.952 ±
Percentage of	28.487 ±	31.193 ± 12.702	29.217 ±	26.824 ±	24.647 ±
Entropy_AP	1.321 ± 0.42	1.648 ± 0.345	1.486 ±	1.472 ±	1.232 ±
Entropy_ML	1.375 ±	1.73 ± 0.258	1.764 ±	1.667 ± 0.35	1.795 ±
Entropy_Vert	1.809 ±	2.003 ± 0.205	1.825 ±	1.677 ±	1.619 ±
FoG_Percent_StraightL	61.506 ±	38.288 ± 38.614	43.9 ±	32.094 ±	32.394 ±
HR_AP	0.442 ±	0.509 ± 0.277	0.784 ±	0.621 ±	0.805 ±
HR_ML	1.657 ±	2.497 ± 1.794	1.869 ±	2.424 ± 2.01	2.377 ±
HR_Vert	0.41 ± 0.326	0.5 ± 0.322	0.58 ± 0.279	0.708 ±	0.511 ±
Speed	0.574 ±	0.613 ± 0.56	0.545 ±	0.56 ± 0.27	0.85 ± 0.506
Speed_Variability	181.156 ±	150.871 ±	153.233 ±	115.971 ±	132.839 ±
Stance_Time_Percent_	37.564 ±	17.649 ± 14.73	28.454 ±	28.907 ±	14.946 ±
Stance_Time	52.758 ±	68.393 ± 5.153	58.204 ±	60.273 ±	65.531 ±
Step_Length_Asymme	42.588 ±	41.413 ± 29.666	53.308 ±	53.264 ±	34.784 ±
Step_Length_Variabilit	47.904 ±	31.528 ± 16.47	45.73 ±	42.708 ±	46.747 ±
Step_Lengt	13.239 ±	20.017 ± 11.369	18.124 ±	23.877 ±	22.338 ±
Step_Time_Asymmetr	67.652 ±	39.657 ± 38.143	34.938 ±	30.207 ±	26.827 ±
Step_Time_Variability	73.036 ±	48.449 ± 46.757	65.709 ±	51.52 ±	29.98 ±
Step_Time	0.973 ±	0.675 ± 0.223	1.011 ±	0.731 ±	0.538 ±
Step_Width	13.56 ±	16.175 ± 5.116	15.535 ±	18.221 ±	20.47 ±
Step_Width_Variability	44.366 ±	38.801 ± 11.953	50.527 ±	39.345 ±	30.843 ±
Swing_Time_Asymmet	24.301 ±	18.795 ± 13.702	23.451 ±	26.213 ±	15.232 ±
Swing_Time_Variabilit	39.634 ±	40.28 ± 33.813	42.977 ±	36.183 ±	23.923 ±
Swing_Time	47.242 ±	31.607 ± 5.153	41.796 ±	39.727 ±	34.469 ±

Data are expressed as mean and STD. Abbrev: COM RMS, Center-of-Mass; AP, Antero-Posterior; Vert; Vertical; ML, Medio-lateral; HR, Harmonic-ratio; FoG, freezing of gait; MedOFF-StimOFF, Medication OFF-Stimulation OFF; MedOFF-StimON, Medication OFF-Stimulation ON; MedON-StimOFF, Medication ON-Stimulation OFF; MedON-StimON 130 Hz, Medication ON-Stimulation ON 130 Hz; MedON-StimON 60 Hz, Medication ON-Stimulation ON 60 Hz

Discussion

The emergence and management of severe FOG in the best functional state after surgery remains a challenge in the long-term follow-up of STN-DBS patients. In this study, we aimed to understand the impact of stimulation and LD on post-surgery FOG, in patients previously responsive to LD. We have found that FOG presenting in the Best-Functional state after surgery is mostly a therapy-resistant FOG, and that stimulation and medication are still able to partially improve the severe gait alterations observed in the treatment-OFF condition. Importantly, a strong heterogeneity in FOG responses to specific treatments is observed. Despite the lack of benefit in the number of FOG episodes with LFS, axial scores were significantly improved, suggesting a role on LFS in the management of gait.

Individual subjects have distinct FOG responses to Stimulation or Levodopa

In our study, we identified that best functional state FOG is mostly a treatment-resistant FOG and not treatment-induced FOG. Consequently, severe FOG and associated gait impairments observed in the off-treatment condition are, to a certain extent,rescued by therapy in all patients.

We found that either LD or stimulation improved OFF/OFF FOG, and that a synergistic effect was observed when they were combined. This suggests that patients presenting FOG in MedON/StimON state 7 years after DBS still benefit from the effects of stimulation and LD, even if with a lower magnitude of response than before surgery: Additionally, these findings do not suggest, at least at a group level, a deleterious effect of stimulation. and do not suggest, at least at a group level, a deleterious effect of stimulation. This observation aligns with prior research findings, indicating that while FOG may persists in the MedON/StimON condition, both its severity and frequency decrease in comparison to the OFF treatment-state.[303,335,339,382,461]

We hypothesized that this attenuated response to treatment is related to disease progression, with a decline in LD sensitivity reflecting the extension of the neurodegenerative process to non-dopaminergic pathways.[127,351] The lower magnitude of motor response in the post-op LCT compared to pre-op LCT, particularly regarding axial symptoms, as well the increased severity of motor scores in the treatment OFF states, supports this argument. This is in line with previous studies in STN-DBS patients, where a progressive decline in axial symptoms, including freezing was observed in the medium to long-term follow-ups. [303,327,336] However, our study does not inform us whether patients would have equivalent benefit compared to pre-DBS were much higher doses of LD used for the pos-DBS LCT.

Different effects of STN-DBS and LD at motor outcomes[462–465] have been described and, more recently, STN-DBS and Levodopa were shown to modulate brain motor circuits differently.[466] Here, we expand these observations by proposing that symptom-specific improvements must be accounted when addressing disease mechanisms. Our observations may have practical clinical implications: currently, patients with LD-resistant FOG and gait impairment are currently excluded from surgical programs[206,321] even if some isolated finding have suggested that axial non-LD responsive signs may improve with STN-DBS [334]. Our quasi-experimental design may complement these findings. We describe a subgroup of ~30% of patients in our cohort whose FOG was not improved with medication but was rescued with stimulation. In fact, in these patients the number of FOG episodes nearly doubled while on medication, even if bradykinesia and rigidity improved. Although we can't exclude that a low dose of LD was used in the LCT, the pattern of response suggests a lack of effect of LD and an effect of STN-DBS specifically in axial signs. This may suggest that exclusion of DBS surgery based solely on the response to LD may limit their accessibility to an effective treatment.

Interestingly, the dissociation between therapy-specific responses is observed mostly for axial signs, suggesting that FOG and axial symptoms may behave differently than the rest of PD motor symptoms.

The exact pathophysiologic mechanisms involved in FOG are not well understood, with multiple theoretical models[122] and clinical triggers identified[194]. By systematically exploring the response of the same patient in the same self-paced scenario across multiple therapeutic manipulations, we are limited to extract conclusions regarding freezing in other contexts but we benefit from constraining contextual variability. This allow us to argue that it is very likely that therapeutic responses of FOG can be obtained by manipulating different nodes of circuit dysfunction (with stimulation or medication). [467,468]

Stimulation Frequency can lead to important differences in FOG response to stimulation

LFS has been appointed as a possible strategy to manage refractory-FOG in STN-DBS patients.[338–340,342,469] These studies have different designs and outcome measures, but from most of them the clinical variability in FOG response is clear, even if they focus on younger and less severe patients than our sample. In our study, we found no difference between HFS and LFS, even if LFS was associated with a significant reduction in axial MDS-UPDRS III scores. The benefits of LFS in axial scores, including improvements in symptoms such as dysarthria and dysphagia, have also been previously demonstrated. .[340,376] Although variability, unblinding and small sample limited comparisons, nearly 60% of patients had less FOG episodes with LFS at equivalent delivered energy levels than HFS.

In this subgroup of patients, when LFS and HFS were compared, a significant reduction in MDS-UPDRS III axial scores with a trend for an increase in non-axial was also seen. The effect of LFS on axial symptoms was also captured by the kinematic analysis. Here, variables reflecting mostly the overall gait bradykinesia (as speed or step length) were not specifically modulated by LFS, whilst variables known to be associated with axial signs[153,212,231,436], such as gait cycle variability metrics, were reduced by 60 Hz stimulation, in accordance with a previous observation with 80 Hz stimulation.[470] Previous studies have shown that the optimal contacts for 60 Hz stimulation were situated more ventrally than the ones used for 130 Hz stimulation.[338,471] Here, one can envisage that whilst HFS of the descending nigropontine projections and outflow tracts of the pedunculopontine nucleus

(PPN) can negatively impact gait, LFS stimulation of the same structure will have a positive impact, as suggested by the beneficial effects on gait observed with PPN-DBS at low frequency stimulation (25 Hz).[471–473]

We used the same contacts for both HFS and LFS, suggesting that even using the same contact location, different FOG responses can be obtained. It would be crucial to characterize the distinct circuit engagement related to symptom improvement in order to refine stimulation targeting and refinement.

Nonetheless it appears to be clear that axial signs are specifically prone to modulation by LFS, suggesting that axial and appendicular symptoms may emerge from distinct brain circuits involved in motor control.

Our results reinforce the clinical evidence that different patients will benefit from different therapeutic strategies and that an individualized and systematic approach exploring patients under both medication and stimulation conditions may help in individualizing the role of stimulation and levodopa resistance in the etiology of FOG **(Fig 6.10).** This heterogeneity might be a source of bias in clinical trials assessing stimulation parameters strategies and should be considered when calculating sample size.

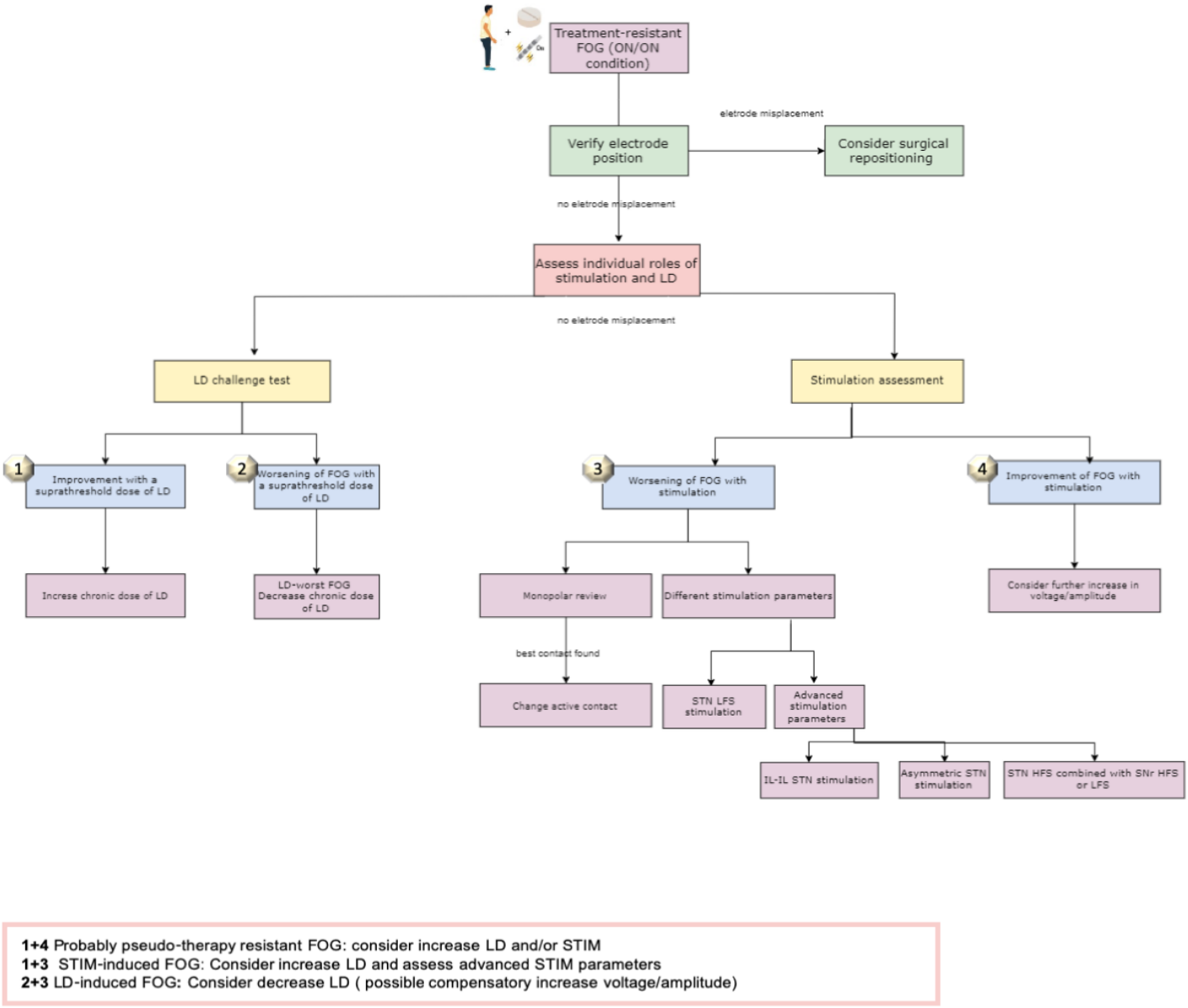


Figure 6.10: A multi-step approach to evaluate patients presenting with FOG in the Best Functional State after STN-DBS surgery, is proposed. FOG: Freezing of Gait; MedON/StimON: Medication ON/Stimulation ON; LD: Levodopa; STN: Subthalamic nucleus; LFS: 60 Hz-Low Frequency Stimulation; HFS: 130 Hz, High Frequency Stimulation; SNr: Subtantia Nigra

Automatic FOG detection correlates well with clinical FOG metrics

FOG detection and quantification have traditionally been carried out using clinical scales, often relying on retrospective self-assessment.[208,242,474] Even when evaluated by a trained clinician, a significant inter-rater variability concerning both the number and duration of FOG episodes exists.[475] To find more robust and objective metrics, wearable devices, such as IMUs, have been increasingly used for FOG quantification and detection.[208]

Additionally, machine-learning algorithms have been increasingly used to provide an automated detection of FOG.[476,477] We created a model for FOG detection using the continuous IMU data from previously assessed PD patients[381] , which was fed into a convolutional neural network (CNN), an approach that has previously proved its capacity in capturing complex movement and accurately detecting FOG.[478] The results where then applied to the current sample of DBS patients. Our model for automatic FOG detection has shown to capture well the clinical phenomenon, with a good correlation with clinical detection of FOG episodes across all experimental conditions, which comes in line with previous works showing good correlation between automatic-FOG detection methods and clinical metrics.[477] In addition, the automatic detection of the percentage of FOG in gait significantly decreased from Med OFF / Stim OFF condition to Med ON / Stim ON condition, suggesting it is sensitive to treatment modulation. In future, replication of our results in different populations and bigger sample is needed, as well as the assessment of its ability to detect subclinical FOG.

A discussion about the true episodic nature of FOG and the artificial split between episodic and continuous gait disorders, is ongoing.[122] Objective gait analysis, especially when performed in ambulatory settings throughout long time-periods, can provide useful insights regarding the overall gait structure, clarifying how the presence of continuous alterations on the background gait may predispose to the emergence of a clinical episode of FOG. PD patients with FOG present higher gait variability and asymmetry than PD patients without FOG, even outside FOG episodes.[210,213–215] An increase in gait variability has been linked to an elevated risk of negative gait outcomes, including risk of falls,[229,436,479] suggesting that increased gait variability discloses a significant disruption of normal gait patterns. Here one can picture that the presence of this severe background and continuous gait deficits will progressively accumulate until a certain threshold is achieved and a FOG episode occurs – threshold model. [122]

In our work, the gait metrics who were most strongly associated with both clinical or automatic FOG metrics were gait variability, asymmetry, and non-linear metrics, with this holding true across all tested conditions This was also evident with PC1, that being

mostly composed by variability and asymmetry metrics, showed a significant decrease with medication and stimulation closely followed the behavior of clinical observed freezing events. This may argue that the existence of severe gait alterations will be associated to a decrease on the freezing threshold, and "normalization" of this background gait alterations could potentially translate into a lower likelihood of FOG.

Our kinematic gait analysis was made including freezing episodes, that may potentially contribute to the estimation of kinematic variables. Importantly, in the LFS/HFS scenario, the number of FOG episodes is similar, and kinematic patterns distinct, suggesting that even in this scenario kinematics can captures non-FOG changes. To properly ascertain the background gait in PD freezers a comparison with an age and disease duration-matched non-freezer group should be performed. Our results favors the idea that cumulative and severe gait alterations will culminate on a clinical FOG event, that will only represent the "tip of the iceberg" of profound and subclinical gait disturbances. Recently, stride time variability was used as a biomarker to modulate adaptative DBS, with positive effects in FOG.[480] Enriching this "kinematic biomarker" with comprehensive set of gait variables known to capture FOG could provide an attractive treatment strategy.

Several limitations should be considered when interpreting the findings of this study. Firstly, the small sample size restricts the generalizability of the results and may diminish statistical power to detect significant effects. Additionally, the absence of randomization and blinding in the evaluation process introduces potential biases into the study design. The LD dose administered during the LCT was determined based on pre-surgery assessments and may underestimate the actual dosage required. Accurately estimating the post-surgery LD dose post STN-DBS surgery is challenging due to post-surgery LEDD reduction. Consequently, many STN-DBS studies employ fixed LD doses of 200-250 mg for the LCT. In this study, an average LD dose of 433 mg was utilized, exceeding the dosages typically employed in prior research. Our kinematic gait analysis incorporated freezing episodes, potentially impacting the observed results. Nevertheless, consistent relationships between analyzed metrics and FOG were observed in all the analysis performed, aligning with prior research findings. [157,211,212]

In summary, at a group level, post-surgery FOG still responds to LD and DBS, even if the LD-induced improvement observed pre-surgery cannot be fully reproduced. A high inter-individual variability exists on response to treatment, claiming for an individualized approach to FOG. Importantly, freezers who not response to medication may still respond to stimulation: a pivotal observation regarding patients' selection for surgery. Automatic detection of FOG is reliable and correlates well with clinical assessment. The identification of an association between gait variability-related metrics and FOG may provide valuable insights into the biomechanics of gait in FOG patients and may be used in the future to monitor disease progression and optimize therapeutic strategies.

Supplementary Material - Chapter VI

Supplementary Table S6.1– Comparison between OFF/OFF and ON/ON HFS and ON/ON HFS and ON/ON LFS conditions using individual paired-Wilcoxons test

Variable	OFF/OFF vs ON/ON HFS	ON/ON HFS vs ON/ON LFS
MDS-UPDRS part III	0.0003	0.3921
Axial score	0.0064	0.0339
Item 3.10	0.0890	0.0708
Item 3.11	0.0077	0.2985
Item 3.12	0.0119	0.1814
SWS time (s)	0.0179	0.8361
SWS nº FOG events	0.0258	0.4103
H&Y	0.0477	0.0947
AIMS score	0.0104	0.3598
FoG %	0.0174	0.6777
Cadence	0.1089	0.0448
COM_RMS_AP	0.1743	0.7467
COM_RMS_ML	0.1202	0.6777
COM_RMS_Vert	0.2435	0.3778
Cycle_Time	0.0569	0.5171
Cycle_Time_Variability	0.0150	0.0448
Double_Support Asymmetry	0.1454	0.0174
Double_Support Variability	0.7119	0.0232
Percentage Double_Support	0.6777	0.1454
Entropy_AP	0.2247	0.2842
Entropy_ML	0.1901	0.0348
Entropy_Vert	0.4586	0.7119
HR_AP	0.5171	0.5171
HR_ML	0.4307	0.4307
HR_Vert	0.8536	0.8536
Speed	0.3778	0.3778
Speed_Variability	0.7819	0.7819
Stance_Time_Percent_Variability_ws	0.0714	0.0714
Stance_Time	0.0174	0.0174
Step_Length_Asymmetry	0.0984	0.0984
Step_Length_Variabilit	0.2435	0.2435
Step_Length	0.5791	0.5791
Step_Time_Asymmetry	0.9632	0.9632
Step_Time_Variability	0.6777	0.6777
Step_Time	0.1454	0.1454
Step_Width	0.0202	0.0202
Step_Width_Variability	0.0984	0.0984
Swing_Time_Asymmetry	0.4874	0.4874
Swing_Time_Variability	0.1454	0.1454
Swing_Time	0.0267	0.0267

OFF/OFF, Medication OFF-Stimulation OFF ; ON/ON HFS, Medication ON-Stimulation ON 130 Hz; ON/ON LFS, Medication ON-Stimulation ON 60 Hz; MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SWS, Stand-Walk sit test; FOG, Freezing of gait; H&Y, Hoehn and Yahr Scale; AIMS, Abnormal Involuntary Movement Scale; FOG%; % of FOG in straight line; Center-of-Mass; AP, Antero-Posterior; Vert; Vertical; ML, Medio-lateral; HR, Harmonic-ratio

Supplementary Table S6.2 – Clinical variable under analysis in the Levodopa-resistant patients, n=5

	Summary statistics (Mean ± SD)			Friedman test	Multiple comparisons		
Variable	**OFF/OFF**	**ON/OFF**	**OFF/ON**		**OFF/OFF vs ON/OFF**	**OFF/OFF vs OFF/ON**	**ON/OFF VS OFF/ON**
#FOG episodes	8.80 ± 8.044	15.80 ± 6.834	1.800 ± 2.490	0.002	0.206	0.082	0.003
SWS time (s)	108.00± 87.75	198.2±84.32	55.00 ±183.2	0.039	0.6177	0.6177	0.0342
MDS-UPDRS III score	61.80 ± 15.47	53.40 ± 13.16	46.60 ± 8.142	0.0216	0.2460	0.0342	>0.9999
MDS-UPDRS non axial	54.00 ± 13.67	43.80 ± 10.62	40.40 ±7.197	0.0239	0.0342	0.0806	>0.9999
MDS-UPDRS axial	7.800 ± 4.817	9.600 ± 3.975	6.200 ± 4.438	0.0278	0.4642	>0.9999	0.0489
AIMS score	8.400 ± 13.45	12.40 ± 12.12	6.400 ± 11.08	0.1111	>0.9999	0.8051	0.2460

Data are expressed as mean & SD. Abbrev: MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SWS, Stand-Walk sit test; FOG, Freezing of gait; H&Y, Hoehn and Yahr Scale; AIMS, Abnormal Involuntary Movement Scale; MedOFF-StimOFF, Medication OFF-Stimulation OFF; MedOFF-StimON, Medication OFF-Stimulation ON; MedON-StimOFF, Medication ON-Stimulation OFF; MedON-StimON 130 Hz, Medication ON-Stimulation ON 130 Hz; MedON-StimON 60 Hz, Medication ON-Stimulation ON 60 Hz

Supplementary Table S6.3– Clinical variable under analysis in Stimulation-resistant patients, n=3

	Summary statistics (Mean ± SD)			Friedman test	Multiple comparisons		
Variable	**OFF/OFF**	**ON/OFF**	**OFF/ON**		**OFF/OFF vs ON/OFF**	**OFF/OFF vs OFF/ON**	**ON/OFF VS OFF/ON**
#FOG episodes	13.61± 6.727	4.546 ± 2.858	26.00 ±11.53	<0.0001	0.0008	0.0201	11.56 ± 12.86
SWS time (s)	287.0 ± 239.9	113.8 ± 126.8	359.3 ± 119.0	0.0029	0.0286	0.0065	137.4 ± 140.6
MDS-UPDRS III	67.33 ± 8.083	52.67 ± 12.86	53.33 ± 6.028	<0.0001	0.0553	0.0002	43.11 ± 8.638
MDS-UPDRS non axial	55.00 ± 6.083	44.00 ± 10.82	42.67 ± 8.505	<0.0001	0.0400	0.0003	35.67 ± 7.583
MDS-UPDRS axial	12.33 ± 3.786	8.667 ± 5.508	10.67 ± 3.055	0.0123	0.1354	0.0286	7.444 ± 2.789
AIMS score	0.000 ± 0.000	10.00 ± 10.00	10.00 ± 10.00	0.1070	0.5846	>0.9999	2.889 ± 5.011

Data are expressed as mean & SD. Abbrev: MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SWS, Stand-Walk sit test; FOG, Freezing of gait; H&Y, Hoehn and Yahr Scale; AIMS, Abnormal Involuntary Movement Scale; MedOFF-StimOFF, Medication OFF-Stimulation OFF; MedOFF-StimON, Medication OFF-Stimulation ON; MedON-StimOFF, Medication ON-Stimulation OFF; MedON-StimON 130 Hz, Medication ON-Stimulation ON 130 Hz; MedON-StimON 60 Hz, Medication ON-Stimulation ON 60 Hz

Supplementary Table S6.4 – Clinical variable under analysis in patients responsive to both stimulation and medication, n=9

	Summary statistics (Mean ± SD)			Friedman test	Multiple comparisons		
Variable	**OFF/OFF**	**ON/OFF**	**OFF/ON**		**OFF/OFF vs ON/OFF**	**OFF/OFF vs OFF/ON**	**ON/OFF VS OFF/ON**
#FOG episodes	22.78 ± 19.36	6.210 ± 6.575	11.56 ± 12.86	<0.0001	0.0008	0.0201	>0.9999
SWS time (s)	280.9 ± 220.6	99.37 ± 80-54	137.4 ± 140.6	0.0029	0.0286	0.0065	>0.9999
MDS-UPDRS III score	60.33 ± 6.801	46.00 ± 7.969	43.11 ± 8.638	<0.0001	0.0553	0.0002	0.2969
MDS-UPDRS non axial	50.22 ± 5.718	38.44 ± 7.055	35.67 ± 7.583	<0.0001	0.0400	0.0003	0.4719
MDS-UPDRS axial	10.11 ± 3.018	7.556 ± 2.603	7.444 ± 2.789	0.0123	0.1354	0.0286	>0.9999
AIMS score	3.111 ± 3.756	7.222 ± 8.182	2.889 ± 5.011	0.1070	0.5846	>0.9999	0.3765

Data are expressed as mean & SD. Abbrev: MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SWS, Stand-Walk sit test; FOG, Freezing of gait; H&Y, Hoehn and Yahr Scale; AIMS, Abnormal Involuntary Movement Scale; MedOFF-StimOFF, Medication OFF-Stimulation OFF; MedOFF-StimON, Medication OFF-Stimulation ON; MedON-StimOFF, Medication ON-Stimulation OFF; MedON-StimON 130 Hz, Medication ON-Stimulation ON 130 Hz; MedON-StimON 60 Hz, Medication ON-Stimulation ON 60 Hz

Supplementary Table S6.5: Correlation between automatic FOG detection (%FOG) and clinical FOG assessment (#FOG episodes and SWS time)

	Correlation coefficient (r)	p-value
%FOG x #FOG epsiodes MedOFFStimOFF	0.807	<0.001
%FOG x #FOG epsiodes MedONStimOFF	0.741	<0.001
%FOG x #FOG epsiodes MedOFFStimON	0.782	<0.001
%FOG x #FOG epsiodes MedONStimON LFS	0.802	<0.001
%FOG x #FOG epsiodes MedONStimON LFS	0.543	0.024
% FOG x SWS time MedOFFStimOFF	0.828	<0.001
% FOG x SWS time MedONStimOFF	0.760	<0.001
% FOG x SWS time MedOFFStimON	0.924	<0.001
% FOG x SWS time MedONStimON HFS	0.796	<0.001
% FOG x SWS time MedONStimON LFS	0.429	0.087

Abbrev: %FOG: percentage of FOG detected by a automatic model; #FOG episodes: number of FOG episodes during the SWS test; SWS time: time needed to perform de SWS test; MedOFFStimOFF: Medication OFF/Stimulation OFF; MedONStimOFF: Medication ON/Stimulation OFF; MedOFFStimON: Medication OFF/Stimulation ON; MedONStimON: Medication ON/Stimulation ON

Supplementary Table S6.6: Correlation between each individual kinematic variable and automatic FOG detection (%FOG)

	Correlation coefficient	P-value
Cadence x %FOG MedOFFStimOFF	-0.475	0.056
Cadence x %FOG MedONStimOFF	-0.629	0.008
Cadence x %FOG MedOFFStimON	-0.456	0.068
Cadence x %FOG MedONStimON HFS	-0.211	0.415
Cadence x %FOG MedONStimON LFS	-0.022	0.936
Speed x %FOG MedOFFStimOFF	-0.174	0.503
Speed x %FOG MedONStimOFF	-0.549	0.024
Speed x %FOG MedOFFStimON	-0.201	0.438
Speed x %FOG MedONStimON HFS	-0.439	0.079
Speed x %FOG MedONStimON LFS	0.252	0.327
Step Width x %FOG MedOFFStimOFF	-0.721	0.002
Step Width x %FOG MedONStimOFF	-0.216	0.404
Step Width x %FOG MedOFFStimON	-0.230	0.372
Step Width x %FOG MedONStimON HFS	-0.395	0.118
Step Width x %FOG MedONStimON LFS	0.047	0.861
Cycle Time x %FOG MedOFFStimOFF	0.537	0.028
Cycle Time x %FOG MedONStimOFF	0.593	0.014
Cycle Time x %FOG MedOFFStimON	0.502	0.042
Cycle Time x %FOG MedONStimON HFS	0.399	0.113
Cycle Time x %FOG MedONStimON LFS	-0.044	0.869
Step Time x %FOG MedOFFStimOFF	0.522	0.034
Step Time x %FOG MedONStimOFF	0.348	0.171
Step Time x %FOG MedOFFStimON	0.277	0.281
Step Time x %FOG MedONStimON HFS	0.245	0.342
Step Time x %FOG MedONStimON LFS	-0.091	0.729
Swing Time x %FOG MedOFFStimOFF	0.846	0
Swing Time x %FOG MedONStimOFF	0.534	0.029
Swing Time x %FOG MedOFFStimON	0.422	0.093
Swing Time x %FOG MedONStimON HFS	0.544	0.026
Swing Time x %FOG MedONStimON LFS	0.118	0.653
% Double Support x %FOG MedOFFStimOFF	0.804	0.001
% Double Support x %FOG MedONStimOFF	0.311	0.223
% Double Support x %FOG MedOFFStimON	0.787	0.001
% Double Support x %FOG MedONStimON HFS	0.561	0.021
% Double Support x %FOG MedONStimON LFS	0.610	0.011
% Stance Time x %FOG MedOFFStimOFF	-0.873	0
% Stance Time x %FOG MedONStimOFF	-0.537	0.028
% Stance Time x %FOG MedOFFStimON	-0.422	0.093
% Stance Time x %FOG MedONStimON HFS	-0.542	0.027
% Stance Time x %FOG MedONStimON LFS	-0.118	0.653
Step Lenght x %FOG MedOFFStimOFF	-0.907	0
Step Lenght x %FOG MedONStimOFF	-0.637	0.007
Step Lenght x %FOG MedOFFStimON	-0.686	0.003
Step Lenght x %FOG MedONStimON HFS	-0.564	0.020
Step Lenght x %FOG MedONStimON LFS	-0.395	0.118
Speed Variability x %FOG MedOFFStimOFF	0.848	0
Speed Variability x %FOG MedONStimOFF	0.730	0.001
Speed Variability x %FOG MedOFFStimON	0.819	<0.001
Speed Variability x %FOG MedONStimON HFS	0.556	0.022
Speed Variability x %FOG MedONStimON LFS	0.5	0.043
Step Width Variability x %FOG MedOFFStimOFF	0.578	0.017
Step Width Variability x %FOG MedONStimOFF	0.108	0.680
Step Width Variability x %FOG MedOFFStimON	0.431	0.085
Step Width Variability x %FOG MedONStimON HFS	0.341	0.181
Step Width Variability x %FOG MedONStimON LFS	0.216	0.404
Cycle time Variability x %FOG MedOFFStimOFF	0.757	<0.001
Cycle time Variability x %FOG MedONStimOFF	0.576	0.017
Cycle time Variability x %FOG MedOFFStimON	0.804	<0.001
Cycle time Variability x %FOG MedONStimON HFS	0.458	0.066
Cycle time Variability x %FOG MedONStimON LFS	0.551	0.024
Step time Variability x %FOG MedOFFStimOFF	0.797	<0.001
Step time Variability x %FOG MedONStimOFF	0.544	0.026
Step time Variability x %FOG MedOFFStimON	0.831	<0.001
Step time Variability x %FOG MedONStimON HFS	0.365	0.149
Step time Variability x %FOG MedONStimON LFS	0.608	0.011
Swing time Variability x %FOG MedOFFStimOFF	0.740	0.001
Swing time Variability x %FOG MedONStimOFF	0.309	0.227
Swing time Variability x %FOG MedOFFStimON	0.762	<0.001

Swing time Variability x %FOG MedONStimON HFS	0.566	0.019
Swing time Variability x %FOG MedONStimON LFS	0.475	0.055
Double support Variability x %FOG MedOFFStimOFF	0.799	<0.001
Double support Variability x %FOG MedONStimOFF	0.458	0.066
Double support Variability x %FOG MedOFFStimON	0.804	<0.001
Double support Variability x %FOG MedONStimON HFS	0.404	0.109
Double support Variability x %FOG MedONStimON LFS	0.451	0.071
Stance time Variability x %FOG MedOFFStimOFF	0.777	<0.001
Stance time Variability x %FOG MedONStimOFF	0.453	0.06
Stance time Variability x %FOG MedOFFStimON	0.812	<0.001
Stance time Variability x %FOG MedONStimON HFS	0.576	0.017
Stance time Variability x %FOG MedONStimON LFS	0.368	0.147
Step Lenght Variability x %FOG MedOFFStimOFF	0.583	0.016
Stance time Variability x %FOG MedONStimOFF	0.301	0.239
Step Lenght Variability x %FOG MedOFFStimON	0.409	0.104
Step Lenght Variability x %FOG MedONStimON HFS	0.221	0.393
Step Lenght Variability x %FOG MedONStimON LFS	0.377	0.136
Step Lenght Variability x %FOG MedOFFStimOFF	0.706	0.002
Step Lenght Variability x %FOG MedONStimOFF	0.343	0.178
Step Lenght Variability x %FOG MedOFFStimON	0.767	<0.001
Step Lenght Variability x %FOG MedONStimON HFS	0.485	0.050
Step Lenght Variability x %FOG MedONStimON LFS	0.446	0.074
Step Time Asymmetry x %FOG MedOFFStimOFF	0.588	0.015
Step Time Asymmetry x %FOG MedONStimOFF	0.392	0.120
Step Time Asymmetry x %FOG MedOFFStimON	0.311	0.223
Step Time Asymmetry x %FOG MedONStimON HFS	0.453	0.069
Step Time Asymmetry x %FOG MedONStimON LFS	-0.598	0.013
Step length Asymmetry x %FOG MedOFFStimOFF	0.502	0.042
Step length Asymmetry x %FOG MedONStimOFF	0.495	0.045
Step length Asymmetry x %FOG MedOFFStimON	0.412	0.102
Step length Asymmetry x %FOG MedONStimON HFS	0.439	0.079
Step length Asymmetry x %FOG MedONStimON LFS	0.259	0.313
Swing Time Asymmetry x %FOG MedOFFStimOFF	-0.331	0.1944
Swing Time Asymmetry x %FOG MedONStimOFF	- 0.4632	0.063
Swing Time Asymmetry x %FOG MedOFFStimON	-0.181	0.485
Swing Time Asymmetry x %FOG MedONStimON HFS	-0.108	0.680
Swing Time Asymmetry x %FOG MedONStimON LFS	0	1
Double Support Asymmetry x %FOG MedOFFStimOFF	0.238	0.357
Double Support Asymmetry x %FOG MedONStimOFF	0.027	0.921
Double Support Asymmetry x %FOG MedOFFStimON	0.251	0.332
Double Support Asymmetry x %FOG MedONStimON HFS	0.532	0.030
Double Support Asymmetry x %FOG MedONStimON LFS	-0.319	0.212
Antero-Posterior Entropy x %FOG MedOFFStimOFF	0.184	0.479
Antero-Posterior Entropy x %FOG MedONStimOFF	0.088	0.737
Antero-Posterior Entropy x %FOG MedOFFStimON	0.139	0.592
Antero-Posterior Entropy x %FOG MedONStimON HFS	0.509	0.039
Antero-Posterior Entropy x %FOG MedONStimON LFS	-0.108	0.680
Vertical Entropy x %FOG MedOFFStimOFF	-0.735	0.001
Vertical Entropy x %FOG MedONStimOFF	- 0.635	0.007
Vertical Entropy x %FOG MedOFFStimON	- 0.610	0.011
Vertical Entropy x %FOG MedONStimON HFS	- 0.336	0.188
Vertical Entropy x %FOG MedONStimON LFS	- 0.483	0.052
Medio-lateral Entropy x %FOG MedOFFStimOFF	-0.691	0.003
Medio-lateral Entropy x %FOG MedONStimOFF	-0.647	0.006
Medio-lateral Entropy x %FOG MedOFFStimON	-0.542	0.027
Medio-lateral Entropy x %FOG MedONStimON HFS	-0.449	0.073
Medio-lateral Entropy x %FOG MedONStimON LFS	-0.103	0.694
Anterio-posterior Harmonic Ratio x %FOG MedOFFStimOFF	-0.691	0.191
Anterio-posterior Harmonic Ratio x %FOG MedONStimOFF	-0.647	0.585
Anterio-posterior Harmonic Ratio x %FOG MedOFFStimON	-0.542	0.016
Anterio-posterior Harmonic Ratio x %FOG MedONStimON HFS	-0.449	0.029

Anterio-posterior Harmonic Ratio x %FOG MedONStimON LFS	-0.103	0.579
Vertical Harmonic Ratio x %FOG MedOFFStimOFF	-0.333	0.065
Vertical Harmonic Ratio x %FOG MedONStimOFF	-0.142	0.004
Vertical Harmonic Ratio x %FOG MedOFFStimON	-0.581	0.281
Vertical Harmonic Ratio x %FOG MedONStimON HFS	-0.534	0.091
Vertical Harmonic Ratio x %FOG MedONStimON LFS	-0.145	0.021
Medio-lateral Harmonic Ratio x %FOG MedOFFStimOFF	-0.461	0.012
Medio-lateral Harmonic Ratio x %FOG MedONStimOFF	-0.674	0.883
Medio-lateral Harmonic Ratio x %FOG MedOFFStimON	-0.277	0.006
Medio-lateral Harmonic Ratio x %FOG MedONStimON HFS	-0.424	0.043
Medio-lateral Harmonic Ratio x %FOG MedONStimON LFS	-0.561	0.817
Antero-posterior COM x %FOG MedOFFStimOFF	-0.603	0.118
Antero-posterior COM x %FOG MedONStimOFF	-0.039	0.268
Antero-posterior COM x %FOG MedOFFStimON	-0.652	0.073
Antero-posterior COM x %FOG MedONStimON HFS	-0.501	0.162
Antero-posterior COM x %FOG MedONStimON LFS	0.061	0.497
Vertical COM x %FOG MedOFFStimOFF	-0.395	0.082
Vertical COM x %FOG MedONStimOFF	-0.284	0.004
Vertical COM x %FOG MedOFFStimON	-0.448	0.010
Vertical COM x %FOG MedONStimON HFS	-0.355	0.126
Vertical COM x %FOG MedONStimON LFS	0.176	0.653
Medio-lateral COM x %FOG MedOFFStimOFF	-0.436	0.082
Medio-lateral COM x %FOG MedONStimOFF	-0.672	0.004
Medio-lateral COM x %FOG MedOFFStimON	-0.618	0.009
Medio-lateral COM x %FOG MedONStimON HFS	-0.387	0.126
Medio-lateral COM x %FOG MedONStimON LFS	0.118	0.653

Abbrev: %FOG: percentage of FOG detected by a automatic model; MedOFFStimOFF: Medication OFF/Stimulation OFF; MedONStimOFF: Medication ON/Stimulation OFF; MedOFFStimON: Medication OFF/Stimulation ON; MedONStimON: Medication ON/Stimulation ON

Supplementary Table S6.7: Correlation between PC1 and clinical FOG assessment (#FOG episodes and SWS time) and automatic FOG detection (%FOG)

	Correlation coefficient	pvalue
PC1 x #FOG episodes MedOFF/StimOFF	0.951	<0.05
PC1 x #FOG episodes MedON/StimOFF	0.089	>0.05
PC1 x #FOG episodes MedOFF/StimON	0.393	>0.05
PC1 x #FOG episodes MedON/StimON HFS	0.585	<0.05
PC1 x #FOG episodes MedON/StimON LFS	0.596	<0.05
PC1 x SWS time MedOFF/StimOFF	0.912	<0.05
PC1 x SWS time MedON/StimOFF	0.132	>0.05
PC1 x SWS time MedOFF/StimON	0.608	<0.05
PC1 x SWS time MedON/StimON HFS	0.706	<0.05
PC1 x SWS time MedON/StimON LFS	0.551	<0.05
PC1 x %FOG MedOFF/StimOFF	0.875	<0.05
PC1 x %FOG MedON/StimOFF	0.501	<0.05
PC1 x %FOG MedOFF/StimON	0.387	>0.05
PC1 x %FOG MedON/StimON HFS	0.539	<0.05
PC1 x %FOG MedON/StimON LFS	0.468	>0.05

Abbrev: %FOG: percentage of FOG detected by a automatic model; PC1, Principal Component 1; #FOG episodes: number of FOG episodes during the SWS test; SWS time: time needed to perform de SWS test; MedOFFStimOFF: Medication OFF/Stimulation OFF; MedONStimOFF: Medication ON/Stimulation OFF; MedOFFStimON: Medication OFF/Stimulation ON; MedONStimON: Medication ON/Stimulation ON

Supplementary Table S6.8: Comparison between conditions using Friedman test with adjustment for multiple comparisons

Variable	Friedman test	Multiple comparisons adjustment		
	p-value	OFFOFF vs OFFON	OFFOFF vs ONOFF	OFFON vs ONOFF
UPDRS_III	0.000001	0.00072	0.00072	0.05873
Item_3_10	0.367879	0.27	0.61	0.61
Item_3_11	0.035973	0.023	0.229	0.229
Item_3_12	0.001503	0.036	0.05	0.346
SWS_time_s	0.019425	0.054	0.107	0.927
SWS_N_FOG_Events	0.016473	0.074	0.074	0.552
HY	0.094078	0.14	0.3	0.89
AXIAL_score	0.010567	0.019	0.108	0.291
FoG%	0.000281193	0.000046	0.076	0.459
Cadence	0.011440584	0.052	1	0.085
Speed	0.942873144	0.96	0.96	0.96
Speed_Variability	0.034981316	0.29	0.29	0.68
Step_Time_Asymmetry	0.05939594	0.045	0.12	0.548
Step_Length_Asymmetry	0.290749235	0.75	0.75	0.75
Swing_Time_Asymmetry	0.58895131	0.73	0.89	0.73
Double_Support_Percent_Asymmetry	0.120314388	1	0.16	0.16
Step_Width	0.390168543	0.3	0.37	0.58
Step_Width_Variability	0.838223432	0.61	0.75	0.61
Cycle_Time	0.10085034	0.067	0.12	0.067
Cycle_Time_Variability	0.327048416	0.17	0.18	0.22
Entropy_AP	0.012133747	0.0063	0.5791	0.5791
Entropy_Vert	0.10085034	0.059	0.89	0.052
Entropy_ML	0.056002836	0.03	0.024	0.712
HR_AP	0.013648609	0.579	0.039	0.261
HR_Vert	0.161454903	0.33	0.27	0.33
HR_ML	0.009589766	0.12	0.68	0.12
COM_RMS_AP	0.05939594	0.678	0.12	0.12
COM_RMS_Vert	0.465470814	0.62	1	1
COM_RMS_ML	0.161454903	0.78	0.06	0.31
GDI_Percent	0.662480135	0.93	0.4	0.65
Step_Time	0.012133747	0.039	0.927	0.04
Step_Time_Variability	0.04694289	0.07	1	0.24
Swing_Time	0.001376467	0.002	0.19	0.002
Swing_Time_Variability	0.838223432	0.82	0.82	0.82
Double_Support_Percent	0.079705892	0.36	0.85	0.57
Double_Support_Percent_Variability	0.120314388	0.33	0.33	0.33
Stance_Time_Percent	0.001376467	0.002	0.19	0.002
Stance_Time_Percent_Variability	0.079705892	0.017	0.12	0.12
Step_Length	0.056002836	0.12	0.37	0.68
Step_Length_Variability	0.034981316	0.028	0.89	0.18

OFF/OFF, Medication OFF-Stimulation OFF ; OFF/ON H, Medication OFF-Stimulation ON; ON/OFF, Medication ON-Stimulation OFF; MDS UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; SWS, Stand-Walk sit test; FOG, Freezing of gait; H&Y, Hoehn and Yahr Scale; AIMS, Abnormal Involuntary Movement Scale; FOG%; % of FOG in straight line; Center-of-Mass; AP, Antero-Posterior; Vert; Vertical; ML, Medio-lateral; HR, Harmonic-ratio

Chapter VII – General Discussion

The introduction of DBS 30 years ago has changed the life of PD patients with bothersome levodopa-induced motor complications. However, and despite the significative improvement on motor symptoms, quality of life and motor fluctuations, the results on axial signs, specially gait and freezing remained far from optimal.

The nature of gait and freezing that emerge after DBS-STN surgery in patients with well controlled appendicular symptoms is still not clear. It has been hypothesized that stimulation spreading to neighboring structures could be implicated on the emergence/ worsening of gait and freezing. It has also been hypothesized that gait impairment and freezing would appear after STN-DBS surgery as a consequence of disease progression. In this case, the loss of benefit of stimulation (and medication) would be attributed to the involvement of non-dopaminergic systems, not amenable to modulation by these therapies.

However, the true burden of freezing of gait (FOG) and gait impairment after surgery remains unclear. Additionally, pre-surgery metrics that can aid in identifying patients with a higher probability of developing gait disturbance during medium and long-term follow-up have not yet been elucidated.

Additionally, the best strategy to manage the patients who evolve to present FOG and gait disorders is still not completely defined.

Our work addresses the question of gait impairment and FOG after STN-DBS by evaluating the PD patient at different points, along their pathway from the pre-surgery assessment to the long-term follow up. Evaluation at different moments enabled us to answer different, but interconnected, questions, all aiming to understand the nature of gait disorders after stimulation.

The frequency and risk factors for gait impairment and FOG after STN-DBS surgery: introducing Freezing as a disability milestone

Freezing is a common symptom in PD non-STN DBS patients, with prevalence increasing with disease progression, being estimated that 50-70% of patients will present FOG after 10 years of diseases. Due to the fact that gait and FOG were not primary outcomes in previous large-scale, randomized controlled trials, the frequency of FOG in patients submitted to STN-DBS is still not clear. Studies employing retrospective designs with FOG assessment relying mostly on item 14 of the UPDRS part II, have generated data predominantly focused on the STN-DBS impact on FOG severity.[312,336,377] Some more recent studies, have employed more objective metrics to assess the impact of stimulation on FOG, both in severity and incidence [481] but we are still lacking in information regarding the prevalence of FOG after surgery. Several studies indicate an overall FOG prevalence ranging from 34% to 56% post-surgery, with results varying with follow-up duration (1 to 7 years follow-up have been reported) ,assessment method employed and the type of medication- condition(off or on-medication) state.[312,481,482]

In this thesis we have studied the frequency of FOG after STN-DBS surgery in two different samples. For both studies, FOG was assessing using the item 3.11 of the MDS-UPDRS part III score, providing a more clinician, instead of patient, -based assessment of the presence of FOG.

In our initial retrospective study, we assessed the prevalence of FOG in a cohort of patients with a follow-up of 8 years after STND-DBS surgery. We found that at the end of the follow-up 47% of the patients presented FOG with FOG appearing relatively earlier after surgery (on average 3 years). In this study we were also able to determinate that older age at surgery and higher UPDRS II OFF scores were the main predictors of post-surgery FOG. Freezers had also higher OFF gait scores (item 29) in the pre-surgery evaluation than non-freezers. The importance of the severity of axial signs in the OFF conditions, had already been shown by previous studies [327,482] and we reinforce it here. Our results seem to suggest that it's the pre-surgery disease severity, independently of their responsiveness to LD, that will mainly impact the development of FOG after surgery.

In this study, patients had been observed under routine medication and stimulation since the assessment has been made during a routine clinic evaluation. Despite providing an important information regarding the patient's habitual state it didn't enable us to pinpoint with precision which type of FOG were we facing, since the effects of stimulation and LD could not be specifically manipulated.

To address this issue, we conducted a second study, with a prospective design where both the presence, severity and type of FOG (OFF FOG, OFFON-FOG or ON FOG) [204] could be assess in different treatment conditions. Here, in the best-functional condition, FOG was present in 28% of the patients, a lower value than the one found in our retrospective study (47%). Different follow-up times (18 months vs 8 years) may justify the difference found, and hint to the role of disease progression on the emergence of axial signs not completely responsive do therapy.

Stimulation was able to improvr the percentage and severity of Off-medication FOG, when compared to the baseline (pre-surgery assessment) but also with the OFF-state at the end of FUP. This comes in line with previous works, showing the efficacity of stimulation in improving off-medication FOG outcomes. [312,336,481,482] We couldn't observe the same effect of stimulation in the ON-medication condition, where, on the reverse, a mild, non-significative worsening was observed. Again, the lack of benefit in the on-medication condition has been previously ascertained in other studies, and attributed to disease progression. In the Best-On condition 28% of the patients presented FOG contrasting with only 11% on the Best-ON condition at baseline. A significant reduction on levodopa responsiveness was also observed in this work, which may lead one to think that disease progression, with loss of levodopa sensitivity due to extension of the neuropathologic process to non-dopaminergic pathways, would be the explanation. However, previous works have also highlighted the role of post-surgery desensitization of the postsynaptic dopaminergic receptors on the observed decrease response to LD. [351] Even if both mechanisms may be present, an overall increase in motor scores from the baseline OFF to the post-surgery OFF condition suggests that disease progression is present even at 18 months after surgery and may be responsible for progression in freezing severity.

In this prospective study FOG was also assessed using the FOG-Questionnaire (FOG-Q), with 72% of the patients reporting the presence of FOG during the previous. Even if the lack of a baseline, pre-surgery data on FOG-Q constitutes an important limitation, precluding assessing the evaluation of this percentage throughout the follow-up, this data provides meaningful insights. First, it shows that FOG is a frequent complain in STN-DBS patients, even in the early follow-up. Secondly, there is a discordance between the percentage of self-reported FOG and clinical-observed FOG. This may be due to the fact that a clinical evaluation of FOG represents a limited snapshot of the overall motor behavior of the patient. In addition an improvement in FOG during medical visits has been previous reported, with clinicians failing to ascertain the presence and severity of the symptom.[192,242,474,483] On the other hand, a patient's subjective assessment of FOG will encompass a broader spectrum of conditions and a more extensive timeframe, which may increase the likelihood of detecting paroxysmal phenomena such as FOG. However, it is important to note that self-reports include a subjective component that can be influenced by the patient's interpretation of FOG symptoms, recall bias, and subjective experiences.This supports the case for a more ecological and objective assessment of FOG emphasizing the evaluation and monitoring of patients in ambulatory settings over time.[133,192,208]

In our retrospective study, falls were used as an indicator of the presence of gait impairment. This decision was influenced by the retrospective nature of the study and the lack of systematic descriptions of gait in clinical records. Conversely, falls were consistently documented and considered a proxy for gait impairment. Our findings revealed that 73% of patients experienced falls within 8 years of undergoing STN-DBS, with older and more severely affected patients at baseline exhibiting a greater likelihood of becoming fallers
In our prospective study, gait impairment was assessed using the item 3.10 of the MDS-UPDRS III. Mimicking the results observed for FOG, an overall increase in the percentage of gait impairment was observed, with the majority of patients (78%) presenting a therapy-resistant gait impairment, whilst before surgery only 1 patient had a therapy-resistant gait impairment. Consequently, the percentage of patients with gait changes in

the Best-Functional condition significantly increased. The effects of stimulation were less effective than for FOG, and didn't follow the same pattern as observed in previous studies [336,484]. In our study stimulation was associated to a worsening in gait outcomes both in off and on-medication conditions. The kinematic results further validate these findings, with a worsening in kinematic metrics with stimulation in different gait domains. If these findings are solely due to disease progression or also represent a stimulation-induced side effect, deserve further exploration.[387,462,485] Our small sample size precludes further conclusions and it is warranted that studies in larger, independent cohorts be pursued to replicate these findings.

Overall, when pooling together the results from both cohorts, there is a decrease in levodopa (LD) responsiveness and an increase in overall motor scores from baseline to post-operative assessment in both the OFF and ON conditions. Additionally, there is a progressive increase in FOG frequency, rising from 28% at 18 months to 47% at 8 years after surgery. These findings collectively suggest that disease progression is the main cause for the increased FOG and gait impairment after surgery.

Markers of disease progression are extremely important in the management of neurodegenerative diseases since they enable us to monitor disease evaluation, define patient health status, adjust therapeutic strategies and helps clinicians (and patients and caregivers) to predict disease course, adjust behaviors and expectations.[61,486]

In PD, the emergence of falls, hallucinations, cognitive impairment and institutionalization, has been regarded as signaling the presence of a late-stage disease, with these symptoms clustering together and closely preceding death.[63,79,80] The prevalence and timing of emergence of these disability milestones has been well described in non-DBS cohorts [79,80,487–489] and more recently in DBS cohorts.[305,306,354,361,362,364,365,369,490] Across all studies, falls and dementia are the disability milestones more frequently assessed on the long-term PD cohorts. [491] Even if FOG is not classically recognized as a disability milestone (DM), we believe that it should be included in this set of symptoms associated with disease progression. First, FOG, as a symptom, is associated to a significant loss of autonomy, quality of life and increased morbidity.[173,193,373,444] Secondly, a temporal relationship

between FOG and the presence of other disability milestones has been found in our study, with the emergence of FOG being closed followed by the emergence of Falls. Moreover, in our findings, FOG preceded death by 3 years, which is a time lag similar to other disability milestones [79,80]. This reinforces the idea that FOG is part of this group of late-stage symptoms, appearing on the 4-5 years before death and sharing pathophysiology mechanisms, mostly non-dopamine dependent.

Specially in DBS cohorts, systematically assessing FOG may reinforce the notion of the existence of a "long-term DBS syndrome". This term, introduced by Fasano, describes the long-term PD patients submitted to DBS surgery that will evolve to a distinct phenotype where the main determinants of patients' autonomy and quality of live is the presence of axial signs and NMS, while rigidity, bradykinesia, tremor and levodopa-induced MC would have only a minorl impact . [127] The recognition of this phenotype of patients its particularly important since it enables clinicians to adjust patients' expectations and adopt measures that will help patients and caregivers to better cope with disability. Additionally, it emphasizes a group of unmet needs to improve patients' condition, which deserves much research.

With that in mind, this thesis supports the idea that 1) despite the initial good response to LD at baseline, FOG and gait impairment will emerge during the follow-up of PD STN-DBS patients, progressively increasing over time 2) FOG should be regarded as a disability milestone, claiming that future studies both in DBS and non-DBS patients should specifically assess its prevalence and risk factors.

The clinical relevance of objective movement assessment in PD STN-DBS patients:

Increasing accessibility to fine motor assessment through wearable devices

Motor assessment is a cornerstone in PD research and clinical practice. It remains the central element of PD diagnosis [44,220] and despite gait impairment, FOG and postural instability not being considered "necessary" for the diagnosis of PD, they represent major landmarks of PD staging, progression and prognosis[121,492–495] The current state-of-art for motor assessment is the Movement Disorders Society Unified Parkinson's Disease Ratings Scale (MDS-UPDRS) part III[220].

Although with high reliability and construct validity, [220] this assessment depends on proper training of raters and the dislocation of the rater and the subject to the same place. Proper assessment can take up to 20 minutes and it can only be performed when the 2 subjects (rater and ratee) meet. Inter-rater and intra-rater variability in motor assessment may contribute to MDS-UPDRS III over or underestimation[425,496], with a limited capacity to capture disease progression[425] and presenting an important floor effect and lack of granularity in early stage disease assessment .[497]

Acute drug challenge tests such as the LCT have been used since the 1980s for various clinical and experimental purposes. A positive response to LCT is still used as one of the main criteria for inclusion in surgical protocols, with levodopa responsiveness being considered an absolute requirement in the screening process for DBS.[321,328]. In addition, LCT can be used to differentiate idiopathic PD from other forms of parkinsonism. However, performance of the LCT requires a certain degree of expertise that is not present in all the clinical centers, which may preclude some patients to receive this type of assessment. [328]

Studying patients undergoing an LCT (**Chapter V**), we were able to show that kinematic-related metrics capture well the transition between medication-states, being able to clearly distinguish the OFF-medication state from the ON-medication state. This holds true when the LD challenge test was preformed either before (**Chapter V**) or after surgery (**Chapter IV**), with significative improvements from the OFF to the Medication-ON

condition in the globality of gait metrics, mimicking what happened with the MDS-UPDRS III scores.

In **Chapter IV**, we found that despite a clinical significant improvement in gait when using clinical metrics (item 3.10 MDS-UPDRS III), when dissecting gait into its several subcomponents, a uniform response to LD was not observed across all gait subcomponents, with some gait metrics not being improvedby LD. Whilst the effect of LD in spatiotemporal gait metrics had been already described,[152,404,405,498,499] its effect on metrics reflecting variability, smoothness and rhythmicity of gait has been less well explored.[154,462,500–502] In two of our cohorts (one assessing patients before surgery and other assessing patients at 18 months after surgery) spatiotemporal gait metrics as speed, stride length and step length significantly improved with LD whie its effect on gait variability and asymmety metrics, Harmonic Ratios and Entropy was less remarkable. One may speculate that while these latter gait metrics reflect more than the dopaminergic deficit,their dysfunction also being a the product of deregulation in other non-dopaminergic structures, and consequently less responsive to LD.

When assessing advanced, axial post-surgery PD patients (**chapter VI**), an overall decrease on the response to LD was observed across all kinematic-driven gait metrics. At the same time, clinical gait assessment also failed to capture a significant benefit from LD. In this cohort of older patients with longer disease duration, one can envisage that his loss of LD responsiveness can be related with disease progression. Here, again, we reinforce the idea that kinematic-related metrics relate well with the clinical observation and it can be used to assess transition (or lack of it) between states.

The role of LCT in predicting post-surgical outcomes, special gait axial outcomes has been discussed[206,323,324] , which led some authors to consider the use of kinematic-based LCT to predict post-surgery gait outcomes. In line with this, a previous study has shown that a preoperative LD response of stride length and range of movement at the lower limb was significantly correlated with favorable FOG outcomes.[335] Thought limited by the small sample size we have found that the response of specific kinematic gait-metrics to a pre-surgery LCT was correlated to the post-surgery outcomes of FOG. Moreover,

some of these gait metrics showed stronger correlation with the FOG outcomes than the LD response of the MDS-UPDRS III. In Cebi and colleagues' paper, the majority of the kinematic metrics studied pertained to the spatiotemporal and angular domains..[335] Based on a growing body of evidence that points to variability, asymmetry and gait metrics reflecting overall gait smoothness and regularity as particularly altered in freezer-patients, we included these metrics in our analysis. Remarkably Entropy, HR, stride time variability and stride time asymmetry were the metrics that best correlated with the outcome of FOG.

The use of wearable devices has shown the potential to increase objectivity in motor analysis whilst reducing inter and intra-rater variability. [395,396,424]In addition, it may democratize the access of patients to this fine motor assessment otherwise only possible in the presence of expert-raters, once wearables become more economic accessible to most centers and countries [395,396,424] The assessment of levodopa response during a LCT using wearable devices may enhance the evaluation of patients, offering a high-quality assessment of motor symptoms across different centers and reducing rater-dependent variability without requiring an expert rater. However, there will always be a need for a Parkinson's disease expert to interpret the data collected by the wearable device within the context of the patient's clinical history, providing it with clinical significance

In this thesis, studies assessing the role of wearable devices in motor assessment were conducted on a highly specific population of advanced Parkinson's disease (PD) patients experiencing motor fluctuations, all of whom were either candidates for or had already undergone subthalamic nucleus deep brain stimulation (STN-DBS) surgery. While internal validity was ensured through a strict study protocol and experimental manipulation of levodopa (LD) and stimulation, allowing for the establishment of causal relationships between the observed kinematic results, external validation of our findings remains necessary. Further studies involving larger cohorts, assessing patients at various disease stages, and conducted in ambulatory settings should be pursued to strengthen the generalizability of the results.

The role of automatic models for FOG detection

The currently gold-standard method for FOG assessment and quantification reposes on a video scoring of a gait test by independent experts. [208,242,249] However, no uniformity is found between centers, with some scoring FOG episodes by their clinical severity/duration whileothers reporting the percentage of gait time spent infreezing.[208,242,249] Whilst the reliability of inter-rater agreement was acceptable for the percent time frozen (ICC: 0.73), the inter-rater agreement for the number of freezing events was only moderate (intraclass correlation coefficient [ICC]: 0.63.[251] In addition, these scoring approaches remain time consuming, dependent on the presence of expert raters and still susceptible to individual variability and bias. The latter one may render difficult the comparison of scoring from raters working in different centers, which may assume particular importance when looking at multicentric studies. [208,242,249,251]

Thus, significant efforts have been made to use more objective FOG metrics, namely wearable devices (most commonly accelerometers).[132,133,208,424] In addition to increase objectivity, reduce inter-rater variability, this kind of measurement of gait also offers the possibility of assessing patients in ambulatory setting, which is highly desirable specially in the case of FOG, an episodic phenomenon often not observed during clinical evaluation.

A model for automatic quantification of the % of FOG during straight gait, previous validated in an independent cohort of 21 PD, was applied in our cohort of PD STN-DBNS patients presenting with severe FOG after surgery (**Chapter VI**). A high correlation between the % of FOG automatically detected by our model and clinical FOG metrics was found across all conditions tested. In addition, and mimicking the behavior of clinical metrics (e.g., number of FOG episodes and gait time) the % of FOG declined from the OFF condition to the Best-functional condition. This suggest that our model is not only able to capture well the presence of FOG but also is sensitive to the change of FOG with interventions. This finding require further validation, but they align with previous reports indicating that models utilizing wearable devices in conjunction with machine learning

techniques achieve high sensitivity, specificity, and accuracy when evaluating PD-FOG patients.[476,477,503,504]

In addition to the automatic assessment of FOG, a kinematic study of gait was also performed, enabling us to understand the behavior of different kinematic-driven gait metrics in these FOG patients. Previous studies comparing PD freezers vs non-freezers have found that the formers had higher levels of gait variability and asymmetry then their non-freezers counterpart.[210–215] Variability and asymmetric gait metrics were also the gait metrics that better explained gait alterations in our cohort of FOG patients. This holds true for the assessment of individual gait metrics but also when a PCA is applied in order to reduce the number of variables and facilitate interpretation of data. These variables correlated well with the presence of FOG (both assessed clinical or by our automatic model), changing across treatment conditions, according to the behavior of FOG, as assessed by the different clinical methods.

We recognize that the lack of a non-FOG control group and the fact that kinematic gait analysis was performed across all gait moments, including FOG episodes, may contaminate the analyses of the background gait and limit some of the results found. Even so, and similar to previous works, it appears that increase gait variability and asymmetry may be associated to the presence of FOG, probably reflecting the presence of alterations on background gait. Interestingly, these gait variables seem to be relatively unaffected by levodopa or even stimulation.

In **chapter VI** distinct profiles of patients regarding their responsiveness to therapy have been identified. These distinct profiles of response are also seen at a kinematic level, with some gait metrics being specifically modulated by LD, HFS, LFS.

Over the past decade, precision medicine approaches have received significant investment in order to tailor medical care and interventions to the specific characteristics of each patient, allowing for more accurate and effective treatments.[505,506]

Precision medicine can leverage advanced technologies, such as wearable sensors and gait analysis tools, to monitor and analyze a patient's gait pattern. Objective data from wearable devices can provide valuable insights into the specific characteristics of gait and

freezing episodes and help tailor interventions based on the specific gait characteristics of each patient.[480] For example, knowing that specific gait metrics respond better to specific gait interventions, may help adapt therapeutic regimens according to the gait metrics most profoundly altered.

However, despite the allure of having abundant data with a higher level of detail, particularly in a world increasingly reliant on vast amounts of data and precise information, it is imperative to remember that this data relates to an individual human being—a single patient.[507]. Duysens, a retired researcher on FOG, recently reported its own personal perspective on FOG, presenting a view how freezing could be beneficial when handled appropriately. [508]

While objective gait metrics offer valuable insights into FOG, they may not fully capture the subjective experiences and perceived difficulties encountered by individuals with PD in their daily lives. Despite providing objective data, these metrics often lack the contextual understanding that patient-reported metrics offer. For instance, while accelerometers can monitor walking behavior in real-life situations, they may not capture the nuanced challenges experienced by individuals with PD during episodes of FOG. Additionally, patient-reported metrics provide insight into nonmotor factors such as self-efficacy and depressive symptoms, which significantly influence FOG but may not be reflected in objective gait assessments alone. Therefore, integrating patient-reported metrics alongside objective gait metrics is essential for a comprehensive understanding of FOG, ensuring that interventions address the holistic needs of individuals with PD and promoting patient-centered care approaches.[509–511]

The role of STN-DBS and dopaminergic therapy on post-surgery FOG and gait impairment

Whilst Subthalamic Nucleus Deep Brain Stimulation (STN DBS) has proven to be an efficacious treatment for controlling cardinal motor symptoms in both short and long-term follow-ups[84,87,299,301,302], its sustained efficacy in addressing axial signs such as gait and FOG remains a subject of controversy.[127] The follow-up of STN-DBS patients reveals a gradual emergence of gait impairment and FOG, even in the best-functional state (Medication ON/Stimulation ON), resistant to therapy optimization.[303,327,336] These therapy-resistant symptoms pose a significant therapeutic challenge for clinicians managing STN-DBS patients. Understanding their etiology and devising corresponding therapeutic strategies is one of the major unmet need in the field of movement disorders surgery.[127]

Numerous studies have focused on PD STN-DBS patients with post-surgery gait disorders or FOG, primarily to elucidate the role of alternative stimulation paradigms as treatment approaches.[310,338–340,343,347,452,512] Starting by the premise that loss of benefit on axial signs could be attributed to a direct side effect of stimulation, these works delve into its modulation as a strategy to improve gait.

However, long-term follow-up studies reveal a general decrease in the effectiveness of both stimulation and LD on motor symptoms after surgery.[303,327] Interestingly, despite a reduction in magnitude, especially when compared with pre-surgery LD-responsiveness, the magnitude of effects of LD and stimulation tend to be similar, suggesting an overall lack of disease responsivity to treatment, likely due to disease progression. [351]This effect is more evident for axial signs, but the same principle holds true for non-axial symptoms.

It is crucial to discern whether the observed gait disorders that exist in the Best-Functional condition post-surgery are induced by therapy (stimulation and/or LD) or represent treatment-resistant features (present in the OFF state and not totally improved by treatment). To address this, we undertook a comprehensive study involving a highly selected cohort of 17 patients with severe FOG in the best-functional condition **(Chapter VI)**. We assessed them in five different therapeutic conditions, enabling the evaluation of the OFF state, the isolated effects of LD and stimulation, the synergistic effect of both, and

an additional condition to determine the role of Low-Frequency Stimulation (LFS) on FOG. Most previous works have not conducted such a comprehensive evaluation, often focusing primarily on the effects of stimulation.[339,340,347] Given the non-negligible role of disease progression in the development of axial signs, assessing the response to LD and comparing it with the pre-surgery response is a critical step towards understanding the etiology of the loss of therapeutic benefit in these patients. Accordingly, assessing patients in the MedOFF/StimOFF state is of paramount importance to understand where the patient stands in their disease evolution.

Akin to Moreau patients[339], ourspresented significative more FOG episodes in the OFF-state than in the Best-functional state. This suggests that, despite the benefit observed in the pre-surgery LCT cannot be reproduced, patients still benefit from treatment. Interestingly, when compared with the pre-surgery evaluation, there is a significant decreased in the motor response to LD, accompanied by a significant increase in both overall motor and axial scores in both OFF and ON conditions.. This suggests that there is, at least in part, a component of disease progression that explains the incomplete response of FOG to both stimulation and LD. The emergence of axial signs and FOG after surgery appears to be linked to the progressive loss of LD sensitivity with a consequently reduced responsiveness to stimulation due to disease progression outside the dopaminergic system.

To disentangle the specific effects of stimulation and medication, our sample was evaluated under stimulation-only and under medication-only conditions. While there was an overall group level benefit on FOG, individual responses varied, revealing specific profiles of patients: LD-induced FOG patients, stimulation-induced FOG patients and stimulation and LD-improvement patients.

In non-DBS patients, the notion that FOG could be induced/worsened by LD has already been discussed with these patients representing a very small proportion of PD-FOG patients.[183,204] Here, we introduced the concept that some of the post-surgery FOG observed in the best-functional state could be induced and/or worsened by LD. Interestingly, these patients will experience FOG improvement with stimulation, indicating

a distinct sensitivity to therapeutic strategies. Importantly, this dissociation between LD and stimulation response isn't observed for non-axial signs, which are equally improved by LD or stimulation. We are led to conclude that this LD-worsening behavior is specific for axial signs, and that therapeutic modulation of axial signs follows different pathways then non-axial symptoms, probably reflecting the distinct pathophysiologic mechanisms underlying them.

This diametrically opposed patterns of response to stimulation and LD have led us to question the role of the LCT. A LCT is traditionally performed to predict surgery outcomes being the most important criteria for patient selection.[206,321] Despite criticisms of its role in predicting axial outcomes[324,327,351,389,513], patients with LD-resistant axial signs, including FOG, are still classically excluded from surgical programs.[206] Our results question the exclusion of patients with insufficient LD response from surgical programs, as distinct responses to stimulation and medication may be observed. We recognize that, at baseline, all these patients were responsive to Levodopa (LD) concerning axial outcomes. This prevents us from directly addressing the question of whether pre-surgery axial signs that were not responsive to LD would improve with stimulation. However, a previous work has found the same dissociation between pre-surgery LD response and post-surgery stimulation-response, suggesting that some of the non-LD responsive patients may come to improve with stimulation, despite the initial lack of LD sensitivity. [334]

Our study also identifies a subgroup of patients whose FOG is worsened by stimulation whilst significantly improved with LD. Here one can envisage that current spread to the neighboring structures could have led to gait worsening.[341,448] Here, one can envisage that whilst HSF of the descending nigropontine projections and outflow tracts of the pedunculopontine nucleus can negatively impact gait, LFS stimulation of the same structure will have a positive impact, as suggested by the beneficial effects on gait observed with PPN-DBS at low frequency stimulation (25 Hz).[471–473]

Even though the small number of patients in our sample prevents further conclusions, one can hypothesize that the patients with stimulation-induced FOG, would be the ones most likely to benefit from different or alternative stimulation paradigms.

Modulating the stimulation field, either by reducing or reshaping the volume of tissue activated (VTA) area or by recruiting different axonal fibers, could help limit the adverse effects of stimulation.

In line with the hypothesis that post-surgery FOG could be stimulation-induced, several studies have explored the effectiveness of low-frequency stimulation (generally 60 or 80 Hz) in improving axial signs.[339,340,343,512] Previous works have found a significative effect of LFS on FOG outcomes specially in short-term follow-up, but with less consistent long-term results. [339,340,343,512] In our work we couldn't reproduce the benefice of LFS in FOG metrics using a 60 Hz-stimulation, but LFS was associated to significant lower axial scores. Despite the lack of benefit at a group level, a subgroup of patients appeared to be particularly improved by LFS regarding FOG. This benefit is extensive to other axial signs, with non-axial signs not being modulated by LFS, suggesting a specificity of low frequencies to modulate brain circuits related to axial signs.

We advocate that in STN-DBS PD patients experiencing FOG post-surgery, a "one-size-fits-all" approach is insufficient. Both the etiological causes of freezing and the therapeutic strategies to address them require a tailored approach and individualized assessments of LD and stimulation effects are crucial, considering the diverse responses observed among patients.

Conclusion

Our study contributes valuable insights into gait impairment and FOG after STN-DBS in PD patients. By conducting assessments at various time points, from pre-surgery to long-term follow-ups, we gained a comprehensive understanding of the nature of gait disorders following stimulation.

We observed that FOG is a prevalent symptom in PD patients undergoing STN-DBS, with its occurrence increasing as the disease progresses, affecting a substantial percentage of patients after 8 years. In our retrospective study, we found older age and higher pre-

surgery disease severity were significant predictors of post-surgery gait and FOG outcomes. Furthermore, our prospective study provided insights into the role of the LCT on predicting gait outcomes, suggesting that response of specific kinematic gait metrics may be better correlated with FOG outcomes than the overall motor response during the LCT.

We showed that automatic models for FOG detection using wearable devices and machine learning techniques have high sensitivity and specificity, offering a scalable approach to monitoring FOG in PD patients. In addition, the presence of FOG appears to correlate with higher gait variability and asymmetry.

Importantly, we identified distinct patient profiles in response to therapy, with some patients exhibiting worsened FOG under stimulation but improved responses to medication.

This underscores the need for personalized approaches in managing post-surgery FOG and emphasizing the importance of evaluating both medication and stimulation effects individually.

Implications for Clinical Practice

Therapy-refractory FOG and gait impairment emerge during the follow-up of STN-DBS PD patients, despite an initial good response to LD prior to surgery. Their emergence appears to be dictated mostly by disease progression, despite a continued benefit on stimulation specially on the off-medication FOG.

Healthcare professionals should, therefore, advise patients considering STN-DBS sthat, following the procedure, axial signs may continue to progress and remain partially resistant to treatment. Nonetheless, it should also be remarked that this doesn't preclude an overall benefit in terms of motor fluctuations and dyskinesias, reduction of medication on improvement in overall motor scores.

In patients who developed FOG in the best-functional condition (MedON/StimON) an individualized evaluation should be prioritized, where the individual effects of stimulation and LD are assessed. This may enable the clinician to identify specific points for intervention, where modulation of one or another therapeutic modality may be sufficient to improve the clinical picture. At the same time, when managing severe post-surgery FOG, one should consider the potential detrimental effects of chronic HFS and the possibility of benefiting from fine adjustments to stimulation parameters should be considered. Here, LFS appear to specifically modulate axial signs without significant effects on non-axial motor symptoms. In line with this, LFS should be tried in patients with post-surgery FOG and gait impairment.

Here, the advancements in DBS technology hold promise for improving the management of these patient. Directional DBS leads feature may enable a better modulation of the electric field in order to a more precise targeting of neural circuits implicated in FOG.[285,317,333] The integration of closed-loop DBS systems represents another significant advancement, with a recent paper using stride time variability as a biomarker to modulate adaptive DBS, with positive effects in FOG. This enables a real-time assessment of the state of gait and an adapted *online* correction.[317,333,480]

The understanding of FOG and gait complexity, their behavior and response to treatment demands an objective, observed-independent assessment. Patient-reported

FOG outcomes and clinician-based clinical assessment, may not be sufficient to fully capture this complexity. Wearable devices can provide real-time, quantifiable data on a patient's movements, allowing also for continuous monitoring outside the clinical setting. Machine learning models, trained on these objective metrics, can accurately identify and classify episodes of FOG, during long periods of time, enabling a more ecologic assessment of FOG. This technology offers clinicians a valuable tool for gaining deeper insights into patients' motor state and response to treatments, enabling personalized and data-driven interventions.

Implications for research

FOG significantly impacts the life of PD submitted to STN-DBS surgery, and despite significant efforts, our current treatments are often unable to prevent sufferers from losing their independence and quality of live. Consequently, FOG is one of the major unmet needs in clinical research, and a collective effort to understand the etiology of FOG and the therapeutic strategies that can be adopted should be undertaken.

Up to now, the assessment of post-surgery FOG has relied in the retrospective assessment of small cohorts, with different follow-up times, and with FOG assessment based on self-reported questionnaires. While ethical concerns may pose limitations on conducting randomized controlled trials (RCTs) specially with medium and long-term follow-ups to compare STN-DBS with BMT, it is feasible to prospectively assess multicentric cohorts of Parkinson's disease (PD) patients to evaluate the prevalence of post-surgery FOG and gait impairment. In these cohorts, an objective assessment of FOG should be prioritized, ideally using wearable devices and machine-learning techniques for an objective, automatic FOG detection. Additionally, studies with larger samples are needed to test our hypothesis that there is heterogeneity within subjects regarding the response of FOG to stimulation, including different frequencies of stimulation and medication.

Patients whose symptoms emergence it associated to either brain lesions[514] or brain stimulation[318,319,515] are particularly well placed to establish a link between the clinical observed symptom and the underlying responsible brain circuits. Using normative functional connectomes acquired in large samples either "lesion network mapping" and "Deep Brain Stimulation (DBS) network mapping" have been used to investigate networks that are affected by lesions and stimulation and identify key nodes related to symptoms. [318,319,514,515] Using a normative connectome, functional connectivity of DBS sites associated of patients with FOG could be analyzed and compared with the functional connectome of STN-DBS PD patients without FOG. This could enable to identify brain regions related to FOG, providing insights into circuit dysfunction in STN-DBS FOG.

DBS frequency manipulation provides a strategy to reduce FOG with no major impact on other motor symptoms, with an increasing body of evidence showing the efficacy of LFS to improve FOG and other axial symptoms. [337–340,343,512] This provides an optimal scenario to causally assess FOG-specific changes in complex networks. New imaging techniques can be also used to study the effects of different stimulation frequency in modulating brain networks. Studying PD STN-DBS patients under HSF and LFS with fMRI functional may identify within subject response at a brain circuit level to the different stimulation frequencies, helping to clarify how the different frequencies modulate the clinical signs but also which brain circuits are involved in the emergence of axial alterations.

Wearable devices and kinematic-driven gait metrics have been increasingly used in clinical practice. [221,395,396] However, when looking to data regarding the effects of stimulation and LD in individual gait metrics, contradictory results are found across studies, with most of these studies assessing a limited number of patients. Efforts from the scientific and medical community should be undertaken in order to create bigger cohorts, or to gather data from different small cohorts, in order to generate bigger data sets, from which more consist and robust outcomes can be obtained.

Finally, although significant progress has been made since Kinnier Wilson referred to the basal ganglia as 'the dark chamber of the brain,' the journey to fully comprehend the pathophysiological mechanisms underlying FOG and gait impairment is still far from its conclusion.

Leveraged by technological advances, ranging from new imaging techniques to wearable devices for gait analysis, novel research avenues are opening up for a more profound understanding of post-surgery FOG and gait impairment. Ideally, these insights could translate into improved treatments and an enhanced quality of life for PD STN-DBS.

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