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**“The effect of Deep Brain Stimulation on Electroencephalographic
activity and Local Field Potentials in Parkinson’s disease”**

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“We can imagine that this complicated array of moving things which constitutes ‘the world’ is something like a great chess game [...], and we are observers of the game. We do not know what the rules of the game are; all we are allowed to do is to watch the playing. Of course, if we watch long enough, we may eventually catch on to a few of the rules”.

Richard Feynman
Physics Lectures (1964)

“[...] counsels scientific writers to govern themselves by the following rules: 1) Have something to say; 2) Say it; 3) Stop once it is said; 4) Give the article a suitable title and order of arrangement”.

Santiago Ramón y Cajal,
Reglas y Consejos sobre Investigación Científica (1897)

“Chronic remorse, as all the moralists are agreed, is a most undesirable sentiment. If you have behaved badly, repent, make what amends you can and address yourself to the task of behaving better next time. On no account brood over your wrongdoing. Rolling in the muck is not the best way of getting clean”.

Aldous Huxley
Brave New World (1932)

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Abbreviations

aDBS: adaptive Deep Brain Stimulation; **BEM**: Boundary Element Method; **cFU**: clinical Follow-Up; **CP**: Clinical Programming; **DBS**: Deep Brain Stimulation; **ECoG**: Electrocorticography; **EKG**: Electrocardiography; **EMG**: Electromyography; **FC**: Functional Connectivity; **FDR**: False Discovery Rate; **fMRI**: functional Magnetic Resonance Imaging; **FTG**: Finely-Tuned Gamma; **GPI**: Globus Pallidus internus; **HC**: Healthy Controls; **HD-EEG**: High-Density Electroencephalography; **H&Y**: Hohen & Yahr; **ICA**: Independent Component Analysis; **IP**: Initial Programming; **IPG**: Implantable Pulse Generator; **IQR**: Interquartile range; **LEDD**: Levodopa Equivalent Daily Dose; **LFP**: Local Field Potentials; **MDS-UPDRS**: Movement Disorder Society – Unified Parkinson’s Disease Rating Scale; **MEG**: Magnetoencephalography; **MoCA**: Montreal Cognitive Assessment; **MRI**: Magnetic Resonance Imaging; **NBS**: Network-based Statistic; **PAC**: Phase-Amplitude Coupling; **PD**: Parkinson’s Disease; **PSD**: Power Spectral Density; **ROI**: Region Of Interest; **RS**: Random Selection; **SD**: Standard Deviation; **SEM**: Standard Error of the Mean; **STN**: Subthalamic Nucleus; **SVD**: Singular Value Decomposition; **T1-w MPRAGE**: T1-weighted Magnetization-Prepared Rapid Acquisition Gradient-Echo; **wMNE**: weighted Minimum Norm Estimation; **wPLI**: weighted Phase Lag Index.

1. Abstract

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus internus (GPi) represents a well-established treatment for patients with advanced Parkinson's disease (PD) experiencing suboptimal control of symptoms despite optimized pharmacological therapy. By delivering targeted electrical stimulation, DBS is thought to disrupt pathological patterns of neural activity within the basal ganglia and related cortico-basal networks. Despite clinical effectiveness, the neurophysiological mechanisms underlying DBS therapeutic effects remain incompletely understood, given the modulation of both local and wider network-level brain dynamics.

This thesis addresses these knowledge gaps by examining the effects of DBS on electroencephalographic (EEG) activity and local field potentials (LFP) in patients with PD, while also exploring the translational clinical potential of LFP-based biomarkers across three complementary studies. The first study directly compared beta-band activity in LFPs recorded in the STN and GPi, providing novel insights into oscillatory signatures across these two main DBS targets in PD, as well as their modulation with stimulation and dopaminergic medication. The second study investigated the effect of both acute and long-term DBS on cortico-cortical functional connectivity in high-density electroencephalography (HD-EEG) recordings in patients receiving STN- and GPi-DBS, demonstrating how stimulation induces widespread and frequency-specific neurophysiological changes beyond the basal ganglia. The third study explored the translational application of beta-band peaks in LFP recordings for DBS contact selection, highlighting their potential to guide faster, objective and individualized programming strategies.

Together, these studies contribute to advancing the understanding of the neurophysiological mechanisms of DBS in PD, supporting differential subcortical effects and network-level modulation outside the sensorimotor areas. Furthermore, the thesis highlights the translational value of beta oscillations as a bridge between mechanistic insights and clinical practice, ultimately supporting the development of next-generation, patient-tailored approaches to DBS programming.

2. Introduction

2.1 DBS as an advanced treatment for PD

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is characterized by prominent motor symptoms (bradykinesia, tremor and rigidity) alongside a broad range of non-motor manifestations¹⁻⁵. While dopaminergic medication provides substantial and stable symptom control in the early and intermediate stages of disease, many patients eventually develop motor complications, including daily fluctuations in symptom severity and involuntary movements (dyskinesias), which define the advanced stage of PD (Figure 1)⁶⁻¹⁰. When pharmacological therapy becomes suboptimal in controlling these manifestations, patients are typically considered for advanced treatments^{8,11}. Among those, Deep Brain Stimulation (DBS) has become a well-established therapeutic option^{12,13}. As a neuromodulation therapy, DBS consists of the delivery of continuous, high-frequency electrical current via neurosurgically implanted intracranial electrodes connected through extension cables to an implantable pulse generator (IPG) placed subcutaneously in the chest or abdomen¹⁴⁻¹⁶.

Although DBS has been approved for several neurological and psychiatric disorders, advanced PD represents the most frequent clinical indication, supported by evidence on its long-term efficacy, extending up to 15 years, and consolidated experience in many specialized centers¹⁷⁻²⁰. Numerous clinical studies have demonstrated that DBS can markedly reduce motor symptoms severity and complications, improve quality of life, and enable substantial reductions in dopaminergic medication dosages²¹⁻²⁶.

The therapeutic benefit of DBS depends critically on careful postoperative programming^{27,28}. This process involves selective active electrode contacts and setting stimulation parameters (amplitude, pulse width and frequency), to maximize clinical benefit while minimizing side effects^{29,30}. Traditionally, this is performed through a clinical-based process in which clinicians systematically test different parameter combinations and assess changes in motor symptoms^{31,32}. Technological advances in electrode design and stimulation modalities have significantly expanded the range of available configurations, but at the same time, increased complexity³³⁻³⁵. As a result, programming remains a time-consuming, largely trial-and-error process, requiring multiple outpatient visits^{30,36,37}. To address these challenges, recent efforts have focused on the development of objective strategies aimed at making programming more efficient and personalized³⁸⁻⁴².

The two main approved targets for DBS in PD are the subthalamic nucleus (STN) and the globus pallidus internus (GPi). Both structures represent key nodes within the cortico-basal-thalamo-cortical loops, play essential roles in motor control and are functionally involved in PD^{11,43,44}. Although STN is currently the most widely used target worldwide, randomized controlled trials have consistently shown comparable benefits in terms of motor symptom control with GPi-DBS⁴⁵⁻⁴⁷. However, some differences in specific therapeutic outcomes have been reported between the two targets⁴⁸. Patients receiving STN-DBS often achieve greater reductions in dopaminergic medication, whereas GPi-DBS has proven particularly advantageous in patients with troublesome OFF dystonia^{26,45,47,49}. Differences in neuropsychiatric and cognitive outcomes have also been described, with some studies suggesting a higher risk of mood and cognitive side effects after STN-DBS, though these findings remain heterogeneous and not uniformly replicated⁴⁸⁻⁵².

Thus, while DBS has proved a highly effective treatment strategy for advanced PD, understanding how it produces these outcomes requires closer examination of both the mechanisms of stimulation and the pathophysiological processes modulated.

2.2 Mechanisms of DBS in the context of PD pathophysiology

Mechanisms underlying DBS and the pathophysiology of PD are closely intertwined. By directly targeting abnormal neural activity in basal ganglia–cortical circuits, DBS not only alleviates motor symptoms but also serves as a unique experimental tool to probe the dysfunctional dynamics that generate them⁵³⁻⁵⁷. In turn, advances in understanding PD pathophysiology provide the conceptual framework to refine stimulation strategies, develop next-generation adaptive neuromodulation approaches, and guide hypotheses about how DBS exerts its therapeutic effects^{53,54,58,59}. This bidirectional relationship has transformed DBS into both a treatment and an investigative instrument^{55,56,60}. Importantly, insights derived from intraoperative and perioperative recordings in patients undergoing DBS surgery and studies on the effects of stimulation have reshaped our understanding of PD pathophysiology^{44,61}. The classic “rate model,” which emphasized an imbalance between firing rates in competing basal ganglia pathways (“direct” and “indirect”), has proven insufficient to fully account for the clinical features of PD or the widespread impact of DBS⁶¹⁻⁶⁴. Instead, PD is now increasingly conceptualized as a “circuit disorder” characterized by abnormal activity patterns within

distributed cortico-basal-thalamo-cortical networks^{60,64–66}. Within this framework, PD has been described as an “oscillopathy,” in which pathological neural oscillations emerge as a central functional feature of the disease^{67,68}.

Currently, imbalances in oscillatory activity leading to abnormal information processing and transfer have been proposed as a key mechanism underlying the development of symptoms in PD^{53,69,70}. Within this framework, DBS is thought to exert its therapeutic effects by disrupting pathological oscillations, inducing what has been defined as an “informational lesion” and restoring more physiological patterns of activity^{71,72}. Recent observations also indicate that DBS acts through multifactorial mechanisms, including immediate neuromodulatory effects, synaptic plasticity, and long-term neuronal reorganisation^{60,72–74}. Importantly, these effects extend beyond the stimulated deep brain target: emerging evidence suggests that DBS influences oscillatory dynamics across broader cortico-subcortical loops and cortico-cortical networks^{75–78}.

2.2.1 Oscillatory activity in the basal ganglia

Abnormal oscillatory activity in the basal ganglia has emerged as one of the most consistent neurophysiological hallmarks of PD^{68,79–81}. Exaggerated synchronization in the beta frequency band (13–30 Hz) has been repeatedly observed in local field potential (LFP) recordings from the STN and GPi of PD patients undergoing DBS surgery (Figure 2)^{82–84}. LFPs represent the summed activity of small neuronal populations around the recording electrode, represented by their extracellular potentials^{82,85,86}. Unlike action potentials, which capture the firing of individual neurons, LFPs primarily represent synchronized synaptic inputs, dendritic processing, and oscillatory dynamics in local basal ganglia circuits^{85,87,88}. Beta activity has a physiological role in normal motor control, as beta oscillations become highly synchronized at rest and during movement preparation, and their increase is not specific to PD or even pathological *per se*^{89–91}. The excessive beta activity in PD likely reflects a pathological alteration of this physiological synchronization phenomenon, involved in dynamic brain state transitions and movement inhibition, and these pathological abnormalities limit computation capacity and information coding of local neuronal populations in the basal ganglia^{82,92–95}. In PD, abnormal synchronization in the beta band is now considered a biomarker of brady-/hypokinetic motor state, as it has been consistently related to the severity of motor symptoms and it is suppressed by L-Dopa and DBS, paralleling the improvement of bradykinesia and rigidity^{79,81,83,96–98}.

However, the relationship between beta synchronization and bradykinesia appears to go beyond PD, as abnormal beta activity was also related to this symptom in patients with dystonia receiving DBS and experiencing a hypokinetic state as a side-effect of medications and in Huntington's disease patients^{99–102}.

Overall, pathological beta activity has been more extensively characterized in PD with respect to other neurological and psychiatric disorders; however, it is not the only oscillatory abnormality in PD. Increases in theta (4–8 Hz) and alpha (8–12 Hz) activity have been reported in the STN and linked to gait dysfunction, cognitive impairment, and mood disorders, whereas gamma-band activity (30–90 Hz), which normally supports movement execution, is attenuated in PD and restored by L-Dopa and DBS^{103–107}. Notably, DBS induces finely-tuned gamma (FTG) oscillations that appear as a narrowband activity at half the stimulation frequency, which are reliably induced by L-Dopa, and have been associated with dyskinesia^{107–109}. Moreover, cross-frequency interactions such as beta–gamma coupling within the basal ganglia suggest that pathological synchronization extends across multiple bands, interfering with the integration of motor commands^{110–112}. A growing body of evidence has shown that beta activity is not uniform and suggested that different sub-bands may reflect distinct aspects of pathological local circuit dynamics^{77,98,113,114}. In fact, within the beta range, a distinction is commonly made between low beta (13–20 Hz) and high beta (21–30 Hz) activity. Both sub-bands have been implicated in PD pathophysiology, yet current evidence suggests that in the STN, low beta oscillations are more strongly linked to the hypodopaminergic state and to the expression of motor impairment^{79,114–116}. High beta activity, by contrast, is thought to reflect and mediate long-range brain communications, including functional interhemispheric coupling between basal ganglia and subcortical-cortical interactions^{77,113,117}.

Furthermore, beta oscillations in LFPs recorded in both STN and GPi are not stationary but rather occur in the form of phasic bursts, representing intermittent and transient epochs of heightened synchrony^{118,119}. In the dopamine-depleted (“OFF”) state, beta bursts are both more frequent, longer in duration and bigger in amplitude compared to those observed after L-Dopa administration^{114,118,120–122}. Importantly, changes in burst duration after medication were found to correlate with bradykinesia and rigidity improvements^{118–120}. Similarly, it was previously demonstrated that in the STN, DBS modulated burst characteristics, shortening their duration, reducing burst probability and amplitude^{121,123}.

Taken together, these findings have pointed to beta oscillations as a neurophysiological biomarker (“physiomarker”) of PD and have been translated into applications of beta activity in clinical practice, including intraoperative guiding of electrode localization and closed-loop adaptive stimulation approaches^{59,124–127}.

However, most of the current understanding of beta dynamics in PD derives from intraoperative or perioperative LFP recordings in patients undergoing DBS surgery targeting the STN^{15,53,128}. Although DBS lead implantation is usually performed in awake subjects, intraoperative neurophysiology can be influenced by anaesthetic administration (e.g., propofol), which is known to alter neural activity^{129,130}. Similarly, recordings obtained in the early postoperative period (typically 3–7 days after surgery) may be confounded by microlesional, or “stun”, effects within the target structures^{131,132}.

The advent of sensing-enabled DBS devices has opened new opportunities to overcome these limitations and directly monitor pathological neural dynamics in chronic conditions and in more ecological settings^{109,133,134}. By chronically recording LFPs from implanted electrodes, these devices enable the acquisition of neurophysiological activity beyond the perioperative period, enabling the evaluation of temporal fluctuations of pathological oscillations, their relation to motor states, and their modulation by therapies^{33,109,115}. Importantly, sensing-enabled systems have allowed the implementation of adaptive (closed-loop) DBS into clinical practice, where stimulation is delivered in real-time in response to beta activity recorded from target structures^{59,134–136}.

Yet, despite these advances, a central question remains: where does beta activity originate, and what are the principal targets of DBS modulation mediating its clinical efficacy? Several lines of evidence have postulated a cortical origin of pathological beta activity and its maintenance within cortico-basal loops^{76,77,137}. These aspects will be discussed in the following section.

2.2.2 Cortical and network-level modulation

Several lines of evidence increasingly indicate that pathological beta synchronization cannot be fully understood by focusing solely on subcortical structures^{53,95}. Rather, beta activity might emerge from cortical sources, particularly the motor cortex, and be sustained within distributed cortico-basal-thalamo-cortical loops^{53,72,77}. Animal studies have suggested that direct axonal activation of cortical afferents to the STN may

be important in the therapeutic effects of STN DBS^{138,139}. Complementary studies in PD patients undergoing DBS have demonstrated effective anterograde transmission of subthalamic stimulation to the motor cortex, further supporting strong functional coupling between these regions^{140,141}. Analyses of directional information flow have shown that cortical activity precedes and potentially drives beta synchronization in the STN and GPi⁷⁶. In addition, differences in temporal delays between subthalamic- and pallidal-cortical interactions corroborated the existence of a monosynaptic “hyperdirect” pathway linking cortex to the STN^{76,142,143}. Importantly, based on the evidence of differential and dynamic effects of DBS on motor symptoms, neuroplastic cortical changes were also hypothesized and observed in some previous studies^{144,145}. These findings have led to the hypothesis that in PD the hypodopaminergic state may reflect a vulnerability of the basal ganglia to cortical synchronization, which disrupts flexible information transfer across the cortical–basal networks⁵³. This accumulating evidence has further shifted attention toward cortical and network-level dynamics, as both sources and critical targets of experimental assessment and modulation, paving the way for a network-level perspective on PD pathophysiology and the mechanisms of DBS^{53,57,72,77,93}. Furthermore, the potential of cortical activity in guiding closed-loop DBS approaches is currently under investigation^{146–151}. Cortical activity in PD has been assessed using both invasive and non-invasive techniques, including electrocorticography (ECoG), magnetoencephalography (MEG), electroencephalography (EEG), and functional MRI (fMRI)^{57,152–156}. Among these, EEG stands out as a practical and versatile assessment tool due to its excellent temporal granularity (in the order of milliseconds) and good spatial resolution when using high-density montages and source reconstruction methods to localize cortical dynamics and to probe oscillatory activity both within specific cortical regions and across distributed cortical networks^{157–160} (Figure 2). EEG signals represent the summation of excitatory and inhibitory post-synaptic potentials of large populations of cortical neurons, recorded non-invasively with electrodes placed on the scalp^{161–163}. Specifically, signals are mainly generated by ionic currents in the dendritic membrane of the pyramidal neurons in cortical layers IV-V, and largely reflect thalamic and cortical inputs to these cells^{161–163}. Rhythmic EEG activity reflects synchronized excitability fluctuations of local neuronal ensembles, and is believed to facilitate the flow of neural information between nodes in the network when the oscillations are synchronized between those nodes and contribute to the establishment of long-range

communication^{161,164,165}. Therefore, the brain could dynamically coordinate information flow by changing the strength, pattern, or frequency with which different brain areas engage in oscillatory synchrony¹⁶⁶.

EEG has revealed that the cortical activity in PD is characterized less by absolute increases in beta power and more by abnormal synchronization patterns and coupling phenomena^{155,156,167}. For example, while STN LFP recordings consistently show exaggerated beta power in the medication OFF state, cortical beta power measured with EEG tends to be more variable across patients and often less strongly elevated^{153,168,169}. One of the pathological cortical signatures of PD is abnormal phase–amplitude coupling (PAC), where high-frequency cortical activity becomes excessively locked to the phase of the beta rhythm^{75,156,170}. This abnormal PAC has been associated with impaired motor performance and reduced movement initiation, supporting the idea that cortical beta may interfere with local information coding rather than simply reflecting an increase in oscillatory power^{53,156,171}.

A crucial aspect for implementing this technique is the assessment of cortico-cortical functional connectivity (FC), which refers to the statistical dependence between neural signals recorded from distinct cortical areas and used to evaluate their dynamic interactions^{160,172}. FC can be quantified using a variety of analytical methods, including measures of coherence, phase-locking, Granger causality, and amplitude–amplitude correlations, each capturing different aspects of neural coordination, from frequency-specific synchronization to directionality of information flow^{160,172,173}. In PD, such approaches have consistently demonstrated abnormal patterns of cortical connectivity, particularly within motor and premotor regions, reflecting excessive synchronization that is postulated to contribute to impaired motor functions^{174–176}. Recent methodological advances have allowed connectivity analyses to extend beyond isolated connections, enabling a shift into a more comprehensive network-based framework. Tools such as Network-Based Statistics (NBS) allow the identification of clusters of connections that differ significantly between groups or conditions, while controlling for multiple comparisons within the high-dimensional connectivity space^{177,178}. This shift has been critical for uncovering distributed patterns of dysregulation in PD, highlighting that pathological synchronization is not restricted to single circuit nodes but involves alterations across entire cortico-cortical networks. Using phase-correlation-based approaches to measure FC in HD-EEG recordings and this network-based approach, previous studies demonstrated increased beta coherence in PD patients compared to healthy control (HC) subjects since the early disease stages^{174–176,179}. Of note, dysfunctional

beta-band cortical networks differentiating patients from HC were not confined to sensorimotor areas but extended to multiple non-motor regions^{174,176}. In a subsequent study, it was observed that specific FC networks in the alpha and theta bands could differentiate PD patients with body-first and brain-first phenotypes¹⁷⁹. Therefore, this approach proved useful to evaluate network-level brain changes in PD and holds the potential to evaluate cortical DBS-induced connectivity changes. A previous study in a limited cohort of PD patients treated with STN-DBS showed that stimulation acutely reduced beta cortical FC compared to the stimulation off condition¹⁸⁰.

Taken together, converging evidence indicates that pathological beta synchronization in PD cannot be fully explained by local mechanisms in the basal ganglia, but instead reflects aberrant interactions within distributed cortico-basal-thalamo-cortical loops^{53,154,169,170}. Cortical inputs appear to play a key role in generating and sustaining abnormal oscillations, and DBS may exert part of its therapeutic effect by modulating, cortico-subcortical interactions, cortical frequency coupling and cortico-cortical communication^{60,75,156}. HD-EEG, particularly when combined with source modelling and network-based analytical frameworks, provides a powerful non-invasive tool to investigate these dynamics *in vivo*^{53,54,155,158}. By capturing both oscillatory signatures and large-scale connectivity patterns, EEG can reveal how pathological synchronization disrupts information flow across cortical networks and possible long-term neuroplastic effects^{158,181}. Furthermore, this network-level perspective not only advances mechanistic understanding of PD but also yields the potential to identify possible biomarkers and guide the development of physiology-based, adaptive DBS strategies^{53,57,134}.

2.2.3 Aims and Objectives

This thesis aims to integrate mechanistic and clinical perspectives of DBS in PD as both an investigative tool and therapeutic intervention, bridging understanding of pathological oscillations with their potential clinical translation into physiology-guided neuromodulation strategies. To this end, three complementary studies were conducted, investigating the effects of DBS on neurophysiological activity at both subcortical and cortical levels, and evaluating the translational potential of beta band activity in LFPs. The first study directly compared LFP beta-band activity between STN and GPi, with the objective to characterize target-specific oscillatory signatures, their modulation by both dopaminergic medication and DBS and their clinical

correlates, to test possible differential pathophysiological characteristics of these two DBS targets. The second study investigated the acute and long-term effects of stimulation on cortico-cortical dynamics using HD-EEG in PD patients treated with STN- or GPi-DBS, by evaluating cortico-cortical FC and group-specific network changes. The third study addressed the translational application of LFP beta peaks for stimulation contact selection for STN and GPi, to define an objective, efficient, and individualized tool to streamline and optimize DBS programming.

3. Experimental part

3.1 Study 1: Pathophysiologically relevant beta activity differs between Subthalamic Nucleus and Globus Pallidus internus in Parkinson's disease

3.1.1 Introduction

Assessing the activity of neuronal populations in the basal ganglia using DBS electrodes has offered direct insights into neurophysiological abnormalities in PD, deepening the understanding of its pathophysiology^{53,61}. Most evidence comes from studies assessing LFPs recorded from the STN, the most common target for DBS in PD worldwide. It is now largely demonstrated that hypersynchronous activity in the beta band (13-30 Hz) within the STN represents a neurophysiological hallmark of PD^{182,183}, is suppressed by L-Dopa and DBS and correlates with motor symptoms^{80,114,184}. Notably, beta activity is not uniform: low-beta oscillations (13-20 Hz) have been more directly implicated in motor impairment, while high-beta activity (20-30 Hz) has been related to long-range cortico-basal communication^{76,77}. Additionally, beta oscillations occur in phasic bursts, whose duration and amplitude are reduced by L-Dopa^{114,118,120} and DBS^{121,123,185}. Despite its proven clinical efficacy as an alternative DBS target in PD and approved indication for aDBS, the neurophysiological characteristics of GPi have been less investigated^{84,112,122,186–188}. Only a few studies have explored the dynamics of pallidal beta oscillations in PD, highlighting the presence of exaggerated beta-band activity^{84,122,186,188,189}. Importantly, all previous studies were performed during surgery or in the early postoperative period, with many aiming to assess differences between PD and other movement disorders (e.g., dystonia and Tourette syndrome)^{119,188,190}. Only two studies directly compared neurophysiological features of GPi and STN, though in limited PD patient cohorts^{122,186}. Notably, chronic DBS-induced modulation of beta-band activity and the combined effects of L-Dopa and DBS in GPi have never been assessed and compared to the STN.

Neurophysiological similarities between STN and GPi might be supported by the fact that both targets are part of the same cortico-subcortical networks and have several direct and indirect connections^{66,191}. Also, the equivalent benefit of DBS on motor symptoms favours similar pathophysiological changes in the two nuclei^{45,46}. On the other hand, the two targets have distinct neural populations, neurotransmitter systems,

local and longer-range synaptic connections that could support the hypothesis of distinct neurophysiological features and reactivity to therapeutic interventions (L-Dopa and DBS). Investigating the possible differences between the STN and GPi is relevant to better understand pathophysiological mechanisms in PD. Also, it may have an impact on the use of beta-band activity as a physiomaer for guiding GPi-aDBS.

In this study, we investigated and compared for the first time the beta band modulation induced by L-Dopa, DBS, and their combination in two cohorts of PD patients chronically treated with STN- or GPi-DBS. To provide a comprehensive assessment of beta dynamics, we evaluated changes in beta power spectrum, peak amplitude, and burst characteristics in response to medication and stimulation. Finally, we assessed the possible correlation between changes in neurophysiological measures and PD motor symptoms.

3.1.2 Materials and methods

Participants

Twenty-one patients with advanced PD treated with bilateral STN- (5 females, 24 hemispheres) or GPi-DBS (4 females, 18 hemispheres) were included. The assessments were performed in a chronic stimulation setting, i.e., >6 months after surgery and at least 1 month after stable stimulation parameters (Table 1). All patients were implanted with the sensing-enabled Medtronic Percept™ PC neurostimulator and SenSight™ directional leads (B33005, with 0.5 mm inter-contact spacing)¹⁹⁰. All subjects gave their written informed consent to participate in the study, and research was completed in accordance with the Declaration of Helsinki. Clinical and demographic characteristics of patients are summarized in Table 1.

Experimental protocol and data acquisition

Each subject was evaluated in a single session in the clinical OFF condition (i.e., >6 hours after the last levodopa intake, M-OFF) and 1 hour after the administration of the usual L-Dopa dose (M-ON). In each medication condition, patients were assessed before and 5 minutes after switching off DBS (S-ON and S-OFF, respectively), resulting in four different conditions: i) M-OFF/S-ON; ii) M-OFF/S-OFF; iii) M-ON/S-ON and iv) M-ON/S-OFF (Figure 3). Clinical and neurophysiological data were collected in each condition. Appendicular motor signs were evaluated using the rigidity (3.3), bradykinesia (3.4-3.8), and tremor (3.15-3.18) subitems of the third section of the Movement Disorder Society Unified Parkinson's Disease Rating

Scale (MDS-UPDRS III)¹⁹². Neurophysiological data were acquired with patients at rest seated in an armchair. LFPs were recorded using the BrainSense™ Streaming feature from the contact pair adjacent to the patient's chronic stimulating level (either 1-3 or 0-2) with a sampling frequency of 250 Hz. Stimulation parameters (amplitude, pulse width and frequency) used for chronic DBS were used in S-ON conditions. Data were exported as .json files for further offline analyses.

Data analysis

All data were analysed offline in MATLAB v.2022b (The MathWorks Inc., Natick, Massachusetts). LFPs were extracted with the open-source Perceive Toolbox (<https://github.com/neuromodulation/perceive/>). For each subject, 120 s of data were selected for each condition for further analyses. A 5th-order Butterworth filter was applied at 5 Hz high- and 98 Hz low-pass to minimize movement- and stimulation-related artifacts. Filtered signals were then visually inspected for electrocardiogram (EKG) or stimulation contamination. When EKG artifacts were detected, signals were further processed using a customized Template Subtraction Method, in which R-peaks from the QRS complex were identified and then subtracted from the original LFP trace¹⁹³. Power spectral density was estimated using Welch's method with 1-s windows and 50% overlap¹⁹⁴. Spectra were normalized to the total power as a sum across the frequency range 5–45 Hz and expressed as a percentage of the total sum^{77,97,98}. Beta peaks within the 13-30 Hz range were identified using the *findpeaks* MATLAB function, then visually inspected, reviewed and modified if needed¹¹⁵. Beta bursts were computed for each frequency (1 Hz) across the whole beta range (13-30 Hz) by applying a bandpass filter (± 2 Hz) around each frequency bin, allowing a frequency-resolved characterization of bursting activity¹¹⁴. Bursts were calculated separately for each condition, as this approach has been shown to minimize signal distortions compared to the application of a single threshold across conditions¹⁹⁵. To detect bursts, the Hilbert envelope of the filtered signal was computed, and bursts were defined as segments where amplitude exceeded the 75th percentile threshold^{118–120}. To control for frequency-dependent effects, a minimum burst length of 2/frequency (s) was applied¹⁹⁶. For each condition, burst duration (time between consecutive threshold crossings in seconds) and rate (number of bursts/second) were calculated¹¹⁸. In a separate additional analysis, bursts were computed within the ± 3 Hz range around the individual beta peak

frequency in the M-OFF/S-OFF condition. Thresholds were again calculated separately for each condition, and bursts were characterized using the same methodology described above¹⁹⁵. Other frequency bands were not characterized.

Statistical-analysis

The Fisher exact and Mann-Whitney U tests were used to analyse possible differences in clinical and demographic characteristics between STN- and GPi-DBS cohorts. Separate cluster-based permutation tests were performed to assess differences in spectral power and burst characteristics (duration and rate) across the beta range (13-30 Hz) and around the beta peak (± 3 Hz): i) between different conditions in STN and GPi (paired tests), and ii) between targets (unpaired tests). In all cases, differences were randomly permuted 10000 times for a subset of hemispheres. For each frequency point, the z-statistic of the actual mean gradient/gradient difference was computed based on the distribution of the 10000 permutations¹⁰³. The supra-threshold clusters (pre-cluster threshold: $p < 0.05$) were determined for each permutation, and the sum of the z-statistics within these clusters was stored to form a distribution. Spearman's correlation was performed to assess possible clinical-neurophysiological relationships. To this purpose, spectral characteristics and burst parameters were correlated with the MDS-UPDRS III lateralized composite bradykinesia+rigidity, and tremor subscores. To control for multiple comparisons, p -values were FDR (false discovery rate) corrected using the Benjamini-Hochberg procedure¹⁹⁷. Statistical analyses were performed with custom MATLAB scripts. A $p \leq 0.05$ was considered significant in the statistical analyses.

3.1.3 Results

Demographic and clinical characteristics

The STN- and GPi-DBS patient cohorts were comparable in sex distribution, age, disease duration at implantation, severity of motor symptoms (MDS-UPDRS III scores, M-OFF) and of motor complications (MDS-UPDRS IV), and Levodopa Equivalent Daily Doses (LEDD) before surgery. The percentage improvement in motor symptoms (M-OFF before vs. M-OFF/S-ON) and complications severity after DBS surgery did not differ between groups, while LEDD reduction was greater in the STN- than GPi-DBS cohort (Table 1).

When considering changes in cardinal motor symptoms in our specific experimental setting, L-Dopa administration (M-OFF/S-OFF vs. M-ON/S-OFF) similarly reduced MDS-UPDRS III composite scores (bradykinesia+rigidity+tremor) in STN- ($p<0.001$, mean change: -34.4%) and GPi-DBS ($p<0.001$, mean change: -31.9%) cohorts, with no between-group differences ($p=0.2$). Similarly, DBS (M-OFF/S-OFF vs. M-OFF/S-ON) improved motor scores to a comparable extent in the two groups (STN-DBS: $p<0.001$, mean change: -31.1%; GPi-DBS: $p<0.001$, mean change: -29.2%, STN-DBS vs. GPi-DBS: $p=0.1$).

Differences in beta activity and reactivity to L-Dopa and DBS between STN and GPi,

In the M-OFF/S-OFF condition, no significant frequency-wise differences in beta power or burst characteristics were observed between STN and GPi (Figure 4). However, when comparing these parameters computed around the individual beta peak, we found that beta peak amplitude was higher, and bursts were longer in the STN than GPi (Figure 4A). L-Dopa (M-ON/S-OFF vs. M-OFF/S-OFF condition) modulated beta power in both targets, but a frequency specificity emerged in its effect. Indeed, medication selectively reduced low-beta power in the STN (13-18 Hz), while suppressing higher beta frequencies in the GPi (20-23 Hz). This difference was also confirmed when directly comparing the two cohorts, where a significant cluster at 13-15 Hz was present between targets (Table 2, Figure 5). Frequency-specific effects of L-Dopa were also found in the bin-wise analysis of bursts, which showed reduced duration and increased rate in the low-beta range when considering the STN (13-18 Hz), and no change in the GPi (Table 2, Figures 6 and 7). In line with the within-group results, between-target comparison showed a significant cluster at 14–16 Hz (Figures 6 and 7). The analysis performed around the beta peak disclosed that L-Dopa reduced peak amplitude and burst duration in both nuclei, but the magnitude of peak amplitude reduction was greater in the STN than GPi (Table 3, Figures 8A, 9 and 10).

DBS (M-OFF/S-ON vs. M-OFF/S-OFF condition) induced a broadband beta power reduction in the STN (14-30 Hz), and a more restricted high-beta suppression in the GPi (20-27 Hz), with significant between-target differences in the low-beta range (15-16 Hz, Table 2 and Figure 5). Similarly, beta bursts duration shortening and burst rate increase involved a beta broadband in the STN (13-17 Hz and 20-27 Hz for both measures), while it impacted only the high-beta sub-band in the GPi (20-22 Hz, Figures 6 and 7). When

specifically considering the individual beta peaks, DBS suppressed peak amplitude and shortened beta bursts in both targets, with a stronger effect in the STN for the former parameter (Table 3, Figures 8, 9 and 10)

Combined effects of L-Dopa and DBS in the STN and GPi

The combination of L-Dopa and DBS (M-ON/S-ON vs. M-OFF/S-OFF condition) induced a broadband beta power decrease in both STN (13-30 Hz) and GPi (16-29 Hz), with a comparable extent between targets (Table 2, Figure 5). Similarly, beta bursts modulation involved both the low- and high-beta sub-bands in both targets (Table 2, Figures 6 and 7). Individual peak amplitude and around-the-peak burst duration decreased in both STN and GPi. However, the degree of beta peak suppression, burst shortening and rate increase was again higher in the STN (Table 3, Figures 8, 9 and 10).

Adding L-Dopa to DBS (M-ON/S-ON vs. M-OFF/S-ON) determined neurophysiological effects on beta power overlapping those produced by L-Dopa alone. That is, the medication selectively suppressed low-beta power in the STN (13-14 Hz) and higher frequencies in the GPi (19-21 Hz), with a significant difference in the low-beta range (13-14 Hz) between targets (Table 2, Figure 3). Importantly, L-Dopa add-on to DBS further decreased beta peak amplitude in the STN, but that effect was not evident in the GPi cohort (Table 3, Figure 8A). No change in beta bursts characteristics was found in STN and GPi, both when computing frequency-wise and around-the-peak analyses (Table 3, Figures 9 and 10)-

Finally, adding DBS to L-Dopa (M-ON/S-ON vs. M-ON/S-OFF) reduced beta power (STN: 20-30 Hz; GPi: 18-30 Hz), burst duration, and rate selectively in the high-beta range (for both measures: STN: 20-23 Hz and 27-29 Hz; GPi: 19-20 Hz and 23-27 Hz), and to a comparable extent between STN and GPi (Table 2). The beta peak amplitude was also further suppressed by adding the stimulation to the medication alone, without significant between-target differences, while burst duration and rate computed around the individual peak remained unchanged in both targets (Table 3).

Clinical-neurophysiological correlations

In the M-OFF/S-OFF condition, the severity of bradykinesia+rigidity compound MDS-UPDRS III subscore correlated positively with low-beta power in the STN (15 Hz: $R=0.64$, $p=0.001$; 16 Hz: $R=0.52$, $p=0.02$) and the power in a higher beta frequency range in the GPi (19 Hz: $R=0.51$, $p=0.03$, Figure 4A). A similar

frequency-specific relationship was also present with beta burst duration (STN, 12-15 Hz: $0.55 < R < 0.82$, $0.001 < p < 0.03$; GPi, 20 Hz, $R=0.53$, $p=0.03$, Figure 4A).

Importantly, the relationship between clinical measures and beta power in different sub-frequency ranges based on the cohort tested was consistent even when considering changes induced by medication and stimulation (Figure 5). Indeed, both L-Dopa-induced, DBS-induced and combined L-Dopa+DBS-induced changes in bradykinesia+rigidity severity were related to the amount of reduction in low-beta power for the STN (medication effect, 15 Hz: $R=0.51$, $p=0.03$, and 16 Hz: $R=0.58$, $p=0.007$; stimulation effect, 16 Hz: $R=0.57$, $p=0.01$; medication+stimulation effect, 14 Hz: $R=0.61$, $p=0.01$) and in the power of a higher beta frequency for the GPi (medication effect, 20 Hz: $R=0.54$, $p=0.02$; stimulation effect, 20 Hz: $R=0.51$, $p=0.04$, and 21 Hz: $R=0.63$, $p=0.02$, medication+stimulation effect, 21 Hz: $R=0.52$, $p=0.03$)

Finally, in the STN cohort, we found a direct relationship between beta peak amplitude in the M-OFF/S-OFF condition and the amount of beta peak amplitude suppression induced by L-Dopa, DBS and their combination (medication: $R=0.52$, $p=0.03$; stimulation: $R=0.75$, $p<0.001$; medication+stimulation: $R=0.81$, $p<0.001$, Figure 8B). That is, the higher the beta peak amplitude, the greater the treatment-induced modulation. Similar correlations were not observed in the GPi cohort (medication: $R=-0.29$, $p=0.23$; stimulation: $R=-0.41$, $p=0.09$; medication+stimulation: $R=-0.42$, $p=0.08$).

We did not find any other relationship between neurophysiological and clinical measures, including tremor severity, or their changes induced by L-Dopa or DBS.

3.1.4 Discussion

In the present study, we assessed and compared beta activity in chronic LFPs recorded from the STN and GPi in PD patients and its modulation by L-Dopa and DBS. We found that beta power and burst characteristics did not differ at baseline across the beta band between targets, whereas L-Dopa and DBS induced frequency-specific effects depending on the target. In the STN, L-Dopa reduced low-beta activity, and DBS determined a broad beta band power suppression, while in the GPi, both L-Dopa and DBS selectively modulated higher beta frequencies. The pattern of L-Dopa and DBS-induced modulation of beta bursts' characteristics in STN and GPi generally paralleled the effects observed in beta power. Combining medication and stimulation induced a similar beta broadband suppression and beta bursts modulation in both

targets. Importantly, clinical-neurophysiological correlations pointed towards a more relevant pathophysiological role of higher beta oscillations in the GPi with respect to the STN.

The main novel result of our study concerns the differential responsiveness between STN and GPi to L-Dopa and DBS. At baseline (M-OFF/S-OFF condition), beta power and bursting characteristics were similar between the two structures, in line with previous intraoperative LFP studies^{122,186}. This observation might reflect the fact that both nuclei are embedded in the same cortico-basal-thalamo-cortical network. As such, they are likely exposed to and shaped by common aberrant beta oscillations that pathologically emerge within this circuit in PD^{76,122}. However, L-Dopa administration had distinct frequency-specific effects in the two structures. In the STN, the suppression was selective for low-beta oscillations, in line with their established association to the hypodopaminergic state^{79,114,115}, while in the GPi, we observed a specific reduction of higher beta frequencies. The effects of L-Dopa on pallidal beta activity have been poorly characterized, and a few studies have reported a global reduction of beta mean power^{84,198}, while direct comparison with the STN was never performed. Indirectly supporting a differential dopaminergic modulation in the two nuclei, one prior study compared STN and GPi under medication ON condition and showed greater high-beta power in the STN than GPi⁷⁶. Further supporting the differential effect of L-Dopa, we observed that medication modulated burst characteristics (duration and rate) in the low-beta range in the STN, while it suppressed only bursts around the beta peak in the GPi¹²⁰. The latter finding is concordant with a previous work¹¹⁹, although methodological differences in burst detection (i.e., peak selection, thresholding) might account for inconsistencies in mean burst duration modulation across frequencies¹⁹⁵. Importantly, the differential effect of L-Dopa between targets was also present during the stimulation (M-OFF/S-ON vs. M-ON/S-ON conditions). Overall, our observations suggest a differential effect of L-Dopa on beta dynamics in the two structures.

For the first time, in our study, we also compared changes in beta power and bursts in response to DBS between the two targets. In line with several previous research studies^{71,97,115,185}, we observed a broad beta band suppression and burst shortening in the STN, while in the GPi the modulation of spectral power and bursting characteristics (duration and rate) selectively involved higher beta frequencies¹⁸⁸.

Another novel finding concerns the combined effect of medication and stimulation (M-OFF/S-OFF vs. M-ON/S-ON comparison) that has never been assessed in the GPi. Interestingly, both STN and GPi exhibited a

similar broadband modulation of beta power and burst characteristics. Our results are consistent with a recent study in PD patients chronically treated with STN-DBS¹¹⁵. This might indicate that although medication and stimulation might differently affect STN and GPi activity, their combination converges into a common suppression of pathological beta activity.

Importantly, the significant correlation observed between beta power changes in specific frequency sub-band and bradykinesia-rigidity improvement suggests that observed neurophysiological differences between targets are pathophysiologically relevant in PD^{98,115,120}. In the STN, lateralized bradykinesia-rigidity severity at baseline as well as after L-Dopa and DBS was selectively related to low-beta activity, while in the GPi, the relationship was shifted toward high-beta frequencies^{98,120,189}. These data indicate that the activity of different beta sub-bands in the STN and GPi may have clinically relevant implications in the pathophysiology of cardinal motor symptoms in PD. While the relationship between pallidal beta activity and motor symptoms at baseline was previously documented¹⁸⁶, our frequency-resolved analysis reconciles findings from previous studies reporting a significant correlation only with low beta mean power or with the high-beta power^{189,198}.

Overall, our results indicate that pathological beta oscillations in the GPi might be prevalent at higher beta frequencies than in the STN. In the cortico-basal networks as well as in interhemispheric communication between basal ganglia, high-beta oscillations have been linked to long-range information processing^{76,77}. A first speculative hypothesis could be that pathological oscillations occur at a higher frequency in the GPi, the main output structure of the basal ganglia, to favour communication with the motor thalamus. The different spectral modulation with the two interventions in each target might depend on the shaping based on the distinct anatomical connections of the STN and GPi, particularly when considering that LFPs predominantly reflect synaptic inputs. Although both nuclei are part of the same network, they differ significantly in their local and long-range (i.e., cortical) inputs. The STN likely receives direct projections from the motor cortex^{76,77}, while the GPi is believed to lack direct cortical inputs and is located downstream in the basal ganglia circuit as a main output nucleus⁷⁶. Consequently, the GPi activity might be more strongly influenced by basal ganglia afferents (including the STN) and indirectly by cortical inputs.

This anatomical divergence is important considering the recent hypothesis of cortical driving of beta oscillations in both the STN and GPi that might contribute to the distinct spectral local modulation from L-Dopa and DBS^{76,77}. In this regard, in STN-DBS patients, it was hypothesized that L-Dopa and DBS might

have differential effects and mechanisms of action⁷⁷. We here speculate that in the GPi these mechanisms might display a higher overlap, potentially mediated by the converging influence from other structures, reflecting the functional role of the nucleus as the main basal ganglia output structure.

L-Dopa might exert widespread effects across the cortico-basal-thalamo-cortical circuit, primarily by restoring dopaminergic tone in the striatum and enhancing the activity of the indirect pathway. Therefore, the specific connection of each target may be more relevant in determining the L-Dopa-induced modulation. DBS likely produces more focal and direct effects on the target structure, modulating both afferent and efferent activity¹⁹⁹. The strong anatomical connections between the two structures and the previous observations pallidal beta activity suppression from stimulation applied to the STN might explain the similar modulation of high beta frequencies and the lack of difference in DBS-induced effects^{81,200}.

Another novel result of our study concerns the differences in beta peaks between STN and GPi and their modulation by L-Dopa and DBS. At baseline (MOFF/SOFF condition), we found more prominent peaks in the STN compared to GPi. This finding might be attributed to its smaller anatomical size compared to the GPi, given that identical recording electrodes were used for both targets. This might result in a higher signal-to-noise ratio for detecting synchronized activity. Alternatively, this difference may reflect higher neural beta synchronization in the STN in our cohort.

Importantly, medication and stimulation suppressed beta peaks in both targets, suggesting that, despite frequency-specific effects, each intervention might act by reducing the dominant pathological synchronization in both targets. The observed stronger peak amplitude reduction in the STN with medication, stimulation and their combination might likely depend on the greater peak prominence at baseline, as demonstrated by neurophysiological correlations.

Our results have translational relevance for the development of tailored aDBS strategies for PD. While supporting the use of beta activity as a robust physiomarker for pallidal aDBS, our findings suggest that higher beta frequencies could be more appropriate for guiding stimulation in the GPi compared to the STN^{116,122,186}. Although aDBS has been recently approved in PD for GPi, the reactivity of beta oscillations to medication under chronic DBS has never been assessed. Our results offer the theoretical basis to test the effects of guiding aDBS with different beta frequencies. The difference we observed in beta peak prominence and reactivity to combined L-Dopa and DBS between STN and GPi also has clinical relevance.

The use of the beta peak as a feedback signal is indeed a crucial step for aDBS programming^{134,135}. Our results might suggest that narrower stimulation windows might be more appropriate when programming GPi- compared to STN-aDBS, as beta peak amplitude appears less sensitive to the combined effects of medication and stimulation.

Confoundings and limitations

Patients were evaluated at least 6 months after surgery and after DBS surgery and stimulation parameter optimization, while maintaining chronic stimulation parameters. This allowed us to evaluate the best response to DBS as established by multiple clinical visits. Also, patients were given their usual L-Dopa dose (≥ 100 mg) to account for individual differences in medication response. Importantly, there were no demographic and clinical differences between STN and GPi patients, and the acute L-Dopa doses and the washout period from medication and stimulation were similar between groups. Importantly, this is the first study assessing neurophysiological changes of GPi in response to medication and stimulation using chronic LFP recordings^{84,119,122,186,188}. Most previous works assessed these signals during or immediately after DBS surgery. However, intraoperative LFPs might be affected by propofol administration, while recordings from externalized leads might be influenced by the “stun effect” resulting from electrode implantation^{130,131,201}. In contrast, chronic recordings provide a more stable, ecological and physiologically representative assessment of neural activity, avoiding these acute peri-operative confounds. However, our study has some limitations. First, only lateralized motor symptoms were assessed across the four experimental conditions, which prevents evaluating the relationships between beta dynamics and axial symptoms or overall clinical changes. Second, the effect of L-Dopa was assessed after a withdrawal period of ≥ 5 hours (clinical OFF condition) rather than following a longer overnight withdrawal (≥ 12 hours). Due to the severity of motor symptoms and the development of OFF-state troublesome phenomena, some patients would indeed not have tolerated longer withdrawal periods. However, STN- and GPi-DBS patients were evaluated after similar periods from the last L-Dopa dose, ensuring consistency across groups. Similarly, the effects of stimulation were observed 15-20 minutes after DBS was turned off. Although residual effects cannot be entirely excluded, this interval is likely sufficient, as a previous study documented that beta-band activity re-emerges within seconds of DBS cessation⁹⁷. Finally, our sample size was relatively small, reflecting the inherent challenges of

recruiting well-characterized PD patients treated with DBS. While this is a common limitation in similar studies, it may limit the generalizability of our findings and the power to detect more subtle effects, which should be further addressed by future studies. A further limitation is that only beta activity was assessed, while oscillations in the theta, alpha, and gamma bands were not analyzed. However, this is justified by the role of beta oscillations as disease biomarker and their application as control signals for aDBS. Future studies should compare the activity in other frequency bands between targets.

3.1.5 Conclusions

Our study reveals that while the STN and GPi show similar beta activity at baseline, they respond differently to L-Dopa and DBS. The STN is more sensitive to low-beta modulation, whereas the GPi shows selective suppression at higher beta frequencies. These frequency-specific effects extend to beta bursts and correlate with motor symptom improvement. Importantly, combining medication and stimulation leads to a broadband beta suppression in both targets. These findings highlight that pathophysiologically relevant beta-band oscillations might occur at higher frequencies in the GPi compared to the STN and support differential biomarker selection approaches in adaptive DBS in the two targets. Overall, our results underscore the need for frequency-tailored neuromodulation strategies based on target-specific beta dynamics.

3.2 Study 2: Acute and long-term modulation of cortico-cortical functional connectivity by DBS in Parkinson's Disease

3.2.1 Introduction

Understanding cortical network modulation in PD is clinically and mechanistically relevant. The cortex is the final common pathway for movement generation and a major recipient of basal ganglia output signals^{43,44,95,191}. Therefore, changes in cortical synchronization and large-scale network oscillatory activity might play a role in determining PD motor symptoms and mediating the effects of therapeutic interventions that alleviate them^{53,140,202,203}. Moreover, DBS targets (STN and GPi) engage partially different anatomical loops and afferent/efferent projections, suggesting that they might have different impact on cortical and cortico-basal circuit dynamics^{43,76,191,204,205}. Prior studies have reported abnormal resting-state connectivity patterns in PD compared to HC, as well as DBS-related alterations in cortical synchrony, particularly within the beta band^{76,77,174,180,206}. However, systematic comparisons between STN- and GPi-DBS, and investigations of both longitudinal and acute stimulation effects, remain scarce.

HD-EEG combined with individualized source reconstruction methods and graph theory approaches provides a non-invasive window onto cortical network organization in patients with chronically implanted DBS systems^{157,158,180}. When paired with metrics of FC less sensitive to volume conduction, such as the weighted phase-lag index (wPLI), and inferential approaches controlling for multiple comparisons, such as NBS, HD-EEG enables frequency-specific characterization of large-scale cortico-cortical FC networks at specific frequencies^{159,173,177,207}. This framework is particularly suited to test whether DBS induces target- and frequency-dependent reconfiguration of cortical coupling, and whether these changes differ between the acute and chronic phases of stimulation.

From a therapeutic standpoint, disentangling the cortical signatures of STN- and GPi-DBS could help explain their comparable efficacy on motor symptoms as well as target-specific benefits observed in clinical practice^{23,45,46}. Mechanistically, demonstration of frequency- and network-specific cortical modulation would support models in which DBS alleviates symptoms by suppressing pathological beta-band synchronization and facilitating restoration of more physiological patterns of information flow across sensorimotor and associative circuits^{77,208,209}.

In this pilot study, we combined HD-EEG with NBS to investigate cortical network changes in PD patients undergoing DBS. We pursued three objectives: (i) to confirm disease-related FC alterations in PD compared to HC; (ii) to characterize longitudinal changes in cortical connectivity after DBS surgery; and (iii) to assess acute network effects of DBS by comparing stimulation ON and OFF states in the chronic phase. We hypothesized that DBS would reduce pathological beta-band hyperconnectivity both longitudinally and acutely, with potential differences between STN- and GPi-DBS cohorts. By addressing these aims, our work seeks to clarify how DBS reshapes cortical networks acutely over time, providing insights that may inform mechanistic models of therapy and guide future optimization strategies.

3.2.2 Materials and Methods

Participants

Twenty-eight PD patients (mean age $\pm$ SD: 60.5 $\pm$ 9.75 years) treated with bilateral STN- (n=16, 4 females) or GPi-DBS (n=12, 4 females), and twenty-five age- and sex-matched HC (mean age $\pm$ SD 62.5 $\pm$ 10.2 years, 9 females) were included. In PD patients, assessments were performed in the chronic phase after DBS implantation, i.e., more than 6 months after surgery and at least 1 month after stable stimulation parameters. All patients were implanted with directional leads (Medtronic B33005 or Boston Scientific Cartesia). Patients with cognitive impairment, as indicated by a Montreal Cognitive Assessment (MoCA) score ≥ 22 ²¹⁰ were excluded from the study. Inclusion criteria for HC were the absence of major neurological or psychiatric conditions and no evidence of cognitive impairment (MoCA score ≥ 22)²¹⁰. Clinical and demographic characteristics of participants are reported in Table 4.

Experimental protocol and clinical evaluation

Each PD patient underwent a single experimental session in the clinical OFF state (M-OFF) after overnight withdrawal of L-Dopa (>12 hours). Clinical and neurophysiological assessments were conducted before and 10 minutes after switching off DBS (S-ON and S-OFF, respectively; Figure 11). In the S-ON condition, individual chronic DBS stimulation settings (amplitude, pulse width, frequency and active stimulating contacts) were applied. The severity of motor and non-motor symptoms was evaluated using the MDS-UPDRS I-IV¹⁹², and the disease was staged using the modified Hoehn and Yahr (H&Y) scale²¹¹. In each

condition, motor symptom severity (MDS-UPDRS III) and HD-EEG data were collected. Cognitive function was assessed at the beginning of each session using the MoCA scale²¹⁰. A subgroup of PD patients (11 STN-DBS, 9 GPi-DBS) had also undergone a clinical-neurophysiological assessment 2-6 weeks before DBS surgery in the M-OFF condition (T0) in addition to the DBS chronic evaluation (T1). HC completed a single experimental session that included MoCA administration and HD-EEG recordings.

EEG data acquisition

HD-EEG data were recorded using a 64-channel system (NeurOne, Bittium, Kuopio, Finland), with electrodes placed according to the 10-10 International System (IS)²¹². In each condition, signals were recorded for 10 minutes at a sampling rate of 1024 Hz and band-pass filtered between 1 and 100 Hz. Electrode impedances were kept below 5 k Ω . Recordings were performed in the eyes-closed resting state condition with participants instructed to remain awake and relaxed for 10 minutes, as in previous studies^{175,179,213}. To exclude epileptiform activity, eye-opening reactivity and activation manoeuvres were assessed. Vertical and horizontal electro-oculogram (EOG), electrocardiogram (EKG) and bilateral wrist flexor electromyography (EMG) were recorded simultaneously with HD-EEG.

Cortico-cortical functional connectivity analysis

Data preprocessing was performed on MATLAB v.2022b (The MathWorks, Natick, Massachusetts) using the Brainstorm open-source toolbox (Figure 12)²¹⁴. HD-EEG recordings were segmented into 30-second epochs for visualization. The first epoch of each recording was discarded. For each subject, six consecutive epochs with minimal artifacts (total duration: 180 seconds) were selected for further analysis^{175,176,179}. Residual artifacts were removed using independent component analysis (ICA)²¹⁵. EEG source localization was then performed. All participants underwent a presurgical brain MRI on a 3T system (Achieva, Philips Medical Systems) equipped with an eight-channel phased-array head coil. The 3D T1-weighted (T1w) magnetisation-prepared rapid gradient echo (MPRAGE) sequence (acquisition matrix, 224x224; TR=4800 ms; TE=340 ms; TI=1650 ms; flip angle, 90°; slice thickness, 1.12 mm) was used to compute the head model and the cortex surface for each subject, using CAT12 software (parameters: vertices on the cortex surface 15,000; cortical thickness 12 mm; folding measures 20 mm)²¹⁶. Next, personal T1-w MPRAGE MRI

sequence and EEG data were co-registered using anatomical landmarks. The boundary element method (BEM) was used to solve the forward problem, and the inverse problem was addressed with weighted minimum-norm estimation (wMNE)^{217–219}. Cortical sources obtained were parcellated into 68 brain regions (Regions of interest, ROI) using the Desikan–Killiany atlas²²⁰. Phase information from the preprocessed EEG signals was obtained using the Hilbert transform. FC was calculated in source space using the weighted phase lag index (wPLI), a measure that minimizes the influence of volume conduction, noise, and small sample bias^{173,207}. FC was estimated across the following frequency bands: theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and low-gamma (30–48 Hz). The delta band was excluded due to its limited relevance in awake, cognitively unimpaired patients with PD⁶⁷. Dynamic FC matrices were calculated between all pairs of regions in the selected EEG frequency bands using Welch’s method (1-s segments, 50% overlap)¹⁹⁴. Finally, dynamic connectivity matrices were averaged across time epochs to obtain static FC matrices.

Statistical analysis and cross-validation algorithm

Group differences in demographic characteristics between PD patients and HC, as well as between the STN-DBS and GPi-DBS cohorts, were assessed with Fisher’s exact test (categorical variables) and the Mann–Whitney U test (continuous variables). Clinical changes after surgery and the motor effects of DBS stimulation at T1 were assessed within each cohort using the Wilcoxon test. To compare these effects between STN- and GPi-DBS patients, percentage changes of each variable were computed as $(T0-T1)/T0 \times 100$ post and compared using the Mann-Whitney U test.

The NBS algorithm was used to detect differences in FC and possible differential networks between i) PD patients at T0 (n=19) and HC; ii) before and after DBS surgery (n=19); iii) S-OFF and S-ON conditions at T1. NBS controls the family-wise error rate at the component (subnetwork) level by first applying a component-forming threshold (τ) to edge-wise test statistics and then using permutation testing to assign significance to the size of connected edge components¹⁷⁷. The mean network connectivity (mNC) of the identified differential networks was then compared between groups using the Wilcoxon test. For PD patients, the comparison between STN- and GPi-DBS was performed by calculating and comparing the percentage change in mNC of the identified networks. All analyses were implemented using custom MATLAB scripts

in combination with the Brainstorm, NBS, and NBS-Predict toolboxes^{177,214,221}. P values <0.05 were considered significant for NBS and in all statistical comparisons.

3.2.3 Results

Demographic and clinical characteristics

No significant differences in age ($p=0.87$) and sex (0.72) were observed between HC and PD patients. Among PD patients treated with STN- or GPi-DBS, there were no between-group differences in age ($p=0.22$), sex distribution ($p=0.90$), disease duration at surgery ($p=0.07$), MDS-UPDRS III preoperative ($p=0.53$) and post-operative ($p=0.87$) scores, in MDS-UPDRS IV pre-operative ($p=0.36$) and post-operative ($p=0.28$) scores and LEDD pre-operatively ($p=0.63$) and post-operatively ($p=0.17$, Figure 13). Within both targets, MDS-UPDRS III scores significantly decreased after surgery when stimulation was on (MDS-UPDRS III M-OFF vs. MDS-UPDRS III M-OFF S-ON, STN: $p<0.001$, GPi: $p=0.001$) with no between-target differences ($p=0.66$). Conversely, post-operative MDS-UPDRS III scores with stimulation turned off (S-OFF) were higher with respect to preoperative scores in both groups. However, STN-DBS patients' MDS-UPDRS III changes were bigger compared to GPi-DBS patients ($p=0.04$). LEDD significantly decreased in both groups after surgery (STN: $p<0.001$, GPi: $p=0.001$), with no significant between-target difference in percentage changes ($p=0.09$), although the mean reduction was higher in STN-DBS patients (60.1%) than GPi-DBS (47.4%). Furthermore, MDS-UPDRS IV was significantly reduced in both groups with surgery (STN: $p<0.001$, GPi $p=0.009$), with no difference between targets ($p=0.9$).

Finally, acutely switching DBS on produced a significant acute reduction in MDS-UPDRS III scores in both groups (STN: $p<0.001$, GPi: $p=0.001$), with no significant between-target differences in percentage change ($p=0.32$).

Differences in FC between PD and HC

The NBS analysis applied to differentiate PD patients assessed at T0 and HC identified a large FC network in the beta band (56 nodes and 99 links, $\tau=2.8$) in which connectivity was significantly stronger in PD than in HC ($p=0.0016$; Figure 14 A). The network was bilaterally distributed with a slight left-predominance ($\approx 56\%$). ROIs with a higher degree were located in prefrontal/orbitofrontal cortices (left caudal middle

frontal, pars orbitalis, bilateral lateral orbitofrontal), sensorimotor regions (bilateral paracentral), parietal (bilateral inferior parietal and left superior parietal), occipital (bilateral lateral occipital and pericalcarine), and limbic (right entorhinal and bilateral cingulate) cortices. The mNC within this network was significantly higher in PD patients than in HC ($p=0.002$; Figure 14 A).

An additional network was detected in the alpha band (51 nodes, 107 links, $\tau=2.6$) in which FC was significantly stronger in HC than in PD ($p=0.0006$; Figure 14 B). The network was bilateral with a slight predominance in the right hemisphere ($\approx 55\%$). Higher-degree ROIs were part of the prefrontal cortex (right middle frontal and pars triangularis), orbitofrontal cortex (right medial and lateral orbitofrontal, right pars orbitalis), sensorimotor areas (bilateral paracentral, right precentral, and left postcentral), parietal (bilateral supramarginal and right inferior parietal), and temporal (right temporal pole and inferior temporal, right fusiform) lobes. The mNC of this alpha-band network was significantly higher in HC compared to PD ($p<0.0001$; Figure 14 B).

Longitudinal FC changes after DBS surgery

To assess longitudinal changes in PD patients after DBS surgery, we compared T0 and T1 in the S-OFF condition. NBS analysis revealed a network in the beta band (37 nodes and 46 links, $\tau=2.2$) in which FC was significantly higher at T0 compared to T1 ($p=0.03$; Figure 15 A). This network had bilateral distribution with left-hemisphere predominance ($\approx 59\%$). High-degree ROIs were part of the cingulate (left caudal anterior cingulate), sensorimotor (bilateral precentral), and orbitofrontal (right lateral orbitofrontal) areas. Network mNC was significantly higher at T0 compared to T1 ($p=0.0004$), consistently across targets (STN-DBS: $p=0.005$; GPi-DBS: $p=0.01$) with no significant between-target difference in T0-T1 percentage change ($p=0.96$; Figure 15 A).

In the theta band, NBS analysis identified a network (44 nodes and 62 links, $\tau=2.3$) in which FC was significantly higher at T1 than at T0 ($p=0.02$; Figure 15 B). The network was bilaterally distributed with a right-hemisphere predominant ($\approx 55\%$). ROIs with a higher degree were located in the temporal (right inferior temporal and temporal pole), prefrontal (right pars triangularis), and parietal (bilateral supramarginal) cortices. The mNC of this theta network was significantly higher at T1 compared to T0

($p=0.0002$), and this held for both STN-DBS ($p=0.01$) and GPi-DBS ($p=0.004$), with no significant differences in percentage changes between targets ($p=0.32$; Figure 15 B).

Acute DBS-induced FC changes

When assessing the acute changes induced by DBS (T1 S-ON vs. T1 S-OFF, $n=28$), NBS analysis identified a FC network in the beta band (19 nodes, 18 links, $\tau=2.0$) where FC was significantly higher in S-OFF than S-ON (Figure 16). The observed network had a bilateral symmetrical distribution between hemispheres. Regions with a higher degree were located in the temporal lobe (right superior temporal sulcus and bilateral temporal pole), prefrontal cortex (left caudal and right rostral middle frontal), sensorimotor areas (left precentral and postcentral), and parietal cortex (bilateral superior/inferior parietal). The mNC of the identified network was significantly higher in the S-OFF compared to the S-ON condition ($p=0.0004$), consistently within both targets (STN-DBS: $p=0.005$; GPi-DBS: $p=0.01$) without between-target differences in percentage change ($p=0.58$, Figure 16).

3.2.4 Discussion

This study investigated large-scale cortico-cortical FC patterns in PD patients treated with DBS of the STN or GPi, compared to age- and sex-matched HC. Using HD-EEG combined with source reconstruction and NBS, our preliminary results indicate frequency-specific cortical network alterations after DBS surgery and in response to stimulation.

First, in line with previous findings, PD patients exhibited hyperconnectivity in the beta band and hypoconnectivity in the alpha band compared to HC, with involved prefrontal, sensorimotor, parietal, and limbic regions^{175,176,179}. Longitudinal analyses revealed that chronic DBS was associated with a reduction of pathological beta-band FC and a relative enhancement of theta-band networks, independently of stimulation target (STN or GPi). Acute stimulation (S-ON vs. S-OFF) produced a decrease in beta-band FC, consistent with DBS-induced network-level modulation. Importantly, clinical outcomes confirmed robust improvements in motor symptoms and reduction of dopaminergic medication following surgery in both STN- and GPi-DBS groups, with no major between-target differences except for slightly larger medication reduction and off-stimulation motor worsening in STN-DBS patients.

The observed widespread beta hyperconnectivity at baseline in PD patients relative to HC confirms previous observations and further underscores the distributed nature of this abnormality, involving not only sensorimotor but also prefrontal and limbic regions^{77,175,179}. Such widespread beta coupling may reflect maladaptive recruitment of interconnected cortical circuits^{53,175,222}.

Conversely, the alpha-band hypoconnectivity in PD compared to HC supports evidence that alpha oscillations are diminished in PD and have been demonstrated since the early phase of the disease, while they have also been correlated with cognitive decline^{153,176,179,223}. In our study, participants with overt cognitive impairment were excluded, confirming that alpha deficits may be present even in cognitively preserved PD subjects, representing an early biomarker of network dysfunction^{175,179}.

Longitudinally, chronic DBS was associated with reduced beta-band and increased theta-band connectivity compared to the pre-operative condition in both STN and GPi cohorts. Theta activity has been implicated in cognitive control, working memory, and cortico-striatal communication²²⁴. The observed theta enhancement after surgery may indicate partial network reorganization or restoration of cross-frequency dynamics disrupted in PD^{113,137}. This resonates with MEG studies showing that STN-DBS can increase cortico-frontal theta synchronization, possibly reflecting adaptive network plasticity in the chronic stimulation phase¹¹³.

Acute DBS-induced suppression of beta connectivity is consistent with a previous study performed on a limited cohort of PD STN-DBS patients but extends findings to GPi patients. These abnormalities also mirror LFP studies reporting acute desynchronization of pathological beta oscillations upon stimulation^{97,98,225}. Importantly, the identified beta FC network was not restricted to sensorimotor regions, but involved multiple cortical areas, further strengthening the view that DBS acts not only locally but also reshapes large-scale distributed cortical connectivity patterns²²⁵. The lack of significant differences between STN- and GPi-DBS on network-level metrics parallels the clinical equivalence observed in motor outcomes, reinforcing the notion that both targets modulate overlapping pathological circuits despite distinct anatomical entry points^{23,45,46}.

Confoundings and limitations

Several factors must be considered when interpreting these findings. First, the study cohort was relatively small, particularly when stratified by DBS target, which limits statistical power to detect subtle between-

target effects or associations with clinical symptoms and disease subtypes. Although directional leads were uniformly used, variability in electrode positioning, stimulation parameters, and disease phenotype (e.g., presence and severity of gait abnormalities) may have introduced heterogeneity^{179,226,227}.

Second, EEG-based source localization, while improved by individual MRI co-registration, was performed offline based on anatomical landmarks and is generally also constrained by limited spatial resolution and potential residual confounds from volume conduction^{157,228–230}. Although we minimized these using the wPLI, caution is warranted when interpreting specific regional differences.

Third, the exclusion of cognitively impaired patients restricts generalizability, as connectivity alterations in alpha/theta bands may be more pronounced in PD with mild cognitive impairment or dementia^{5,231,232}. Medication state was controlled by overnight withdrawal, but chronic medication effects on network plasticity cannot be fully excluded. Furthermore, the use of resting-state paradigms, while reproducible, limits the evaluation of beta activity and the functional inference about task-related or behaviorally relevant network dynamics.

Future perspectives

Future research should aim to address these findings in larger patient cohorts, ideally integrating multimodal approaches (LFP, MEG, fMRI, EEG) to capture complementary aspects of network dynamics^{77,113,128,233}. Importantly, coupling electrophysiological connectivity measures with behavioural and cognitive assessments may help disentangle the clinical relevance of alpha and theta network changes.

In addition, emerging closed-loop DBS strategies, which adjust stimulation parameters in real time based on neurophysiological biomarkers, could leverage cortical or network-level activities to optimize therapy^{147,148,151,234,235}. While most clinical aDBS trials have focused on subcortical beta activity as a control signal, recent work has shown that specific signal features of cortical recordings, particularly from the motor cortex, provide potential biomarkers^{146,149–151}. Personalized connectivity-guided targeting (Horn et al., 2017) and cross-frequency coupling analyses may further refine our understanding of DBS mechanisms and support individualized patient selection for STN versus GPi implantation.

3.2.5 Conclusions

This study demonstrates that PD is associated with widespread beta-band hyperconnectivity and alpha-band hypoconnectivity at rest, extending beyond motor networks. DBS, irrespective of target, reduces pathological beta synchronization both acutely and chronically, while enhancing theta-band connectivity in the chronic phase, suggesting large-scale network reorganization. These electrophysiological changes parallel clinical improvements, supporting the concept of DBS as a circuit therapy. Despite methodological limitations and modest sample size, our findings add to converging evidence that oscillatory connectivity biomarkers may serve as objective indicators of disease state and treatment response in PD. Future research should validate these markers in larger cohorts, integrate them into adaptive DBS paradigms, and explore their utility for predicting long-term clinical and cognitive outcomes.

3.3 Study 3: Local field potentials fast survey to guide DBS programming in Parkinson's disease

3.3.1 Introduction

A critical step for DBS optimization and tailoring is programming, which currently relies on clinical evaluation of motor symptoms and adverse effects during the titration of stimulation parameters (i.e., monopolar review)^{31,236}. Although this conventional clinical programming (CP) is considered the *gold standard*, it is time- and resource-consuming, prone to subjective errors, and requires specialized training, making it largely restricted to experienced centers^{31,33,37,40}. Additionally, CP often follows heterogeneous in-house procedural pipelines and is not standardized across centers³⁰.

A possible strategy to overcome these limitations is using imaging-guided programming^{40,41}. However, the identification of the dorsolateral (sensorimotor) area of target nuclei with conventional Magnetic Resonance Imaging (MRI) remains challenging and requires advanced image post-processing^{41,237}. Several factors can affect lead localization accuracy and the overall reliability of these approaches, including movement-related artifacts during MRI acquisition, susceptibility artifacts around electrodes, limited spatial resolution and potential distortions of low-field (i.e., 1.5 and 3T) MRI in deep brain structures, and potential errors introduced by co-registration pipelines²³⁸. Furthermore, there is evidence that the structurally defined sensorimotor regions do not necessarily coincide with the functional domain in the individual patient^{39,239,240}. Previous studies using intraoperative and early postoperative LFP recordings showed that lead contacts exhibiting prominent beta activity frequently showed the largest therapeutic window and may therefore be used for chronic stimulation^{124,241–244}. Sensing-enabled DBS systems, allowing fast neurophysiological assessments in chronically implanted patients, can now facilitate LFP-based contact selection^{133,245}. To date, only a few studies have investigated the efficacy of beta-guided programming in PD^{39,42,246}, with one randomized controlled trial demonstrating similar motor outcomes to conventional CP and imaging-guided programming³⁸. However, these studies did not include both short- and long-term neurophysiological assessments. Also, the method used to identify the best stimulating contact remains a key challenge in implementing LFP-guided programming in clinical practice.

In this longitudinal study, we assessed and compared three different neurophysiological methods in selecting optimal stimulation contact, applicable in real-time without signal post-processing for STN- and GPi-DBS PD patients, with conventional clinical programming (CP). This selection may halve the contacts needed for clinical testing by determining whether beta sources fall more ventrally (contacts 0 and 1) or dorsally (contacts 2 and 3). The overall assessment period spanned from initial programming (IP) to long-term clinical follow-ups (cFU) (i.e., after determining the optimal chronic stimulation setting). The study objectives were to (i) evaluate the performance of different LFP-based methods relative to CP (gold standard) using three complementary evaluation metrics (correlation strength, agreement level, and selection similarity) and validate it against a random selection (RS) model; (ii) assess the stability of contact selection and beta activity over time; and (iii) determine the ability of each method to predict the clinical stimulating contact at follow-up, and iv) to compare the best-performing neurophysiological approach against imaging-guided programming.

3.3.2 Materials and Methods

Participants and clinical evaluations

Nineteen PD patients (9 females, mean age 55.8 ± 7.5 years) treated with bilateral STN- (12 subjects) or GPi-DBS (7 subjects) were included. All were implanted with the sensing-enabled Medtronic Percept™ PC neurostimulator and quadripolar segmented leads (model B33005; 0.5 mm intercontact spacing) identical for both STN and GPi. Monopolar review was performed after L-Dopa withdrawal (>1 hour beyond the usual interdose interval, in the clinical OFF condition), and all four lead levels were tested in a monopolar configuration (i.e., using the pulse generator as anode and the tested level as cathode), separately for each hemisphere^{29,236}. The therapeutic window was assessed by increasing stimulation amplitude in 0.2 mA steps and evaluating the effect on parkinsonian motor symptoms (bradykinesia, rigidity, and tremor), with bradykinesia severity most frequently used as the target symptom, given its consistent presence across patients. The level with the widest therapeutic window was selected for chronic stimulation. Importantly, CP was solely based on clinical assessment, blinded to LFP data or imaging guidance. Due to technical constraints of bipolar recordings of the Percept™ PC, it is currently impossible to obtain a real-time, reliable estimate of beta power sources located at the most cranial and caudal contact levels (i.e., 0 and 3). Therefore,

since the aim was to compare neurophysiology-based vs. clinical-based programming, only patients showing the widest therapeutic window at one of the two central levels were included. All patients underwent multiple on-demand follow-up visits (mean: 5.7, range 4-8 visits), and stimulation was optimized, if needed (i.e., side effects or unsatisfactory clinical improvement). The last cFU was always performed ≥ 6 months after surgery and >1 month after stable stimulation parameters and contacts (mean time from IP to cFU: 9 months, range 6-13 months). Clinical and demographic characteristics of patients and the timing of assessments are reported in Table 5.

Data acquisition and analysis

Immediately after clinical assessment at IP and cFU, LFPs were acquired with patients at rest with their eyes open, two minutes after turning off the stimulation. Recordings from each hemisphere (38 nuclei) were obtained using the BrainSense™ Survey (BSS) feature separately between level pairs (0-3, 0-2, 1-3, 0-1, 1-2, and 2-3), and individual segment pairs (1A-1B, 1B-1C, 1A-1C, 2A-2B, 2B-2C and 2A-2C) (Figure 17). Briefly, BSS captures LFPs sampled at 250 Hz for ≈ 40 seconds with stimulation turned off and displays power spectra of each bipolar recording^{133,245}. Data were stored locally on the Clinician Programmer and exported as .json files for offline analyses, which were performed using MATLAB v.2022b (The MathWorks Inc., Natick, Massachusetts). And a 5th-order Butterworth filter was applied (5-98 Hz). Power spectra were computed with Welch's method (1s window length, 50% overlap) and beta peaks (13-30 Hz) were detected with the *findpeaks* MATLAB function, visually inspected and manually adjusted if needed. Two hemispheres (both STN) were excluded from subsequent analyses since no clear beta peak could be detected. Consequently, a total of 36 hemispheres were included in the final analyses. In cases where two distinct beta peaks were present (observed in seven hemispheres), the peak with the highest power was selected for subsequent analysis. Each identified peak was then classified into the low-beta (13–20 Hz) or high-beta (21–30 Hz) sub-band. Then, bipolar recordings from levels and horizontally paired segments were ranked in descending order based on the power spectral density (PSD) of the identified beta peaks. To evaluate possible longitudinal changes of beta activity, signals were z-scored before performing spectral decomposition using Welch's method. Beta peak amplitude, mean PSD in the beta, low and high beta ranges were then computed and compared between IP and cFU¹⁹⁴.

Neurophysiological methods for beta-based level selection

LFP-based contact selection between middle segmented levels (1 vs. 2) was performed by evaluating beta peak amplitude using three methods comparing LFPs recorded by contact pairs with the same distance (i.e., 0-2 vs. 1-3, 0-1 vs. 2-3, 1A/B/C-1B/C/A vs. 2A/B/C-2B/C/A, Figure 17). Importantly, all programming strategies were specifically designed for direct application as a bedside tool solely using the Clinician Programmer without requiring offline data processing.

Three different contact selection methods were evaluated and compared in this work (Figure 17). The Broad-Bipolar and Narrow-Bipolar methods include both central and peripheral contacts (non-adjacent 0-2/1-3 pairs and adjacent 0-1/2-3 pairs, respectively), and are based on the assumption that beta activity is higher when one contact is inside the source of beta activity and the other outside²⁴⁶. Therefore, they allow to discriminate whether the source of beta activity is located more ventrally (beta peak 0-2>1-3 or 0-1>2-3) or dorsally (beta peak 1-3>0-2 or 2-3>1-2). For Broad-Bipolar, if the beta peak from the 0-2 recording was higher, 1 was selected as the “best” level; if the peak from the 1-3 recording was more prominent, level 2 was chosen, as in a previous study^{38,39}. In the Narrow-Bipolar method, 1 or 2 was considered as the “best” level depending on whether the greatest beta peak was from 0-1 or 2-3 bipolar recording, respectively. Notably, despite the same general assumption, the key difference between broad-bipolar and narrow-bipolar methods was the width of the bipolar recording.

Finally, in the Segment-Bipolar method, the optimal stimulation level was identified by comparing the beta peak power in recordings from horizontally paired segments (i.e., A-B, B-C, A-C) between levels 1 and 2 (1A-1B vs. 2A-2B; 1B-1C vs. 2B-2C; 1A-1C vs. 2A-2C, Figure 17)³⁸. Here, the level showing higher beta peak amplitude in at least two of the three comparisons was considered the “best” level.

Neuroimaging data acquisition and contact selection

All patients underwent a pre-surgical brain MRI (including 0.9mm iso 3D-MPRAGE, 0.9 mm iso 3D-T2-weighted and 2D-Susceptibility Weighted Imaging sequences) within one month of the implant on a 3T Philips Ingenia (Philips Healthcare, Amsterdam, Netherlands). Post-operative head CT scans (slice thickness ≤ 1 mm, no gap between slices; reconstruction slice thickness ≤ 0.625 mm; soft tissue reconstruction kernel)

were obtained >3 months after surgery to minimize pneumocephalus and brain shift artifacts. DBS electrodes were localized using Lead-DBS v3.1, an open-source MATLAB toolbox that integrates pre-operative MRI with post-operative CT scans²⁴⁷.

Electrodes and subcortical targets were visualized using the DISTAL atlas²⁴⁸. An experienced rater (LR), blinded to the patients' clinical, neurophysiological and programming information, identified the two “best” levels^{41,249} based on spatial proximity to the sensorimotor subregion of the target and distance from other neighbouring structures (e.g., internal capsule and substantia nigra). This approach accounts for the common clinical scenario where multiple lead levels are near the anatomical target and ensures that at least one of the two middle-segmented contacts is selected as the “best” level.

Statistical analysis

The performance of each beta-based method was evaluated using three different complementary metrics: correlation, agreement and selection similarity, to provide a comprehensive assessment of each selection strategy. Correlation captures the strength and direction of relationships between each method and CP, agreement quantifies the degree of concordance in selected levels, reflecting how closely each method replicates the gold standard, while similarity provides a proportion of exact matches in contact selection. The correlation strength between LFP-based methods and the CP-based level selection was evaluated using the phi(ϕ) coefficient, a measure of binary correlation suitable for categorical agreement. Correlation was considered very weak for $0.01 \leq |\phi| < 0.2$, weak for $0.2 \leq |\phi| < 0.3$, moderate for $0.3 \leq |\phi| < 0.4$, strong for $0.4 \leq |\phi| < 0.7$, and very strong for $|\phi| \geq 0.7$ ²⁵⁰. The level of agreement between LFP-based methods and CP-based selection was estimated with the Quadratic Weighted Kappa (QWK). The agreement was considered slight for $0 < \text{QWK} \leq 0.2$, fair for $0.2 < \text{QWK} \leq 0.4$, moderate for $0.4 < \text{QWK} \leq 0.6$, substantial for $0.6 < \text{QWK} \leq 0.8$, and almost perfect for $0.8 < \text{QWK} \leq 1$ ²⁵¹. QWK p-values were derived using permutation testing (1000 permutations) implemented via the `sklearn.metrics.cohen_kappa_score` function. Confidence intervals were estimated using bootstrap resampling with 1000 iterations. Finally, the degree of similarity between contact selection performed by LFP-based methods and CP was quantified by computing a custom similarity function that assigns a score of 1 or 0 based on the presence of a match between selections. To assess the statistical significance of similarity measures, a bootstrap hypothesis testing approach was employed. For

each similarity measure, 25,000 bootstrap samples were generated by resampling with replacement from the original dataset. Unlike permutation-based approaches, which are limited by the number of unique label rearrangements, the bootstrap allows for a far larger set of resamples, providing robust estimation even with relatively small sample sizes. The mean similarity was calculated for each bootstrap sample, forming a bootstrap distribution for each measure. A one-sided hypothesis t-test was then conducted to compare the observed mean similarity of each measure against the bootstrap distribution of a RS. The null hypothesis assumed that the observed mean similarity was not significantly greater than the mean similarity from RS. The p-value was calculated as the proportion of bootstrap samples from RS $\geq$ to the observed mean similarity for the given measure.

Correlation strength, agreement, and similarity levels between LFP-based methods at IP and CP at cFU were used to estimate the ability of each neurophysiological method to predict the level selected after multiple follow-up visits. These measures were also used to compare the overall performance of the best LFP-based method to the imaging-based approach we tested. Additionally, to evaluate possible differences between STN and GPi in the performance of each LFP-based method, we compared the proportion of cases with neurophysiology-CP concordant level selection between DBS targets using Fisher's exact test. The same approach was used to assess possible differences when considering peaks in the low- or high-beta sub-bands. To verify whether the changes in the stimulation level from IP to cFU (i.e., from 1 to 2 or vice versa) had a similar distribution to those occurring using the LFP-based methods, we applied the Chi-squared test. To evaluate the stability of beta-band activity over time, we assessed the recordings from contact pairs included in the best LFP-based method (Narrow-Bipolar). The bipolar recording displaying the highest beta peak at IP was selected, and the beta peak amplitude, frequency, and low- and high-beta mean PSD were compared between IP and cFU. The Shapiro-Wilk test for normality was used to assess data distribution in the various analyses. Parametric or non-parametric tests were applied accordingly, with the significance level set at $p < 0.05$. Statistical analyses were implemented using Python 3.13 libraries (scipy, sklearn) and MATLAB v.2022b.

3.3.3 Results

Performance of neurophysiological methods at initial programming

At IP, the ϕ correlation and QWK analyses demonstrated varying levels of association strength and agreement levels in contact selection between the different LFP-based methods and clinical-based programming (Figure 18). The Narrow-Bipolar method showed strong correlation ($\phi=0.7$) and substantial agreement (QWK=0.65, 95% CI: 0.39, 0.86, $p<0.001$) with monopolar review. Segment-Bipolar showed a strong correlation ($\phi=0.56$) and moderate agreement (QWK=0.54; 95% CI: 0.24, 0.76, $p=0.003$), while Broad-Bipolar did not correlate ($\phi=0.01$) and had only slight agreement (QWK=0.11; 95% CI: -0.25, 0.41, $p=0.38$) with monopolar review.

When assessing the observed mean similarity between the bootstrap distribution of levels selected by LFP-based strategies and monopolar review, we observed that Narrow-Bipolar had higher mean similarity (0.9) than Segment-Bipolar (0.86) and Broad-Bipolar (0.75). When testing the difference between mean similarity of the LFP-based strategies with CP and a random bootstrap distribution, the Narrow-Bipolar and Segment-Bipolar methods were significantly superior to RS ($p<0.001$ for both comparisons), and Broad-Bipolar ($p=0.17$) did not statistically differ from RS (Figure 19 and Table 6).

Finally, no significant differences were observed in the distribution of levels matching with CP between STN and GPi (Narrow-Bipolar: STN 15/22, GPi 11/14, $p=0.70$; Segment-Bipolar: STN 13/22, GPi 9/14, $p=1.00$; Broad-Bipolar: STN 12/22, GPi 7/14, $p=1.00$).

Stability of contact selection over time and performance of neurophysiological methods at clinical follow-up

When assessing the stability of clinical contact selection over time, we observed that the level activated at IP corresponded to that chronically used at cFU in 75% of cases (27/36 hemispheres, Figure 20). Among the different LFP-based methods tested, Narrow-Bipolar demonstrated the highest stability between IP and cFU (88.8%, 32/36 hemispheres). Furthermore, the distribution of contact changes over time was similar to CP ($p=0.56$). In contrast, Segment-Bipolar (69.4%, 25/36 hemispheres) and Broad-Bipolar (58.3%, 21/36 hemispheres) showed lower stability over time, and the distribution of contact changes from IP to cFU differed from CP (Broad-Bipolar vs. CP: $p<0.01$; Segment-Bipolar vs. CP: $p=0.01$). When evaluating the stability of beta activity over time, we found that beta peak amplitude ($p=0.18$), frequency ($p=0.40$), low-beta mean power ($p=0.07$), and high-beta mean power ($p=0.62$) did not change between IP and cFU (Figure 20).

The level of correlation and agreement with CP improved for all the LFP-based strategies at cFU compared to IP (Figure 18). Narrow-Bipolar showed a very strong correlation ($\phi=0.86$) and substantial agreement (QWK=0.78; 95% CI: 0.59, 0.99, $p<0.001$), Segment-Bipolar showed very strong correlation ($\phi=0.79$) and substantial agreement (QWK=0.74; 95% CI: 0.49, 0.93, $p<0.001$), while the correlation between Broad-Bipolar and CP was very weak ($\phi=0.06$) and the agreement was slight (QWK=0.12; 95% CI: -0.23, 0.43, $p=0.37$). Finally, the distribution of levels matching with CP was similar when considering peaks in the low- or high-beta sub-bands (Narrow-Bipolar: low-beta 20/24, high-beta 9/12, $p=0.66$; Segment-Bipolar: low-beta 19/24, high-beta 9/12, $p=0.54$; Broad-Bipolar: low-beta 9/24, high-beta 9/12, $p=0.08$) and between STN and GPi (Narrow-Bipolar: STN 17/22, GPi 12/14, $p=0.68$; Segment-Bipolar: STN 16/22, GPi 12/14, $p=0.44$; Broad-Bipolar: STN 13/22, GPi 5/14, $p=0.30$).

Ability of neurophysiological methods to predict contact selection at cFU

Narrow-Bipolar selection at IP showed a very strong correlation ($\phi=0.79$) and substantial agreement (QWK=0.75; 95% CI: 0.53, 0.93, $p<0.001$) with CP at cFU (Figure 18). Segment-Bipolar showed strong correlation ($\phi=0.50$) and moderate agreement (QWK=0.51; 95% CI: 0.19, 0.76, $p=0.02$), while Broad-Bipolar did not correlate ($\phi=0.05$) and had slight agreement (QWK=0.13; 95% CI: -0.22, 0.42, $p=0.34$) with CP at cFU (Figure 18). When assessing the observed mean similarity between the bootstrap distribution of levels selected by LFP-based strategies at IP and CP at cFU, we found that the Narrow-Bipolar method had a very high similarity to CP (0.93, Table 6, Figure 19). Segment-Bipolar and Broad-Bipolar methods showed lower similarity levels (0.87 and 0.75, respectively). The comparison between the observed mean similarity of the LFP-based strategies and the random bootstrap distribution disclosed that the Narrow-Bipolar and Segment-Bipolar methods were significantly superior to RS ($p<0.01$) (Figure 19, Table 6). Overall, these results suggest that the Narrow-Bipolar method had good predictive ability in identifying the level clinically selected after multiple follow-up visits.

Performance of the imaging-based approach and comparison with the best neurophysiological method

At IP, imaging-based level selection showed a strong correlation ($\phi=0.64$) and substantial agreement (QWK=0.65; 95% CI: 0.36, 0.86, $p<0.001$) with CP. The observed mean similarity between the bootstrap

distribution of contacts selected by the imaging-based approach and CP was 0.9, which was significantly greater than the corresponding value for RS ($p < 0.01$) (Table 6). At cFU, the correlation between imaging-based selection and CP was very strong ($\phi = 0.79$) and the agreement substantial (QWK = 0.76; 95% CI: 0.53, 0.94, $p < 0.001$). The observed mean similarity to CP was 0.83, and, unlike the Narrow-Bipolar method, this value did not differ from that obtained with RS ($p = 0.43$) (Table 6). When directly comparing the bootstrap distribution of similarity (with CP) between the Narrow-Bipolar and imaging-based methods, we found no differences between the two approaches, both at IP ($p = 0.99$) and cFU ($p = 0.82$).

3.3.4 Discussion

This longitudinal clinical-neurophysiological study compares the performance of three different beta-based DBS programming methods for identifying the best stimulation lead level compared to the current *gold standard* (CP) at both IP and after several follow-up visits (cFU). Broad-Bipolar method compared beta activity recorded between non-adjacent rings, Narrow-Bipolar included adjacent rings, while Segment-Bipolar was based on the comparison of horizontally paired segments. We found that Narrow-Bipolar outperformed the other methods in identifying the clinically selected level at IP and cFU in all metrics tested (correlation strength, agreement, and similarity level) and proved able to predict the level used over time. The performance of Narrow-Bipolar was comparable to an imaging-based method at both time points and did not change when considering the DBS target (STN or GPi). Performance was also unaffected by whether the dominant beta peak fell in the low- or high-beta sub-band. Overall, these findings suggest that LFP fast survey using a Narrow-Bipolar method can reliably guide DBS programming in PD.

The first novel finding of our study concerns the observation of different performances of three distinct beta-based methods in identifying the lead level selected at initial clinical programming, as per the standard monopolar review. The Narrow-Bipolar method demonstrated a strong correlation and substantial agreement with CP, Segment-Bipolar showed a strong correlation and substantial agreement, while Broad-Bipolar exhibited a slight agreement. Narrow-Bipolar also reached the highest similarity with CP in contact selection, and it proved superior to a simulated random selection. The reason for the diverging performances among methods likely depends on the different combinations of bipolar recording pairs used to compare the beta peak amplitude. The different spacing of contact pairs considered in each method might affect spatial

resolution, resulting in different abilities in discriminating the source of beta oscillations between central levels. Bipolar recordings capture the differences in electric potentials between recording sites. Therefore, the amplitude of the signal will be higher when only one of the two recording locations is close to the source of beta oscillations, and lower when both contacts are either close or distant from it⁸⁸. In this context, bipolar recordings between central and peripheral levels (Narrow-Bipolar) will provide information on the central contact closer to the source of beta oscillations, while sampling a relatively small target volume, thus retaining spatial resolution. Conversely, recordings from non-adjacent contacts (Broad-Bipolar) will achieve lower spatial resolution by capturing the activity of broader target volumes. Furthermore, since both levels 1 and 2 fall within the volume captured by 1-3 and 0-2 pairs, Broad-Bipolar might specifically have a reduced ability to discriminate the source of beta oscillations between central levels. Notably, while previous studies assumed that the source of beta activity might be localized between recording contact pairs, this hypothesis was originally based on multichannel EEG studies and may not necessarily be translated into LFP signals. Finally, consistent with the findings of a recent study, the performance of Segment-Bipolar was good³⁸. Indeed, recordings from horizontally paired segments span small target volumes, thus potentially providing an optimal spatial resolution⁸⁸. The lower performance than Narrow-Bipolar may be due to cases where the source of beta activity is symmetrically distributed around the electrode, resulting in small potential differences between recording segments and, in turn, low beta activity.

An additional strength of our study is that clinical and neurophysiological information was assessed multiple times, allowing us to compare IP and the last cFU. Clinically, we found that the levels selected using monopolar review at IP were maintained after multiple follow-up visits (cFU) in 75% of cases. Further supporting its superiority among beta-based selection strategies, Narrow-Bipolar was the approach demonstrating the highest selection stability from IP to cFU. The longitudinal design of our study also allowed us to assess the temporal stability of beta activity²⁵². We observed no significant differences in beta peak frequency, peak amplitude, or mean power in the low- and high-beta bands when comparing IP and cFU recordings. This finding aligns with a recent study by Fasano et al.²⁵³, which examined beta oscillations at various time points following STN-DBS surgery in PD patients. That study reported an initial increase in mean beta power, followed by sustained stability in subsequent assessments, whose timing mirrored the schedule used in our research. Altogether, these results underscore the importance of timing in LFP

recordings for DBS programming. By performing monopolar review at >3 weeks after surgery, we aimed to minimize the influence of the post-operative “stun” (microlesional) effect on beta oscillations^{131,253}. The observed beta stability in space (i.e., lead level), frequency, and power over the following months suggests that beta activity may serve as a reliable support for level selection when measured beyond this post-surgical period.

Another key finding of our study relates to the ability of LFP-guided programming using Narrow-Bipolar to predict the clinically selected contact after multiple follow-up visits. This has relevant translational implications when considering the possibility of integrating LFPs into the earliest phases of DBS programming. The fact that beta activity at IP is a good predictor of the optimal level determined after multiple clinical assessments highlights the reliability and robustness of this approach. Furthermore, the concordance with initial monopolar review of the Narrow-Bipolar method was not inferior to imaging-guided level selection, which is currently considered another valuable alternative to conventional CP^{38,40,41,237}. However, Narrow-Bipolar achieved even greater performances in predicting clinically selected levels at cFU than the imaging-based approach. This result might reflect the different identification strategy between the two approaches. While imaging can inform lead placement by providing static guidance of sensorimotor anatomical subregion, LFPs offer a dynamic and physiology-based confirmation of the functional sweet spot within the target. Functional rather than structural guidance may thus be more sensitive in identifying the optimal target site^{240,242}. In this context, our results highlighting the potential of beta activity in DBS programming are overall consistent with previous studies on intraoperative and early postoperative LFP recordings^{42,242–244}. From a practical standpoint, our overall findings point to the potential usefulness of the Narrow-Bipolar approach in halving the number of contacts requiring clinical testing. Indeed, when beta activity at contacts 0–1 exceeds 2–3, a more ventral beta source is suggested, and thus only contacts 0, 1A, 1B, and 1C could be tested. Conversely, the opposite pattern would suggest a more dorsal source, and clinical testing may be limited to contacts 2A, 2B, 2C, and 3. Figure 21 shows a proposal algorithm for a possible neurophysiologically-oriented fast DBS programming based on our data.

Confounding factors and limitations

The methods for data collection allowed us to exclude several factors potentially affecting our results. First, the monopolar review was always performed before neurophysiological recordings, and data were analysed offline to identify the highest beta peak. Therefore, the clinician performing the initial programming was blind to the “best” LFP-based contact level. Also, the “stun” effect likely impacts LFP recordings by inducing a transient decrease in beta activity in the first weeks after surgery^{30,131,132}. However, we performed the monopolar review at a time when the “stun” effect was likely subsiding¹³¹, and our finding of beta power stability over months supports this idea. To minimize possible post-stimulation effects, DBS was turned off two minutes before LFP recordings, as beta-band power generally returns to baseline within this timeframe⁹⁷. Importantly, since the distance between recording sites is known to affect signal amplitude, each Method included only contact pairs with the same interelectrode distance (e.g., 1-3 vs. 0-2 and 0-1 vs. 2-3). Similarly, the dimension of the recording surface influences the amplitude of the recorded signal; thus, segments and rings were compared independently. Because of the technological limitations of available sensing-enabled DBS systems, LFP signals were recorded using a bipolar montage, which yields intrinsic ambiguity and limitations in localizing the source of the beta oscillations, especially for extreme levels (0 and 3)⁸⁸. However, we enrolled only patients in whom one of the two central levels had the widest therapeutic window at monopolar review, but this inclusion criterion limits the generalizability of our findings for cases where upper- or lowermost levels are clinically optimal. It should be noted, however, that surgical placement of directional leads is typically planned so that central segmented contacts (enabling more precise current steering) are positioned within the optimal functional target region^{254,255}. Consequently, the *a priori* likelihood that the central levels (1 and 2) fall within the optimal target location is higher compared to the peripheral contacts (0 and 3). Importantly, since the Narrow-Bipolar method indicates a more ventral beta source when activity at contacts 0–1 exceeds 2–3, and a more dorsal source when the opposite pattern is observed, this method may halve the number of contacts requiring clinical testing (contacts 0 and 1 for ventral sources; contacts 2 and 3 for dorsal sources, see Figure 21 for the proposed flow-chart for a possible neurophysiologically-oriented fast DBS programming). Another limitation is that neurophysiological data were not correlated to clinical thresholds. Finally, recent DBS systems allow measuring LFPs from individual contacts independently by referencing to the contralateral DBS lead. However, such monopolar LFP recordings need to be validated

for application in clinical practice, and the method presented here might be useful for this aim. Furthermore, monopolar recordings are not applicable in specific cases (i.e., unilateral DBS lead or altered impedances on one electrode) where bipolar LFP signals might still be informative and are more sensitive to artifacts. Therefore, it is likely that combining monopolar and bipolar recordings will provide the most comprehensive and accurate neurophysiological information, leveraging the spatial resolution of monopolar LFPs and the robustness of bipolar signals to noise and artifacts.

3.3.5 Conclusions

Our study provides real-world evidence supporting the use of LFPs to assist DBS contact selection in PD. Specifically, evaluating beta peak amplitude using the Narrow-Bipolar beta-based method might offer a valid, practical, and physiologically grounded approach to orient clinical programming, halving the number of levels to test. Conventional CP can be time-consuming, subjective, and highly dependent on clinician expertise and patient feedback, which might be confounded by fatigue, cognitive impairment, speech disturbances, or delayed onset of clinical improvement. Using beta-based approaches would reduce programming times and follow-up visits, thus decreasing patient discomfort and healthcare system burden, while providing a simplified and more broadly applicable strategy in resource-limited centers.

4. Discussion

The present thesis aimed to investigate the neurophysiological mechanisms by which DBS exerts its therapeutic effects in PD, and to explore the translational potential of beta oscillations in the basal ganglia as a biomarker for clinical application. Across three complementary studies, were examined (i) target-specific differences in subcortical beta activity and its modulation by dopaminergic medication and DBS (Study 1), (ii) large-scale cortical network reorganization induced by DBS in the acute and chronic phases (Study 2), and (iii) the feasibility of leveraging beta-band activity in LFPs to streamline DBS programming (Study 3). Together, these investigations offer insights into the mechanistic underpinnings of DBS, supporting the view of PD as a circuit disorder with pathophysiologically relevant oscillatory abnormalities, and translationally underscoring the role of beta activity in the basal ganglia as a clinically useful biomarker.

4.1 Mechanistic insights into DBS: target-specific and network-level effects

This thesis work stems from the emerging concept that DBS exerts its therapeutic effects through both local and distributed network-level mechanisms^{53,151,209,256}. Results from Study 1 provided evidence that while both the STN and GPi exhibit exaggerated beta activity at baseline, their reactivity to dopaminergic medication and stimulation differs. Specifically, low-beta oscillations (13–20 Hz) in the STN were more sensitive to L-Dopa, whereas higher beta oscillations were preferentially modulated in the GPi. Importantly, these target-specific spectral differences correlated with motor improvements: compound bradykinesia/rigidity severity paralleled low-beta power in the STN and higher beta power in the GPi. These findings reinforce the concept that the two nuclei, while embedded in overlapping cortico-basal loops, subserve partially distinct roles in motor control, with the STN being more tightly linked to the local basal dynamics and information processing and the GPi, as the main output structure of basal ganglia, reflecting longer-range information processing for information transmission to the thalamus and the cortex.

These observations contribute to refining our mechanistic models of DBS. Rather than producing uniform desynchronization across all oscillatory bands, stimulation appears to act on frequency-specific pathological activities that show different reactivity in the STN and GPi. The convergence of dopaminergic and stimulation effects onto broadband suppression when combined suggests a shared downstream pathway, yet the frequency selectivity may reflect the unique anatomical inputs and outputs of each structure. This target-

specific physiology provides a rationale for tailoring adaptive DBS (aDBS) strategies, with low-beta being a more reliable control signal in the STN and higher beta frequencies potentially more informative in the GPi. Study 2 expanded the mechanistic focus from subcortical to cortical networks. Using HD-EEG, source modelling and network-level connectivity analyses, our preliminary results confirmed widespread beta hyperconnectivity and alpha hypoconnectivity in PD relative to HC. Crucially, DBS reduced pathological beta synchronization both acutely and chronically, while enhancing theta-band connectivity in the chronic phase. These results further support findings indicating that DBS is not confined to producing local effects but instead reorganizes large-scale brain networks^{53,74,140,170,179,226}. Such reconfiguration was observed irrespective of target (STN or GPi), aligning with clinical findings of equivalent motor benefits between STN- and GPi-DBS and similar cortical-level dynamics at baseline. From a mechanistic perspective, the suppression of beta-band hyperconnectivity supports the model of DBS as an “informational lesion,” disrupting pathological synchrony that impedes motor execution^{53,71}. Furthermore, the presence of long-term beta suppression after surgery suggests the possibility of a cortical neuroplastic effect of DBS, which will need further confirmation.

Taken together, Studies 1 and 2 converge on the view of DBS as a circuit therapy: its efficacy derives not only from modulating activity within the stimulated nucleus but also from reshaping oscillatory communication across cortico-basal loops.

4.2 Translational implications: toward physiology-guided and adaptive DBS

A second key contribution of this thesis lies in bridging mechanistic insights with clinical practice. The identification of beta oscillations as robust biomarkers of motor impairment and treatment response has already translated into the development of aDBS systems, in which stimulation is modulated in real time based on LFP recordings^{59,125,126,134,148,187}. In Study 3, the usefulness of beta peaks in bipolar LFPs recorded with sensing-enabled devices from STN and GPi in supporting clinical DBS programming^{38,39,42,246}. Our findings showed that using specific approaches like the “Narrow-Bipolar” method, based on comparing beta peak amplitude between adjacent contact pairs, reliably predicted the clinically optimal stimulation level both at initial programming and after prolonged clinical follow-up. The performances of this approach were similar to the imaging-based contact selection strategy while being faster, more accessible, and requiring no

offline signal processing^{38,39,41,238}. Importantly, beta activity was stable over months, reinforcing its reliability as a programming tool.

These results have several practical implications. First, LFP-guided programming could reduce reliance on time-consuming clinical monopolar reviews, shorten clinical visits, and decrease patient burden. Second, by providing an objective physiological metric, it could help standardize and streamline programming across centers. By further demonstrating that beta dynamics not only index disease state and treatment response but also directly guide therapeutic decision-making, this thesis supports the clinical utility of oscillatory biomarkers as a bridge between mechanistic neuroscience and individualized therapy.

4.3 Methodological strengths and limitations

The studies presented here share several methodological strengths. They leveraged sensing-enabled neurostimulators to record chronic LFPs in ecological conditions, overcoming the perioperative confounds of anaesthesia and stun effects^{39,97,115,131–133,201}. The use of advanced analytical techniques, such as frequency-resolved burst detection and NBS, allowed us to capture both transient and distributed aspects of pathological synchrony^{114,177,178}. Importantly, all analyses were conducted in well-characterized cohorts of PD patients with chronic DBS, ensuring clinical relevance.

Nonetheless, some limitations must be acknowledged. Sample sizes were modest, reflecting the challenges of recruiting patients with implanted devices, and may have limited statistical power to detect more subtle differences, especially between targets. While HD-EEG source reconstruction and wPLI reduced confounds from volume conduction, residual limitations in spatial resolution cannot be excluded^{173,228–230}. Clinical assessments focused primarily on motor symptoms, and non-motor outcomes such as cognition and mood were not systematically considered. Finally, the generalizability of beta-guided programming methods remains to be validated in larger, multicenter trials, assessed after stimulation reprogramming and including patients with optimal stimulation levels located at extreme electrode contacts.

4.4 Future directions

Building on these findings, several possibilities for future research can be identified. First, larger multicenter studies are needed to validate the reliability of low- versus high-beta oscillations as target-specific

physiomarkers and to extend analyses to other frequency bands, which may capture non-motor domains of PD^{103–105,108,109,257}. A second priority is the integration of these biomarkers into adaptive DBS: future work should determine whether higher target-specific beta frequencies can effectively guide stimulation in real time for the GPi. Concerning cortical dynamics, it should be assessed whether incorporating cortical connectivity measures could further enhance the performance of closed-loop algorithms^{146,148,150,151}. Coupling neurophysiological recordings with behavioural and cognitive assessments will be crucial to disentangle the clinical relevance of these network dynamics. Finally, combining imaging-based connectomics with physiology-based markers may enable connectivity-guided targeting and contact selection tailored to each patient's oscillatory profile^{57,209}. Such approaches hold promise not only for optimizing therapy in PD but also for advancing DBS strategies in other neurological and psychiatric indications.

5. Conclusions

The work presented in this thesis highlights the dual significance of DBS: it is both a therapeutic intervention and a neuroscientific probe. Mechanistically, DBS differentially modulates low- and high-beta activity in the STN and GPi in PD, while reorganizing large-scale cortical connectivity. Clinically, beta oscillations provide reliable biomarkers that can streamline programming, inform adaptive stimulation, and ultimately support next-generation personalized DBS therapies.

By integrating subcortical physiology, cortical network dynamics, and translational applications, this thesis underscores the value of oscillatory biomarkers as a bridge between basic pathophysiological insights and practical clinical innovation in PD.

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7. Tables

Table 1: Demographic and clinical characteristics of patients included in Study 1. Bottom lines report the median and interquartile range (IQR) for STN- and GPi-DBS PD patients. P values of between-group statistical comparisons are also reported in the bottom line. *Disease duration at DBS surgery, in years (y).

ID	Target	Age	Sex	PD duration (y)*	UPDRS III MOFF pre	UPDRS III MOFF- SON post	UPDRS III MOFF- SOFF post	UPDRS IV pre	UPDRS IV post	LEDD pre-	LEDD post-
1	STN	62	M	12	46	38	59	8	7	1290	595
2	STN	65	M	14	48	41	57	7	11	1507	839
3	STN	51	M	14	36	34	47	8	2	661	505
4	STN	70	F	12	45	35	48	9	3	1260	280
5	STN	50	F	17	44	38	59	15	7	1186	80
6	STN	53	F	4	26	29	48	12	3	1305	400
7	STN	58	M	13	56	45	69	12	2	1055	200
8	STN	65	F	9	41	22	41	15	8	700	325
9	STN	47	M	7	45	34	57	10	6	1502	550
10	STN	61	M	12	45	23	38	11	4	1327	570
11	STN	62	M	13	54	42	59	9	4	2100	850
12	STN	68	F	7	57	42	54	14	5	945	320
13	GPi	57	F	11	76	53	72	10	4	1550	720
14	GPi	62	F	17	54	42	57	13	6	1185	835
15	GPi	60	M	13	41	38	48	10	8	1243	855
16	GPi	64	F	17	56	47	68	16	4	1325	500
17	GPi	45	M	9	74	62	78	15	10	875	425
18	GPi	71	F	9	38	28	60	7	1	690	450
19	GPi	68	M	23	62	50	59	11	7	1113	955
20	GPi	54	M	13	47	37	53	14	4	850	400
21	GPi	43	M	16	29	12	30	3	1	580	220
<i>Median (IQR) STN</i>	-	61 (11)	-	13 (3)	46 (4.5)	38 (8)	57 (11.5)	11 (3.5)	4 (3)	1243 (294)	505 (280)
<i>Median (IQR) GPi</i>	-	61 (8.7)	-	13 (6.5)	55 (19.5)	44.5 (10.7)	59.5 (13)	12 (4.2)	5 (3.2)	1149 (394.7)	610 (396.2)
<i>P values</i>	-	0.69		0.42	0.08	0.09	0.07	0.26	0.47	0.35	0,21

Table 2: Results of frequency-resolved cluster-based permutation test of power spectra, burst durations and rates. Only significant clusters with their relative frequency range (Hz) and corresponding p -values are reported for comparisons within the STN and GPi-DBS groups (unpaired permutation tests between pairs of conditions), as well as on differences between groups (STN vs. GPi, paired permutation tests on differences between conditions). “n.s.” indicates that no significant cluster was detected. The following comparisons are reported: Medication: M-OFF/S-OFF vs. M-ON-SOFF, Add-on medication: M-OFF/S-ON vs. M-ON/S-ON; Stimulation: M-OFF/S-OFF vs. M-OFF/S-ON; Add-on stimulation: M-ON/S-OFF vs. M-ON/S-ON; Medication+Stimulation: M-OFF/S-OFF vs. M-ON/S-ON.

		STN		GPi		STN vs. GPi	
		<i>cluster range</i>	<i>p value</i>	<i>cluster range</i>	<i>p value</i>	<i>cluster range</i>	<i>p value</i>
Medication	power	13-18 Hz	0.002	19 - 23 Hz	0.01	13 - 15 Hz	0.03
	burst duration	13-18 Hz	0.0001	n.s.		14 - 16 Hz	0.02
	burst rate	13 - 18 Hz	<0.0001	n.s.		n.s.	
Add-on Medication	power	13- 14 Hz	0.001	19 - 21 Hz	0.03	13 - 14 Hz	0.02
	burst duration	n.s.		n.s.		n.s.	
	burst rate	n.s.		n.s.		n.s.	
Stimulation	power	14 - 30 Hz	0.0008	19 - 27 Hz	0.0001	15 - 16 Hz	0.03
	burst duration	13 - 17 Hz 20 - 27 Hz	0.002 <0.0001	20 - 22 Hz	0.01	n.s.	
	burst rate	15 - 27 Hz	0.0001	20 .22 Hz 26 - 27 Hz	0.01 0.03	n.s.	
Add-on Stimulation	power	20 - 30 Hz	0.001	18 - 30 Hz	0.02	n.s.	
	burst duration	20 - 23 Hz 27- 29 Hz	0.007 0.01	19 - 20 Hz 23 - 27 Hz	0.03 0.002	n.s.	
	burst rate	20 - 23 Hz 27- 29 Hz	0.005 0.01	19 - 20 Hz 23 - 27 Hz	0.04 0.001	n.s.	
Medication + Stimulation	power	13 - 30 Hz	0.0001	16 - 29 Hz	0.0002	n.s.	
	burst duration	13 - 17 Hz 19 - 29 Hz	0.003 0.0007	14 - 20 Hz 24 - 28 Hz	0.001 0.006	n.s.	
	burst rate	13 - 21 Hz 23 - 27 Hz	0.0004 0.003	16 - 20 Hz 24 - 27 Hz	0.004 0.01	n.s.	

Table 3: Results of cluster-based permutation test on spectral power and bursts computed ± 3 Hz around the individual beta peak frequency. Only significant clusters with their relative frequency range (Hz) and corresponding p values are reported for comparisons within the STN and GPi-DBS groups (unpaired permutation tests between pairs of conditions), as well as on differences between groups (STN vs. GPi, paired permutation tests on differences between conditions). “n.s.” indicates that no significant cluster was detected. The following comparisons are reported: Medication: M-OFF/S-OFF vs. M-ON-SOFF, Add-on medication: M-OFF/S-ON vs. M-ON/S-ON; Stimulation: M-OFF/S-OFF vs. M-OFF/S-ON; Add-on stimulation: M-ON/S-OFF vs. M-ON/S-ON; Medication+Stimulation: M-OFF/S-OFF vs. M-ON/S-ON.

		STN		GPi		STN vs. GPi	
		<i>cluster range</i>	<i>p value</i>	<i>cluster range</i>	<i>p value</i>	<i>cluster range</i>	<i>p value</i>
Medication	power	-3 / 3 Hz	<0.0001	-2 / 2 Hz	0.0002	-1 / 0 Hz	0.03
	burst duration	-1 / 0 Hz	0.01	-1 / 0 Hz	0.01	n.s.	
	burst rate	-1 / 1Hz	0.003	- 1 / 0 Hz	0.02	n.s.	
Add-on Medication	power	0 / 2 Hz	0.001	n.s.		n.s.	
	burst duration	n.s.		n.s.		n.s.	
	burst rate	n.s.		n.s.		n.s.	
Stimulation	power	-2 / 3 Hz	<0.0001	-2 / 2 Hz	0.002	-1 / 1 Hz	0.004
	burst duration	-1 / 1 Hz	0.002	-1 / 2 Hz	0.0009	n.s.	
	burst rate	-1 / 3 Hz	<0.0001	0 / 2 Hz	0.003	n.s.	
Add-on Stimulation	power	-1 / 3 Hz	0.0004	0 / 1 Hz	0.03	n.s.	
	burst duration	n.s.		n.s.		n.s.	
	burst rate	n.s.		n.s.		n.s.	
Medication+ Stimulation	power	-2 / 3 Hz	<0.0001	-2 / 3 Hz	0.0003	-1 / 1 Hz	0.0003
	burst duration	-1 / 2 Hz	<0.0001	-1 / 2 Hz	0.002	n.s.	
	burst rate	-1 / 2 Hz	0.0009	-3 / 2 Hz	0.0004	n.s.	

Table 4: Demographic and clinical characteristics of patients included in Study 2. Bottom lines report the median values (interquartile range) of clinical and demographical data for the STN- and GPi-DBS subgroups, for the whole PD group and for healthy controls (HC). *Disease duration at DBS surgery, in years (y). °Refers to the presence of neurophysiological assessment before surgery (T0).

ID	Target	Age	Sex	PD dur (y)*	UPDRS III T0**	UPDRS III SON T1§	UPDRS III SOFF T1§	UPDRS IV T0	UPDRS IV T1	LEDD T0	LEDD T1	T0 °
1	STN	62	M	12	48	38	59	8	7	1290	595	Yes
2	STN	58	M	7	23	16	25	11	4	500	330	Yes
3	STN	51	M	14	36	28	40	8	2	661	505	Yes
4	STN	68	F	7	57	42	58	14	5	945	320	Yes
5	STN	50	F	17	44	35	52	15	7	1186	80	Yes
6	STN	53	F	6	29	25	38	12	3	1305	400	Yes
7	STN	58	M	13	59	45	69	12	2	1055	200	Yes
8	STN	65	F	9	41	22	42	15	8	700	325	Yes
9	STN	48	M	7	45	34	57	10	6	1502	550	Yes
10	STN	61	M	12	42	23	38	11	4	1327	570	Yes
11	STN	62	M	13	54	42	59	9	4	2100	850	Yes
12	STN	54	M	12	29	16	32	8	3	1520	580	No
13	STN	56	M	13	61	41	58	16	5	1740	740	No
14	STN	65	M	14	48	39	55	10	7	1507	839	No
15	STN	71	F	12	45	35	48	9	3	1260	280	No
16	STN	59	M	14	35	24	40	11	8	1200	420	No
17	GPi	75	M	16	46	31	48	6	2	1090	720	Yes
18	GPi	56	M	13	52	32	47	10	6	1950	750	Yes
19	GPi	64	F	17	56	44	59	16	4	1325	500	Yes
20	GPi	62	F	17	54	42	57	13	6	1185	835	Yes
21	GPi	43	M	16	29	19	30	3	1	580	220	Yes
22	GPi	54	M	13	47	32	53	14	4	850	400	Yes
23	GPi	68	M	23	62	50	59	14	7	1113	955	Yes
24	GPi	60	M	13	41	35	43	10	8	1243	855	No
25	GPi	71	F	9	38	22	40	7	1	690	450	No
26	GPi	70	M	9	30	21	32	4	5	1560	580	No
27	GPi	66	M	15	37	26	45	8	3	1000	300	No
28	GPi	57	F	11	76	53	72	10	4	1550	720	No
STN	-	58.5 (9)	4 F	12 (4.75)	44.5 (13.7)	34.5 (15.7)	50 (18.5)	11 (3.5)	4.5 (4)	1275 (475.5)	462.5 (280)	11
GPi	-	63 (11.7)	4 F	14 (3.7)	46.5 (16.7)	32 (17.5)	47.5 (15.2)	10 (6.5)	4 (3.2)	1149 (418.7)	650 (333)	8
PD	-	60.5 (9.7)	8 F	13 (3.7)	45 (17.2)	33 (17.5)	48 (18)	10 (5.25)	4 (3.25)	1221.5 (517)	527 (96.2)	19
HC		62 (8.5)	7 F	-	-	-	-	-	-	-	-	-

Table 5: Demographic and clinical characteristics of patients included in Study 3. *Disease duration at DBS surgery, in years. **Performed before surgery, in the OFF-medication condition; ***Performed one year after surgery, in the OFF-medication, ON-stimulation condition. Abbreviations: cFU: clinical follow-up; LEDD: Levodopa Equivalent Daily Dose; IP: initial programming; SD: standard deviation.

ID	Target	Sex	Age	PD duration (y)*	Age at onset (y)	UPDRS III pre-DBS*	UPDRS III post-DBS**	n° visits	Time after implant (at cFU, mo)
1	STN	F	50	17	32	54	18	6	9
2	GPI	F	63	17	45	51	42	7	13
3	STN	F	58	6	51	42	33	5	8
4	STN	M	54	9	43	29	17	8	16
5	STN	M	62	12	50	46	27	5	6
6	GPI	F	70	9	60	38	26	6	8
7	STN	M	52	14	37	36	23	7	11
8	GPI	M	45	9	35	84	62	8	12
9	GPI	F	52	19	12	55	40	7	12
10	STN	M	56	11	44	61	32	7	13
11	GPI	F	64	17	47	56	47	4	8
12	STN	F	66	19	46	74	45	6	9
13	STN	M	58	13	45	56	45	4	7
14	STN	M	60	12	48	45	31	5	7
15	STN	F	53	4	48	29	26	5	6
16	STN	F	65	9	56	41	22	5	6
17	GPI	M	69	23	45	62	43	6	6
18	GPI	M	54	13	41	47	37	5	8
19	STN	M	47	7	40	40	26	4	6
Mean ± SD			55.8 ± 7.5	12.6 ± 5	43.4 ± 10.1	49.8 ± 14.2	33.8 ± 11.6	5.7 ± 1.2	9 ± 2.9

Table 6: Similarity between LFP-based and imaging-based methods and clinical programming and difference from random selection. Left columns: mean similarity values of each selection method with clinical programming (CP) at initial programming (IP) and differences between the bootstrap similarity and the random selection (RS). Right columns: mean similarity values of each selection method performed at IP with CP at the last clinical follow-up (cFU), and differences between the bootstrap similarity and random selection (RS). Significant values ($p < 0.05$) are displayed in bold.

	<i>Selection method vs. CP at IP</i>		<i>Selection method at IP vs. CP at cFU</i>	
	Mean similarity	Bootstrap similarity vs. RS (p value)	Mean similarity	Bootstrap similarity vs. RS (p value)
<i>Broad-Bipolar</i>	0.75	0.2	0.75	0.34
<i>Narrow-Bipolar</i>	0.9	<0.001	0.93	<0.001
<i>Segment-Bipolar</i>	0.86	0.001	0.87	0.02
<i>Imaging-based</i>	0.9	0.006	0.83	0.43
<i>RS</i>	0.7	-	0.82	-

8. Figures

Figure 1: Schematic representation of the PD course, from diagnosis to the advanced stage. In the early stage of the disease, patients present with cardinal motor symptoms (bradykinesia, rigidity and tremor), which are initially well controlled with dopaminergic medication such as levodopa, providing stable and sustained benefit. During the progression from intermediate to advanced stage, motor complications develop, including OFF-ON fluctuations and involuntary movements (dyskinesia, Dys). In the advanced stage, motor symptoms and complications become increasingly disabling, and pharmacological treatment alone is insufficient. At this stage, DBS provides significant improvement in both motor symptoms and treatment-related complications.

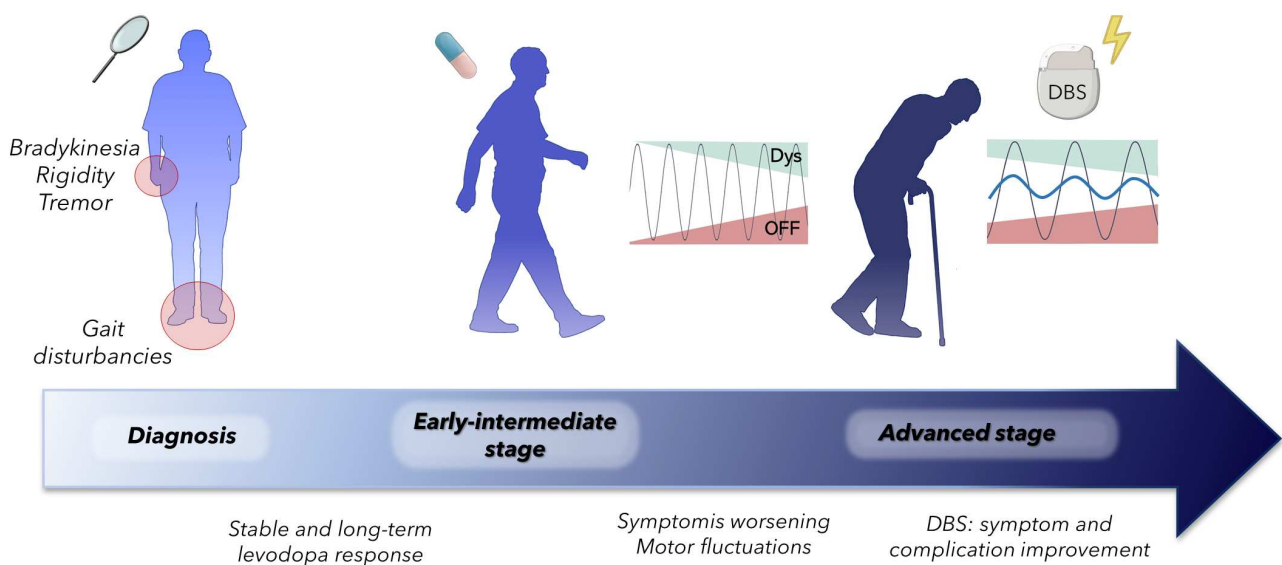


Figure 2: Overview of neurophysiological recordings and analyses used in the present thesis work in Parkinson's disease (PD) patients treated with DBS. Top: Local field potentials (LFPs) recorded from DBS electrodes in the target nuclei (Subthalamic Nucleus, STN, or Globus Pallidus Internus, GPi). LFPs are analyzed in the frequency domain with spectral decomposition and in the time-domain to characterize beta-band (13-30 Hz) bursting activity. Bottom: High-density EEG (HD-EEG) acquired in DBS-treated PD patients. Cortical signals are used to estimate cortico-cortical functional connectivity in different frequency bands, obtaining frequency-resolved connectivity matrices and network-level analyses across cortical regions.

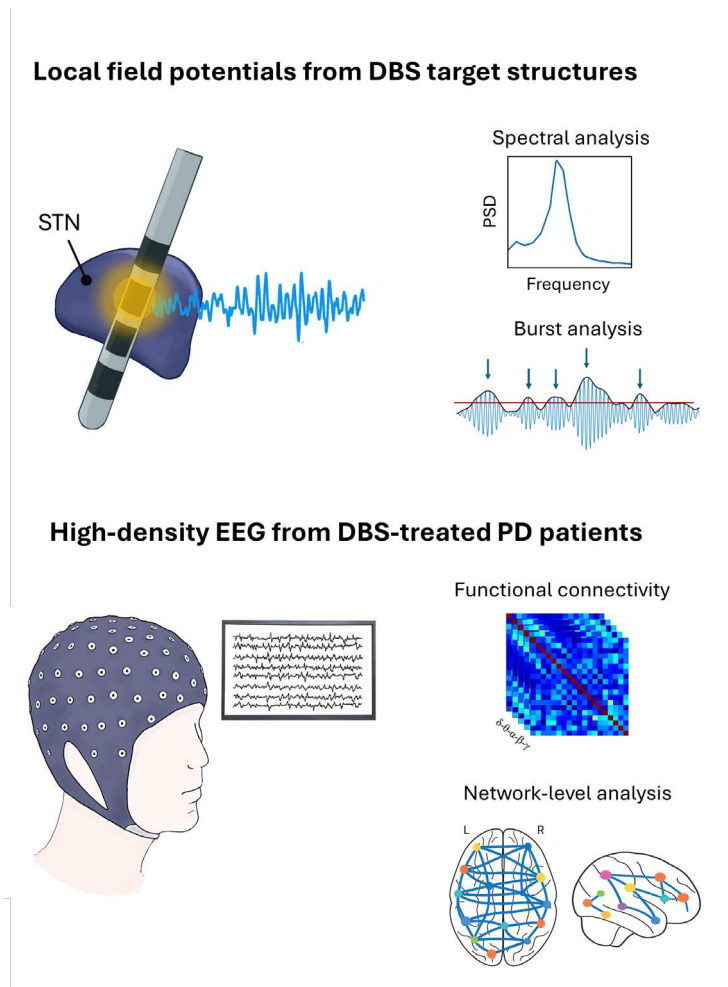


Figure 3: Data acquisition protocol for Study 1. LFPs were recorded from DBS electrodes implanted in STN or GPi in four different conditions with respect to medication (L-Dopa) and stimulation: M-OFF/S-OFF (red exemplary raw signal and filtered around the individual beta peak, showed with envelope), M-OFF/S-ON (purple signals), M-ON/S-OFF (blue signals) and M-ON/S-ON (green signals).

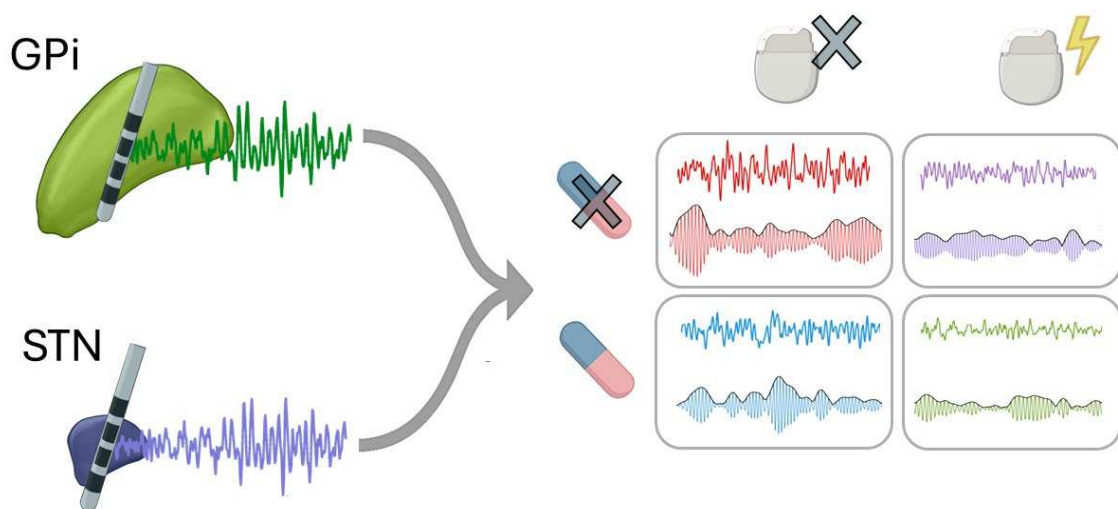


Figure 4: Baseline differences between DBS targets. **A)** Left panels: mean power spectra (top) and frequency-resolved mean burst durations (bottom) at baseline (M-OFF/S-OFF) for STN (blue) and GPi (green). Middle panels: unpaired cluster-based permutation tests revealed no significant differences. Frequency-wise Spearman's correlations with bradykinesia/rigidity sub-scores are shown for the STN (blue histograms) and GPi (green histograms), with significant correlations ($p < 0.05$) marked by red asterisks. Right panels: averaged power spectra and burst durations within ± 3 Hz around individual beta peak frequencies, showing significantly higher peak power and longer burst durations in STN (blue) compared to GPi (green, cluster-based permutation test). Shaded areas represent standard error of the mean (SEM), and yellow shaded areas mark significant differences ($p < 0.05$). **B)** Frequency distribution of individual beta peaks in the M-OFF/S-OFF condition in the STN (left blue histogram) and GPi (right green histogram).

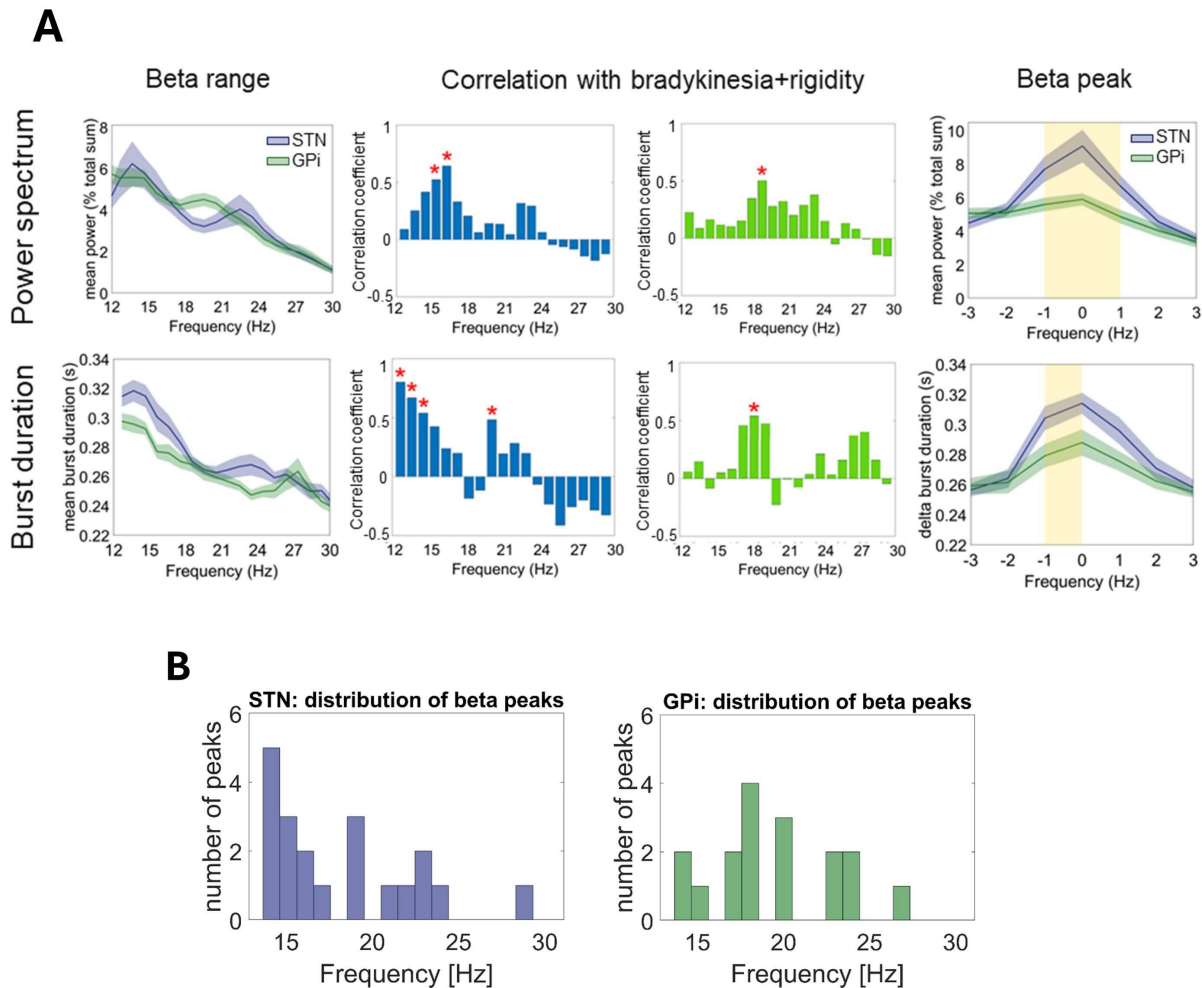


Figure 5: Frequency-resolved beta power modulation and clinical-neurophysiological correlations.

Averaged power spectra across medication and stimulation conditions are shown for the STN (top row) and GPi (middle row), together with results of the paired cluster permutation tests. Below is the distribution of Spearman's correlation coefficients between power at each beta frequency bin and bradykinesia and rigidity sub-scores for the STN (blue histograms) and GPi (green histograms). The bottom row shows results of unpaired cluster-based permutations comparing beta power changes (delta) between STN (blue line) and GPi (green line). Shaded areas indicate standard error of the mean (SEM). Vertical yellow shaded areas mark significant differences ($p < 0.05$). Conditions: MED: M-OFF/S-OFF vs. M-ON/S-OFF; STIM: M-OFF/S-OFF vs. M-OFF/S-ON; MED (STIM ON): M-OFF/S-ON vs. M-ON/S-ON; MED + STIM: M-OFF/S-OFF vs. M-ON/S-ON.

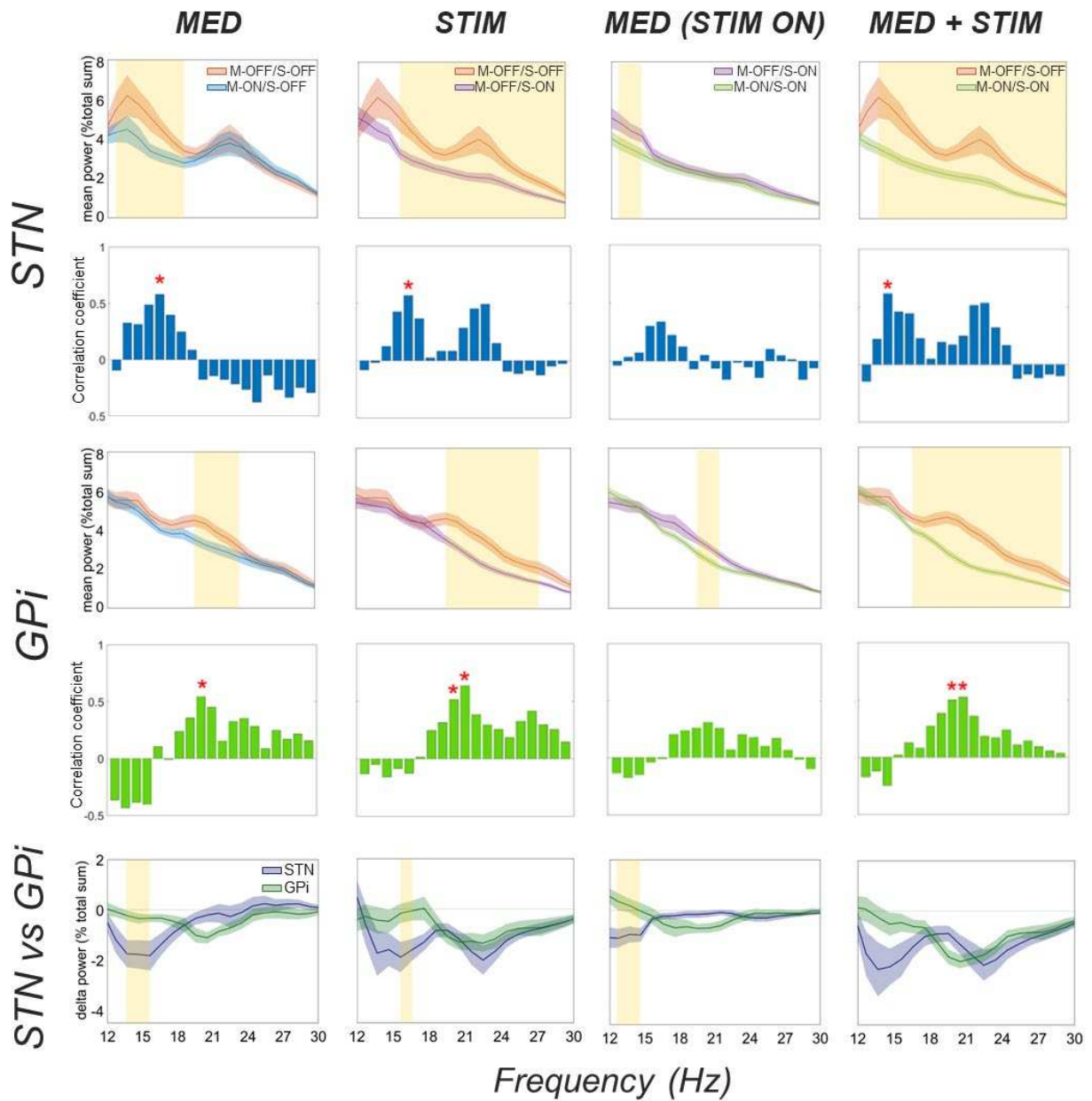


Figure 6: Frequency-resolved modulation of beta burst durations and clinical-neurophysiological correlations. Top and middle rows: averaged frequency-wise beta burst durations (s) across medication and stimulation in the STN (top) and GPi (middle), with results of cluster-permutation tests. Below each plot: distributions of Spearman's correlation coefficients between burst durations at each beta frequency bin and bradykinesia-rigidity sub-scores for STN (blue histograms) and GPi (green histograms). Bottom row: unpaired cluster-based permutation results comparing changes (delta) between STN (blue line) and GPi (green line). Shaded areas indicate standard error of the mean (SEM). Vertical yellow shaded areas mark significant differences ($p < 0.05$). Conditions: MED: M-OFF/S-OFF vs. M-ON/S-OFF; STIM: M-OFF/S-OFF vs. M-ON/S-OFF; MED (STIM ON): M-OFF/S-ON vs. M-ON/S-ON; MED+STIM: M-OFF/S-OFF vs. M-ON/S-ON.

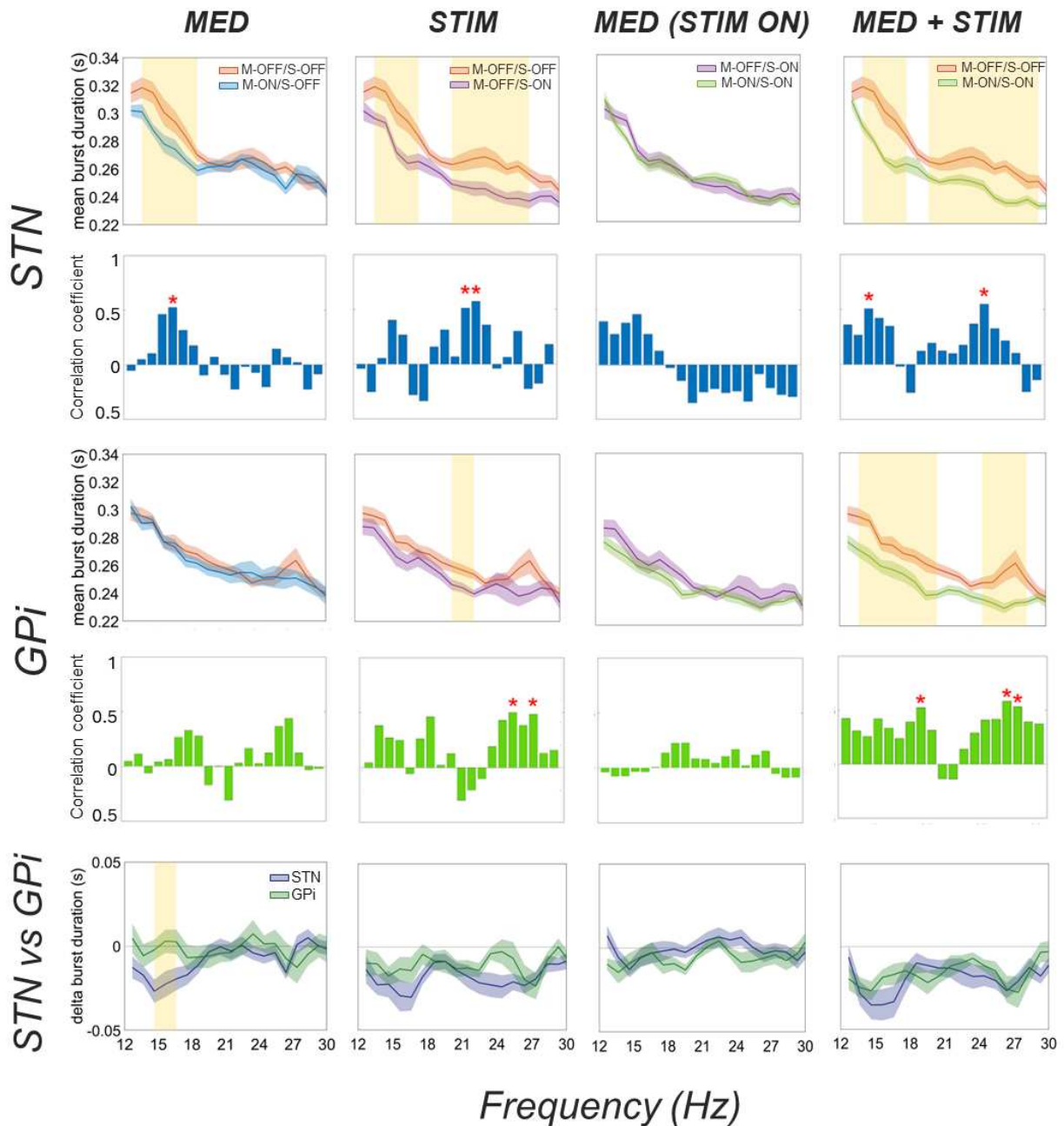


Figure 7: Frequency-resolved modulation of beta burst rates. Top and middle rows: averaged frequency-wise beta burst rates (bursts/s) across medication and stimulation in the STN (top) and GPi (middle), with results of cluster-permutation tests. Bottom row: unpaired cluster-based permutations results comparing changes (delta) between STN (blue line) and GPi (green line). Shaded areas indicate standard error of the mean (SEM). Vertical yellow shaded areas mark significant differences ($p < 0.05$). Conditions: MED: M-OFF/S-OFF vs. M-ON/S-OFF; STIM: M-OFF/S-OFF vs. MO-OFF/S-ON; MED (STIM ON): M-OFF/S-ON vs. M-ON/S-ON; MED+STIM: M-OFF/S-OFF vs. M-ON/S-ON.

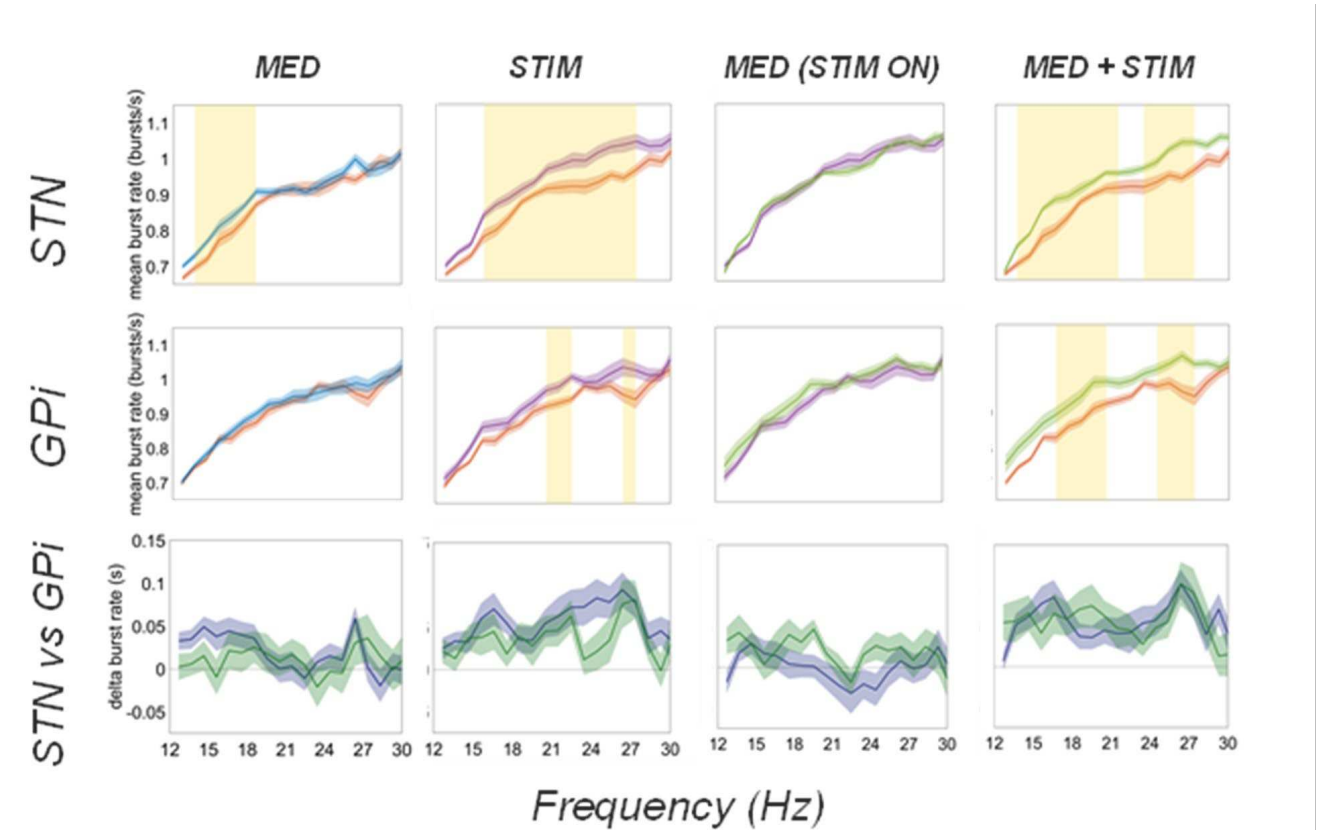


Figure 8: Modulation of beta peak amplitude in STN and GPi, and differences between targets. A) Cluster-based permutation test results on averaged power spectra across medication and stimulation conditions within ± 3 Hz around individual beta peaks for the STN (upper plots) and GPi (middle plots). Lower plots depict the differences (delta) between STN (blue) and GPi (green). Shaded areas represent standard error of the mean (SEM), and vertical yellow areas mark significant differences ($p < 0.05$). **B)** Spearman's correlation between peak power changes with each intervention and baseline peak amplitude (M-OFF/S-OFF) in the STN and GPi. Correlations were significant only for the STN. Conditions: MED: M-OFF/S-OFF vs. M-ON/S-OFF; STIM: M-OFF/S-OFF vs. M-OFF/S-ON; MED+STIM: M-OFF/S-OFF vs. M-ON/S-ON.

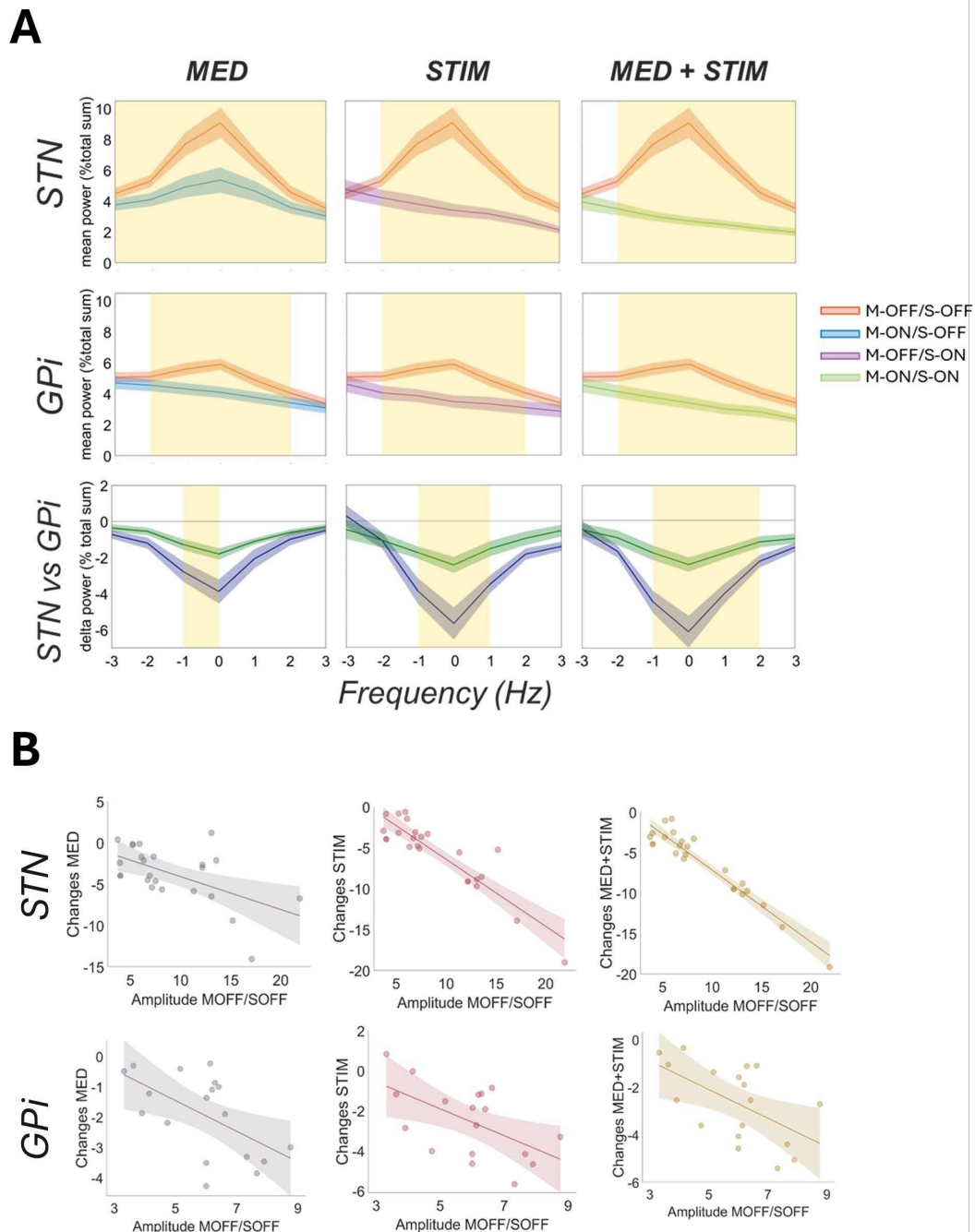


Figure 9: Modulation of beta burst durations around beta peak in STN and GPi, and differences between targets. Cluster-based permutations result on averaged beta burst durations (s) across medication and stimulation conditions within ± 3 Hz around individual beta peaks for the STN (upper plots) and GPi (middle plots). Lower plots depict differences (delta) between STN (blue) and GPi (green). Shaded areas represent the standard error of the mean (SEM). Significant differences ($p < 0.05$) are marked with yellow areas. MED: M-OFF/S-OFF vs. M-ON/S-OFF; STIM: M-OFF/S-OFF vs. M-OFF/S-ON; MED+STIM: M-OFF/S-OFF vs. M-ON/S-ON.

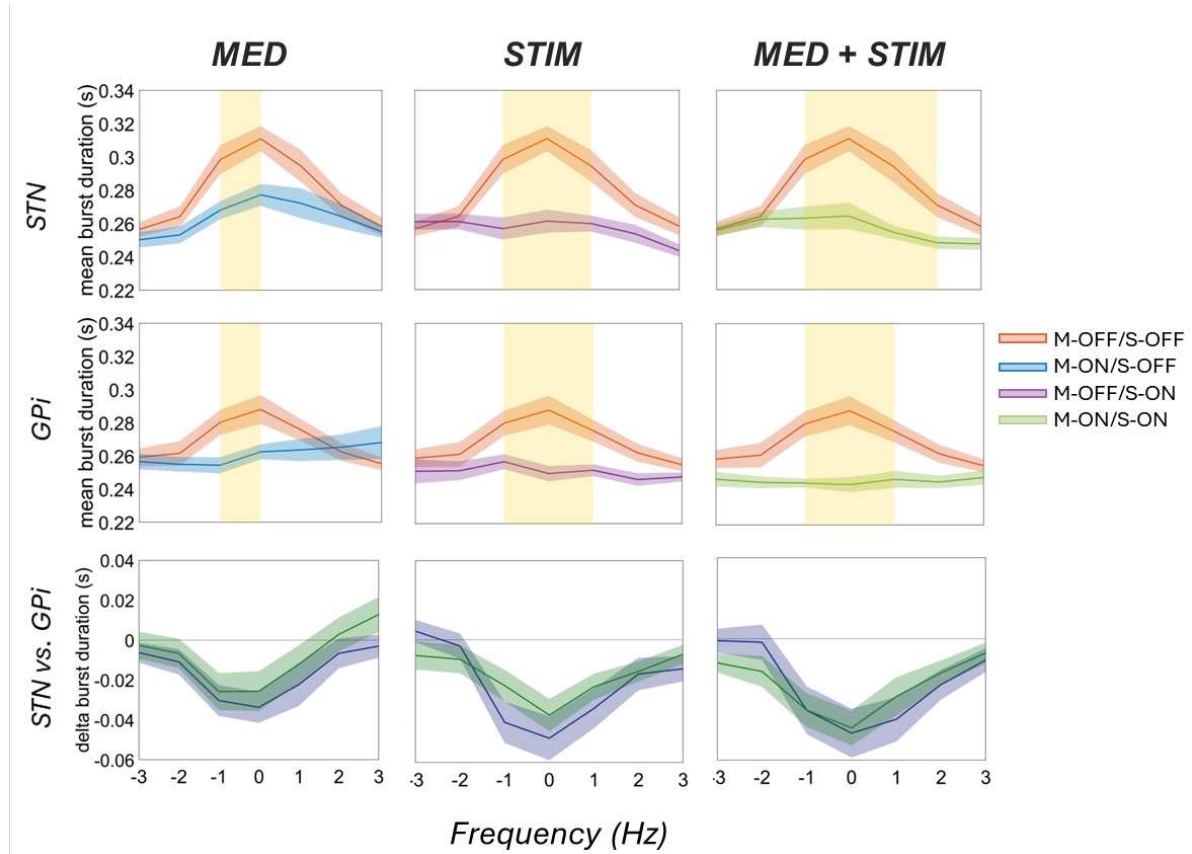


Figure 10: Modulation of beta burst rates around beta peak in STN and GPi, and differences between targets. Cluster-based permutations result on averaged beta burst rates (bursts/s) within ± 3 Hz around individual beta peaks for the STN (top) and GPi (middle). Bottom plots show differences (delta) between STN (blue) and GPi (green). Shaded areas represent the standard error of the mean (SEM). Significant differences ($p < 0.05$) are marked with yellow areas. MED: M-OFF/S-OFF vs. M-ON/S-OFF; STIM: M-OFF/S-OFF vs. M-OFF/S-ON; MED+STIM: M-OFF/S-OFF vs. M-ON/S-ON. MED (STIM ON): M-OFF/S-ON vs. M-ON/S-ON; STIM (MED ON): M-ON/S-OFF vs. M-ON/S-ON.

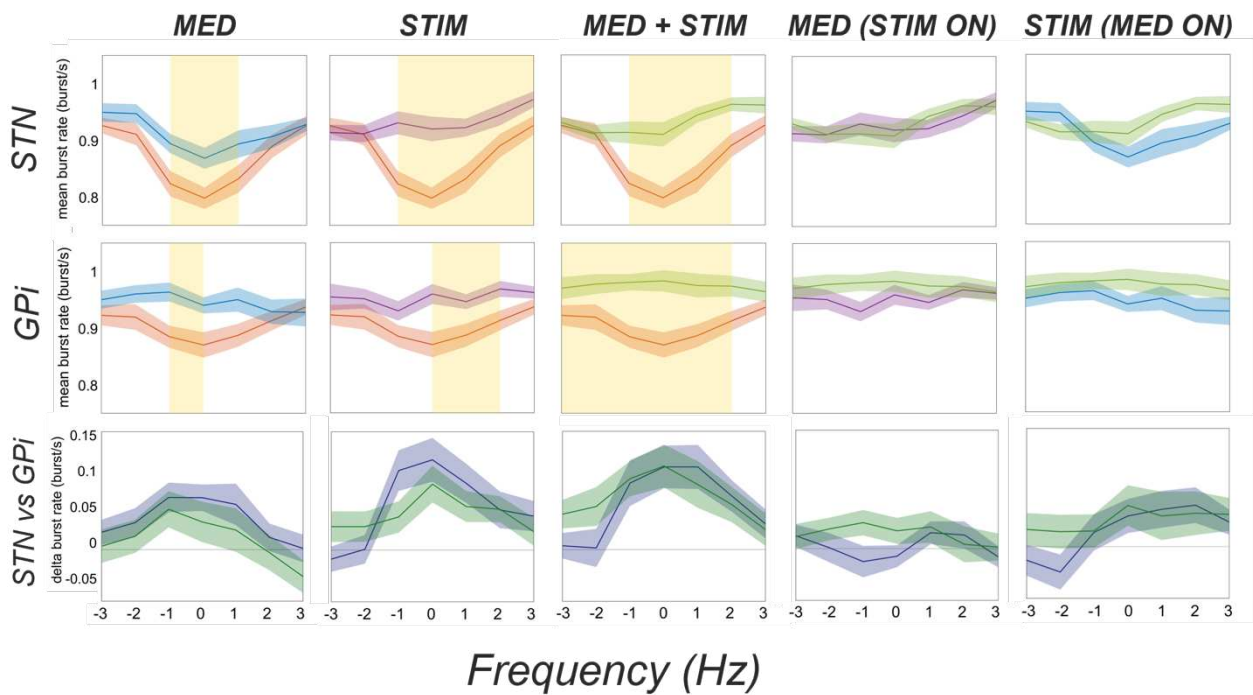


Figure 11: Experimental protocol for PD patients. At baseline (T0, 2–6 weeks before surgery), all patients underwent presurgical screening, including brain MRI, clinical assessment and EEG recordings after overnight L-Dopa withdrawal (MED OFF). After surgery (T1, 6–12 months after implantation), EEG recordings were repeated in MED OFF condition, with stimulation turned ON (DBS-ON) and after switching it off (DBS OFF). In each condition, motor symptoms were clinically assessed with the MDS-UPDRS III.

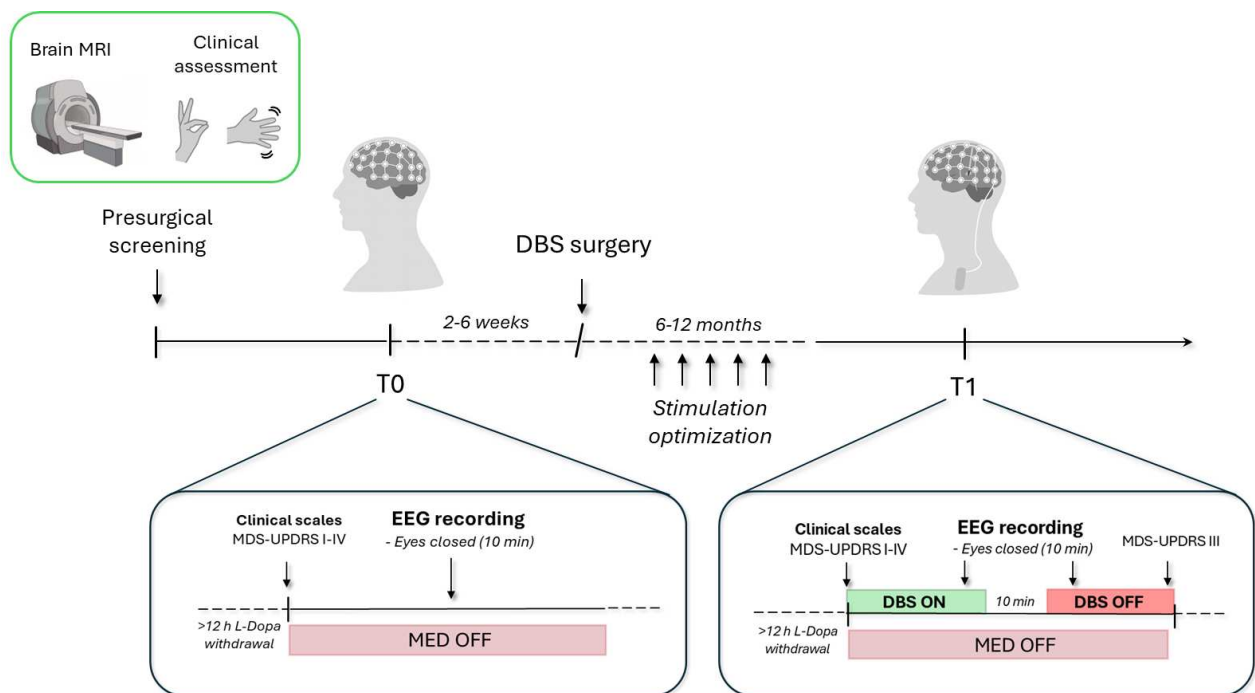


Figure 12: Pipeline for data preprocessing and connectivity analysis. EEG signals underwent standard preprocessing. Processed EEG data were co-registered with individual brain MRIs using anatomical landmarks, and source reconstruction was performed using the boundary element method and weighted minimum-norm estimation. Brain regions were then defined according to the Desikan-Killiany atlas, allowing for MRI parcellation. Functional connectivity (FC) was estimated with the weighted phase-lag index (wPLI), yielding connectivity matrices. Statistical group comparisons of brain networks were then performed using Network-Based Statistics (NBS).

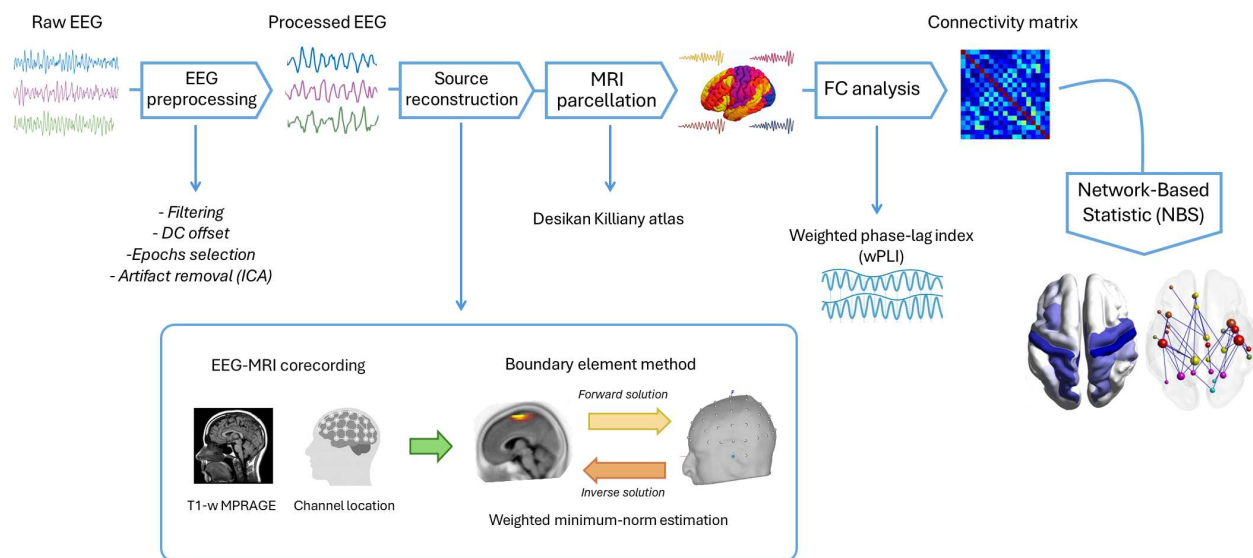


Figure 13: Clinical outcomes before (T0) and after (T1) surgery in STN- and GPi PD patients. No between-target differences were observed in all comparisons. Top left: MDS-UPDRS III motor scores significantly decreased from T0 to T1 with DBS turned on (S-ON) condition. Top right: L-Dopa equivalent daily dose (LEDD) was significantly reduced after surgery (T1) compared to T0. Bottom left: MDS-UPDRS IV scores improved at T1 relative to T0. Bottom right: at T1, MDS-UPDRS III scores were significantly lower in the S-ON condition compared to the stimulation OFF (S-OFF) condition. Gray lines indicate individual patient trajectories. * $p < 0.05$.

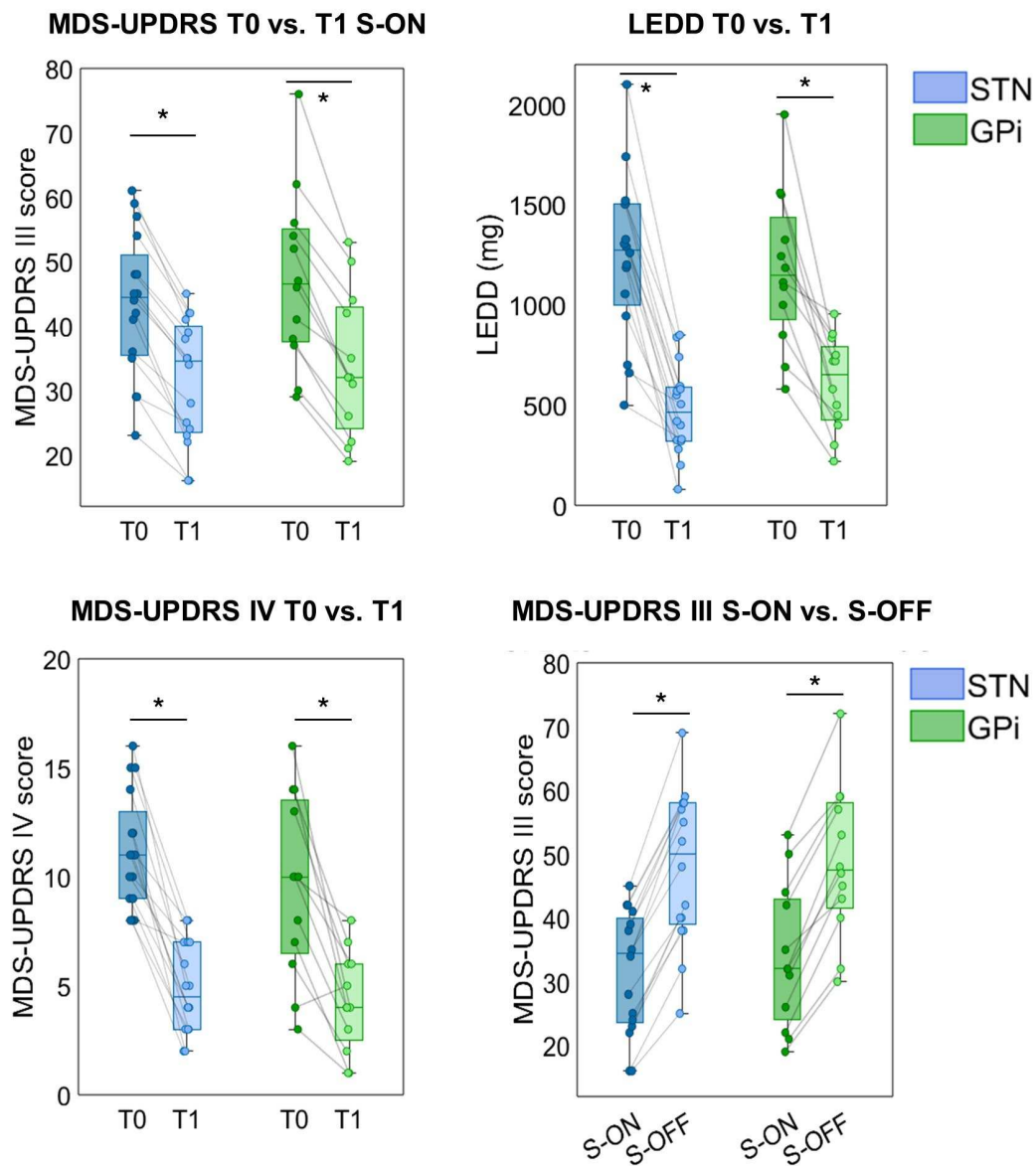


Figure 14: Differential cortical networks between healthy controls (HC) and Parkinson's disease (PD) patients before DBS surgery. Box plots represent the mean network connectivity (mNC) values in HC (grey) and PD patients before DBS surgery (T0, blue) groups in the network identified with the network-based statistic (NBS) in the beta (13-30 Hz, A), and alpha (8-12 Hz, B) frequency bands. In the beta network, mNC was significantly higher in PD with respect to HC, while in alpha network mNC values were significantly higher in the HC group. *** indicates $p < 0.0001$. Graph and map representations of regions of interest (ROI) degrees on the model brain surface of the differential networks between HC and PD patients in the beta (A), and alpha (B) bands. Spheres' colours represent different brain lobes: orange= fronto-insular, red= sensorimotor, yellow= limbic, green= temporal, magenta= parietal, light blue= occipital. Sphere diameters are directly proportional to ROI degrees.

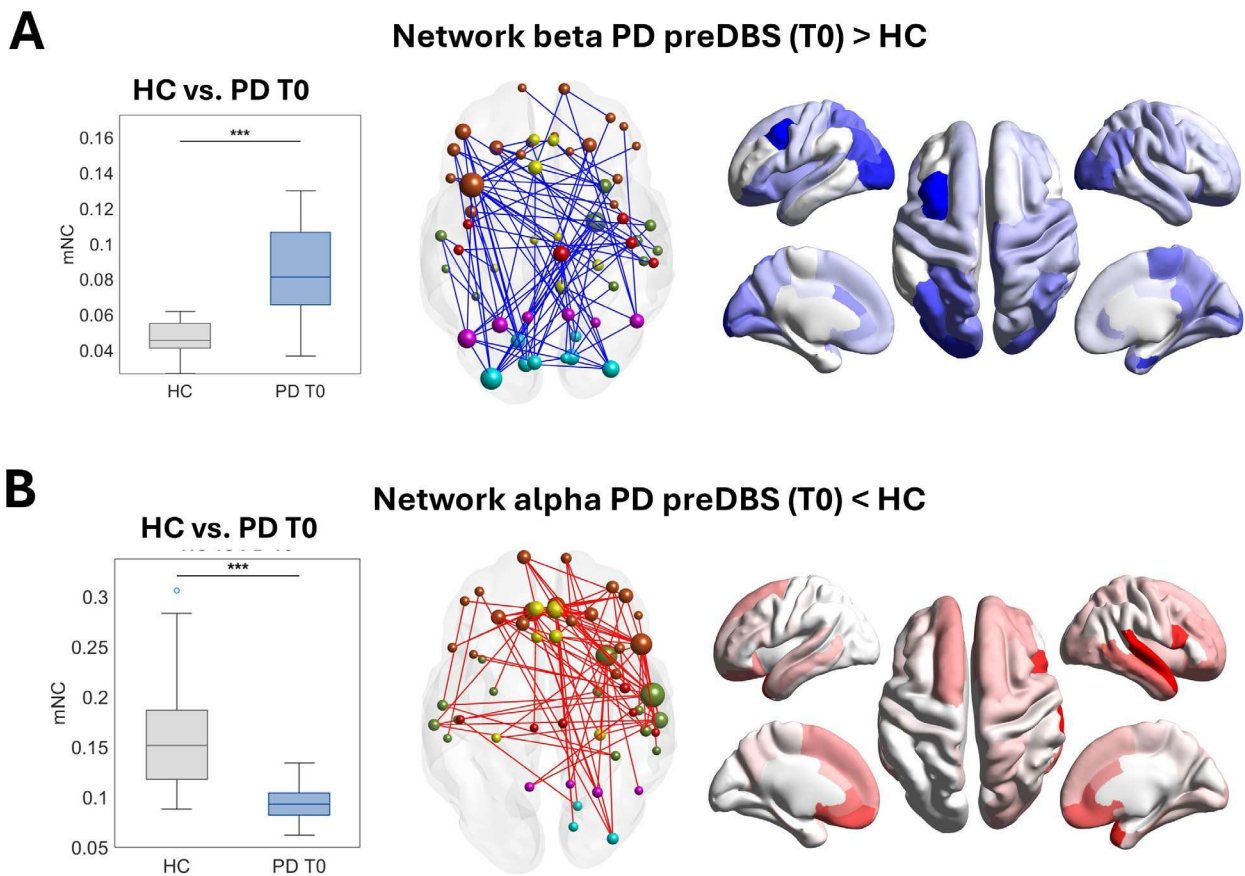
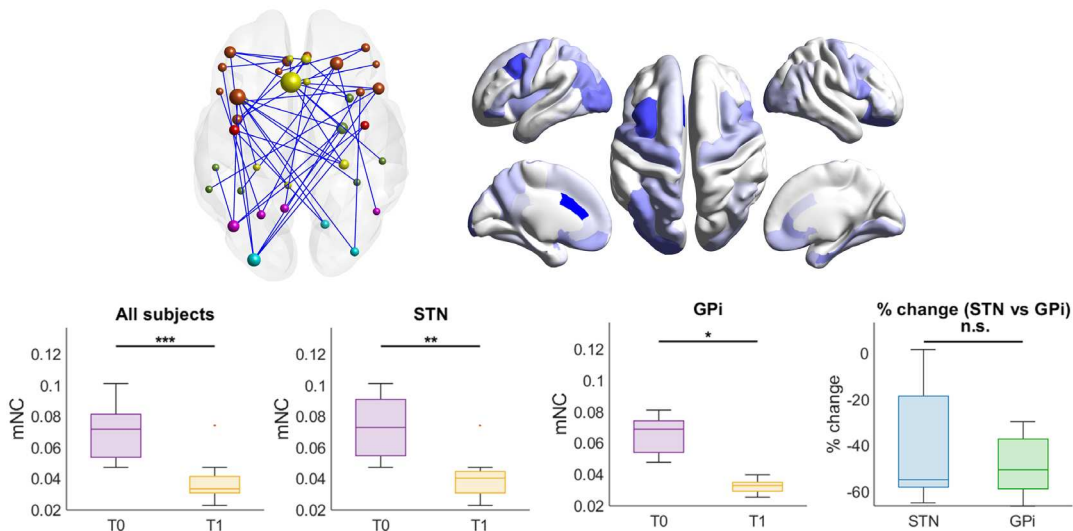


Figure 15: Differential cortical networks in Parkinson's disease (PD) patients between T0 and T1 in the stimulation OFF condition. Graph (top left) and map (top right) representations of regions of interest (ROI) degrees on model brain surface of the differential networks in PD patients before (T0) and after (T1) surgery with the stimulation turned OFF (S-OFF) in the beta (13-30 Hz, A), and theta (4-7 Hz, B) frequency bands. As for Figure 14, spheres' colours represent different brain lobes, and diameters are directly proportional to ROI degrees. Box plots represent the mean network connectivity (mNC) values at T0 (purple) and T1 (yellow) in networks identified in the beta (A), and theta (B) bands. A significant mNC reduction was observed at T1 compared to T0 when considering all PD subjects, as well as STN and GPi sub-groups separately. No significant differences were observed when comparing mNC between STN (blue boxplot) and GPi (green boxplot) subgroups. * $p < 0.01$, ** $p < 0.001$, and *** $p < 0.0001$.

A

Network beta PD preDBS (T0) > postDBS (T1) S-OFF



B

Network theta PD preDBS (T0) < postDBS (T1) S-OFF

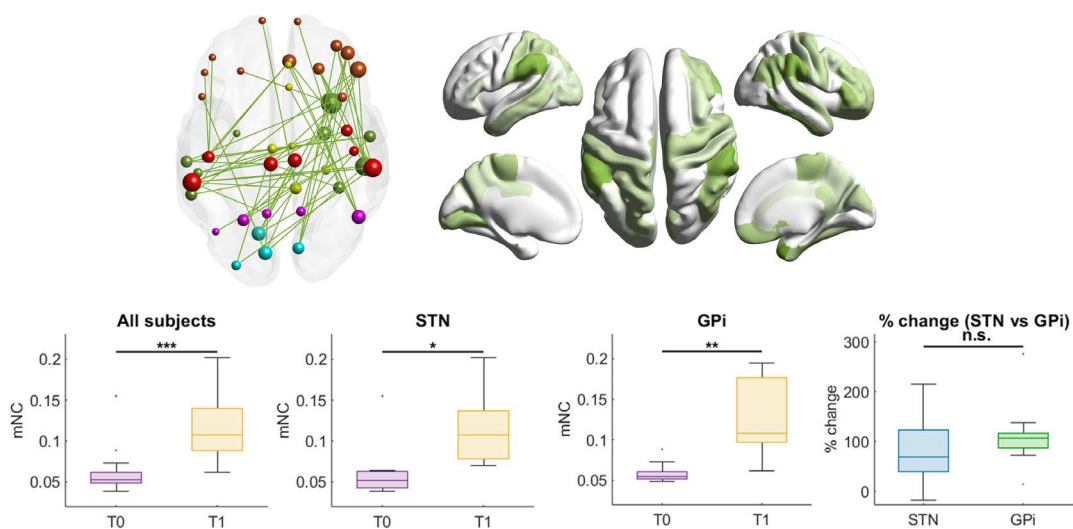


Figure 16: Differential cortical networks in Parkinson's disease (PD) patients at T1 between DBS stimulation switched ON and OFF. Graph (top left) and map (top right) representation of regions of interest (ROI) degrees on the model brain surface of the differential networks in the beta band in PD patients after DBS surgery (T1) with the stimulation turned OFF (S-OFF) and ON. As for Figures 14 and 15, sphere colours represent different brain lobes, and diameters are directly proportional to ROI degrees. Box plots represent the mean network connectivity (mNC) values in the S-OFF (red) and S-ON (orange) in the identified network in the beta band. A significant mNC reduction after turning ON the stimulation when considering all PD subjects, as well as STN and GPi sub-groups separately. No significant differences were observed when comparing mNC between STN (blue boxplot) and GPi (green boxplot) subgroups. * $p < 0.01$, ** $p < 0.001$, and *** $p < 0.0001$.

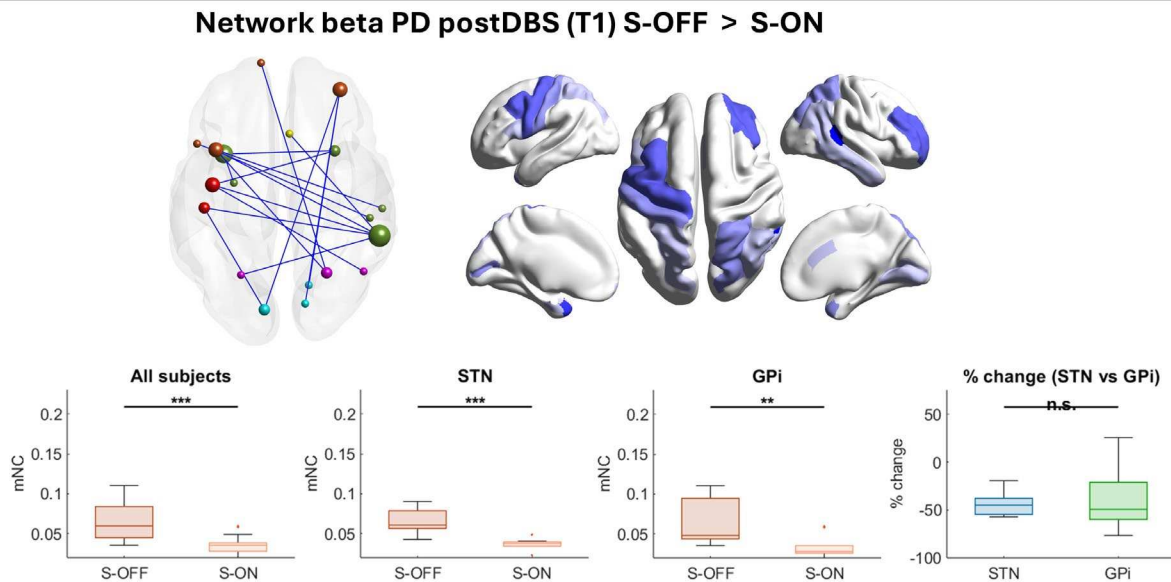


Figure 17: Experimental protocol for Study 3. Before surgery, all patients underwent a brain MRI and clinical motor evaluation using MDS-UPDRS-III. Bipolar LFPs were recorded 3-4 weeks after surgery at initial programming (IP) and after ≥ 6 months of clinical follow-up (cFU). The beta peak amplitude, computed on LFPs recorded from contact pairs, was compared according to the three different methods: Broad-Bipolar (1-3 vs. 0-2), Narrow-Bipolar (2-3 vs. 0-1), and Segment-Bipolar (1A-1B, 1B-1C, 1A-1C, 2A-2B, 2B-2C and 2A-2C). Power spectra from a PD patient are shown in the bottom: in this case, level 2 was selected in all methods.

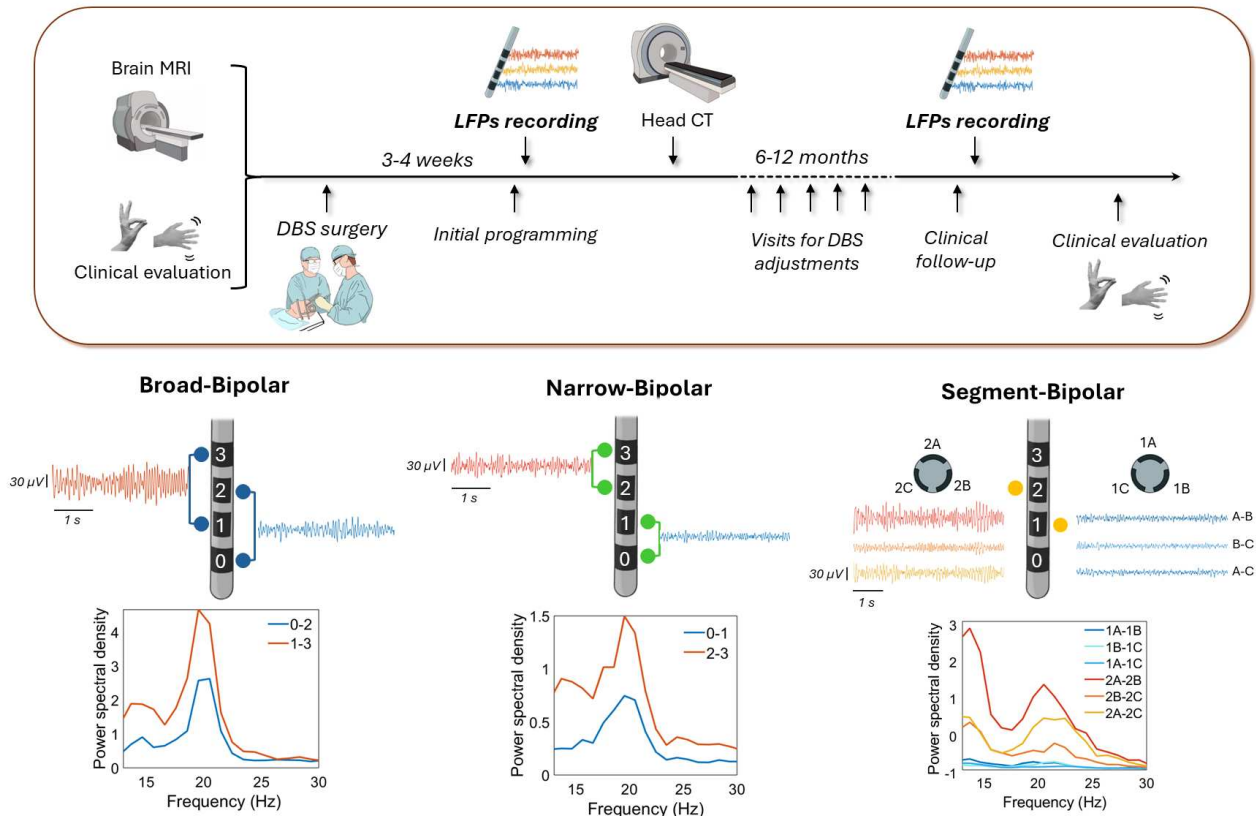


Figure 18: Correlation and agreement between beta-based contact selection methods and clinical programming. Phi correlation coefficient (panel A) and Quadratic Weighted Kappa (QWK, panel B) between LFP-based methods and clinical selection at initial programming (IP), last clinical follow-up (cFU). The figure also includes the same measures computed between contacts selected using LFP-based methods at IP and those selected clinically at cFU (IP/cFU). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

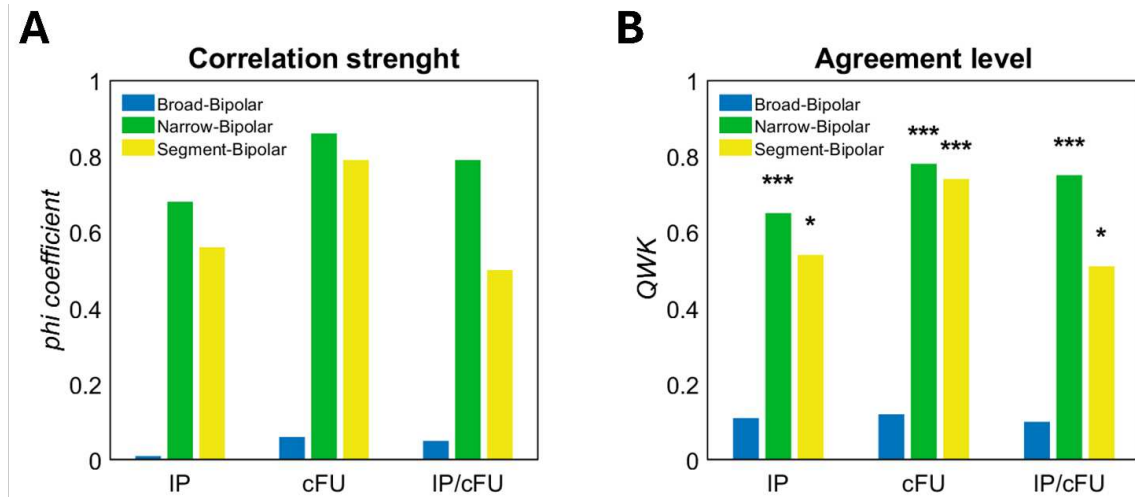


Figure 19: Similarity of LFP-based methods with clinical programming. A) Bootstrap distributions illustrating the mean similarity with clinical programming of each method and random selection (RS) at initial monopolar review. B) Bootstrap distribution of mean similarity of each method at initial programming and clinical selection at the last follow-up. Dashed lines represent the mean similarity of each method and random distribution.

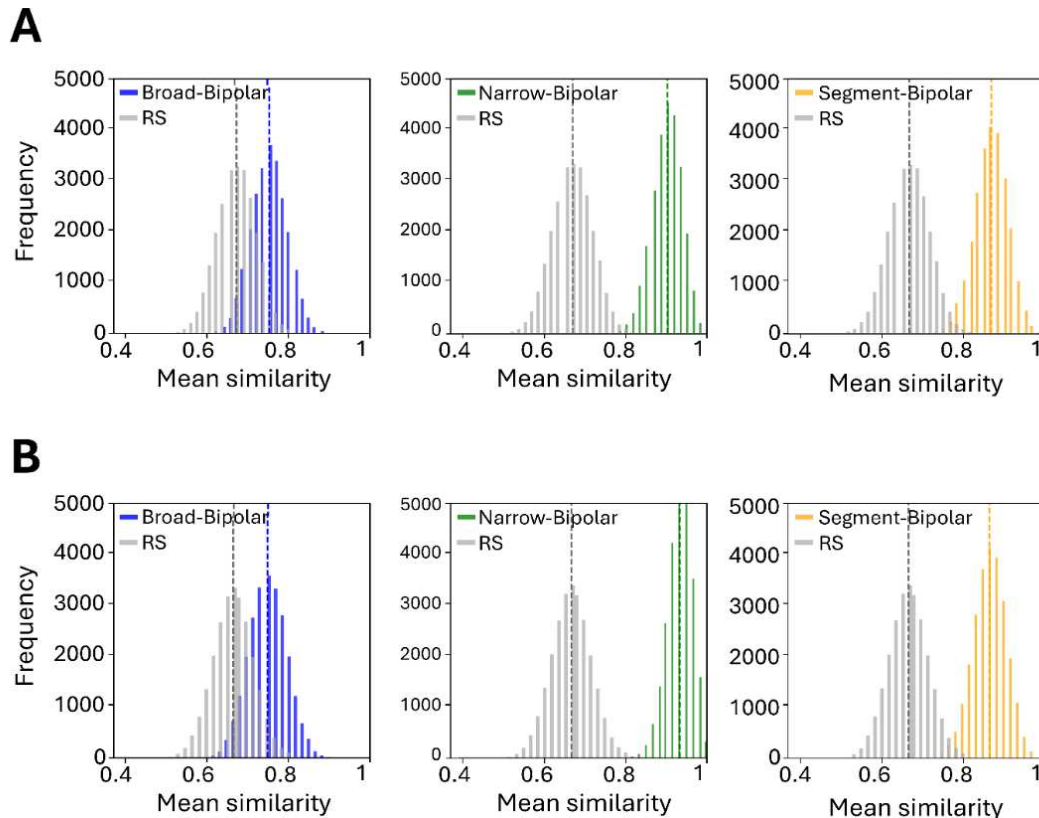


Figure 20: Longitudinal changes in beta activity. A) Donut charts represent the stability of contact selection between initial programming (IP) and the last clinical follow-up (cFU) for clinical programming and each LFP-based method. Colored segments indicate the number and percentage of cases (36 in total), in which the same contact was retained at cFU. B) Violin plots show changes in beta activity (amplitude and frequency of the beta peak, and beta power) from IP to cFU. Gray markers and lines indicate a decrease at cFU compared to IP, while green indicates an increase.

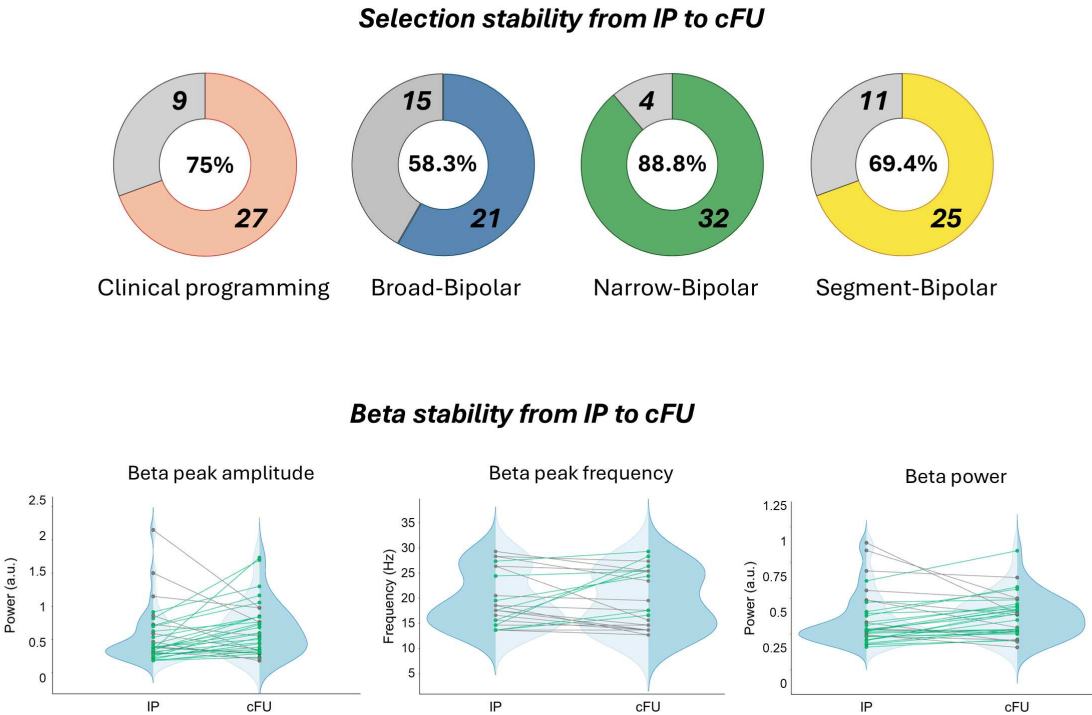


Figure 21: Flow-chart for application of LFP-based level selection using Narrow-Bipolar method, comparing beta peak amplitude in bipolar recordings from 0-1 and 2-3 contact pairs

