

UNIVERSIDAD POLITÉCNICA DE MADRID
Escuela Técnica Superior de Ingenieros de Telecomunicación



Oscillatory and non-oscillatory beta activity in Parkinson's disease

DOCTORAL THESIS

Submitted for the degree of Doctor by:

Jesús Pardo Valencia

Master's degree in Biomedical Engineering

Madrid, 2025



UNIVERSIDAD POLITÉCNICA DE MADRID
Escuela Técnica Superior de Ingenieros de
Telecomunicación

Doctoral Degree in Biomedical Engineering

Oscillatory and non-oscillatory beta activity in Parkinson's disease

DOCTORAL THESIS

Submitted for the degree of Doctor by:

Jesús Pardo Valencia

Master's degree in Biomedical Engineering

Under the supervision of:

Dr Guglielmo Foffani

Madrid, 2025

Title: Oscillatory and non-oscillatory beta activity in Parkinson's disease

Author: Jesús Pardo Valencia

Doctoral Programme: Biomedical Engineering

Thesis Supervision:

Dr Guglielmo Foffani, Principal Investigator and Scientific Coordinator at Centro Integral de Neurociencias Abarca-Campal (HM CINAC).

External Reviewers:

Thesis Defense Committee:

Thesis Defense Date:

This thesis was supported by "Fundación La Caixa" (grant LCF/PR/HR20/52400012) with co-funding by the European Regional Development Fund (ERDF) of the European Union (grant PID2021-128623OB-100) and by Comunidad de Madrid (fellowship PEJ-2018-AI/BMD-11787).

A mi abuelo, Ofelio.

Agradecimientos

Esta tesis es el fruto de años de trabajo, durante los cuales muchas personas han contribuido, de una u otra manera, a su culminación. Me gustaría agradecer en estas líneas el tremendo impacto que estas personas han tenido en la tesis y en mí mismo.

Por supuesto, muchas gracias al Dr. Guglielmo Foffani, director de esta tesis, de cuya imaginación surgió este trabajo y sin el cual nada de esto existiría. Me siento muy agradecido por la dedicación y apoyo que ha brindado a este trabajo, por el respeto a mis sugerencias e ideas y por la dirección y el rigor que ha facilitado a las mismas. Has sido y sigues siendo para mí un excelente maestro en múltiples ámbitos. Al final, conseguimos terminar una *bellissima* tesis.

Muchas gracias a la gente del HM CINAC, de quienes he aprendido un montón sobre diversos temas (desde astrofísica hasta los mejores productos de peluquería, pasando, por supuesto, por neurociencia), y que me han ayudado en todo lo posible desde el principio hasta el último momento. Muchos de ellos, con el tiempo, se han convertido en grandes amigos, que me han acompañado tanto en las dulces victorias como en las amargas derrotas. Estoy muy agradecido de haberos conocido y de poder llamaros amigos. Espero que sigáis formando parte de mi vida por muchos años. Me gustaría también agradecer al propio centro, el HM CINAC, y al director de este, el Dr. José A. Obeso, por acogerme y darme la oportunidad de avanzar en mi carrera laboral e investigadora.

Muchas gracias a mis padres José Vicente y Rocío, que me dieron raíces para crecer y alas para volar. No creo que hubiera llegado hasta donde estoy sin el esfuerzo y trabajo que dedicaron para que mi hermana Sandra y yo pudiéramos estudiar. En cuanto a ella, deseo que pronto también tenga la oportunidad de defender su tesis doctoral y pueda regresar a casa.

Muchas gracias a mis abuelos José, Felisa, Ofelio y Jara, que nos disteis tanto habiendo recibido tan poco. Habéis hecho todo lo posible para darnos un futuro próspero y mejores oportunidades. Vosotros me habéis enseñado que, con

constancia, humildad y trabajo duro, se pueden conseguir grandes cosas. Siempre os llevo en mi recuerdo.

Muchas gracias a Marieta, que ha escuchado estoicamente una y otra vez mis monólogos sobre ingeniería, neurociencia y estadística, poniendo todo de su parte para aprender y así poder ayudarme. Tu punto de vista, tus opiniones y tus consejos han sido y son muy importantes para mí. Eres uno de mis mayores apoyos, en esto y en todo lo demás.

Muchas gracias a mis amigos, con quienes siempre puedo contar, que se han preocupado desde el principio por el desarrollo de la tesis, me han brindado apoyo moral y se han interesado en comprender todo lo que está escrito en estas páginas. Ojalá que lo podamos celebrar juntos dentro de muy poco tiempo.

A todos vosotros, muchas gracias.

Abstract

Parkinson's disease is a neurodegenerative disorder that primarily affects the cortico-basal ganglia circuit in the brain. Patients suffering from this disease present several motor signs such as bradykinesia, rigidity and tremor, which largely reduce their quality of life. This motor impairment in patients seems to be related to exaggerated beta band (13-35 Hz) neural activity in the cortico-basal ganglia circuit, being considered a hallmark of the disease. For decades, it has been widely accepted that neural oscillatory activity at beta frequencies would be the sole component related to the disease' pathophysiology. However, recent studies suggest that also the non-oscillatory component may intervene in the pathological processes of Parkinson's disease.

This thesis aims to identify the role of the oscillatory and non-oscillatory parts of beta activity in the pathophysiology and pathogenesis of Parkinson's disease, by means of developing a principled framework that allows us to properly investigate both components.

Beta band activity in patients' recordings is typically assessed with classical spectral analysis. However, the power spectrum ambiguously measures both oscillatory and non-oscillatory components. Several algorithms have been developed to overcome this ambiguity. Most of them estimate the oscillatory activity indirectly by subtracting the estimated non-oscillatory component from the total power spectrum. Despite these advances, accurately estimating non-oscillatory activity in real neurophysiological signals remains a challenge. Here we introduce a new principled framework designed to separately analyse oscillatory and non-oscillatory activity in biological signals. The approach is rigorously supported by mathematical justification and validated using simulated data.

Subthalamic local field potentials from patients were studied using the developed framework to identify the relative contribution, dopamine dependency, response to neuromodulation and clinical relevance of oscillatory and non-oscillatory subthalamic beta activity in Parkinson's disease. We found that only the oscillatory component of subthalamic beta activity is dopamine dependent,

while deep brain stimulation primarily modulates non-oscillatory activity in the subthalamic nucleus of patients. Additionally, we showed that the oscillatory component of subthalamic beta activity, particularly in the low-beta range, is related to the parkinsonian akinetic-rigid clinical phenotype, and may play a key role in both the pathophysiology and the progression of Parkinson's disease.

Therefore, we demonstrated that using our new principled framework it is possible to separately assess the impact of the different components of subthalamic beta activity, i.e., oscillatory and non-oscillatory, in Parkinson's disease.

Resumen

La enfermedad de Parkinson es un trastorno neurodegenerativo que afecta principalmente al circuito cortico-basal del cerebro. Los pacientes que padecen esta enfermedad presentan varios signos motores como bradicinesia, rigidez y temblor, que reducen en gran medida su calidad de vida. Este deterioro motor parece estar relacionado con un aumento de actividad neuronal en la banda beta (13-35 Hz) en el circuito cortico-basal, considerándose un sello distintivo de la enfermedad. Durante décadas, se ha aceptado ampliamente que la actividad neural oscilatoria en frecuencias beta sería el único componente relacionado con la fisiopatología de la enfermedad. Sin embargo, estudios recientes sugieren que la componente no oscilatoria también podría intervenir en los procesos patológicos de la enfermedad de Parkinson.

Esta tesis tiene como objetivo identificar el papel de las partes oscilatoria y no oscilatoria de la actividad beta en la fisiopatología y patogénesis de la enfermedad de Parkinson, mediante el desarrollo de un marco fundamentado que nos permita investigar adecuadamente ambos componentes.

La actividad de la banda beta en registros de pacientes suele evaluarse con el análisis espectral clásico. Sin embargo, el espectro de potencia mide de forma ambigua tanto las componentes oscilatorias como las no oscilatorias. Se han desarrollado varios algoritmos para superar esta ambigüedad. La mayoría de ellos estiman la actividad oscilatoria indirectamente restando el componente no oscilatorio estimado del espectro de potencia total. A pesar de estos avances, la estimación precisa de la actividad no oscilatoria en señales neurofisiológicas reales sigue siendo un reto. En el presente trabajo presentamos un nuevo marco fundamentado diseñado para analizar por separado la actividad oscilatoria y no oscilatoria en señales biológicas. El planteamiento se apoya rigurosamente en una justificación matemática y se valida mediante datos simulados.

Se estudiaron potenciales de campo locales subtalámicos de pacientes utilizando el marco desarrollado para identificar la contribución relativa, la dependencia de la dopamina, la respuesta a la neuromodulación y la relevancia

clínica de la actividad beta subtalámica oscilatoria y no oscilatoria en la enfermedad de Parkinson. Encontramos que sólo el componente oscilatorio de la actividad beta subtalámica es dependiente de la dopamina, mientras que la estimulación cerebral profunda modula principalmente la actividad no oscilatoria en el núcleo subtalámico de los pacientes. Además, demostramos que la componente oscilatoria de la actividad beta subtalámica, particularmente en el rango beta bajo, está relacionada con el fenotipo clínico acinético rígido parkinsoniano, y que puede desempeñar un papel clave tanto en la fisiopatología como en la progresión de la enfermedad de Parkinson.

Demostramos, por tanto, que con nuestro nuevo marco fundamentado es posible evaluar por separado el impacto de los diferentes componentes de la actividad beta subtalámica, es decir, oscilatoria y no oscilatoria, en la enfermedad de Parkinson.

Table of Contents

1. Introduction.....	1
1.1. Overall perspective.....	1
1.2. Motivation of the thesis	2
1.3. Objectives of the thesis.....	4
2. State of the art	5
2.1. Organization of the cortico-basal ganglia circuit.....	5
2.2. Parkinson's disease: pathogenesis and pathophysiology.....	7
2.3. Antiparkinsonian therapies	11
2.4. Beta activity in Parkinson's disease	14
2.5. Non-oscillatory neural activity in Parkinson's disease.....	17
2.6. Separating oscillatory and non-oscillatory components.....	19
3. Materials and methods	21
3.1. Beta activity model details	21
3.2. Non-oscillatory activity model details	22
3.3. Oscillatory activity model details.....	23
3.4. Subthalamic LFP recordings from PD patients: HM CINAC	25
3.5. Subthalamic LFP recordings from PD patients: NeuroRestore	29
3.6. Spectral analysis in the frequency domain	32
3.7. Beta burst analysis in the time domain	33
3.8. FOOOF details.....	34
3.9. Estimation of the periodicity spectrum.....	36
3.10. Estimation of the Bayesian periodicity spectrum	38
3.11. Statistics	39

4. Signal processing principled framework	41
4.1. Modelling of oscillatory and non-oscillatory beta activity	41
4.2. Bayesian periodicity spectrum	43
4.3. Periodicity spectrum of non-oscillatory activity	44
4.4. Periodicity spectrum of oscillatory activity	45
5. Disambiguation of beta activity components in Parkinson's disease	49
5.1. Effect of dopaminergic medication on subthalamic beta activity	49
5.2. Effect of deep brain stimulation on subthalamic beta activity	54
5.3. Beta activity across clinical phenotypes	58
5.4. Clinical correlations.....	64
6. Discussion and conclusions.....	71
6.1. Beta bursts, spectral measures and oscillatory/non-oscillatory activity	72
6.2. The Bayesian periodicity spectrum.....	73
6.3. Dopamine dependency of oscillatory <i>vs.</i> non-oscillatory beta activity	76
6.4. Neuromodulation of oscillatory <i>vs.</i> non-oscillatory beta activity	78
6.5. Beta activity across clinical phenotypes	80
6.6. Clinical correlations.....	82
6.7. Conclusions	85
References	87
Annexes.....	117
Validation of beta activity modelling	117
Supplementary figures.....	125
Publication associated to the thesis.....	127

List of Figures

Figure 1. Parallel loops of the cortico-basal ganglia circuit.....	6
Figure 2. Schematic representation of the direct, indirect and hyperdirect pathways of the cortico-basal ganglia circuit in healthy conditions	7
Figure 3. Schematic representation of the direct, indirect and hyperdirect pathways of the cortico-basal ganglia circuit in the parkinsonian state	8
Figure 4. Bottom-up and top-down models of Parkinson's disease pathogenesis.....	9
Figure 5. Parkinson's disease motor signs and non-motor symptoms associated with disease progression	11
Figure 6. Evolution of levodopa therapeutic effect	12
Figure 7. Representation of fully implanted deep brain stimulation device into the subthalamic nucleus.....	14
Figure 8. Schematic representation of the oscillation model of Parkinson's disease ..	15
Figure 9. Non-oscillatory component in electrophysiology recordings.....	17
Figure 10. IRASA and FOOOF algorithms.	19
Figure 11. Periodicity spectrum	37
Figure 12. Modelling of oscillatory and non-oscillatory beta activity.....	42
Figure 13. Power spectrum and periodicity spectrum of non-oscillatory activity	44
Figure 14. Power spectrum and periodicity spectrum of oscillatory activity	46
Figure 15. Frequency resolution in power spectra and periodicity spectra	47
Figure 16. Oscillatory and non-oscillatory components in PD patients off and on medication.....	50
Figure 17. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease off and on medication.....	52
Figure 18. Correlations between periodicity, Bayesian periodicity, and spectral and beta bursts measures off and on medication.....	53
Figure 19. Oscillatory and non-oscillatory components in PD patients off and on DBS	

Figure 20. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease off and on DBS.....	56
Figure 21. Correlations between periodicity, Bayesian periodicity, and spectral and beta bursts measures off and on DBS.	57
Figure 22. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease presenting different clinical phenotypes off DBS	60
Figure 23. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease presenting akinetic-rigid phenotype off and on DBS	62
Figure 24. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease presenting akinetic-rigid with tremor and tremor dominant phenotypes off and on DBS	63
Figure 25. PD motor progression and beta activity I	68
Figure 26. PD motor progression and beta activity II	69
Figure 27. Verification of beta modelling I: beta oscillations in PD patients off medication.	120
Figure 28. Correlations between spectral and beta bursts measures off medication	121
Figure 29. Verification of beta modelling II: beta oscillations in PD patients off and on medication.....	123
Figure 30. Correlations between spectral and beta bursts measures off and on medication.....	124
Figure 31. Power spectrum and periodicity spectrum of non-oscillatory activity (CWT)	125
Figure 32. Power spectrum and periodicity spectrum of oscillatory activity (CWT)	126
Figure 33. Frequency resolution in power spectra and periodicity spectra (CWT)...	126

List of Tables

Table 1. Clinical details (HM CINAC).....	25
Table 2. Electrophysiological recordings details (HM CINAC)	26
Table 3. Clinical details (NeuroRestore).....	29
Table 4. Electrophysiological recordings details (NeuroRestore)	31
Table 5. Dopamine dependency of oscillatory and non-oscillatory beta activity with n = 21 nuclei.....	50
Table 6. DBS dependency of oscillatory and non-oscillatory beta activity with n = 58 nuclei	54
Table 7. Effect of DBS on beta activity depending on the clinical phenotype.....	58
Table 8. Clinical correlations.....	64
Table 9. Rate of motor progression of the disease	66

Abbreviations and Acronyms

ANTs	Advanced Normalization Tools
ANOVA	Analysis of variance
α -syn	Alpha-synuclein
AR	Akinetic-rigid
AR+T	Akinetic-rigid with tremor features
AR(2)	Second-order autoregressive
BF	Bayes factor
CAPSIT	Core assessment program for surgical interventional therapies
CT	Computed tomography
CWT	Continuous wavelet transform
DBS	Deep brain stimulation
DFT	Discrete Fourier transform
FIR	Finite impulse response
FOOOF	Fitting oscillations and one-over-f
FWHM	Full width, half-maximum
GPe	Globus pallidus pars externa
GPI	Globus pallidus pars interna
Hz	Hertz
IPG	Implantable pulse generator
IIR	Infinite impulse response
IRASA	Irregular resampling auto-spectral analysis
LAS	Less affected side
LFP	Local field potential
M1	Primary motor cortex

MAS	More affected side
MRI	Magnetic resonance imaging
MSN	Medium spiny neuron
NMDA	N-methyl-D-aspartate
PD	Parkinson's disease
PIGD	Postural instability/gait difficulty
PMC	Premotor cortex
PSD	Power spectral density
REM	Rapid eye movement
S1	Primary somatosensory cortex
SMA	Supplementary motor area
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STFT	Short-time Fourier transform
STN	Subthalamic nucleus
TD	Tremor-dominant
UPDRS	Unified Parkinson's disease rating scale
VTA	Ventral tegmental area

Thesis structure

This document is organized in seven differentiated parts. In the first part, a brief introduction to the thesis is given, along with the motivation and objectives of this work. This sets the stage for the second section, which reviews the state of the art. Here, foundational concepts related to Parkinson's disease, neural activity and current analytical approaches are presented to establish a baseline understanding for the reader. Materials available and methodology followed in the thesis are described in the third part of the manuscript. The fourth part of the document is devoted to reporting on the development of the signal processing principled framework. Then, this framework is applied to subthalamic recordings obtained from Parkinson's disease patients, illustrating its practical utility and validating its design, which can be found in the fifth section of the manuscript. The sixth section provides an in-depth discussion of the results, emphasizing their implications for understanding the pathophysiology and pathogenesis of Parkinson's disease, as well as their potential contributions to improving disease management, and the conclusions are presented. Finally, in the last part of the document, the reader may find the references, and also the annexes which offer additional context and supporting information that extends beyond the scope of the main manuscript.

1. Introduction

1.1. Overall perspective

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the basal ganglia (Kalia & Lang, 2015). The dramatic reduction of this neuronal population affects the whole brain, especially the structures that are part of the cortico-basal ganglia circuit which show altered neural activity (Obeso *et al.*, 2000*b*; Poewe *et al.*, 2017). These alterations in neural activity result in a change in the connections between brain structures in the cortical-basal ganglia circuit compared to the healthy state, generating excessive neuronal synchronization (Gatev *et al.*, 2006). Increased patterns of neural activity at certain frequencies within the cortico-basal ganglia circuit are related to several motor signs and non-motor symptoms of PD (Brown, 2003). Recently, it has been proposed that abnormal corticostriatal activity may also contribute to the death of nigral dopaminergic neurons (Foffani & Obeso, 2018).

The most studied cortico-basal ganglia neural pattern in PD corresponds to the beta band activity (13-35 Hz), which spreads throughout the entire circuit (Marsden *et al.*, 2001; Brown, 2003; Lalo *et al.*, 2008) although it is mostly studied in the subthalamic nucleus (STN) (Group, 2001; Benabid *et al.*, 2009). Exaggerated beta band activity within the cortico-basal ganglia circuit is considered a hallmark of the disease (Priori *et al.*, 2004; Little & Brown, 2014) and is highly related to motor signs, particularly rigidity and bradykinesia (Pogosyan *et al.*, 2009; Neumann *et al.*, 2016; Lofredi *et al.*, 2019*b*). Beta band oscillatory activity both modulates and is modulated by voluntary movement (Cassidy *et al.*, 2002; Foffani *et al.*, 2005; Alegre *et al.*, 2005; Androulidakis *et al.*, 2007; Tsang *et al.*, 2012; Vissani *et al.*, 2021). Altogether these findings suggest that neuronal synchronization at beta frequencies is tightly involved in motion, and that the

presence of excessive beta band activity in the cortico-basal ganglia circuit would promote a hypokinetic state in PD patients.

Nevertheless, it must be considered that neural activity, as recorded by local field potentials (LFPs) (Buzsáki *et al.*, 2012), is comprised of the ambiguous combination of oscillatory and aperiodic, or non-oscillatory activity (He *et al.*, 2010; Donoghue *et al.*, 2020). Oscillatory activity mainly reflects periodic biological fluctuations while non-oscillatory activity is known to reflect spiking activity and synaptic balance between excitation and inhibition (Manning *et al.*, 2009; He *et al.*, 2010; Gao *et al.*, 2017; Donoghue *et al.*, 2020) but also non-biological noise, e.g., changes of impedance. Although only the beta oscillatory component was considered as detrimental in PD (Stein & Bar-Gad, 2013; Little & Brown, 2014), over the last few years more and more studies were focused on the cortico-basal ganglia non-oscillatory part of beta band activity, which seems to be altered in PD patients (Martin *et al.*, 2018; Belova *et al.*, 2021; Darmani *et al.*, 2022; Kim *et al.*, 2022; Zhang *et al.*, 2022; Wiest *et al.*, 2023).

The role of the different parts of the beta band activity i.e., oscillatory synchronizations and non-oscillatory components, in both the pathophysiology and pathogenesis of PD remain unclear. Throughout the present work, we will investigate the properties of subthalamic beta activity from PD patients in order to fully address the main objective of this thesis.

1.2. Motivation of the thesis

Power spectrum analysis is ambiguously sensitive to both oscillatory and non-oscillatory activity, which can stem from different biological and non-biological sources (He *et al.*, 2010; Donoghue *et al.*, 2022; Pardo-Valencia *et al.*, 2024). This ambiguity arises because the power spectrum captures the overall energy distribution across frequencies, but it cannot differentiate true oscillatory signals, which are periodic, from other non-oscillatory sources of signal variance, such as non-oscillatory “noise” of non-biological or biological origin, e.g., $1/f$ noise. Consequently, the power at a given frequency does not necessarily indicate genuine oscillations; it might also reflect non-oscillatory fluctuations at the same frequency

(Miller *et al.*, 2009a; He *et al.*, 2010; Buzsáki & Wang, 2012; Voytek *et al.*, 2015; Donoghue *et al.*, 2020), complicating the biological interpretation of spectral data (Donoghue *et al.*, 2022). The most common strategies for addressing this ambiguity involve estimating the non-oscillatory component of the power spectrum, either through resampling procedures in the time domain (Yamamoto & Hughson, 1991, 1993; Wen & Liu, 2016) or by fitting the $1/f$ aperiodic activity in the frequency domain (Blankertz *et al.*, 2010; Hughes *et al.*, 2012; Gao, 2016; Martin *et al.*, 2018; Donoghue *et al.*, 2020). The oscillatory component in the power spectrum can then be indirectly estimated by subtracting the non-oscillatory component. However, in real neurophysiological data, estimating the non-oscillatory activity can be challenging (Gerster *et al.*, 2022). If the primary interest is oscillations, the ideal spectral analysis method would be one that is sensitive only to oscillatory activity.

We aimed to overcome all these limitations by developing a new principled framework that allows to accurately investigate beta band oscillatory and non-oscillatory dynamics. First, we simulated beta band activity in an ideal scenario, i.e., signals that comprised of only non-oscillatory activity and a single oscillatory peak within the beta band. Second, we analysed this simulated beta band activity using classical methodologies, i.e., beta bursts measures in the time domain (Tinkhauser *et al.*, 2017a, 2017b) and spectral measures in the frequency domain. Third, we developed a novel phase-based spectral analysis methodology based on the variability of the instantaneous frequency which we named “periodicity spectrum”. It is derived from the mathematical intuition that the instantaneous frequency at a certain frequency of a random noise signal would present maximum variability, whereas in the case of a pure sinusoid signal that variability would be zero. We used Bayesian statistics for the design of the “Bayesian periodicity spectrum” so we could provide the level of evidence for the presence or the absence of oscillatory activity in biological signals (Keysers *et al.*, 2020). Fourth, we determined the best strategy to study and disambiguate beta activity oscillatory and non-oscillatory components based on the results obtained with simulated signals. Fifth, we applied this framework to analyse beta activity present in actual STN LFPs recordings from PD patients on vs. off dopaminergic medication and on

vs. off continuous deep brain stimulation (DBS). Finally, we studied the oscillatory and non-oscillatory components of subthalamic beta band activity in order to unveil their relevance in PD.

1.3. Objectives of the thesis

The main objective is to identify the relative contribution, dopamine dependency, response to neuromodulation and clinical relevance of oscillatory and non-oscillatory subthalamic beta activity in PD. The central hypothesis is that the oscillatory component, rather than the non-oscillatory component, of subthalamic beta activity is the hallmark of PD.

Specific objective 1. Establish a principled framework to discern oscillatory synchronizations from non-oscillatory components in stationary signals.

Specific objective 2. Investigate cortico-basal ganglia oscillatory synchronizations and non-oscillatory components in PD patients.

Significance statement: This doctoral thesis furthers previous understanding about the different components of subthalamic beta activity, i.e., oscillatory and non-oscillatory, in PD. Through the development of a novel principled signal processing framework, we provide new insights on the neural activity characteristics underlying the pathophysiology of PD. We unveiled how these oscillatory and non-oscillatory components are related to dopamine levels, therapeutic interventions and clinical outcomes. Our findings highlight the oscillatory component of beta activity as a hallmark of the disease while clarifying the role of non-oscillatory dynamics. This deeper comprehension advances our ability to pinpoint the onset and progression of PD, as well as the potential for targeted neuromodulation strategies.

2. State of the art

In this section, a comprehensive overview of the current knowledge, research and development related to this thesis is provided. Here, we explore the interplay between the cortico-basal ganglia circuit, the pathophysiology of PD and antiparkinsonian therapeutic interventions, integrating insights into beta activity dynamics with advanced analytical approaches for disentangling oscillatory and non-oscillatory components.

2.1. Organization of the cortico-basal ganglia circuit

The cortico-basal ganglia circuit is a network of parallel loops (motor, associative and limbic domains) integrated by cortical and subcortical brain structures connected by the thalamus (Figure 1) (Alexander *et al.*, 1986, 1991). Due to its anatomical and functional organization, the cortico-basal ganglia circuit is responsible for functions such as movement control, attention, learning, habit formation and time estimation (Obeso *et al.*, 2008*b*). The structure and function of the motor loop is the most studied and better understood in PD, since motor manifestations represented the major clinical output of the flawed cortico-basal ganglia circuit in the past years (Gibb & Lees, 1988; Hughes *et al.*, 1992; Obeso *et al.*, 2008*b*; Marras & Lang, 2013). Cortical structures of the cortico-basal ganglia motor loop include supplementary motor area (SMA), primary somatosensory cortex (S1), cingulate motor cortex, and premotor (PMC) and primary motor (M1) cortices. Conversely, the basal ganglia are a group of subcortical nuclei composed of the striatum (caudate and putamen), globus pallidus pars externa (GPe) and pars interna (GPi), the STN, and the substantia nigra pars compacta (SNc) and pars reticulata (SNr) (Obeso *et al.*, 2008*b*, 2008*a*; Poewe *et al.*, 2017).

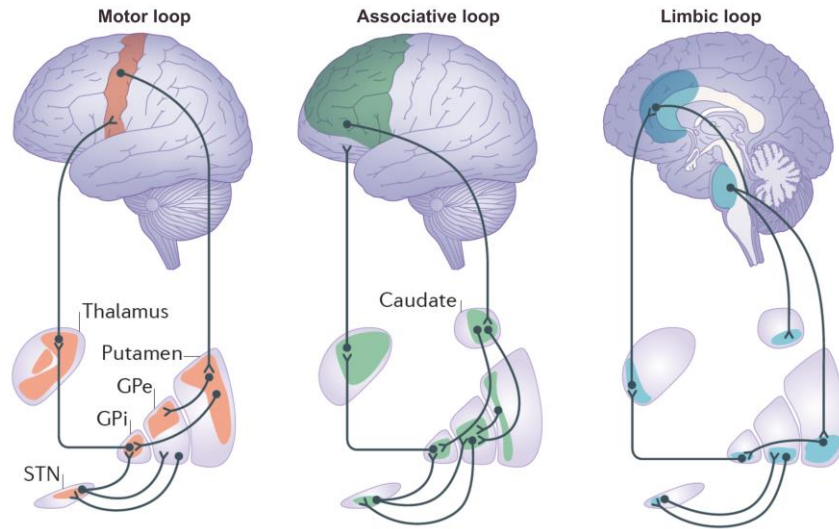


Figure 1. Parallel loops of the cortico-basal ganglia circuit (Jahanshahi *et al.*, 2015). GPe: Globus pallidus pars externa, GPi: Globus pallidus pars interna, STN: Subthalamic nucleus.

The cortico-basal ganglia motor loop is associated with voluntary movement, and in healthy conditions is regulated by the equilibrium between the direct, indirect and hyperdirect pathways (Figure 2). Direct and indirect pathways provide cortical inputs in a somatotopic fashion to medium spiny neurons (MSNs) into the striatum. Two main MSNs populations can be identified depending on their dopamine receptors. MSNs with D1 dopamine receptors form the direct pathway, and they connect the striatum directly to the GPi and SNr. On the other hand, MSNs with D2 dopamine receptors shape the indirect pathway, and they connect the striatum to the GPi and SNr through the GPe and the STN. The direct pathway promotes locomotion and movement while the indirect pathway acts as a movement inhibitor (Albin *et al.*, 1989; DeLong, 1990; Obeso *et al.*, 2000b; DeLong & Wichmann, 2007; Calabresi *et al.*, 2014). Complementing these pathways, the hyperdirect pathway is a monosynaptic neuronal connection from the cortex directly into the STN, bypassing the striatum (Nambu *et al.*, 2000). This pathway acts as a faster mechanism of movement inhibition compared to the indirect pathway, quickly stopping unintended motor actions (Nambu *et al.*, 2002; Chen *et al.*, 2020a). Together, these interconnected pathways maintain a fine-tuned balance, which is essential for the precise regulation of motor activity.

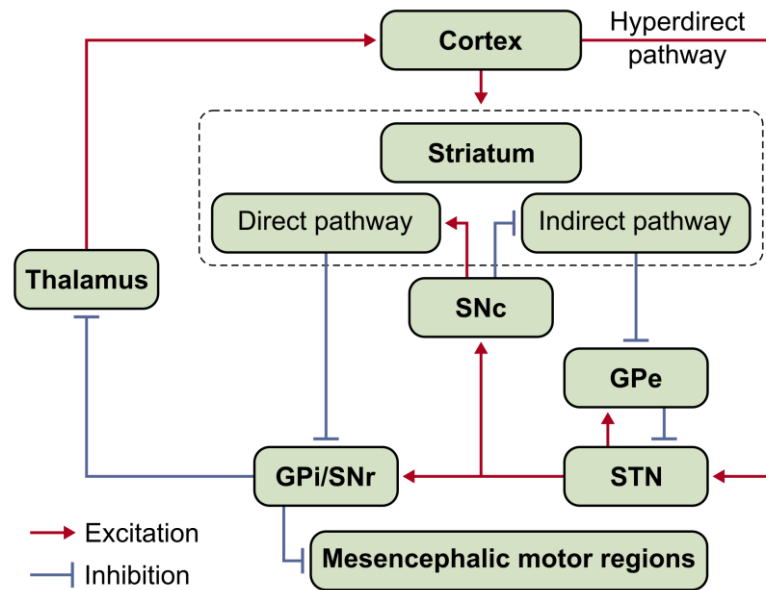


Figure 2. Schematic representation of the direct, indirect and hyperdirect pathways of the cortico-basal ganglia circuit in healthy conditions (Obeso *et al.*, 2000a, 2000b; Poewe *et al.*, 2017). GPe: Globus pallidus pars externa, GPi: Globus pallidus pars interna, SNc: Substantia nigra pars compacta, SNr: Substantia nigra pars reticulata, STN: Subthalamic nucleus.

The regulation of this circuit is highly dependent on dopamine (Hornykiewicz, 1966). The major input of this neurotransmitter into the striatum comes from the dopaminergic cells of the SNc, but also from the ventral tegmental area (VTA) (Rice *et al.*, 2011). Dopamine acts differentially depending on the striatal MSNs receptors D1 and D2, facilitating and inhibiting the direct and the indirect pathway, respectively (Keeler *et al.*, 2014). Dopamine release into the striatum plays a key role in motor control, reward, cognition and learning (Yin & Knowlton, 2006; Haber, 2014). Thus, dopamine serves as a critical modulator of striatal function, orchestrating a delicate, essential balance for both motor and cognitive processes.

2.2. Parkinson's disease: pathogenesis and pathophysiology

The smooth performance of the cortico-basal ganglia circuit is disrupted in PD by the loss of dopaminergic neurons in the SNc which project to the striatum (Figure 3) (Dauer & Przedborski, 2003). Generally, this dopaminergic deficiency in PD progresses gradually over the years. It is estimated that striatal dopamine

depletion reaches around 70–80% by the time the first motor signs appear in PD patients (Bernheimer *et al.*, 1973; Riederer & Wuketich, 1976; Fearnley & Lees, 1991), although recently published results suggest that these numbers are around 35-45% at the onset of motor manifestations (Heng *et al.*, 2023). Striatal dopamine depletion tends to follow a pattern in PD, being more prominent in the posterior-dorsal part of the putamen, which is associated to the motor loop of the cortico-basal ganglia circuit (Figure 1) (Wang *et al.*, 2007; Jeong *et al.*, 2023). The pathogenesis of the nigrostriatal dopaminergic system degeneration is still under debate, as several factors such as genetics, mitochondrial dysfunction, neuroinflammation, oxidative stress and protein misfolding are thought to play a role in this process (Olanow, 2007; Shulman *et al.*, 2011; Hirsch *et al.*, 2013).

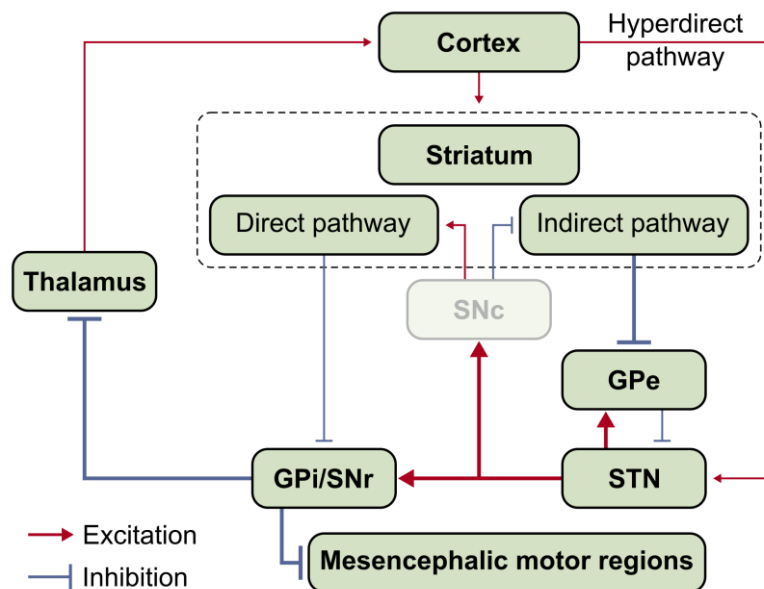
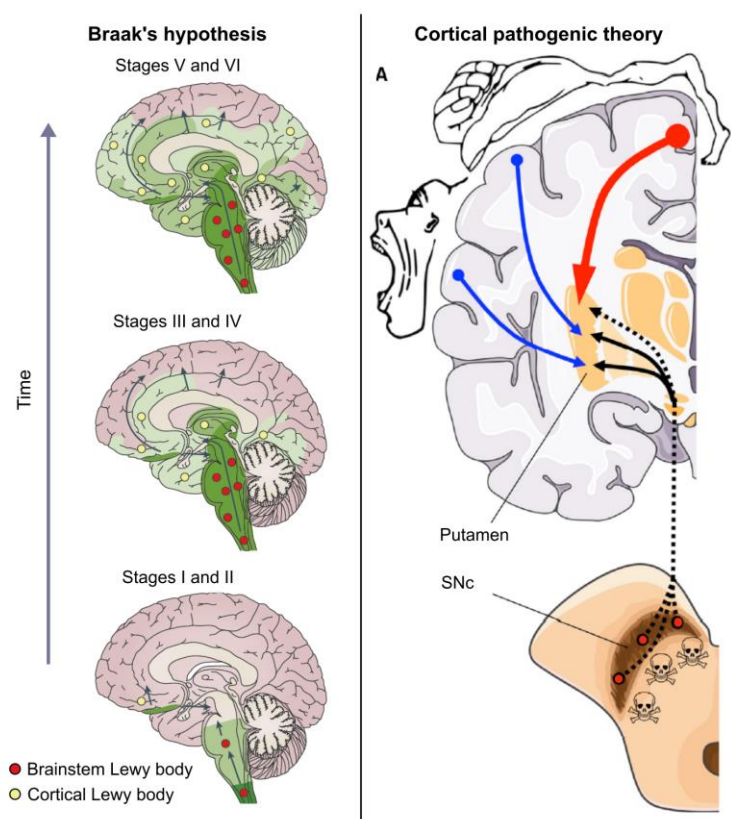


Figure 3. Schematic representation of the direct, indirect and hyperdirect pathways of the cortico-basal ganglia circuit in the parkinsonian state (Obeso *et al.*, 2000a, 2000b; Poewe *et al.*, 2017). Thicker lines represent greater excitation/inhibition while thinner lines represent the opposite. GPe: Globus pallidus pars externa, GPi: Globus pallidus pars interna, SNc: Substantia nigra pars compacta, SNr: Substantia nigra pars reticulata, STN: Subthalamic nucleus.

Nowadays, Braak’s hypothesis is the most accepted description for nigrostriatal degeneration in PD (Braak *et al.*, 2006). This hypothesis involves Lewy bodies, which are intracellular inclusions of protein aggregates, being alpha-synuclein (α -syn) their main component (Spillantini *et al.*, 1997). According to the

postulations of Braak and colleagues, toxic α -syn species propagate from the olfactory bulb, the gut and the peripheral nervous system into the brain in a bottom-up caudo-rostral direction to cortical areas over 6 progressive stages (I-VI) (Figure 4) (Braak *et al.*, 2006; Kim *et al.*, 2019). Nevertheless, recent studies performed in non-human primate models of PD showed that toxic α -syn species can propagate bidirectionally in the gut-brain axis (Arotcarena *et al.*, 2020) and also from cortical areas into deeper brain structures (Teil *et al.*, 2023). More importantly, two main features of PD cannot be explained by Braak's hypothesis: the selective vulnerability of SNc dopaminergic neurons that project to the motor part of the striatum (Kordower *et al.*, 2013) and the typical focal onset of motor signs (Monje *et al.*, 2021). In order to solve this paradox, a recent work proposes that corticostriatal activity would act a somatotopic top-down stressor, which may co-exist with the bottom-up progression of PD (Figure 4) (Foffani & Obeso, 2018).

Figure 4. Bottom-up and top-down models of Parkinson's disease pathogenesis (Poewe *et al.*, 2017; Foffani & Obeso, 2018). The different stages of Braak's hypothesis (I-VI) are represented on the left side of the figure (Braak *et al.*, 2006). On the right side, a representation of how corticostriatal activity may act as a somatotopic stressor which promotes nigrostriatal degeneration according to the cortical pathogenic theory (Foffani & Obeso, 2018). SNc: Substantia nigra pars compacta.



Be that as it may, the degeneration of nigrostriatal dopaminergic neurons triggers a change both in the connections of the cortico-basal ganglia circuit and in the neural activity of its components. According to the classical “fire rate” model

(Albin *et al.*, 1989; DeLong, 1990; Obeso *et al.*, 2000*b*), the reduction of striatal dopaminergic inputs leads to a decrease of D1-MSNs excitation, which reduces the activity of the direct pathway; and to a reduced inhibition of D2-MSNs, that increases the activity of the indirect pathway (Obeso *et al.*, 2008*a*; Poewe *et al.*, 2017; Wichmann, 2019). In turn, all these alterations drive an over-inhibition of the GPe, an increase of excitatory neuronal firing in the STN and, therefore, an increase of excitation with lack of inhibition of GPi/SNr. It has been also observed a breakdown in cortico-subthalamic projections, affecting the integrity of the hyperdirect pathway and thus reducing its activity as a consequence of striatal dopaminergic depletion (Obeso *et al.*, 2008*a*; Villalba *et al.*, 2015; Chu *et al.*, 2017). The overall result is an increase of neuronal activity of the basal ganglia output, which excessively inhibits motor systems (Obeso *et al.*, 2000*b*).

All these changes in the cortico-basal ganglia circuit induce a pathological motor impairment in PD patients characterized by bradykinesia, i.e., slowness of movement, rigidity, rest tremor, postural impairment and gait disturbances (Figure 5) (Tolosa *et al.*, 2006; Kalia & Lang, 2015; Postuma *et al.*, 2015). In recent years, the non-motor symptoms of the disease have been gaining more and more relevance (Chaudhuri & Schapira, 2009; Stern *et al.*, 2012; Kalia & Lang, 2015) since some of them may occur several years before motor manifestations and be highly disabling, such as depression, rapid eye movement (REM) sleep behaviour disorder, constipation and hyposmia (Figure 5) (Chaudhuri & Schapira, 2009; Kalia & Lang, 2015; Poewe *et al.*, 2017). Both motor signs and non-motor symptoms in PD are generally assessed by neurologists following certain worldwide accepted guidelines, such as the Unified Parkinson's disease rating scale (UPDRS) (Goetz *et al.*, 2008). Understanding both motor signs and non-motor symptoms is crucial for comprehensive management of PD disease, enabling earlier diagnosis and more effective therapeutic strategies.

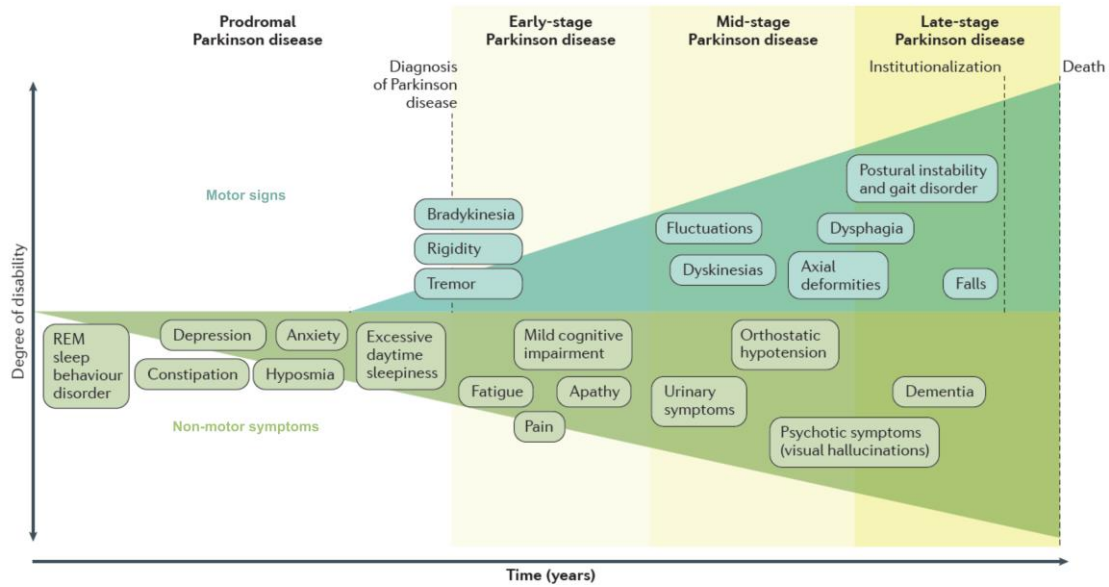


Figure 5. Parkinson's disease motor signs and non-motor symptoms associated with disease progression (Poewe *et al.*, 2017).

2.3. Antiparkinsonian therapies

Since the first description of the “shaking palsy” published by James Parkinson in 1817 (Parkinson, 2002), there were several attempts to develop a therapy that would alleviate PD signs and symptoms. In the first half of the past century, ablative brain surgery was considered as a feasible strategy to treat the symptomatology of the disease (Walter & Vitek, 2004). Different brain areas were studied as suitable spots for neurosurgery, such as the primary motor cortex, the caudate or the pallidum (Bucy & Case, 1939; Meyers, 1951).

It was not until the discovery of striatal dopamine depletion in PD during the 1960s (Ehringer & Hornykiewicz, 1960) that dopamine replacement therapy was considered a better option for the treatment of PD symptomatology. The gold standard for pharmacological treatment in PD is levodopa, and it is prescribed to virtually every patient at some point (Tolosa *et al.*, 1998; Witt & Fahn, 2016). Levodopa is the synthetic precursor of dopamine (Fahn, 2008) which can be administered orally (Cotzias & Papavasiliou, 1967) or by pump infusion (Stocchi *et al.*, 2005). This drug is converted into dopamine upon reaching the brain, achieving a striatal dopamine concentration closer to physiological levels for a certain period of time (Fahn, 2008; Witt & Fahn, 2016). Levodopa administration

is one of the best treatments for motor signs and some aspects of non-motor symptoms during the early stages of the disease in most cases (Schapira *et al.*, 2009; Sprenger & Poewe, 2013).

However, dopaminergic medication typically tends to produce complications after 5-10 years after therapy implementation (Obeso *et al.*, 2000a; Jankovic, 2005), although they may appear much sooner (Ahlskog & Muenter, 2001; Stocchi *et al.*, 2010). These complications include progressive decline of symptomatic effect and narrowing of therapeutic window (Figure 6) (Jankovic, 2005), dyskinesias, i.e., involuntary movements (Obeso *et al.*, 2000a; Castela & Hernandez, 2021), end-of-dose wearing-off, i.e., predictable decline in motor function at the end of dose with previously stable response (Rajput *et al.*, 2002), and on-off phenomenon, i.e., sudden and unpredictable pronounced short-duration worsening of parkinsonian features which resolved spontaneously (Rajput *et al.*, 2002). Therapy duration, disease severity and the degree of striatal dopamine depletion are related to the emergence of levodopa-related complications (Obeso *et al.*, 2000a; Stocchi *et al.*, 2010). It must also be considered that some PD patients are non-responsive to levodopa treatments (Hauser & Auinger, 2011).

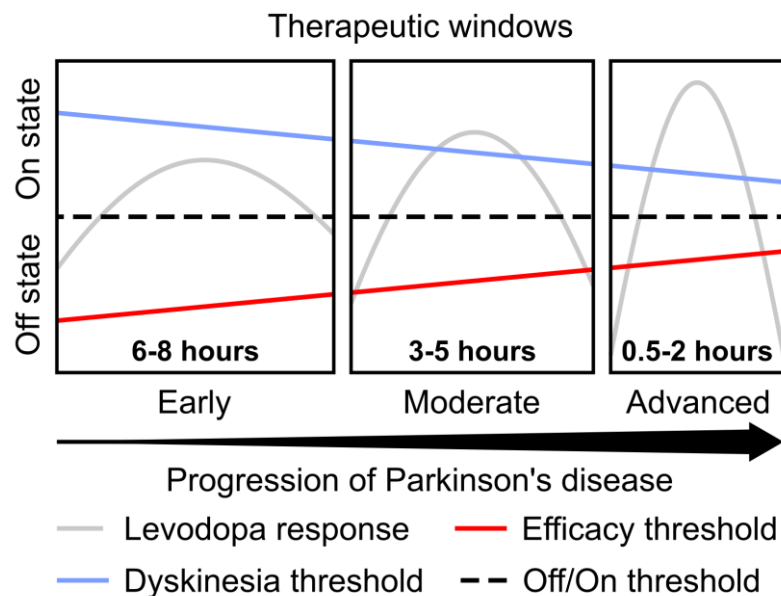


Figure 6. Evolution of levodopa therapeutic effect (Jankovic, 2005). The effective levodopa response and the window width of therapeutic effect tend to worsen as the disease progresses over time.

These complications related to the response to dopaminergic medication prompted the development of alternative surgical procedures to improve the quality of life of PD patients. According to the literature, disrupting the activity of specific brain regions such as the GPi, the thalamus, or the STN can help restore balance within the cortico-basal ganglia motor circuit, providing therapeutic improvement (Meyers, 1940; Alexander *et al.*, 1986, 1991; Albin *et al.*, 1989; DeLong, 1990). Importantly, disrupting activity in these brain structures does not necessarily require their removal. Instead, modern surgical approaches such as DBS have become the most widely used and effective treatments for alleviating PD manifestations.

DBS consists of the chronic placement of an electrode inside the brain, targeting a particular structure, which in the case of PD is within the basal ganglia (Tasker, 1998; Group, 2001; Benabid *et al.*, 2009). The choice of target may differ depending on the patient's clinical phenotype, i.e., the dominant motor sign (Kang *et al.*, 2005; Stebbins *et al.*, 2013), whether is tremor-dominant (TD), akinetic-rigid (AR), or postural instability/gait difficulty (PIGD). Nevertheless, the most common target in PD patients is the STN (Figure 7). Once the electrode is placed, neurosurgeons can apply a tuneable electric stimulation at a certain frequency that disrupts the pathological activity of the target brain structure (Benabid, 2003). Thus, instead of irreversibly damaging brain structures as in traditional ablative brain surgery, modern approaches like DBS modulate the activity of such structures. This surgical procedure has been also proposed as a possible successful disease-modifying therapy i.e., an intervention that change the natural clinical course of the disease if applied soon after diagnosis (Wallace *et al.*, 2007; Musacchio *et al.*, 2017; Lang & Espay, 2018). The rationale behind this statement is that STN projections are mainly excitatory and glutamatergic (Smith & Parent, 1988), and the neuronal activity of this structure is increased in PD (Bergman *et al.*, 1994) maybe even before motor signs appear (Bezard *et al.*, 1999). This particular combination promotes glutamate-mediated excitotoxicity, which is involved in the pathogenesis of neurodegenerative diseases (Meldrum & Garthwaite, 1990; Ambrosi *et al.*, 2014), that would lead to the degeneration of dopaminergic neurons

in the SNc projecting to the striatum (Figure 3). An early intervention would reduce the overactivity in the STN and therefore slow down the neurodegenerative process.

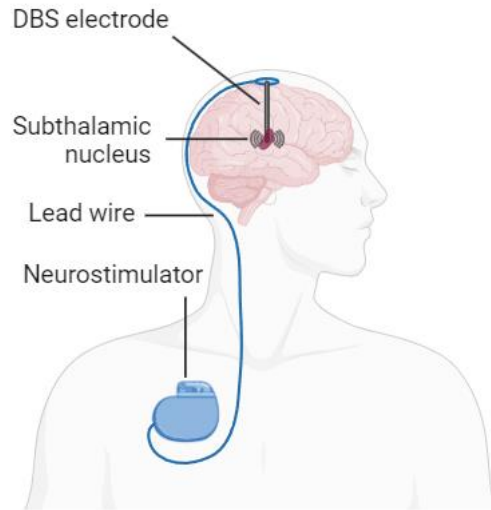


Figure 7. Representation of fully implanted deep brain stimulation device into the subthalamic nucleus (Pardo-Valencia *et al.*, 2024). DBS: deep brain stimulation.

From the beginning of the DBS era, this electric stimulation was applied continuously (Moro *et al.*, 2002) providing short-, mid- and long-term significant improvements in PD patients (Ghika *et al.*, 1998; Lagrange *et al.*, 2002; Temperli *et al.*, 2003; Rodriguez-Oroz *et al.*, 2005). However, several efforts have been made over the years in order to develop adaptive DBS implementations, so the devices are more effective and efficient, thus providing better therapeutic results (Little *et al.*, 2013; Beudel & Brown, 2016; Little & Brown, 2020). Although DBS implantation is an invasive procedure, it has demonstrated effectiveness as a therapy for PD patients, and has offered valuable insights into basal ganglia electrophysiological activity in humans (Foffani & Alegre, 2022).

2.4. Beta activity in Parkinson's disease

Electrodes implanted for DBS in the basal ganglia of PD patients have allowed researchers to better characterize the cortico-basal ganglia circuit pathophysiology in PD. The first classical “fire rate” model of PD (Figure 3) is a simplification of the cortico-basal ganglia circuit, which is based on changes of firing rates because of striatal dopamine depletion (Albin *et al.*, 1989; DeLong, 1990; Obeso *et al.*, 2000b).

Although this model supported the idea that lesioning either the GPi or the STN would provide motor improvement in PD patients (Lozano *et al.*, 1995; Fine *et al.*, 2000; Alvarez *et al.*, 2005), lesions in certain structures such as the motor thalamus are expected to impair voluntary movement, which is not the case (Marsden & Obeso, 1994). The study of basal ganglia activity in PD patients allowed the development of an alternative interpretation of the cortico-basal ganglia circuit in the beginning of this century, based on firing patterns rather than firing rates (Figure 8) (Brown, 2003; Hutchison *et al.*, 2004).

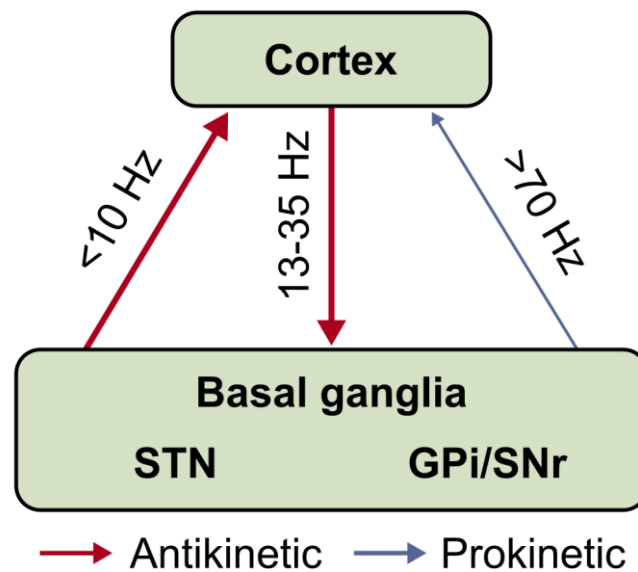


Figure 8. Schematic representation of the oscillation model of Parkinson's disease (Brown, 2003; Hutchison *et al.*, 2004). The arrows represent the dominating direction of connectivity in each frequency band. Thicker lines mean increased activity while thinner mean reduced activity. GPi: Globus pallidus pars interna, SNr: Substantia nigra pars reticulata, STN: Subthalamic nucleus.

It was observed that striatal dopamine depletion induces a pathological state of synchronization in the cortico-basal ganglia circuit at certain frequencies (Guridi & Alegre, 2017). The most recognized altered cortico-basal ganglia activity in PD corresponds to the beta oscillations (13-35 Hz), which spread throughout the entire circuit (Marsden *et al.*, 2001; Brown, 2003; Lalo *et al.*, 2008). Beta band activity within the cortico-basal ganglia motor loop is highly related to preparation and execution of voluntary movement (Tzagarakis *et al.*, 2010; Khanna & Carmena, 2015; Chung *et al.*, 2017) and in physiological conditions, it allows to accurately

perform motor actions (Dostrovsky & Bergman, 2004; Engel & Fries, 2010; Khanna & Carmena, 2017). Conversely, there is an exaggerated increase of activity in the beta range in PD, observable at multiple nodes of cortico-basal ganglia motor loop, and it has emerged as a pathophysiological hallmark of the disease (Little & Brown, 2014).

Increased cortico-basal ganglia beta activity in PD can be measured through electrophysiology recordings using the classical power spectrum in the frequency domain (Marsden *et al.*, 2001; Priori *et al.*, 2004; Neumann *et al.*, 2016; Darcy *et al.*, 2022). Alternatively, in recent years it has been developed a new approach to quantify beta bursts in the time domain based on the instantaneous amplitude of beta activity (Tinkhauser *et al.*, 2017*a*, 2017*b*). On average, beta activity power is decreased by dopaminergic medication (Brown *et al.*, 2001; Levy *et al.*, 2002; Priori *et al.*, 2004*a*; Weinberger *et al.*, 2006; Alonso-Frech *et al.*, 2006; Tinkhauser *et al.*, 2017*b*), DBS (Wingeier *et al.*, 2006; Kühn *et al.*, 2008*a*; Ray *et al.*, 2008*a*; Bronte-Stewart *et al.*, 2009; Quinn *et al.*, 2015; Tinkhauser *et al.*, 2017*a*; Anidi *et al.*, 2018; Kehnemouyi *et al.*, 2021*a*) as well as movement execution (Cassidy *et al.*, 2002*a*; Foffani *et al.*, 2005*a*; Alegre *et al.*, 2005; Kühn *et al.*, 2006*a*; Vissani *et al.*, 2021) and it correlates with motor deficits, particularly bradykinesia and rigidity (Kühn *et al.*, 2006*b*, 2008*b*; Ray *et al.*, 2008*b*; Pogosyan *et al.*, 2009; Neumann *et al.*, 2016*a*; Lofredi *et al.*, 2019*b*, 2023*a*). Beta activity thus became a consolidated neurophysiological biomarker of the parkinsonian rigid/akinetic motor state, offering an attractive feedback variable for clinical applications of adaptive DBS (Priori *et al.*, 2013; Beudel & Brown, 2016; Krauss *et al.*, 2020).

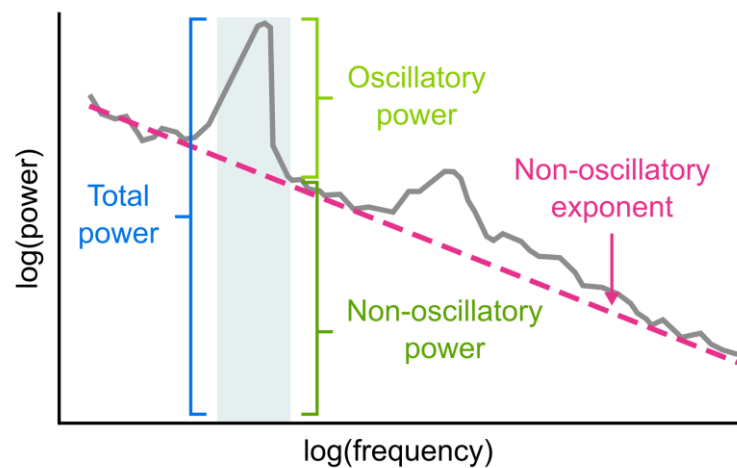
In turn, beta activity was subdivided into two components: low-beta (13-20 Hz) and high-beta (21-35 Hz) (Priori *et al.*, 2004; Yin *et al.*, 2021). This division was made as it is thought that they would represent distinct neural mechanisms. In fact, low-beta and high-beta activities are differentially modulated in the STN by dopaminergic medication (Priori *et al.*, 2004; López-Azcárate *et al.*, 2010), subthalamic low-beta activity is much more correlated with motor impairment compared with the total beta band activity within the STN (Neumann *et al.*, 2016) and there are shorter delays between the motor cortex and the STN in the high-

beta band compared to the low-beta band (Alexander & Crutcher, 1990; Blumenfeld *et al.*, 2017; Ozturk *et al.*, 2020). In this context, low-beta activity would represent the over-inhibition of the striatum applied onto the GPe through the indirect pathway which ultimately alters the microcircuitry between the STN and the GPe (Bevan *et al.*, 2002), while high-beta activity would be the electrophysiological signature of the hyperdirect pathway (Oswal *et al.*, 2021). The distinct modulation and functional significance of both low-beta and high-beta activities provide critical insights into the neural mechanisms underlying motor control and the pathophysiology of PD.

2.5. Non-oscillatory neural activity in Parkinson's disease

In contrast to oscillatory activity, the aperiodic, or non-oscillatory, part of electrophysiology recordings has gained more and more relevance in the study of brain activity in recent years (He, 2014). In the frequency domain, the non-oscillatory exponent describes a straight line when the X-axis, i.e., spectral density, and the Y-axis, i.e., frequency, are set in log-log scale, following which is called a power-law distribution (Figure 9) (He *et al.*, 2010).

Figure 9. Non-oscillatory component in electrophysiology recordings (Donoghue *et al.*, 2020). Example of neural power spectrum with peaks of oscillatory activity and the corresponding non-oscillatory exponent.



It is often referred to as “1/f noise”, though it reflects different biological processes such as spiking neuronal activity (Manning *et al.*, 2009; Ray & Maunsell, 2011), the balance between excitation and inhibition (Gao *et al.*, 2017; Donoghue *et al.*, 2020), sensory stimulation (El Boustani *et al.*, 2009) or task performance (He, 2011). Non-oscillatory activity seems to be different between cortical and

subcortical structures, maybe due to cytoarchitectonic and functional differences (Bush *et al.*, 2024). Also, non-oscillatory components of neural activity change with age (Voytek *et al.*, 2015; Dave *et al.*, 2018), under sleep/anaesthesia conditions (Muthukumaraswamy & Liley, 2018; Colombo *et al.*, 2019; Miskovic *et al.*, 2019; Lendner *et al.*, 2020), across cortical regions (Muthukumaraswamy & Liley, 2018; Chaoul & Siegel, 2021) and even with respiration (Kluger *et al.*, 2023). However, the generative mechanisms of the non-oscillatory activity in the brain are not very clear (Buzsáki *et al.*, 2012), but it may be due to a combination of factors which include synaptic currents, cell membrane leaks and N-methyl-D-aspartate (NMDA) receptors binding (Gibb & Colquhoun, 1991; Wong & Wang, 2006; Miller *et al.*, 2009b).

With regard to PD, non-oscillatory components of neural activity have been studied within cortical and subcortical areas and in different conditions. At cortical level, non-oscillatory activity is altered compared to healthy controls (Rosenblum *et al.*, 2023; Vinding *et al.*, 2024), even across cortical regions (Helson *et al.*, 2023). Whether dopaminergic medication changes the non-oscillatory component of cortical activity in PD is still under debate, since published results are contradictory (Wang *et al.*, 2022; Helson *et al.*, 2023; McKeown *et al.*, 2024). At subcortical level, most studies are focused on subthalamic non-oscillatory activity. The slope of non-oscillatory activity within the STN is decreased by voluntary movement (Belova *et al.*, 2021), increases over time (Darmani *et al.*, 2022) and is informative of motor signs and predict the response to DBS in PD patients (Clark *et al.*, 2023). Moreover, DBS would increase the slope of non-oscillatory subthalamic activity in the short- and long-term (Darmani *et al.*, 2022; Wiest *et al.*, 2023). Related to dopamine levels, as it was seen at cortical level, there is still controversy about the effect of medication on subthalamic non-oscillatory activity (Darmani *et al.*, 2022; Kim *et al.*, 2022; Wiest *et al.*, 2023). These findings underscore the complexity of non-oscillatory neural activity and its modulation in PD, highlighting the need for further research to clarify its generative mechanisms and the effects of dopaminergic medication and DBS on cortical and subcortical dynamics.

2.6. Separating oscillatory and non-oscillatory components

The disambiguation of oscillatory activity from non-oscillatory components in electrophysiology recordings represents a great opportunity for investigating the two parts of neural activity separately. Typically, the main strategy is to identify the $1/f$ slope of the power spectrum, which would be the limit between oscillatory and non-oscillatory components. This approach is based on the assumption that power above the $1/f$ slope corresponds to oscillatory activity power. The easiest way to calculate the non-oscillatory slope is by simply fitting this $1/f$ exponent using linear regression in log-log (Gao *et al.*, 2017) or semi-log scale (Voytek *et al.*, 2015). Paradoxically, this strategy is susceptible to failure when oscillatory activity is present in the power spectra (Gerster *et al.*, 2022). More sophisticated algorithms were developed in recent years. Two of the most used algorithms in several studies nowadays are “fitting oscillations and one-over- f ”, or “FOOOF” (Donoghue *et al.*, 2020), and “irregular resampling auto-spectral analysis”, or “IRASA” (Wen & Liu, 2016) (Figure 10).

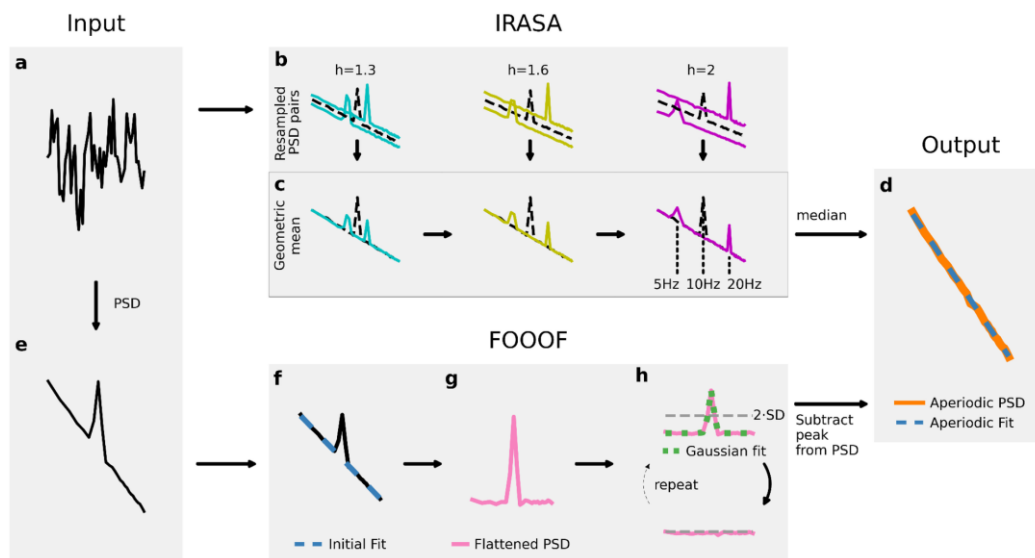


Figure 10. IRASA and FOOOF algorithms (Gerster *et al.*, 2022). Schematic representation of workflow pipelines for the algorithms “irregular resampling auto-spectral analysis” (IRASA) and “fitting oscillations and one-over- f ” (FOOOF).

Regarding FOOOF, first a linear robust fit of the $1/f$ exponent is calculated and subtracted from the power spectrum. Then, the method repeatedly applies Gaussian fits to each oscillatory component to create a model of the oscillatory part.

This model is then subtracted from the spectrum to isolate a purely aperiodic component which is again fitted, obtaining the final fit of the $1/f$ slope. On the other hand, IRASA is based on the fractal nature of non-oscillatory activity. Because of their fractal nature, non-oscillatory time series are resistant to the effects of resampling, while oscillatory components are significantly altered by it. IRASA leverages this difference to "remove" the periodic parts from a spectrum. The resulting, ideally pure, non-oscillatory spectrum can then be used to fit the $1/f$ slope.

By employing advanced algorithms like FOOOF and IRASA, it is possible to separate oscillatory and non-oscillatory components more accurately, providing a deeper understanding of neural activity. Nevertheless, these algorithms face several challenges when they are applied to real-world electrophysiology recordings and may not effectively separate both components (Gerster *et al.*, 2022). These limitations call for the development of alternative signal processing approaches, such as our novel Bayesian periodicity spectrum.

3. Materials and methods

This section outlines the experimental and analytical approaches used to investigate beta activity components in STN LFP recordings from PD patients. To complement these empirical observations, computational models were used to simulate and analyse beta activity under controlled conditions. Several analytical techniques were considered to investigate oscillatory and non-oscillatory components of beta activity, including our novel Bayesian periodicity spectrum which development is described in here.

3.1. Beta activity model details

The second-order autoregressive (AR(2)) model (Yule, 1927; Walker, 1931; Neumaier & Schneider, 2001) can be expressed as:

$$y_t = a_1 y_{t-1} + a_2 y_{t-2} + \varepsilon_t \quad (1)$$

where a_1 and a_2 are the AR(2) coefficients; y_t , y_{t-1} , and y_{t-2} are the values of the simulated signal y in time and ε_t is a white noise input with variance σ^2 . The input variance σ^2 is related to the output variance σ_y^2 through the following equation:

$$\sigma^2 = \frac{\sigma_y^2(1 + a_2)(1 - a_1 - a_2)(1 + a_1 - a_2)}{1 - a_2} \quad (2)$$

An AR(2) model can also be interpreted as an infinite impulse response (IIR) digital filter characterized by its two conjugate poles p_1 and p_2 :

$$p_1 = \rho e^{-j\theta 2\pi}, p_2 = \rho e^{j\theta 2\pi} \quad (3)$$

where ρ is the radius (from 0 to 1) and θ the normalized oscillation frequency.

In order to produce our AR(2) models, we needed to determine the conjugate poles p_1 and p_2 , from which we obtained the AR(2) coefficients a_1 and a_2 (from p_1

and p_2 using MATLAB function *zp2tf* and consequently the input noise variance σ^2 (from equation (2)) to create the simulated signal y_t , which is the oscillatory component of our simulated signals.

In the first part, when the simulations were performed in a model-driven fashion to establish correspondences between beta burst and spectral measures, we set the beta frequency to 15 Hz and the variance of the input noise to 1×10^{-2} mV². To modulate the oscillatory component in our simulated signals, we changed the radius of the poles from 0.81 to 0.99 units in steps of 0.02 units. To generate the non-oscillatory component, we used the MATLAB System object *dsp.ColoredNoise*, setting the inverse exponent to 1, i.e., pink noise. To modulate the variance of non-oscillatory component, we multiplied the normalized signals by a value from 0.1 to 0.9, in steps of 0.1, with the radius of the AR(2) fixed at 0.95 units.

Once the models were determined, we generated 1000 simulated signals per case in order to provide reliable estimates.

3.2. Non-oscillatory activity model details

We used the MATLAB System object *dsp.ColoredNoise* for the simulation of non-oscillatory activity in the validation of the periodicity spectrum. Further details about this methodology are provided below (see “Estimation of the periodicity spectrum” and “Estimation of the Bayesian periodicity spectrum”). In order to study periodicity in signals without oscillatory activity, we generated 100 signals (sampling frequency = 128 Hz) for each studied condition i.e., changing the variance of the signal, the 1/f slope and the signal duration. We used either the short-time Fourier transform (STFT) (window type = Hanning, window length = 128 samples, overlapping = 127 samples, number of DFT points = 128) or the continuous wavelet transform (CWT) (Morlet wavelet, 16 voices per octave) to decompose simulated signals.

In the first part, we set the signals’ amplitudes from 1 to 5 mV in steps of 1 mV (fixed values: signal duration = 60 seconds, 1/f^a slope = 1 mV²/Hz). In the second part, we modulated the decay of power in the frequency domain in simulated

signals i.e., the $1/f^\alpha$ slope of their power spectra, by gradually increasing the α value (inverse exponent of MATLAB System object *dsp.ColoredNoise*) from 0 to 2 mV^2/Hz in steps of 0.5 mV^2/Hz (fixed values: signal duration = 60 seconds, signal variance = 1 mV^2). In the third part, we changed the duration of simulated signals from 30 to 150 seconds in steps of 30 seconds (fixed values: signal variance = 1 mV^2 , $1/f^\alpha$ slope = 1 mV^2/Hz).

In the part where we provide the level of evidence of absence of oscillatory activity in simulated signals, we previously generated 1000 simulated signals following the same procedures previously reported for each case to obtain the asymptotic value $\Psi_{non-oscillatory}(f)$. In the case of real-world signals, i.e., STN LFP recordings from PD patients, we generated 1000 simulated signals (sampling frequency = 128 Hz) in slots of 100 signals with variable duration starting from the shortest signal duration in each case and ending for the longest signal duration in 10 steps, increasing signal duration by the same length. Normalized periodicity spectra $\Psi_{norm}(f)$ is calculated as the mean periodicity from the 10 steps.

For periodicity estimation, we iteratively median-filtered instantaneous frequency traces, using ten time windows from 10 ms to 100 ms and increasing the window width by 10 ms each iteration in all cases. Also, we divided instantaneous frequency traces in segments of 1 s.

3.3. Oscillatory activity model details

Conversely, oscillatory activity in simulated signals was generated through different means in order to validate the periodicity spectrum. Further details about this methodology are provided below (see “Estimation of the periodicity spectrum” and “Estimation of the Bayesian periodicity spectrum”). We modelled continuous oscillatory activity using AR(2) models and sinusoid functions. In the case of autoregressive models, the amount of oscillatory activity is modulated by changing the radius of the conjugated poles that characterize the AR(2) modelling. On the other hand, when sinusoid functions were used to add oscillatory activity, we modulated the amplitude of the sinusoid. In all simulations where only one

oscillatory component is present, we set the frequency of the oscillatory activity at 15 Hz.

Previous to the analysis of periodicity of oscillatory activity we simulated 1000 signals comprised only of non-oscillatory activity (sampling frequency = 128 Hz) using the MATLAB System object *dsp.ColoredNoise* to obtain the asymptotic value $\Psi_{non-oscillatory}(f)$. In order to study periodicity in signals with oscillatory activity, we generated 100 signals (sampling frequency = 128 Hz) using MATLAB System object *dsp.ColoredNoise* for the simulation of non-oscillatory activity and adding oscillatory activity for each studied condition i.e., changing the variance of the non-oscillatory component and of the oscillatory component, and the level of oscillatory activity in signals i.e., the decay rate of the oscillatory component, modulated from the radius of the pole in the AR(2) process.

In the first part, we set the non-oscillatory component amplitude from 1 to 5 mV in steps of 1 mV, using sinusoid functions to simulate oscillatory activity (fixed values: signal duration = 60 seconds, $1/f^\alpha$ slope = 1 mV²/Hz, sinusoid variance = 0.25 mV²). In the second part, we modulated the variance of the oscillatory component by changing the amplitude of sinusoids from 0.2 to 1.0 mV in steps of 0.2 mV (fixed values: signal duration = 60 seconds, non-oscillatory component variance = 1 mV², $1/f^\alpha$ slope = 1 mV²/Hz). In the third part, we modelled oscillatory activity using AR(2) modelling, and we changed the level of oscillatory activity in simulated signals by changing the radius of the AR(2) process from 0.91 to 0.99 units in steps of 0.02 units, and fixing the power peak value to 1 mV² (fixed values: signal duration = 60 seconds, non-oscillatory component variance = 1 mV², $1/f^\alpha$ slope = 1 mV²/Hz).

In the part where two oscillatory components are present in simulated signals, we generated 100 signals (sampling frequency = 128 Hz) using MATLAB System object *dsp.ColoredNoise* for the simulation of non-oscillatory activity (fixed values: signal duration = 60 seconds, $1/f^\alpha$ slope = 1 mV²/Hz), and changing oscillatory activity the level of oscillatory activity of the two components using the same radius of the AR(2) processes, from 0.85 to 1 units in steps of 0.01 units. We evaluated the minimum radius that allowed to discriminate the two oscillatory

peaks in both power and periodicity spectra, setting the difference between central frequencies from 1 to 3 Hz in steps of 0.2 Hz around 15 Hz.

We also used either the STFT (window type = Hanning, window length = 128 samples, overlapping = 127 samples, number of DFT points = 128) or the CWT (Morlet wavelet, 16 voices per octave) to decompose simulated signals. For periodicity estimation, we iteratively median-filtered instantaneous frequency traces, using ten time windows from 10 ms to 100 ms and increasing the window width by 10 ms each iteration. Also, we divided instantaneous frequency traces in segments of 1 s.

3.4. Subthalamic LFP recordings from PD patients: HM CINAC

These datasets and their associated information were already published (Pardo-Valencia *et al.*, 2024). We recorded post-operative LFPs from 21 PD patients (18 men, 3 women) who underwent surgery for DBS implantation. We performed bilateral recordings in 12 patients and unilateral recordings in nine. We collected two datasets: (1) in all patients ($n = 33$ nuclei) we recorded STN LFPs off medication; (2) in 13 patients ($n = 21$ nuclei) we also recorded STN LFPs on medication. Clinical details of these patients are provided in Table 1. Details about electrodes implanted, contacts analysed in each patient and beta peak frequencies detected for the analyses are provided in Table 2.

Table 1. Clinical details (HM CINAC)

Patient	Gender	Age (years)	Disease duration (years)	LEDD (mg)	Pre-op UPDRS-III off/on	Pre-op UPDRS-III MAS/LAS off	Post-op UPDRS-III MAS/LAS off
HM1	M	60	4	650	30/18	12/7	9/10
HM2	M	44	6	1006	34/21	9/9	10/9
HM3	F	70	11	970	36/14	12/9	16/14
HM4	M	45	5	2308	55/11	22/20	12/9
HM5	M	37	4	930	32/10	14/12	12/4
HM6	M	68	14	2484	42/13	13/12	15/11

HM7	M	64	9	1336	26/19	-/-	-/-
HM8	M	46	12	400	59/39	25/17	5/3
HM9	M	52	14	1060	25/8	10/7	12/11
HM10	M	56	7	955	53/45	22/20	15/6
HM11	F	44	6	985	34/8	9/9	7/7
HM12	M	58	15	976	19/2	8/6	6/0
HM13	M	69	8	1231	62/28	19/15	18/12
HM14	M	61	15	1212	47/37	22/19	21/18
HM15	M	60	7	1264	18/4	10/3	7/1
HM16	M	70	20	1488	38/20	8/8	15/13
HM17	F	58	20	2017	50/13	21/17	10/6
HM18	M	57	11	1050	25/13	15/7	-/-
HM19	M	64	5	1440	28/9	12/9	-/-
HM20 ^a	M	53	12	1380	39/17	18/11	-/-
HM21	M	50	6	1060	35/7	16/9	-/-
Mean ± SD		56.5 ± 9.6	10.0 ± 4.9	1247.7 ± 500.8	37.5 ± 12.8/17.0 ± 11.6	14.9 ± 5.4/11.3 ± 5.0	11.9 ± 4.6/8.4 ± 4.9

^aAll patients with LFP recordings in the on state received levodopa, except for this patient who received apomorphine.

M = male, F = female, Pre-op = preoperative, Post-op = postoperative, LEDD = levodopa equivalent daily dose, UPDRS = Unified Parkinson's disease rating scale, MAS = more affected side, LAS = less affected side

Table 2. Electrophysiological recordings details (HM CINAC)

Patient	Electrode	Selected contact (MA STN/LA STN)	Beta peak frequency (Hz) (MA STN/LA STN)	Off recording (s) (MA STN/LA STN)	Off/on recording (s) (MA STN/LA STN)
HM1	4-contacts	1-2/0-1	17/17	100/100	100/100
HM2	4-contacts	1-2/2-3	13/13	200/200	200/200
HM3	8-contacts	7-8/-	18/-	200/-	-/-
HM4	8-contacts	3-4/-	17/-	78/-	78/-
HM5	Directional	1-3/-	20/-	70/-	-/-
HM6	Directional	8-6/-	13/-	118/-	-/-
HM7	Directional	1-4/1-4	13/13	200/200	-/-

HM8	Directional	1-2/1-3	13/13	94/94	-/-
HM9	Directional	8-7/8-6	15/14	200/80	200/80
HM10	Directional	1-4/1-2	13/16	66/66	-/-
HM11	Directional	8-5/1-4	13/14	121/121	121/121
HM12	Directional	1-2/1-2	13/13	170/170	170/170
HM13	4-contacts	2-3/1-2	16/14	200/120	200/-
HM14	4-contacts	0-1/-	26/-	200/-	-/-
HM15	4-contacts	0-1/0-1	17/24	200/100	200/-
HM16	4-contacts	1-2/2-3	16/16	110/110	60/60
HM17	4-contacts	2-3/2-3	17/13	190/-	190/190
HM18	8-contacts	3-4/-	27/-	200/-	-/-
HM19	4-contacts	2-3/1-2	13/15	100/100	200/200
HM20	4-contacts	2-3/-	16/-	180/-	180/-
HM21	Directional	2-3/-	16/-	75/-	75/-
Mean $\pm$ SD			16.3 $\pm$ 4.0/15.0 $\pm$ 3.0	146.3 $\pm$ 54.1/121.8 $\pm$ 44.5	151.8 $\pm$ 56.0/140.1 $\pm$ 56.8

MA STN = more affected subthalamic nucleus (contralateral to the more affected side), LA STN = less affected subthalamic nucleus (ipsilateral to the more affected side).

All patients met CAPSIT criteria (Defer *et al.*, 1999): a diagnosis of idiopathic PD, at least 5 years' disease duration (this criterion was relaxed for two highly fluctuating patients with 4 years' disease duration), at least 33% decrease of the third part of the UPDRS, or UPDRS-III, to levodopa challenge (note that in Table 1, three patients display a slightly lower response at the formal pre-operative clinical evaluation, but they were included due to their good response to levodopa at previous evaluations), no cognitive deterioration, severe depression or major behavioural disorder. Patients were referred to DBS in order to manage motor fluctuations and they underwent DBS surgery for bilateral STN stimulation at Hospital Clínico San Carlos. All patients gave written informed consent, and all procedures were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee at Hospital Clínico San Carlos (internal code 13/316).

The motor STN area was accurately identified by tractographic projection from the motor cortex to the nucleus using a computed tomography (CT)–magnetic resonance imaging (MRI) fusion-based technique (Framelink software 5, and advanced visualization and planning application Stealthviz, Medtronic Iberica, Madrid, Spain) and through intraoperative microelectrode recordings and micro/macro stimulation (Fernández-García *et al.*, 2022). Emphasis was placed on best defining the dorsolateral region of the STN. Patients were implanted with either four-contact leads (model 3389, Medtronic, Minneapolis, MN, USA), or eight-contact leads (Vercise DBS Lead, Boston Scientific, Valencia, CA, USA), or directional leads (Vercise Cartesia Directional Lead, Boston Scientific, Valencia, CA, USA). Definitive placement of leads was assessed by postoperative volumetric CT, which was then fused to preoperative MRI. The leads were not initially connected to the pulse generator, to allow LFPs to be recorded postoperatively.

Bipolar LFP recordings were performed 3–5 days later, using custom-made external connections, with a bipolar montage between adjacent contacts (4-contact and 8-contact leads) or between the lowest ring electrode and every inferior segmented electrode and between the highest ring electrode and every superior segmented electrode (directional leads). Recordings were performed at rest, after overnight withdrawal of dopaminergic medication ($n = 21$ patients), before and after administration of 200–375 mg oral fast-acting levodopa ($n = 12$ patients) or 3 mg of apomorphine ($n = 1$ patient). LFPs were filtered (0.5–1,000 Hz/1–3,000 Hz) and amplified (10,000/100,000) with a D360 amplifier (Digitimer, Welwyn Garden City, UK) and then sampled (5 kHz/10 kHz) using a CED 1401 plus A/D converter (Cambridge Electronic Design, Cambridge, UK). Since three types of DBS electrodes were implanted, depending on the patient, only the contact pair with the highest mean power in the beta band in the off state was used for the analyses.

Before any signal processing, artifact removal in STN LFPs from the HM CINAC dataset was done by visual inspection using Spike2 software (Cambridge Electronic Design). Further analyses were performed using MATLAB (version R2021a, The MathWorks, Natick, MA, USA). All LFPs were normalized by dividing each signal by the square root value of its 460–490 Hz spectral power

(conceptually similar to previous works (Foffani *et al.*, 2003; Priori *et al.*, 2004)). This normalization is intended to eliminate at least some of the non-biological contributions to non-oscillatory activity, i.e., multiplicative factors such as differences in gain/impedance, while maintaining the possible biological contributions, e.g., biological 1/f noise. Normalized LFPs were then bandpass filtered at 1–90 Hz and resampled at 200 Hz.

3.5. Subthalamic LFP recordings from PD patients: NeuroRestore

This dataset consists of 29 patients with Parkinson’s disease (20 men, 9 women) who had DBS leads implanted bilaterally (Medtronic 3389) whose STN LFPs were recorded 2–9 days after surgery, thus obtaining a dataset of 58 recorded nuclei. All patients were implanted with a Percept PC stimulator (Medtronic, USA) in the right abdominal area, and were recorded using the sensing capabilities offered by the device. Patients were predominantly in the off-medication condition (>12h), although depending on their severity, some of them may retained some dopamine agonist medication. Clinical details of these patients are provided in Table 3.

Table 3. Clinical details (NeuroRestore)

Patient	Gender	Age (years)	Disease duration (years)	More affected side	LEDD pre-op (mg)	Phenotype	Pre-op UPDRS-III off/on
NR1	M	73	6	Left	723	AR	31/25
NR2	M	73	20	Left		AR	40/18
NR3	M	64	13	Right	1490	AR+T	32/8
NR4	F	73	11	Left	800	TD	25/3
NR5	M	56	12	-	1450	-	-/3
NR6	F	60	6	Right	437	TD	36/9
NR7	F	56	8	Right	700	AR+T	35/11
NR8	F	75	17	Right	491	AR	-/22
NR9	M	67	10	Right	1600	AR	22/7
NR10	M	65	4	Right	774	-	-/-

NR11	M	59	9	Right	1400	AR	17/4
NR12	M	71	9	Left	1208	AR+T	36/6
NR13	M	58	7	Left	0	AR+T	20/-
NR14	F	45	12	Right	1698	AR	40/17
NR15	M	68	5	Left	625	AR	34/20
NR16	M	67	-	Both	250	AR	49/8
NR17	M	58	17	Both	2160	AR+T	40/10
NR18	M	63	10	Left	1650	AR	53/32
NR19	M	55	8	Left	1862	AR+T	54/18
NR20	F	61	5	Right	750	AR+T	-/-
NR21	M	72	7	Right	875	AR+T	-/28
NR22	F	69	9	-	1615	AR	67/22
NR23	F	71	9	-	1313	AR+T	48/16
NR24	M	69	8	-	819	AR+T	-/-
NR25	M	-	17	-	1049	AR	49/16
NR26	F	60	10	-	941	AR+T	47/11
NR27	M	74	8	Left	1738	AR	37/19
NR28	M	63	17	Right	1667	AR	24/8
NR29	M	62	11	Right	1300	AR	-/-
Mean $\pm$ SD		64.5 $\pm$ 7.2	10.2 $\pm$ 4.2		1120.9 $\pm$ 537.6		38.9 $\pm$ 12.1/12.8 $\pm$ 8.0

M = male, F = female, Pre-op = preoperative, LEDD = levodopa equivalent daily dose, UPDRS = Unified Parkinson's disease rating scale, AR = akinetic-rigid, AR+T = akinetic-rigid with tremor, TD = tremor-dominant

According to the NeuroRestore centre procedures (Thenaisie *et al.*, 2022), lead localization was computed using the processing pipeline in the Lead-DBS MATLAB toolbox (Horn & Kühn, 2015; Horn *et al.*, 2019), using pre-operative T1 and T2-weighted MRIs and a post-operative CT-scan as inputs. The post-operative CT scan was linearly co-registered with the pre-operative MRI using Advanced Normalization Tools, or ANTs (Avants *et al.*, 2011). Co-registrations were visually inspected and manually adjusted if necessary. A brain shift correction was performed as implemented in Lead-DBS. Pre-operative volumes were used to achieve precise multi-spectral normalization to the ICBM 2009b NLIN asymmetric

space (Fonov *et al.*, 2009) via ANTs SyN Diffeomorphic Mapping (Avants *et al.*, 2008), using the “effective: low variance default + subcortical refinement” preset. DBS contacts were initially reconstructed with the phantom-validated, fully automated PaCER method (Husch *et al.*, 2017) and subsequently verified on an individual basis.

STN LFPs were recorded at a sampling frequency of 250 Hz in both off and on continuous DBS conditions. The duration of the recordings was paired between DBS conditions for both nuclei of each patient. Further details can be found in Table 4. Recordings at rest were performed in the *BrainSense Streaming* mode, which is restricted to one contact pair per hemisphere. Prior to the first recording session with each patient, they performed a *BrainSense Survey* and visually inspected the power spectral density (PSD) of each pair. They also determined the contact and intensity which provide the best motor improvement in PD patients. The recording contact pair was selected using the contacts immediately above and below the active contact. They further ensured that the selected contact pair was not labelled as “artefacted” by the system. Finally, the synchronization with external devices was performed by applying a transient DBS burst (130Hz, 60us, 1mA) at both the beginning and the end of each recording, which induced artifacts in an external electromyographic sensor placed on the chest of the patient, in the vicinity of the implantable pulse generator (IPG) (Thenaisie *et al.*, 2021).

Table 4. Electrophysiological recordings details (NeuroRestore)

Patient	Active contact (Left STN/Right STN)	Selected contact (Left STN/Right STN)	Beta peak frequency (Hz) (Left STN/Right STN)	Off/on recording (s) (Left STN/Right STN)
NR1	2/2	1-3/1-3	17/15	129/129
NR2	2/2	1-3/1-3	15/17	71/71
NR3	2/2	1-3/1-3	19/15	63/63
NR4	1/1	0-2/0-2	15/15	62/62
NR5	2/2	0-3/1-3	15/16	68/68
NR6	2/2	1-3/1-3	21/14	122/122
NR7	2/2	1-3/1-3	15/15	132/132
NR8	2/2	1-3/1-3	20/18	128/128

NR9	2/2	1-3/1-3	15/28	125/125
NR10	2/2	1-3/1-3	17/18	123/123
NR11	1/1	0-2/0-2	14/15	123/123
NR12	2/2	0-3/1-3	14/23	45/45
NR13	1/1	0-2/0-2	16/15	123/123
NR14	1/1	0-2/0-2	23/14	101/101
NR15	2/2	1-3/1-3	23/14	63/63
NR16	1/1	0-2/0-2	16/16	59/59
NR17	1/1	0-2/0-2	15/14	40/40
NR18	1/1	0-2/0-2	18/15	76/76
NR19	1/1	0-2/0-2	14/14	98/98
NR20	2/2	1-3/1-3	21/22	78/78
NR21	2/2	1-3/1-3	25/28	60/60
NR22	2/2	1-3/1-3	14/14	60/60
NR23	2/2	1-3/1-3	24/25	47/47
NR24	2/2	1-3/1-3	26/14	58/58
NR25	2/2	1-3/1-3	22/15	51/51
NR26	2/1	1-3/0-2	20/20	53/53
NR27	2/2	1-3/1-3	15/18	54/54
NR28	2/2	1-3/1-3	14/15	62/62
NR29	1/1	0-2/0-2	30/19	54/54
Mean $\pm$ SD			18.4 $\pm$ 4.4/17.3 $\pm$ 4.1	80.3 $\pm$ 31.4/80.3 $\pm$ 31.4

STN = Subthalamic nucleus.

3.6. Spectral analysis in the frequency domain

All power spectra used to measure beta peak power, sharpness of the beta peak, and oscillatory and non-oscillatory power were estimated using Welch's method (Welch, 1967) using a 1-s window with zero overlap. We used two direct power spectrum measures to quantify beta oscillations: (1) the beta peak power, i.e., the maximum power value of the spectral peak, and (2) a new metric that we called "sharpness" of the peak, calculated by simply dividing the peak power by the total spectral power of the beta-filtered signal (or equivalently of the ± 3 Hz band

around the peak in the frequency domain). This spectral sharpness intuitively assesses how close is a spectral peak to the limit case of a pure sinusoid (sharpness = 1). This measure was computed with power spectrum values in mV^2 , and then log-transformed by adding 1 and applying the natural logarithm. We have chosen to use the peak power because it is less dependent on the signal filtering or the exact beta band definition.

We also used two decomposed power spectrum measures: (1) the oscillatory component and (2) the non-oscillatory component of the beta peak. We specifically applied the FOOOF method (Donoghue et al., 2020) to fit the $1/f$ noise-like non-oscillatory component eliminating the peaks of the power spectrum in semi-log scale from 1 to 95 Hz. The resulting function, which models the non-oscillatory $1/f$ noise-like component, represents the boundary between the non-oscillatory power and the oscillatory power of the beta peak. From the same function we also extracted the exponent of the $1/f$ slope. Further details about the beta peak power decomposition and sensitivity analysis are provided below (see “FOOOF details”).

3.7. Beta burst analysis in the time domain

We used two main measures to quantify beta bursts in the time domain: burst amplitude and burst duration. In order to extract beta bursts, we followed the same methodology used by Tinkhauser and colleagues (Tinkhauser *et al.*, 2017*a*, 2017*b*). This methodology is based on amplitude thresholds, which are defined as percentiles of the rectified amplitude distributions. For this study, the 75th percentile of the corresponding amplitude distributions was set as threshold in all cases. When signals were analysed in both off and on therapeutic conditions, the beta peak off medication was used to define the beta range for both off and on conditions, and the same amplitude threshold was applied to extract beta bursts across conditions, i.e., the mean of the 75th percentile of both off and on amplitude distributions. Beta bursts were characterized as the number of wavelet amplitude values from a signal, either recorded or simulated, surpassing the defined amplitude threshold. Bursts with duration shorter than 100 ms were not studied to limit the possible contribution of noise. We thus quantified the average values

of burst amplitude and burst duration in each recorded or simulated signal. Throughout the thesis, for each recorded or simulated beta oscillations, average burst amplitude and average burst duration are simply referred to as burst amplitude and burst duration, unless otherwise specified. Additionally, we also studied burst duration distributions, dividing them into eight time windows of 100 ms, starting from 100 ms to 900 ms, and a ninth time window which includes burst duration greater than 900 ms.

In order to study beta bursts in each STN, the beta peak frequency was determined as the one corresponding to the highest peak of the power spectrum in the beta band during the off state. LFPs were then bandpass filtered around the beta peak frequency, using a bandwidth of ± 3 Hz. We refer to the resulting signal as “recorded beta oscillations”. Consistent with (Tinkhauser *et al.*, 2017b), the instantaneous beta power amplitude of the beta-filtered signals was obtained using a Wavelet transformation (ft_specest_wavelet script in Fieldtrip – Morlet Wavelet, width = 10, gwidth = 5; (Oostenveld *et al.*, 2011)). Wavelet amplitudes were then smoothed using a moving average filter of 0.2 s and DC corrected by subtracting the very same signal filtered with a moving average filter of 20 s, to adjust signals for baseline shifts and eliminate slow fluctuations.

3.8. FOOF details

To decompose the beta peak power into oscillatory and non-oscillatory beta power, we followed the FOOF method (Donoghue *et al.*, 2020). According to this method, the PSD can be expressed as the sum of a non-oscillatory component and one or more peaks, which represent the oscillatory activity:

$$PSD = L + \sum_{n=0}^N G_n \quad (4)$$

where L is the non-oscillatory component and G_n represents one or more (N) Gaussian distributions, which are the peaks. The non-oscillatory component is modelled as a Lorentzian function:

$$L = b - \log(k + F^x) \quad (5)$$

where b is the offset, k is a parameter for the bending in the non-oscillatory component and χ is the exponent at which the PSD decays as a function of frequency F . We consider the slope of the non-oscillatory component as the negative value of the exponent χ .

On the other hand, the Gaussian distributions that are used to model the peaks are characterized by their mean and standard deviation. The mean of each distribution corresponds to their peak frequency, whereas the standard deviation is estimated from the full width, half-maximum (FWHM) around the peak, dividing this value by $2\sqrt{2\log(2)}$. The distributions are multiplied by a factor a , which is the power of the peak in logarithmic scale.

The FOOOF method is an iterative process, which we adapted to our data following the recommendations provided by Gerster and colleagues (Gerster *et al.*, 2022). First, we modelled the non-oscillatory component in semi-log scale, i.e. power spectral density in logarithmic scale, frequencies in linear scale between 1 and 95 Hz. We did not consider the frequencies between 13 and 60 Hz in the case of the HM CINAC dataset (beta band activity and line noise) and frequencies between 13 and 35 Hz in the NeuroRestore dataset for they could bias our first estimations. Once the non-oscillatory component was modelled, we subtracted it from the original power spectrum, obtaining a residual. Now we identified spectral peaks between 13 and 40 Hz that surpassed a certain threshold, which in this study was set to the mean of this residual plus its standard deviation. If a peak was detected, it was modelled as a Gaussian distribution and then subtracted from the residual, resetting the threshold. This process was repeated until there was no peak that could be detected. The Gaussian distributions that were modelled were subtracted to the original power spectrum, and then the non-oscillatory component was modelled again. In this second estimation we included all frequencies between 1 and 95 Hz except for the line noise band present in the recordings of the HM CINAC dataset, between 40 and 60 Hz.

In the control sensitivity analysis about non-oscillatory component and the $1/f$ slope between medication conditions, we estimated the $1/f$ slope linearly, similar to other works (Martin *et al.*, 2018). We modelled the power spectrum on a

log–log scale, i.e., power spectral density and frequencies on a logarithmic scale, by fitting a linear function:

$$L = k_1 + k_2 \log(F) \quad (6)$$

where k_1 is the offset and k_2 is the $1/f$ slope.

3.9. Estimation of the periodicity spectrum

For the practical implementation of the periodicity spectrum, the first step is to decompose the time series $s(t)$ into its distinct frequency components, using the STFT, the CWT or any other time-frequency decomposition (Figure 11A). For illustration purposes, we also show the inverse transform $z_f(t)$ of a representative frequency component (Figure 11B), as well as the instantaneous amplitude and imaginary part, i.e., the Hilbert transform $H[z_f(t)]$ (Hilbert, 1912) of the corresponding analytic signal (Figure 11C). For each frequency f , the instantaneous phase $\phi_f(t)$ is extracted directly from the time frequency decomposition (or alternatively from the corresponding analytic signal) (Figure 11D). The instantaneous frequency $f_{inst}(t)$ for frequency f is then calculated as the time derivative of the unwrapped instantaneous phase and expressed in Hz based on the sampling frequency F_s (Figure 11E), i.e.,

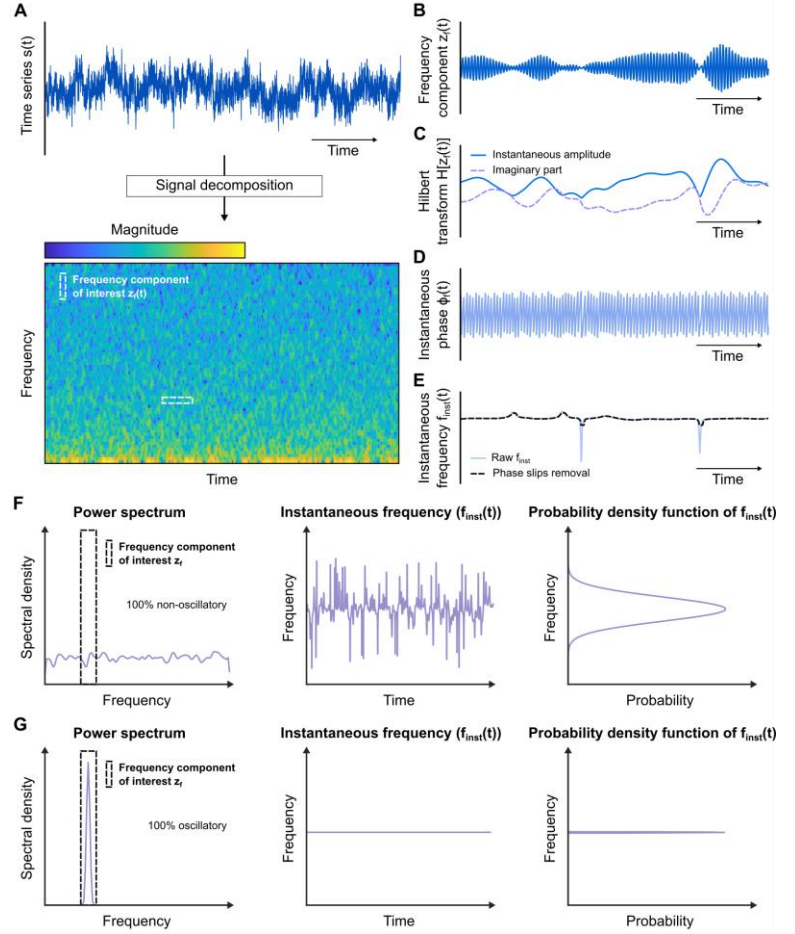
$$f_{inst}(t) = \frac{\Delta(\text{unwrap}(\phi_f(t)))}{2\pi \Delta t} \quad (7)$$

where Δt is the sampling period, i.e., the inverse of the sampling frequency F_s . It is crucial to rectify $f_{inst}(t)$ if needed, particularly in frequencies close to the Nyquist limit. We evaluated instantaneous frequency traces for sudden changes ($\pm 2\pi$ multiplied by F_s), and depending on the direction of the jump, i.e., positive or negative, we rectified $f_{inst}(t)$ by either adding or subtracting 2π multiplied by F_s from the jump location to the end of the trace. This process is done iteratively from beginning to end of $f_{inst}(t)$, since we could find several instantaneous frequency jumps in a single trace. To ensure stabilization of the instantaneous frequency variance throughout frequencies, positive and negative spikes of instantaneous frequency due to phase slips (Hurtado *et al.*, 2004) should be eliminated by

recurrently applying median filtering to the instantaneous frequency traces, increasing the window size with each iteration (Cohen, 2014) (Figure 11E).

Figure 11. Periodicity spectrum.

A, Time series $s(t)$ decomposed into their different frequency components. B, Portion example of a random frequency component $z_f(t)$. C, Instantaneous amplitude and imaginary part of the Hilbert transform function of $z_f(t)$. D, Instantaneous phase $\phi_f(t)$ from $z_f(t)$. E, Instantaneous frequency $f_{inst}(t)$ before and after phase slips removal (iterative median-filtering). F and G, Power spectra, and instantaneous frequencies and the corresponding probability density functions of the same frequency component from a simulated gaussian noise signal and a simulated sinusoidal signal, respectively.



The periodicity spectrum is based on the variability (variance) of the resulting instantaneous frequency $Var(f_{inst}(t))$. Intuitively, $Var(f_{inst}(t))$ at a certain frequency – assuming non-positive second derivative in the power spectrum at that frequency – would be maximum for a random noise (100% non-oscillatory, Figure 11F), whereas it would be zero for a pure sinusoid (100% oscillatory, Figure 11G). To maintain the intuitive convention of greater values indicating more oscillatory activity, we define periodicity as the multiplicative inverse of $Var(f_{inst}(t))$, logarithm-transformed to ensure normality.

Note that the estimation of the periodicity spectrum is affected by several factors that do not depend on the time series, such as the frequency decomposing methodology, the time-frequency resolution of such methodology, or the recursive

median filtering for phase slips removal. These factors must be considered when comparing between different time series or when interpreting the periodicity spectrum.

3.10. Estimation of the Bayesian periodicity spectrum

For the estimation of the Bayesian periodicity spectrum, the time series $s(t)$ is divided into n segments, the periodicity $\Psi_i(f)$ is estimated for each segment i , and $BF_\Psi(f)$ is estimated from the Bayes factor BF_{+0} of a directional one sample t-test between $\Psi_i(f)$ against zero, considering segments as samples.

Specifically, we used the general equation for the Bayes factor based on the observed data d proposed by Rouder and colleagues (Rouder *et al.*, 2009, 2012) founded on the works of Jeffreys (Jeffreys, 1998), and Zellner and Siow (Zellner & Siow, 1980), which was later extended by Gronau, Ly and Wagenmakers (Gronau *et al.*, 2020), which can be used in one-sample and two-samples t-tests by adjusting the corresponding parameters for each case:

$$BF_{10}(d) = \frac{\int T_\nu(t | n_\delta \delta) \pi(\delta) d\delta}{T_\nu(t)} \quad (8)$$

where t is the observed t-value, $T_\nu(t | a)$ represents the probability density function of a t-distribution with ν degrees of freedom and a non-centrality parameter a (in this case, $a = n_\delta \delta$), n_δ is the sample size (one-sample t-test) or the effective sample size (two-sample t-test), δ is the effect size, $T_\nu(t)$ is the probability density function of a standard t-distribution with ν degrees of freedom, and $\pi(\delta)$ is the prior distribution of the effect size δ , which is set as a zero-centered normal distribution with variance σ_δ^2 distributed as an inverse chi-square probability density function with one degree of freedom. The choice of the inverse chi-square for the prior distribution on σ_δ^2 is made in order to obtain a Cauchy prior distribution on the effect size δ (Rouder *et al.*, 2009). The current standard for Bayesian statistics is a zero-centred Cauchy prior with scale parameter γ equal to $1/\sqrt{2}$ (Gronau *et al.*, 2020). In Bayesian statistics it is allowed (and recommended) to include prior knowledge to the hypothesis testing, particularly regarding the

direction of the expected effect (Keyzers *et al.*, 2020). We thus adapted equation (8) to obtain the directional Bayes factor (Morey & Wagenmakers, 2014):

$$BF_{\pm 0}(d) = k \frac{\int T_v(t | n_\delta \delta) \pi(\delta) d\delta}{T_v(t)} \quad (9)$$

where k is $(2 - p)$ if the Bayes factor is right-sided (BF_{+0} , $\delta > 0$) or p if it is left-sided (BF_{-0} , $\delta \leq 0$). The parameter p is the two-sided p-value of the corresponding t-test. For the Bayesian periodicity spectrum $BF_\Psi(f)$ we used the right-sided version of equation (9).

At the population level, the single Bayesian periodicity spectra obtained for individual time series can be multiplied across time series at the same frequency to obtain population Bayes factors (Ly *et al.*, 2019) and then dividing the obtained Bayes factors by the number of time series evaluated.

When comparing the periodicity between two populations y_1 and y_2 , we performed a Bayesian two-samples t-test for each frequency component, being the effective sample size $n_\delta = (1/n_1 + 1/n_2)^{-1}$ and setting the prior knowledge (BF_{+0} or BF_{-0}) according to each case.

Evidence in favour of alternative hypothesis ($BF > 1$) or of the null hypothesis ($BF < 1$) is described according to standard levels: anecdotal ($1/3 < BF < 3$), moderate ($<1/3$ or >3), strong ($<1/10$ or >10), very strong ($<1/30$ or >30), and extremely strong ($<1/100$ or >100). We represented the values of the Bayesian periodicity spectrum using the logarithm with the base of 10 in order to improve the visualization of the results.

3.11. Statistics

All analyses were performed with Bayesian statistics (Keyzers *et al.*, 2020) using JASP statistical software (version 0.14.1.0; JASP Team, 2020). Correlations between measures were assessed with either Pearson or Kendall correlation coefficient and reported using the one-tailed Bayes factor BF_{+0} . Comparisons between therapeutic states, i.e., off vs. on medication and off vs. on DBS, were performed with Bayesian t-tests, using default effect size priors (Cauchy scale 0.707), and results are reported using the one-tailed Bayes factor BF_{-0} expressing

the likelihood ratio between the alternative hypothesis and the null hypothesis. Note that one-tailed testing is typically preferred in Bayesian statistics because it provides a faired balance between the ability to support the null or the alternative hypothesis (Keysers *et al.*, 2020). Bayesian analyses of variance (ANOVAs) were conducted with default priors, and effects are reported as the Bayes factor for the inclusion of a particular effect (BF_{incl}), calculated as the ratio between the likelihood of the data given the model with vs. the next simpler model without the effect, comparing across matched models. In the dataset of LFPs recorded both off and on DBS, we performed two-way repeated-measures ANOVAs, with two levels reflecting the clinical phenotype of PD patients (PHENOTYPE: AR vs. AR+T) and the DBS therapy factor (DBS: off vs. on). Evidence in favour to alternative hypothesis ($BF > 1$) or to the null hypothesis ($BF < 1$) is described according to standard levels: anecdotal ($1/3 < BF < 3$), moderate ($< 1/3$ or > 3), strong ($< 1/10$ or > 10), very strong ($< 1/30$ or > 30), and extremely strong ($< 1/100$ or > 100).

4. Signal processing principled framework

This section presents the outcomes of analysing beta activity in simulated signals, which served as a controlled environment to test and refine our signal processing approaches. The insights from these analyses led to the development of a principled framework for accurately studying oscillatory and non-oscillatory components of beta activity from PD patients.

4.1. Modelling of oscillatory and non-oscillatory beta activity

We first simulated beta activity in a model-driven fashion by combining AR(2) models with additive $1/f$ non-oscillatory noise to understand how conventional measures of beta band activity, i.e., beta bursts and power spectrum, would be affected by a modulation of oscillatory and/or non-oscillatory components. More details are provided in the methods (see “Beta activity model details”). We separately manipulated the oscillatory component, i.e., the radius of the AR(2) poles, and the non-oscillatory component, i.e., the variance of the $1/f$ noise, of simulated beta activity and investigated the impact of these manipulations on beta burst measures and spectral measures. We further validated this modelling of subthalamic beta activity, i.e., the sum of a $1/f$ noise and an oscillatory signal, in actual STN LFP recordings from PD patients (See “Validation of beta activity modelling” in the annexes).

Subthalamic beta activity in LFPs from PD patients is typically measured using either classical spectral measures in the frequency domain or more recent measures of beta burst dynamics in the time domain. It is often assumed, explicitly or implicitly, that those measures of beta activity provide different pathophysiological information. We found that in our simulations both burst amplitude and burst duration increased when increasing the oscillatory

component of beta activity (Figure 12A and B). Conversely, when increasing the non-oscillatory component of beta activity (Figure 12C) only burst amplitude increased, whereas burst duration remained essentially unchanged (Figure 12D). These results show that burst duration is specifically sensitive to oscillatory activity, whereas burst amplitude is sensitive to both oscillatory and non-oscillatory activity.

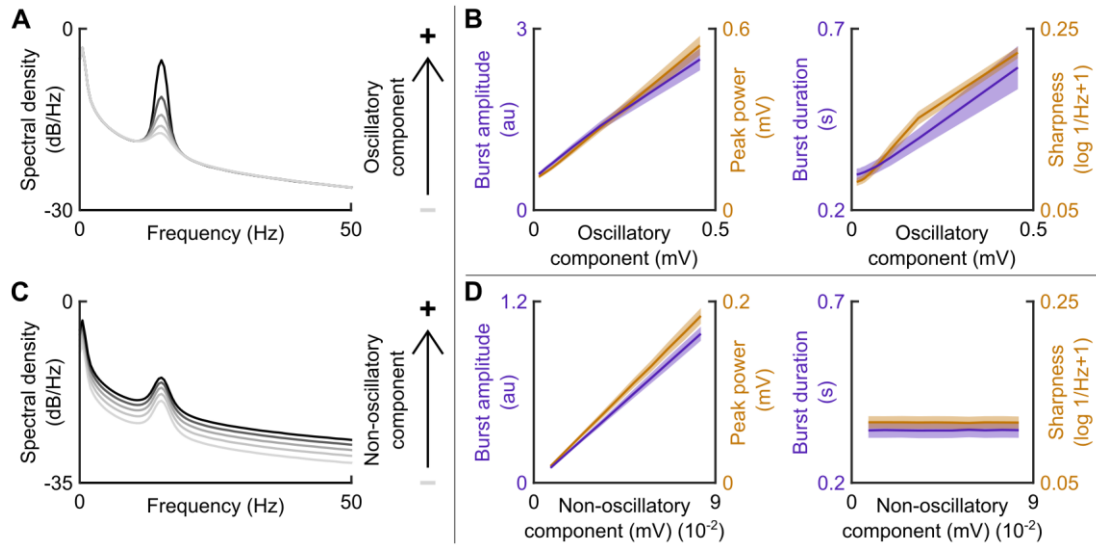


Figure 12. Modelling of oscillatory and non-oscillatory beta activity. A–D, modulation of oscillatory and non-oscillatory components of beta activity in simulated signals. A, the oscillatory component is modulated by changing the radius of the AR(2) poles. C, the non-oscillatory component is modulated by changing the variance of the $1/f$ noise, simulating a change of non-oscillatory fluctuations. B and D, changes in beta burst measures (average burst amplitude and duration) and spectral measures (beta peak power and sharpness) as a function of the oscillatory or the non-oscillatory components of simulated signals. Shaded area represents the standard deviation.

Similar results were observed in the frequency domain. When increasing the oscillatory component of beta activity (Figure 12A), both the power and the sharpness of the spectral peak increased (Figure 12B). On the other hand, when increasing the non-oscillatory component of beta activity (Figure 12C), only the power increased whereas the sharpness remained essentially unchanged (Figure 12D).

Together, these results establish the direct correspondence between beta burst measures in the time domain and spectral measures in the frequency

domain: burst amplitude and duration correspond with the power and the sharpness of the beta peak in the power spectrum, respectively. Overall, our results in simulated beta activity indicate that burst duration and spectral sharpness specifically measure oscillatory activity while burst amplitude and spectral power ambiguously measure both oscillatory and non-oscillatory activity.

4.2. Bayesian periodicity spectrum

We developed the periodicity spectrum based on the results obtained in the previous section from simulated beta activity. This novel methodology relies on the frequency modulation, rather than on the amplitude modulation, since only employs phase information to unambiguously assess the level of oscillatory activity at each frequency. The method arises from the intuition that temporal variability of the instantaneous frequency serves as an inverse measure of oscillatory activity (Averna *et al.*, 2022; Pardo-Valencia *et al.*, 2024): it is zero for a pure sinusoid, reflecting perfect periodicity, and maximal for random noise, which lacks periodic structure.

For a given stationary time series or signal $s(t)$, we define the periodicity $\Psi(f)$ at frequency f as the logarithmic inverse of the variance of the instantaneous frequency $f_{inst}(t)$ of the signal at that frequency, i.e.,

$$\Psi(f) = -\log(\text{Var}(f_{inst}(f, t))) \quad (10)$$

The periodicity spectrum is the function $\Psi(f)$ evaluated across all frequencies.

We also define the Bayesian periodicity $BF_\Psi(f)$ at frequency f as the ratio between the likelihood of the observed periodicity under the alternative hypothesis of oscillatory activity (H_1) against the null hypothesis of non-oscillatory activity (H_0), i.e.,

$$BF_\Psi(f) = \frac{P(\Psi(f)|H_1)}{P(\Psi(f)|H_0)} \quad (11)$$

The Bayesian periodicity spectrum is the function $BF_\Psi(f)$ evaluated across all frequencies and assesses the evidence favouring the presence ($BF_\Psi(f) > 1$) or

the absence ($BF_\Psi(f) < 1$) of oscillatory activity at each frequency of an individual time series.

4.3. Periodicity spectrum of non-oscillatory activity

We first characterized the periodicity spectrum of non-oscillatory activity, which we simulated using coloured noises. More details are provided in the methods (see “Non-oscillatory activity model details”). Differently from the classical power spectrum (Figure 13A), at least the first two moments of the periodicity spectrum (mean and standard deviation) are independent of the variance of non-oscillatory activity (Figure 13B).

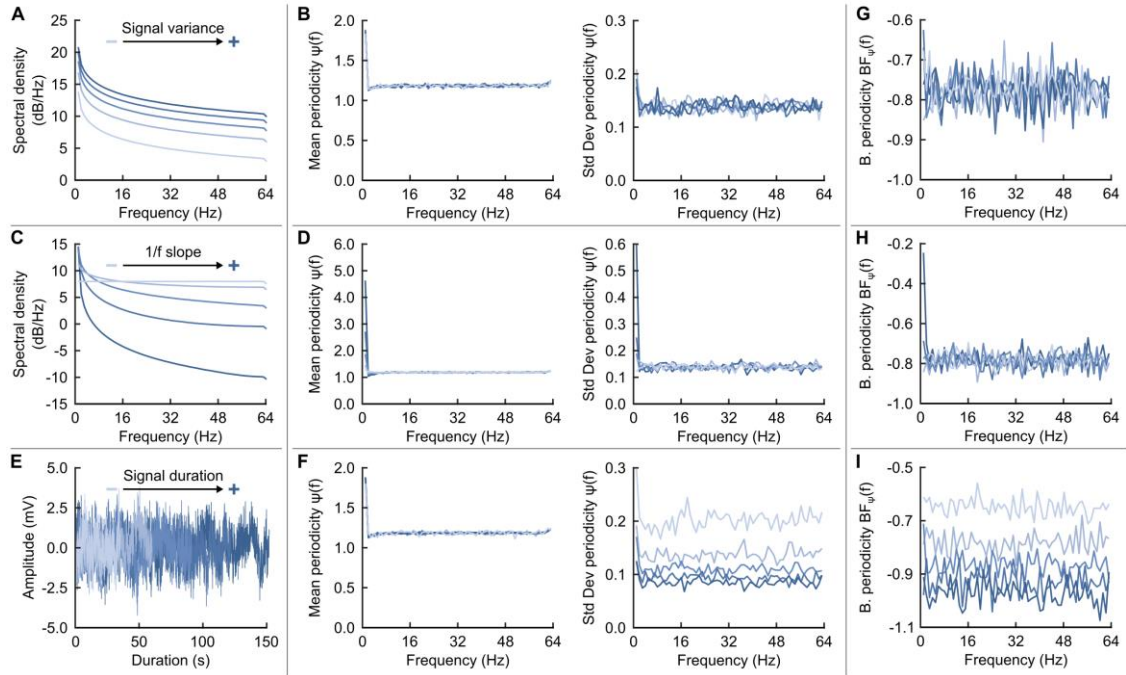


Figure 13. Power spectrum and periodicity spectrum of non-oscillatory activity. A-F, Modulation of signal variance, 1/f slope and signal duration, and their corresponding effect on periodicity (mean value and standard deviation (Std. Dev.)) in simulated signals using the short-time Fourier transform (STFT). G-I, Corresponding Bayesian periodicity spectra.

The same independence is also true for the 1/f exponent of the non-oscillatory activity, which clearly affects the power spectrum (Figure 13C), but not the periodicity spectrum (Figure 13D). The mean of the periodicity spectrum is also independent of the duration of the signal, whereas its standard deviation

expectedly decreases as the signal duration increases (Figure 13E and F). In all cases, the Bayesian periodicity spectrum provides the expected evidence of absence of oscillatory activity (Figure 13G-I). Similar results were obtained when both power spectra and periodicity spectra were estimated from the STFT (Figure 13) or from the CWT (Figure 31 in the Annexes).

Importantly, in absence of oscillatory activity the periodicity spectrum depends only on the time-frequency resolution used for the spectral estimation. As a consequence, when the estimation is based on the STFT, which has constant time-frequency resolution at all frequencies, the periodicity spectrum of non-oscillatory activity is constant at all frequencies, excluding edge effects (Figure 13B). Conversely, when the estimation is based on the CWT, in which the frequency resolution decreases with frequency, the periodicity spectrum of non-oscillatory activity also decreases with frequency (Figure 31B). The asymptotic periodicity spectrum of non-oscillatory activity $\Psi_{non-oscillatory}(f)$ can thus be subtracted to define a normalized version of the periodicity spectrum $\Psi_{norm}(f)$, in which zero represents absence of oscillatory activity and positive values indicate oscillatory activity, i.e.,

$$\Psi_{norm}(f) = \Psi(f) - \Psi_{non-oscillatory}(f) \quad (12)$$

In all subsequent analyses and experimental results, we consistently use the normalized version of the periodicity spectrum. The Bayesian periodicity spectrum is not affected by the normalization.

4.4. Periodicity spectrum of oscillatory activity

We then characterized the periodicity spectrum in presence of both oscillatory and non-oscillatory activity, by simulating signals composed by the sum of coloured noise for the non-oscillatory component and either a sinusoid or a second-order autoregressive AR(2) process for the oscillatory component. More details are provided in the methods (see “Oscillatory activity model details”). Consistently with the previous simulations, and again differently from the power spectrum (Figure 14A), the periodicity spectrum is independent of the variance of the non-

oscillatory component (Figure 14B). Conversely, the periodicity spectrum is expectedly sensitive to the variance of the oscillatory component (Figure 14C and D). It is also sensitive to the oscillatory level of the signal, i.e., the decay rate of the oscillatory component, modulated from the radius of the pole in the AR(2) process, which is reflected by the sharpness of the peak in the power spectrum (Figure 14E and F) (Pardo-Valencia *et al.*, 2024). The Bayesian periodicity spectrum provides the expected evidence of presence of oscillatory activity at the oscillation frequency and absence of oscillatory activity at all other frequencies (Figure 14G-I). Again, similar results were obtained when the estimates were based on the STFT (Figure 14) or on the CWT (Figure 32 in the Annexes).

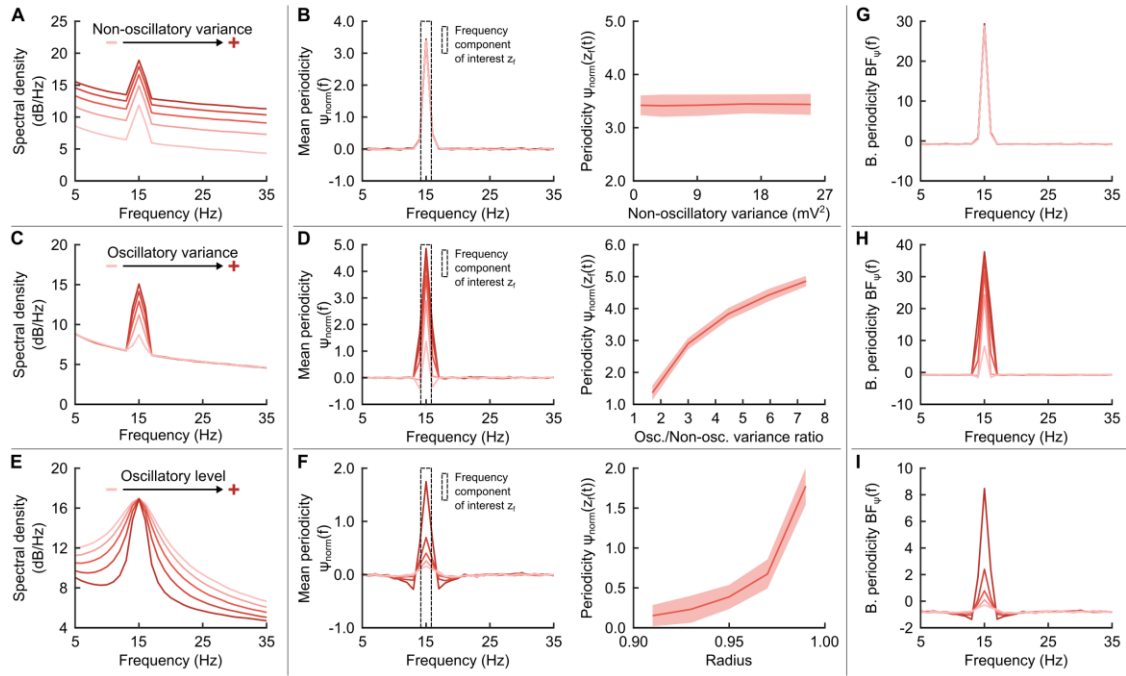


Figure 14. Power spectrum and periodicity spectrum of oscillatory activity. A-F, Modulation of non-oscillatory component variance, oscillatory component variance and the oscillatory level, and the corresponding effect on the periodicity spectrum and the change of periodicity (or the absence of it) in the frequency component of interest $z_f(t)$ (15 Hz) in simulated signals using the short-time Fourier transform (STFT). G-I, Corresponding Bayesian periodicity spectra.

Importantly, at frequencies adjacent to the main frequency of an oscillatory activity, the variance of the instantaneous frequency can be higher compared to non-oscillatory activity, leading to negative values in the normalized periodicity spectrum. This makes the periodicity spectrum more frequency-selective compared

to the power spectrum under the same time-frequency resolution conditions and spectral estimation parameters (Figure 14F left and Figure 14I). To make this point more explicit, we performed simulations with two AR(2) processes oscillating at close frequencies around 15 Hz, modulating their oscillatory level, i.e., the radius of both poles. The power spectrum was very ambiguous about the presence of two oscillatory processes, with two peaks starting to appear only at very-high oscillatory levels (Figure 15A). Conversely, in the periodicity spectrum the presence of two oscillatory processes at nearby frequencies was evident from the lowest oscillatory levels (Figure 15B). To generalize this observation, we performed simulations with a range of frequency differences between the two oscillatory processes, and we found that for each frequency difference, the minimum oscillatory level that was necessary to detect two processes was in general substantially lower with the periodicity spectrum compared to the power spectrum (Figure 15C). Again, similar results were obtained when the estimates were based on the STFT (Figure 15) or on the CWT (Figure 33 in the Annexes).

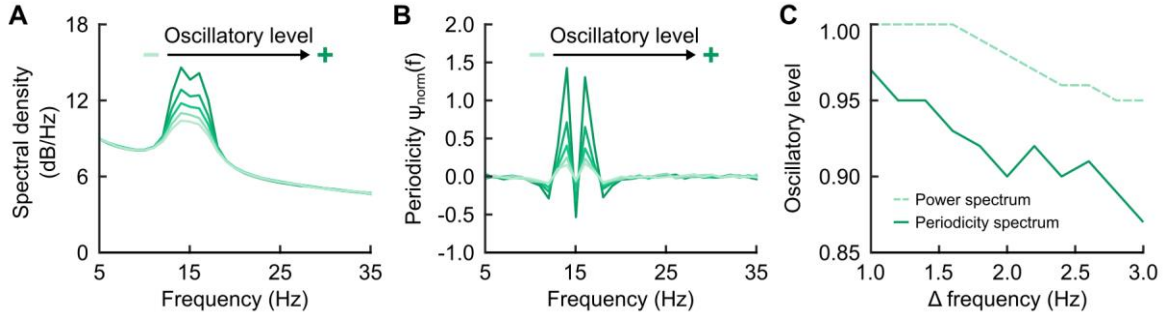


Figure 15. Frequency resolution in power spectra and periodicity spectra. A and B, Modulation of the oscillatory level of two close oscillatory components, and the corresponding effect on the power spectrum and the periodicity spectrum. C, Relationship between the distance between oscillatory peaks and the minimum oscillatory level (measured as the radius of the AR(2) models) needed to discriminate the two oscillatory components in the power spectrum and the periodicity spectrum from simulated signals measured using the short-time Fourier transform (STFT).

These simulations show that while the power spectrum is sensitive to both oscillatory and non-oscillatory activity, the (Bayesian) periodicity spectrum is specifically sensitive only to oscillatory activity (same as burst duration and sharpness of the peak) and has better frequency resolution properties.

5. Disambiguation of beta activity components in Parkinson's disease

In this section, we present the findings from analysing STN LFP recordings from PD patients off therapy and undergoing dopaminergic medication and DBS. The results highlight the effects of these therapies on oscillatory and non-oscillatory components of beta activity, and their relationships with clinical outcomes. These insights provide a deeper understanding of subthalamic neural activity in the pathophysiology of PD.

5.1. Effect of dopaminergic medication on subthalamic beta activity

After the theoretical insight and experimental validations of our framework (see also “Validation of beta activity modelling” in the Annexes and the publication associated to this thesis), we are in position to rigorously test whether dopaminergic medication separately modulates the oscillatory and non-oscillatory components of beta activity in the STN of PD patients ($n = 21$ nuclei, HM CINAC) (Table 5). Dopaminergic medication reduced with strong-to-extreme evidence both the power (paired t test, $BF_{-0} = 45.1$; Figure 16A) and the sharpness of the beta peak ($BF_{-0} = 26.1$; Figure 16B), as well as both burst amplitude ($BF_{-0} = 13.6$; Figure 16C) and burst duration ($BF_{-0} = 1641.1$; Figure 16D). These results by themselves convincingly suggest that dopaminergic medication reduces the oscillatory component of beta activity, but they remain ambiguous about the non-oscillatory component.

Table 5. Dopamine dependency of oscillatory and non-oscillatory beta activity with $n = 21$ nuclei

Measure	N	t-stat	Degrees of freedom	BF_0	Cohen's d	95% credibility interval for Cohen's d	
						Lower	Upper
Peak power	21	3.617	20	45.1	0.789	0.290	1.274
Sharpness		3.342		26.1	0.729	0.239	1.205
Burst amplitude		3.008		13.6	0.657	0.177	1.123
Burst duration		5.367		1641.1	1.171	0.603	1.722
Oscillatory component		4.692		409.3	1.024	0.484	1.547
Non-oscillatory component		-0.232		0.193	-0.051	-0.478	0.378
1/f slope		-0.151		0.256	0.033	-0.395	0.460

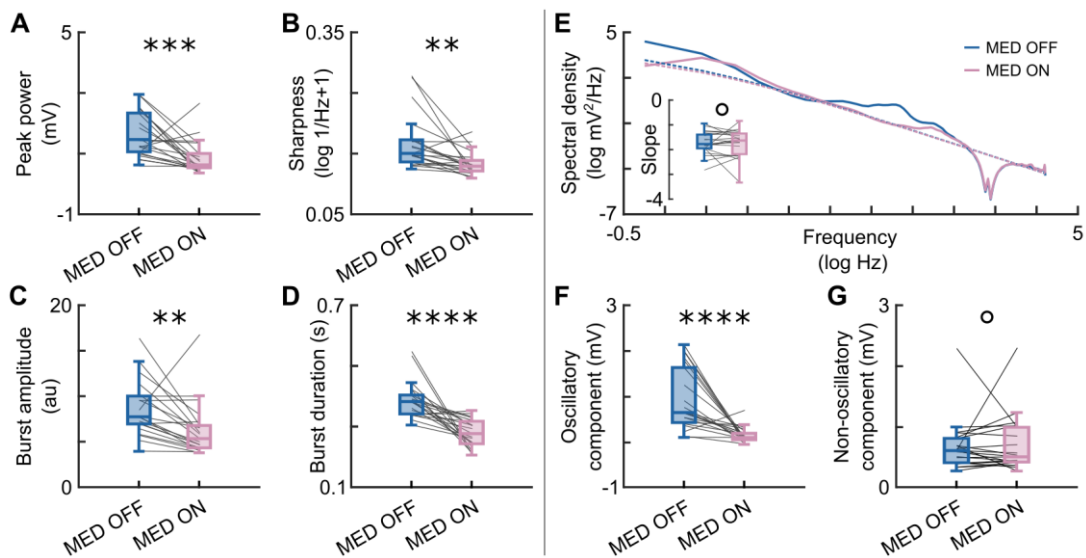


Figure 16. Oscillatory and non-oscillatory components in PD patients off and on medication. A-D, box plots of beta peak power and sharpness, and of burst amplitude and duration off and on medication ($^{**}BF_{-0} > 10$, $^{***}BF_{-0} > 30$, $^{****}BF_{-0} > 100$). E and F, box plots of oscillatory and non-oscillatory components off and on medication ($^{\circ}BF_{-0} < 1/3$, $^{****}BF_{-0} > 100$). G, average log-log 1–100 Hz spectrum of recorded STN LFPs and average estimation of non-oscillatory components off and on medication (dashed lines). The box plot represents the absence of an increase in the 1/f slope between medication conditions. ($^{\circ}BF_{-0} < 1/3$).

The decomposed spectral measures confirmed that levodopa reduced with extreme evidence the power of the oscillatory component ($BF_0 = 409.3$; Figure 16E). Conversely, we found moderate evidence that levodopa did not decrease the power of the non-oscillatory component ($BF_0 = 0.193$; Figure 16F), and did not increase the exponent of the $1/f$ slope, i.e., it did not make the slope more negative ($BF_0 = 0.256$; Figure 16G). As control sensitivity analysis, similar evidence of absence of an effect was obtained when the power of the non-oscillatory component of beta activity and the $1/f$ slope were estimated not with the FOOOF method but by fitting the log-log spectrum in different frequency bands: 1–100 Hz excluding the beta band and the line noise ($BF_0 < 0.211$); 1–100 Hz excluding 13–60 Hz ($BF_0 < 0.214$); 35–100 Hz excluding the line noise ($BF_0 < 0.344$); 60–100 Hz ($BF_0 < 0.179$).

Then, we applied the Bayesian periodicity spectrum to these LFPs recorded from STN in PD patients. We aimed to obtain a clearer view of the beta oscillatory dynamics in the STN and of their response to dopaminergic medication. All spectral estimations were performed from the CWT (Morlet wavelet, 16 voices per octave).

The power spectrum displayed more or less evident peaks within low-beta and high-beta frequencies off medication, with the expected power decrease on medication (Figure 17A and B). Note that, as seen above, the power spectrum per se is ambiguous about the underlying level of non-oscillatory activity and about the contribution of oscillatory vs. non-oscillatory activity in the dopaminergic modulation (Pardo-Valencia *et al.*, 2024). Notably, the power spectrum did not convincingly separate low-beta from high-beta activity in the off-medication state (Figure 17B), and suggested a dopaminergic modulation that is more prominent in the low-beta band, but extends into high-beta frequencies (Figure 17B), consistent with previous reports (Priori *et al.*, 2004). The periodicity spectrum explicitly quantified only the oscillatory activity off and on medication (Figure 17C and D). The Bayesian periodicity spectrum quantified the actual level of evidence for the presence or absence of oscillatory activity at the different frequencies off and on medication, both at the single nucleus level (Figure 17E) and at the population

level (Figure 17F). Specifically at the population level, off medication there was extreme evidence of oscillatory activity within the two frequency bands – low-beta and high-beta – with moderate-to-strong evidence of absence of oscillatory activity between sub-bands (Figure 17F). Conversely, on medication there was extreme evidence of oscillatory activity only in the high-beta band and strong evidence of absence of oscillatory activity in the low-beta band (Figure 17F).

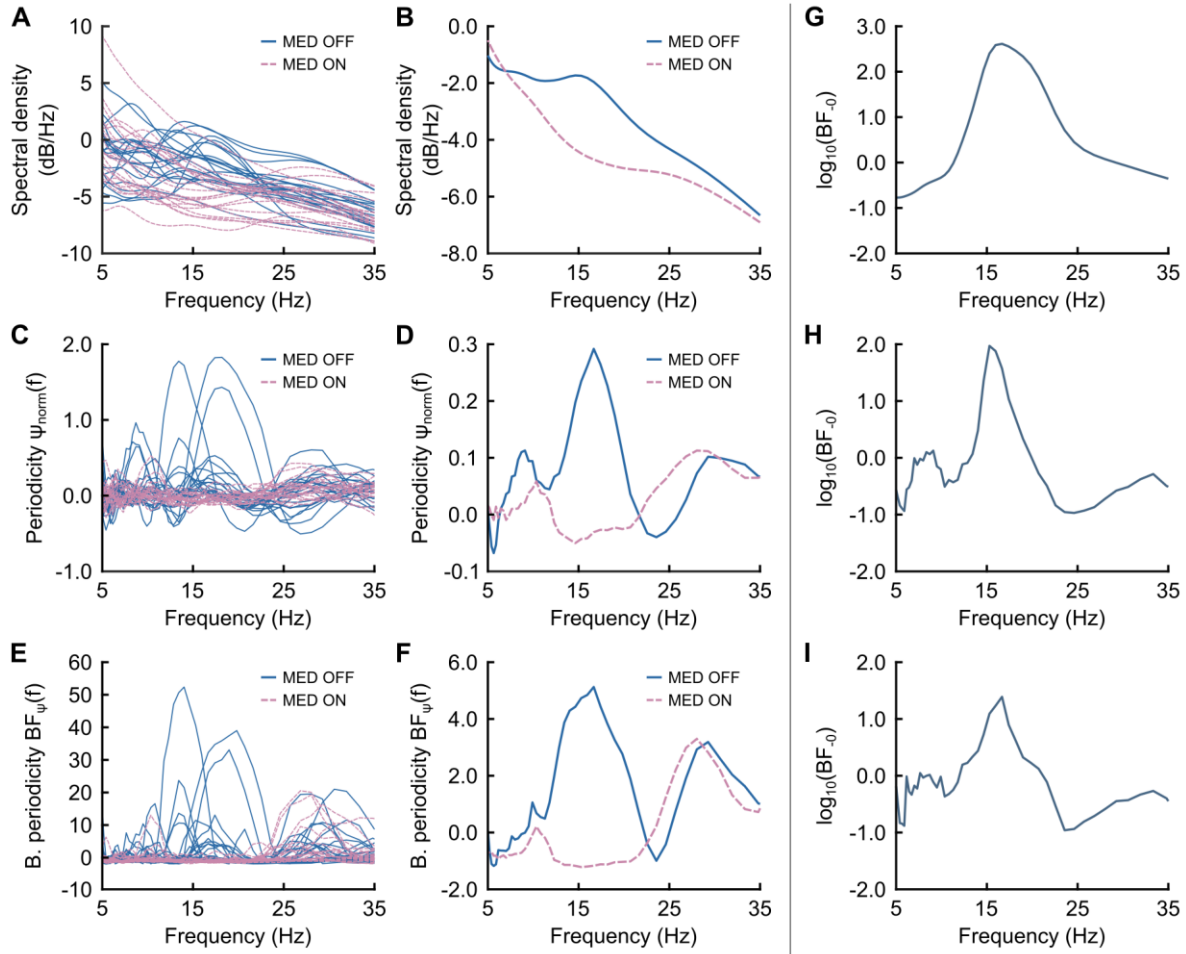


Figure 17. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease off and on medication. A-F, Superimposed and average power spectra (A and B), periodicity spectra (C and D) and Bayesian periodicity spectra (E and F) of subthalamic local field potentials (STN LFPs) recorded off and on medication ($n = 21$ nuclei). G-I, Group level comparison of values on vs. off medication (two-sample Bayesian t-tests, BF_{-0}) for the power spectrum (G), the periodicity spectrum (H) and the Bayesian periodicity spectrum (I).

Overall, the (Bayesian) periodicity spectrum resolved better the two frequency bands compared to the power spectrum. Accordingly, the evidence of a decrease of

oscillatory activity with dopaminergic medication (BF_{-0}) extended from the low-beta to the high-beta band when assessed with the power spectrum (Figure 17G), whereas it was restricted to the low-beta band – with evidence of absence of modulation in the high-beta band – when assessed with the periodicity spectrum (Figure 17H) or with the Bayesian periodicity spectrum (Figure 17I).

As corollary results, we also confirmed robust correlations between periodicity and Bayesian periodicity with measures that specifically reflect oscillatory activity, i.e., burst duration and spectral sharpness, and weaker correlations with measures that ambiguously reflect oscillatory and non-oscillatory activity, i.e., burst amplitude and peak power (Figure 18).

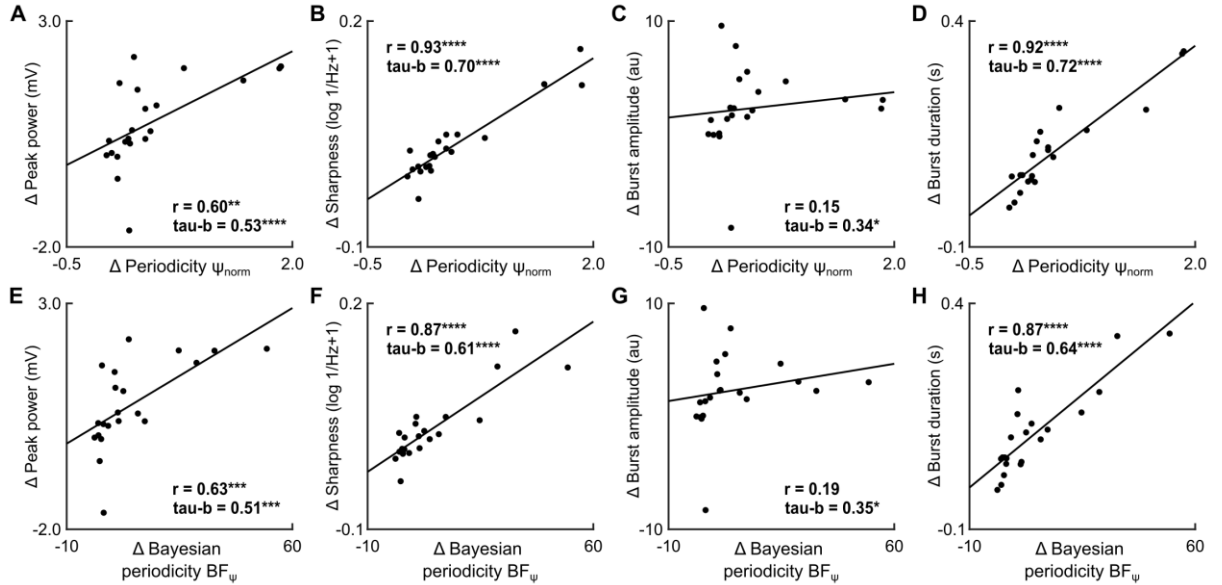


Figure 18. Correlations between periodicity, Bayesian periodicity, and spectral and beta bursts measures off and on medication. A-H, correlations between periodicity and Bayesian periodicity values, and spectral and beta burst measures off/on medication. In this case, we calculated correlations using the difference in measures between off and on medication (* $BF_{+0} > 3$, ** $BF_{+0} > 10$, *** $BF_{+0} > 30$, **** $BF_{+0} > 100$).

These results collectively suggest that primarily the oscillatory, and not the non-oscillatory component, of STN beta activity is modulated by dopaminergic medication in PD.

5.2. Effect of deep brain stimulation on subthalamic beta activity

Once the effect of dopaminergic medication in subthalamic beta activity was identified, we investigated whether the application of electrical stimulation through DBS electrodes would also affect differentially the oscillatory and non-oscillatory components of subthalamic beta activity in PD patients ($n = 58$ nuclei, NeuroRestore) (Table 6).

Table 6. DBS dependency of oscillatory and non-oscillatory beta activity with $n = 58$ nuclei

Measure	N	t-stat	Degrees of freedom	BF ₀	Cohen's d	95% credibility interval for Cohen's d	
						Lower	Upper
Peak power	58	1.577	57	0.861	0.207	-0.054	0.466
Sharpness		-0.406		0.108	-0.053	-0.311	0.204
Burst amplitude		2.442		4.3	0.321	0.055	0.583
Burst duration		2.617		6.3	0.344	0.077	0.607
Oscillatory component		0.319		0.187	0.042	-0.216	0.299
Non-oscillatory component		3.389		43.4	0.445	0.173	0.713
1/f slope		-2.859		0.039	-0.375	-0.640	-0.108

In contrast to the results reported on dopaminergic medication, DBS did not reduced neither the power (paired t test, $BF_{-0} = 0.861$; Figure 19A) nor the sharpness of the beta peak ($BF_{-0} = 0.108$; Figure 19B), though it decreased with moderate evidence both burst amplitude ($BF_{-0} = 4.0$; Figure 19C) and burst duration ($BF_{-0} = 6.6$; Figure 19D). The results are somehow unexpected, since both spectral measures, i.e., power and sharpness of the beta peak, and beta bursts measures, i.e., burst amplitude and burst duration, should follow the same tendency due to their direct relationships (Pardo-Valencia *et al.*, 2024). The decomposed spectral measures revealed the inverse effect on oscillatory and non-oscillatory beta activity compared to that of levodopa. DBS did not reduce the power of the oscillatory component ($BF_{-0} = 0.015$; Figure 19E). On the other hand,

we found very strong evidence for a reduction in the power of the non-oscillatory component due to DBS ($BF_{-0} = 43.4$; Figure 19F). We also found that DBS did not increase the exponent of the $1/f$ slope, i.e., it did not make the slope more negative, ($BF_{-0} = 0.039$; Figure 19G), but the opposite: strong evidence for a decrease of the exponent of the $1/f$ slope ($BF_{+0} = 11.2$; Figure 19G). We also evaluated the non-oscillatory beta activity power and the exponent of the $1/f$ slope using a linear fitting of the log-log spectra in a reliable frequency range, between 35 and 95 Hz (Gerster *et al.*, 2022). In this case, we reported an extreme increase of the exponent of the $1/f$ slope, ($BF_{+0} = 5.5 \times 10^9$), as well as an extreme reduction of the non-oscillatory part of the beta activity power ($BF_{-0} = 2.9 \times 10^6$).

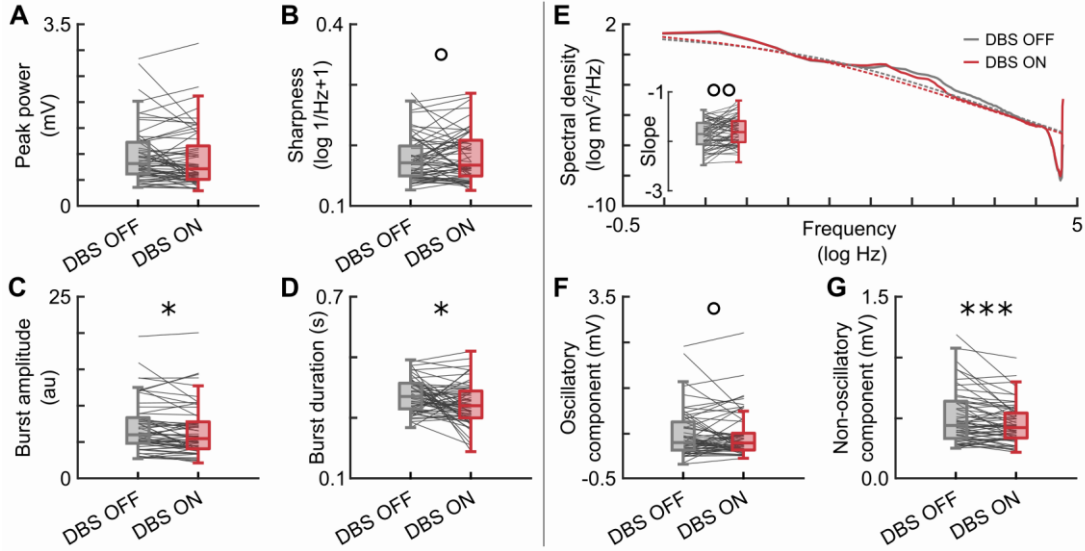


Figure 19. Oscillatory and non-oscillatory components in PD patients off and on DBS. A-D, box plots of beta peak power and sharpness, and of burst amplitude and duration off and on DBS (${}^0BF_{-0} < 1/3$, ${}^*BF_{-0} > 3$). E and F, box plots of oscillatory and non-oscillatory components off and on medication (${}^0BF_{-0} < 1/3$, ${}^{***}BF_{-0} > 30$). G, average log-log 1–125 Hz spectrum of recorded STN LFPs and average estimation of non-oscillatory components off and on DBS (dashed lines). The box plot represents the absence of an increase in the $1/f$ slope between medication conditions. (${}^{oo}BF_{-0} < 1/10$).

We also applied the Bayesian periodicity spectrum to this dataset of STN LFPs from PD patients. Hopefully, our novel methodology would provide a better understanding of the beta oscillatory dynamics in the STN when electrical stimulation is applied to brain tissue. All spectral estimations were performed from the CWT (Morlet wavelet, 16 voices per octave).

The power spectrum showed the usual peaks within low-beta and high-beta frequencies off DBS in PD, with the expected power decrease in the beta band on DBS (Figure 20A and B). It is observable that, at these wavelet characteristics, we cannot find a proper separation between low-beta from high-beta activity in the off DBS state (Figure 20B) and suggested a modulation which primarily affects high-beta frequencies, with a lesser effect in the low-beta band (Figure 20B) (Chen *et al.*, 2020b; Feldmann *et al.*, 2022).

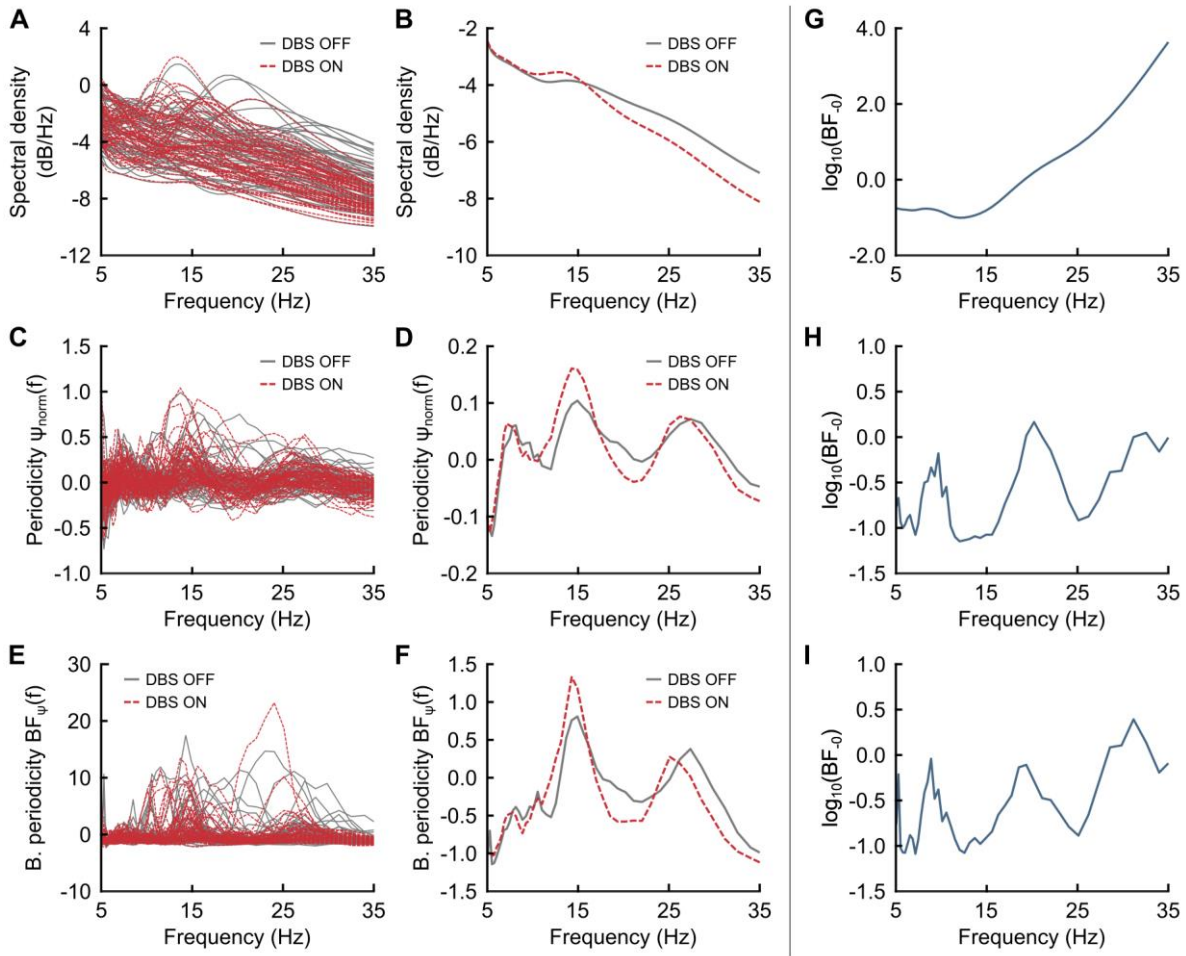


Figure 20. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease off and on DBS. A-F, Superimposed and average power spectra (A and B), periodicity spectra (C and D) and Bayesian periodicity spectra (E and F) of subthalamic local field potentials (STN LFPs) recorded off and on DBS ($n = 58$ nuclei). G-I, Group level comparison of values on vs. off DBS (two-sample Bayesian t-tests, BF_{-0}) for the power spectrum (G), the periodicity spectrum (H) and the Bayesian periodicity spectrum (I).

The periodicity spectrum quantified only the oscillatory activity off and on DBS (Figure 20C and D). The Bayesian periodicity spectrum assessed the level of evidence for the presence or absence of oscillatory activity across frequencies, both at the single-nucleus (Figure 20E) and population levels (Figure 20F). At the population level, off DBS, there was anecdotal-to-moderate evidence of oscillatory activity in the low-beta and high-beta bands, with anecdotal evidence of its absence between sub-bands (Figure 20F). Conversely, there was anecdotal-to-strong evidence of oscillatory activity in both bands and moderate evidence of its absence between them on DBS (Figure 20F).

In this case, the (Bayesian) periodicity spectrum and the power spectrum revealed different patterns of beta activity modulation due to DBS. Evidence for a decrease in oscillatory activity with DBS (BF_{-0}) increased from the low-beta to the high-beta band in the power spectrum (Figure 20G). In contrast, the periodicity spectrum (Figure 20H) and the Bayesian periodicity spectrum (Figure 20I) showed no reduction in beta activity, with anecdotal-to-strong evidence.

The correlations obtained between periodicity, Bayesian periodicity, and spectral and beta bursts measures in the LFPs recorded off and on medication extended to the modulation due to DBS (Figure 21).

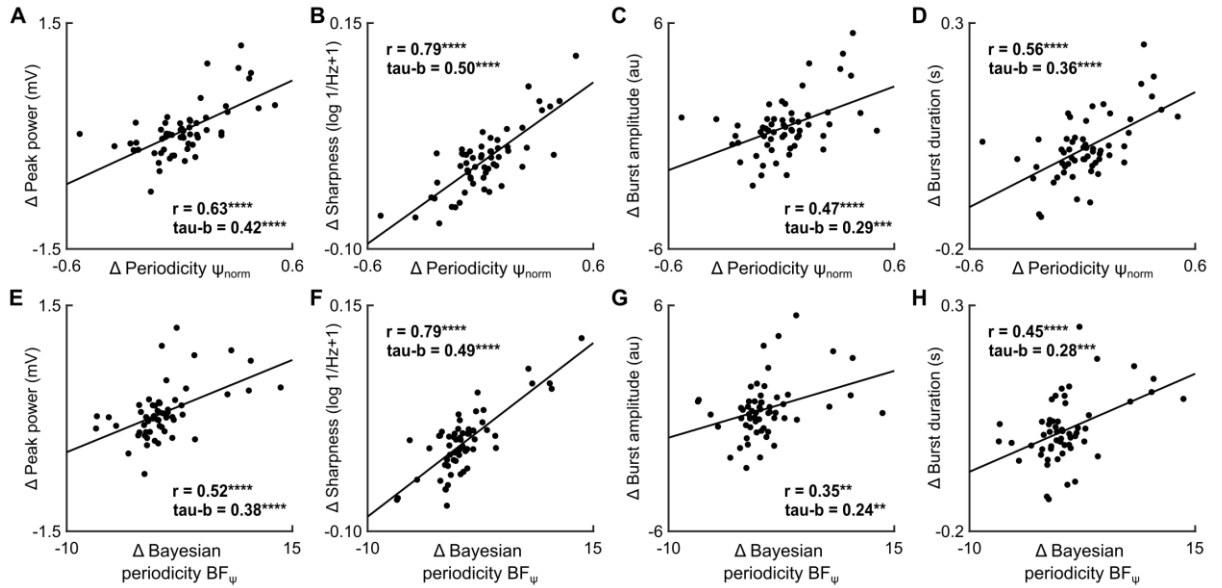


Figure 21. Correlations between periodicity, Bayesian periodicity, and spectral and beta bursts measures off and on DBS. A-H, correlations between periodicity and Bayesian

periodicity values, and spectral and beta burst measures off/on DBS. In this case, we calculated correlations using the difference in measures between off and on DBS ($**BF_{+0} > 10$, $***BF_{+0} > 30$, $****BF_{+0} > 100$).

Taken together, all these results mostly suggest that DBS would modulate the non-oscillatory component and not the oscillatory component of beta activity in PD patients.

5.3. Beta activity across clinical phenotypes

In order to further characterize subthalamic beta activity components depending on patients' dominant clinical motor signs, we divided the subjects of the NeuroRestore dataset into two different groups. The first group is composed of patients presenting a pure AR phenotype ($n = 28$ nuclei), whereas the second group consists of patients with AR phenotype with tremor features (AR+T) ($n = 22$ nuclei), and TD patients ($n = 4$ nuclei) which we included as part of the AR+T group.

We found that the modulatory effect of DBS, or the lack of it, on oscillatory and non-oscillatory components previously reported in the whole dataset remains when it is divided into both clinical phenotype groups (Table 7). However, we did not report any difference between groups in the classical measures of beta activity, nor an interaction between factors, i.e., DBS and PHENOTYPE (Table 7).

Table 7. Effect of DBS on beta activity depending on the clinical phenotype

Factor: DBS				
Measure	F	Degrees of freedom	BF_{incl}	η^2
Peak power	3.002	1	0.712	0.006
Sharpness	0.309		0.227	0.001
Burst amplitude	7.529		4.73	0.007
Burst duration	6.844		5.644	0.054
Oscillatory component	0.157		0.214	0.001
Non-oscillatory component	13.388		31.896	0.026
1/f slope	8.759		7.0	0.036

Factor: PHENOTYPE				
Measure	F	Degrees of freedom	BF _{incl}	η²
Peak power	0.106	1	0.475	0.002
Sharpness	0.102		0.342	0.001
Burst amplitude	1.143		0.653	0.020
Burst duration	2.368		0.542	0.023
Oscillatory component	0.392		0.512	0.012
Non-oscillatory component	0.211		0.790	0.026
1/f slope	1.707		0.651	0.024
Interaction: DBS * PHENOTYPE				
Measure	F	Degrees of freedom	BF _{incl}	η²
Peak power	0.668	1	0.351	0.001
Sharpness	0.658		0.376	0.003
Burst amplitude	0.813		0.362	0.001
Burst duration	0.632		0.379	0.005
Oscillatory component	0.006		0.271	0.001
Non-oscillatory component	4.481		1.5	0.008
1/f slope	1.365		0.489	0.006

A broader analysis of beta activity was performed applying the Bayesian periodicity spectrum to the STN LFPs recorded from PD patients in the NeuroRestore dataset off and on DBS. All spectral estimations were performed from the CWT (Morlet wavelet, 16 voices per octave).

First, we considered the STN LFP recordings only in the off DBS condition. The power spectrum showed greater activity within the low-beta band in AR patients compared to AR+T patients off DBS, with a relative similar power within the high beta band between groups (Figure 22A and B). As we showed previously, the separation between low-beta from high-beta activity using the classical power spectrum in both groups is not quite clear (Figure 22B). On the other hand, the periodicity spectrum unambiguously provides the oscillatory activity off DBS in both groups of STN LFP recordings, being clearly higher within the low-beta band in the AR group compared to the AR+T group (Figure 22C and D). The Bayesian

periodicity spectrum quantified the actual level of evidence for the presence or absence of oscillatory activity at the different frequencies both at single nucleus level and population level (Figure 22E and F). At the population level, we reported anecdotal of oscillatory activity within the high-beta band and moderate-to-strong evidence of oscillatory activity in the case of the low-beta band for the AR group off DBS with moderate evidence of absence of oscillatory activity between sub-bands (Figure 22F). On the other hand, there was anecdotal-to-moderate evidence of oscillatory activity in the overall beta band for the AR+T group, without any clear evidence of absence of oscillatory activity between sub-bands. (Figure 22F).

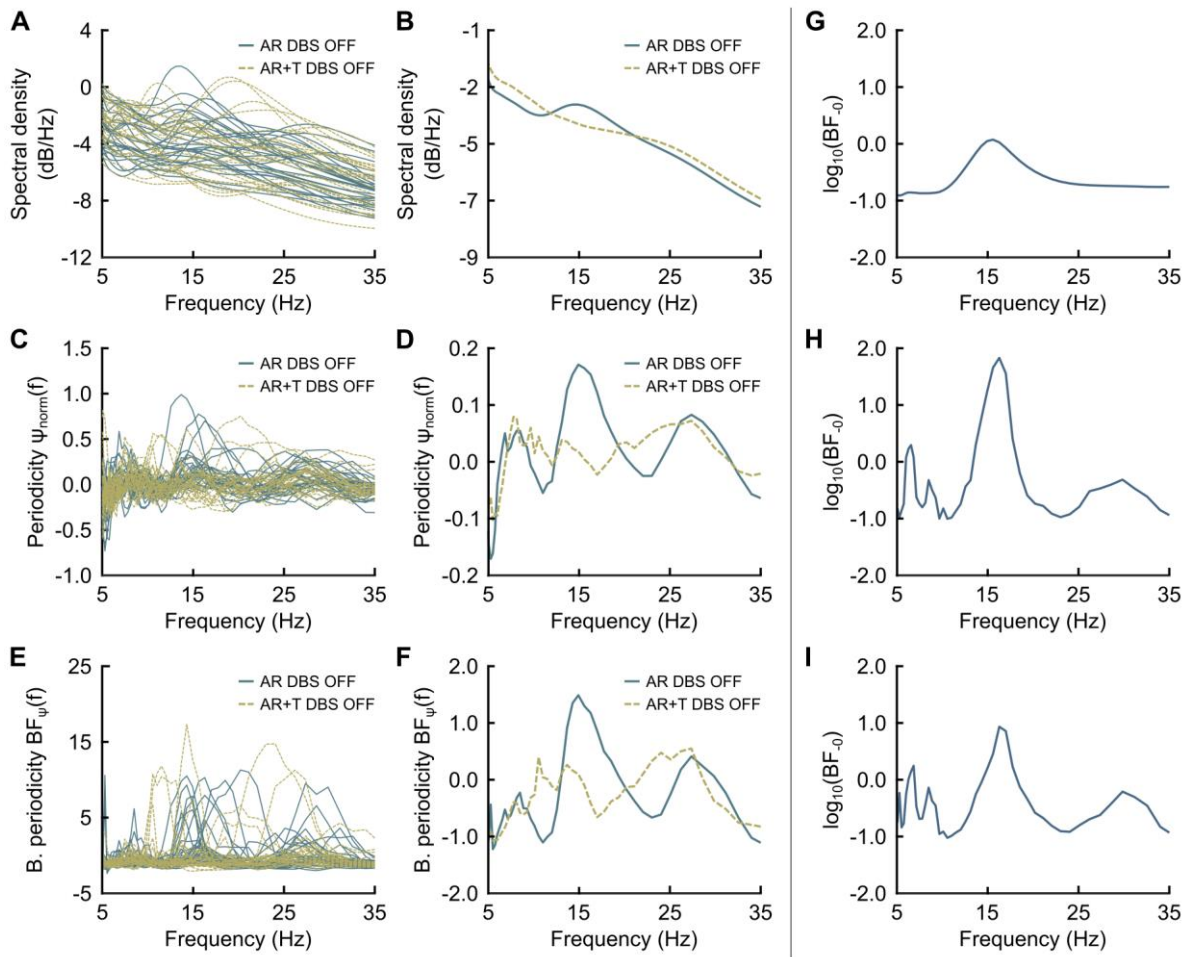


Figure 22. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease presenting different clinical phenotypes off DBS. A-F, Superimposed and average power spectra (A and B), periodicity spectra (C and D) and Bayesian periodicity spectra (E and F) of subthalamic local field potentials (STN LFPs) recorded off DBS from akinetic-rigid (AR) patients ($n = 28$ nuclei), and AR patients presenting tremor and tremor-dominant (TD) patients (AR+T, $n = 26$ nuclei) with

Parkinson's disease (PD). G-I, Group level comparison of values AR+T vs. AR (two-sample Bayesian t-tests, BF_{-0}) for the power spectrum (G), the periodicity spectrum (H) and the Bayesian periodicity spectrum (I).

We compared our measures in terms of power, periodicity and Bayesian periodicity between groups. The alternative hypothesis in all cases is that values from the AR group are higher than values from the AR+T group. In this case, the (Bayesian) periodicity spectrum revealed the difference in subthalamic oscillatory beta activity between clinical phenotypes. In turn, the power spectrum failed to separate the two groups based on the analysis of beta band activity. There was no evidence for a higher power in the AR group compared to the AR+T off DBS (BF_{-0}) in all beta frequency components (Figure 22G). On the other hand, when assessed with the periodicity spectrum (Figure 22H) or with the Bayesian periodicity spectrum (Figure 22I) we reported higher oscillatory beta activity in the AR group compared to the AR+T group with moderate-to-very-strong evidence.

Then, we studied the STN LFP recordings of both groups separately in the off and on DBS conditions in order to unveil the modulatory effects of this therapy across phenotypes. The power spectrum in both cases showed a similar pattern of power decrease in the beta band on DBS (Figure 23A and B, Figure 24A and B). together with a similar high-beta band power (Figure 23A and B, Figure 24A and B). As seen previously in the analysis of the whole NeuroRestore dataset, this power reduction primarily affects high-beta frequencies (Figure 23B, Figure 24B). Conversely, the periodicity spectrum offers an alternative view on oscillatory activity in both clinical phenotype groups off and on DBS. In these cases, we reported similar peaks of oscillatory activity within the beta band in both clinical phenotype groups on DBS. (Figure 23C and D, Figure 24C and D). Furthermore, using the Bayesian periodicity spectrum off DBS there was evidence of oscillatory activity – moderate-to-very-strong for AR group, moderate for AR+T group – within the two frequency bands – low-beta and high-beta – with moderate evidence of absence of oscillatory activity between sub-bands. These results were obtained both at single nucleus level (Figure 23E, Figure 24E) and population level (Figure 23F, Figure 24F).

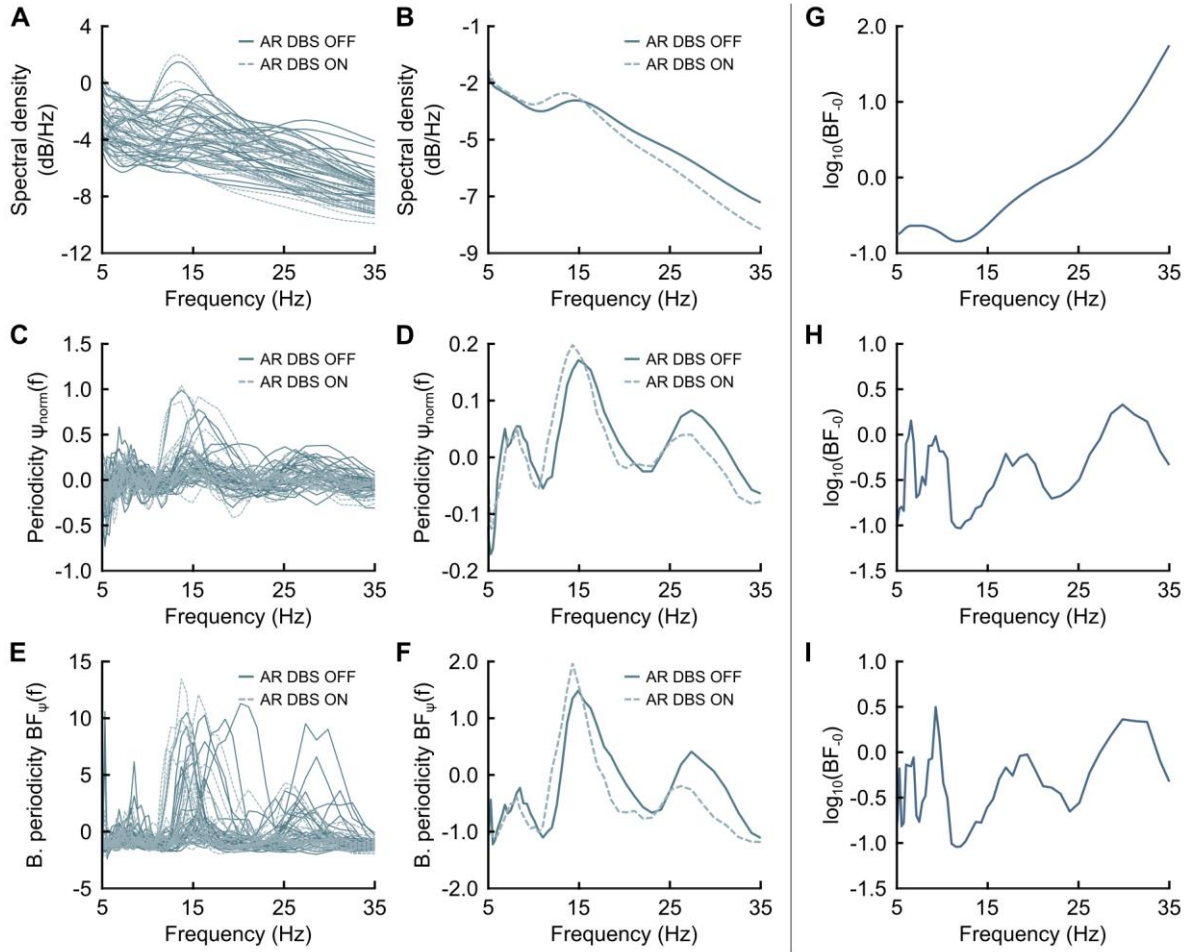


Figure 23. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease presenting akinetic-rigid phenotype off and on DBS. A-F, Superimposed and average power spectra (A and B), periodicity spectra (C and D) and Bayesian periodicity spectra (E and F) of subthalamic local field potentials (STN LFPs) recorded off and on DBS from akinetic-rigid (AR) patients with Parkinson's disease (PD) ($n = 28$ nuclei). G-I, Group level comparison of values on vs. off DBS (two-sample Bayesian t-tests, BF_0) for the power spectrum (G), the periodicity spectrum (H) and the Bayesian periodicity spectrum (I).

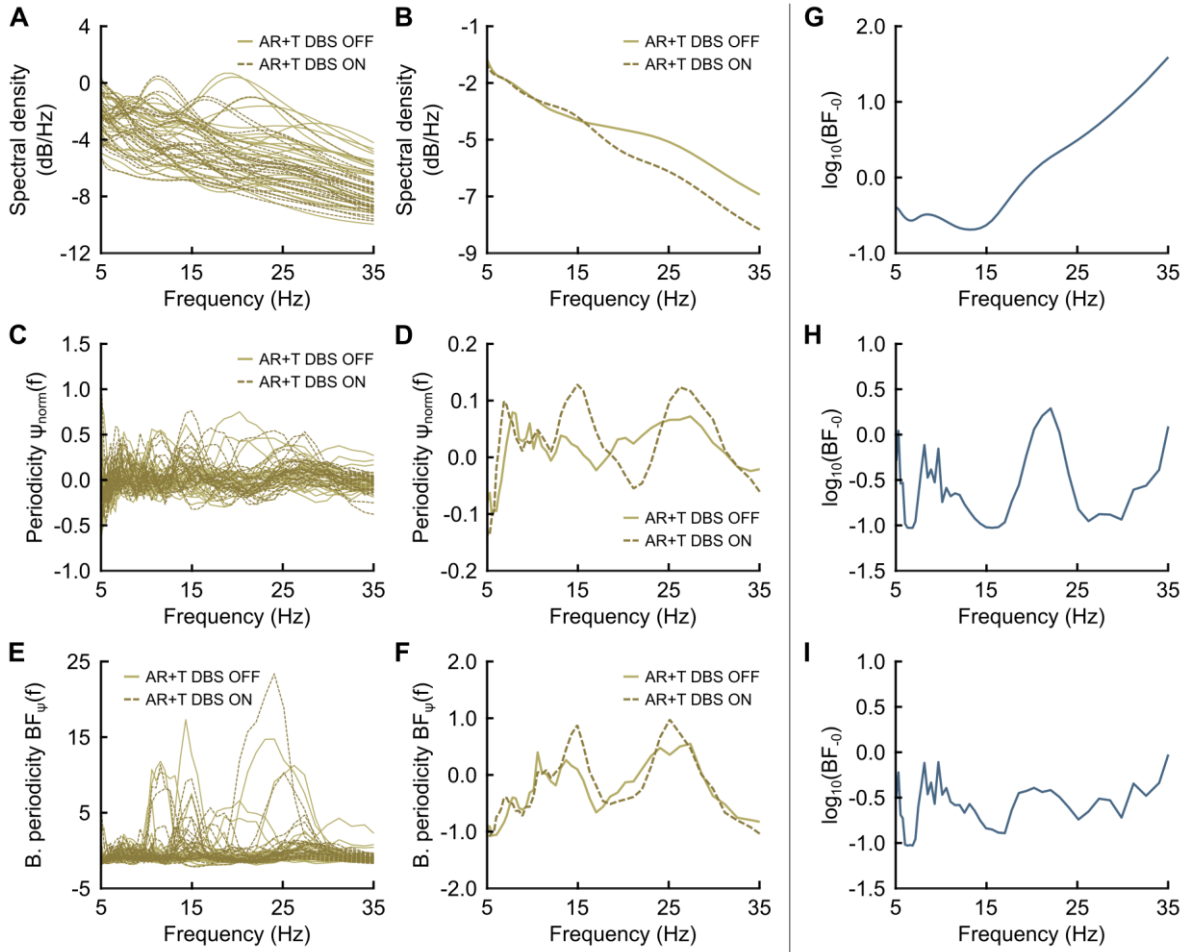


Figure 24. Application of Bayesian periodicity spectrum to subthalamic recordings from patients with Parkinson's disease presenting akinetic-rigid with tremor and tremor dominant phenotypes off and on DBS. A-F, Superimposed and average power spectra (A and B), periodicity spectra (C and D) and Bayesian periodicity spectra (E and F) of subthalamic local field potentials (STN LFPs) recorded off and on DBS from akinetic-rigid with tremor (AR+T) and tremor-dominant (TD) patients with Parkinson's disease (PD) ($n = 26$ nuclei). G-I, Group level comparison of values on vs. off DBS (two-sample Bayesian t-tests, BF_{-0}) for the power spectrum (G), the periodicity spectrum (H) and the Bayesian periodicity spectrum (I).

Finally, as seen previously studying the whole NeuroRestore dataset, the (Bayesian) periodicity spectrum and the power spectrum showed different patterns of beta activity modulation between off and on DBS conditions in both clinical phenotype groups. On the one hand, when we compared power measures for each frequency component on vs. off DBS (BF_{-0}), we reported similar moderate-to-very-strong evidence for a reduction in power in the high-beta band in both groups (Figure 23G, Figure 24G). On the other hand, we reported a lack of reduction of

oscillatory activity in the whole beta band in both the AR and AR+T groups with moderate evidence on DBS compared to off DBS (BF_{+0}) measured either using the periodicity spectrum (Figure 23H, Figure 24H) or the Bayesian periodicity spectrum (Figure 23I, Figure 24I).

All results collectively suggest that increased oscillatory activity within the low-beta band is characteristic of the AR phenotype in PD patients, and that DBS therapy would restore at some point the pattern of pathological subthalamic beta oscillations in PD patients presenting tremor features.

5.4. Clinical correlations

We finally tested whether the oscillatory and non-oscillatory components of beta activity from STN LFPs in PD patients of the HM CINAC datasets correlated either with the motor severity or with the motor progression of the disease.

We did not find any clear correlation between measures of beta activity and motor severity, as measured with UPDRS-III scores (Table 8). We calculated these correlations in several ways: between more affected nuclei and total pre-operative UPDRS-III scores off-medication; between all available nuclei and lateralized pre-operative or post-operative UPDRS-III scores off-medication; and same combinations with the difference between measures and clinical scores off and on medication.

Most of the evidence, either in favour of the presence or of the absence of correlations, remained in the anecdotal range, which does not allow drawing any firm conclusion (Table 8).

Table 8. Clinical correlations

More affected STNs off						
<i>Pre-op UPDRS-III off (n=21)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF_{+0})	0.27 (0.889)	0.04 (0.304)	0.28 (0.968)	-0.04 (0.239)	0.20 (0.603)	0.23 (0.721)
Kendall's tau-b (BF_{+0})	0.25 (1.7)	0.14 (0.671)	0.26 (1.9)	-0.03 (0.244)	0.14 (0.671)	0.12 (0.584)

More affected STNs Δ off/on						
Δ Pre-op UPDRS-III off/on (n=13)	Δ Peak power	Δ Sharpness	Δ Burst amplitude	Δ Burst duration	Δ Oscillatory component	Δ Non-oscillatory component
Pearson's r (BF ₊)	0.13 (0.477)	0.01 (0.345)	0.14 (0.495)	0.13 (0.489)	0.16 (0.522)	-0.04 (0.313)
Kendall's tau-b (BF ₊)	0.01 (0.366)	0.19 (0.834)	0.17 (0.726)	0.14 (0.637)	0.07 (0.449)	0.17 (0.726)
More and less affected STNs off						
Pre-op UPDRS-III MAS/LAS off (n=31)	Peak power	Sharpness	Burst amplitude	Burst duration	Oscillatory component	Non-oscillatory component
Pearson's r (BF ₊)	0.17 (0.550)	-0.09 (0.159)	0.28 (1.3)	-0.19 (0.118)	0.06 (0.296)	0.29 (1.3)
Kendall's tau-b (BF ₊)	0.10 (0.505)	0.00 (0.235)	0.14 (0.711)	-0.18 (0.099)	0.06 (0.338)	0.10 (0.505)
Post-op UPDRS-III MAS/LAS off (n=26)	Peak power	Sharpness	Burst amplitude	Burst duration	Oscillatory component	Non-oscillatory component
Pearson's r (BF ₊)	0.13 (0.420)	-0.10 (0.173)	0.24 (0.819)	-0.04 (0.210)	0.21 (0.659)	-0.12 (0.163)
Kendall's tau-b (BF ₊)	0.00 (0.252)	-0.14 (0.134)	0.16 (0.857)	-0.05 (0.194)	0.15 (0.760)	-0.16 (0.125)
More and less affected STNs Δ off/on						
Δ Pre-op UPDRS-III MAS/LAS off/on (n=21)	Δ Peak power	Δ Sharpness	Δ Burst amplitude	Δ Burst duration	Δ Oscillatory component	Δ Non-oscillatory component
Pearson's r (BF ₊)	0.10 (0.393)	-0.08 (0.212)	0.18 (0.559)	-0.01 (0.265)	0.05 (0.322)	0.12 (0.422)
Kendall's tau-b (BF ₊)	0.04 (0.351)	-0.02 (0.260)	0.18 (0.897)	-0.04 (0.228)	0.07 (0.416)	0.18 (0.897)
Δ Post-op UPDRS-III MAS/LAS off/on (n=17)	Δ Peak power	Δ Sharpness	Δ Burst amplitude	Δ Burst duration	Δ Oscillatory component	Δ Non-oscillatory component
Pearson's r (BF ₊)	-0.05 (0.259)	-0.19 (0.189)	0.09 (0.392)	-0.14 (0.210)	-0.11 (0.226)	0.06 (0.363)
Kendall's tau-b (BF ₊)	-0.11 (0.206)	0.02 (0.330)	0.06 (0.409)	0.05 (0.380)	0.02 (0.330)	0.12 (0.569)

UPDRS = Unified Parkinson's Disease Rating Scale, MAS = More affected side, LAS = less affected side, STN = subthalamic nucleus, Pre-op = preoperative, Post-op = postoperative.

Interestingly, we found moderate-to-strong evidence that measures of beta oscillatory activity off medication were inversely correlated with disease duration,

and moderate evidence that disease duration did not correlate with the non-oscillatory component (Table 9). Importantly, our patients are not a random sample of PD patients, in the sense that they represent the specific disease stage in which they are candidate for DBS surgery. Consequently, in this sample disease duration is not a measure of disease severity, but rather an inverse measure of the rate of disease progression, i.e., patients with longer disease duration progressed more slowly to the stage at which they became candidates for DBS surgery. Making this relationship more explicit, we found moderate-to-strong evidence that all beta measures correlated with the rate of motor progression of the disease, as assessed by dividing off UPDRS-III scores by disease duration, both considering patients and nuclei (Table 9). Similar correlations were observed when the rate of motor progression was assessed by dividing on UPDRS-III scores by disease duration.

Table 9. Rate of motor progression of the disease

More affected STNs						
<i>Pre-op UPDRS-III off/disease duration (n=21)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF ₊)	0.46 (3.9)	0.48 (5.1)	0.35 (1.6)	0.41 (2.7)	0.53 (9.3)	0.07 (0.343)
Kendall's tau-b (BF ₊)	0.35 (5.5)	0.37 (7.2)	0.33 (4.3)	0.34 (4.9)	0.43 (17.1)	0.05 (0.369)
<i>Pre-op UPDRS-III on/disease duration (n=21)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF ₊)	0.50 (6.5)	0.46 (4.1)	0.44 (3.5)	0.53 (9.1)	0.47 (4.8)	0.257 (0.840)
Kendall's tau-b (BF ₊)	0.28 (2.3)	0.30 (2.9)	0.26 (1.9)	0.33 (4.1)	0.32 (3.6)	-0.01 (0.266)
More and less affected STNs						
<i>Pre-op UPDRS-III MAS/LAS off/disease duration (n=31)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF ₊)	0.43 (7.4)	0.34 (2.2)	0.44 (7.9)	0.23 (0.828)	0.43 (6.7)	0.16 (0.499)
Kendall's tau-b (BF ₊)	0.29 (5.5)	0.31 (8.2)	0.31 (7.6)	0.24 (2.5)	0.31 (8.9)	0.11 (0.510)

<i>Post-op UPDRS-III MAS/LAS off/disease duration (n=26)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF ₊)	0.53 (18.6)	0.46 (6.8)	0.50 (12.0)	0.34 (1.9)	0.65 (194.7)	-0.07 (0.193)
Kendall's tau-b (BF ₊)	0.21 (1.4)	0.28 (3.2)	0.29 (4.1)	0.26 (2.7)	0.42 (36.3)	-0.11 (0.150)
<i>Pre-op UPDRS-III MAS/LAS on/disease duration (n=31)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF ₊)	0.33 (2.1)	0.29 (1.3)	0.33 (2.0)	0.22 (0.746)	0.30 (1.5)	0.19 (0.613)
Kendall's tau-b (BF ₊)	0.17 (0.991)	0.21 (1.61)	0.16 (0.855)	0.12 (0.572)	0.19 (1.2)	0.04 (0.310)
<i>Post-op UPDRS-III MAS/LAS on/disease duration (n=16)</i>	<i>Peak power</i>	<i>Sharpness</i>	<i>Burst amplitude</i>	<i>Burst duration</i>	<i>Oscillatory component</i>	<i>Non- oscillatory component</i>
Pearson's r (BF ₊)	0.55 (5.8)	0.66 (21.9)	0.37 (1.4)	0.54 (5.3)	0.60 (10.2)	-0.22 (0.187)
Kendall's tau-b (BF ₊)	0.20 (0.952)	0.39 (4.9)	0.24 (1.2)	0.49 (16.5)	0.34 (3.4)	-0.19 (0.168)

UPDRS = Unified Parkinson's Disease Rating Scale, MAS = More affected side, LAS = less affected side, STN = subthalamic nucleus, Pre-op = preoperative, Post-op = postoperative.

These correlations were driven by the oscillatory component of beta activity, which displayed up to extremely strong evidence of correlation with the rate of motor progression (Figure 25A and Table 9). Conversely, we obtained moderate evidence that the non-oscillatory component did not correlate with the rate of motor progression of the disease (Figure 25B and Table 9).

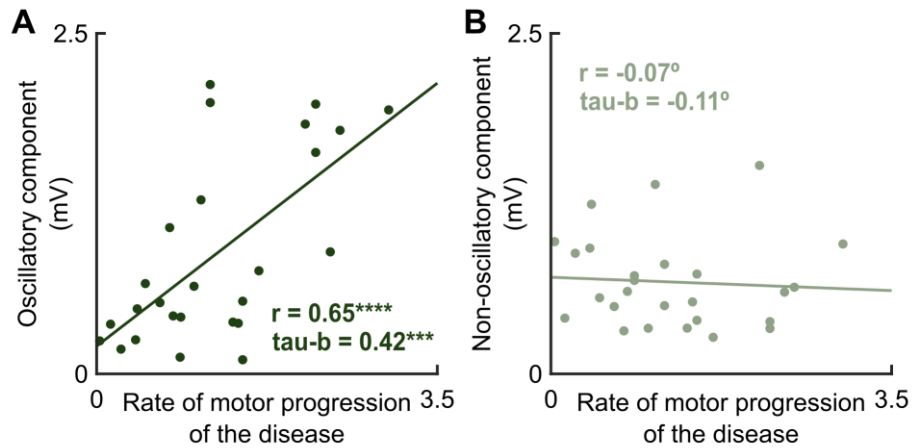


Figure 25. PD motor progression and beta activity I. A and B, correlations between the rate of motor progression of the disease and the oscillatory and non-oscillatory components of beta activity in PD. For this representation, the rate of motor progression of the disease was calculated as the lateralized post-operative off medication UPDRS-III scores divided by the corresponding disease duration ($^{\circ}BF_{+0} < 1/3$, $^{***}BF_{+0} > 30$, $^{****}BF_{+0} > 100$).

We further expanded these results, investigating the correlation of power and periodicity measures for each frequency component within the beta band range in PD with both the UPDRS-III scores and the rate of motor progression. We used the lateralized post-operative off and on medication UPDRS-III scores divided by the corresponding disease duration as the measure of motor progression.

We calculated both Pearson's and Kendall's correlation coefficient for each frequency component between power, periodicity and Bayesian periodicity measures and motor progression following a Bayesian approach (Figure 26). The rate of motor progression of the disease correlated positively with the power of the low beta band off medication, with moderate evidence of positive correlation. On the other hand, we reported moderate-to-extreme positive correlation between the rate of motor progression of the disease and both periodicity and Bayesian periodicity of the low beta band off medication, specifically around 15 Hz.

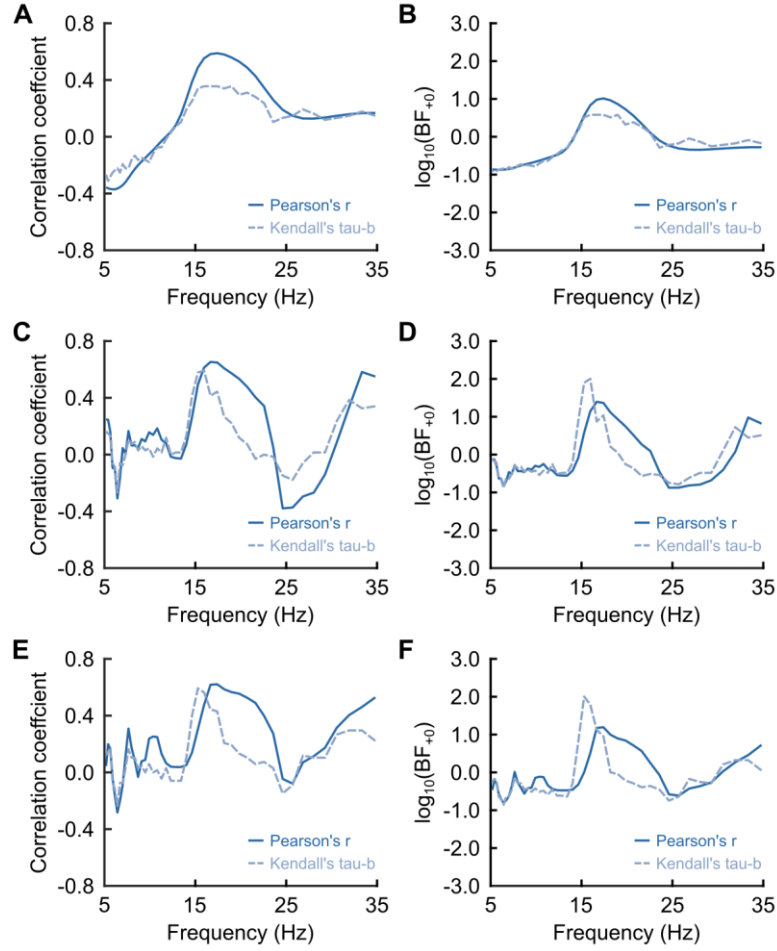


Figure 26. PD motor progression and beta activity II. A-F, Pearson's and Kendall's correlation coefficients and correspondent BF_{+0} values obtained from the correlation between power (A and B), periodicity (C and D), and Bayesian periodicity (E and F) in the 5-35 Hz range from STN LFPs recorded off medication ($n = 17$ nuclei) and rate of motor progression. The rate of motor progression of the disease was calculated as the lateralized post-operative off medication UPDRS-III scores divided by the corresponding disease duration.

In summary, these findings suggest that specifically the oscillatory component of the low beta band activity is related to the progression rate of motor impairment in PD patients.

6. Discussion and conclusions

This doctoral thesis unveils the relative contribution, dopamine dependency, response to neuromodulation and clinical relevance of oscillatory vs. non-oscillatory STN beta activity in PD. We first showed in simulated data that burst duration and spectral sharpness specifically measure oscillatory activity, whereas burst amplitude and spectral power ambiguously measure both oscillatory and non-oscillatory activity. We confirmed these relationships in experimental LFP data from PD patients off and on medication. We then obtained strong-to-extreme evidence that the oscillatory component of STN beta activity is reduced in PD patients on vs. off medication, and moderate evidence for absence of a modulation of the non-oscillatory component. Conversely, we found the opposite results on vs. off DBS: extreme evidence that the non-oscillatory component of STN beta activity is reduced, and moderate evidence for absence of a modulation of the oscillatory component. To solve the ambiguity of power spectrum analysis about oscillatory vs. non-oscillatory components of signal variance, here we introduced the periodicity spectrum. This method employs only phase information to directly assess oscillatory activity at each frequency without requiring any estimation or assumption about the underlying non-oscillatory activity. We further incorporated a Bayesian framework to formally assess the presence or absence of oscillatory activity at each frequency. We fully characterized and validated the Bayesian periodicity spectrum in simulated data, and we applied it to subthalamic local field potential recordings in patients with Parkinson’s disease, confirming our previous findings. Our results show that the Bayesian periodicity spectrum not only addresses the ambiguity of the power spectrum, but also outperforms it in terms of frequency selectivity, providing sharper resolution of oscillatory processes in both simulated and real data. Overall, the Bayesian periodicity spectrum offers a rigorous approach to quantifying oscillatory activity in biological signals. We

finally showed that specifically the oscillatory component of beta activity, particularly within the low-beta band, and not the non-oscillatory component, characterizes the AR clinical phenotype of PD, and correlates with the rate of motor progression of the disease.

6.1. Beta bursts, spectral measures and oscillatory/non-oscillatory activity

Our model-driven simulations clarify the theoretical correspondence between beta burst measures and spectral measures, and their relationships with oscillatory vs. non-oscillatory activity.

Previous studies have typically modelled beta oscillations with mechanistic approaches, by simulating the activity of neuronal populations in cortico-basal ganglia loops. For example, models at the cellular level allowed different aspects of beta oscillations to be investigated, such as their origin and generation, their synchrony within the basal ganglia network and their underlying mechanisms (Terman *et al.*, 2002; Nevado-Holgado *et al.*, 2014; Pavlides *et al.*, 2015; Schroll & Hamker, 2016; Mirzaei *et al.*, 2017; Bahuguna *et al.*, 2020). Other modelling studies have bridged the gap between the cellular level and the LFP level in order to gain deeper understanding of beta oscillatory activity in PD (Lempka & McIntyre, 2013; Fleming *et al.*, 2020). However, these studies did not investigate the oscillatory vs. non-oscillatory components of beta “oscillations”. We thus adopted a simpler statistical modelling approach, simulating beta activity by AR(2) models with additive 1/f noise. Note that autoregressive models represent the well-known basis for parametric power spectrum estimation (Akaike, 1969), which has been previously applied to basal ganglia LFP recordings in PD patients (Cassidy *et al.*, 2002; Foffani *et al.*, 2004, 2005). Importantly, our models allowed us to separately manipulate the oscillatory and non-oscillatory components of the simulated activity, and thus to assess the theoretical impact of these components on beta burst measures and spectral measures, as well as to map the correspondences between measures in the time and frequency domains. Burst duration corresponds to spectral sharpness, and they specifically measure

oscillatory activity. Burst amplitude corresponds to spectral power, and they ambiguously measure both oscillatory and non-oscillatory activity.

Spectral sharpness is also intuitively related to the frequency modulation, i.e., the variability of the instantaneous frequency, of the oscillation, which was recently characterized for STN beta activity as a predictor of the dopaminergic state (Averna *et al.*, 2022). This intuition was further confirmed by the correlations we found here between spectral sharpness and (Bayesian) periodicity measures. In general, measures of temporal stability that are invariant to the amplitude of the signal, e.g., burst duration, spectral sharpness or frequency modulation (Averna *et al.*, 2022), are primarily measuring the oscillatory component of the activity, whereas measures that are sensitive to the amplitude of the signal e.g., burst amplitude, spectral power or amplitude modulation (Averna *et al.*, 2022), are ambiguously measuring both the oscillatory and non-oscillatory components of the activity. The simplicity of spectral sharpness makes it an attractive new biomarker, which could be readily implemented in adaptive DBS devices. Spectral sharpness may thus foster the development of optimized adaptive DBS algorithms.

6.2. The Bayesian periodicity spectrum

The periodicity spectrum is built on the intuition that the temporal stability of instantaneous frequency serves as a direct measure of oscillatory activity (Averna *et al.*, 2022; Pardo-Valencia *et al.*, 2024). Since instantaneous frequency is derived purely from phase, the periodicity spectrum possesses a fundamental property: it is scale-invariant with respect to amplitude. This scale invariance means that the periodicity spectrum identifies oscillations independently of signal strength or gain, allowing it to distinguish oscillatory components even in presence of amplitude fluctuations from noise or other non-oscillatory sources. This amplitude scale invariance provides several advantages compared to the classical power spectrum. First, it makes the periodicity spectrum insensitive to non-oscillatory (aperiodic) components: random noise, which has high instantaneous frequency variance, translates to low periodicity values that do not depend on noise amplitude or $1/f$ exponent, allowing for a reliable distinction between oscillatory

activity and non-oscillatory background signals. This property reduces interpretative ambiguity and enables selective quantification of oscillations in scenarios where traditional power-based methods may be confounded by amplitude variations (Donoghue *et al.*, 2022). Second, insensitivity to non-oscillatory activity makes the periodicity spectrum well suited to integration within a probabilistic framework, because the null distribution (absence of oscillatory activity) is known *a priori*. This allowed us to incorporate a Bayesian framework (Zellner & Siow, 1980; Jeffreys, 1998; Rouder *et al.*, 2009, 2012; Morey & Wagenmakers, 2014; Gronau *et al.*, 2020), enabling quantification of evidence for both the presence and the absence of oscillatory activity at each frequency on a single-signal level – a challenge with power-based methods. Third, amplitude scale invariance contributes to greater frequency selectivity. By focusing on frequency stability, the periodicity spectrum avoids amplitude-related interference, allowing for more accurate frequency resolution compared to the power spectrum under similar conditions. This selectivity is particularly valuable in biological signals, where distinct frequency bands can carry specific functional or physiological significance.

While the Bayesian periodicity spectrum has important advantages, it also presents certain limitations. The method is non-linear; specifically, the periodicity spectrum of the sum of two independent signals does not equal the sum of their periodicity spectra. Additionally, is not a formal transform, unlike Fourier or wavelet transforms (Daubechies, 1990), since it lacks the mapping properties between domains. These limitations restrict some mathematical operations, such as direct additive synthesis across signal components or convolution-multiplication transformation between domains, which are available in power spectrum analysis. The Bayesian periodicity spectrum assumes stationarity but can also be naturally extended to track time-varying dynamics by estimating local variance of instantaneous frequency across time. This could be useful, for example, to reassess event-related changes in brain oscillations (Pfurtscheller & Lopes da Silva, 1999) without confounding shifts in non-oscillatory activity.

The Bayesian periodicity spectrum fundamentally differs from power-spectrum-based methods developed to address the spectral ambiguity between

oscillatory and non-oscillatory activity, such as IRASA (Wen & Liu, 2016), FOOOF (Donoghue *et al.*, 2020) and earlier techniques (Yamamoto & Hughson, 1991, 1993; Blankertz *et al.*, 2010; Hughes *et al.*, 2012; Gao, 2016; Martin *et al.*, 2018). These methods offer algorithmic solutions to estimate the non-oscillatory component within the power spectrum, enabling indirect estimation of the oscillatory component by subtracting the non-oscillatory estimate in the frequency domain. This approach is particularly useful when estimating the non-oscillatory component is a primary goal. However, these methods rely on two main assumptions: (1) that non-oscillatory activity follows a $1/f$ noise structure across the frequency range of interest, which may not always hold experimentally; and (2) that the $1/f$ component can be estimated accurately, which is not always feasible in practice (Gerster *et al.*, 2022). Consequently, any inaccuracies in estimating the non-oscillatory component – for example when it does not have a $1/f$ structure or cannot be fitted in the available band – impact the estimation of the oscillatory component. In contrast, the periodicity spectrum does not rely on assumptions about the structure of the non-oscillatory component. It directly quantifies the presence of oscillatory activity at each frequency, independently of other frequencies. Rather than representing a new algorithm for estimating an existing measure, the periodicity spectrum represents a new measure of oscillatory stability and periodicity in its own right, with broad applicability in biology.

Regarding estimation algorithms, a large engineering literature exists about the problem of estimating the instantaneous frequency of a signal (Boashash, 1992a, 1992b; Huang *et al.*, 2009; Stanković *et al.*, 2014). We used the STFT and the CWT, both of which provide a compact way to estimate the instantaneous frequency across frequencies and also allow for estimation of the power spectrum for direct comparison. Importantly, the time-frequency resolution should be carefully matched to the oscillatory processes in the target frequency range to obtain reliable estimates and to avoid edge effects (near zero or the Nyquist frequency). Other time-frequency decompositions and filter-bank approaches with Hilbert transform (Huang *et al.*, 1998) are equally valid options for estimating the periodicity spectrum. In principle, periodicity spectra could also be constructed

from other measures of oscillatory activity, such as the local sharpness of the power spectrum in the frequency domain or the “burst duration” of band-pass filtered signals in the time domain (Tinkhauser *et al.*, 2017c; Pardo-Valencia *et al.*, 2024). However, variance of instantaneous frequency remains a robust, elegant choice, as it quantifies oscillatory stability intuitively and captures the core periodic nature without amplitude-based or threshold-dependent metrics.

6.3. Dopamine dependency of oscillatory *vs.* non-oscillatory beta activity

The deeper understanding gained about beta burst measures, spectral measures and periodicity puts us in a position to rigorously answer the critical question about the oscillatory *vs.* non-oscillatory nature of parkinsonian beta activity, as a reappraisal at the mesoscopic scale of the classical dualism between firing patterns and firing rates in the pathophysiology of PD (Bevan *et al.*, 2002; Wichmann & DeLong, 2003; Wichmann, 2019). Importantly, the use of Bayesian statistics allowed us to assess both the evidence supporting a dopaminergic modulation and the evidence supporting the absence of a dopaminergic modulation, thereby disambiguating the unsatisfactory absence of evidence that is typically offered by frequentist statistics in case of “non-significant” results (Keysers *et al.*, 2020). We found that specifically the oscillatory component and not the non-oscillatory component of STN beta activity, specifically in the low-beta range, is disrupted by levodopa in PD patients. This specificity has important pathophysiological and translational implications.

From a pathophysiological perspective, the dopamine dependence of the oscillatory component of beta activity is completely consistent with more than two decades of literature on LFP recordings in PD (Brown *et al.*, 2001; Levy *et al.*, 2002; Priori *et al.*, 2004; Weinberger *et al.*, 2006; Alonso-Frech *et al.*, 2006; Tinkhauser *et al.*, 2017b). True STN “oscillations” in the beta range (and particularly in the low-beta range; (Priori *et al.*, 2004)) likely represent reverberant cortically driven activity (Williams *et al.*, 2002; Fogelson *et al.*, 2006; Lalo *et al.*, 2008; Litvak *et al.*, 2011; De Hemptinne *et al.*, 2013; Shimamoto *et al.*, 2013; Oswal *et al.*, 2016)

entering the striatum (Singh & Papa, 2020), where they are amplified by the hypersynchronization due to dopamine depletion (McCarthy *et al.*, 2011; Kondabolu *et al.*, 2016), thereby reaching the STN through the classical indirect pathway. The frequency of beta oscillations is too high to directly entrain muscle activity (which is the case for the slower tremor-related activity), but exaggerated beta oscillations seem sufficient to bring the cortico-basal ganglia motor circuits into a state of pathological equilibrium that is difficult to perturb, which manifests into a hypokinetic pathological state. The existence of two distinct cortico-subcortical beta rhythms – low-beta and high-beta – has long been postulated, based on higher sensitivity to dopaminergic medication in the low-beta band (Priori *et al.*, 2004), though it has not been definitively established. Our findings confirm that the Bayesian periodicity spectrum successfully identified two distinct beta rhythms in patients off medication, with dopaminergic modulation evident in the low-beta but not in the high-beta rhythm.

On the other hand, the absence of a dopamine dependency in the non-oscillatory component of beta activity was less expected. Non-oscillatory activity is believed to reflect the overall firing rate of underlying neurons (Manning *et al.*, 2009) and the local ratio between excitation and inhibition (Gao *et al.*, 2017). In rodent models of PD, dopaminergic medication decreases the firing rate of STN neurons (Kreiss *et al.*, 1997; Hassani & Feger, 1999), thereby moving the excitation–inhibition ratio toward inhibition. This dopamine-dependent decrease of subthalamic excitation is thus expected to decrease the power and increase the $1/f$ slope of non-oscillatory activity (Kim *et al.*, 2022). But the dopaminergic modulation of subthalamic firing rates is more controversial in primate models of PD (Gilmour *et al.*, 2011) and in PD patients (Levy *et al.*, 2001; Stefani *et al.*, 2002). In disagreement with our results, dopamine dependency in the non-oscillatory component of subthalamic beta activity was recently reported in PD patients (Wiest *et al.*, 2023). In that dataset, however, the total power in the beta band decreased with dopaminergic medication, but the peak power did not (Figure 2B in (Wiest *et al.*, 2023)), which is somewhat puzzling and at odds with a consolidated literature (Brown *et al.*, 2001; Levy *et al.*, 2002; Priori *et al.*, 2004; Weinberger *et*

al., 2006; Alonso-Frech *et al.*, 2006; Tinkhauser *et al.*, 2017b), rendering their results on the non-oscillatory component difficult to interpret. Admittedly, we only analysed the contact pair displaying maximum beta power off medication, so we cannot exclude a dopamine dependency of the non-oscillatory components at less optimal contact pairs. Still, the dopamine independence of the non-oscillatory component of beta activity observed in the present study suggests that subthalamic aperiodic fluctuations at the mesoscopic scale play a relatively minor role in the dopaminergic pathophysiology of PD. Our results thus support the concept of cortico-basal ganglia dopaminergic alterations in PD as an oscillopathy (Foffani & Alegre, 2022).

From a translational perspective, the specificity of dopamine dependency for the oscillatory component beta activity has important implications for adaptive DBS. If the aim is to adapt the stimulation to the dopamine-dependent clinical motor state of the patient, our results suggest (1) that neurophysiological biomarkers that track the non-oscillatory component are unlikely to be informative at the level of individual patients, and (2) that biomarkers that specifically track the oscillatory component (burst duration, spectral sharpness, periodicity and Bayesian periodicity, frequency modulation; (Averna *et al.*, 2022)) are in principle more robust than ambiguous biomarkers (burst amplitude, spectral power, amplitude modulation; (Averna *et al.*, 2022)), because oscillatory-specific biomarkers are less likely to be contaminated by non-dopaminergic and non-biological fluctuations of beta activity. Investigating the possible DBS-dependent alterations of these biomarkers would be important to define the overall control dynamics of a possible adaptive DBS system.

6.4. Neuromodulation of oscillatory *vs.* non-oscillatory beta activity

The findings showed throughout this work about DBS effects on neuronal activity and motor circuitry dynamics allows to thoroughly address the elusive question of how DBS modulates pathological synchronizations, abnormal firings and their interaction with cortical-basal ganglia loops in PD (Benabid *et al.*, 2009;

Lozano & Lipsman, 2013). Importantly, the application of advanced statistical frameworks, such as Bayesian modelling, enabled us to assess not only the evidence supporting the modulatory effects of DBS but also the evidence against such effects, providing clarity beyond the binary thresholds of significance often used in frequentist approaches (Keysers *et al.*, 2020). Specifically, we found that DBS does not modulate the oscillatory component of the beta band though it reduces non-oscillatory power, particularly within the high-beta frequency range. This selective effect on oscillatory and non-oscillatory beta components has profound implications for our understanding of PD pathophysiology and for optimizing therapeutic strategies.

Over the years, the underlying mechanisms of action of DBS have been investigated across multiple levels of analysis (Agnesi *et al.*, 2013; Ashkan *et al.*, 2017) from diverse perspectives (McIntyre & Hahn, 2010; McIntyre & Foutz, 2013; Jakobs *et al.*, 2019; Neumann *et al.*, 2023), in order to build a comprehensive understanding of its therapeutic effect in PD. Recent studies suggest that DBS would act by inhibiting the cortical excitatory inputs into the STN and promoting inhibition through the GPe (Steiner *et al.*, 2019, 2022; Neumann *et al.*, 2023), thus reducing subthalamic pathological beta oscillations. However, there is some evidence which indicates that DBS may not reduce subthalamic neural activity in the beta band (Foffani *et al.*, 2006; Blumenfeld *et al.*, 2017; Schmidt *et al.*, 2020). According to our own results on spectral and (Bayesian) periodicity measures, the latter hypothesis, i.e., DBS would not diminish beta oscillatory activity in PD, could be true. In this work, we found moderate evidence for a reduction in beta burst amplitude and duration on DBS. Though adaptive DBS may reduce at some point pathological subthalamic beta bursts (Tinkhauser *et al.*, 2017a), it seems that beta bursts characteristics should not be affected by continuous DBS (Schmidt *et al.*, 2020). It must also be considered that both burst amplitude and duration measures could be biased depending on the followed methodology (Anderson *et al.*, 2020; Duchet *et al.*, 2021) as well as the chosen amplitude threshold (Tinkhauser *et al.*, 2017b). Be that as it may, the new insights presented in this work primarily

suggest that DBS does not reduce pathological beta oscillatory activity as dopaminergic medication

On the other hand, we reported a dramatic reduction in non-oscillatory activity on DBS with very strong evidence, along with a strong reduction of the $1/f$ slope exponent of the power spectrum. This critical reduction of the non-oscillatory part of the power spectrum may have led to the conclusion that DBS abolish subthalamic beta oscillations. However, the advent of biomarkers that specifically target oscillatory components such as frequency modulation (Averna *et al.*, 2022) or sharpness of the peak (Pardo-Valencia *et al.*, 2024), and algorithms which separate oscillatory from non-oscillatory components such as FOOOF (Donoghue *et al.*, 2020) helped to better understand the effects of DBS on subthalamic activity. We further confirmed the lack of modulation on beta oscillatory components due to DBS using the Bayesian periodicity spectrum. This specificity suggests that the observed effects are confined to non-oscillatory activity. It has been established that the non-oscillatory component of the power spectrum would reflect the excitation/inhibition ratio in neuronal populations (Gao *et al.*, 2017). Contrary to our findings, recent studies propose that DBS promotes inhibition, reflected by an increase in the $1/f$ slope exponent (Darmani *et al.*, 2022; Wiest *et al.*, 2023). However, it is critical to note that these studies included the beta band in the slope estimation frequency range, a methodological choice that may bias the results (Gerster *et al.*, 2022). In this regard and according to our results, DBS would induce a net increase of excitation in STN neurons (Vitek, 2002; Galati *et al.*, 2008; Velarde *et al.*, 2017). Yet, our findings leave open the possibility that the observed effects on non-oscillatory activity and $1/f$ slope could reflect alterations in tissue impedance due to the energy delivered by DBS, rather than direct changes in neuronal excitation. Further studies must be conducted in order elucidate the true mechanism of action of DBS in PD.

6.5. Beta activity across clinical phenotypes

The characterization of subthalamic beta activity components according to the dominant clinical phenotype of PD patients further expands our knowledge about

the neural activity involved in the motor manifestations of the disease. Using the Bayesian periodicity spectrum, we found that increased oscillatory activity, specifically within the low-beta band, is characteristic of the AR phenotype in PD patients. This result was quite expected due to a number of previous published findings about the relationship between beta band activity, and bradykinesia and rigidity (Kühn *et al.*, 2006b, 2008b; Ray *et al.*, 2008b; Pogosyan *et al.*, 2009; Neumann *et al.*, 2016a; Lofredi *et al.*, 2019b, 2023a). The link between the oscillatory component of beta activity and hypokinetic parkinsonian motor features is supported by previous studies attempting to estimate this oscillatory component explicitly in the frequency domain (Martin *et al.*, 2018), or implicitly in the time domain, where burst duration seems to better reflect the clinical severity of motor features than burst amplitude (Tinkhauser *et al.*, 2017a, 2017b; Deffains *et al.*, 2018; Lofredi *et al.*, 2019a; Duchet *et al.*, 2021). Nevertheless, recent studies suggest that the pathophysiological mechanisms underlying bradykinesia and rigidity are at least partially independent (Zampogna *et al.*, 2024). To this effect, bradykinesia primarily would be a sign produced by dysfunction within the cortico-basal ganglia-thalamocortical loop (Michely *et al.*, 2015; De Hemptinne *et al.*, 2015; Wilkins *et al.*, 2023). Conversely, rigidity seems to be associated to functional alterations in specific brainstem circuits and descending pathways to the spinal cord (Delwaide *et al.*, 2000; Linn-Evans *et al.*, 2020; Asci *et al.*, 2023). A more exhaustive and deeper analysis of subthalamic oscillatory activity within the low beta band would certainly help in the understanding of these nuances.

The lack of reduction in subthalamic beta oscillatory activity due to DBS is consistently present in LFP recordings from PD patients presenting both clinical phenotypes, as well as the evident reduction of non-oscillatory power at high beta frequencies. Interestingly, the application of DBS in the STN of PD patients with tremor induced the manifestation of two distinguishable peaks of oscillatory activity in the beta band on average, i.e., one in the low-beta range and another one within the high-beta band, only observable through the Bayesian periodicity spectrum. It seems to exist a negative correlation between beta activity in the basal ganglia-cortical loop and rest tremor in PD patients, suggesting a functional

relationship between tremor dynamics and beta activity suppression (Hirschmann *et al.*, 2016, 2017). Moreover, decreased subthalamic beta activity relates to worsening of rest tremor in PD patients (Asch *et al.*, 2020). These findings support a model in which tremor contributes to the reduction of beta band synchronization within the basal ganglia-cortical circuit (Qasim *et al.*, 2016). This compensatory-like role of tremor implies that the suppression of rest tremor through DBS could partially promote the resurgence of pathological low-beta oscillatory activity in the STN. Furthermore, the observed reduction in non-oscillatory high-beta power highlights the complex interplay between oscillatory and non-oscillatory components in shaping the therapeutic effects of DBS. Future studies should aim to unravel the specific mechanisms driving these beta dynamics and their relationship to motor impairment, which could improve the personalization of therapeutic approaches such as optimizing DBS parameters or pharmacological treatments for hypokinetic *vs.* trembling manifestations.

6.6. Clinical correlations

Finally, we investigated the clinical correlations of the oscillatory and non-oscillatory components of beta activity.

Somewhat surprisingly, we did not find any clear correlation between measures of beta activity and motor severity. These results are not necessarily in contrast with previous studies (Kühn *et al.*, 2006; Ray *et al.*, 2008; Neumann *et al.*, 2016; Martin *et al.*, 2018; Lofredi *et al.*, 2023), since our correlations with motor severity are not conclusive and the evidence may accumulate toward the presence of correlation with larger sample sizes.

Interestingly, we did find moderate to extremely strong evidence that stronger beta oscillatory activity, specifically within the low-beta band, correlates with faster motor progression of the disease. This relationship emerged as an inverse correlation between beta oscillatory activity and disease duration, and was confirmed as a positive correlation between beta oscillatory activity and UPDRS-III scores divided by disease duration. These results support the robustness of the periodicity spectrum in delineating clinically meaningful oscillatory dynamics,

emphasizing its potential for detecting functionally relevant oscillatory activity and its modulation in clinical applications. On the one hand, our patients represent the specific disease stage at which they are candidate for DBS surgery, making disease duration a reasonable inverse measure of progression rate in our sample. On the other hand, UPDRS-III scores divided by disease duration admittedly have the limitations related to the cross-sectional assessments of progression rate (Marinus *et al.*, 2014). Future studies with longitudinal assessments of progression rate are thus warranted to confirm this relationship between beta oscillatory activity and rate of disease progression.

With all due caveats of correlative findings in a cross-sectional cohort, this intriguing relationship may have at least two possible explanations. A first possibility is that faster motor progression of the disease may cause stronger beta oscillatory activity due to subtype-specific pathophysiological mechanisms in cortico-basal ganglia circuits (Fereshtehnejad *et al.*, 2015, 2017; Belvisi *et al.*, 2021). For example, patients with more aggressive motor progression may have a lower (residual) long-duration response to levodopa and, consequently, stronger beta oscillatory activity after overnight withdrawal of dopaminergic medication, as in our off-medication recordings. A pathophysiological subtype specificity would also be consistent with beta oscillatory activity being stronger in the more aggressive PIGD phenotype compared to the less aggressive TD phenotype (Godinho *et al.*, 2021; Neuville *et al.*, 2021; Fim Neto *et al.*, 2022), although this is not always observed (Telkes *et al.*, 2018). A second possibility is that the causality is reversed in such a way that faster motor progression of the disease may actually be caused by stronger beta oscillatory activity. This view would be in agreement with classic STN-mediated excitotoxicity (Rodriguez *et al.*, 1998), and with the more recent cortical pathogenic theory of Parkinson's disease, according to which an excess of cortico-basal ganglia activity may act a stress factor for vulnerable dopaminergic terminals in the striatum (Foffani & Obeso, 2018). A pathogenic role of cortico-basal ganglia oscillatory beta activity could also contribute to explaining the neuroprotective effects observed with STN DBS or subthalamotomy in animal

models of PD, providing a possible rationale for early interventions toward disease modification (Foffani *et al.*, 2019).

6.7. Conclusions

1. Spectral sharpness is a novel and easy-to-implement approach that specifically measures oscillatory activity in biological signals which may represent the solution for the development of optimised adaptive DBS implementations.
2. The Bayesian periodicity spectrum offers a new paradigm for studying oscillatory activity, advancing our ability to characterize and interpret complex oscillatory dynamics in biological systems.
3. Primarily the oscillatory component of subthalamic beta activity, specifically in the low-beta range, at the mesoscopic scale is dopamine dependent.
4. The mechanism of action of DBS in PD does not involve the disruption of pathological beta oscillations in the STN, contrary to dopaminergic medication, and it is more related to modulatory effects on non-oscillatory neural dynamics.
5. PD clinical phenotypes are reflected in distinctive subthalamic beta profiles, which are informative of their underlying neural mechanisms and should be considered for the development of personalized therapies.
6. The oscillatory component of subthalamic beta activity may play a role not only in the pathophysiology but also in the progression of PD.

References

- Agnesi F, Johnson MD & Vitek JL (2013). Deep brain stimulation: how does it work? *Handb Clin Neurol* **116**, 39–54.
- Ahlskog JE & Muenter MD (2001). Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* **16**, 448–458.
- Akaike H (1969). Power spectrum estimation through autoregressive model fitting. *Ann Inst Stat Math* **21**, 407–419.
- Albin RL, Young AB & Penney JB (1989). The functional anatomy of basal ganglia disorders. *Trends Neurosci* **12**, 366–375.
- Alegre M, Alonso-Frech F, Rodríguez-Oroz MC, Guridi J, Zamarbide I, Valencia M, Manrique M, Obeso JA & Artieda J (2005). Movement-related changes in oscillatory activity in the human subthalamic nucleus: Ipsilateral vs. contralateral movements. *Eur J Neurosci* **22**, 2315–2324.
- Alexander GE & Crutcher MD (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* **13**, 266–271.
- Alexander GE, Crutcher MD & DeLong MR (1991). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. *Prog Brain Res* **85**, 119–146.
- Alexander GE, DeLong MR & Strick PL (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* **9**, 357–381.
- Alonso-Frech F, Zamarbide I, Alegre M, Rodríguez-Oroz MC, Guridi J, Manrique

- M, Valencia M, Artieda J & Obeso JA (2006). Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain* **129**, 1748–1757.
- Alvarez L, Macias R, Lopez G, Alvarez E, Pavon N, Rodriguez-Oroz MC, Juncos JL, Maragoto C, Guridi J, Litvan I, Tolosa ES, Koller W, Vitek J, DeLong MR & Obeso JA (2005). Bilateral subthalamotomy in Parkinson's disease: initial and long-term response. *Brain* **128**, 570–583.
- Ambrosi G, Cerri S & Blandini F (2014). A further update on the role of excitotoxicity in the pathogenesis of Parkinson's disease. *J Neural Transm* **121**, 849–859.
- Anderson RW, Kehnemouyi YM, Neuville RS, Wilkins KB, Anidi CM, Petrucci MN, Parker JE, Velisar A & Brontë-Stewart HM (2020). A novel method for calculating beta band burst durations in Parkinson's disease using a physiological baseline. *J Neurosci Methods* **343**, 108811.
- Androulidakis AG, Kühn AA, Chen CC, Blomstedt P, Kempf F, Kupsch A, Schneider GH, Doyle L, Dowsey-Limousin P, Hariz MI & Brown P (2007). Dopaminergic therapy promotes lateralized motor activity in the subthalamic area in Parkinson's disease. *Brain* **130**, 457–468.
- Arotcarena ML et al. (2020). Bidirectional gut-to-brain and brain-to-gut propagation of synucleinopathy in non-human primates. *Brain* **143**, 1462–1475.
- Asch N, Herschman Y, Maoz R, Auerbach-Asch CR, Valsky D, Abu-Snineh M, Arkadir D, Linetsky E, Eitan R, Marmor O, Bergman H & Israel Z (2020). Independently together: subthalamic theta and beta opposite roles in predicting Parkinson's tremor. *Brain Commun*; DOI: 10.1093/BRAINCOMMS/FCAA074.
- Asci F, Falletti M, Zampogna A, Patera M, Hallett M, Rothwell J & Suppa A (2023). Rigidity in Parkinson's disease: evidence from biomechanical and neurophysiological measures. *Brain* **146**, 3705–3718.
- Ashkan K, Rogers P, Bergman H & Ughratdar I (2017). Insights into the

- mechanisms of deep brain stimulation. *Nat Rev Neurol* 2017 139 **13**, 548–554.
- Avants BB, Epstein CL, Grossman M & Gee JC (2008). Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* **12**, 26–41.
- Avants BB, Tustison NJ, Song G, Cook PA, Klein A & Gee JC (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage* **54**, 2033–2044.
- Averna A, Marceglia S, Priori A & Foffani G (2022). Amplitude and frequency modulation of subthalamic beta oscillations jointly encode the dopaminergic state in Parkinson’s disease. *npj Park Dis* 2022 81 **8**, 1–12.
- Bahuguna J, Sahasranamam A & Kumar A (2020). Uncoupling the roles of firing rates and spike bursts in shaping the STN-GPe beta band oscillations. *PLOS Comput Biol* **16**, e1007748.
- Belova EM, Semenova U, Gamaleya AA, Tomskiy AA & Sedov A (2021). Voluntary movements cause beta oscillations increase and broadband slope decrease in the subthalamic nucleus of parkinsonian patients. *Eur J Neurosci*, DOI: 10.1111/ejn.14715.
- Belvisi D, Fabbrini A, De Bartolo MI, Costanzo M, Manzo N, Fabbrini G, Defazio G, Conte A & Berardelli A (2021). The Pathophysiological Correlates of Parkinson’s Disease Clinical Subtypes. *Mov Disord* **36**, 370–379.
- Benabid AL (2003). Deep brain stimulation for Parkinson’s disease. *Curr Opin Neurobiol* **13**, 696–706.
- Benabid AL, Chabardes S, Mitrofanis J & Pollak P (2009). Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson’s disease. *Lancet Neurol* **8**, 67–81.
- Bergman H, Wichmann T, Karmon B & DeLong MR (1994). The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J Neurophysiol* **72**, 507–520.
- Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K & Seitelberger F (1973).

- Brain dopamine and the syndromes of Parkinson and Huntington Clinical, morphological and neurochemical correlations. *J Neurol Sci* **20**, 415–455.
- Beudel M & Brown P (2016). Adaptive deep brain stimulation in Parkinson’s disease. *Parkinsonism Relat Disord* **22**, S123–S126.
- Bevan MD, Magill PJ, Terman D, Bolam JP & Wilson CJ (2002). Move to the rhythm: oscillations in the subthalamic nucleus–external globus pallidus network. *Trends Neurosci* **25**, 525–531.
- Bezard E, Boraud T, Bioulac B & Gross CE (1999). Involvement of the subthalamic nucleus in glutamatergic compensatory mechanisms. *Eur J Neurosci* **11**, 2167–2170.
- Blankertz B, Sannelli C, Halder S, Hammer EM, Kübler A, Müller K-R, Curio G & Dickhaus T (2010). Neurophysiological predictor of SMR-based BCI performance. *Neuroimage* **51**, 1303–1309.
- Blumenfeld Z, Koop MM, Prieto TE, Shreve LA, Velisar A, Quinn EJ, Trager MH & Brontë-Stewart H (2017). Sixty-hertz stimulation improves bradykinesia and amplifies subthalamic low-frequency oscillations. *Mov Disord* **32**, 80–88.
- Boashash B (1992a). Estimating and interpreting the instantaneous frequency of a signal. I. Fundamentals. *Proc IEEE* **80**, 520–538.
- Boashash B (1992b). Estimating and interpreting the instantaneous frequency of a signal. II. Algorithms and applications. *Proc IEEE* **80**, 540–568.
- El Boustani S, Marre O, Béhuret S, Baudot P, Yger P, Bal T, Destexhe A & Frégnac Y (2009). Network-State Modulation of Power-Law Frequency-Scaling in Visual Cortical Neurons. *PLOS Comput Biol* **5**, e1000519.
- Braak H, Bohl JR, Müller CM, Rüb U, de Vos RAI & Del Tredici K (2006). Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson’s disease reconsidered. *Mov Disord* **21**, 2042–2051.
- Brown P (2003). Oscillatory nature of human basal ganglia activity: Relationship to the pathophysiology of Parkinson’s disease. *Mov Disord* **18**, 357–363.

- Brown P, Oliviero A, Mazzone P, Insola A, Tonali P & Di Lazzaro V (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci* **21**, 1033–1038.
- Bucy PC & Case TJ (1939). TREMOR: PHYSIOLOGIC MECHANISM AND ABOLITION BY SURGICAL MEANS. *Arch Neurol Psychiatry* **41**, 721–746.
- Bush A, Zou JF, Lipski WJ, Kokkinos V & Richardson RM (2024). Aperiodic components of local field potentials reflect inherent differences between cortical and subcortical activity. *Cereb Cortex* **34**, bhae186.
- Buzsáki G, Anastassiou CA & Koch C (2012). The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nat Rev Neurosci* **13**, 407–420.
- Buzsáki G & Wang X-J (2012). Mechanisms of Gamma Oscillations. *Annu Rev Neurosci* **35**, 203–225.
- Calabresi P, Picconi B, Tozzi A, Ghiglieri V & Di Filippo M (2014). Direct and indirect pathways of basal ganglia: a critical reappraisal. *Nat Neurosci* **17**, 1022–1030.
- Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Lazzaro V Di & Brown P (2002). Movement-related changes in synchronization in the human basal ganglia. *Brain*.
- Castela I & Hernandez LF (2021). Shedding light on dyskinesias. *Eur J Neurosci* **53**, 2398–2413.
- Chaoul AI & Siegel M (2021). Cortical correlation structure of aperiodic neuronal population activity. *Neuroimage* **245**, 118672.
- Chaudhuri KR & Schapira AH (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* **8**, 464–474.
- Chen W, de Hemptinne C, Miller AM, Leibbrand M, Little SJ, Lim DA, Larson PS & Starr PA (2020a). Prefrontal-Subthalamic Hyperdirect Pathway Modulates Movement Inhibition in Humans. *Neuron* **106**, 579-588.e3.
- Chen Y, Gong C, Tian Y, Orlov N, Zhang J, Guo Y, Xu S, Jiang C, Hao H, Neumann

- WJ, Kühn AA, Liu H & Li L (2020*b*). Neuromodulation effects of deep brain stimulation on beta rhythm: A longitudinal local field potential study. *Brain Stimul* **13**, 1784–1792.
- Chu HY, McIver EL, Kovaleski RF, Atherton JF & Bevan MD (2017). Loss of Hyperdirect Pathway Cortico-Subthalamic Inputs Following Degeneration of Midbrain Dopamine Neurons. *Neuron* **95**, 1306-1318.e5.
- Chung JW, Ofori E, Misra G, Hess CW & Vaillancourt DE (2017). Beta-band activity and connectivity in sensorimotor and parietal cortex are important for accurate motor performance. *Neuroimage* **144**, 164–173.
- Clark DL, Khalil T, Kim LH, Noor MS, Luo F & Kiss ZH (2023). Aperiodic subthalamic activity predicts motor severity and stimulation response in Parkinson disease. *Parkinsonism Relat Disord* **110**, 105397.
- Cohen MX (2014). Fluctuations in Oscillation Frequency Control Spike Timing and Coordinate Neural Networks. *J Neurosci* **34**, 8988–8998.
- Colombo MA, Napolitani M, Boly M, Gosseries O, Casarotto S, Rosanova M, Brichant J-F, Boveroux P, Rex S & Laureys S (2019). The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. *Neuroimage* **189**, 631–644.
- Cotzias GC & Papavasiliou PS (1967). THERAPEUTIC STUDIES OF PARKINSONIAN PATIENTS: LONG TERM EFFECTS OF D, L, AND L DOPA. ; DOI: 10.2172/10116180.
- Darcy N, Lofredi R, Al-Fatly B, Neumann WJ, Hübl J, Brücke C, Krause P, Schneider GH & Kühn A (2022). Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. *Exp Neurol* **356**, 114150.
- Darmani G, Drummond NM, Ramezanpour H, Saha U, Hoque T, Udupa K, Sarica C, Zeng K, Cortez Grippe T, Nankoo JF, Bergmann TO, Hodaie M, Kalia SK, Lozano AM, Hutchison WD, Fasano A & Chen R (2022). Long-Term Recording

- of Subthalamic Aperiodic Activities and Beta Bursts in Parkinson's Disease. *Mov Disord*. DOI: 10.1002/MDS.29276.
- Daubechies I (1990). The wavelet transform, time-frequency localization and signal analysis. *IEEE Trans Inf Theory* **36**, 961–1005.
- Dauer W & Przedborski S (2003). Parkinson's disease: Mechanisms and models. *Neuron* **39**, 889–909.
- Dave S, Brothers TA & Swaab TY (2018). 1/f neural noise and electrophysiological indices of contextual prediction in aging. *Brain Res* **1691**, 34–43.
- Defer G, Widner H, Marié R, Rémy P & Levivier M (1999). Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord Off J Mov Disord Soc* **14**, 572–584.
- Deffains M, Iskhakova L, Katabi S, Israel Z & Bergman H (2018). Longer β oscillatory episodes reliably identify pathological subthalamic activity in Parkinsonism. *Mov Disord* **33**, 1609–1618.
- DeLong MR (1990). Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* **13**, 281–285.
- DeLong MR & Wichmann T (2007). Circuits and Circuit Disorders of the Basal Ganglia. *Arch Neurol* **64**, 20–24.
- Delwaide J, Pepin JL, De Pasqua V & De Noordhout AM (2000). Projections from basal ganglia to tegmentum: A subcortical route for explaining the pathophysiology of Parkinson's disease signs? *J Neurol Suppl* **247**, 75–81.
- Donoghue T, Haller M, Peterson EJ, Varma P, Sebastian P, Gao R, Noto T, Lara AH, Wallis JD, Knight RT, Shestyuk A & Voytek B (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nat Neurosci* **23**, 1655–U288.
- Donoghue T, Schaworonkow N & Voytek B (2022). Methodological considerations for studying neural oscillations. *Eur J Neurosci* **55**, 3502–3527.
- Dostrovsky J & Bergman H (2004). Oscillatory activity in the basal ganglia—relationship to normal physiology and pathophysiology. *Brain* **127**, 721–722.

- Duchet B, Ghezzi F, Weerasinghe G, Tinkhauser G, Kühn AA, Brown P, Bick C & Bogacz R (2021). Average beta burst duration profiles provide a signature of dynamical changes between the ON and OFF medication states in Parkinson's disease ed. Gutkin BS. *PLOS Comput Biol* **17**, e1009116.
- Ehringer H & Hornykiewicz O (1960). Verteilung Von Noradrenalin Und Dopamin (3-Hydroxytyramin) Im Gehirn Des Menschen Und Ihr Verhalten Bei Erkrankungen Des Extrapiramidalen Systems. *Klin Wochenschr* **38**, 1236–1239.
- Engel AK & Fries P (2010). Beta-band oscillations — signalling the status quo? *Curr Opin Neurobiol* **20**, 156–165.
- Fahn S (2008). The history of dopamine and levodopa in the treatment of Parkinson's disease. *Mov Disord*; DOI: 10.1002/MDS.22028.
- Fearnley JM & Lees AJ (1991). AGEING AND PARKINSON'S DISEASE: SUBSTANTIA NIGRA REGIONAL SELECTIVITY. *Brain* **114**, 2283–2301.
- Feldmann LK, Lofredi R, Neumann WJ, Al-Fatly B, Roediger J, Bahnert BH, Nikolov P, Denison T, Saryyeva A, Krauss JK, Faust K, Florin E, Schnitzler A, Schneider GH & Kühn AA (2022). Toward therapeutic electrophysiology: beta-band suppression as a biomarker in chronic local field potential recordings. *NPJ Park Dis*; DOI: 10.1038/S41531-022-00301-2.
- Fereshtehnejad SM, Romenets SR, Anang JBM, Latreille V, Gagnon JF & Postuma RB (2015). New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. *JAMA Neurol* **72**, 863–873.
- Fereshtehnejad SM, Zeighami Y, Dagher A & Postuma RB (2017). Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain* **140**, 1959–1976.
- Fernández-García C, Monje MHG, Gómez-Mayordomo V, Foffani G, Herranz R, Catalán MJ, González-Hidalgo M, Matias-Guiu J & Alonso-Frech F (2022). Long-term directional deep brain stimulation: Monopolar review vs. local field

- potential guided programming. *Brain Stimul* **15**, 727–736.
- Fim Neto A, de Luccas JB, Bianqueti BL, da Silva LR, Almeida TP, Takahata AK, Teixeira MJ, Figueiredo EG, Nasuto SJ, Rocha MSG, Soriano DC & Godinho F (2022). Subthalamic low beta bursts differ in Parkinson’s disease phenotypes. *Clin Neurophysiol* **140**, 45–58.
- Fine J, Duff J, Chen R, Hutchison W, Lozano AM & Lang AE (2000). Long-Term Follow-up of Unilateral Pallidotomy in Advanced Parkinson’s Disease. *N Engl J Med* **342**, 1708–1714.
- Fleming JE, Dunn E & Lowery MM (2020). Simulation of Closed-Loop Deep Brain Stimulation Control Schemes for Suppression of Pathological Beta Oscillations in Parkinson’s Disease. *Front Neurosci* **0**, 166.
- Foffani G & Alegre M (2022). Brain oscillations and Parkinson’s disease. In *Handbook of Clinical Neurology*.
- Foffani G, Ardolino G, Egidio M, Caputo E, Bossi B & Priori A (2006). Subthalamic oscillatory activities at beta or higher frequency do not change after high-frequency DBS in Parkinson’s disease. *Brain Res Bull*; DOI: 10.1016/j.brainresbull.2005.11.012.
- Foffani G, Bianchi AM, Baselli G & Priori A (2005). Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. *J Physiol* **568**, 699–711.
- Foffani G, Bianchi AM, Priori A & Baselli G (2004). Adaptive autoregressive identification with spectral power decomposition for studying movement-related activity in scalp EEG signals and basal ganglia local field potentials. *J Neural Eng* **1**, 165.
- Foffani G & Obeso JA (2018). A Cortical Pathogenic Theory of Parkinson’s Disease. *Neuron* **99**, 1116–1128.
- Foffani G, Priori A, Egidio M, Rampini P, Tamma F, Caputo E, Moxon KA, Cerutti S & Barbieri S (2003). 300-Hz subthalamic oscillations in Parkinson’s disease. *Brain* **126**, 2153–2163.

- Foffani G, Trigo-Damas I, Pineda-Pardo JA, Blesa J, Rodríguez-Rojas R, Martínez-Fernández R & Obeso JA (2019). Focused ultrasound in Parkinson's disease: A twofold path toward disease modification. *Mov Disord* **34**, 1262–1273.
- Fogelson N, Williams D, Tijssen M, Van Bruggen G, Speelman H & Brown P (2006). Different Functional Loops between Cerebral Cortex and the Subthalamic Area in Parkinson's Disease. *Cereb Cortex* **16**, 64–75.
- Fonov V, Evans A, McKinstry R, Almlí C & Collins D (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *Neuroimage* **47**, S102.
- Galati S, Scarnati E, Mazzone P, Stanzione P & Stefani A (2008). Deep brain stimulation promotes excitation and inhibition in subthalamic nucleus in Parkinson's disease. *Neuroreport* **19**, 661–666.
- Gao R (2016). Interpreting the electrophysiological power spectrum. *J Neurophysiol* **115**, 628–630.
- Gao R, Peterson EJ & Voytek B (2017). Inferring synaptic excitation/inhibition balance from field potentials. *Neuroimage*; DOI: 10.1016/j.neuroimage.2017.06.078.
- Gatev P, Darbin O & Wichmann T (2006). Oscillations in the basal ganglia under normal conditions and in movement disorders. *Mov Disord* **21**, 1566–1577.
- Gerster M, Waterstraat G, Litvak V, Lehnertz K, Schnitzler A, Florin E, Curio G & Nikulin V (2022). Separating Neural Oscillations from Aperiodic 1/f Activity: Challenges and Recommendations. *Neuroinformatics* **20**, 991–1012.
- Ghika J, Villemure JG, Fankhauser H, Favre J, Assal G & Ghika-Schmid F (1998). Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. *J Neurosurg* **89**, 713–718.
- Gibb AJ & Colquhoun D (1991). Glutamate activation of a single NMDA receptor-channel produces a cluster of channel openings. *Proceedings Biol Sci* **243**, 39–

45.

- Gibb WRG & Lees AJ (1988). The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* **51**, 745–752.
- Gilmour TP, Lieu CA, Nolt MJ, Piallat B, Deogaonkar M & Subramanian T (2011). The effects of chronic levodopa treatments on the neuronal firing properties of the subthalamic nucleus and substantia nigra reticulata in hemiparkinsonian rhesus monkeys. *Exp Neurol* **228**, 53–58.
- Godinho F, Fim Neto A, Bianqueti BL, de Luccas JB, Varjão E, Terzian Filho PR, Figueiredo EG, Almeida TP, Yoneyama T, Takahata AK, Rocha MS & Soriano DC (2021). Spectral characteristics of subthalamic nucleus local field potentials in Parkinson's disease: Phenotype and movement matter. *Eur J Neurosci* **53**, 2804–2818.
- Goetz CG et al. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord* **23**, 2129–2170.
- Gronau QF, Ly A & Wagenmakers EJ (2020). Informed Bayesian t-Tests. *Am Stat* **74**, 137–143.
- Group TD-BS for PDS (2001). Deep-Brain Stimulation of the Subthalamic Nucleus or the Pars Interna of the Globus Pallidus in Parkinson's Disease. *N Engl J Med* **345**, 956–963.
- Guridi J & Alegre M (2017). Oscillatory activity in the basal ganglia and deep brain stimulation. *Mov Disord* **32**, 64–69.
- Haber SN (2014). The place of dopamine in the cortico-basal ganglia circuit. *Neuroscience* **282**, 248.
- Hassani O-K & Feger J (1999). Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: an electrophysiological and c-Fos study. *Neuroscience* **92**, 533–543.
- Hauser RA & Auinger P (2011). Determination of minimal clinically important

- change in early and advanced Parkinson's disease. *Mov Disord* **26**, 813–818.
- He BJ (2011). Scale-Free Properties of the Functional Magnetic Resonance Imaging Signal during Rest and Task. *J Neurosci* **31**, 13786–13795.
- He BJ (2014). Scale-free brain activity: past, present and future. *Trends Cogn Sci* **18**, 480.
- He BJ, Zempel JM, Snyder AZ & Raichle ME (2010). The temporal structures and functional significance of scale-free brain activity. *Neuron* **66**, 353–369.
- Helson P, Lundqvist D, Svenningsson P, Vinding MC & Kumar A (2023). Cortex-wide topography of 1/f-exponent in Parkinson's disease. *NPJ Park Dis*; DOI: 10.1038/S41531-023-00553-6.
- De Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, Ostrem JL, Galifianakis NB & Starr PA (2013). Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. *Proc Natl Acad Sci USA* **110**, 4780–4785.
- De Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB & Starr PA (2015). Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci* **18**, 779–786.
- Heng N, Malek N, Lawton MA, Nodehi A, Pitz V, Grosset KA, Ben-Shlomo Y & Grosset DG (2023). Striatal Dopamine Loss in Early Parkinson's Disease: Systematic Review and Novel Analysis of Dopamine Transporter Imaging. *Mov Disord Clin Pract* **10**, 539.
- Hilbert D (1912). *Grundzüge einer allgemeinen Theorie der linearen Integralgleichungen*. BG Teubner.
- Hirsch EC, Jenner P & Przedborski S (2013). Pathogenesis of Parkinson's disease. *Mov Disord* **28**, 24–30.
- Hirschmann J, Butz M, Hartmann CJ, Hoogenboom N, Özkurt TE, Vesper J, Wojtecki L & Schnitzler A (2016). Parkinsonian Rest Tremor Is Associated With Modulations of Subthalamic High-Frequency Oscillations. *Mov Disord*

- 31, 1551–1559.
- Hirschmann J, Schoffelen JM, Schnitzler A & van Gerven MAJ (2017). Parkinsonian rest tremor can be detected accurately based on neuronal oscillations recorded from the subthalamic nucleus. *Clin Neurophysiol* **128**, 2029–2036.
- Horn A & Kühn AA (2015). Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. *Neuroimage* **107**, 127–135.
- Horn A, Li N, Dembek TA, Kappel A, Boulay C, Ewert S, Tietze A, Husch A, Perera T, Neumann WJ, Reisert M, Si H, Oostenveld R, Rorden C, Yeh FC, Fang Q, Herrington TM, Vorwerk J & Kühn AA (2019). Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. *Neuroimage* **184**, 293–316.
- Hornykiewicz O (1966). DOPAMINE (3-HYDROXYTYRAMINE) AND BRAIN FUNCTION. *Pharmacol Rev.*
- Huang NE, Shen Z, Long SR, Wu MC, Snin HH, Zheng Q, Yen NC, Tung CC & Liu HH (1998). The empirical mode decomposition and the Hubert spectrum for nonlinear and non-stationary time series analysis. *Proc R Soc A Math Phys Eng Sci* DOI: 10.1098/rspa.1998.0193.
- Huang NE, Wu Z, Long SR, Arnold KC, Chen X & Blank K (2009). On instantaneous frequency. *Adv Adapt Data Anal* DOI: 10.1142/S1793536909000096.
- Hughes AJ, Ben-Shlomo Y, Daniel SE & Lees AJ (1992). What features improve the accuracy of clinical diagnosis in parkinson’s disease: A clinicopathologic study. *Neurology* **42**, 1142–1146.
- Hughes AM, Whitten TA, Caplan JB & Dickson CT (2012). BOSC: A better oscillation detection method, extracts both sustained and transient rhythms from rat hippocampal recordings. *Hippocampus* DOI: 10.1002/hipo.20979.
- Hurtado JM, Rubchinsky LL & Sigvardt KA (2004). Statistical Method for Detection of Phase-Locking Episodes in Neural Oscillations. *J Neurophysiol*

91, 1883–1898.

- Husch A, V. Petersen M, Gemmar P, Goncalves J & Hertel F (2017). PaCER - A fully automated method for electrode trajectory and contact reconstruction in deep brain stimulation. *NeuroImage Clin* **17**, 80–89.
- Hutchison WD, Dostrovsky JO, Walters JR, Courtemanche R, Boraud T, Goldberg J & Brown P (2004). Neuronal Oscillations in the Basal Ganglia and Movement Disorders: Evidence from Whole Animal and Human Recordings. *J Neurosci* **24**, 9240–9243.
- Jahanshahi M, Obeso I, Rothwell JC & Obeso JA (2015). A fronto–striato–subthalamic–pallidal network for goal-directed and habitual inhibition. *Nat Rev Neurosci* **2015** *1612* **16**, 719–732.
- Jakobs M, Fomenko A, Lozano AM & Kiening KL (2019). Cellular, molecular, and clinical mechanisms of action of deep brain stimulation—a systematic review on established indications and outlook on future developments. *EMBO Mol Med*. DOI: 10.15252/EMMM.201809575/ASSET/6CD26C70-0244-4704-A38A-F0F83ECEC1D2/ASSETS/GRAPHIC/EMMM201809575-FIG-0007-M.PNG.
- Jankovic J (2005). Motor fluctuations and dyskinesias in Parkinson’s disease: clinical manifestations. *Mov Disord*. DOI: 10.1002/MDS.20458.
- Jeffreys H (1998). *The theory of probability*. OuP Oxford.
- Jeong SH, Park CW, Lee HS, Kim YJ, Yun M, Lee PH, Sohn YH & Chung SJ (2023). Patterns of striatal dopamine depletion and motor deficits in de novo Parkinson’s disease. *J Neural Transm* **130**, 19–28.
- Kalia L V. & Lang AE (2015). Parkinson’s disease. *Lancet* **386**, 896–912.
- Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA & Ritz B (2005). Clinical characteristics in early Parkinson’s disease in a central California population-based study. *Mov Disord* **20**, 1133–1142.
- Keeler JF, Pretsell DO & Robbins TW (2014). Functional implications of dopamine D1 vs. D2 receptors: A ‘prepare and select’ model of the striatal direct vs. indirect pathways. *Neuroscience* **282**, 156–175.

- Keyzers C, Gazzola V & Wagenmakers EJ (2020). Using Bayes factor hypothesis testing in neuroscience to establish evidence of absence. *Nat Neurosci* 2020 **23**, 788–799.
- Khanna P & Carmena JM (2015). Neural oscillations: beta band activity across motor networks. *Curr Opin Neurobiol* **32**, 60–67.
- Khanna P & Carmena JM (2017). Beta band oscillations in motor cortex reflect neural population signals that delay movement onset. *Elife*; DOI: 10.7554/ELIFE.24573.
- Kim J, Lee J, Kim E, Choi JH, Rah JC & Choi JW (2022). Dopamine depletion can be predicted by the aperiodic component of subthalamic local field potentials. *Neurobiol Dis*; DOI: 10.1016/j.nbd.2022.105692.
- Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, Lee JH, Kim WR, Kook M, Foss CA, Shen C, Lee H, Kulkarni S, Pasricha PJ, Lee G, Pomper MG, Dawson VL, Dawson TM & Ko HS (2019). Transneuronal Propagation of Pathologic α -Synuclein from the Gut to the Brain Models Parkinson's Disease. *Neuron* **103**, 627–641.e7.
- Kluger DS, Forster C, Abbasi O, Chalas N, Villringer A & Gross J (2023). Modulatory dynamics of periodic and aperiodic activity in respiration-brain coupling. *Nat Commun* **14**, 4699.
- Kondabolu K, Roberts EA, Bucklin M, McCarthy MM, Kopell N & Han X (2016). Striatal cholinergic interneurons generate beta and gamma oscillations in the corticostriatal circuit and produce motor deficits. *Proc Natl Acad Sci U S A* **113**, 3159–3168.
- Kordower JH, Olanow CW, Dodiya HB, Chu Y, Beach TG, Adler CH, Halliday GM & Bartus RT (2013). Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain* **136**, 2419–2431.
- Kreiss DS, Mastropietro CW, Rawji SS & Walters JR (1997). The response of subthalamic nucleus neurons to dopamine receptor stimulation in a rodent model of Parkinson's disease. *J Neurosci* **17**, 6807–6819.

- Kühn AA, Kupsch A, Schneider G-H & Brown P (2006). Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur J Neurosci* **23**, 1956–1960.
- Lagrange E, Krack P, Moro E, Ardouin C, Van Blercom N, Chabardes S, Benabid AL & Pollak P (2002). Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology* **59**, 1976–1978.
- Lalo E, Thobois S, Sharott A, Polo G, Mertens P, Pogosyan A & Brown P (2008). Patterns of Bidirectional Communication between Cortex and Basal Ganglia during Movement in Patients with Parkinson Disease. *J Neurosci* **28**, 3008–3016.
- Lang AE & Espay AJ (2018). Disease Modification in Parkinson's Disease: Current Approaches, Challenges, and Future Considerations. *Mov Disord* **33**, 660–677.
- Lempka SF & McIntyre CC (2013). Theoretical Analysis of the Local Field Potential in Deep Brain Stimulation Applications. *PLoS One* **8**, e59839.
- Lendner JD, Helfrich RF, Mander BA, Romundstad L, Lin JJ, Walker MP, Larsson PG & Knight RT (2020). An electrophysiological marker of arousal level in humans. *Elife* **9**, e55092.
- Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM & Dostrovsky JO (2002). Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain* **125**, 1196–1209.
- Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD & Lozano AM (2001). Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. *J Neurophysiol* **86**, 249–260.
- Linn-Evans ME, Petrucci MN, Amundsen Huffmaster SL, Chung JW, Tuite PJ, Howell MJ, Videnovic A & MacKinnon CD (2020). REM sleep without atonia is associated with increased rigidity in patients with mild to moderate Parkinson's disease. *Clin Neurophysiol* **131**, 2008–2016.
- Little S & Brown P (2014). The functional role of beta oscillations in Parkinson's disease. *Parkinsonism Relat Disord* **20**, S44–S48.

- Little S & Brown P (2020). Debugging Adaptive Deep Brain Stimulation for Parkinson's Disease. *Mov Disord* **35**, 555.
- Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, Foltynie T, Limousin P, Ashkan K, FitzGerald J, Green AL, Aziz TZ & Brown P (2013). Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* **74**, 449–457.
- Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K & Brown P (2011). Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain* **134**, 359–374.
- Lofredi R, Neumann W-J, Brücke C, Huebl J, Krauss JK, Schneider G-H & Kühn AA (2019a). Pallidal beta bursts in Parkinson's disease and dystonia. *Mov Disord* **34**, 420–424.
- Lofredi R, Okudzhava L, Irmen F, Brücke C, Huebl J, Krauss JK, Schneider G-H, Faust K, Neumann W-J & Kühn AA (2023). Subthalamic beta bursts correlate with dopamine-dependent motor symptoms in 106 Parkinson's patients. *npj Park Dis* 2023 91 **9**, 1–9.
- Lofredi R, Tan H, Neumann WJ, Yeh CH, Schneider GH, Kühn AA & Brown P (2019b). Beta bursts during continuous movements accompany the velocity decrement in Parkinson's disease patients. *Neurobiol Dis* **127**, 462–471.
- López-Azcárate J, Tainta M, Rodríguez-Oroz MC, Valencia M, González R, Guridi J, Iriarte J, Obeso JA, Artieda J & Alegre M (2010). Coupling between Beta and High-Frequency Activity in the Human Subthalamic Nucleus May Be a Pathophysiological Mechanism in Parkinson's Disease. *J Neurosci* **30**, 6667–6677.
- Lozano AM, Lang AE, Galvez-Jimenez N, Miyasaki J, Duff J, Hutchison WD & Dostrovsky JO (1995). Effect of GPi pallidotomy on motor function in Parkinson's disease. *Lancet (London, England)* **346**, 1383–1387.
- Lozano AM & Lipsman N (2013). Probing and Regulating Dysfunctional Circuits Using Deep Brain Stimulation. *Neuron* **77**, 406–424.
- Ly A, Etz A, Marsman M & Wagenmakers E-J (2019). Replication Bayes factors

- from evidence updating. *Behav Res Methods* **51**, 2498–2508.
- Manning JR, Jacobs J, Fried I & Kahana MJ (2009). Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *J Neurosci*; DOI: 10.1523/JNEUROSCI.2041-09.2009.
- Marinus J, van der Heeden JF & van Hilten JJ (2014). Calculating clinical progression rates in Parkinson’s disease: Methods matter. *Parkinsonism Relat Disord* **20**, 1263–1267.
- Marras C & Lang A (2013). Parkinson’s disease subtypes: lost in translation? *J Neurol Neurosurg Psychiatry* **84**, 409–415.
- Marsden CD & Obeso JA (1994). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson’s disease. *Brain* **117** (Pt 4), 877–897.
- Marsden JF, Limousin-Dowsey P, Ashby P, Pollak P & Brown P (2001). Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson’s disease. *Brain* **124**, 378–388.
- Martin S, Iturrate I, Chavarriaga R, Leeb R, Sobolewski A, Li AM, Zaldivar J, Peciú-Florianu I, Pralong E, Castro-Jiménez M, Benninger D, Vingerhoets F, Knight RT, Bloch J & Millán J del R (2018). Differential contributions of subthalamic beta rhythms and 1/f broadband activity to motor symptoms in Parkinson’s disease. *NPJ Park Dis*; DOI: 10.1038/S41531-018-0068-Y.
- McCarthy MM, Moore-Kochlacs C, Gu X, Boyden ES, Han X & Kopell N (2011). Striatal origin of the pathologic beta oscillations in Parkinson’s disease. *Proc Natl Acad Sci U S A* **108**, 11620–11625.
- Mcintyre CC & Foutz TJ (2013). Computational modeling of deep brain stimulation. *Handb Clin Neurol* **116**, 55–61.
- McIntyre CC & Hahn PJ (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol Dis* **38**, 329–337.
- McKeown DJ, Jones M, Pihl C, Finley AJ, Kelley N, Baumann O, Schinazi VR, Moustafa AA, Cavanagh JF & Angus DJ (2024). Medication-invariant resting

- aperiodic and periodic neural activity in Parkinson's disease. *Psychophysiology*; DOI: 10.1111/PSYP.14478.
- Meldrum B & Garthwaite J (1990). Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol Sci* **11**, 379–387.
- Meyers R (1940). Surgical procedure for postencephalitic tremor, with notes on the physiology of premotor fibers. *Arch Neurol Psychiatry* **44**, 455–459.
- Meyers R (1951). Surgical experiments in the therapy of certain “extrapyramidal” diseases: a current evaluation. *Acta Psychiatr Neurol Suppl.*
- Michely J, Volz LJ, Barbe MT, Hoffstaedter F, Viswanathan S, Timmermann L, Eickhoff SB, Fink GR & Grefkes C (2015). Dopaminergic modulation of motor network dynamics in Parkinson's disease. *Brain* **138**, 664–678.
- Miller KJ, Sorensen LB, Ojemann JG & Den Nijs M (2009a). Power-law scaling in the brain surface electric potential. *PLoS Comput Biol*; DOI: 10.1371/journal.pcbi.1000609.
- Miller KJ, Sorensen LB, Ojemann JG & Den Nijs M (2009b). Power-Law Scaling in the Brain Surface Electric Potential. *PLOS Comput Biol* **5**, e1000609.
- Mirzaei A, Kumar A, Leventhal D, Mallet N, Aertsen A, Berke J & Schmidt R (2017). Sensorimotor Processing in the Basal Ganglia Leads to Transient Beta Oscillations during Behavior. *J Neurosci* **37**, 11220–11232.
- Miskovic V, MacDonald KJ, Rhodes LJ & Cote KA (2019). Changes in EEG multiscale entropy and power-law frequency scaling during the human sleep cycle. *Hum Brain Mapp* **40**, 538–551.
- Monje MHG, Sánchez-Ferro Á, Pineda-Pardo JA, Vela-Desojo L, Alonso-Frech F & Obeso JA (2021). Motor Onset Topography and Progression in Parkinson's Disease: the Upper Limb Is First. *Mov Disord* **36**, 905–915.
- Morey RD & Wagenmakers E-J (2014). Simple relation between Bayesian order-restricted and point-null hypothesis tests. *Stat Probab Lett* **92**, 121–124.
- Moro E, Esselink RJA, Xie J, Hommel M, Benabid AL & Pollak P (2002). The impact on Parkinson's disease of electrical parameter settings in STN

- stimulation. *Neurology* **59**, 706–713.
- Musacchio T, Rebenstorff M, Fluri F, Brothie JM, Volkmann J, Koprach JB & Ip CW (2017). Subthalamic nucleus deep brain stimulation is neuroprotective in the A53T α -synuclein Parkinson's disease rat model. *Ann Neurol* **81**, 825–836.
- Muthukumaraswamy SD & Liley DTJ (2018). 1/f electrophysiological spectra in resting and drug-induced states can be explained by the dynamics of multiple oscillatory relaxation processes. *Neuroimage* **179**, 582–595.
- Nambu A, Tokuno H, Hamada I, Kita H, Imanishi M, Akazawa T, Ikeuchi Y & Hasegawa N (2000). Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *J Neurophysiol* **84**, 289–300.
- Nambu A, Tokuno H & Takada M (2002). Functional significance of the cortico–subthalamo–pallidal ‘hyperdirect’ pathway. *Neurosci Res* **43**, 111–117.
- Neumaier A & Schneider T (2001). Estimation of parameters and eigenmodes of multivariate autoregressive models. *ACM Trans Math Softw* **27**, 27–57.
- Neumann W-J, Degen K, Schneider G-H, Brücke C, Huebl J, Brown P & Kühn AA (2016). Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Mov Disord* **31**, 1748–1751.
- Neumann WJ, Steiner LA & Milosevic L (2023). Neurophysiological mechanisms of deep brain stimulation across spatiotemporal resolutions. *Brain* **146**, 4456–4468.
- Neuville RS, Petrucci MN, Wilkins KB, Anderson RW, Hoffman SL, Parker JE, Velisar A & Bronte-Stewart HM (2021). Differential Effects of Pathological Beta Burst Dynamics Between Parkinson's Disease Phenotypes Across Different Movements. *Front Neurosci*; DOI: 10.3389/FNINS.2021.733203.
- Nevado-Holgado AJ, Mallet N, Magill PJ & Bogacz R (2014). Effective connectivity of the subthalamic nucleus–globus pallidus network during Parkinsonian oscillations. *J Physiol* **592**, 1429–1455.
- Obeso JA, Marin C, Rodríguez-Oroz C, Blesa J, Benitez-Temiño B, Mena-Segovia J, Rodríguez M & Olanow CW (2008a). The basal ganglia in Parkinson's

- disease: current concepts and unexplained observations. *Ann Neurol*; DOI: 10.1002/ANA.21481.
- Obeso JA, Olanow CW & Nutt JG (2000a). Levodopa motor complications in Parkinson's disease. *Trends Neurosci*; DOI: 10.1016/S1471-1931(00)00031-8.
- Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C & Rodríguez M (2008b). Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Mov Disord* **23**, S548–S559.
- Obeso JA, Rodríguez-Oroz MC, Rodríguez M, Lanciego JL, Artieda J, Gonzalo N & Olanow CW (2000b). Pathophysiology of the basal ganglia in Parkinson's disease. *Trends Neurosci* **23**, S8–S19.
- Olanow CW (2007). The pathogenesis of cell death in Parkinson's disease – 2007. *Mov Disord* **22**, S335–S342.
- Oostenveld R, Fries P, Maris E & Schoffelen JM (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Comput Intell Neurosci* **2011**, 156869.
- Oswal A, Cao C, Yeh CH, Neumann WJ, Gratwicke J, Akram H, Horn A, Li D, Zhan S, Zhang C, Wang Q, Zrinzo L, Foltynie T, Limousin P, Bogacz R, Sun B, Husain M, Brown P & Litvak V (2021). Neural signatures of hyperdirect pathway activity in Parkinson's disease. *Nat Commun*; DOI: 10.1038/S41467-021-25366-0.
- Oswal A, Jha A, Neal S, Reid A, Bradbury D, Aston P, Limousin P, Foltynie T, Zrinzo L, Brown P & Litvak V (2016). Analysis of simultaneous MEG and intracranial LFP recordings during Deep Brain Stimulation: a protocol and experimental validation. *J Neurosci Methods* **261**, 29–46.
- Ozturk M, Abosch A, Francis D, Wu J, Jimenez-Shahed J & Ince NF (2020). Distinct subthalamic coupling in the ON state describes motor performance in Parkinson's disease. *Mov Disord* **35**, 91–100.
- Pardo-Valencia J, Fernández-García C, Alonso-Frech F & Foffani G (2024). Oscillatory vs. non-oscillatory subthalamic beta activity in Parkinson's

- disease. *J Physiol* **602**, 373–395.
- Parkinson J (2002). An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci*; DOI: 10.1176/JNP.14.2.223.
- Pavlidis A, Hogan SJ & Bogacz R (2015). Computational Models Describing Possible Mechanisms for Generation of Excessive Beta Oscillations in Parkinson's Disease ed. Graham LJ. *PLOS Comput Biol* **11**, e1004609.
- Pfurtscheller G & Lopes da Silva FH (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* **110**, 1842–1857.
- Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, Schrag A-E & Lang AE (2017). Parkinson disease. *Nat Rev Dis Prim* **3**, 17013.
- Pogosyan A, Gaynor LD, Eusebio A & Brown P (2009). Boosting Cortical Activity at Beta-Band Frequencies Slows Movement in Humans. *Curr Biol* **19**, 1637–1641.
- Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH & Deuschl G (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* **30**, 1591–1601.
- Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, Locatelli M, Moxon KA & Villani RM (2004). Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol*; DOI: 10.1016/j.expneurol.2004.06.001.
- Qasim SE, de Hemptinne C, Swann NC, Miocinovic S, Ostrem JL & Starr PA (2016). Electrocorticography reveals beta desynchronization in the basal ganglia-cortical loop during rest tremor in Parkinson's disease. *Neurobiol Dis* **86**, 177–186.
- Rajput AH, Fenton ME, Birdi S, Macaulay R, George D, Rozdilsky B, Ang LC, Senthilselvan A & Hornykiewicz O (2002). Clinical-pathological study of levodopa complications. *Mov Disord* **17**, 289–296.

- Ray NJ, Jenkinson N, Wang S, Holland P, Brittain JS, Joint C, Stein JF & Aziz T (2008). Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Exp Neurol* **213**, 108–113.
- Ray S & Maunsell JHR (2011). Different Origins of Gamma Rhythm and High-Gamma Activity in Macaque Visual Cortex. *PLOS Biol* **9**, e1000610.
- Rice ME, Patel JC & Cragg SJ (2011). Dopamine release in the basal ganglia. *Neuroscience* **198**, 112.
- Riederer P & Wuketich S (1976). Time course of nigrostriatal degeneration in parkinson's disease - A detailed study of influential factors in human brain amine analysis. *J Neural Transm* **38**, 277–301.
- Rodriguez-Oroz MC et al. (2005). Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain* **128**, 2240–2249.
- Rodriguez MC, Obeso JA & Olanow CW (1998). Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: a target for neuroprotection. *Ann Neurol*. DOI: 10.1002/ANA.410440726.
- Rosenblum Y, Shiner T, Bregman N, Giladi N, Maidan I, Fahoum F & Mirelman A (2023). Decreased aperiodic neural activity in Parkinson's disease and dementia with Lewy bodies. *J Neurol* **270**, 3958–3969.
- Rouder JN, Morey RD, Speckman PL & Province JM (2012). Default Bayes factors for ANOVA designs. *J Math Psychol* **56**, 356–374.
- Rouder JN, Speckman PL, Sun D, Morey RD & Iverson G (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychon Bull Rev* **16**, 225–237.
- Schapira AHV, Emre M, Jenner P & Poewe W (2009). Levodopa in the treatment of Parkinson's disease. *Eur J Neurol* **16**, 982–989.
- Schmidt SL, Peters JJ, Turner DA & Grill WM (2020). Continuous deep brain stimulation of the subthalamic nucleus may not modulate beta bursts in patients with Parkinson's disease. *Brain Stimul* **13**, 433–443.

- Schroll H & Hamker FH (2016). Basal Ganglia dysfunctions in movement disorders: What can be learned from computational simulations. *Mov Disord* **31**, 1591–1601.
- Shimamoto SA, Ryapolova-Webb ES, Ostrem JL, Galifianakis NB, Miller KJ & Starr PA (2013). Subthalamic Nucleus Neurons Are Synchronized to Primary Motor Cortex Local Field Potentials in Parkinson's Disease. *J Neurosci* **33**, 7220–7233.
- Shulman JM, De Jager PL & Feany MB (2011). Parkinson's Disease: Genetics and Pathogenesis. <https://doi.org/10.1146/annurev-pathol-011110-130242> **6**, 193–222.
- Singh A & Papa SM (2020). Striatal Oscillations in Parkinsonian Non-Human Primates. *Neuroscience* **449**, 116–122.
- Smith Y & Parent A (1988). Neurons of the subthalamic nucleus in primates display glutamate but not GABA immunoreactivity. *Brain Res* **453**, 353–356.
- Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R & Goedert M (1997). α -Synuclein in Lewy bodies. *Nat* 1997 3886645 **388**, 839–840.
- Sprenger F & Poewe W (2013). Management of motor and non-motor symptoms in parkinson's disease. *CNS Drugs* **27**, 259–272.
- Stanković L, Djurović I, Stanković S, Simeunović M, Djukanović S & Daković M (2014). Instantaneous frequency in time–frequency analysis: Enhanced concepts and performance of estimation algorithms. *Digit Signal Process* **35**, 1–13.
- Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK & Tilley BC (2013). How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord* **28**, 668–670.
- Stefani A, Bassi A, Mazzone P, Pierantozzi M, Gattoni G, Altibrandi MG, Giacomini P, Peppe A, Bernardi G & Stanzione P (2002). Subdyskinetic

- apomorphine responses in globus pallidus and subthalamus of parkinsonian patients: lack of clear evidence for the ‘indirect pathway.’ *Clin Neurophysiol* **113**, 91–100.
- Stein E & Bar-Gad I (2013). Beta oscillations in the cortico-basal ganglia loop during parkinsonism. *Exp Neurol* **245**, 52–59.
- Steiner LA, Kühn AA, Geiger JR, Alle H, Popovic MR, Kalia SK, Hodaie M, Lozano AM, Hutchison WD & Milosevic L (2022). Persistent synaptic inhibition of the subthalamic nucleus by high frequency stimulation. *Brain Stimul* **15**, 1223–1232.
- Steiner LA, Tomás FJB, Planert H, Alle H, Vida I & Geiger JRP (2019). Connectivity and dynamics underlying synaptic control of the subthalamic nucleus. *J Neurosci* **39**, 2470–2481.
- Stern MB, Lang A & Poewe W (2012). Toward a redefinition of Parkinson’s disease. *Mov Disord* **27**, 54–60.
- Stocchi F, Jenner P & Obeso JA (2010). When do levodopa motor fluctuations first appear in Parkinson’s disease? *Eur Neurol* **63**, 257–266.
- Stocchi F, Vacca L, Ruggieri S & Olanow CW (2005). Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. *Arch Neurol* **62**, 905–910.
- Tasker RR (1998). Deep brain stimulation is preferable to thalamotomy for tremor suppression. *Surg Neurol* **49**, 145–153.
- Teil M, Dovero S, Bourdenx M, Arotcarena ML, Darricau M, Porras G, Thiolat ML, Trigo-Damas I, Perier C, Estrada C, Garcia-Carrillo N, Herrero MT, Vila M, Obeso JA, Bezard E & Dehay B (2023). Cortical Lewy body injections induce long-distance pathogenic alterations in the non-human primate brain. *npj Park Dis* **2023** 91 **9**, 1–13.
- Telkes I, Viswanathan A, Jimenez-Shahed J, Abosch A, Ozturk M, Gupte A, Jankovic J & Ince NF (2018). Local field potentials of subthalamic nucleus contain electrophysiological footprints of motor subtypes of Parkinson’s

- disease. *Proc Natl Acad Sci U S A* **115**, E8567–E8576.
- Temperli P, Ghika J, Villemure JG, Burkhard PR, Bogousslavsky J & Vingerhoets FJG (2003). How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neurology* **60**, 78–81.
- Terman D, Rubin JE, Yew AC & Wilson CJ (2002). Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *J Neurosci* **22**, 2963–2976.
- Thenaisie Y, Lee K, Moerman C, Scafa S, Gálvez A, Pirondini E, Burri M, Ravier J, Puiatti A, Accolla E, Wicki B, Zacharia A, Jiménez MC, Bally JF, Courtine G, Bloch J & Moraud EM (2022). Principles of gait encoding in the subthalamic nucleus of people with Parkinson’s disease. *Sci Transl Med*; DOI: 10.1126/SCITRANSLMED.ABO1800.
- Thenaisie Y, Palmisano C, Canessa A, Keulen BJ, Capetian P, Jiménez MC, Bally JF, Manferlotti E, Beccaria L, Zutt R, Courtine G, Bloch J, Van Der Gaag NA, Hoffmann CF, Moraud EM, Isaias IU & Contarino MF (2021). Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. *J Neural Eng*; DOI: 10.1088/1741-2552/AC1D5B.
- Tinkhauser G, Pogosyan A, Little S, Beudel M, Herz DM, Tan H & Brown P (2017*a*). The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson’s disease. *Brain* **140**, 1053–1067.
- Tinkhauser G, Pogosyan A, Tan H, Herz DM, Kühn AA & Brown P (2017*b*). Beta burst dynamics in Parkinson’s disease OFF and ON dopaminergic medication. *Brain* **140**, 2968–2981.
- Tinkhauser G, Pogosyan A, Tan H, Herz DM, Kühn AA & Brown P (2017*c*). Beta burst dynamics in Parkinson’s disease off and on dopaminergic medication. *Brain* **140**, 2968–2981.
- Tolosa E, Martí MJ, Valldeoriola F & Molinuevo JL (1998). History of levodopa and dopamine agonists in Parkinson’s disease treatment. *Neurology*; DOI:

10.1212/WNL.50.6_SUPPL_6.S2.

- Tolosa E, Wenning G & Poewe W (2006). The diagnosis of Parkinson's disease. *Lancet Neurol* **5**, 75–86.
- Tsang EW, Hamani C, Moro E, Mazzella F, Lozano AM, Hodaie M, Yeh IJ & Chen R (2012). Movement related potentials and oscillatory activities in the human internal globus pallidus during voluntary movements. *J Neurol Neurosurg Psychiatry* **83**, 91–97.
- Tzagarakis C, Ince NF, Leuthold AC & Pellizzer G (2010). Beta-Band Activity during Motor Planning Reflects Response Uncertainty. *J Neurosci* **30**, 11270–11277.
- Velarde OM, Mato G & Dellavale D (2017). Mechanisms for pattern specificity of deep-brain stimulation in Parkinson's disease. *PLoS One* **12**, e0182884.
- Villalba RM, Mathai A & Smith Y (2015). Morphological changes of glutamatergic synapses in animal models of Parkinson's disease. *Front Neuroanat* **9**, 156509.
- Vinding MC, Waldthaler J, Eriksson A, Manting CL, Ferreira D, Ingvar M, Svenningsson P & Lundqvist D (2024). Oscillatory and non-oscillatory features of the magnetoencephalic sensorimotor rhythm in Parkinson's disease. *NPJ Park Dis*; DOI: 10.1038/S41531-024-00669-3.
- Vissani M, Palmisano C, Volkmann J, Pezzoli G, Micera S, Isaias IU & Mazzoni A (2021). Impaired reach-to-grasp kinematics in parkinsonian patients relates to dopamine-dependent, subthalamic beta bursts. *NPJ Park Dis* **2021** *7*, 1–10.
- Vitek JL (2002). Mechanisms of deep brain stimulation: Excitation or inhibition. *Mov Disord* **17**, S69–S72.
- Voytek B, Kramer MA, Case J, Lepage KQ, Tempesta ZR, Knight RT & Gazzaley A (2015). Age-related changes in 1/f neural electrophysiological noise. *J Neurosci* **35**, 13257–13265.
- Walker GT (1931). On periodicity in series of related terms. *Proc R Soc London Ser A, Contain Pap a Math Phys Character* **131**, 518–532.

- Wallace BA, Ashkan K, Heise CE, Foote KD, Torres N, Mitrofanis J & Benabid AL (2007). Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. *Brain* **130**, 2129–2145.
- Walter BL & Vitek JL (2004). Surgical treatment for Parkinson's disease. *Lancet Neurol* **3**, 719–728.
- Wang J, Zuo CT, Jiang YP, Guan YH, Chen ZP, Xiang J De, Yang LQ, Ding ZT, Wu JJ & Su HL (2007). 18F-FP-CIT PET imaging and SPM analysis of dopamine transporters in Parkinson's disease in various Hoehn & Yahr stages. *J Neurol* **254**, 185–190.
- Wang Z, Mo Y, Sun Y, Hu K, Peng C, Zhang S & Xue S (2022). Separating the aperiodic and periodic components of neural activity in Parkinson's disease. *Eur J Neurosci* **56**, 4889–4900.
- Weinberger M, Mahant N, Hutchison WD, Lozano AM, Moro E, Hodaie M, Lang AE & Dostrovsky JO (2006). Beta Oscillatory Activity in the Subthalamic Nucleus and Its Relation to Dopaminergic Response in Parkinson's Disease. *J Neurophysiol* **96**, 3248–3256.
- Wen H & Liu Z (2016). Separating Fractal and Oscillatory Components in the Power Spectrum of Neurophysiological Signal. *Brain Topogr* **29**, 13–26.
- Wichmann T (2019). Changing views of the pathophysiology of Parkinsonism. *Mov Disord* **34**, 1130–1143.
- Wichmann T & DeLong MR (2003). Pathophysiology of Parkinson's disease: the MPTP primate model of the human disorder. *Ann N Y Acad Sci* **991**, 199–213.
- Wiest C, Torrecillos F, Pogosyan A, Bange M, Muthuraman M, Groppa S, Hulse N, Hasegawa H, Ashkan K, Baig F, Morgante F, Pereira EA, Mallet N, Magill PJ, Brown P, Sharott A & Tan H (2023). The aperiodic exponent of subthalamic field potentials reflects excitation/inhibition balance in Parkinsonism. *Elife*; DOI: 10.7554/ELIFE.82467.
- Wilkins KB, Kehnemouyi YM, Petrucci MN, Anderson RW, Parker JE, Trager MH,

- Neuville RS, Koop MM, Velisar A, Blumenfeld Z, Quinn EJ & Bronte-Stewart HM (2023). Bradykinesia and Its Progression Are Related to Interhemispheric Beta Coherence. *Ann Neurol* **93**, 1029–1039.
- Williams D, Tijssen M, Van Bruggen G, Bosch A, Insola A, Di Lazzaro V, Mazzone P, Oliviero A, Quartarone A, Speelman H & Brown P (2002). Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain* **125**, 1558–1569.
- Witt PAL & Fahn S (2016). Levodopa therapy for Parkinson disease: A look backward and forward. *Neurology* **86**, S3–S12.
- Wong KF & Wang XJ (2006). A recurrent network mechanism of time integration in perceptual decisions. *J Neurosci* **26**, 1314–1328.
- Yamamoto Y & Hughson RL (1991). Coarse-graining spectral analysis: New method for studying heart rate variability. *J Appl Physiol*, DOI: 10.1152/jappl.1991.71.3.1143.
- Yamamoto Y & Hughson RL (1993). Extracting fractal components from time series. *Phys D Nonlinear Phenom*; DOI: 10.1016/0167-2789(93)90083-D.
- Yin HH & Knowlton BJ (2006). The role of the basal ganglia in habit formation. *Nat Rev Neurosci* 2006 **7**, 464–476.
- Yin Z, Zhu G, Zhao B, Bai Y, Jiang Y, Neumann WJ, Kühn AA & Zhang J (2021). Local field potentials in Parkinson’s disease: A frequency-based review. *Neurobiol Dis*; DOI: 10.1016/J.NBD.2021.105372.
- Yule GU (1927). VII. On a method of investigating periodicities disturbed series, with special reference to Wolfer’s sunspot numbers. *Philos Trans R Soc London Ser A, Contain Pap a Math or Phys Character* **226**, 267–298.
- Zampogna A, Suppa A, Bove F, Cavallieri F, Castrioto A, Meoni S, Pelissier P, Schmitt E, Chabardes S, Fraix V & Moro E (2024). Disentangling Bradykinesia and Rigidity in Parkinson’s Disease: Evidence from Short- and Long-Term Subthalamic Nucleus Deep Brain Stimulation. *Ann Neurol* **96**, 234–246.

Zellner A & Siow A (1980). Posterior odds ratios for selected regression hypotheses. *Trab estadística y Investig Oper* **31**, 585–603.

Zhang J, Villringer A & Nikulin V V. (2022). Dopaminergic Modulation of Local Non-oscillatory Activity and Global-Network Properties in Parkinson's Disease: An EEG Study. *Front Aging Neurosci* **14**, 381.

Annexes

Validation of beta activity modelling

The results from simulated data provide testable experimental predictions and rely on a crucial mechanistic assumption. The predictions are that, in real data, burst duration and spectral sharpness should specifically correlate with the oscillatory component of beta activity, whereas burst amplitude and spectral power should correlate with both the oscillatory and the non-oscillatory components of beta activity. The assumption is that the AR(2) model with additive 1/f noise reproduces well the temporal dynamics of beta activity. The mechanistic implication of this assumption is that beta activity would not consist of transient bursts of isolated oscillatory events, but rather of sustained stochastic oscillations.

For modelling the oscillatory component of beta activity in a data-driven fashion, we first subtracted from the recorded spectrum the non-oscillatory component that we obtained using the FOOOF method (see “FOOOF details” in the main manuscript). Then, we set the output variance of the simulated beta oscillations σ_y^2 as the variance corresponding to the resulting beta power spectrum (total spectral power in the beta range multiplied by square root of 2 and divided by 2). We then set the normalized frequency θ as the beta peak frequency of the recorded beta oscillations. We finally determined the radius ρ imposing that the simulated signals should have the same spectral peak power (in addition to the same total beta power) and, therefore, the same spectral sharpness as the recorded beta oscillations. To this end, the radius ρ was estimated with the following fitting approach using equations (2 and (3: (1) for each possible value of r (radius) in steps of 0.0025 units from 0.9 to 0.995, we simulated 100 signals with a total power equal to their corresponding recorded beta oscillation and we measured the peak power value; (2) using the mean peak power value x obtained at each value of r , we fitted a curve with equation $r = ax^b + c$; (3) finally, ρ was determined by entering the

actual peak power value of the recorded signal into the obtained equation. Following this approach, we ensure that both power and sharpness of the beta peak of the simulated signals, as well as the beta peak frequency, are the same as their corresponding recorded signal.

Note that if the reduction of total beta power after the non-oscillatory component subtraction is more than 97%, this fitting approach does not work properly, at least in our datasets. In such cases, we considered that there was no oscillatory component to be modelled (which is not uncommon in recordings on medication).

To generate the non-oscillatory component in the data-driven simulations, we designed a finite impulse response (FIR) digital filter whose frequency response was the $1/f$ slope corresponding to the non-oscillatory component from each recorded signal. Gaussian white noise was then filtered to obtain the $1/f$ signal. Finally, the resulting $1/f$ signal was normalized by its square root value at the beta peak frequency, and then multiplied by the square root value of the non-oscillatory component estimated at the beta peak frequency.

Once the models were determined, we generated 1000 simulated signals per case in order to provide reliable estimates.

All analyses were performed with Bayesian statistics (Keysers *et al.*, 2020) using JASP statistical software (version 0.14.1.0; JASP Team, 2020). Correlations between measures were assessed with either Pearson or Kendall correlation coefficient and reported using the one-tailed Bayes factor BF_{+0} . Beta bursts measures were separately compared between recorded and simulated signals using paired t-tests (HM CINAC dataset 1 off medication) and analysis of variance (ANOVA) (HM CINAC dataset 2 off-on medication). Bayesian ANOVAs were conducted with default priors, and effects are reported as the Bayes factor for the inclusion of a particular effect (BF_{incl}), calculated as the ratio between the likelihood of the data given the model with vs. the next simpler model without the effect, comparing across matched models. In the dataset of LFPs recorded both off and on medication (HM CINAC dataset 2), we performed two-way repeated-measures ANOVAs, with two levels reflecting the type of beta oscillations

considered (TYPE: recorded vs. simulated) and the dopaminergic medication factor (MED: off vs. on). Evidence in favour to alternative hypothesis ($BF > 1$) or to the null hypothesis ($BF < 1$) is described according to standard levels: anecdotal ($1/3 < BF < 3$), moderate ($< 1/3$ or > 3), strong ($< 1/10$ or > 10), very strong ($< 1/30$ or > 30), and extremely strong ($< 1/100$ or > 100).

We first considered the dataset of STN LFPs recorded in patients off medication ($n = 33$ nuclei, HM CINAC). The LFP power spectra presented typical peaks of activity in the beta band (13–35Hz), particularly in the low-beta range (13–20Hz), with the expected variability across patients (Figure 27A and B). LFPs were thus filtered around their maximum beta peak to obtain the recorded beta oscillations, from which we extracted direct spectral measures, i.e., power and sharpness of the beta peak, decomposed spectral measures, i.e., power of the oscillatory and non-oscillatory components of the beta peak, and beta bursts measures, i.e., average amplitude and duration of beta bursts. As predicted by the model, burst amplitude and spectral power correlated with both the oscillatory component of beta activity (Figure 27C) and the non-oscillatory component (Figure 27D). Also consistent with the model predictions, burst duration and spectral sharpness correlated with the oscillatory component of beta activity (Figure 27E) and not with the non-oscillatory component (Figure 27F). These findings experimentally confirm the specificity of burst duration and spectral sharpness for the oscillatory component of beta activity, as well as the ambiguity of burst amplitude and spectral power between oscillatory and non-oscillatory components.

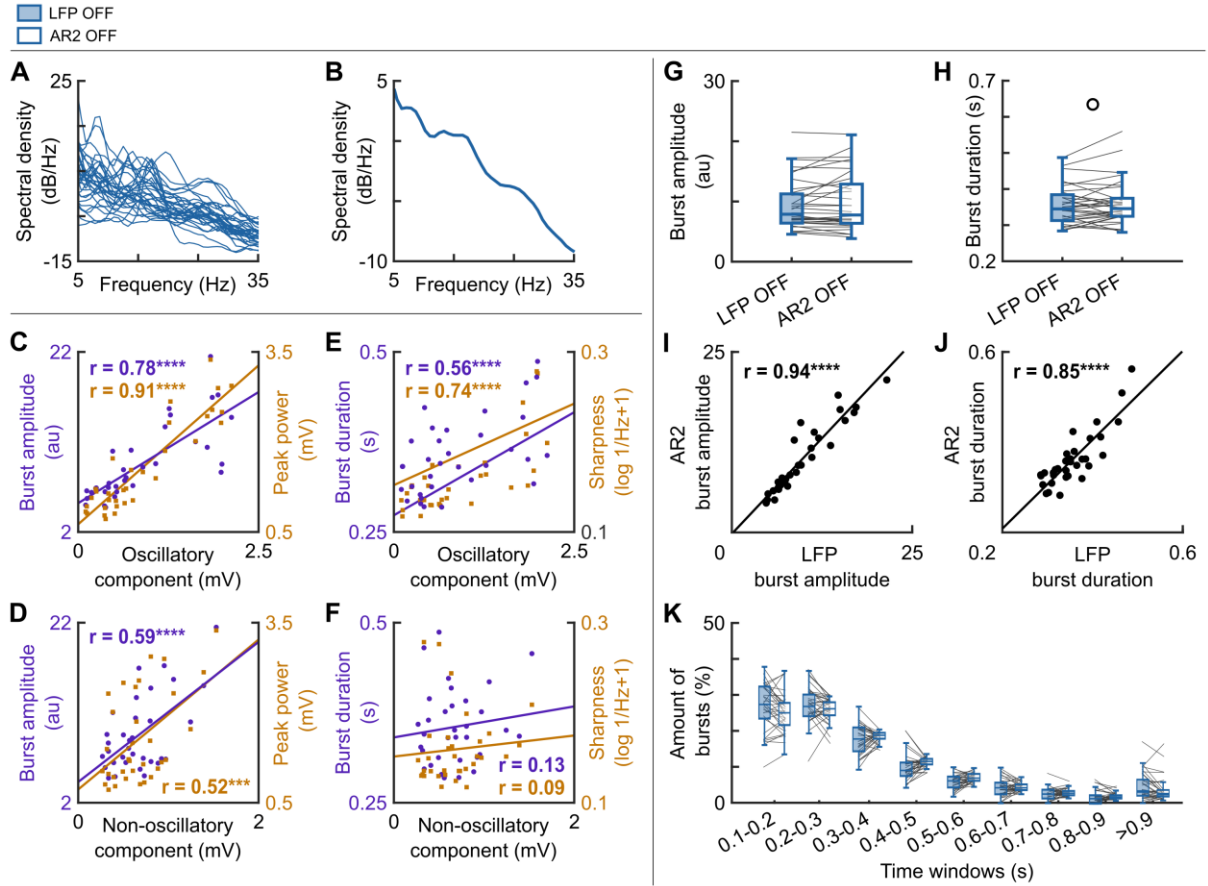


Figure 27. Verification of beta modelling I: beta oscillations in PD patients off medication.

A and B, superimposed spectra and average spectrum of STN LFPs recorded off medication. C–F, correlations between recorded oscillatory and non-oscillatory components (x-axes), and recorded spectral measures and beta burst measures (y-axes) ($^{***}BF_{+0} > 30$, $^{****}BF_{+0} > 100$). G and H, box plots of burst amplitude and burst duration in recorded and simulated beta oscillations ($^{\circ}BF < 1/3$). I and J, correlations between recorded beta oscillations (LFP, x-axes) and simulated beta oscillations (AR(2), y-axes) for burst amplitude and burst duration ($^{****}BF_{+0} > 100$). K, recorded and simulated burst duration distributions.

As corollary predictions, we also confirmed robust correlations between corresponding measures, i.e., burst amplitude and spectral power, burst duration and spectral sharpness, and weaker correlations between non-corresponding measures, i.e., burst amplitude and spectral sharpness, burst duration and spectral power (Figure 28).

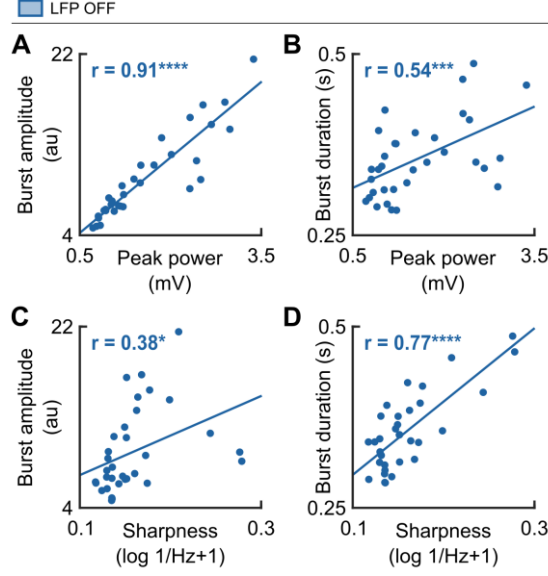


Figure 28. Correlations between spectral and beta bursts measures off medication. A-D, correlations between spectral and beta burst measures off medication (* $BF_{+0} > 3$, *** $BF_{+0} > 30$, **** $BF_{+0} > 100$).

To verify the mechanistic assumption that the AR(2) model with additive $1/f$ noise describes well the temporal dynamics of beta activity, we performed data-driven simulations, by setting the parameters of the model from the spectral measures extracted from the real LFPs. We thus tested whether the beta oscillations simulated with the models could reproduce the dynamics of beta bursts, i.e., their average amplitude and duration. We found anecdotal-to-moderate evidence of absence of difference between recorded and simulated beta oscillations in burst amplitude (paired t test, $BF_{10} = 0.394$; Figure 27G) and burst duration ($BF_{10} = 0.283$; Figure 27H). Furthermore, both burst amplitude and burst duration displayed extremely strong correlation across nuclei between recorded and simulated beta oscillations ($r > 0.85$, $BF_{+0} > 5.6 \times 10^7$; Figure 27I and J). Finally, simulated beta oscillations reproduced well the distribution of burst durations within recordings (Figure 27K). AR(2) models with additive $1/f$ noise constructed from the shape of the power spectrum thus reproduced well both (1) the population averages and (2) the dispersions across and within subjects of beta burst dynamics observed in subthalamic LFPs off medication.

The analysis of subthalamic beta oscillations recorded in PD patients off medication thus (1) confirms the relationships between beta burst measures

(amplitude and duration), spectral measures (power and sharpness) and oscillatory/non-oscillatory activity predicted by the modelling and (2) supports the underlying mechanistic assumption that a simple stochastic oscillator provides a satisfactory model, at least as a first approximation, of beta activity.

To test whether the above assumption extended to the well-known dopaminergic modulation of beta activity, we analysed the dataset of LFPs recorded from the STN both off and on medication ($n = 21$ nuclei, HM CINAC). As in the previous dataset, LFPs were filtered to obtain the recorded beta oscillations, from which we extracted spectral measures as well as beta bursts measures, which were expressed as differences between dopaminergic states (off–on Δ).

All results obtained in the LFP recorded off medication extended to their dopaminergic modulation on medication: (1) the specificity of burst duration and spectral sharpness for the oscillatory component of beta activity (Figure 29C-F); (2) the ambiguity of burst amplitude and spectral power between oscillatory and non-oscillatory components (Figure 29C-F); (3) the correspondences between burst measures in time domain and spectral measures in the frequency domain (Figure 30); (4) the verification of the mechanistic assumption that the AR(2) model with additive $1/f$ noise reproduces well the temporal dynamics of beta activity (Figure 29G-K). The analysis of subthalamic beta oscillations recorded in PD patients both off and on medication thus extends the predictions of the model and the validity of its main assumption to the dopaminergic modulation of beta activity.

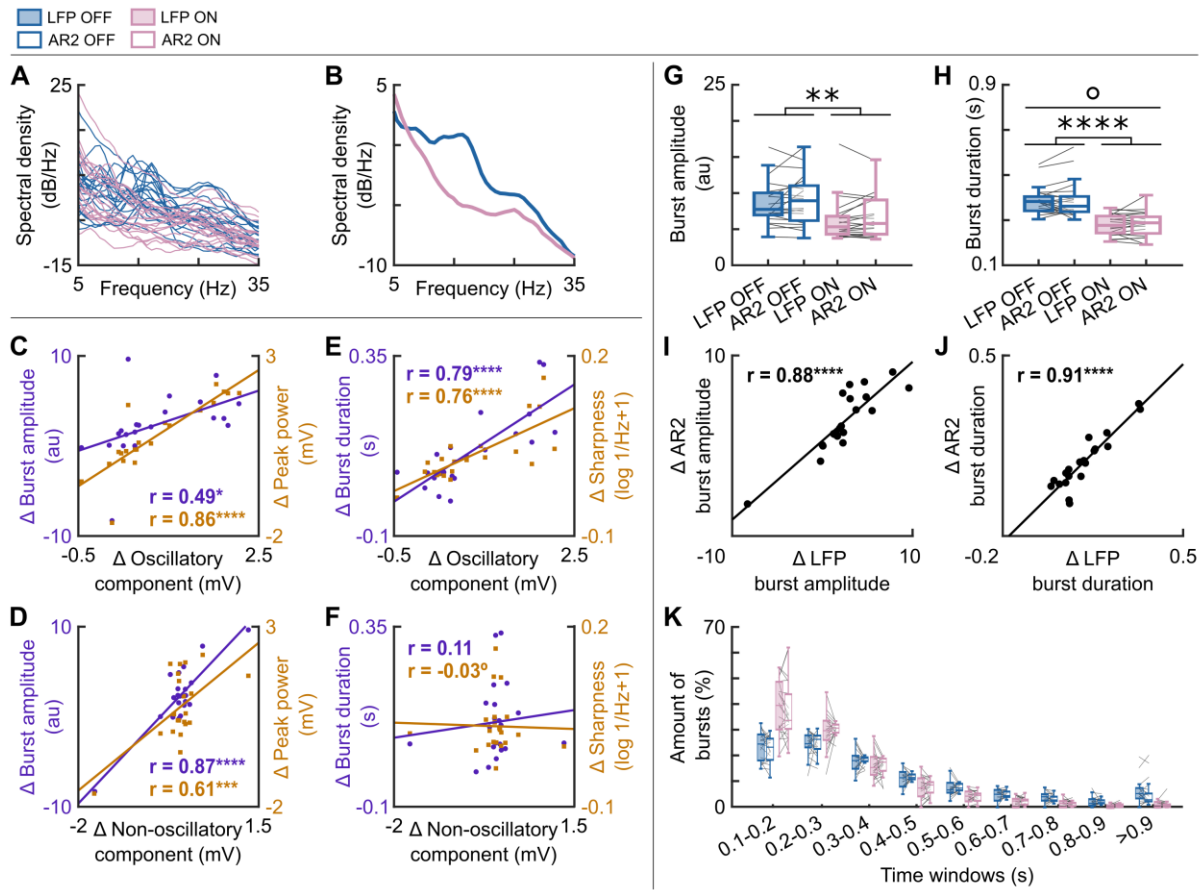


Figure 29. Verification of beta modelling II: beta oscillations in PD patients off and on medication. A and B, superimposed spectra and average spectra of STN LFPs recorded off and on medication. C–F, correlations between recorded oscillatory and non-oscillatory components (x-axes), and recorded spectral measures and beta burst measures (y-axes) in terms of differences (off–on Δ) ($^0BF_{+0} < 1/3$, $^*BF_{+0} > 3$, $^{***}BF_{+0} > 30$, $^{****}BF_{+0} > 100$). G and H, box plots of burst amplitude and burst duration in recorded and simulated beta oscillations ($^0BF_{incl} < 1/3$, $^{**}BF_{incl} > 10$, $^{****}BF_{incl} > 100$). I and J, correlations between recorded beta oscillations (LFP, x-axes) and simulated beta oscillations (AR(2), y-axes) for burst amplitude and burst duration ($^{****}BF_{+0} > 100$). K, recorded and simulated burst duration distributions.

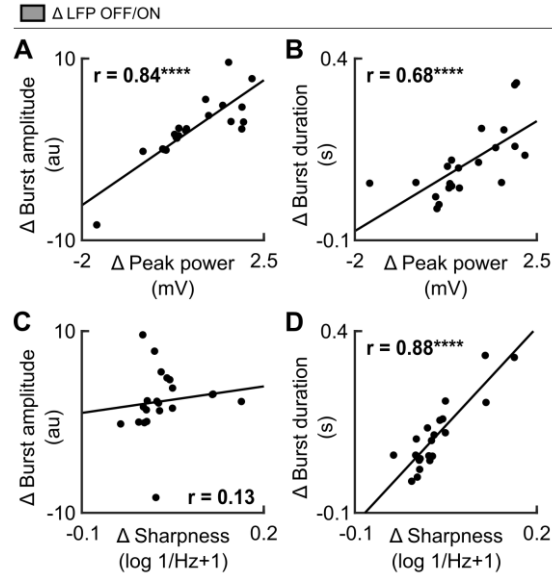


Figure 30. Correlations between spectral and beta bursts measures off and on medication. A-D, correlations between spectral and beta burst measures off/on medication. In this case, we calculated correlations using the difference in measures between off and on medication ($^{****}BF_{+0} > 100$).

Supplementary figures

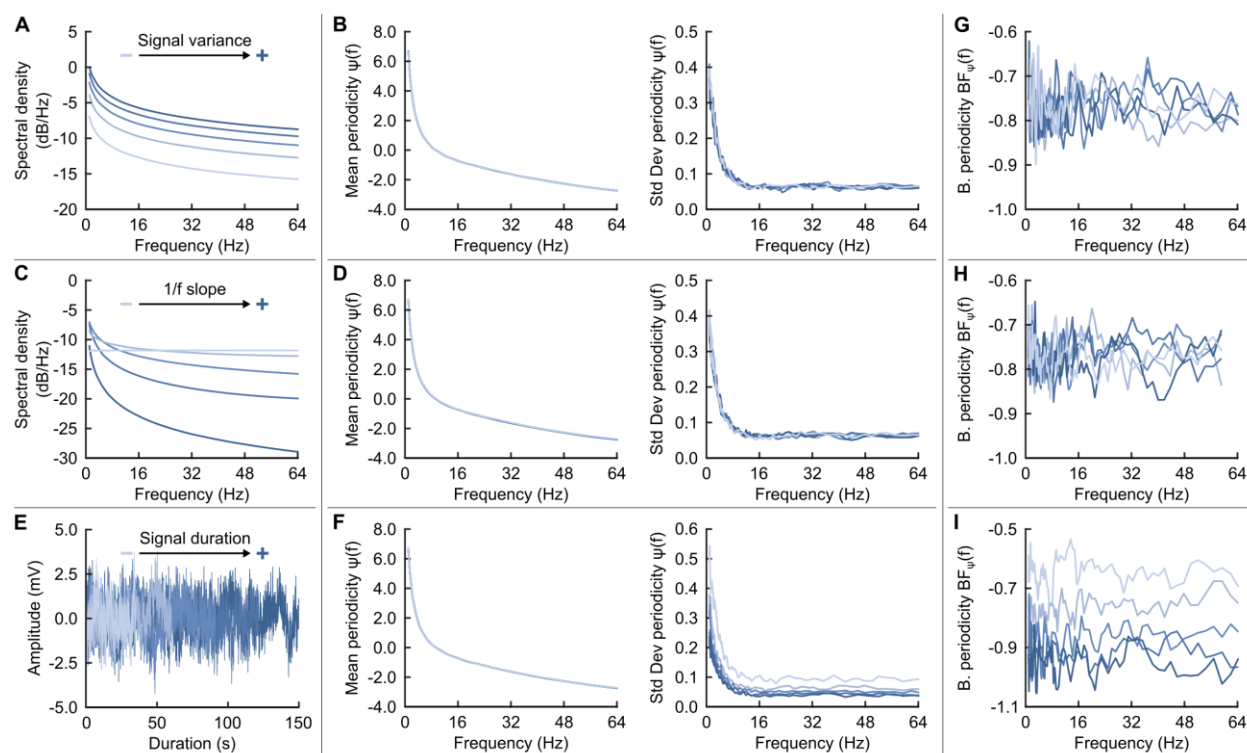


Figure 31. Power spectrum and periodicity spectrum of non-oscillatory activity (CWT). A-F, Modulation of signal variance, 1/f slope and signal duration, and their corresponding effect on periodicity (mean value and standard deviation (Std. Dev.)) in simulated signals using the continuous wavelet transform (CWT). G-I, Corresponding Bayesian periodicity spectra.

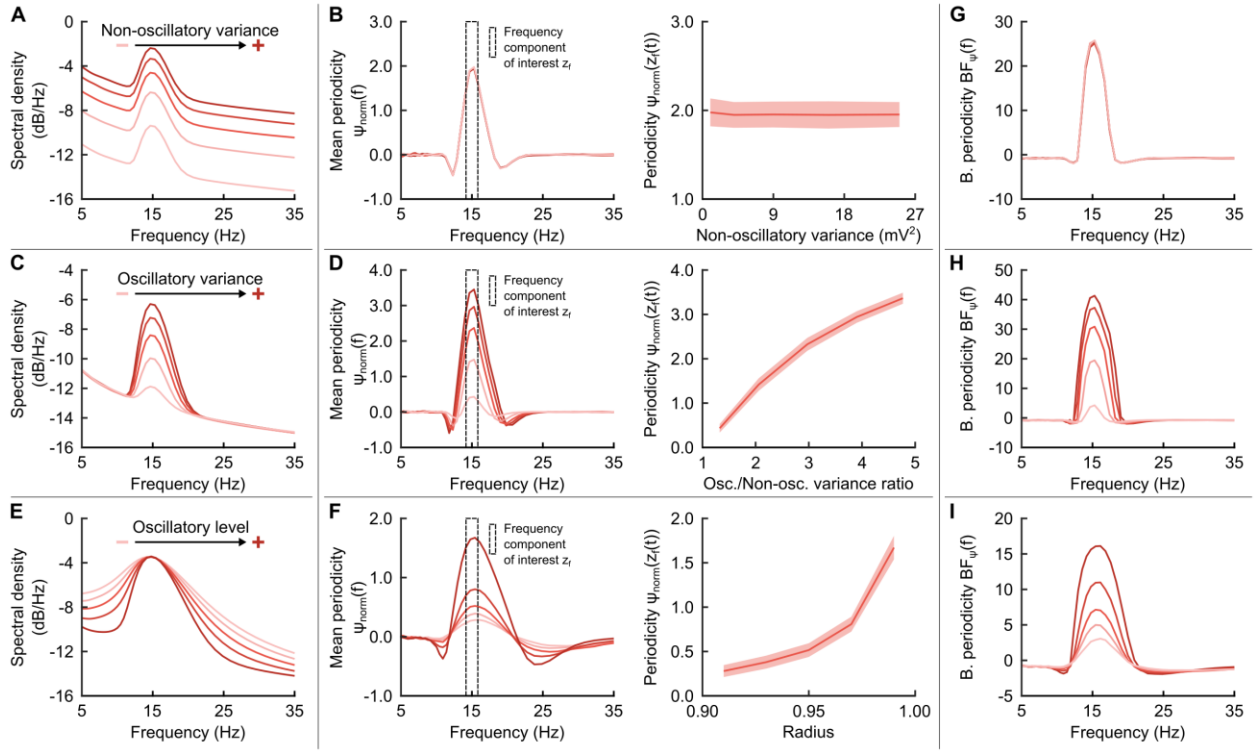


Figure 32. Power spectrum and periodicity spectrum of oscillatory activity (CWT). A-F, Modulation of non-oscillatory component variance, oscillatory component variance and the oscillatory level, and the corresponding effect on the periodicity spectrum and the change of periodicity (or the absence of it) in the frequency component of interest $z_i(t)$ (15 Hz) in simulated signals using the continuous wavelet transform (CWT). G-I, Corresponding Bayesian periodicity spectra.

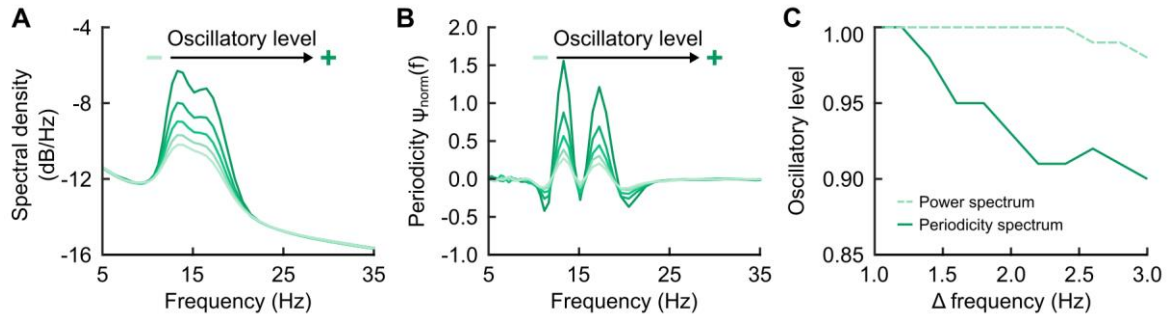


Figure 33. Frequency resolution in power spectra and periodicity spectra (CWT). A and B, Modulation of the oscillatory level of two close oscillatory components, and the corresponding effect on the power spectrum and the periodicity spectrum. C, Relationship between the distance between oscillatory peaks and the minimum oscillatory level (measured as the radius of the AR(2) models) needed to discriminate the two oscillatory components in the power spectrum and the periodicity spectrum from simulated signals measured using the continuous wavelet transform (CWT).

Publication associated to the thesis

Pardo-Valencia, J., Fernández-García, C., Alonso-Frech, F., & Foffani, G. (2024). Oscillatory vs. non-oscillatory subthalamic beta activity in Parkinson's disease. *The Journal of Physiology*, 602(2), 373-395.