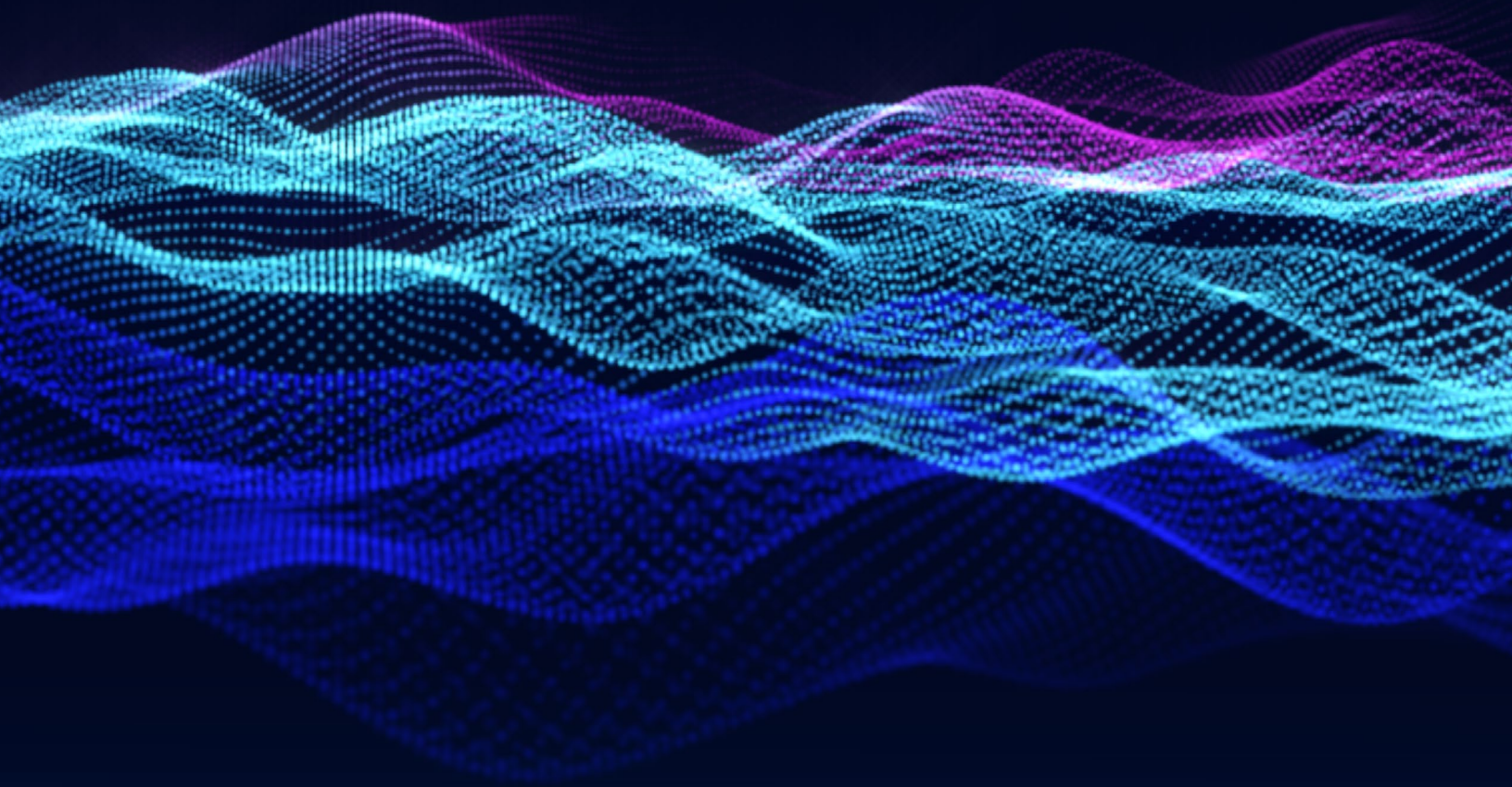
Medtronic

Scientific compendium

Research on brain sensing and BrainSense™ technology

Scientific publications supporting the use of local field potentials (LFPs) as signals of interest in deep brain stimulation (DBS).



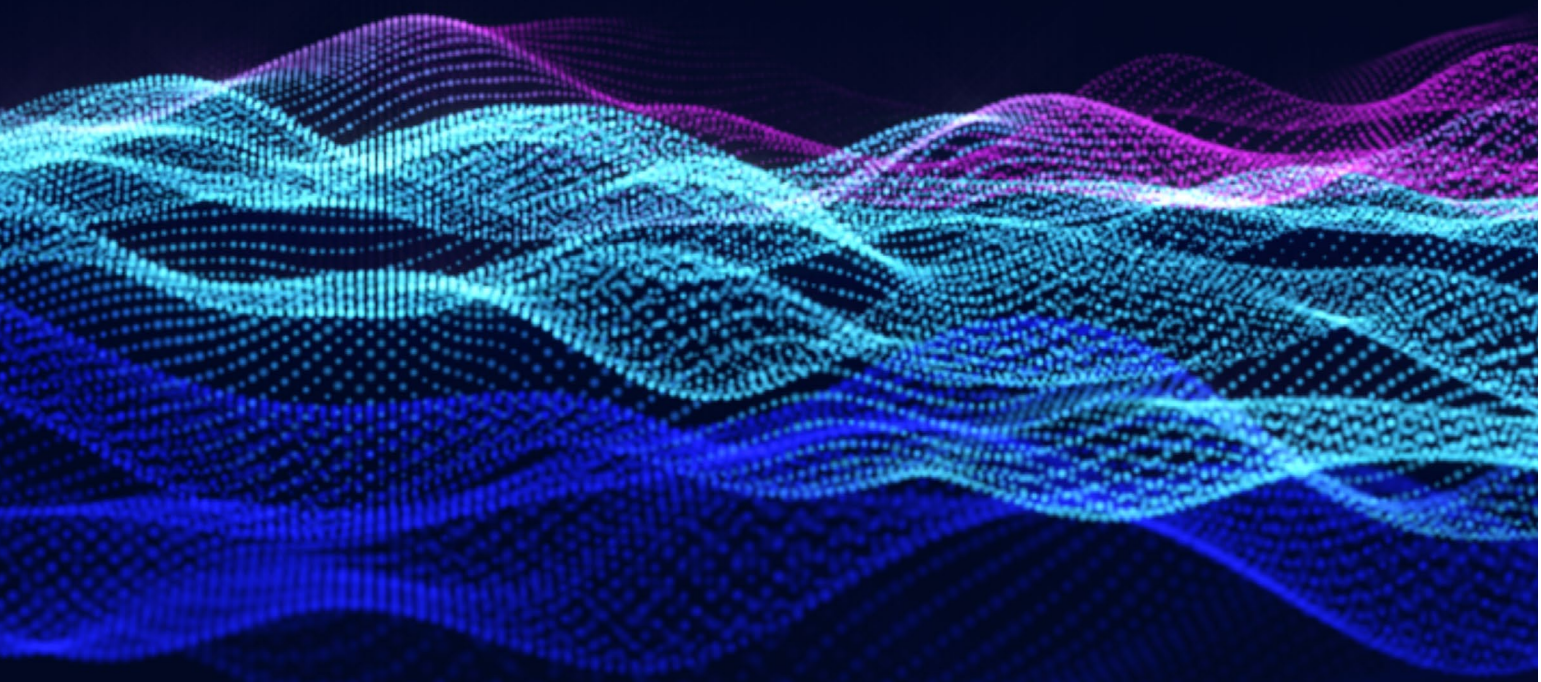
Introduction

This scientific compilation of published literature is intended as an educational resource for healthcare professionals interested in brain sensing and focuses on two objectives.

The first objective is to summarize published literature reporting on the use of BrainSense™ technology† and to provide published examples and guidance for those interested in incorporating BrainSense™ technology into their practice.

The second objective is to provide a scientific overview of the research conducted to investigate and understand local field potentials (LFPs). Years of published literature have helped to set a foundation for the field of brain sensing in Parkinson's disease and sensing related to other disease states is emerging.

The Percept™ PC and Percept™ RC neurostimulators with BrainSense™ technology capture brain signals (LFPs) using an implanted deep brain stimulation (DBS) lead(s).§ The brain signals can be recorded simultaneously while delivering therapeutic stimulation, inside and outside the clinic. Physicians can correlate the brain signals with stimulation and events capturing medication, symptoms, or side effects to deliver personalized, data-driven treatment and adjust stimulation as patients' needs evolve.



† The sensing feature of the Percept™ PC and Percept™ RC systems is intended for use in patients receiving DBS where chronically-recorded bioelectric data may provide useful, objective information regarding patient clinical status. The majority of patients with Parkinson's disease have an identifiable signal.[1] Signal may not be present or measurable in patients treated for essential tremor, dystonia‡, epilepsy or obsessive-compulsive disorder‡.

§ Medtronic's DBS Therapy is approved for 5 indications: Parkinson's disease, essential tremor, dystonia‡, obsessive-compulsive disorder‡ (OCD), and epilepsy. Device indications vary, refer to product labeling.

‡ **Humanitarian Device:** Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated. Authorized by Federal law for use as an adjunct to medications and as alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs). The effectiveness of the devices for this use has not been demonstrated.

1. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022;356:114150.

Limitations

This scientific compilation of published literature is provided for general educational purposes only and should not be considered the exclusive source for this type of information. The articles address common questions and research concepts in the field of brain sensing research.

While brain signals are becoming better characterized and understood, these articles should be appreciated as scientific research with several limitations:

- The articles may be helpful for navigating through the science of brain sensing. There is still much to learn regarding the relationship of LFPs to brain function, disease state, and therapy.
- Interpretation of the data is often limited due to short-term in-clinic testing or small sample sizes.
- Articles were selected as fair and balanced examples of "state of the art" for sensing research. This document does not represent an exhaustive list of brain sensing literature.
- Case reports and case series have provided examples on how BrainSense™ technology may be used to inform clinical decision making. Individual patient outcomes may vary based on the severity of the disease, extent of surgery and patient's response to treatment. Physicians should use their own clinical judgement when implementing use of BrainSense™ technology and deciding how to treat patients with DBS therapy.
- The BrainSense™ features have several limitations themselves:
  - Sensing and stimulation contacts are restricted to predefined combinations; in order to sense, stimulation is limited to the middle contacts. Segmented contacts and surgical planning may help work around this limitation.[2]
  - Cardiac artifact, if present, overlaps with the beta frequency range.[2] Implant location (ie, right side)[2] and leads developed for sensing, such as the SenSight™ lead, help reduce artifact noise.
  - Timeline recordings are restricted to a narrow band around a predefined frequency and could miss frequency shifts or the appearance of new bands.[1,2]
  - LFP signals related to a rapidly-occurring event (ie, a fall, freezing, seizure, aura) may be difficult to capture due to the delay between the event occurrence and marking with the patient programmer.[2]
  - High frequency oscillations, which may also carry information content regarding patient disease state or treatment, are beyond the recording capabilities of the device.[1]

Disclaimers

- Some of the articles describe acute postoperative research investigating brain signals with externalized leads. These scientific findings may or may not be applicable to the utilization of sensing with chronically implanted systems; short-term, in-clinic LFP recording with externalized leads is not common clinical practice and is not endorsed by Medtronic.
- Some of the research contained in this document was conducted with an implanted Activa™ PC+S neurostimulation system for investigational use only and is not FDA approved for commercial DBS Therapy.
- Technical (eg, lead and signal isolation technology) and patient factors (eg, anatomy, disease state, medication state) will influence the ability to detect LFP signals. Signals may not be present in all patients.

1. Jimenez-Shahed J. Device profile of the percept PC deep brain stimulation system for the treatment of Parkinson's disease and related disorders. Expert Rev Med Devices. 2021 Apr;18(4):319-332.
2. Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).

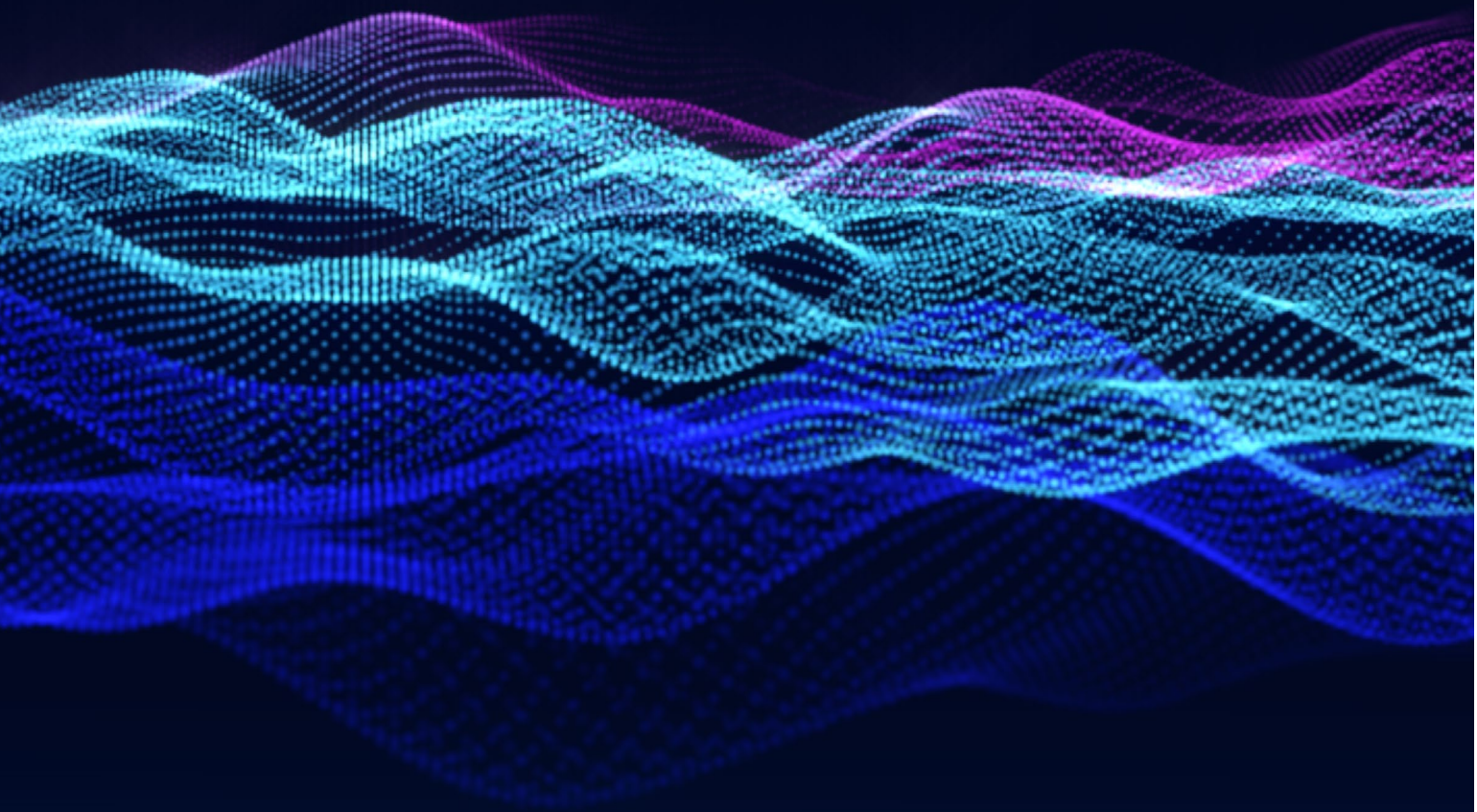
Table of contents

Featured articles

Tables

SECTION 1:

Basics of LFPs



LFP basics

Buzsáki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes. Nat Rev Neurosci. 2012 18;13(6):407-20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4907333/

Herreras O. Local Field Potentials: Myths and Misunderstandings. Front Neural Circuits. 2016 Dec 15;10:101. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5156830/

LFPs in movement disorders

Brown and Williams. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol. 2005;116(11):2510-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=16029963

Rosa M., Marceglia S., Barbieri S., Priori A. Local Field Potential and Deep Brain Stimulation (DBS). In: Jaeger D., Jung R. (eds) Encyclopedia of Computational Neuroscience. Springer, New York, NY; 2014. https://doi.org/10.1007/978-1-4614-7320-6_547-1

Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol. 2013;26(6):662-70. https://www.ncbi.nlm.nih.gov/pubmed/24150222

Eusebio A, Brown P. Synchronisation in the beta frequency-band--the bad boy of parkinsonism or an innocent bystander? Exp Neurol. 2009;217(1):1-3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697315/

Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. Neurobiol Dis. 2021 Jul;155:105372.

Piña-Fuentes D, van Dijk JMC, Drost G, et al. Direct comparison of oscillatory activity in the motor system of Parkinson's disease and dystonia: A review of the literature and meta-analysis. Clin Neurophysiol. 2019 Jun;130(6):917-924.

Blumenfeld Z, Brontë-Stewart H. High Frequency Deep Brain Stimulation and Neural Rhythms in Parkinson's Disease. Neuropsychol Rev. 2015 Dec;25(4):384-97.

Thompson JA, Lanctin D, Ince NF, Abosch A. Clinical implications of local field potentials for understanding and treating movement disorders. Stereotact Funct Neurosurg. 2014;92(4):251-63.

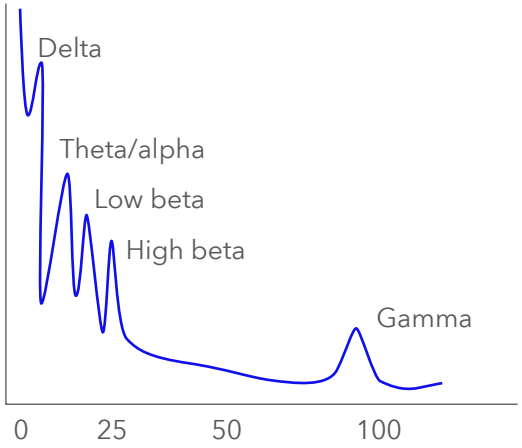
Brittain JS, Brown P. Oscillations and the basal ganglia: motor control and beyond. Neuroimage. 2014;85 Pt 2:637-47.

What is an LFP?

LFPs represent the summed electrical activity from local neuronal transmembrane currents around an electrode. Important factors that contribute to the LFP include the cellular and synaptic cellular architecture and the synchrony of the current sources.

LFPs have been characterized into frequency bands (approximate range, Hz): delta (0-4), theta (4-7), alpha (8-12), beta (13-35), gamma (35-250) and high frequency (> 250), although literature related to oscillatory activity in the basal ganglia broadly describes beta in the 8 to 30 Hz range. While changes in activity within each frequency band contribute to normal brain processing, persistent activity in the beta frequency range has been associated with the withdrawal of antiparkinsonian medication and the return of symptoms in patients with Parkinson's disease. Therefore, persistent beta activity has been considered an "antikinetic" signal. The appearance of frequencies in a gamma range (60-90 Hz) in the basal ganglia may be related to the "vigor or effort" of a motor response and have been called "prokinetic."[1]

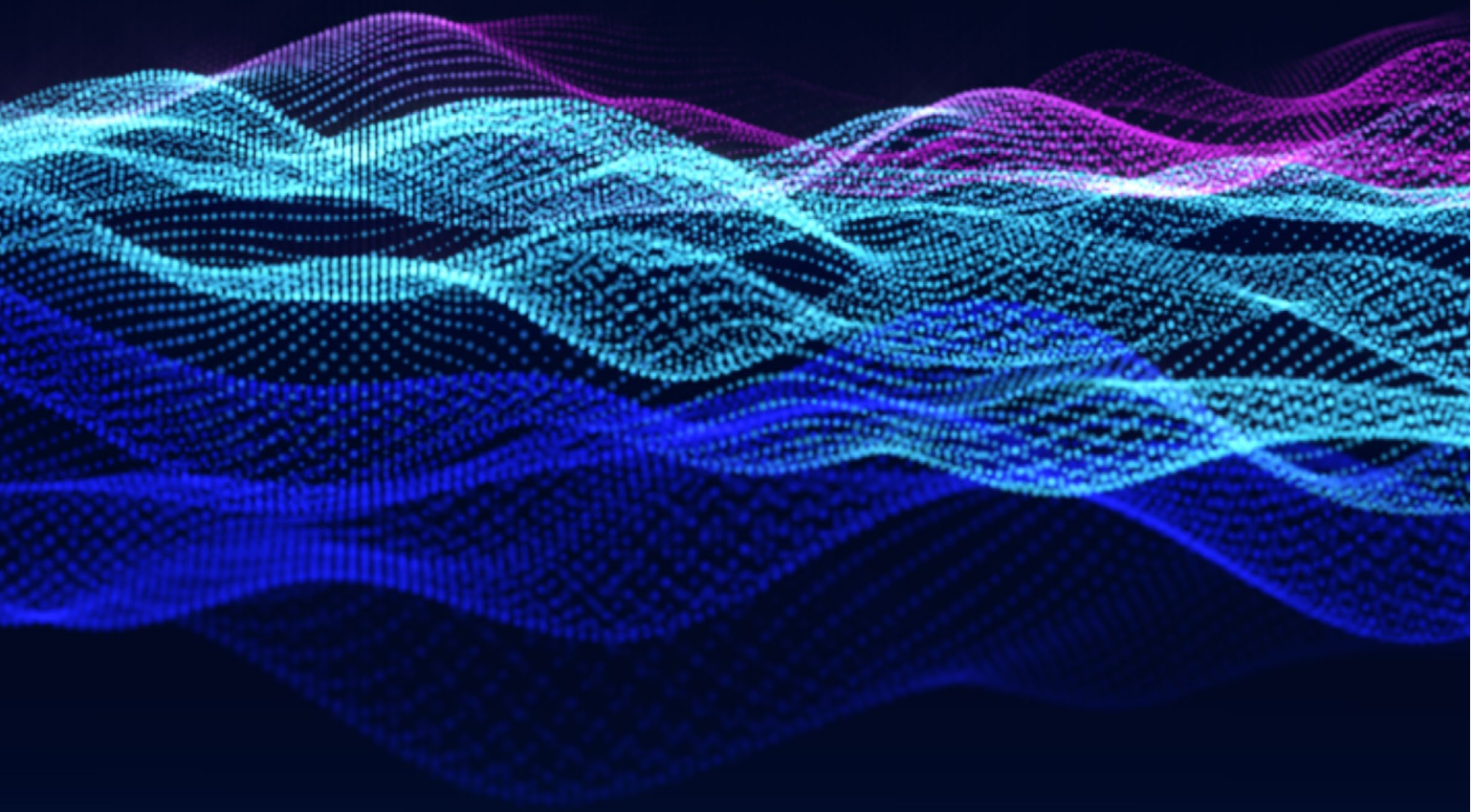
Characterization of LFP bands



1. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. Neurobiology of Disease. 2021;155:105372.

SECTION 2:

BrainSense™ technology: trust, select, optimize and maximize LFP signals



Opportunities for brain sensing in clinical practice

The inclusion of brain sensing within the commercial Percept™ PC and Percept™ RC devices has sparked ideas for incorporating LFP sensing into clinical practice to provide objective data for patient management. Publications discuss:

- Neurophysiologic correlates of disease[1]
- Objective approach to medical management[2,3,5]
- More efficient contact selection[2,4]
- Personalized patient treatment[2,3,5,6]
- Patient monitoring[2,3]

1 Jimenez-Shahed J. Expert Rev Med Devices. 2021 Apr;18(4):319-332.

2 Thenaisie Y, Palmisano C, Canessa A, et al. J Neural Eng. 2021 Aug 31;18(4).

3 Goyal A, Goetz S, Stanslaski S, et al. Biosens Bioelectron. 2021 Mar 15;176:112888.

4 Sirica D, Hewitt AL, Tarolli CG, et al. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.

5 Feldmann LK, Neumann WJ, Krause P, et al. Eur J Neurol PMID: 33675144 PMID: 33675144. 2021.

6 Fasano A, Gorodetsky C, Paul D, et al. Neuromodulation. 2021. Feb;25(2):271-275.

BrainSense™ technology allows clinicians to adapt DBS therapy to patient needs over time with data-driven insights.

Defining trust, select, optimize, and maximize

Using BrainSense™ technology in clinical practice relies on **trusting** that the signal of interest is relevant. The Compendium provides data and research establishing the link between disease states, symptoms, and local field potentials (LFP), which denote the summed electrical activity from regions surrounding an electrode. BrainSense™ technology equips clinicians with tools to identify relevant LFP measures, thereby offering valuable and objective data on a patient's clinical status and informing programming. First, detection of LFP signals can contribute information for contact **selection**. Next, programming may be **optimized** by examining LFP responses to stimulation.

Finally, BrainSense™ technology enables clinicians with data to **maximize** therapy over time through personalized insights from longitudinal LFP monitoring outside the clinic.

Select
(Contacts)

BrainSense™ Survey

Select a contact or directionally shift stimulation in monopolar review or follow up programming

Optimize
(Therapy configurations)

BrainSense™ Streaming

- Identify stimulation-related therapeutic window
- Adjust stimulation parameters to address potentially suboptimal therapy configurations

BrainSense™ Thresholds

Rapidly assess the time spent with or without symptoms when outside the clinic

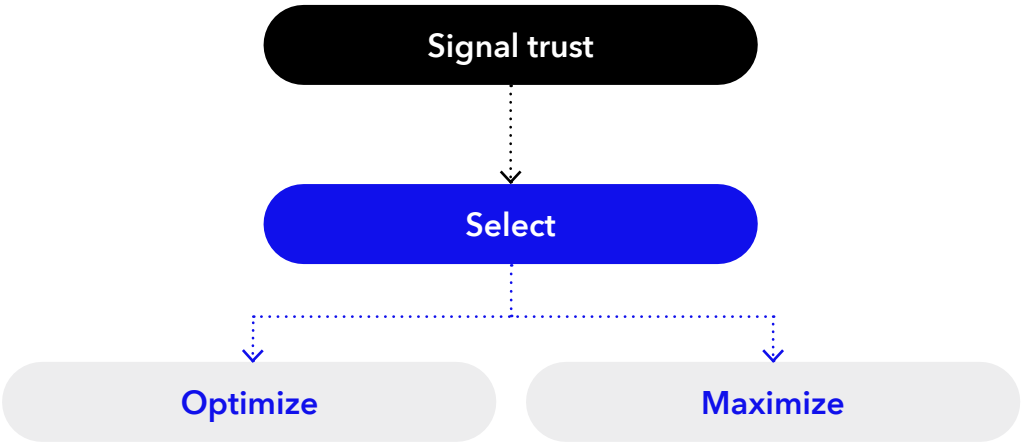
Maximize
(Long-term therapeutic results)

BrainSense™ Timeline

Objective, personalized insights from outside the clinic

BrainSense™ Events

Assess and understand the frequency and magnitude of the signal of interest over time



The BrainSense™ suite of tools offers decision-making support to **select** and **optimize** programming configurations and **maximize** therapeutic results over time.

Building upon LFP signal trust (e.g., LFP peak detection, stability, association to clinical state or subcortical anatomy), the data collected through BrainSense™ technology provides clinicians with decision making support throughout a patient's journey with DBS.

Signal trust

Signals associated with disease states and symptoms

LFPs have been associated with normal physiological brain function as well as pathological brain function and disease states. The majority of research on LFPs within subcortical structures has focused on symptoms related to Parkinson's disease and changes in oscillatory power in untreated versus treated states. Through this research, the beta frequency band has emerged as a robust signal of interest. The relationship of LFP frequency bands to symptoms in other indications is still emerging, though available data generally supports an association of the theta/alpha band with tremor and low frequency bands with dystonia‡. Additionally, recent findings are beginning to highlight potential signals of interest from the anterior nucleus of the thalamus in patients with focal epilepsy. The ensuing table provides an overview of the current understanding of LFPs across movement disorder indications and epilepsy in the context of DBS.

Trust in an LFP signal as it relates to a disease state, symptom, or change in therapy is founded in evidence. The table below provides a summarized overview of LFP signals; the supporting evidence for each indication is variable.

Table 1: LFP frequency bands and disease state

Typical LFP frequency bands associated with symptoms in specific disease states.

	Delta (0-4 Hz)	Theta/Alpha (4-13 Hz)	Low Beta (13-20 Hz)	High Beta (20-35 Hz)	Gamma (35-250 Hz)
PD: Akinetic-Rigid symptoms[1] & symptom severity[2,3]			●	○	○
PD: Tremor symptoms[1]		●			●
PD: UPDRS-III response prediction[3]			○	●	
PD: Levodopa-induced dyskinesia[1]		●			●
Epilepsy[4,5]	○	○	○	○	
Essential Tremor[1]		●	○	○	
Dystonia (tonic)‡[1]	●		○		○ (60-90 Hz)
Dystonia (phasic)‡[1]		●	○		○ (60-90 Hz)

● **likely association of LFP band to disease state (large body of literature supports findings)**

○ **potential association of LFP band to disease state**

‡Humanitarian Device - Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated.

1 Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.

2 van Wijk, B.C.M., de Bie, R.M.A. & Beudel, M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. J Neurol 270, 1162–1177 (2023).

3 Morelli N, Summers RLS. Association of subthalamic beta frequency sub-bands to symptom severity in patients with Parkinson's disease: A systematic review. Parkinsonism Relat Disord. 2023 May;110:105364.

4 Yang AI, Raghu ALB, Isbaine F, Alwaki A, Gross RE. Sensing with deep brain stimulation device in epilepsy: aperiodic changes in thalamic local field potential during seizures. Epilepsia. 2023. Nov;64(11):3025-3035.

5 Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603..

Select: Signals informing contact selection

BrainSense™ Survey determines if a signal is detectable between two contact pairs and may provide objective information for **contact selection**. Since LFP signals have been shown to relate to disease state and symptoms, identifying the contacts with high signal activity may help provide a starting place for the monopolar review for Parkinson's disease or starting contact selection for other indications.

LFPs informing contact selection in Parkinson's disease: page 37

Final contact selection should be determined by the physician along with other medical information.

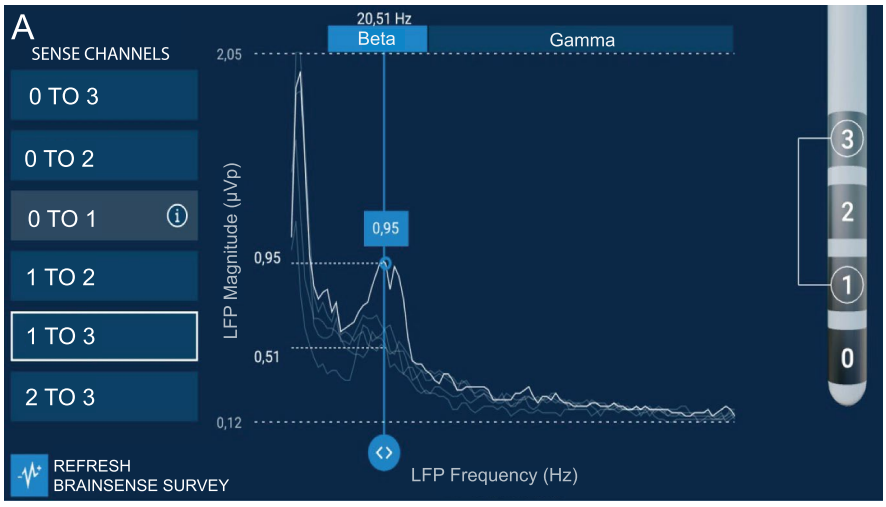
BrainSense™ Survey

Decision-making support

- Provides decision-making support to select recording or therapeutic contact(s), or directionally shift stimulation during monopolar review or follow-up programming sessions.
- Displays frequencies of interest between ~1-100 Hz.

Factors that may impact LFP signals and help explain variability include[1,2,3]:

1. Medications suppressing beta
2. Tremor suppressing beta
3. Lead location
4. Voluntary movement impacting beta
5. Impedance differences and ECG artifact



BrainSense™ Survey example

Screenshot of the BrainSense™ Survey recording from a patient with Parkinson's disease in a Med OFF condition. The tablet displays the LFP magnitude (µ volts peak, µVp) vs frequency (Hz) (about 21 seconds of data for each pair). The highest beta power was seen when recording between contacts 1 and 3. Monopolar stimulation from contact 2 had the best effect on patient symptoms, but also induced dyskinesias. Contact 1 was ultimately chosen for stimulation.

1. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. Neurobiology of Disease. 2021;155:105372.
2. Hirschmann J, Abbasi O, Storzer L, et al. Longitudinal Recordings Reveal Transient Increase of Alpha/Low-Beta Power in the Subthalamic Nucleus Associated With the Onset of Parkinsonian Rest Tremor. Front Neurol. 2019;10:145.
3. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022;356:114150.

Optimize and maximize: Insights over time

BrainSense™ technology uses brain signals to provide a window into a patient's condition, in real-time, over time.

The BrainSense™ suite of tools offers decision-making support to select and optimize programming configurations and to maximize therapeutic results over time.

Optimizing therapy with LFPs in Parkinson's disease: page 45

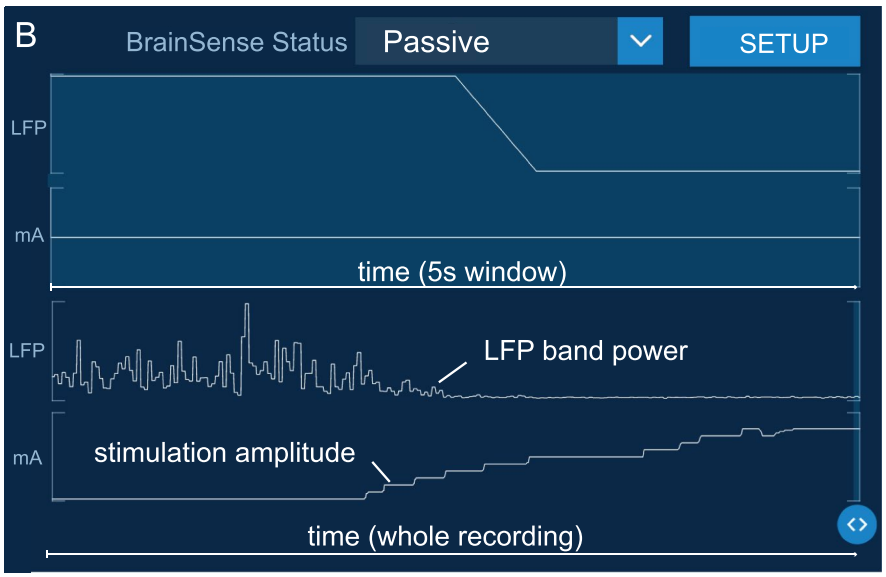
Maximizing therapy with LFPs in Parkinson's disease: page 49

BrainSense™ Streaming

Decision-making support

- Visualize real-time in-clinic changes in LFP signals during active stimulation programming in correlation with patient symptoms and side effects.
- Can assist in finding stimulation-related therapeutic windows.
- Stimulation parameters can be adjusted to address potentially suboptimal therapy configurations using objective patient physiologic data.

BrainSense™ Streaming example 1



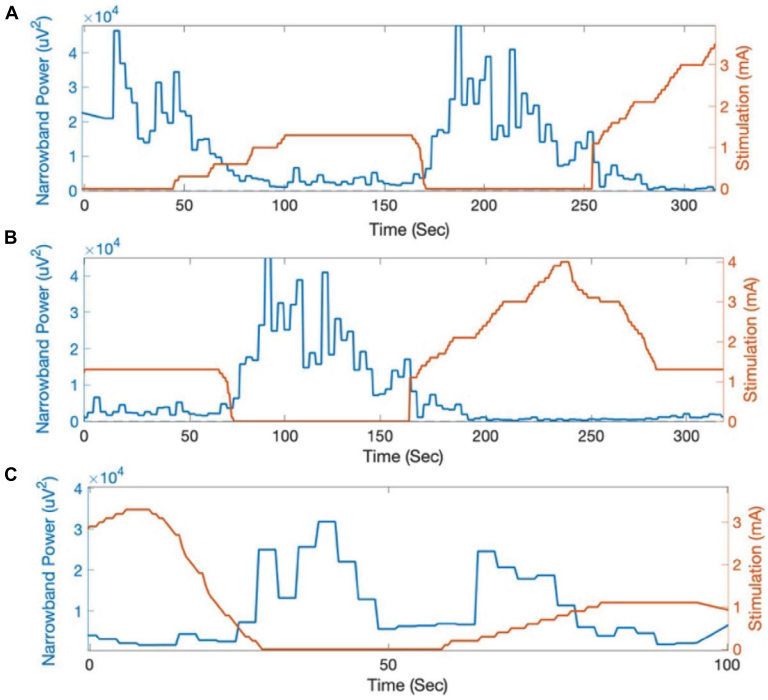
Power in a selected frequency band was tracked in BrainSense™ Streaming mode in a patient with Parkinson's disease. With this feature, the tablet displays the selected power and stimulation amplitude in real-time and over the entire recording. Increasing stimulation amplitude resulted in a decrease in beta-band power, which plateaued after about 2 mA. Simultaneous clinical motor evaluation showed improvement in rigidity as beta power decreased.

Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4). Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). No modifications were made to the material.

BrainSense™ Streaming example 2

This is an example of the type of data that can be recorded with BrainSense™ Streaming and further analyzed from JSON files. Beta power centered around 19.53 Hz was recorded in response to stimulation amplitude during consecutive follow-up periods in a patient with Parkinson's disease. Panels A and B show recordings taken at day 0 after implant and Panel C shows the recording at 9-days post-implant.

Cummins DD, Kochanski RB, Gilron R, et al. Chronic Sensing of Subthalamic Local Field Potentials: Comparison of First and Second Generation Implantable Bidirectional Systems Within a Single Subject. Front Neurosci. 2021 Aug 10;15:725797. Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). No modifications were made to the material.



BrainSense™ Timeline

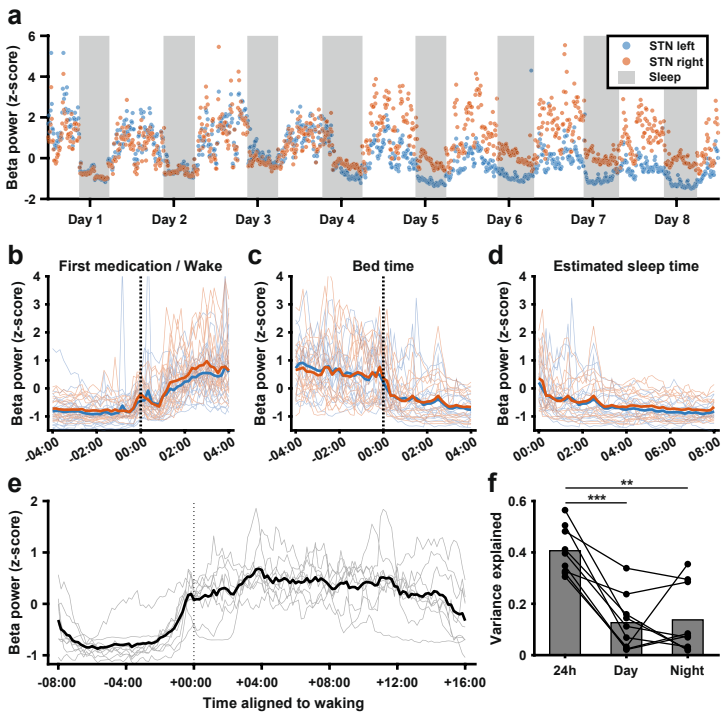
Decision-making support

- Provides objective and personalized information from outside the clinic.
- Allows the ability to observe effects of medication, lifestyle, and stimulation changes on LFP power over time.
- May allow for rapid assessment of the time spent with or without symptoms outside of clinic using BrainSense™ Thresholds and LFP chart.

BrainSense™ Timeline example

A) 8 days - Normalized beta power in the left and right STN of one patient – EVENTS for SLEEP and WAKE. B, C, D) Beta - full 21-day recording period, aligned to the time of waking. E) Average beta power aligned to estimated average wake-up time for all STN time series in the data set (gray lines, n = 9) and mean across all-time series (thick black line). F) Variance explained by time of day across the whole 24 h cycle vs. during the day or night alone. Full 24 h: 0.41 ± 0.092; Day only: 0.13 ± 0.11 (p = 0.039 vs 24 h); Night only: 0.14 ± 0.13 (p = 0.012 vs. 24 h); n = 9 STN time series.

van Rheede, J.J., Feldmann, L.K., Busch, J.L. et al. Diurnal modulation of subthalamic beta oscillatory power in Parkinson's disease patients during deep brain stimulation. npj Parkinsons Dis. 8, 88 (2022). Figure 2 of the paper and supporting legend text are licensed under CC BY 4.0. https://creativecommons.org/licenses/by/4.0/ No changes have been made to the image; figure legend text has been abbreviated.



BrainSense™ Events

Decision-making support

- Acts as a patient's day-to-day digital diary and can track up to 4 programmed events with timestamps and LFP snapshots.
- Can help verify the frequency of interest for chronic tracking.
- Can help understand frequency peaks found associated with specific patient symptoms and the magnitude of those peaks over time.

LFP snapshots can be recorded at a moment in time, showing LFP signal over a range of frequencies (1-100Hz)

The LFP snapshot is recorded when the patient records an event as configured by the clinician. This is used to assess the occurrence of clinician-defined events, and associated LFP activity with those events.

Example event markers for movement disorders:

- Medication intake
- ON state/feeling good
- Main symptom (ie, rigidity, tremor)
- Side effects (eg, dyskinesia, speech)
- Other symptoms

Example event markers for epilepsy:

- Feeling good
- Aura/interictal phase
- Seizure
- Post-ictal phase/interictal phase
- Medication intake

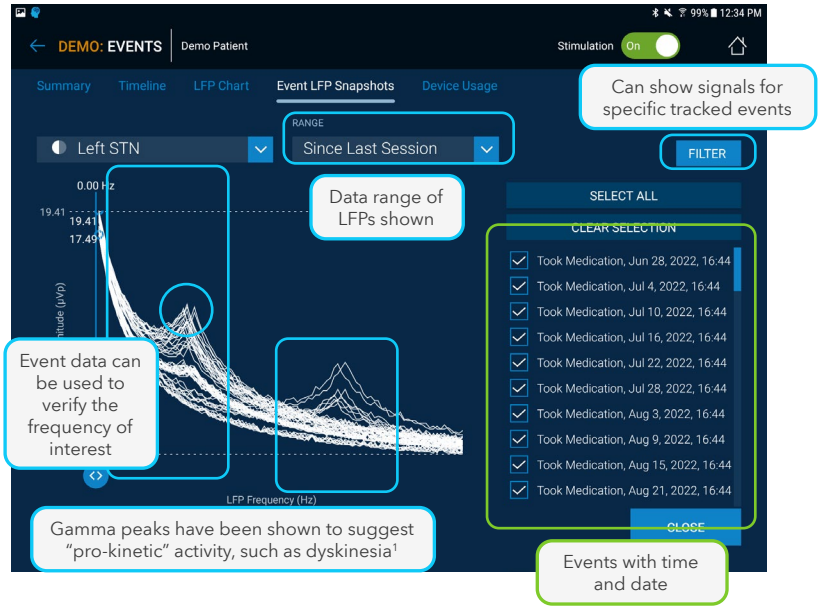
Event marker examples

Event LFP snapshots demo

LFP snapshots can be recorded at a moment in time, showing the magnitude of the LFP signal over a range of frequencies.

The LFP snapshot is recorded when the patient records an event as configured by the clinician. This is used to assess the occurrence of clinician-defined events, and associated LFP activity with those events.

Use: Outside-clinic, the snapshot is representative of a period of approximately 30 seconds after patient marking an event.



BrainSense™ Thresholds

Decision-making support

- Provide helpful context for making clinical judgments when interpreting LFP data.
- May allow for rapid assessment of the time spent with or without symptoms outside of clinic using BrainSense™ Timeline and LFP chart.
- Can be applied immediately in-clinic with BrainSense™ Streaming.

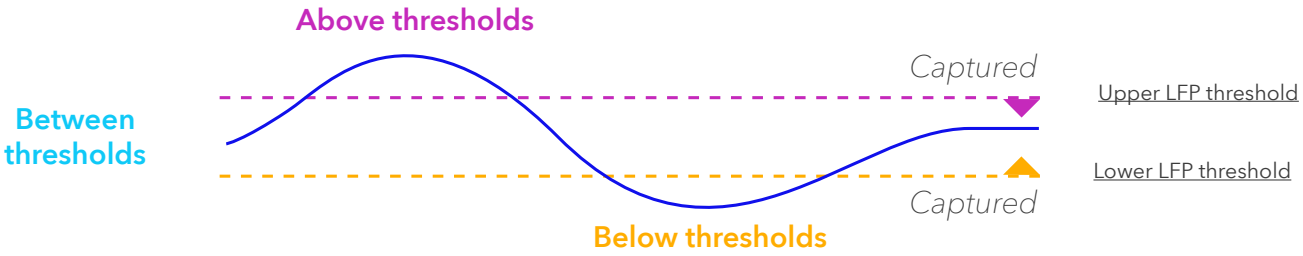
BrainSense™ Threshold interpretation (for Parkinson's disease and a beta signal)

- Upper LFP threshold: could describe the transition from an ON (below upper threshold) to OFF (above upper threshold) state – may be set when stimulation-induced efficacy is first observed.
- Lower LFP threshold: could describe the transition from an ON to overstimulated state – may be set when stimulation-induced side effects are first observed.

BrainSense™ Threshold example

A graphic representation and description of BrainSense™ Timeline and Thresholds.

Example LFP fluctuation



Above thresholds –
patient may be in an **OFF state**, untreated, or symptomatic

Between thresholds –
patient may be in an **ON state**, treated, or asymptomatic

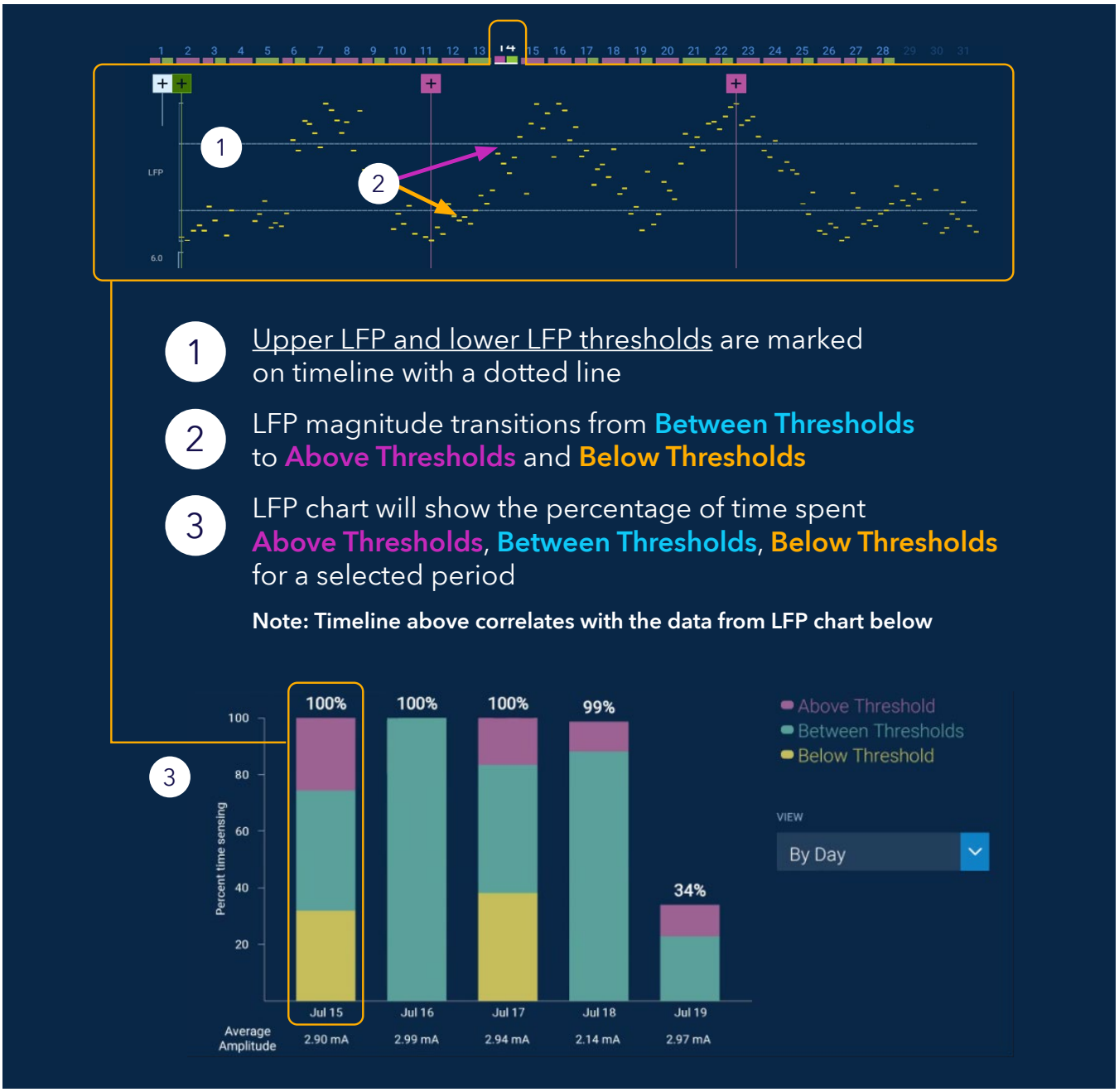
Below thresholds –
More information may be needed. Factors to consider are: treatment, sleep, side-effects, percent of time below threshold and when below threshold occurs.

BrainSense™ Timeline and Thresholds example depicting LFP modulation in response to increased stimulation. After stimulation amplitude was adjusted, LFP power spent greater time within the predetermined thresholds.

*The tablet image presented here is an unpublished example from the BrainSense™ Timeline and Thresholds feature running in a patient with Parkinson's disease with leads in the STN, courtesy of Svjetlana Miocinovic, MD, PhD, Emory University Movement Disorders Program.

BrainSense™ Timeline with thresholds and LFP chart

Delivering personalized insights into patient's symptom fluctuations, which could help therapy management



Battery longevity considerations with BrainSense™ technology

The System Eligibility and Battery Longevity manual (Manual Document Number: M929534A139 Rev A) states that sensing influences battery longevity. The impact of continuous sensing is shown according to overall battery longevity estimates in the table below.

Influence of continuous sensing on battery longevity (All values are approximate)			
Estimated battery longevity	11 years	5 years	2.5 years
Longevity reduction per month of continuous sensing	11.7 days	5.4 days	2.9 days

Source: Manual M929534A139 Rev A

Note: Long clinician telemetry sessions with the Percept™ PC implantable neurostimulator (INS) do have a small impact on the INS longevity.[3] Using BrainSense™ streaming during these telemetry sessions does not add much additional energy usage since the primary energy use is the telemetry session itself. A rough order of magnitude estimate of the telemetry session impact for many patients is: a 1 hour telemetry session has approximately a 1 day impact to INS battery longevity.

For Percept™ RC, the amount of time before the neurostimulator battery requires charging can depend on several factors including programmed parameters and use of sensing. For an implanted Percept™ RC neurostimulator, check the battery level with the Model A610 clinician application to determine recharge interval with the programmed settings. The A610 clinician application also takes into consideration the impact of sensing when calculating the battery recharge intervals. Refer to the A610 clinician application programming guide for instructions.[3]

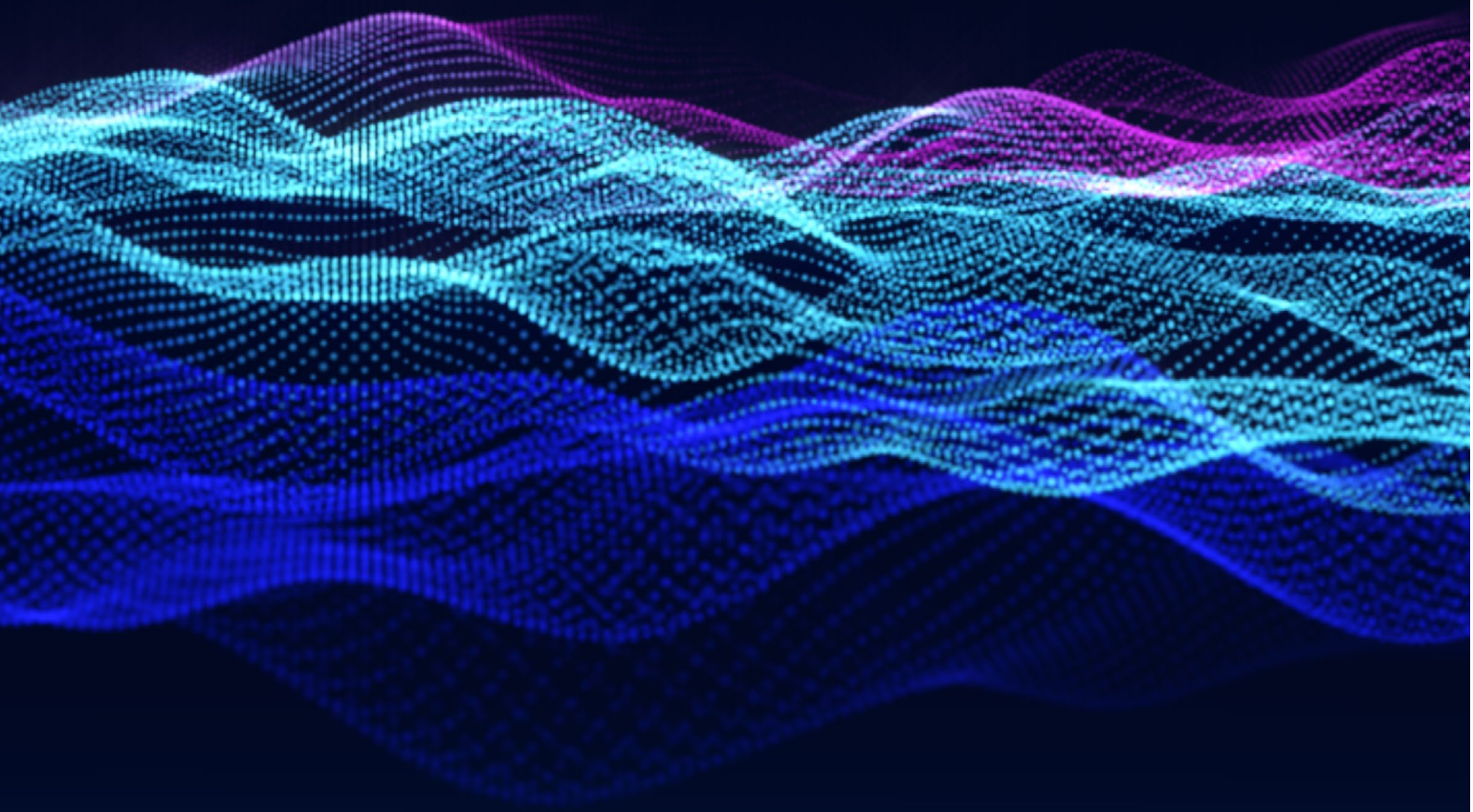
1 For median energy use in DBS for patients with Parkinson's disease, with moderate (up to 2 months per year) BrainSense™ technology usage, longevity impact will be 0.52% per year.

2 For median energy use in DBS for patients with Parkinson's disease, with full time BrainSense™ technology usage, longevity impact will be 3.0% per year.

3 Medtronic System Eligibility and Battery Longevity manual. M929534A139 Rev A. 2022-08-01.

SECTION 3:

Parkinson's disease



Parkinson's disease

Over the past decade, extensive research on local field potentials (LFP) from the subthalamic nucleus (STN) and globus pallidus internus (GPi) in patients with Parkinson's disease (PD) has revealed the diverse applications of these signals in gaining insights into pathophysiology and their potential clinical applications.[1] One key finding from LFP research in PD is the role of beta band (13-30 Hz) hyper-oscillatory activity in the clinical manifestation of motor impairments, principally bradykinesia and rigidity.[2,3] Moreover, LFP measures outside of the beta range are now being explored for their association to clinical symptoms excluding bradykinesia and rigidity.[1,4] As PD is a heterogeneous and progressive disorder, the clinical utility of LFPs as an objective and personalized data source to augment clinical decision making and guide deep brain stimulation (DBS) programming is beginning to be realized.[5,6]

LFPs informing contact selection in Parkinson's disease: page 37

Optimizing therapy with LFPs in Parkinson's disease: page 45

Maximizing therapy with LFPs in Parkinson's disease: page 49

Signal trust

Once available only during intra- and peri-operative settings, LFP data can now be captured using BrainSense™ technology within and outside of the clinic. In order to maximize the utility of information collected through BrainSense™ technology, it is important to understand essential characteristics of the underlying LFP data in patients with PD. As such, this section highlights evidence regarding LFP peak detection, signal stability, clinical correlates of LFP data, LFP responses to common PD-related therapies, and the association of beta to STN anatomy.

LFP peak characteristics

LFP measures from subcortical nuclei in patients with PD can capture either a momentary snapshot in time or longitudinal trends, depending on the modality of data collection. Nevertheless, numerous clinical applications require the detection of a prominent LFP peak. The ensuing evidence reports the prevalence and attributes of LFP peaks in patients with PD. Collectively, this data depicts that LFP peaks can be identified in a wide majority of patients with PD.[7]

1. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. *Neurobiology of Disease*. 2021;155:105372.
2. Morelli N, Summers RLS. Association of subthalamic beta frequency sub-bands to symptom severity in patients with Parkinson's disease: A systematic review. *Parkinsonism & Related Disorders*. 2023;110.
3. van Wijk BCM, de Bie RMA, Beudel M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. *Journal of Neurology*. 2023;270(2):1162-1177.
4. Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.
5. Swinnen BEKS, Stam MJ, Buijink AWG, et al. Employing LFP Recording to Optimize Stimulation Location and Amplitude in Chronic DBS for Parkinson's Disease: A Proof-of-concept Pilot Study. Deep Brain Stimulation. 2023; 2:1-5.
6. Strelow JN, Dembek TA, Baldermann JC, et al. Low beta-band suppression as a tool for DBS contact selection for akinetic-rigid symptoms in Parkinson's disease. Parkinsonism & Related Disorders. 2023;112.
7. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Exp Neurol. 2022 Oct;356:114150.

Table 2: Seminal publications on local field potential peak detection in patients with Parkinson's disease

Publication	Patient Description	Peak Detection Rate	Additional Information
Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).	Patients (N): 11 Recording: Percept™ PC Target: STN Conditions: Med OFF Study design: Single-center Lead Model: 3389 (all but one patient)	**Beta peaks identified in 86% (19 of 22) of leads**	Maximum beta peak was found in contact pair 1–3 or 0–3 in 13/19 STNs. The clinically chosen contact for chronic stimulation was either in between or one of the contact pairs displaying the maximum beta peak in all but 3 leads (of 3 different patients).
Shreve LA, Velisar A, Malekmohammadi M, et al. Subthalamic oscillations and phase amplitude coupling are greater in the more affected hemisphere in Parkinson's disease. Clin Neurophysiol. 2017;128(1):128-137.	Patients (N): 74 Recording: Externalized leads Target: STN Conditions: Med OFF Study design: Single-center Lead Model: 3389 (all but one patient)	**Alpha/beta peaks (8-35 Hz) identified in > 99% (129 of 130) of leads**	Distribution of peak frequency: • Low beta range (13–20 Hz): 64 (51.2%) • High beta range (21-35 Hz): 42 (33.6%) • Alpha range (8–12 Hz): 19 (15.2%)
Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022;356:114150.	Patients (N): 106 Recording: Externalized leads Target: STN Conditions: Med OFF and Med ON Study design: Single-center Lead Model: Medtronic 3389 (n = 80, 3 bipolar channels per electrode), Boston Vercise™ cylindrical (n = 11; 8 cylindric contacts, 7 bipolar channels per electrode) and Vercise Cartesia™* directional leads (n = 15; 8 contacts)	**Patients with a beta peak (Med OFF): 92%** **Hemispheres with a beta peak (Med OFF): 84%** **Hemispheres with a beta peak (Med ON): 79%**	Peaks are detected in a wide majority of patients in both ON and OFF medication states. All tremor-dominant patients (n = 21) had at least one reliable beta peak (PD subtypes determined by UPDRS-III).
Neumann WJ, Degen K, Schneider GH, et al. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. Mov Disord. 2016;31(11):1748-1751.	Patients (N): 63 Recording: Externalized leads Target: STN Conditions: Med OFF Study design: Single-center Lead Model: 3389	**100% of patients had a peak within 8-35 Hz**	Spectral power in the 8-35 Hz range was associated with UPDRS-III scores in the medication OFF state (Spearman's ρ = 0.44, P < .0001).

Table 2: Seminal publications on local field potential peak detection in patients with Parkinson's disease

Publication	Patient Description	Peak Detection Rate	Additional Information
Medtronic conference abstracts			
Case M, Bronte-Stewart H, Kuhn A, et al. A retrospective analysis of multicenter chronic brain signal data recorded in Parkinson subjects implanted with deep brain stimulation leads. Poster presentation at the North American Neuromodulation Society (NANS) Annual Meeting, 2020. Las Vegas, NV.	Patients (N): 63 Recording: Activa™ PC+S, externalized leads (one center) Target: STN Conditions: Med OFF Study design: Multicenter retrospective focused on beta (10 to 35 Hz) with sufficient power for detection (0.8 µV/rtHz)	**82% of patients**	Distribution in patient subtypes: • Akinetic rigid: 79% (38 of 48) • Tremor dominant: 92% (11 of 12) Limitations: • Conference presentation, not peer-reviewed. • Potential patient selection bias
Fasano, A., Witt, T., Bick, S., et al., Local Field Potential Recordings in Patients with Parkinson's Disease: Effect of Lead Type and Target, Peak Detection, and Association to Therapeutic Contact Selection. 9th Annual European Academy of Neurology Congress 2023. Budapest, Hungary	Patients (N): 48 Recording: Percept™ PC Target: STN and GPi Conditions: Stim OFF, Med Unknown Study design: Multi-center, post-market registry Lead Model: 3389/3387 and SenSight™ leads	**At least 1 peak was detected in 93.3% of patients** with bilateral recordings. 76 of 93 **(81.7%)** of nuclei had a peak.	Real-world, multisite data. Limitations: • Conference presentation, not peer-reviewed. • Potential patient selection bias

FEATURED ARTICLE:

Presence of Beta in Patients with Parkinson's Disease

Darcy N, Lofredi R, Al-Fatly B, Neumann WJ, Hübl J, Brücke C, Krause P, Schneider GH, Kühn A. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Exp Neurol. 2022 Oct;356:114150.

Objective

To determine beta signal presence in a large cohort of patients with Parkinson's disease and to understand beta's relationship to the anatomical sweet spot in the subthalamic nucleus (STN).

Methods

- Retrospective study
- 106 patients with bilateral STN-DBS for Parkinson's disease (210 total STN)
- Recordings within a week of lead implant, Meds OFF and ON
- Peaks categorized into alpha (8–12 Hz), low-beta (13–20 Hz), high-beta (21–35 Hz)
- Local field potential (LFP) power was compared to a previously defined anatomical sweet spot[1]

Results

92% of patients had at least one peak in the beta range, OFF medication. 91% and 87% of hemispheres had a peak in the OFF and ON medication state, respectively. Low-beta peak power, but not high-beta, was associated with clinical motor state (i.e., UDPRS-III). High-beta power increased closer to the anatomical sweet spot for the best clinical effect.

Summary and limitations

Peak detection:

- Peaks are detected in a wide majority of patients in both ON and OFF medication states.
- All tremor-dominant patients (n = 21) had at least one reliable beta peak. (PD subtypes determined by UPDRS-III)

Association of Beta Power to UPDRS-III:

- Peak low-beta power correlated significantly with clinical motor score.

Association of Beta Power to STN anatomy:

- Beta power increased closer to the anatomical sweet spot for clinical effect, with high beta being significantly correlated with distance to the sweet spot.

Limitations:

- Micro-lesion effects may limit the ability to detect signals from the tissue.
- Recordings were conducted in a bipolar fashion, potentially causing power in beta to appear lower.
- Beta was analyzed with patients at rest under laboratory conditions.

1 Dembek TA, Roediger J, Horn A, et al. 2019. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. Ann. Neurol. 86, 527–538.

Figure 1. A majority of patients have a signal in both OFF and ON medication states.

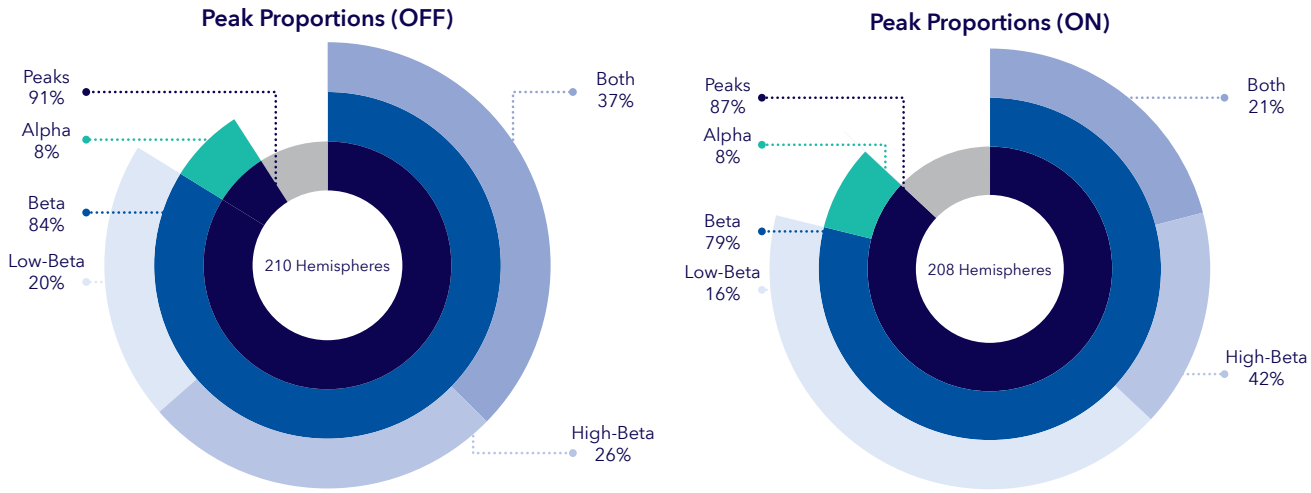
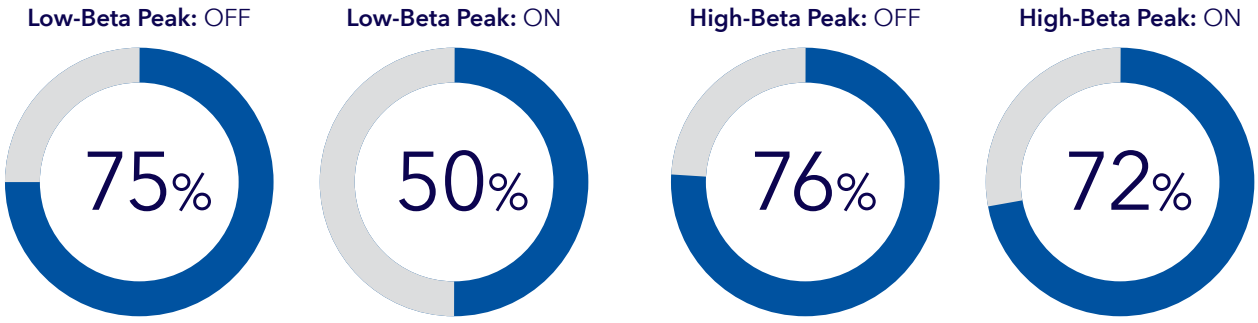


Figure 2. Beta peaks are present in a majority of patients and hemispheres.

Figure 3. Low-beta signals are modulated with medication whereas, high-beta signals persist in OFF and ON medication states.



Clinical significance

The authors found that peaks in the beta range can be found in a majority of patients with Parkinson's Disease, are related to clinical motor state, and are associated to subthalamic anatomy, increasing confidence in the broad relevance of beta in DBS therapy.

All figures have been reproduced from the data in Darcy, et al.

Association of LFP measures to clinical state, response to DBS and meds, and STN anatomy

While LFP peaks are commonly detected in patients with PD[1], extensive literature underscores their significant clinical implications.[2] Specifically, research consistently reports a positive correlation between beta band measures and PD motor symptoms like bradykinesia and rigidity.[3] The exploration of frequency bands beyond beta is also expanding, with studies revealing connections between theta/alpha and gamma activity to tremor and dyskinesia, respectively.[4] Additionally, the response of beta measures to antiparkinsonian medication and DBS is noteworthy; elevated beta activity typically diminishes with treatment, leading to subsequent improvements in UPDRS-III scores.[1] Recent works have found additional frequency band specificity in medication responses, namely, more prominent low-beta band suppression in response to antiparkinsonian medication relative to high-beta.[1] Lastly, given the detectability and functional relevance of these peaks in the majority of patients, numerous studies have delved into their spatial localization within subcortical nuclei.[1] These studies have unveiled the spatial distribution of LFP measures, notably beta, within the subthalamic nucleus, with the aim of propelling the advancement of LFP-guided contact selection.[1] The following is a summary of key literature in the previously noted domains.

1. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022;356:114150.
2. Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.
3. van Wijk BCM, de Bie RMA, Beudel M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. *Journal of Neurology*. 2023;270(2):1162-1177.
4. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. *Neurobiology of Disease*. 2021;155:105372.

Clinical state: symptoms

Beta LFPs correlated with UPDRS-III scores.[1,20]

Beta LFPs correlated with the development of bradykinesia.[2,14]

Alpha/Beta LFPs correlated with akinetic/rigid symptoms and UPDRS-III scores, but not tremor.[3,11,12,13]

Resting tremor tends to attenuate alpha/beta LFPs.[9]

Clinical state: side effects

Theta/alpha LFPs may be correlated with levodopa-induced dyskinesias (LID).[4]

Theta/alpha LFPs may be correlated with impulse control disorders (ICD) and LID.[5]

Therapy: medication

Alpha/beta LFPs correlated with levodopa-induced bradykinesia and rigidity[6,10]

Beta LFPs were attenuated by levodopa.[7,12,13,14,15,18]

Therapy: stimulation

Beta LFPs attenuated proportionally to increasing DBS voltage[8,17]

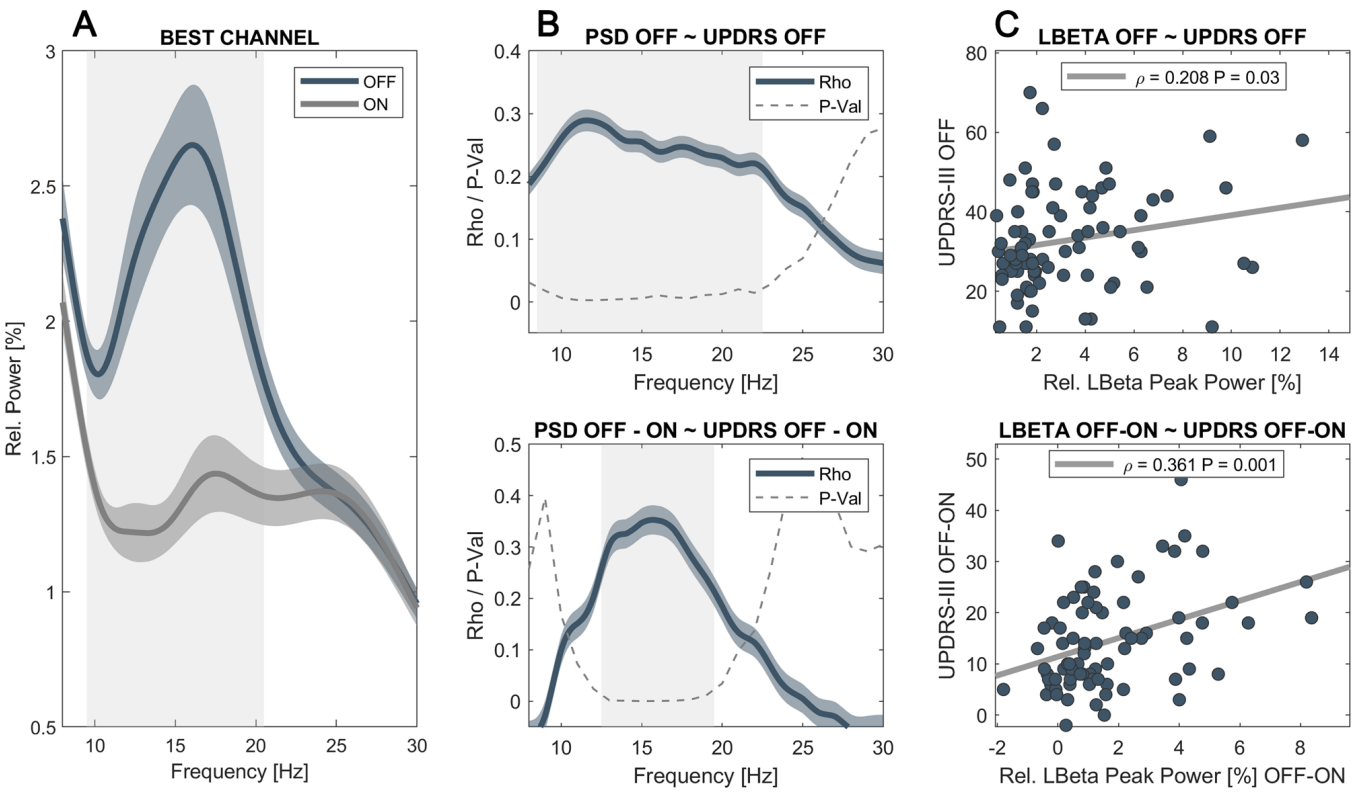
Beta LFPs, but not alpha LFPs, were attenuated by DBS[7,18,19]

Symptom improvement with DBS correlated with reduction in beta activity.[11,16]

Referenced articles

1. Neumann WJ, et al. Mov Disord. 2016a; 31(11):1748-1751.
2. Steiner LA, et al. Mov Disord. 2017; 32(8):1183-1190.
3. Kühn AA, et al. Exp Neurol. 2009; 215(2):380-387
4. Alonso-Frech F, et al. Brain. 2006; 129(Pt 7):1748-1757.
5. Rodriguez-Oroz MC, et al. Brain. 2011; 134(Pt 1):36-49.
6. Kühn AA, et al. Eur JNeurosci. 2006; 23(7):1956-1960.
7. Neumann WJ, et al. Neuromodulation. 2016b; 19(1):20-24.
8. Quinn EJ, et al. Mov Disord. 2015; 30(13):1750-1758.
9. Shreve et al. Clin Neurophysiol. 2017;128(1):128-137.
10. Little et al. Exp Neurol. 2012;236(2):383-8.
11. Kuhn et al. J Neurosci. 2008;28(24):6165-73.
12. Van Wijk et al. Clin Neurophysiol. 2016;127(4):2010-9.
13. Ray et al. Exp Neurol. 2008 Sep;213(1):108-13.
14. Ozturk et al. Mov Disord. 2020 Jan;35(1):91-100.
15. Neumann et al. Clin Neurophysiol. 2017;128(11):2286-2291.
16. Trager et al. NeurobiolDis. 2016;96:22-30.
17. Eusebio et al. Neurol Neurosurg Psychiatry. 2011;82(5):569-73.
18. Giannicola et al. Exp Neurol. 2010;226(1):120-7.
19. Rosa et al. Neurosignals. 2011;19(3):151-62
20. Wiest et al. Neurobiol Dis. 2020 Sep;143:105019.

Beta responds to dopamine: PD symptom severity correlates with reduction of beta power.



Low beta power in the OFF-medication state and its reduction with dopamine correlate with symptom severity.

A) Averaged power spectra across contact pairs in the ON (gray) and OFF (blue) medication state. Relative beta power in the low beta range decreases with dopaminergic medication (gray shading, $p < 0.0001$).

B) The amplitude of frequencies between 9 and 22 Hz shows a significant correlation with motor symptoms as assessed by the UPDRS-III. However, symptom alleviation with dopamine is best reflected by amplitude changes from 13 to 19 Hz, commonly referred to as the low beta band (blue = Rho-values for each frequency bin; gray line = correspondent p-value; significant areas are underlined in gray).

C) There is a significant correlation between symptom severity and averaged low beta power (13–20 Hz) in the dopamine-depleted state. Likewise, the reduction in low beta power with dopamine correlates with symptom alleviation.

Lofredi R, Okudzhava L, Irmen F, Brücke C, Huebl J, Krauss JK, Schneider GH, Faust K, Neumann WJ, Kühn AA. Subthalamic beta bursts correlate with dopamine-dependent motor symptoms in 106 Parkinson's patients. NPJ Parkinsons Dis. 2023 Jan 7;9(1):2. Figure 1 of the paper and supporting legend text are licensed under CC BY 4.0. https://creativecommons.org/licenses/by/4.0/ No changes have been made to the image; figure legend text has been abbreviated.

Review of physiologic and Parkinsonian symptom associations to LFP frequency bands

	Physiological	Pathological Signals in PD
Delta (~0-4 Hz)	Related to slow-wave sleep	-----
Theta/Alpha (~4-13 Hz)	Cognition, emotion, gait regulation	Dyskinesia; tremor
Low beta (~13-20 Hz)	Modulated during movement	Rigidity, bradykinesia, freezing
High beta (~20-35 Hz)	Hyperdirect pathway	
Gamma (~35-250 Hz)	Motor, force	Dyskinesia, resting tremor
Slow HFO (~200-300 Hz)	-----	Akinetic
Fast HFO (~300-400 Hz)	Prokinetic	-----

HFO = high frequency oscillations

Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. Neurobiol Dis. 2021 Jul;155:105372.

Association of LFP frequencies to clinical state in Parkinson's disease

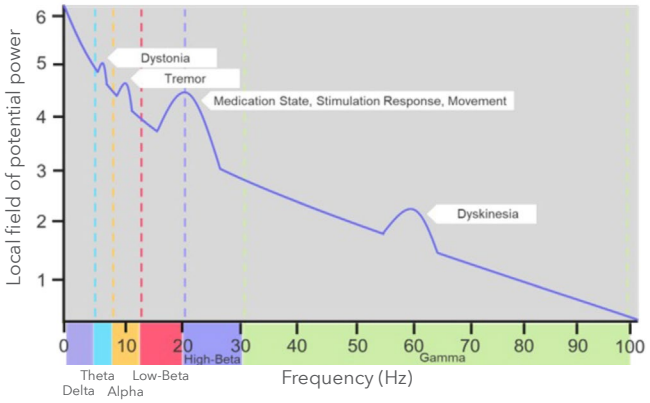


Image adapted from Neumann WJ, Gilron R, Little S, Tinkhauser G. Adaptive Deep Brain Stimulation: From Experimental Evidence Toward Practical Implementation. Mov Disord. 2023 Jun;38(6):937-948.

Gamma and theta band LFPs in Parkinson's disease and relationship to side effects

Gamma activity typically refers to activity in the 30 to 100 Hz range. Finely-tuned gamma (FTG) oscillations in the 60 to 90 Hz range have been induced by parkinsonian medication or DBS in patients with Parkinson's disease. In contrast, movement execution and movement-related events have been shown to induce broad gamma activity. The distinction between these types of gamma is not entirely clear and the two are often discussed interchangeably.

When might a gamma signal appear in patients with PD?[1,2]

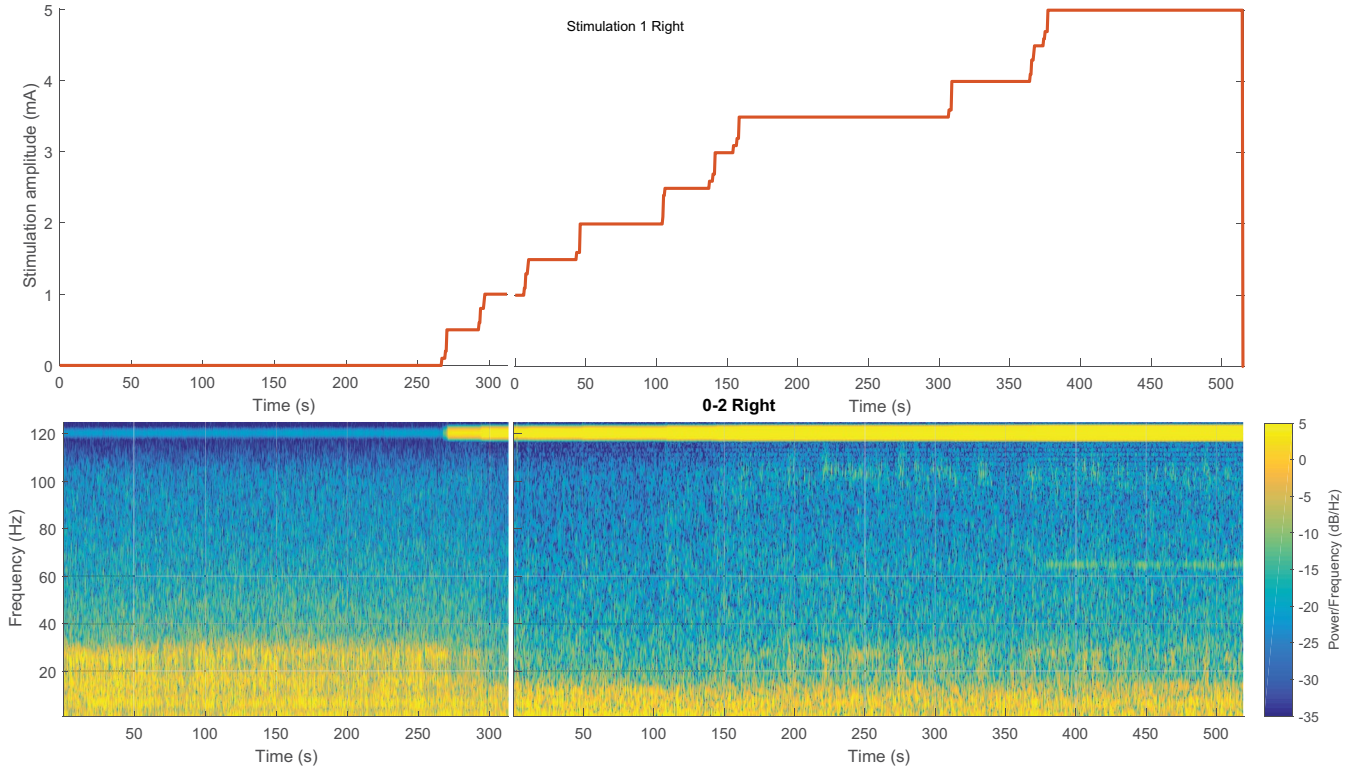
- Levodopa-induced FTG has been observed at rest with slight amplitude and frequency increases during voluntary movement.
- FTG modulation that appears with voluntary movements may reflect healthy motor function.
- Some patients may display levodopa-induced FTG during episodes of dyskinesia.
- Some patients may display FTG when off dopaminergic medication with no observable dyskinesias.
- In patients with DBS, FTG may be apparent when off medication, at the onset of stimulation, or at the offset of stimulation.
- FTG has appeared with peak-dose dyskinesia, but not during diphasic dyskinesias, suggesting a relationship to high dopaminergic stimulation rather than dyskinesias per se.

Related articles

1 Wiest C, Torrecillos F, Tinkhauser G, et al. Finely-tuned gamma oscillations: Spectral characteristics and links to dyskinesia. Exp Neurol. 2022 Feb 7;351:113999.

2 Foffani G, Alegre M. Brain oscillations and Parkinson disease. Handb Clin Neurol. 2022;184:259-271.

- The relationship between dyskinesia and DBS-induced FTG in the STN is not clear.



Data recorded using the Percept™ PC device with BrainSense™ technology shows that power in the beta frequency range (15 to 30 Hz) decreases with increasing DBS stimulation intensity in a patient with Parkinson's disease. Stimulation-related harmonics were seen in this specific patient. Around 4 mA, a 60 Hz oscillation was induced; no dyskinesia was present during the recording.

Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4). Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). No modifications were made to the material.

Theta band oscillations

Oscillations in the theta range (4-7 Hz) have been linked to off-medication rest tremor. In on-medication states, low frequency activity has been associated with levodopa-induced dyskinesias and impulse control disorders.

When might a theta signal appear in a patient with PD?

- With levodopa-induced dyskinesias[1,2]
- Peak-dose and diphasic dyskinesia[3]
- With on-medication impulse control disorders[1]
- During off-medication rest tremor[4]

Related articles

1 Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. Brain. 2011 Jan;134(Pt 1):36-49.

2 Alonso-Frech F, Zamarbide I, Alegre M, Rodríguez-Oroz MC, Guridi J, Manrique M, Valencia M, Artieda J, Obeso JA. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. Brain. 2006 Jul;129(Pt 7):1748-57.

3 Alegre M, López-Azcárate J, Alonso-Frech F, Rodríguez-Oroz MC, Valencia M, Guridi J, Artieda J, Obeso JA. Subthalamic activity during diphasic dyskinesias in Parkinson's disease. Mov Disord. 2012 Aug;27(9):1178-81.

4 Foffani G, Alegre M. Brain oscillations and Parkinson disease. Handb Clin Neurol. 2022;184:259-271.

FEATURED ARTICLE:

Review of Local Field Potential Correlation to Parkinson's Disease Symptoms

van Wijk BCM, de Bie RMA, Beudel M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. J Neurol. 2023 Feb;270(2):1162-1177.

https://doi.org/10.1007/s00415-022-11388-1

Objective

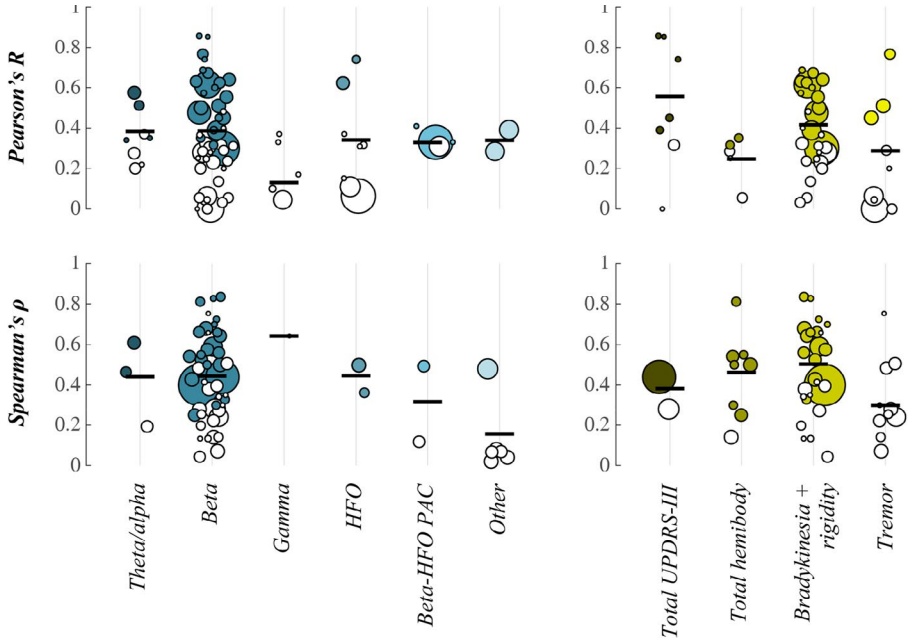
To provide a systematic review of the association of LFPs to PD motor symptoms, show their pooled effect sizes.

Methods

Review of literature that report outcomes of a correlation analysis between subthalamic nucleus (STN) LFP signal features and PD symptoms.

Results

- Pooled together, beta's (~13-30 Hz) estimated correlation value with bradykinesia and rigidity symptoms equaled r=0.416 (p = 0.440) and ρ=0.504 (p = 0.189).
- **Approximately 17% (R^2) of individual variability in symptom severity can be explained by beta-based LFP signal features, suggesting that while beta correlates with motor symptoms, other measures may provide additional insights into a patient's clinical state.**



Distribution of correlation values and pooled effect sizes across publications reporting on beta and UPDRS scores. The size of circles reflects the number of hemispheres that were used in the correlation analysis. Black horizontal lines indicate the pooled effect size estimate across studies. All UPDRS categories include reported correlations for total UPDRS-III, total hemibody (bradykinesia + rigidity + tremor), hemibody bradykinesia + rigidity, and hemibody tremor items. These categories are visualized separately for beta-based LFP features on the right.

Notes and limitations

Clinical ratings used for correlation analysis with LFP are often rater-dependent and, for this reason, not objective. This is especially the case for bradykinesia items in UPDRS scores. The scoring of these items is also nonlinear, meaning that a larger worsening of symptoms is needed to progress from a medium to high score than it is to progress from a low to medium score.

Low correlation values may also result from interindividual differences in LFP signal quality and (patho-) physiology. Suboptimal placement of DBS electrodes, electrode impedance, presence of cardiac or movement artifacts, and hardware failures may affect LFP detection.

FEATURED ARTICLE:

Review of Low And High Beta Correlation to UDPRS-III Scores

Morelli N, Summers RLS. Association of subthalamic beta frequency sub-bands to symptom severity in patients with Parkinson's disease: A systematic review. Parkinsonism Relat Disord. 2023;110:105364. doi:10.1016/j.parkreldis.2023.105364

Objective

The objective of this review is to synthesize literature reporting the association of low- and high-beta characteristics to clinical ratings of motor symptoms in people with PD.

Methods

A systematic review of existing literature, which collected subthalamic nucleus (STN) LFPs using macroelectrodes in people with Parkinson's disease, analyzed low- (13-20 Hz) and high-beta (21-35 Hz) bands, collected UPDRS-III, and reported correlational strength or predictive capacity of LFPs to UPDRS-III scores.

Results

- The initial search yielded 234 articles, with 11 articles achieving inclusion.
- Beta measures included power spectral density, peak characteristics, and burst characteristics.
- **High-beta was a significant predictor of UPDRS-III responses to therapy** in 5 out of 5 (100%) articles that included predictive analyses.
- **Low-beta was significantly associated with UPDRS-III total score** in 3 out of 5 (60%) articles.
- Low- and high-beta associations to UPDRS-III subscores were mixed.

Notes and limitations

This systematic review reinforces previous reports that beta band oscillatory measures demonstrate a consistent relationship to Parkinsonian motor symptoms and ability to predict motor response to therapy.

Continued research is needed to determine which beta sub-band demonstrates the greatest association to motor symptom subtypes and potentially offers clinical utility toward LFP-guided DBS programming.

Findings of studies which report correlations of low- and high-beta to UPDRS-III measures.

UPDRS-III total	Low-beta	High-beta	Strength and direction of association Low-beta
Darcy et al. Exp Neurol. 2022 Oct;356:114150.	Low-beta peak power was significantly correlated with UPDRS-III total score (ρ=0.21, p=0.036).	No association between high-beta measures and UPDRS-III (ρ=0.13, p=0.118).	++
Merk et al. Elife. 2022 May 27;11:e75126.	Significant correlations were found between UPDRS-III and low-beta bursts in STN-LFP signals during motor preparation (ρ=0.63, p=0.02) and movement execution (ρ=0.56, p=0.04)	No association between high-beta measures and UPDRS-III (motor preparation - (ρ=0.27, p=0.21)).	+++
Averna et al. Clin Neurophysiol. 2022 Jan;133:29-38.	No association between low-beta measures and UPDRS-III (correlation values not reported).	No association between high-beta measures and UPDRS-III (correlation values not reported).	NC
Nie et al. Clin Neurophysiol. 2021 Nov;132(11):2789-2797.	Long duration low-beta states were positively correlated (r = 0.736, p = 0.030) with UPDRS-III.	No association between high-beta measures and UPDRS-III.	++++
Chen et al. Front Hum Neurosci. 2022 Sep 8;16:958521.	Low-beta power demonstrated no association to UPDRS-III in the OFF (r= -0.181, p=0.396) or ON (r= 0.283, p=0.181).	High-beta power demonstrated no association to UPDRS-III in the OFF (r=0.010, p=0.961) or ON (r= -.182, p=0.396).	NC

Abbreviations: NC – Not Correlated, UPDRS – Unified Parkinson's Disease Rating Scale; LFP – Local Field Potential; + = positive, negligible association; ++ = positive, weak association; +++ = positive, moderate association; ++++ = positive, strong correlation; +++++ = positive, very strong association; - = negative, negligible association; -- = negative, weak association; --- = negative, moderate association; ---- = negative, strong correlation; ----- = negative, very strong association

Findings of studies which report correlations of low- and high-beta to UPDRS-III measures.

UPDRS-III sub scores	Low-beta	High-beta	Strength and direction of association Low-beta
Belova et al. Eur J Neurosci. 2021 Apr 27.	Low-beta power, specifically 12-16 Hz, demonstrated significant correlation to bradykinesia scores (r= 0.75 - 0.57, p<0.05). This association was consistent with 14-18 (r= 0.59 - 0.54, p>0.05) and 16-20 (r= 0.38 - 0.35, p>0.05) Hz, but was not significant. No significant correlation was found for low-beta to rigidity scores (r= -0.42 - -0.10, p>0.05).	High-beta power ranges demonstrated weak to moderate, primarily negative, non-significant correlation to bradykinesia scores (r= -0.65 - 0.13, p>0.05). High-beta power demonstrated weak, primarily negative correlation to rigidity scores (r= -0.42 - 0.07, p>0.05)	++++
Nie et al. Clin Neurophysiol. 2021 Nov; 132(11):2789-2797.	Long duration low-beta states were positively correlated (r = 0.587, p = 0.028) with tremor and rigidity (r = 0.453, p = 0.045) severity. No correlation was found between low-beta to bradykinesia or axial symptoms.	No association between high-beta measures and UPDRS-III.	+++
Chen et al. Front Hum Neurosci. 2022 Sep 8;16:958521.	The normalized low-beta power was not correlated with the bradykinesia–rigidity score assessed postoperatively in the stimulation-off and medication off state (r= −0.228, p= 0.112).	The normalized high-beta power was not correlated with the bradykinesia–rigidity score assessed postoperatively in the stimulation-off and medication off state (r = −0.025, p= 0.864).	NC
Sure et al. Front Neurosci. 2021 Nov 11;15:724334.	No association to Akinetic-Rigid sub score. (r = -0.20 – 0.13; p > 0.05).	OFF high-beta burst duration of the postero-medial contact demonstrated a significant, positive correlation with the OFF Akinetic-Rigid sub score (r = 0.48, p = 0.03).	NC
UPDRS-III response to therapy	**Low-beta**	**High-beta**	**Strength and direction of association Low-beta**
Averna et al. Clin Neurophysiol. 2022 Jan;133:29-38	Levodopa-induced motor improvement on UPDRS-III positively correlated to LFP variations in low-beta band (r = 0.650, p-value = 0.022, 95% CI [0.200, 0.887]).	No association between high-beta measures and UPDRS-III.	+++
Chen et al. Front Hum Neurosci. 2022 Sep 8;16:958521.	No association was noted between stimulation-related improvement in bradykinesia–rigidity and the maximum power in the low-beta (r= −0.055, p = 0.704) frequency range. No significant relationship to tremor or axial subscales.	High-beta power was positively correlated with the stimulation-related improvement in contralateral bradykinesia–rigidity (r= 0.549, p < 0.0001). No significant correlation to tremor or axial subscales.	NC
	No association was noted between levodopa-related improvement in bradykinesia–rigidity (r= −0.087, p = 0.550) or total UPDRS-III (r= -0.164, p= 0.443) and the maximum power in the low-beta frequency range.	No association was noted between levodopa-related improvement in bradykinesia–rigidity (r= 0.119, p= 0.412) or total UPDRS-III (r= 0.220, p= 0.302) and the maximum power in the low-beta frequency range.	NC

Abbreviations: NC – Not Correlated, UPDRS – Unified Parkinson's Disease Rating Scale; LFP – Local Field Potential; + = positive, negligible association; ++ = positive, weak association; +++ = positive, moderate association; ++++ = positive, strong correlation; +++++ = positive, very strong association; - = negative, negligible association; -- = negative, weak association; --- = negative, moderate association; ---- = negative, strong correlation; ----- = negative, very strong association

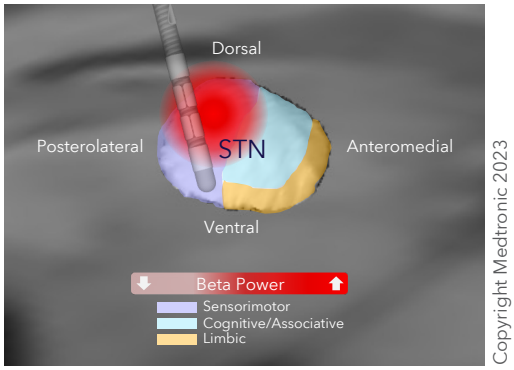
Findings of studies which report predictive capacity of low- and high-beta to UPDRS measures.

	Low-beta	High-beta
Hirschmann et al. Brain Stimul. 2022 May-Jun;15(3):792-802.	Low-beta power did not predict UPDRS-III response to stim.	STN high-beta power was the most important local feature for predicting UPDRS-III response to stim.
Shah et al. Neuromodulation. 2023 Feb;26(2):320-332.	Clinical efficacy (CE) correlated positively with rest low-beta. The most predictive feature for CE for both segmented contacts and all contacts was resting-state fast gamma activity (negative correlation), followed by resting-state low beta activity (positive correlation). Movement-related modulation of low-beta and HFO (both negative correlation) was most predictive for the side-effect threshold for all contacts.	High beta was the second most predictive feature for therapeutic window and segmented contacts.
Khawaldeh et al. Brain. 2022 Mar 29;145(1):237-250.	The change in the occurrence rate of the low-beta states between ON versus OFF levodopa was positively correlated with the change in motor impairment with levodopa, (i.e., decreases in the occurrence of low-beta states were linked to improvements in motor impairment ON meds). Change in the relative occurrence rate of short duration low beta states negatively correlated with change in motor impairment and change in the relative occurrence rate of longer duration low beta states positively correlated with change in motor impairment. Low beta was a stronger predicter of UPDRS improvement compared to high beta.	High-beta was associated with motor improvement, but to a lesser extent than low-beta. Occurrence rate and duration of LFP states in high-beta negatively correlated with motor impairment in patients OFF medication, with medication ON state increasing occurrence rate and duration of high-beta, correlating with improvement in symptoms
Chen et al. Brain Stimul. 2020 Nov-Dec;13(6):1784-1792.	Regression modeling found the most related features at 6 months were found in the 15-18 Hz and 25-26 Hz bands.	Regression modeling found that at month 1, suppression of 29-32 Hz and 35-36 Hz were found to be most related to symptom improvement to stimulation. However, the most predictive feature shifted to 25-32 Hz at month 3.
Chen et al. Front Hum Neurosci. 2022 Sep 8;16:958521.	Low-beta power was not predictive of UPDRS response to DBS.	High-beta power and the distance of the highest high-beta power contact to the contact selected for stimulation accounted for 37.4% of the variance in the therapeutic outcome in contralateral bradykinesia–rigidity [R2 = 0.374, F(2,47) = 14.061, p = 1.6 × 10−5]. In this regression model, the slope coefficient for the maximum high-beta power was 0.425 (95% CI: [0.139, 0.711], p = 0.0045).

Abbreviations: UPDRS – Unified Parkinson's Disease Rating Scale

Association of LFP measures to subcortical anatomy in patients with Parkinson's disease

LFP measures may provide insights into STN anatomy and "sweet spot" proximity in patients with PD. The following publications investigate the spatial distribution of LFP measures within the dorsal STN. Together, highlighting the concentration of beta activity in dorsolateral STN and inversely related to distance from stimulation "sweet spot" for rigidity and bradykinesia symptom control within the dorsolateral STN for patients with STN-DBS for PD.[1,2]



1. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022:114150.
2. Averna A, Debove I, Nowacki A, et al. Spectral Topography of the Subthalamic Nucleus to Inform Next-Generation Deep Brain Stimulation. Mov Disord. 2023;38(5):818-830. doi:10.1002/mds.29381

Table 3: Spatial distribution of LFP measures within the dorsal STN

Publication	Patients	Findings
Xu SS, Sinclair NC, Bulluss KJ, et al. Towards guided and automated programming of subthalamic area stimulation in Parkinson's disease. Brain Communications. 2022;4(1).	Patients: n=14 bilateral STN-DBS for PD	Beta power was greatest at contacts ranked as closer to the nominated ideal anatomical location for stimulation within the STN. • The 'ideal' contact (yielding maximal benefit to tremor, rigidity, or bradykinetic symptoms) was ranked first according to each factor in the following proportion of hemispheres; evoked resonant neural activity 18/28, beta 17/28, anatomy 16/28, high-frequency oscillations 7/28. **Limitations:** LFP data was recorded intraoperatively and could be impacted by microlesion effects.
Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022:114150.	Patients: n=106 bilateral STN-DBS for PD	Contacts with beta peaks were closer to anatomical sweet spot compared to those without beta peaks. • Beta power, specifically high-beta (21-35 Hz) and not low-beta, increased as distance from recording location to anatomical sweet spot decreased. • Heat maps of LFP power denoted a dorsolateral STN concentration of beta power. **Limitations:** Microlesion effects may have influenced the LFP data. Recordings were conducted at rest under laboratory conditions and in a bipolar fashion which may influence the localization of beta power.

Table 3: Spatial distribution of LFP measures within the dorsal STN

Publication	Patients	Findings
Horn A, Neumann W-J, Degen K, Schneider G-H, Kühn AA. Toward an electrophysiological "sweet spot" for deep brain stimulation in the subthalamic nucleus. Human Brain Mapping. 2017;38(7):3377-3390.	Patients: n=54 bilateral STN-DBS for PD	The greatest beta activity was in the dorsolateral part of the STN. • Active contacts of DBS electrodes exhibited significantly higher beta power at rest. • Higher alpha activity was found in the ventromedial aspect of the STN. **Limitations:** Normalization techniques and inter-patient anatomical differences may create inaccuracies in electrode and anatomical coordinates.
Chen P-L, Chen Y-C, Tu P-H, et al. Subthalamic high-beta oscillation informs the outcome of deep brain stimulation in patients with Parkinson's disease. Frontiers in Human Neuroscience. 2022;16.	Patients: n=26 bilateral STN-DBS for PD	DBS efficacy for bradykinesia and rigidity symptoms was correlated with contacts demonstrating the highest high-beta power, but not low-beta power, within the STN. • DBS efficacy for tremor was not associated with STN LFPs. **Limitations:** Imaging was compared to preoperative scans. LFP measures of a single band were compared to STN anatomy, combining measures may provide additional benefit. LFP normalization may be influenced by active tremor in patients.
van Wijk BCM, Pogosyan A, Hariz MI, et al. Localization of beta and high-frequency oscillations within the subthalamic nucleus region. Neuroimage Clin. 2017;16:175-183.	Patients: n=14 bilateral STN-DBS for PD	The greatest beta power was most likely to occur at the surgical target point in the STN. • The greatest beta and high-frequency power occurred at the same recording site in half of STN samples. **Limitations:** Normalization techniques and inter-patient anatomical differences may create inaccuracies in electrode and anatomical coordinates. Recordings were conducted in a bipolar fashion which may influence the localization of beta power
Averna A, Debove I, Nowacki A, et al. Spectral Topography of the Subthalamic Nucleus to Inform Next-Generation Deep Brain Stimulation. Mov Disord. 2023;38(5):818-830. doi:10.1002/mds.29381	Patients: n= 70 bilateral STN-DBS for PD	The strongest segregation of STN LFP data was in the inferior-superior axis superiorly localized beta hot spot, relative to inferiorly located high frequency oscillations. • Both the spatial proximity of contacts to the beta hot spot and the distance to higher-frequency hot spots were predictive for the best rigidity response to DBS. **Limitations:** The topographic distribution was limited to the dorsal part of STN. Clinical assessments focused on rigidity. STN LFP data was collected in the off-medication state and intraoperatively. Normalization techniques and inter-patient anatomical differences may create inaccuracies in electrode and anatomical coordinates.

Abbreviations: STN – subthalamic nucleus, DBS – deep brain stimulation, PD – Parkinson's disease, LFP – local field potentials

Longitudinal stability of LFP measures

DBS is a longitudinal therapy to meet patients' needs throughout their journey with Parkinson's disease.[1,2] Therefore, utilization of patient-specific markers, such as LFPs, in clinical practice requires a stable signal which can be readily detected. This is prudent not only because of the longitudinal nature of DBS therapy, but also the acute effects of electrode implantation (i.e., microlesion effect) which may alter LFP measures. Recent studies have investigated how LFP data changes over time in patients with PD, providing insights into the stability of these signals for longitudinal clinical implementation.

1. Limousin, P., Foltynie, T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Rev Neurol 15, 234–242 (2019).

2. Hitti FL, Ramayya AG, McShane BJ, et al. Long-term outcomes following deep brain stimulation for Parkinson's disease. Journal of Neurosurgery JNS. 2020;132(1):205-210. Doi:10.3171/2018.8.JNS182081

Article summaries: Investigating LFP fluctuations and stability over time.

Neumann WJ, Staub-Bartelt F, Horn A, et al. Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease. Clin Neurophysiol. 2017;128(11):2286-2291.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5779610/

- N=15, LFP recordings at implant, 3 and 8 months post-operatively.
- No statistically significant changes in peak frequency were observed for any time point. The Kruskal-Wallis tests revealed no significance for the effect of timepoint on beta peak power, neither ON, nor OFF medication ($P > 0.1$)

Trager MH, Koop MM, Velisar A, et al. Subthalamic beta oscillations are attenuated after withdrawal of chronic high frequency neurostimulation in Parkinson's disease. NeurobiolDis, 2016;96:22-30.

https://www.ncbi.nlm.nih.gov/pubmed/27553876

- N=17, LFP recordings at initial programming, 6 months, and 12 months
- At the 12 months, there was a trend for a reduction in beta power compared to IP when corrected for multiple comparisons ($\beta = -0.21$, $P = 0.082$ uncorrected, $P = 0.1$ corrected). Beta band power did not change between the 6 months and 12 months time points ($P > 0.05$).

Darmani G, Drummond NM, Ramezanpour H, et al. Long-Term Recording of Subthalamic Aperiodic Activities and Beta Bursts in Parkinson's Disease. Mov Disord. 2023;38(2):232-243. doi:10.1002/mds.29276

- N=10, LFP recordings at six visits during a period of 18 months
- Beta burst duration and amplitude did not differ over time ($P = 0.1$). Aperiodic activity demonstrated a main effect of time ($P < 0.001$), with exponent and offset increasing at 6 months and remaining stable at 18 months after surgery.

Chen Y, Gong C, Tian Y, et al. Neuromodulation effects of deep brain stimulation on beta rhythm: A longitudinal local field potential study. Brain Stimul. 2020;13(6):1784-1792. doi:10.1016/j.brs.2020.09.027

- N=7, LFP recordings at 1, 3, and 6 months after surgery
- Beta power appeared to be slightly lower at month 6 than month 1, especially in the high beta band; however, the difference did not reach statistical significance (N=13, $P > 0.266$ between any two time points).

Wilkins KB, Kehnemouyi YM, Petrucci MN, et al. Bradykinesia and Its Progression Are Related to Interhemispheric Beta Coherence. Ann Neurol. 2023;93(5):1029-1039. doi:10.1002/ana.26605

- N=21, LFP recordings at initial programming and up to 7 years
- Beta power ($P=0.55$) and burst duration ($P=0.54$) remained stable over time, while interhemispheric beta coherence increased with time ($P=0.014$)

FEATURED ARTICLE:

Lack of Progression of Beta Dynamics after Long-term Subthalamic Neurostimulation

Anderson RW, Wilkins KB, Parker JE, et al. Lack of progression of beta dynamics after long-term subthalamic neurostimulation. Ann Clin Transl Neurol. 2021 Nov;8(11):2110-2120.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8607445/

Objective

To investigate the neural and motor features of Parkinson's disease over time, after washout of medication and bilateral STN DBS.

Methods

Patients (N): 18

Recording: Activa™ PC + S

Target: STN

Conditions: Med OFF, DBS OFF

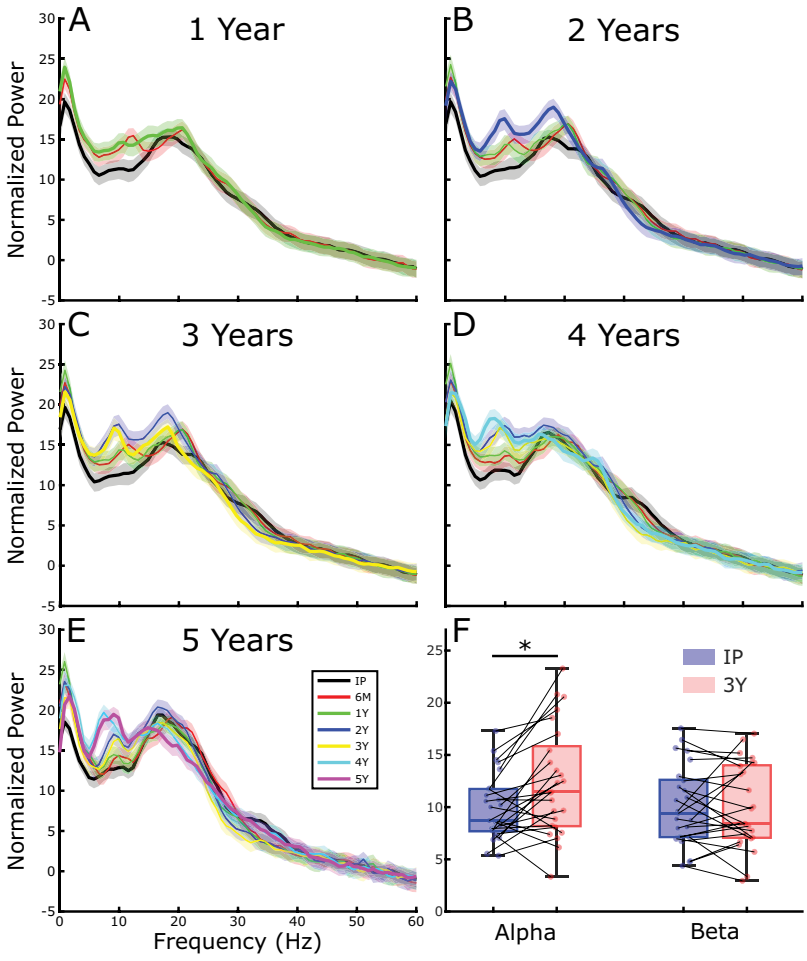
LFP recordings were collected at 1-month (N=18), 6-months (N=18), 1-year (N=18), 2-years (N=14), 3-years (N=14), 4-years (N=9), and 5-years (N=4) after initial programming.

Results

At the 3-year primary endpoint, STN beta (13-30 Hz) was not altered; however, power in the alpha band (8-12 Hz) increased. Results were consistent out to the 5-year follow-up.

Notes and limitations

The authors did not discuss complications. Limitations mentioned in the publication included the lack of a control group and the potential impact of varying levels of medications the patients were taking over the course of the study.



Off therapy average STN LFP power spectral density analysis before and after DBS.

A) 33 STN recordings conducted at initial programming (IP), and 6- and 12-months postimplant. B) 25 STN recordings at 2 years. C) 25 STN recordings at 3 years. D) 16 STN recordings at 4 years. E) 6 STN recordings at 5 years. F) Quantification of alpha (8–12 Hz) and beta (13–30 Hz) spectral bands at IP and after 3 years of DBS (*p = 0.0027). Patients with an akinetic rigid phenotype and a tremor dominant phenotype both displayed the increase in alpha band power.

Select

DBS programming is often time-consuming and heavily reliant on clinical observation.[1,2] Given the high prevalence of peak detection[3], their association to clinical states[3], longitudinal stability[4], and association with subcortical anatomy[3], researchers have explored the utility of LFP data to augment or guide contact selection.[5] Together, these articles suggest identifying contacts with high signal activity may help inform a starting place for the monopolar review.

Learn more about BrainSense™ Survey for informing contact selection: page 12

Final contact selection should be determined by the physician along with other medical information.

1. Volkmann J, Herzog J, Kopper F, Deuschl G. Introduction to the programming of deep brain stimulators. Mov Disord. 2002;17 Suppl 3:S181-S187. Doi:10.1002/mds.10162
2. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. Mov Disord. 2006;21 Suppl 14:S284-S289. Doi:10.1002/mds.20961
3. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022;356:114150.
4. Anderson RW, Wilkins KB, Parker JE, et al. Lack of progression of beta dynamics after long-term subthalamic neurostimulation. Ann Clin Transl Neurol. 2021;8(11):2110-2120. Doi:10.1002/l3.51463
5. Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: A tool to optimize deep brain stimulation. Movement Disorders. 2018;33(1):159-164.

The following section provides a review of recent literature regarding the application of LFP data in guiding contact selection for patients with PD.

Table 4: Association of LFP measures to contact selection in patients with Parkinson's disease

Publication	Patient description/methods	Findings and limitations
Fernández-García C, Monje MHG, Gómez-Mayordomo V, et al. Long-term directional deep brain stimulation: Monopolar review vs. local field potential guided programming. Brain Stimul. 2022;15(3):727-736.	Patients (N): 24 Recording: Intraoperative, externalized, non-Medtronic leads Target: Bilateral STN LFP Guided Contact Selection: Contact ranking based on beta peak power. Additional, non-randomized group based on traditional monopolar review was included.	• A **strong correlation between clinical efficacy and the low-beta** sub-band. • **Contacts with highest beta peaks increased the therapeutic window by 25%.** • Selecting the **two contacts with highest beta peaks provided an 82%** probability of selecting the best clinical contact. • Clinical results showed **similar improvements in the monopolar review group** (motor score, 72% reduction; levodopa equivalent daily dose, 65% reduction) **and LFP group** (72% and 63% reduction, respectively), maintained at long-term follow-up. **Limitations:** No comparison of ring and directional stimulation or monopolar review and beta-guided programming. Evaluations were conducted by different neurologists. Microlesion effect may influence data. Monopolar review done in non-randomized order.

Table 4: Association of LFP measures to contact selection in patients with Parkinson's disease

Publication	Patient description/methods	Findings and limitations
Xu SS, Sinclair NC, Bulluss KJ, et al. Towards guided and automated programming of subthalamic area stimulation in Parkinson's disease. *Brain Communications*. 2022;4(1).	Patients (N): 14 Recording: Immediate postop, externalized Medtronic, 3387 leads. Target: Bilateral STN LFP Guided Contact Selection: LFP recorded in monopolar fashion. Contacts were ranked based on beta power	• **Beta power was greatest at contacts ranked as closer to the nominated ideal anatomical location for stimulation within the STN.** • The 'ideal' contact (yielding maximal benefit to tremor, rigidity, or bradykinetic symptoms) was ranked first according to each factor in the following proportion of hemispheres; evoked resonant neural activity 18/28, beta 17/28, anatomy 16/28, high-frequency oscillations 7/28. **Limitations:** LFP data was recorded intraoperatively and could be impacted by microlesion effects.
Strelow JN, Dembek TA, Baldermann JC, et al. Local Field Potential-Guided Contact Selection Using Chronically Implanted Sensing Devices for Deep Brain Stimulation in Parkinson's Disease. *Brain Sciences*. 2022;12(12):1726.	Patients (N): 7 Recording: BrainSense™ Survey with SenSight™ leads at 3-months ± 6 weeks postop Target: Bilateral STN LFP Guided Contact Selection: 1. Recordings from bipolar contact pairs were obtained. 2. The DETEC algorithm was used to take all possible bipolar recordings and weigh them according to their distance from one another. This resulted in an average spectrogram of each monopolar contact and a method to determine the highest beta contact. 3. Physicians also used a visual approach to determine the location of highest beta. 4. Highest beta contacts were compared to the clinical contacts chosen through a standard monopolar review.	• In all hemispheres, the **stimulation contact with either the highest or second-highest activity in the beta frequency band matched the stimulation** levels with good clinical efficacy. • In 7 out of 14 hemispheres (50%), the stimulation contact with the highest beta activity matched the level with the best clinical efficacy. • **Higher clinical improvement was significantly associated with elevated beta activity**, explaining R^2 = 19% of the variance within the model. • Mean clinical improvement (UPDRS-III item 22, 23, 25) of contacts chosen using the monopolar review was significantly different from contacts chosen using the visual approach ($p = 0.006$) but not significantly differed from contacts chosen using the DETEC algorithm ($p = 0.164$). Further, no statistically significant differences between the visual approach and the DETEC algorithm were determined ($p = 0.403$). **Limitations:** Small sample size. Algorithmic approach to LFP-guided contact ranking requires further development. This study used a modified version of the monopolar contact review with a fixed amplitude of 2 mA rather than assessing the therapeutic windows.

Table 4: Association of LFP measures to contact selection in patients with Parkinson's disease

Publication	Patient description/methods	Findings and limitations
Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: A tool to optimize deep brain stimulation. *Movement Disorders*. 2018;33(1):159-164.	Patients (N): 12 Recording: Intraoperative, externalized, non-Medtronic leads Target: Bilateral STN LFP Guided Contact Selection: Beta peak or low-beta band measures compared to MDS-UPDRS-III rigidity response across contacts.	• **Two contacts with the highest beta activity included the most efficient stimulation contact in up to 92% and that with the widest therapeutic window in 74% of cases.** • A positive relationship ($p < 0.001$) between normalized beta activity and clinical efficacy in 15 of 19 hemispheres. • In 12 of 19 cases (63%) the highest beta contact corresponded to the contact with the highest clinical efficacy. **Limitations:** Only studied those sides with at least two points of upper-limb rigidity and more than a minimum range of responses to stimulation across contacts. Monopolar review may not be predictive of chronic contact settings and subjective. LFP recordings were around 2min and assumed the lead position did not change after recording. Data could be influenced by microlesion effects.
di Biase L, Piano C, Bove F, et al. Intraoperative Local Field Potential Beta Power and Three-Dimensional Neuroimaging Mapping Predict Long-Term Clinical Response to Deep Brain Stimulation in Parkinson Disease: A Retrospective Study. Neuromodulation. 2023. 10:S1094-7159(23)00008-9.	Patients (N): 14 Recording: Intraoperative, externalized, non-Medtronic leads Target: Bilateral STN LFP Guided Contact Selection: Beta power was calculated for all contacts within the STN and compared to programming at one-year postop.	• The **highest beta ranked contact showed a sensitivity of 67% and a negative predictive value of 84%** compared to clinical programming. • Combining LFP and imaging data showed a sensitivity of 87% and a negative predictive value 87% compared to clinical programming. **Limitations:** Small sample size and retrospective design.
Lewis S, Radcliffe E, Ojemann S, et al. Pilot Study to Investigate the Use of In-Clinic Sensing to Identify Optimal Stimulation Parameters for Deep Brain Stimulation Therapy in Parkinson's Disease. Neuromodulation. 2023; 14:S1094-7159(23)00011-9.	Patients (N): 5 Recording: BrainSense™ Survey with Medtronic 3389 leads. Target: Bilateral STN LFP Guided Contact Selection: Contacts with maximal beta peak power were clinically assessed and compared to patients current programming parameters.	• **No clinical difference was seen between stimulation conditions.** • The **clinician and patient preferred settings determined by maximal beta power in 7 of 9 and 5 of 7 hemispheres**, respectively. • The patient's current programming aligned with LFP contacts in 5 of 9 hemispheres. **Limitations:** Small sample size. LFP measures may fluctuate over time.

Table 4: Association of LFP measures to contact selection in patients with Parkinson's disease

Publication	Patient description/methods	Findings and limitations
Swinnen BEKS, Stam MJ, Buijink AWG, et al. Employing LFP Recording to Optimize Stimulation Location and Amplitude in Chronic DBS for Parkinson's Disease: A Proof-of-concept Pilot Study. Deep Brain Stimulation. 2023; 2:1-5.	Patients (N): 4 Recording: BrainSense™ Survey with Medtronic quadripolar leads. Target: Bilateral STN LFP Guided Contact Selection: Contact with highest beta power was compared to patient's current stimulation settings.	• **7 of 8 LFP-guided contacts aligned with clinically determined one.** **Limitations:** LFP recordings can only be collected in bipolar fashion. Clinical assessments were not standardized and multiple longitudinal assessments were lacking. Patient's clinical state (i.e., med state) at LFP recordings was not defined.
Strelow JN, Dembek TA, Baldermann JC, et al. Low beta-band suppression as a tool for DBS contact selection for akinetic-rigid symptoms in Parkinson's disease. Parkinsonism & Related Disorders. 2023; 112:105478.	Patients (N): 7 Recording: BrainSense™ Streaming with SenSight™ leads Target: Bilateral STN LFP Guided Contact Selection: Maximal suppression in theta, alpha, beta, and gamma bands during stimulation titration was used to select contacts and was compared to contacts selected by monopolar review.	• Degree of **low beta-band suppression was significantly associated to improvement of akinetic-rigid symptoms**, but high beta-band suppression was not. • **Low beta-band suppression predicted clinical contact selection with an accuracy probability of 75%.** • Contacts selected through monopolar review did not differ in clinical improvement of akinetic-rigid symptoms (UPDRS-III item 22, 23 and 25) compared to contacts selected through low-beta suppression. **Limitations:** Small sample size. Outcomes for comparison were not longitudinal in nature, are subjective in nature, and were only a subset of outcomes. Directional sensing is limited to middle contacts.

FEATURED ARTICLE:

Feasibility of LFP-guided programming for DBS in PD: A comparison with clinical and neuro-imaging guided approaches

Binder T, Lange F, Pozzi N, et al. Feasibility of local field potential-guided programming for deep brain stimulation in Parkin'on's disease: A comparison with clinical and neuro-imaging guided approaches in a randomized, controlled pilot trial. Brain Stimul. 2023 Aug 22;16(5):1243-1251.

Objective

To determine the potential advantages of beta-guided DBS programming over clinically and image-guided programming in terms of clinical efficacy and programming time.

Methods

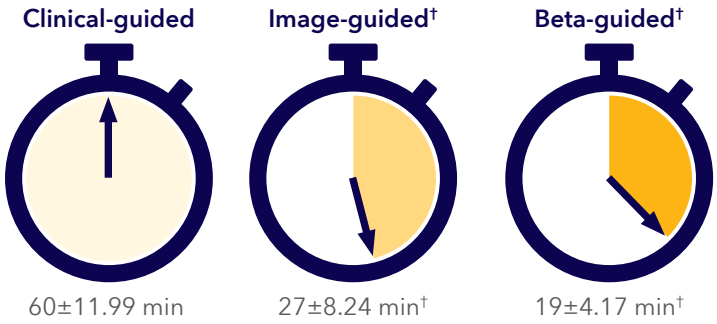
- Randomized, blinded, 3-arm crossover study in 8 patients with Parkinson's disease (PD) and bilateral subthalamic nucleus (STN) DBS with Percept™ PC and SenSight™ leads.
- 3 programming approaches: beta-guided, image-guided, and clinically-guided programming (i.e., shortened monopolar review).
- Tested on 3 different days. Off meds: Dopaminergic (>12 hours) and long-acting dopamine agonists (>72 hours); DBS off, 3 hours prior to baseline MDS-UPDRS-III. Stim applied for 30 min and reassessed with MDS-UPDRS-III, by a blinded rater.

Programming Strategies

Clinically-guided programming Shortened monopolar review	• Four contact levels assessed for effect (including rigidity) and side-effect threshold. • Most effective contact(s) selected. • Programming titrated based on clinical response and patient feedback. • Programming time = entire procedure
Image-guided programming Guide™* XT (Boston Scientific Corporation) and Brainlab Elements (Brainlab AG)	• Preoperative 3T MRI and postoperative CT scans were used for contact localization. • Dorsolateral contacts in the STN were identified. • Default parameters were 60 µs and 130 Hz, adjusted as needed to manage adverse effects or inadequate tremor control. • Programming time = time to load the image series, perform planning, print the anatomical plan, and program the device. **NOTE: The time for obtaining the CT scan was not included in the TFP (time for programming).**
Beta-guided programming Percept™ PC and BrainSense™ technology	• BrainSense™ Setup and Survey were used to collect local field potentials (LFPs). • LFP power was evaluated for elevated beta power, both between levels and within the segmented contacts of a level. • Contacts 0 and 3 were specifically excluded. The authors stated this approach, while not covering all pairs, allowed evaluation of all pairs feasible [for chronic sensing]. • "Low beta" (<20 Hz) was selected if multiple peaks were identified. • The contact pair with the highest beta in the bipolar montage was selected for stimulation and the current equally shared between those contacts. • Initial programming used the default pulse width (60 µs) and frequency (125 Hz), which were adjusted as needed. Amplitude was determined clinically with patient feedback. • Programming time = time to run BrainSense™ Survey and assess ring and segmented LFP data.

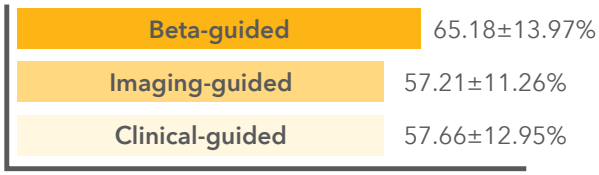
Results

Programming time (min)



N=8; †p<0.001 vs. clinical. No significant differences between image- and beta-guided approaches

MDS-UPDRS-III Improvement (%)



MDS-UPDRS-III Improvement (%)
N=8; No difference between approaches (p>0.05).

All figures have been recreated by Medtronic with data from Binder et al. (2023).

Key takeaways

The authors discussed several study takeaways:

- All three programming paradigms showed similar clinical efficacy after 30 min of stimulation.
- Both image- and beta-guided programming showed a clear and significant reduction in time for programming compared to clinically-guided programming.
- Time for programming with beta-guided programming was approximately 20 min and resulted in similar symptom control and energy consumption compared to imaging-based and clinically-guided approaches.
- Image-guided programming needs additional acquisition equipment that may increase costs and requires expertise in neuroanatomy while beta-guided programming is available in the clinician programmer and can be performed at the bedside. The time for programming for image-guided programming did not include time and resources for image acquisition.

Notes and limitations

The authors discussed several study limitations.

- The number of patients (n = 8) limits generalization of the findings.
- Motor assessment was conducted after only 30 minutes of DBS (in medication-OFF state); long-term side effects would not been detected.
- Beta titration with BrainSense™ Streaming could only be conducted in 5 patients due to signal quality.
- Clinically-guided programming excluded testing of directional contacts with high effect thresholds, which could potentially exclude effective contacts.
- Due to the 3 days required for the study, medication withdrawal durations may have varied between the testing conditions. Randomization was intended to help address this limitation.
- The programming process may have generated cues that could have influenced the blinding process.
- Assessment of clinical efficacy was limited since rigidity outcomes were excluded.
- Beta-guided programming only focused on segmented contacts, not all possible contacts.

FEATURED ARTICLE:

Sensing on Directional Leads

Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: A tool to optimize deep brain stimulation. Mov Disord. 2018 Jan;33(1):159-164.

Objective

To record LFPs from directional contacts and investigate their use as a predictor of contact choice for patients with PD.

Methods

Patients (N): 12

Recording: external Inomed, ISIS IOM system; monopolar recordings from a directional lead (Boston Scientific) with the cannula as a common reference.

PD target: STN

Design: LFPs were recorded during the surgical procedure, after the final lead position. Clinical assessment took place between 17 and 31 weeks post-implant and consisted of % rigidity improvement/stimulation current and therapeutic window (TW) for each directional contact.

Results

Beta and Clinical Assessment

- Normalized beta activity positivity correlated with the contact's clinical efficacy in 15 of 19 hemispheres.
- Contacts with higher beta and had the most clinical symptom reduction when stimulated.
- A clear beta peak was not seen in 7 of 19 cases.

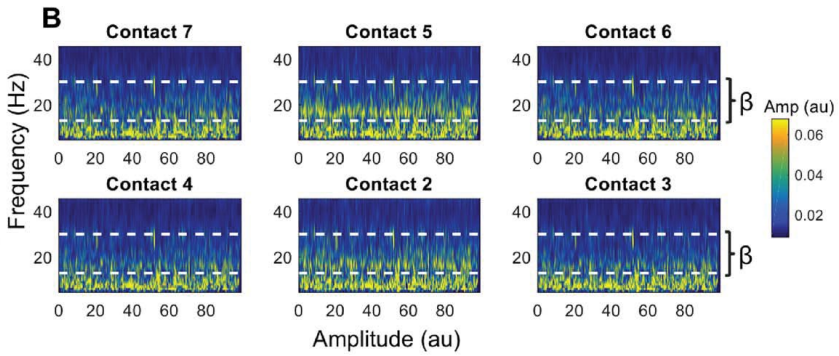
Predictive Value of Beta

- The stimulation contact with the highest beta predicted the contact with the highest clinical efficacy in 63% of cases.
- In 84% of cases, one of the 2 contacts with the highest beta was also the most clinically effective contact.

Notes

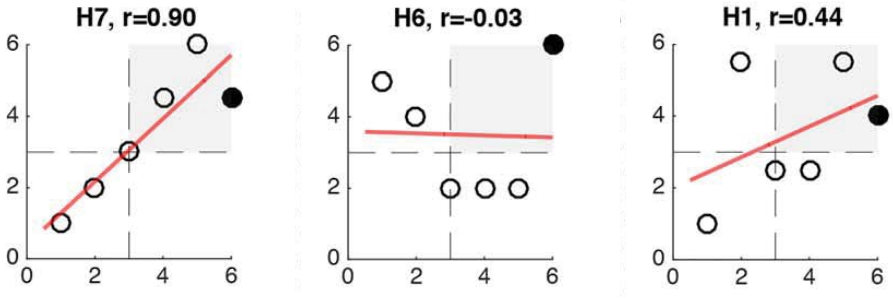
The authors did not report on complications.

Example of a time frequency spectrum from an intraoperative LFP recording (duration, 100 seconds) from 6 directional contacts with the patient awake and at rest. The dashed white line marks the beta frequency band (13-35Hz). LFP beta activity is not equally distributed across directional contacts. Contact 5 shows the highest beta activity, followed by contact 2, with both contacts 5 and 2 oriented in the same direction.



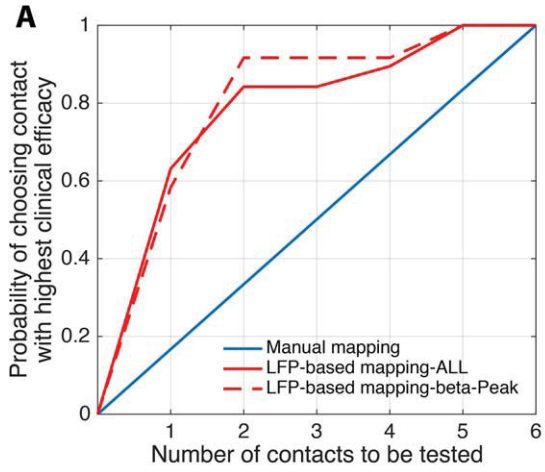
Sensing on Directional Leads *continued*

Example of strong, moderate, and weak correlations (with Spearman correlation coefficients) between ranked clinical efficacy (y-axis) and ranked normalized beta amplitude (x-axis) in 3 example hemispheres. The best electrophysiological contact (contact with highest normalized beta activity) is highlighted in black. The red linear regression fit is shown only for illustration purposes. A total of 15 hemispheres, showed a positive relationship between clinical efficacy and normalized beta activity. In all hemispheres, the contact with the highest beta activity was localized in the upper-right quadrant, where the clinically more efficient contacts are localized.



Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: A tool to optimize deep brain stimulation. Mov Disord. 2018 Jan;33(1):159-164. Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). Only 3 of the 19 hemispheres shown in the original publication from panel C of the publication are displayed. No modifications were made to the content of the individual plots.

The probability of identifying the stimulation contact with the highest clinical efficacy, comparing the conventional (random) test strategy in blue with the LFP-based test strategy in red (full red line: all hemispheres n = 19, dashed red line: only hemispheres with clear beta peak n = 12). For conventional mapping the probability of identifying the most efficient stimulation contact increases by 0.17 with each contact tested, the LFP-based strategy identifies the most efficient contact with a probability of 0.63 if only the contact with the highest beta activity is considered, and with a probability of 0.84 if the two contacts with the highest beta activity are considered. By considering hemispheres with a clear beta peak only, the probability increases up to 0.92 when the two best electrophysiological contacts are considered.



Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: A tool to optimize deep brain stimulation. Mov Disord. 2018 Jan;33(1):159-164. Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). Only panel A of the image is shown. No modifications were made to the content.

Note: This study did not use the SenSight™ directional DBS leads or BrainSense™ technology.

Optimize and maximize

Optimize:

Deep brain stimulation (DBS) programming for individuals with Parkinson's disease (PD) can be a time-consuming endeavor, often necessitating ongoing adjustments to account for disease progression and potential side effects arising from stimulation.[1,2] Given the diversity in motor symptoms, disease progression rates, and the spectrum of side effects, the utilization of local field potentials (LFPs) data may provide patient-specific and objective insights to optimize the clinical decision-making process.

What further adds to the significance of LFP data is the prevalence of beta band detection, its responsiveness to stimulation, and its linkage to bradykinetic-rigidity symptoms.[3,4] This makes LFPs particularly well-suited for probing physiological responses to stimulation both within and beyond the clinical setting for patients with PD, aiding in the determination of optimal stimulation parameters. Considering these insights, the subsequent publications delve into the investigation of how LFP data can be harnessed to facilitate the optimization of stimulation parameters in patients with PD.

Learn more about BrainSense™ Streaming for optimizing therapy: page 13

1. Volkmann J, Herzog J, Kopper F, Deuschl G. Introduction to the programming of deep brain stimulators. Mov Disord. 2002;17 Suppl 3:S181-S187. doi:10.1002/mds.10162

2. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. Mov Disord. 2006;21 Suppl 14:S284-S289. doi:10.1002/mds.20961

3. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022;356:114150.

4. Feldmann LK, Lofredi R, Neumann WJ, et al. Toward therapeutic electrophysiology: beta-band suppression as a biomarker in chronic local field potential recordings. NPJ Parkinsons Dis. 2022 Apr 19;8(1):44.

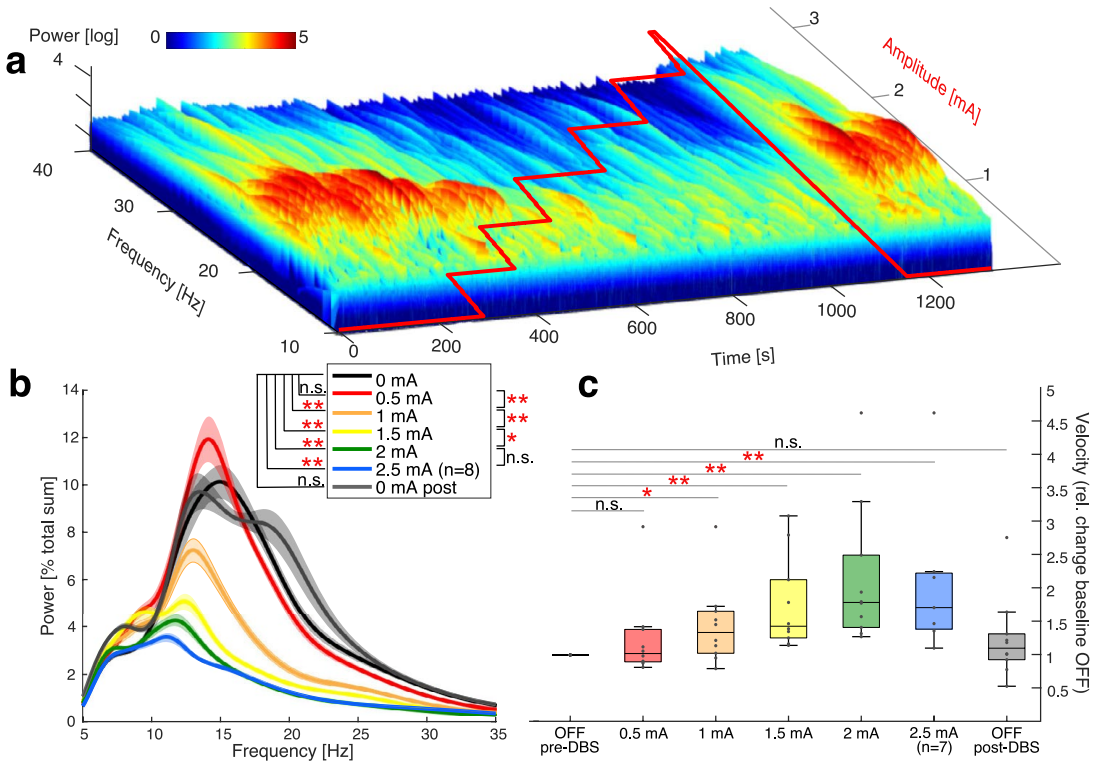
Table 5: Optimizing DBS therapy with BrainSense™ technology in patients with Parkinson's disease

Citation	Patient description/methods	Findings and limitations
Vaou OE, Spidi MD, Raike R, et al. Symptom optimization through sensing local field potentials: Balancing beta and gamma in Parkinson's disease. Deep Brain Stimulation. 2023 Jan 25.	Patients (N): 3 Recording: BrainSense™ Survey, Streaming, and Timeline Target: Bilateral STN Optimization Approach: BrainSense™ features were used to determine LFP frequencies of interest and responses of LFPs to stimulation within and outside of the clinic to optimize therapy for complex motor symptoms.	LFP data collected through **BrainSense™ technology provided objective data to support therapy optimization for dyskinesias** and personalization to motor fluctuations in three patients with PD. **Limitations:** Small sample size. No comparison of settings to objective clinical outcomes (e.g., UDPRS).

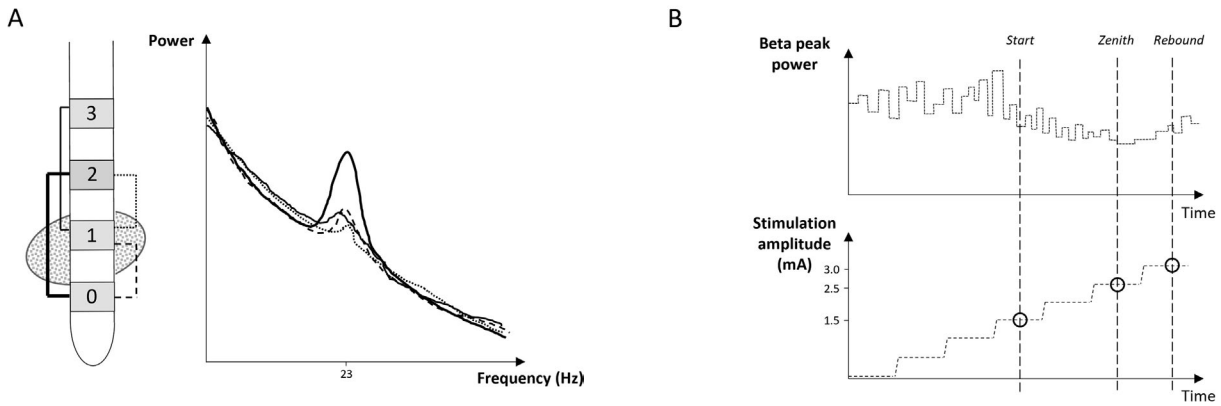
Table 5: Optimizing DBS therapy with BrainSense™ Technology in patients with Parkinson's disease

Citation	Patient description/methods	Findings and limitations
Swinnen BEKS, Stam MJ, Buijink AWG, et al. Employing LFP recording to optimize stimulation location and amplitude in chronic DBS for Parkinson's disease: A proof-of-concept pilot study. Deep Brain Stimulation. 2023; Vol 2:1-5.	Patients (N): 4 Recording: BrainSense™ Survey and Streaming from quadripolar Medtronic leads. Target: Bilateral STN Optimization Approach: • Clinically-guided contact selection and stimulation amplitude via Monopolar review. • LFP-guided contact selection and stimulation amplitudes were determined by BrainSense™ Survey and Streaming data, respectively	**LFP-guided parameter adjustments** were performed in two patients and **resulted in improved motor fluctuations and decreased stimulation induced side effects**, respectively. **Limitations:** Bipolar LFP recordings only. Comparisons of beta-based and monopolar review based therapeutic windows needs further exploration. Clinical assessments were not standardized and multiple longitudinal assessments were lacking. Patients in On Med state at LFP recording.
Binder T, Lange F, Pozzi N, et al. Feasibility of local field potential-guided programming for deep brain stimulation in Parkinson's disease: A comparison with clinical and neuro-imaging guided approaches in a randomized, controlled pilot trial. Brain Stimul. 2023 Aug 22;16(5):1243-1251.	Patient (N): 8 Recording: BrainSense™ Survey and Streaming with SenSight™ leads at 3-months postop Target: Bilateral STN Optimization Approach: Stimulation amplitude adjusted according to the spectral power suppression of an a priori selected β-frequency range (>75% reduction of the original power), namely the β-peak selected from running BrainSense™ Survey.	• **Stimulation amplitude selected after beta titration was below the side effect threshold in all patients.** • Beta-based stimulation titration was possible in five of eight patients. • **Beta titration improved symptom control in four out of five patients**, while one patient showed a worsening of symptom control (–12%). • 6/8 patients were programmed with LFP-based programming within 20 min or less **Limitations:** Approach only possible on 5 patients due to signal quality. Small sample size.
Feldmann LK, Lofredi R, Neumann WJ, et al. Toward therapeutic electrophysiology: beta-band suppression as a biomarker in chronic local field potential recordings. NPJ Parkinsons Dis. 2022 Apr 19;8(1):44. https://www.nature.com/articles/s41531-022-00301-2	Patients (N): 10 Recording: BrainSense™ Survey and Streaming with Medtronic 3389 leads at 3-months postop (N=8) or during routine follow-up outpatient visit (N=2) Target: Bilateral STN Optimization Approach: Stimulation amplitude was increased in steps of 0.5 mA up to the presentation of side effects.	• **Low-beta power was negatively correlated with movement speed and predictive for velocity improvements**, stimulation amplitude for beta suppression. • There was a stepwise suppression of low-beta activity with increasing stimulation intensity. **Limitations:** Motor assessment focused on bradykinesia. Two patients were tremor dominant. ECG artifact noted in 4 nuclei in 4 patients.
Busch, J.L., Kaplan, J., Bahners, et al. Local Field Potentials Predict Motor Performance in Deep Brain Stimulation for Parkinson's Disease. Mov Disord. 2023 https://doi.org/10.1002/mds.29626	Patients (N): 16 Recording: BrainSense™ Survey and Streaming from SenSight™ leads 3-months postop Target: Bilateral STN Optimization Approach: LFP responses to stimulation were assessed using BrainSense Streaming during the monopolar review.	• **Beta power suppression was predictive of the contact with the best motor performance** within individual hemispheres. • Active, blinded **contact selection during long-term clinical programming featured stronger beta power suppression** during DBS. **Limitations:** Offline LFP analyses were restricted to beta. LFP data collected in bipolar fashion. Clinical measures focused on bradykinesia and all data was collected in laboratory setting.

Beta titration measured by the Percept™ PC neurostimulator.



A patient example showing stepwise stimulation increase (red line) with a stepwise suppression of the beta frequency band activity during a monopolar review (a). Resting-state power averaged across 10 patients showed a decrease in beta oscillations with increasing stimulation amplitude (b). Movement velocity improved with increasing stimulation intensity in patients with bradykinesia (c).



Concept of LFP-guided programming. Panel A: hypothetical example of LFP-guided contact selection. The shaded area represents the region of interest, exhibiting beta activity. Beta activity is highest in contact pair 0-2. Panel B: hypothetical example of LFP-guided stimulation titration to determine beta-based therapeutic window. In this fictive case, the beta-based therapeutic window spans from 1.5 mA to 3.0 mA, with optimal beta suppression ('zenith') starting at 2.5 mA.

FEATURED ARTICLE:

Managing Symptoms of Parkinson's Disease Through Optimization with BrainSense™ Technology

Vaou OE, Spidi MD, Raike R, et al. Symptom optimization through sensing local field potentials: Balancing beta and gamma in Parkinson's disease. Deep Brain Stimulation. 2023 Jan 25.

https://www.sciencedirect.com/science/article/pii/S2949669123000015

Objective

To present three patients with complex motor symptoms that could not be managed with adjustment of medications or stimulation parameters. These patients, benefited from information gained from sensing technology, allowing for a more personalized treatment with subsequent optimization of symptom control

Methods

Patients (N): 3

Recording: Percept™ PC

Target: STN

BrainSense™ technology (Survey, Streaming, Timeline, Events) was used to collect LFP data within and outside of the clinic.

Results

Case 1: 72-year-old female with advanced PD with bilateral STN DBS on LEDD 1000mg, implanted with the Percept™ PC device in January 2021. After implant, she continued to experience severe motor fluctuation with significant muscle rigidity and severe motor fluctuations.

BrainSense™ Timeline and LFP Event Capture revealed increased beta oscillation in the morning correlating with patient reported muscle rigidity and bradykinesia. Survey was switched to gamma frequency to better understand pattern and timing of the dyskinesias. By monitoring Timeline and Events, the pattern of motor fluctuations became apparent with consistent peak dose and wearing-off dyskinesias, seen as high LFP gamma peaks, an hour after medication and at the time of the next Levodopa dose.

BrainSense™ technology informed:

- **Medication (adjusted Levodopa morning dose)**
- **DBS parameters (decreased pulse width, increased frequency)**
- **Estimated Battery Life improved from estimated 36 months to 76 months**

Case 2: 66-year-old male with PD, underwent bilateral STN DBS implantation in 2019 to improve motor fluctuations. Despite improvement in motor symptoms, the patient opted to replace his neurostimulator with a Percept™ PC to optimize "ON" time without troublesome dyskinesia.

BrainSense™ Streaming, Timeline, and Event data were used to optimize stimulation settings to increase "ON" time and minimize dyskinesias.

BrainSense™ technology informed:

- **Patient symptom states in real-life context**
- **Daily patterns of pathophysiologic markers of motor fluctuations**
- **Individualized programs which ultimately allowed the patient to better control his symptoms**

Case 3: 65-year-old male with a ten-year history of PD who had bilateral STN DBS implantation in 2017. He was upgraded to a Percept™ PC implanted in July 2020. He continued to have severe dyskinesias, uncontrolled motor fluctuations, frequent and abrupt "OFF" states, speech disturbance, ultimately leading to limited therapeutic on time without troublesome dyskinesias. Due to these symptoms, the patient was mostly wheelchair bound.

BrainSense™ technology informed:

- **Stimulation and medication optimization for a patient with complex motor symptoms**
- **Objective feedback on therapy efficacy and reduction in over-stimulation induced symptoms which allowed patient, previously mostly wheelchair bound, to ambulate without assistance**
- **Stimulation adjustments which resulted in improved battery longevity from 2.5 years to 4 years**

Notes and limitations

LFP data collected through BrainSense™ technology provided objective data to support therapy optimization for dyskinesias, personalization to motor fluctuations in three patients with PD.

Limitations: Small sample size. No comparison of settings to objective clinical outcomes (e.g., UDPRS).

Maximize:

Parkinson's disease (PD) is a chronic, progressive, and fluctuating condition, which can present challenges for clinicians and patients to maximize therapeutic results over time. This underscores the critical need for objective, symptom and patient-specific data for longitudinal insights on patient's journey with PD. One potential solution includes the continuous monitoring of signals of interest which represent salient motor symptoms and responses to common Parkinson's therapies, such as LFPs from subcortical nuclei.[1,2,3] In addition to continuous monitoring of a specified frequency of interest, event-related LFP measures provide an additional avenue for pathophysiologic insights.[4,5] Together, the combined approach of continuous and event-related LFP monitoring can furnish objective and personalized data from real-world settings, which may be used for maximizing therapy over time.

Learn more about BrainSense™ Timeline and Events for maximizing therapy over time: page 14

1. Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.
2. van Wijk BCM, de Bie RMA, Beudel M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. Journal of Neurology. 2023;270(2):1162-1177.
3. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. Neurobiology of Disease. 2021;155:105372.
4. Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).
5. Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. Feb;25(2):271-275.

Table 6: Events and LFPs collected outside of the clinic to maximize data collection in Parkinson's disease

Publication	Target	Chronic LFP monitoring and events	Findings
Goyal A, Goetz S, Stanslaski S, et al. The development of an implantable deep brain stimulation device with simultaneous chronic electrophysiological recording and stimulation in humans. Biosens Bioelectron. 2021 Mar 15;176:112888.	PD STN	BrainSense™ Events • Baseline • Dyskinetic • Good w/o meds • Off symptoms	• Beta power in left hemisphere lower than right during dyskinesia events (p = 0.008) and all other events (p = 0.01). • Across all recording and both hemispheres, "Dyskinetic" had higher beta compared to "Good" (p = 0.04); however, this was due to high beta in the right STN. Within the left STN, beta power was lower during "Dyskinetic" events compared to "Good." • The results for the gamma frequency range (>30 Hz) were similar to those in the beta band.

Table 6: LFP measures collected outside of the clinic

Publication	Target	Chronic LFP monitoring and events	Findings
Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).	PD STN	BrainSense™ Events • Freezing of gait† BrainSense™ Timeline • Out of clinic beta monitoring	• The patient recorded events during freezing of gait; no consistent modulation of the PSD was observed. • Explanations suggested by the authors: 1) the event was not marked exactly during the episode, 2) there may be not PSD modulation related to freezing, or 3) the device could not capture existing modulations. • Circadian rhythm of beta power observed in all three patients. Beta power suppressed overnight.
Vaou OE, Spidi MD, Raike R, et al. Symptom optimization through sensing local field potentials: Balancing beta and gamma in Parkinson's disease. Deep Brain Stimulation. 2023;1:5-14.	PD STN	BrainSense™ Events • Dyskinetic • Off symptoms BrainSense™ Timeline • Out of clinic gamma and beta monitoring	• BrainSense™ event data was used to inform therapy optimization for motor fluctuations through review of event-related LFP profiles. • BrainSense™ timeline data was used to inform therapy optimization and medication regimen for motor fluctuations.
Giannini G, Baldelli L, Leogrande G, et al. Case report: Bilateral double beta peak activity is influenced by stimulation, levodopa concentrations, and motor tasks, in a Parkinson's disease patient on chronic deep brain stimulation. Frontiers in Neurology. 2023;14.	PD STN	BrainSense™ Events • Dyskinesia • Rigidity • Freezing† • "I'm feeling good"	• BrainSense™ event data depicted rigidity and dyskinesia LFP peaks in the beta and gamma ranges, respectively. • Event data was also used to assess LFP responses to medication.

† DBS may contribute to worsening of symptoms such as gait and postural instability. Programming strategies to minimize worsening symptoms may be attempted. Clinical benefits of DBS in treating these symptoms have not been established.

FEATURED ARTICLE:

Diurnal Modulation of STN Beta Oscillatory Power in Parkinson's Disease During DBS

van Rheede, J.J., Feldmann, L.K., Busch, J.L. et al. Diurnal modulation of subthalamic beta oscillatory power in Parkinson's disease patients during deep brain stimulation. npj Parkinsons Dis. 8, 88 (2022) 8;8(1):88.

https://doi.org/10.1038/s41531-022-00350-7

Objective

To analyze long-term (18-59 days) recordings of STN LFP beta-band power during continuous DBS from PD patients implanted with the Medtronic Percept™ PC DBS device and show that beta amplitude can be significantly modulated according to time of day.

Methods

Patients (N): 11

Recording: Percept™ PC

Target: Bilateral STN

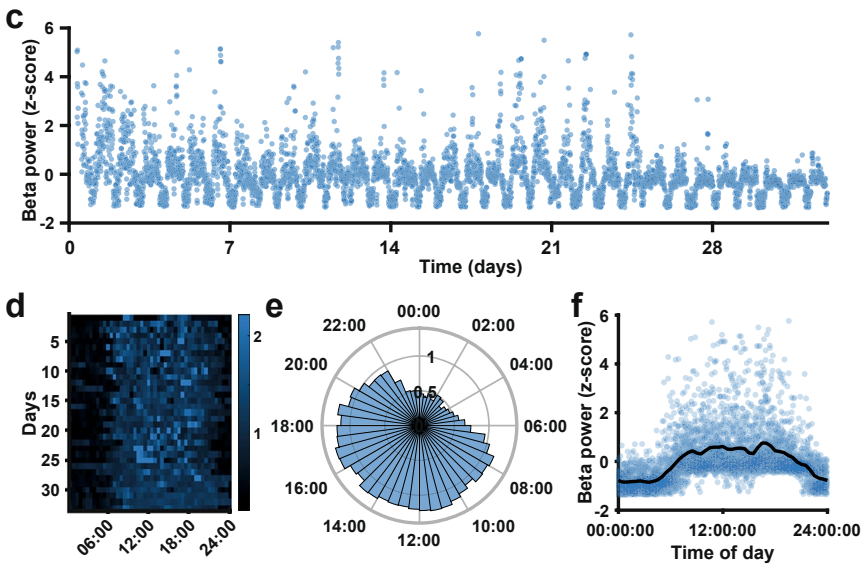
BrainSense™ Signal Test was used to identify frequencies of interest for longitudinal monitoring with BrainSense™ Timeline.

Patients 1–6: Beta power was collected for an average of 34 ± 13.4 days at a stable optimized medication and stimulation regime until the 3-month follow-up.

Patients 7–11: Included for the data set exploring frequency-specificity of the beta band fluctuations in subacute recordings after DBS surgery. Peak beta frequency was selected as described above in one STN, while in the contralateral STN peak power was logged in a 5 Hz window around a theta frequency (7.61 ± 0.43 Hz) for 6.8 ± 3.6 days, irrespective of whether an oscillatory peak was present.

Results

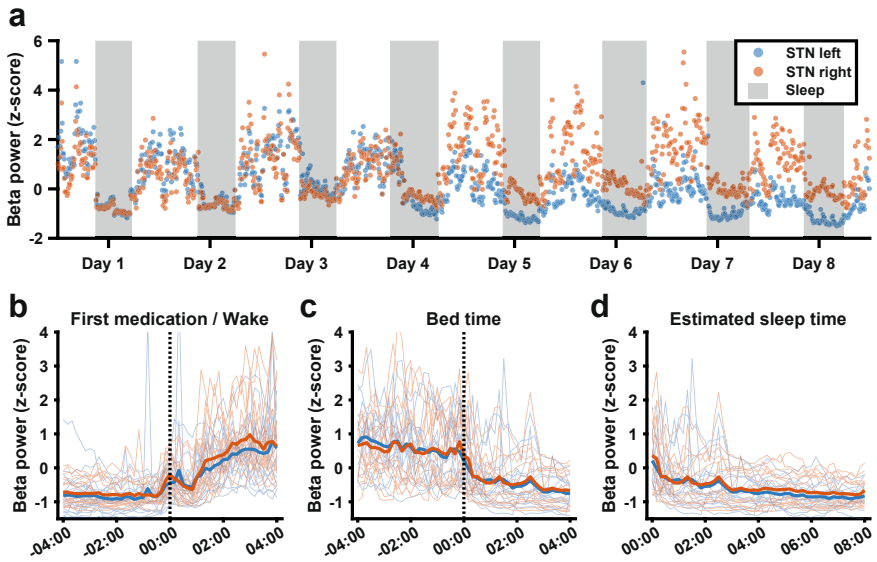
Measured STN beta power fluctuates in a 24-h cycle and is reduced during the night



C) Mean STN beta power (μVp, sampled every 10 min) over a 1-month period. D) Heat map of beta power for the same example STN. E) Detrended (median) beta power across the 24-h diurnal cycle generated from the data in d. F) Normalized beta power measurements plotted against the time of day (black line = linear fit through the mean beta power for the time of day).

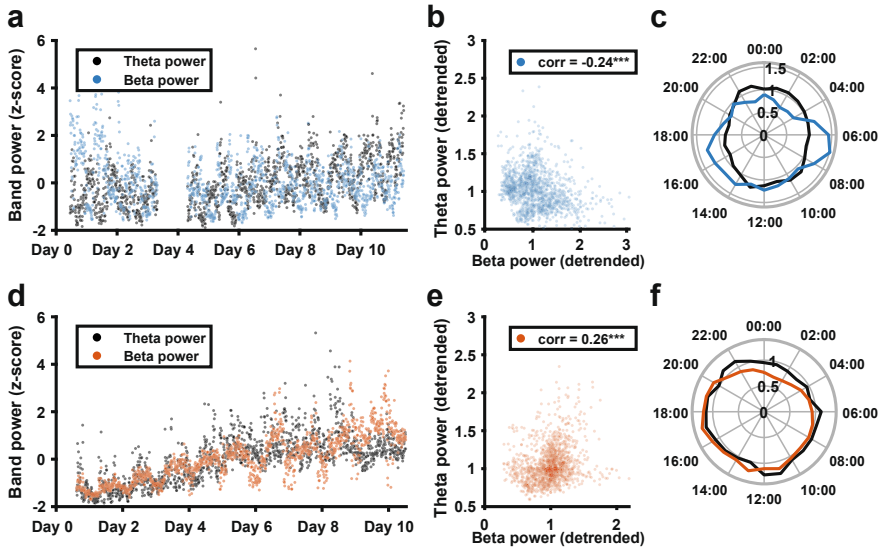
Transitions between sleeping and waking periods are associated with beta fluctuations (n=1)

A) 8 days - Normalized beta power in the left and right STN of one patient – EVENTS for SLEEP and WAKE. B, C, D) Beta - full 21-day recording period, aligned to the time of waking and bed time.



Frequency-specificity of diurnal LFP power modulation

A) Beta / theta power (black) of one example patient. B) Scatter plot. C) Median detrended beta (blue) and theta (black) power across the 24-h diurnal cycle. D) Beta power (orange) and theta power (black) collected concurrently from the left and right STN of a second example patient. E) Scatter plot of detrended beta power vs detrended theta power shown in d showing a positive correlation between beta and theta (r = 0.26, p < 0.001). F) Median beta (orange) and theta (black) power across the 24-h diurnal cycle.



- Beta power was consistently greater during the day and reduced during the night.
- There was a sharp increase in beta power slightly before the first scheduled medication time across patients.
- Beta and theta power could also show different diurnal profiles from each other, with beta demonstrating a more consistent reduction in power at night.

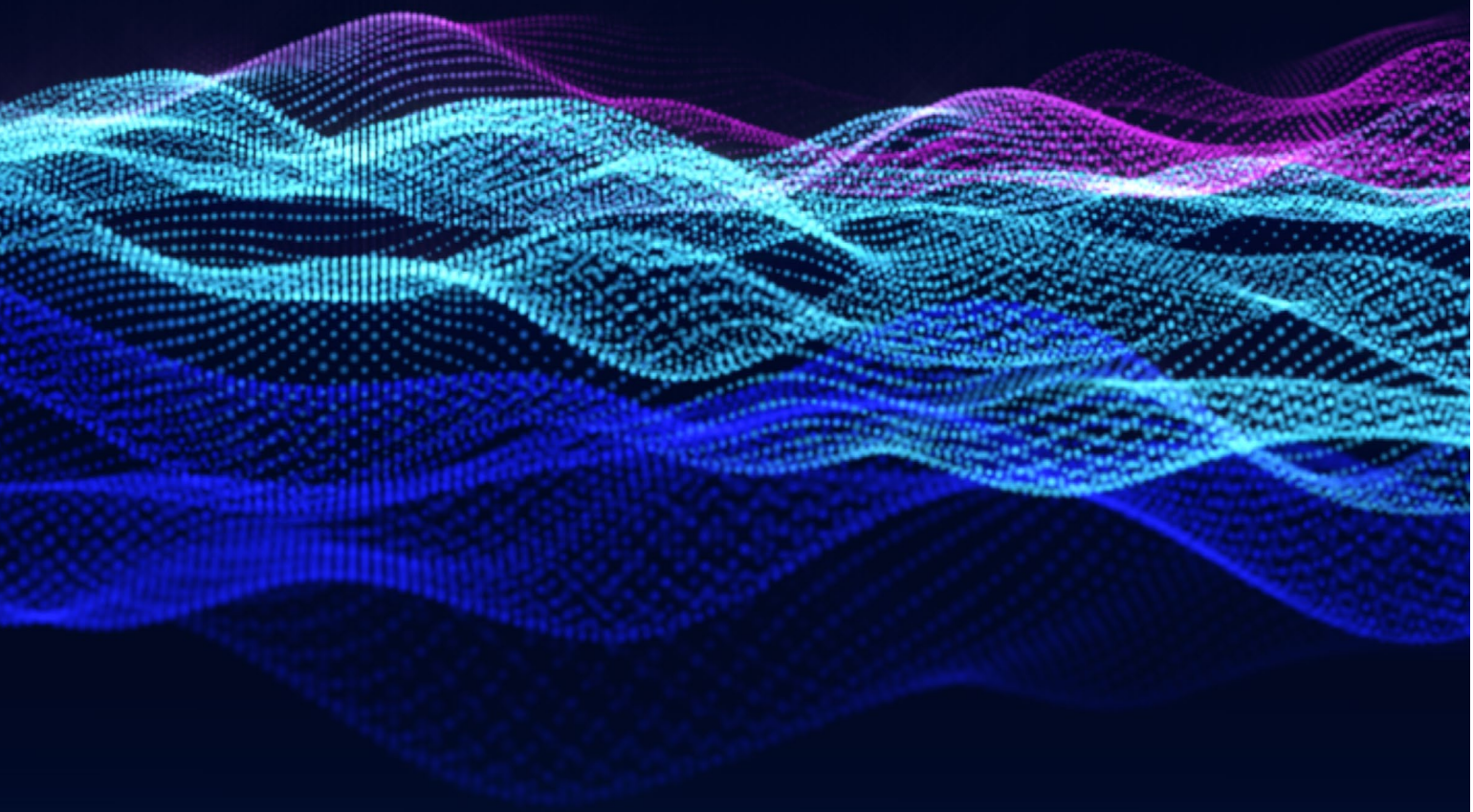
Notes and limitations

Determination of LFP power fluctuations outside of a pre-selected 5 Hz range were limited due to device parameters.

ECG and movements may yield sensing artifacts. Transient movement related artifacts may occur but may have modest impact on longitudinal sensing data.

SECTION 4:

Epilepsy



Epilepsy

Bilateral deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) is approved for the treatment of focal, drug resistant epilepsy resulting in significant reductions of seizure frequency and improved long-term quality of life.[1,2] The ANT belongs to the Papez Circuit, a seizure propagation network in focal epilepsy.[3,4] Local field potentials (LFP), while not as extensively characterized as those in Parkinson's disease, are beginning to be explored in the ANT. To date, publications have focused on the feasibility of identifying and monitoring signals of interest of ictal and inter-ictal states from ANT LFP data.[5,6] The following section presents current evidence of ANT LFP characteristics in patients with focal epilepsy.

1. Salanova V, Sperling MR, Gross RE, et al; SANTÉ Study Group. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021 Jun;62(6):1306–1317.
2. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010 May;51(5):899–908
3. Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res. (1997) 28:89–100. doi: 10.1016/S0920-1211(97)00034-X
4. Mirski MA, Ferrendelli JA. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science. (1984) 226:72–4. doi: 10.1126/science.6433485
5. Yang AI, Raghu ALB, Isbaine F, Alwaki A, Gross RE. Sensing with deep brain stimulation device in epilepsy: aperiodic changes in thalamic local field potential during seizures. Epilepsia. 2023 Nov;64(11):3025-3035.
6. Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603.

Signal trust

Recent publications have started to demonstrate the feasibility of detecting anterior nucleus of thalamus (ANT) local field potential (LFP) peaks in patients undergoing Deep Brain Stimulation (DBS) for focal epilepsy, both during ictal and interictal states. The subsequent section delves into the latest discoveries concerning LFP peak detection rates and frequencies. This data is of paramount significance, as it furnishes compelling evidence regarding the viability of capturing ANT LFPs, thereby paving the way for potential clinical implementation.

Epilepsy	
Common frequencies identified with Percept™ PC associated with seizures.	4 to 11 Hz[1,2,3,4†] 13 to 30 Hz[1,2]

1 Yang AI, Raghu ALB, Isbaine F, Alwaki A, Gross RE. Sensing with deep brain stimulation device in epilepsy: aperiodic changes in thalamic local field potential during seizures. Epilepsia. 2023

2 Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603.

3 Satzer D, Wu S, Henry J, Doll E, Issa NP; Warnke. Ambulatory Local Field Potential Recordings from the Thalamus in Epilepsy: A Feasibility Study. Stereotact Funct Neurosurg. 2023;101(3):195-206.

4 Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. Feb; 25(2): 271-275.

†The theta range of frequencies (5-7 Hz) has also been reported during EEG recording of focal seizures.

Smith SJ. EEG in the diagnosis, classification, and management of patients with epilepsy. J Neurol Neurosurg Psychiatry. 2005 Jun;76 Suppl 2(Suppl 2):ii2-7.

Table 7: Evidence of LFP peaks from the ANT recorded from DBS leads in patients with epilepsy.

<table>
<tr><th>Publication</th><th>Patients</th><th>LFP peaks</th></tr>
<tr><td>Yang AI, Raghu ALB, Isbaine F, Alwaki A, Gross RE. Sensing with deep brain stimulation device in epilepsy: aperiodic changes in thalamic local field potential during seizures. Epilepsia. 2023</td><td>Patients (N): 12
Target: ANT
Recording: Percept™ PC</td><td>Delta (0.5-4 Hz) was the most prevalent peak, detected in 12 out of 12 patients.
Subsets of patients had theta (4-8 Hz), alpha (8-13Hz), beta (13-30 Hz), and gamma (30-80 Hz) oscillations.
Ictal-related peaks detected in 12 out of 12 patients.
Patients and caregivers were instructed to mark seizure events at the start of seizures or as quickly as possible after seizure onset. A subset of patients also marked post-ictal events. Most ictal events showed unilateral peaks; 16.79% (7.71%) of ictal events had bilateral peaks.</td></tr>
<tr><td>Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603.</td><td>Patients (N): 3
Target: ANT
Recording: Percept™ PC</td><td>Alpha (7-11 Hz) and beta (18-22 Hz) were common.
Peaks of interest<table><tr><th></th><th>Left</th><th>Right</th></tr><tr><td>Patient 1</td><td>9.77 Hz
19.53 Hz</td><td>9.77 Hz
21.48 Hz</td></tr><tr><td>Patient 2</td><td>7.81 Hz
18.55 Hz</td><td>7.81 Hz
18.55 Hz</td></tr><tr><td>Patient 3</td><td>21.42 Hz</td><td>10.74 Hz
21.42 Hz</td></tr></table></td></tr>
<tr><td>Satzer D, Wu S, Henry J, Doll E, Issa NP; Warnke. Ambulatory Local Field Potential Recordings from the Thalamus in Epilepsy: A Feasibility Study. Stereotact Funct Neurosurg. 2023;101(3):195-206.</td><td>Patients (N): 1
Target: ANT
Recording: Percept™ PC</td><td>Alpha (6-11 Hz) peaks observed bilaterally</td></tr>
<tr><td>Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. Feb; 25(2): 271-275.</td><td>Patients (N): 1
Target: ANT
Recording: Percept™ PC</td><td>LFPs related to absence and focal seizures were identified.
• 2.93 Hz (absence seizures)
• 8.79 Hz (focal seizures)</td></tr>
<tr><td>Toth E, Kumar S, Ganne C, et al. Machine learning approach to detect focal-onset seizures in the human anterior nucleus of the thalamus. J Neural Eng. 2020 Nov 11;17(6).</td><td>Patients (N): 10
Target: ANT
Recording: SEEG electrodes</td><td>Low frequency (4-16 Hz) power increased in the ANT following seizure onset.
Power in the 32-64 Hz range in the ANT increased in FIAS and FBTCS.
Theta band (4–8 Hz) power increased in the cortex around 26–31 s after seizure onset.</td></tr>
</table>

FBTCS: focal to bilateral tonic-clonic seizures, FIAS: focal onset seizures with impaired awareness, SEEG: stereo-electroencephalography

Select, optimize, and maximize

Publications are increasingly addressing the utilization of local field potentials (LFPs) for clinical applications, including guiding contact selection, facilitating objective neurophysiologic monitoring of relevant signals beyond clinical settings, and capturing neurophysiologic events associated with seizures in patients undergoing Anterior Nucleus of the Thalamus (ANT) Deep Brain Stimulation (DBS). BrainSense™ tools offer valuable support for initial therapy programming and assist in making decisions concerning both DBS and medication therapy over time.

Notably, BrainSense™ Survey serves as a beneficial tool for the initial phase of therapy programming and decision-making by determining the detectability of a signal between two contact pairs. It provides objective information crucial for contact selection, displaying signals across the theta, alpha, beta, and gamma ranges (0 to 96.68 Hz). Signals in the theta/alpha (~4 to 11 Hz) and beta (13 to 30 Hz) range may particularly offer insights into seizure-related information, aiding in informed decisions about lead location and contact selection.[1]

BrainSense™ Timeline, on the other hand, offers a longitudinal representation of a single LFP signal of interest outside the clinical setting. This chronic map aids in identifying daily fluctuations in LFP activity and isolating events that induce changes in the LFP profile, contributing to a more comprehensive understanding of the patient's condition over time.

Lastly, BrainSense™ Events can be effectively employed to assess event-related ANT LFP data in real-world settings, enhancing the ability to evaluate and respond to neurophysiologic events as they occur in the patient's daily life.

Learn more about BrainSense™ Survey for informing contact selection: Page 12

Learn more about BrainSense™ Streaming for optimizing therapy: Page 13

Learn more about BrainSense™ Timeline and Events for maximizing therapy over time: Page 14

Final contact selection should be determined by the physician along with other medical information.

1. Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603.

Table 8: LFPs and contact selection in ANT DBS for epilepsy

Publication	Description of LFP signal informing contact selection
Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603.	The authors reported that stepwise increases in monopolar stimulation were applied while reviewing the LFP power in real-time. Contacts with suppression of LFP power corresponding to increasing stimulation were chosen for stimulation. If no obvious real-time LFP suppression was observed with single monopolar stimulation, programming was switched to double monopolar only if LFP suppression was observed in the double configuration and/or if there was no clinical response to monopolar stimulation by the next clinic visit. Live streaming was used to determine the amplitude for programming that provided maximal LFP suppression. **Patient 1:** Lead localization and LFPs recorded using BrainSense™ Survey informed choice of contact 1 for stimulation in both hemispheres. Contacts 0 and 2 were used for sensing at 9.77 Hz in both hemispheres. **Patient 2:** Lead localization and LFPs recorded using BrainSense™ Survey informed use of contacts 1 and 2 for stimulation in the left hemisphere and contact 1 in the right hemisphere. Sensing on the left hemisphere was between contacts 0 and 3; sensing on the right hemisphere was between contacts 0 and 2 at 7.81 Hz. **Patient 3:** Lead localization and LFPs recorded using BrainSense™ Survey informed choice of contact 2 for stimulation in both hemispheres. Contacts 1 and 3 were used for sensing at 10.74 Hz in both hemispheres.
Lopes EM, Rego R, Rito M, et al. Estimation of ANT-DBS Electrodes on Target Positioning Based on a New Percept™ PC LFP Signal Analysis. Sensors (Basel). 2022 Sep 1;22(17):6601.	The study investigated 2 machine learning classifiers to predict contact location within the ANT. Using data from 1 patient with ANT DBS, contacts inside the ANT could be predicted with an accuracy of 76.6 to 83.33%. Of the 17 extracted features, gamma power (30-100 Hz) was considered a significant variable differentiating between ANT and non-ANT in both classifiers. Alpha power (8-13 Hz) was also equally relevant in the second classifier.

FEATURED ARTICLE:

Cases Series Exploring LFPs in Patients with Epilepsy

Chua MMJ, Vissani M, Liu DD, et al. Initial case series of a novel sensing deep brain stimulation device in drug-resistant epilepsy and consistent identification of alpha/beta oscillatory activity: A feasibility study. Epilepsia. 2023 Oct;64(10):2586-2603

Objective

Retrospective, single-center experience exploring potential LFP signals that may aid DBS programming and outcome tracking in patients with drug-resistant epilepsy.

Methods

Patients with epilepsy and ANT DBS (N): 3

Recording: Percept™ PC

Target: Bilateral ANT

Set-Up:

- Contact selection and configuration and stimulation programming amplitude were informed by BrainSense™ Survey and Streaming in-clinic.
- Out-of-clinic frequency tracking used BrainSense™ Timeline.
- Patients and caregivers recorded events: "aura," "seizure," or "postseizure."

Results

BrainSense™ Survey identified peaks of interest. Lead localization and LFPs recorded using BrainSense™ Survey informed contact choice for all patients. BrainSense™ Streaming was used to determine initial programming amplitudes that maximally suppressed LFP power.

BrainSense™ Timeline recordings in all patients showed a circadian pattern of LFPs at alpha and beta frequencies. In 2 patients, changes in LFP power corresponded to changes in seizure frequency related to adjustments in antiseizure medication.

Patient 1: Chronic BrainSense™ Timeline recordings tracked a 9.77 Hz signal over 12 months. **Active stimulation decreased left hemisphere LFP power and improvement in seizure frequency.** LFP power in the right hemisphere in the **timeline recordings increased when antiseizure medication was discontinued and generalized tonic-clonic seizures re-emerged**. Both hemispheres showed a circadian pattern of LFP amplitudes.

Patient 2: LFP data from **BrainSense™ Streaming was used to aid in contact selection** since lead placement was thought to be suboptimal based on lead reconstruction. Stimulating at contact 1 with sensing between 0 and 2 showed the highest signal suppression in the right hemisphere. Stimulation did not suppress the 7.81 Hz signal in the left hemisphere.

Peaks of interest

	Left	Right
Patient 1	9.77 Hz 19.53 Hz	9.77 Hz 21.48 Hz
Patient 2	7.81 Hz 18.55 Hz	7.81 Hz 18.55 Hz

Chronic **BrainSense™ Timeline tracked a 7.81 Hz** signal. Over the course of treatment, the patient had many changes in antiseizure medication. When placed on Divalproex approximately 11 months after the start of DBS therapy, **seizure frequency decreased and there was a visible reduction in LFP power in the left hemisphere**.

Notes and limitations

Small sample size from single-center limits generalizability. All implants performed by single surgeon, creating potential bias in targeting. Hardware limitations may impact ability to collect low-frequency LFP data.

FEATURED ARTICLE:

Case Report of Event Tracking and LFP Sensing in Epilepsy

Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. Feb; 25(2): 271-275.

Objective

Proof-of-principle pilot study to demonstrate that LFP-based programming can be useful in DBS indications that have a delayed temporal onset of benefit, such as epilepsy.

Methods

Patients with epilepsy (N): 1

Recording: Percept™ PC

Target: Bilateral ANT

Set-Up:

- Prior to therapy activation, sensing and "events" were enabled to look for seizure-related markers.
- Seizure reduction was evaluated using different therapy groups.

Results

Event markers were used to record frequency spectra related to absence seizures, focal/partial seizures, generalized seizures, and medication.

LFPs related to absence and focal seizures were identified.

- 2.93 Hz (absence seizures)
- 8.79 Hz (focal seizures)

Interictal discharges occurred in the theta/delta range in semi-rhythmic runs or bursts lasting up to 3 seconds.

"Split sensing" was used to record different frequencies from each hemisphere.

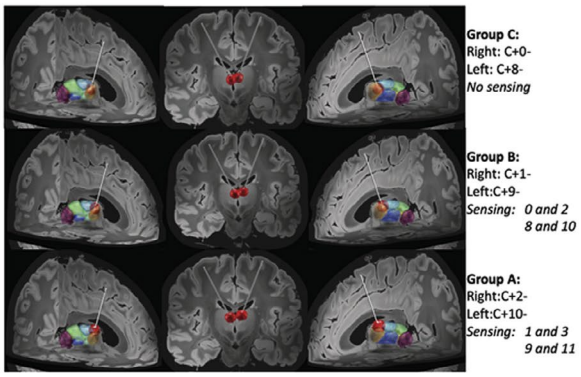
Group A	Group B
1 and 3 sensing at 2.93 Hz	0 and 2 sensing at 2.93 Hz
9 and 11 sensing at 8.79 Hz	8 and 10 sensing at 8.79 Hz

Therapy Groups that were the most effective in seizure reduction were also the most effective in reducing power in the 2.93 frequency band.

Notes and complications

Complications were not discussed by the authors.

a

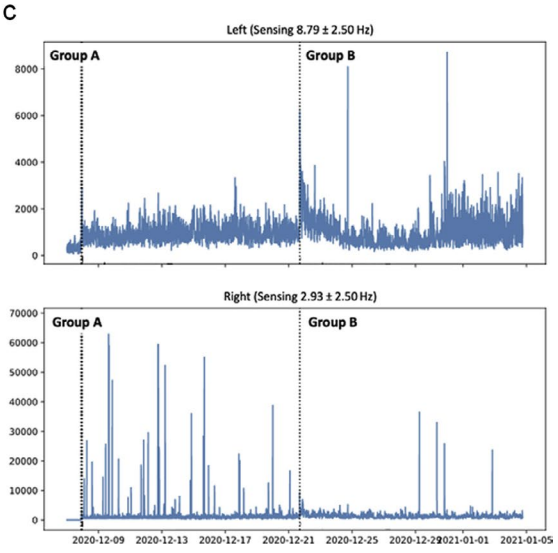


a) Leads and corresponding volume of tissue activation (VTA; red) in the ANT for each stimulation Group (C, B, and A [best to worst]), shown in relation to other nuclei.

b

b) Events of "absence seizure" and "focal/partial seizure" triggered broadband recordings (without ongoing stimulation) in the BrainSense Timeline feature.

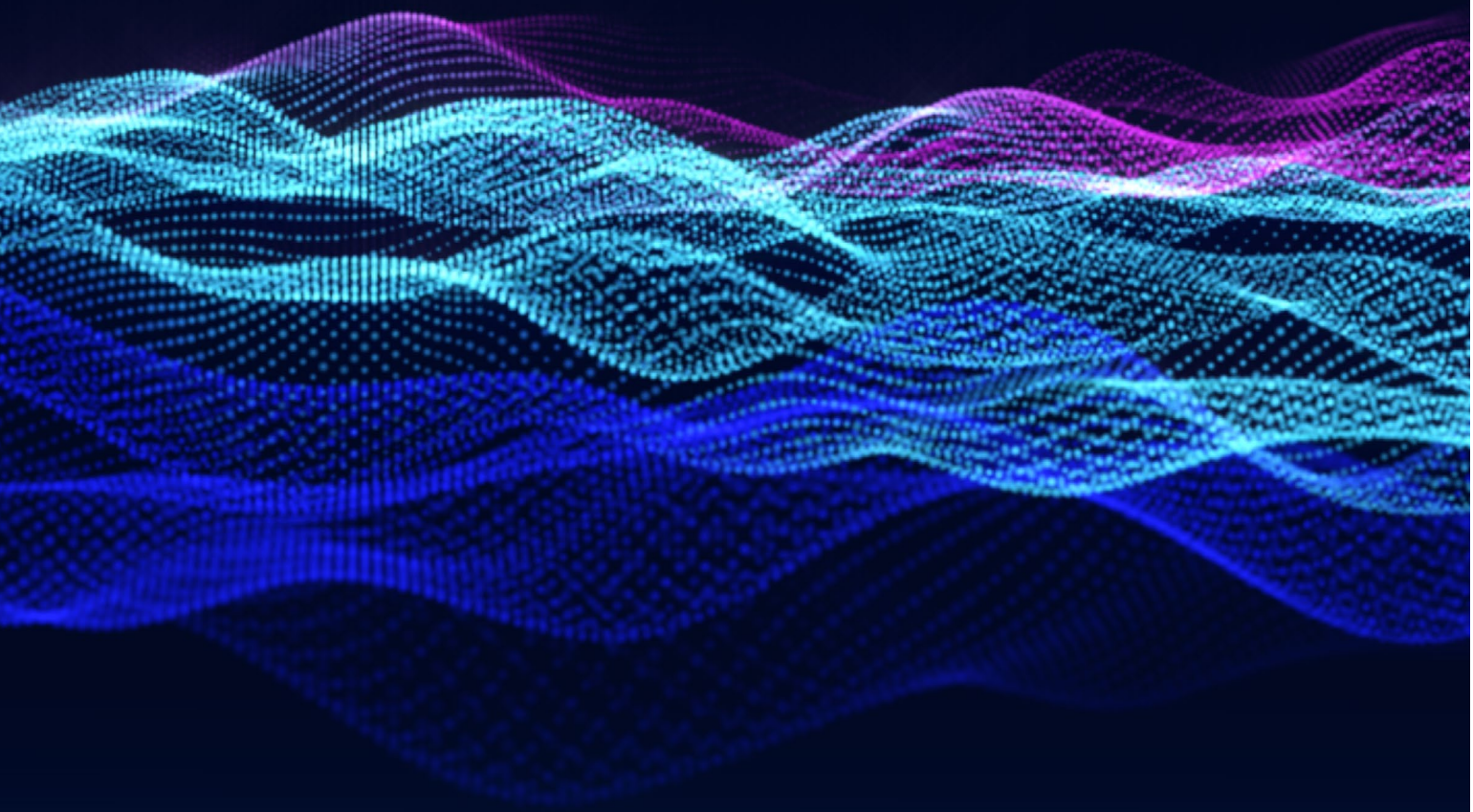
c



c) Chronic recording* of the 2.93 Hz and 8.79 Hz (spit sensing) for groups A and B with ongoing stimulation showing reduced power with Group B which was associated with better seizure control. *Representation of the LFP's unitless power in the sensing frequency band (downloaded as JSON file).

SECTION 5:

Essential tremor



Essential tremor

Signal trust

Review articles have commented on frequencies that have been associated with tremor. Few publications were identified reporting on detection of LFP signals from patients with unilateral ventral intermediate (VIM) nucleus DBS for essential tremor (ET).

Essential tremor	
Common frequencies associated with tremor	4 to 13 Hz[1]
	13 to 35 Hz[1]

1Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.

Related Articles

Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.

Thompson JA, Lanctin D, Ince NF, Abosch A. Clinical implications of local field potentials for understanding and treating movement disorders. Stereotact Funct Neurosurg. 2014;92(4):251-63

Select, optimize, and maximize

BrainSense™ Survey determines if a signal is detectable between two contact pairs and may provide objective information for contact selection. BrainSense™ Survey shows signals in the theta, alpha, beta, and gamma ranges; peak signals may help inform lead location and contact selection. Other BrainSense™ tools may be helpful for initial therapy programming and making DBS and medication therapy decisions over time. Publications reporting on the use of Percept™ PC in patients with unilateral VIM DBS for ET were not identified.

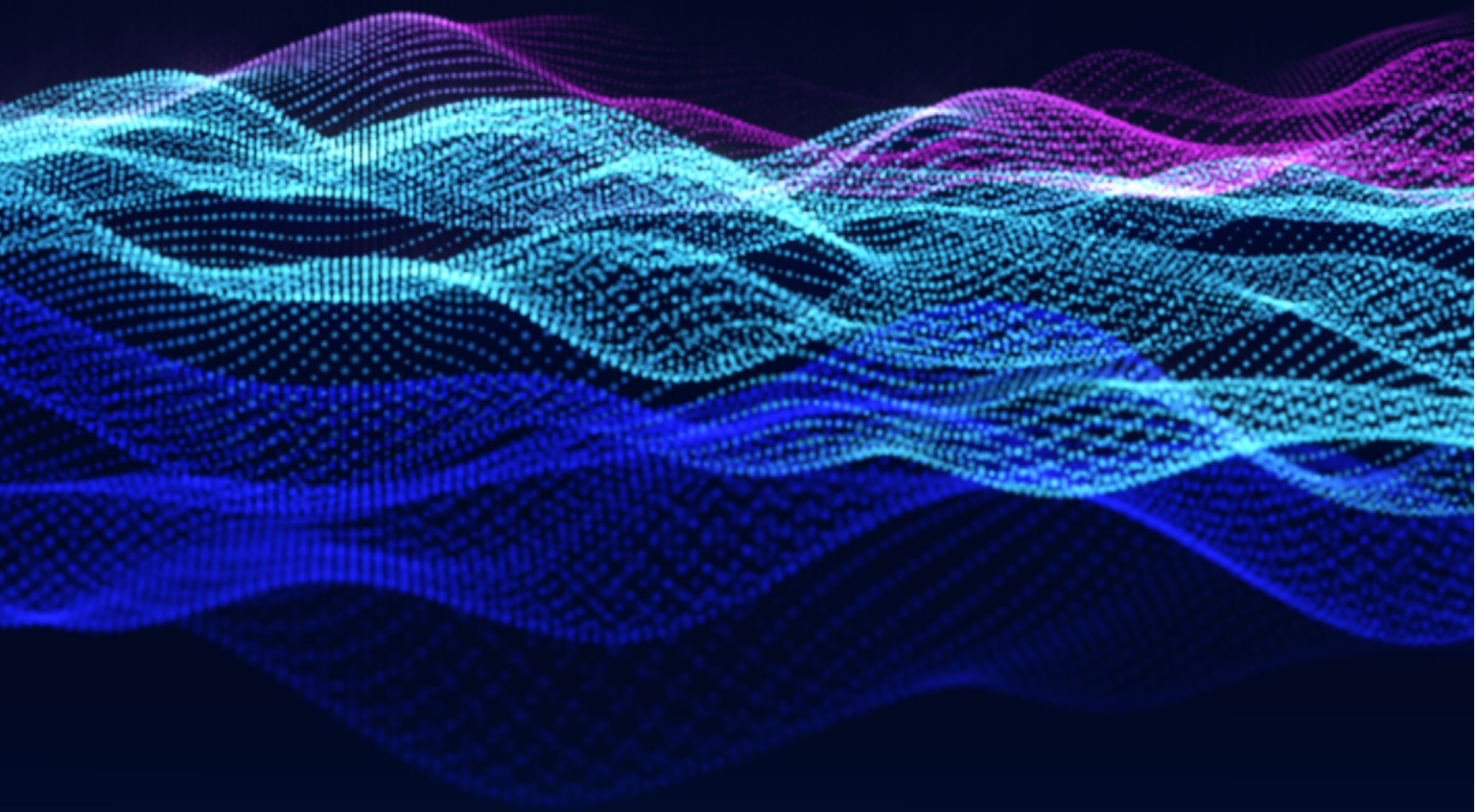
Learn more about BrainSense™ Survey for informing contact selection: page 12

Learn more about BrainSense™ Streaming for optimizing therapy: page 13

Learn more about BrainSense™ Timeline and Events for maximizing therapy over time: page 14

SECTION 6:
Dystonia‡

‡ Dystonia: **Humanitarian Device** – Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated.



Dystonia

Research on local field potentials (LFP) from the globus pallidus internus (GPi) in patients with dystonia has been growing. Review articles have commented on the LFP frequencies associated with dystonia and dystonic symptoms.

Dystonia‡	
Common frequencies associated with dystonic movements, particularly phasic symptoms. Power in these frequencies may relate to symptom severity.	4 to 12 Hz[1,2]
Abnormal synchronization seen in other frequency bands	13 to 35 Hz[1,2] 60 to 90 Hz[1]

1 Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.

2 Lofredi R, Kühn AA. Brain oscillatory dysfunctions in dystonia. Handb Clin Neurol. 2022;184:249-257.

Signal trust

Publications reporting on the association of LFPs in patients with dystonia span back over a decade. Recordings from externalized leads, the Activa™ PC+S device, and Percept™ PC tend to suggest LFPs in the theta/alpha range associate with symptoms of dystonia; however, other frequency bands have also been reported. Several publications reporting on GPi DBS for dystonia are included below.

Table 9: Evidence of LFP peaks from the GPi recorded from DBS leads in patients with dystonia

Publication	Patients	LFP peaks
Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).	Patients with dystonia (N): 5 Bilateral GPi Recording: Percept™ PC	• **Theta/Alpha** peak identified at 5.7±2.1 Hz
Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. Feb; 25(2): 271-275.	Patients with dystonia (N): 1 Bilateral GPi Recording: Percept™ PC	• Left GPi showed a signal in the **delta** range (1.95 Hz) adjacent to contacts 9 and 10.
Scheller U, Lofredi R, van Wijk BCM, et al. Pallidal low-frequency activity in dystonia after cessation of long-term deep brain stimulation. Mov Disord. 2019 Nov;34(11):1734-1739.	Patients with dystonia (N): 9 Bilateral GPi Recording: Activa™ PC+S	• **All patients displayed a peak in at least 1 contact in the 3 to 12 Hz** range at all timepoints after cessation of DBS therapy up to 5 to 7 hours. • Beta peaks (13 – 30 Hz) were detected in all patients but only at some timepoints. • There were no distinct peaks in the higher frequency bands.

‡ Dystonia: **Humanitarian Device** – Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated.

Table 9: Evidence of LFP peaks from the GPi recorded from DBS leads in patients with dystonia

Publication	Patients	LFP peaks
Lofredi R, Scheller U, Mindermann A, et al. Pallidal Beta Activity Is Linked to Stimulation-Induced Slowness in Dystonia. Mov Disord. 2023;38(5):894-899. doi:10.1002/mds.29347	Patients with dystonia (N): 6 Bilateral GPi Recording: Activa PC + S	• **Low-beta peaks (12-20 Hz) were identified in all hemispheres.** • Beta peak contacts mostly overlapped with active DBS contacts (n=9 hemispheres). • Low-beta, but not high-beta, power predicted finger tapping speed.
Yokochi F, Kato K, Iwamuro H, et al. Resting-State Pallidal-Cortical Oscillatory Couplings in Patients With Predominant Phasic and Tonic Dystonia. Front Neurol. 2018;9(MAY):375.	Patients with dystonia (N): 19 Bilateral GPi Recording: externalized leads	• The relative power in the alpha frequency (8-13 Hz) in the phasic group was significantly greater than tonic group ($p < 0.01$). • The relative power in the delta frequency (2-4 Hz) in the tonic group was significantly greater than the phasic group ($p > 0.05$). • No differences were observed in theta and beta between the 2 groups.
Neumann WJ, Horn A, Ewert S, et al. A localized pallidal physiomarker in cervical dystonia. Ann Neurol. 2017;82(6):912-924.	Patients with dystonia (N): 27 Bilateral GPi Recording: externalized leads	• Theta power (4-12 Hz) correlated to Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores prior to DBS ($p = 0.002$) and at the 3-mo follow-up ($p = 0.0176$). • Beta power (13-35 Hz) was not related to TWSTRS scores or improvements.
Liu X, Wang S, Yianni J, et al. The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia. Brain. 2008;131(Pt 6):1562-1573.	Patients with dystonia (N): 15 Bilateral GPi Recording: externalized leads	• Involuntary dystonic muscle spasms were associated with increases in theta (3-8 Hz), alpha (8-12 Hz), and low beta (12-20 Hz) frequencies. • Spasm strength correlated with increased power in the 3 to 20 Hz range. • Power in high beta (20-30 Hz), low gamma (30-60 Hz), and high gamma (60-90 Hz) increased during voluntary movements relative to resting ($p < 0.0001$). • Patients with generalized dystonia displayed broad modulation of 0 to 3 Hz and 30 to 90 Hz bands during voluntary and dystonic movements. Patients with cervical dystonia had a larger desynchronization in the 8 to 20 Hz range during voluntary movement.

FEATURED ARTICLE:

Case Series of Theta-alpha Location and frequency Distribution in Patients with Dystonia

Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).

Objective

Publication overview of the utility and limitations of the Percept™ PC device for LFP recordings. The report aimed to provide clinicians with tips on how to maximize the capabilities of the device for standard clinical practice and for research purposes.

Methods

Patients (N): 20 (14 PD, 5 dystonia, 1 other)

Recording: Percept™ PC

PD target: GPi

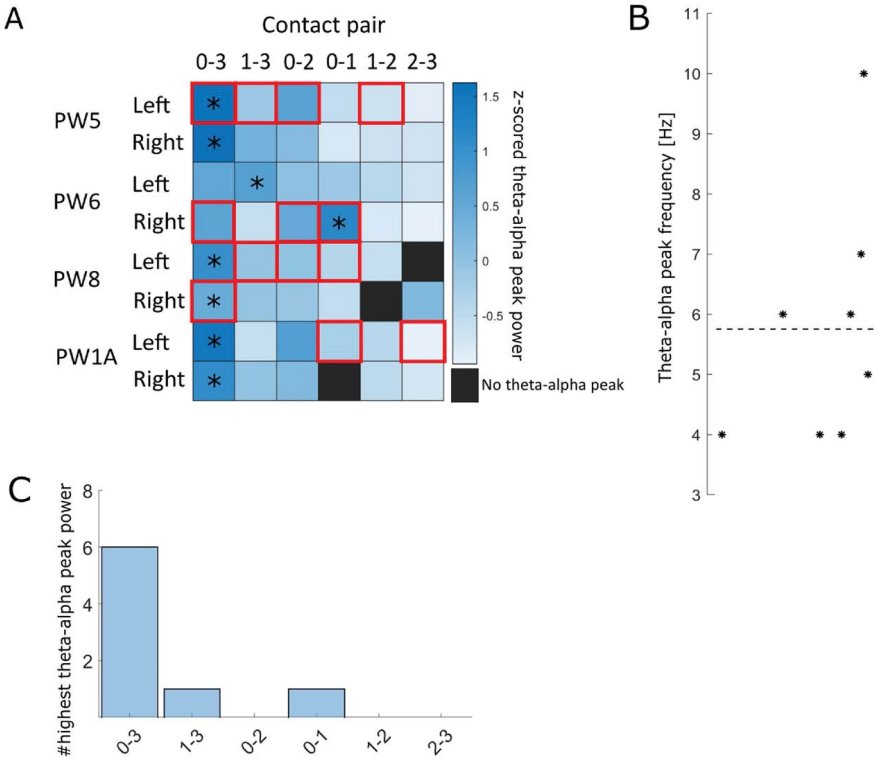
Design: BrainSense™ technology features were used to record LFPs in clinic and during at-home device use.

Results

- **All 8 GPi nuclei displayed a theta-alpha peak.**
- Using the contact pairs with maximum **theta-alpha peak, the average frequency was 5.7 Hz (SD, 2.1) Hz**.
- Contact pair 0-3 had the maximum theta-alpha peak in 6 of 8 GPi.
- The BrainSense™ feature labeled 27% of the contact pairs as containing artifact.
- Consecutive BrainSense™ Survey recordings showed high variability of LFP measurements regarding artifacts. As an example, consecutive sessions in the same patient differentially identified artifact or non-artifact in the same contact pair. This was thought to be due to episodic movement.

Notes

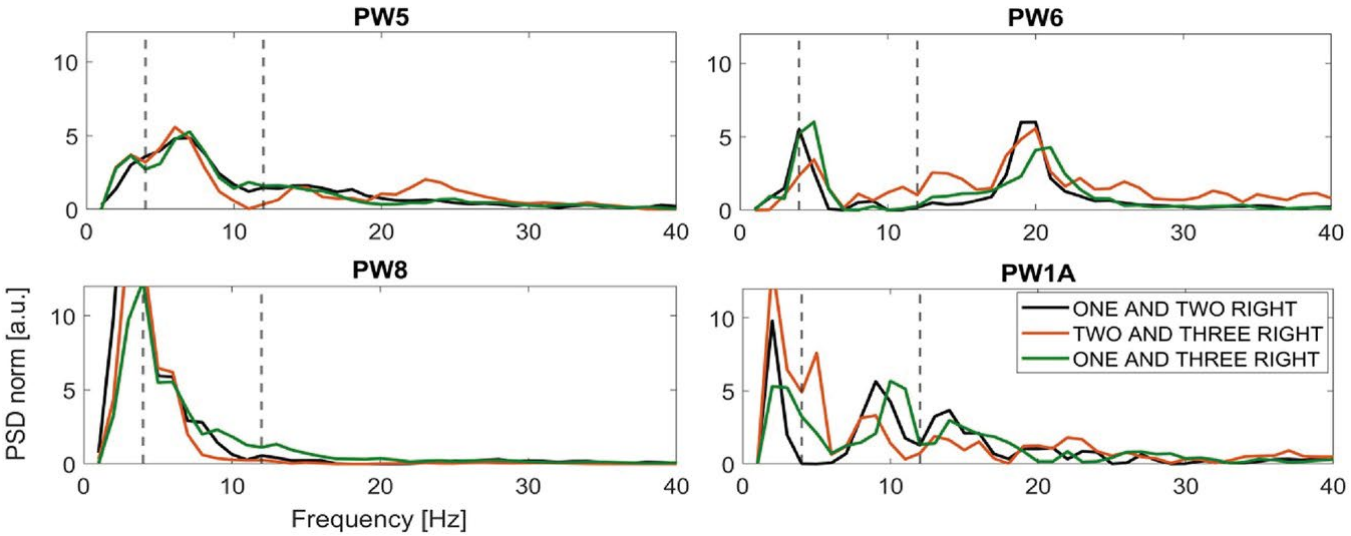
The authors did not report on complications. Signal artifacts, potentially due to movement, were prevalent in the recordings from patients with dystonia.



A) Example of theta-alpha LFPs in patients with dystonia. The Percept™ PC with BrainSense™ technology was used to observe LFP peaks in 8 GPi nuclei of 4 patients with dystonia. DBS was paused for 12 to 72 hours before the recordings were collected and patients were not taking medications during the recording period. Panel A indicates contact pairs displaying theta-alpha peak power (4 to 12 Hz). Black indicates no peak was identified; the star indicates the contact pair with the maximum theta-alpha peak. Red boxes indicate contact pair was labelled by the BrainSense™ system as containing artifact. The authors stated that 27% of the contact pairs in this patient group were labelled as artefactual and consecutive BrainSense™ Survey recordings showed high variability of LFP measurements.

B) The range of theta-alpha frequencies across the 8 nuclei. The dashed line indicates the average frequency.

C) Number of times each of the contact pairs was identified as the one with maximum beta power across the 8 GPi.



Example of theta-alpha LFP peaks in the GPi of patients with dystonia. DBS was paused for 12 to 72 hours before the recordings were collected and patients were not taking medications during the recording period. The Percept™ PC with BrainSense™ technology was used to observe LFP peaks in 4 patients. The vertical lines indicate the range of the theta-alpha band. Clear peaks were seen in all recording pairs in all patients, although less prominently in patient PW8. A beta band peak was also seen in PW6.

Select, optimize, and maximize

BrainSense™ Survey determines if a signal is detectable between two contact pairs and may provide objective information for contact selection. BrainSense™ Survey shows signals in the theta, alpha, beta, and gamma ranges; peak signals may help inform lead location and contact selection. Other BrainSense™ tools may be helpful for initial therapy programming and making DBS and medication therapy decisions over time. Example publications reporting on the use of these features are described here.

Learn more about BrainSense™ Survey for informing contact selection: page 12

Learn more about BrainSense™ Streaming for optimizing therapy: page 13

Learn more about BrainSense™ Timeline and Events for maximizing therapy over time: page 14

Final contact selection should be determined by the physician along with other medical information.

Publication	Description of LFP signal informing contact selection
Lofredi R, Scheller U, Mindermann A, et al. Pallidal Beta Activity Is Linked to Stimulation-Induced Slowness in Dystonia. Mov Disord. 2023;38(5):894-899.	In a case series of 6 patients (12 GPi hemispheres), peak beta overlapped with the active DBS contact in 9 hemispheres. Low beta at a mean of 16 (2.0) Hz was seen in all hemispheres; high beta at a mean of 29 (3.0) Hz was apparent in 9 hemispheres.

FEATURED ARTICLE:

Case Report on LFP Association with Dystonic Symptoms

Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. Feb; 25(2): 271-275.

Objective

Proof-of-principle pilot

Methods

Patients with dystonia (N): 1

Recording: Percept™ PC

Target: bilateral GPi

Set-Up:

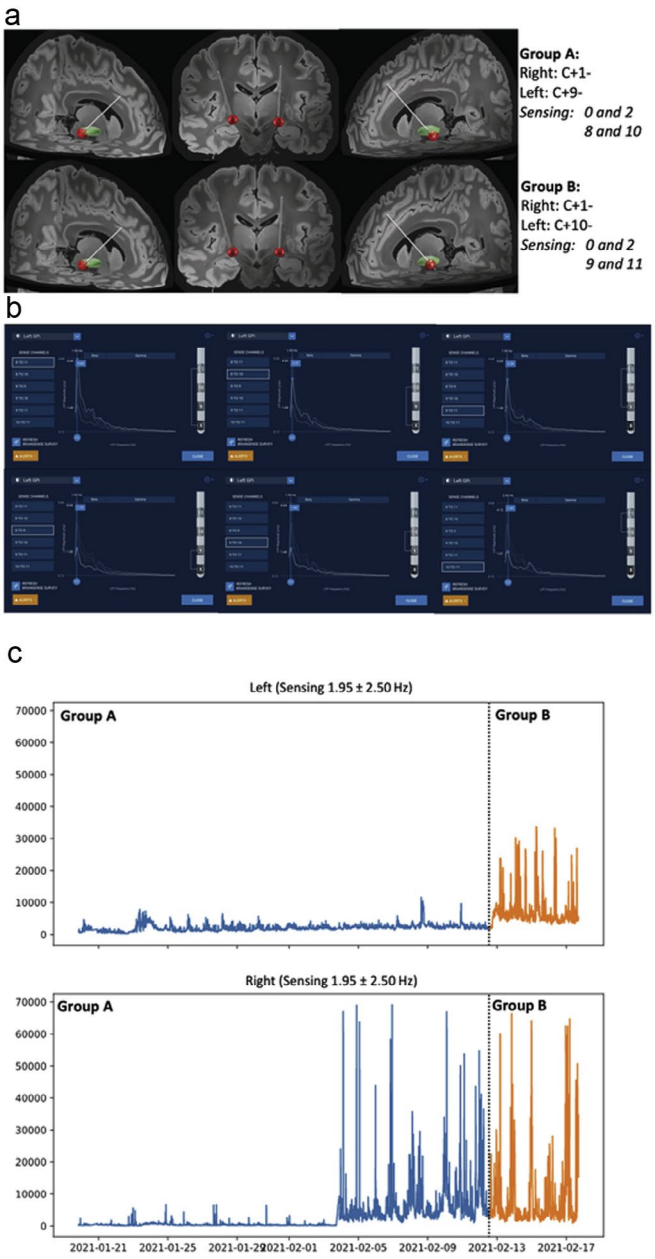
- BrainSense™ Survey was used to look for signals during a dystonic state. The left GPi showed a peak at 1.95 Hz when sensing adjacent to contacts 9 and 10.

Results

- Contact 1 (case +) and contact 9 (case +) were chosen for initial stimulation. Contacts 0 and 2 (right) and contacts 8 and 10 (left) were designated for sensing. This configuration dramatically improved the patient's dystonic symptoms.
- A second program was attempted, stimulating through contact 10, with 9 and 11 as sensing contacts. This program worsened the dystonic symptoms and power in the 1.95 Hz band increased.

Notes and complications

Complications were not discussed by the authors.



a) Leads and corresponding volume of tissue activation (VTA; red) shown in relation to internal globus pallidus (green)

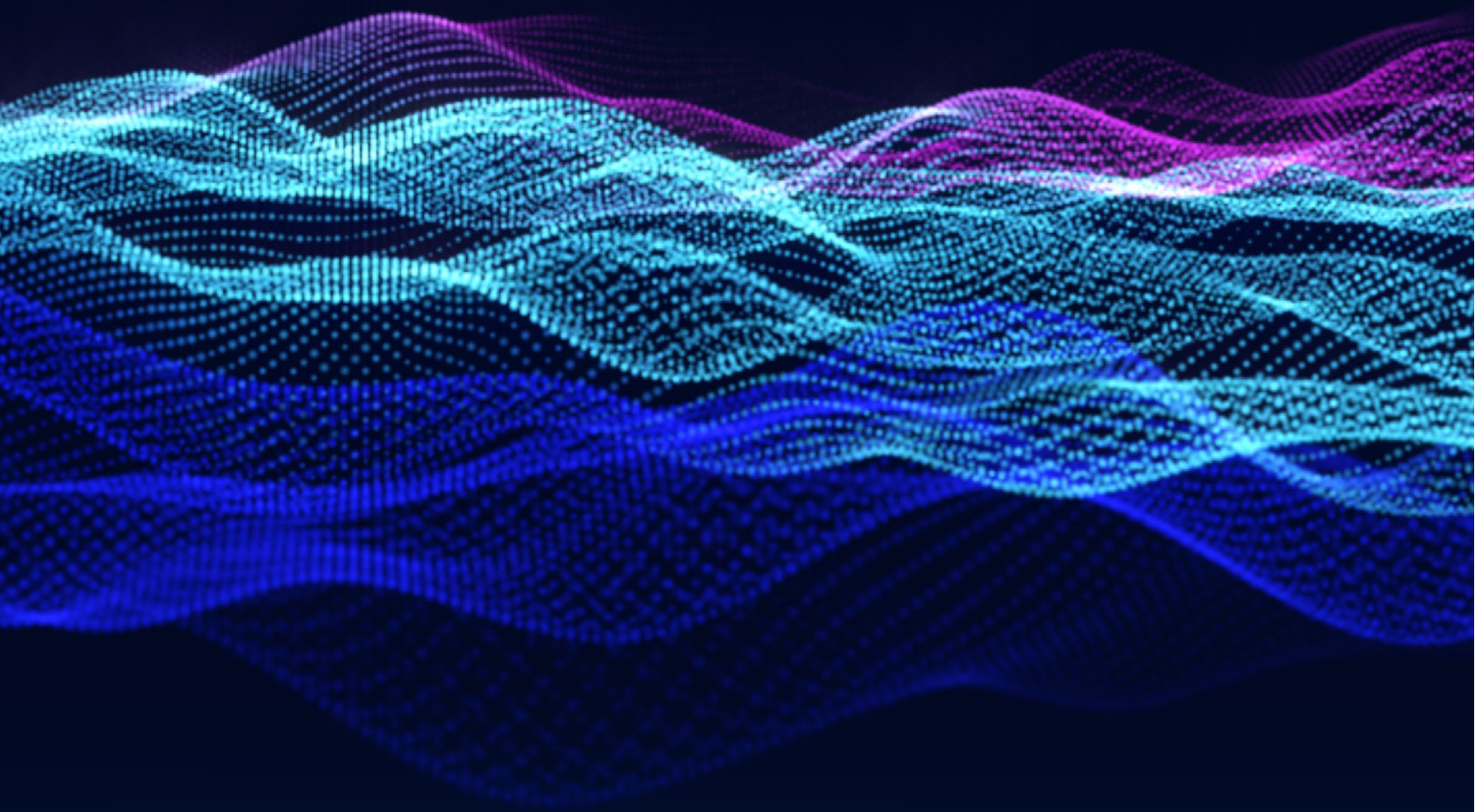
b) A peak in the delta range (1.95 Hz) in the left GPi (no ongoing stimulation) was detected using BrainSense Survey.

c) Chronic recording* of the 1.95 Hz LFP during on-going stimulation with groups A and B. Greater power in the 1.95 Hz band was seen with Group B and was associated with a worsening of dystonia.

*Representation of the LFP's unitless power in the sensing frequency band (downloaded as JSON file).

SECTION 7:

Publications using Percept™ PC



Selected publications on Percept™ PC

Cummins DD, Kochanski RB, Gilron R, et al. Chronic Sensing of Subthalamic Local Field Potentials: Comparison of First and Second Generation Implantable Bidirectional Systems Within a Single Subject. *Front Neurosci*. 2021;15:725797.

http://dx.doi.org/10.3389/fnins.2021.725797

Summary | Case report describing a peak in the beta frequency band (~20 Hz) that could still be identified after an Activa™ PC+S device was replaced with a Percept™ PC device. Recording with DBS ON had less stimulation artifact when using the Percept™ PC device compared with the Activa™ PC+S device.

Binder T, Lange F, Pozzi N, et al. Feasibility of local field potential-guided programming for deep brain stimulation in Parkinson's disease: A comparison with clinical and neuro-imaging guided approaches in a randomized, controlled pilot trial. Brain Stimul. 2023 Aug 22;16(5):1243-1251.

https://doi.org/10.1016/j.brs.2023.08.017

Summary | A comparison of clinically, imaging, and beta-guided programming paradigms demonstrated comparable clinical efficacy in a 30-minute stimulation period. Beta-guided and imaging-guided programming required significantly less time for programming compared to the clinically-guided approach.

Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. *Neuromodulation*. 2021.

http://dx.doi.org/10.1111/ner.13520

Summary | Description of BrainSense™ use in indications that typically take longer to respond to DBS. Two case reports, one epilepsy and one dystonia, are described.

Feldmann LK, Lofredi R, Neumann WJ, et al. Toward therapeutic electrophysiology: beta-band suppression as a biomarker in chronic local field potential recordings. *NPJ Parkinsons Dis*. 2022;8(1):44.

http://dx.doi.org/10.1038/s41531-022-00301-2

Summary | Characterization of LFP activity and STN beta band relationship with bradykinesia in 10 patients with Parkinson's disease. LFPs were recorded with increasing stimulation amplitude during rest and finger tapping. Suppression of low-beta activity was correlated with increasing stimulation intensity and positively correlated with movement speed.

Feldmann LK, Neumann WJ, Krause P, Lofredi R, Schneider GH, Khn AA. Subthalamic beta band suppression reflects effective neuromodulation in chronic recordings. *Eur J Neurol PMID: 33675144 PMID: 33675144*. 2021.

https://pubmed.ncbi.nlm.nih.gov/33675144/

Summary | Case report of a patient with STN DBS and chronic recordings with the Percept™ PC device. Beta was suppressed in response to stimulation while bradykinesia improved.

Koeglsperger T, Mehrkens JH, Botzel K. Bilateral double beta peaks in a PD patient with STN electrodes. *Acta Neurochir (Wien)*. 2020.

http://dx.doi.org/10.1007/s00701-020-04493-5

Summary | Case report of a patient treated with STN DBS for PD displaying two beta peaks. The peaks had varied responses to stimulation and physical movements.

van Rheede JJ, Feldmann LK, Busch JL, et al. Diurnal modulation of subthalamic beta oscillatory power in Parkinson's disease patients during deep brain stimulation. *NPJ Parkinsons Dis*. 2022;8(1):88.

http://dx.doi.org/10.1038/s41531-022-00350-7

Summary | BrainSense™ timeline data demonstrated consistently greater STN beta power during the day and reduced during the night in patients with PD.

Vaou OE, Spidi MD, Raike R, et al. Symptom optimization through sensing local field potentials: Balancing beta and gamma in Parkinson's disease. Deep Brain Stimulation. 2023 Jan 25.

https://doi.org/10.1016/j.jdbs.2023.01.001

Summary | LFP data collected through BrainSense™ technology provided objective data to support therapy optimization for dyskinesias, personalization to motor fluctuations in three patients with PD.

Strelow JN, Dembek TA, Baldermann JC, et al. Low beta-band suppression as a tool for DBS contact selection for akinetic-rigid symptoms in Parkinson's disease. Parkinsonism & Related Disorders. 2023; 112:105478.

https://doi.org/10.1016/j.parkreldis.2023.105478

Summary | Degree of low beta-band suppression, collected through BrainSense™ Streaming was significantly associated to improvement of akinetic-rigid symptoms, but high beta-band suppression was not. Low beta-band suppression predicted clinical contact selection with an accuracy probability of 75%.

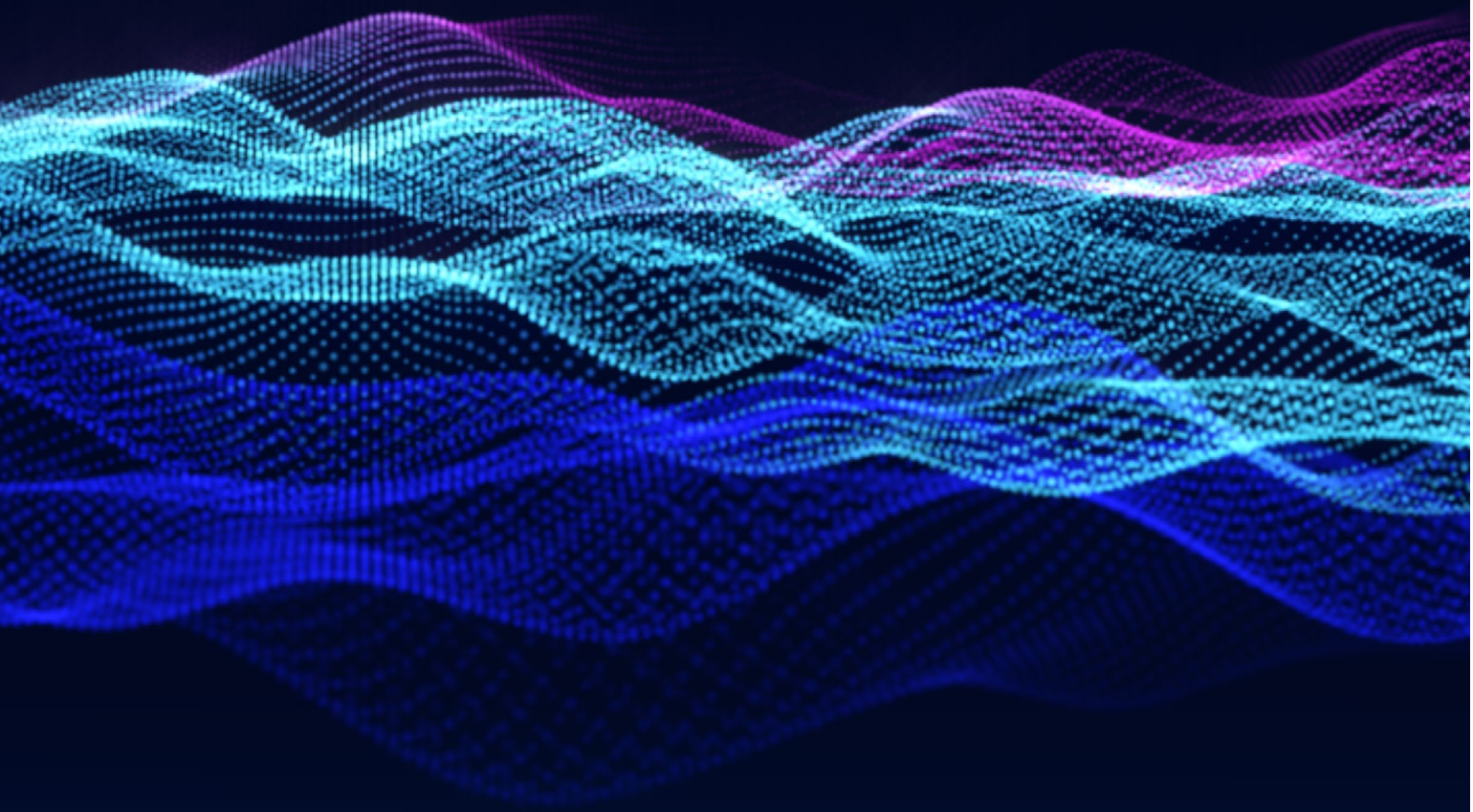
Swinnen BEKS, Stam MJ, Buijink AWG, et al. Employing LFP Recording to Optimize Stimulation Location and Amplitude in Chronic DBS for Parkinson's Disease: A Proof-of-concept Pilot Study. Deep Brain Stimulation. 2023; 2:1-5.

https://www.dbsjournal.com/article/S2949-6691(23)00007-6/fulltext

Summary | BrainSense™ Survey and Streaming were used to select contacts and titrate stimulation amplitudes in patients with STN DBS. The authors found 7 of 8 LFP-guided contacts aligned with clinically determined one.

SECTION 8:

Appendix



Common questions related to artifacts

What artifacts might be seen during BrainSense™ Streaming to investigate beta (or other LFP signal) in relationship to stimulation changes?

Noise transients/artifacts can be observed when changes are made to stimulation amplitude. Small incremental changes will help to decrease these transients, which appear larger when large amplitude changes are made. If ramping stimulation up/down is not possible, an option to avoid such transients is to pause streaming before big stimulation changes take place. Moreover, setting thresholds will help to have a constant reference in the streamed data plots.

Can movement-related artifacts appear in these BrainSense™ Streaming recordings? How should I assess if this is occurring? Can I tell if they are related to EMG sources or mechanical movement of the system/extensions?

Movement artifacts are generated if the neurostimulator, leads or extensions move in a way that creates noise. The artifact is not the physiological change of LFP due to movement. This artifact issue was reported in a cohort of patients with dystonia.[1]

If in doubt, ask the patient to relax and keep still if possible. If there is no movement and the signal displayed on the plots is unchanged, then there is no (significant) artifact related to movement.

Why do ECG artifacts appear and are there ways to manage this artifact?

This artifact is due to leakage of fluid somewhere along the sensing circuit and results in an ECG signal not being rejected as common disturbance; hence, the ECG signal is being recorded on top of the LFP.

The ECG artifact may partially mask the information in the LFP in the frequency band between 0 to 40 Hz.

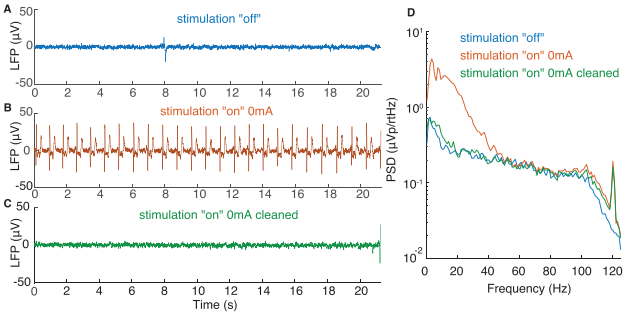
Modeling has suggested that one consideration for managing ECG artifact is the location of the neurostimulator relative to the heart.[2]

BrainSense™ Setup can be used to assess the impact of artifact on the recording.

Are there any ways to understand if artifacts might be influencing the BrainSense™ Timeline data?

It is possible for artifacts like ECG or movement to contaminate the signal. One way to get a sense for a Timeline channel's susceptibility to artifacts is to setup BrainSense™ technology to record LFP in a band which is sensitive to artifacts[3] but may not fluctuate with symptoms or clinical state (e.g., on or off medication in a patient with Parkinson's). For example, if you have recorded or plan to record Timeline data around a signal of interest at 15 Hz, recording a "control band" at 8 Hz for a few days could help to assess how much of the Timeline signal's change might be due to the ECG/motion instead of the actual LFP. Note that only one signal of interest per hemisphere at a time can be collected in the Timeline, hence recording a "control band" for a few days will result in not recording the signal of interest for the same period.

Example of cardiac artifact



Illustrative example of the potential for cardiac artifacts. LFP signals recorded from contacts 1-3 (right) during the BrainSense™ Setup with stimulation OFF (A) and stimulation ON at 0 mA (B). Turning stimulation on caused detection of cardiac-related artifacts that "corrupted the raw signal and covered most frequencies under 50 Hz in the PSD estimate (D)." QRS peaks were removed from the raw signal during a cleaning process (C). The resulting PSD shows that artifact typically contaminates frequencies between 1 and 40 Hz (D).

What are the other sources of noise or artifact that might need to be considered?

Noise from a 2nd stimulation device; for example, interleaving on the contralateral system can create an artifact in the sensing system. When sensing with dual implants, the artifact can be controlled by programming the same stimulation frequency on both neurostimulators.

1 Thenaisie Y, Palmisano C, Canessa A, et al. Towards adaptive deep brain stimulation: clinical and technical notes on a novel commercial device for chronic brain sensing. J Neural Eng. 2021 Aug 31;18(4).

2 Sorkhabi MM, Benjaber M, Brown P, Denison T. Physiological Artifacts and the Implications for Brain-Machine-Interface Design. Conf Proc IEEE Int Conf Syst Man Cybern. 2020;2020:1498-1504.

3 Reasonable bands sensitive to both motion and cardiac artifacts are in the range 1-25Hz.

Common questions related to sensing

What are some considerations when choosing a contact with beta for programming?

The patient response to stimulation is the most important aspect when choosing contacts and programs for therapy.

When using beta (or other signals) as additional information for programming, it can be important to appreciate the signals are differential (so the peak could be high in a region, but it is washed away when compared to a region that also has a high signal).

What are some considerations when using beta as an objective input to programming?

Several considerations have been mentioned by the experts above. In brief, suggestions have included:

When assessing for beta suppression by stimulation, be mindful of overstimulation that could lead to dyskinesia. The goal is not necessarily complete beta suppression; rather take into account initial beta suppression, when beta suppression plateaus, and if gamma appears in the recording.

Gamma does not always indicate dyskinesias. It is important to consider LFP signals within the context of the patient's medical history and symptoms.

It is important to not rely solely on beta to make programming decisions. One should always appreciate the patient's treatment goals and examine the patient's individual symptoms and responses to treatment when determining programming parameters.

A patient with Parkinson's presents with peaks within both the low- and high-beta ranges. What are some factors to consider when determining which one to use as a frequency of interest?

In a recent study, dual-beta peaks were observed in up to 64% of patients (n=106), 35% of all hemispheres (n=210).[1] While low-beta (13-20 Hz) is traditionally associated with akinetic-rigid symptoms and demonstrates marked suppression in response to stimulation, levodopa, and movements; high-beta (21-35 Hz) demonstrates less stimulation related suppression relative to low-beta.[1,2]

Importantly, publications suggest using the low-beta peak as a FOI when both low- and high-beta peaks are present.[3,4]

What are some considerations when using BrainSense™ event markers?

When evaluating signals related to the event, consider relationship between the actual event and the patient-marked event (approximately 30 seconds of recording after the event is marked). For example, patients with a seizure event may indicate the event in the postictal period. Patients with a movement-related event may indicate the event after the event occurred. Providing instructions and/or discussing use of the event marker with patients and caregivers may enable more productive understanding of the event in relationship to the recording.

What are some considerations for using the BrainSense™ Timeline feature?

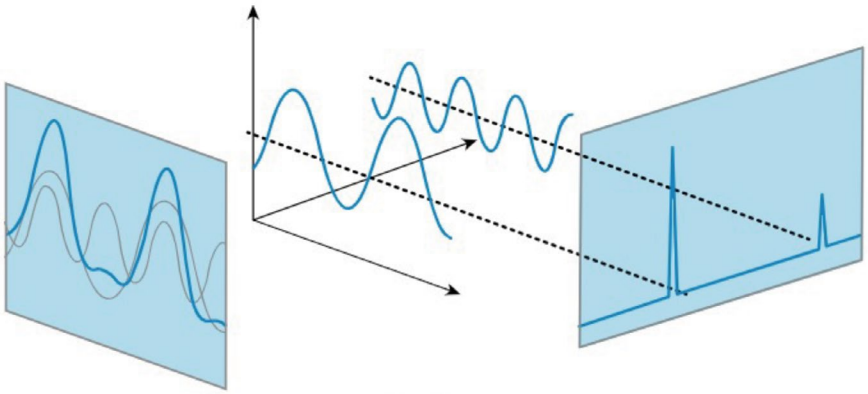
BrainSense™ Timeline is used to assess the data for changes in LFP activity that may occur over the course of a day(s). When the patient leaves the clinic, BrainSense™ LFP power domain data and stimulation amplitude are continuously recorded when a BrainSense™ configured group is active. Be aware that the LFP power and the stimulation amplitudes are the average value measured over a 10 minute interval and these averages are recorded to the neurostimulator memory. Also note that up to 60 days of LFP data and stimulation data can be stored on the device, after which the oldest day is overwritten unless BrainSense™ is turned off or the user changes to a group without BrainSense™ configured.

1. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. Experimental Neurology. 2022:114150.
2. Feldmann LK, Lofredi R, Neumann WJ, et al. Toward therapeutic electrophysiology: beta-band suppression as a biomarker in chronic local field potential recordings. NPJ Parkinsons Dis. 2022 Apr 19;8(1):44.
3. Binder T, Lange F, Pozzi N, et al. Feasibility of local field potential-guided programming for deep brain stimulation in Parkinson's disease: A comparison with clinical and neuro-imaging guided approaches in a randomized, controlled pilot trial. Brain Stimul. 2023 Aug 22;16(5):1243-1251.
4. Strelow JN, Dembek TA, Baldermann JC, et al. Local Field Potential-Guided Contact Selection Using Chronically Implanted Sensing Devices for Deep Brain Stimulation in Parkinson's Disease. Brain Sci. 2022;12(12).

Glossary

Coherence – An assessment of the association between activity recorded at two different sensors.[1]

Fourier transform – a method of "comparing" the data x to sinusoids oscillating at difference frequencies f_j. When the data and sinusoids "match," the power at frequency f_j is large, whereas when the data and sinusoids do not match, the power at frequency f_j is small.[1]



Oscillations – rhythmic repetitive patterns of neural activity in the nervous system that can be recorded as extracellular LFPs.[3]

Phase Amplitude Coupling (PAC) – the ability of the phase of a low-frequency signal to drive the amplitude of a higher oscillation.[2]

Power Spectrum – the magnitude squared of the Fourier transform of the data. The power spectrum indicates the amplitude of rhythmic activity in the data as a function of frequency.[1]

Common Acronyms	
PD	Parkinson's disease
GPi	Internal Globus Pallidus
LFP	Local Field Potential
PC+S	Primary Cell + Sensing
STN	Subthalamic Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
ANT	Anterior nucleus of the thalamus
VIM	Ventral intermediate nucleus

Resources

Refer to product labeling for specific information including indications, safety and warnings. This can be found at: www.medtronic.com/manuals

For technical information regarding BrainSense™ Technology, including access to the data, artifacts, and other technical questions, please see: Percept™ (PC and RC) Neurostimulators with BrainSense™ Technology DBS Sensing White Paper. This Whitepaper is available upon request.

Please note that presentations and webinars on BrainSense™ technology can also be accessed on Medtronic's DBS Academy.

- If you are new to DBS Academy, please send an email to request access: rs.dbstrainingandeducation@medtronic.com
- Returning users, log in with your existing username and password. Go to: rtg.medtronicacademy.com/dbs (Chrome preferred browser). Go to the "search catalog" and type in "Deep Brain" and you will be directed to the DBS Academy home page.
- If you need assistance, please email rs.dbstrainingandeducation@medtronic.com

For any questions or more detailed discussions regarding this content, please contact Medical Affairs: rs.neuromedicalaffairs@medtronic.com

1 Kramer MA. An Introduction to Field Analysis Techniques: The Power Spectrum and Coherence. White Paper. Kramer 2013. Accessed on-line 22July2019.

2 Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol. 2013;26(6):662-70.

3 Thompson JA, Lanctin D, Ince NF, Abosch A. Clinical implications of local field potentials for understanding and treating movement disorders. Stereotact Funct Neurosurg. 2014;92(4):251-63.

Brief Statement: Medtronic DBS Therapy for Parkinson's Disease, Tremor, Dystonia, Obsessive-Compulsive Disorder, and Epilepsy

Product labeling must be reviewed prior to use for detailed disclosure of risks.

INDICATIONS:

Medtronic DBS Therapy for Parkinson's Disease: Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

Medtronic DBS Therapy for Tremor: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Medtronic DBS Therapy for Dystonia*: Unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Dystonia is indicated as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above.

Medtronic DBS Therapy for Obsessive-Compulsive Disorder*: The Medtronic Reclaim™ DBS Therapy is indicated for bilateral stimulation of the anterior limb of the internal capsule, AIC, as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs).

Medtronic DBS Therapy for Epilepsy: Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

CONTRAINDICATIONS: Medtronic DBS therapy is contraindicated for patients who are unable to properly operate the neurostimulator and, for Parkinson's disease and essential tremor, patients for whom test stimulation is unsuccessful. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if they have an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

WARNINGS: There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths and, for Parkinson's disease and essential tremor, a potential risk to drive tremor (cause tremor to occur at the same frequency as the programmed frequency) using low frequency settings. Extreme care should be used with lead implantation in patients with an increased risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as implanted cardiac devices (e.g., pacemaker, defibrillator), external defibrillation/cardioversion, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious and permanent injury including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Abrupt cessation of stimulation should be avoided as it may cause a return of disease symptoms, in some cases with intensity greater than was experienced prior to system implant ("rebound" effect). Onset of status dystonicus, which may be life-threatening, may occur in dystonia patients during ongoing or loss of DBS therapy.

For epilepsy, cessation, reduction, or initiation of stimulation may potentially lead to an increase in seizure frequency, severity, and new types of seizures. For epilepsy, symptoms may return with an intensity greater than was experienced prior to system implant, including the potential for status epilepticus. For Parkinson's disease or essential tremor, new onset or worsening depression, suicidal ideation, suicide attempts, and suicide have been reported. For dystonia or epilepsy, depression, suicidal ideations and suicide have been reported, although no direct cause-and-effect relationship has been established. For epilepsy, preoperatively, assess patients for depression and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients closely for new or changing symptoms of depression and manage these systems appropriately. Patients should be monitored for memory impairment. Memory impairment has been reported in patients receiving Medtronic DBS Therapy for epilepsy, although no direct-cause-and effect relationship has been established. The consequences of failing to monitor patients are unknown. When stimulation is adjusted, monitor patients for new or increased seizures, tingling sensation, change in mood, or confusion. For obsessive-compulsive disorder, patients should be monitored for at least 30 minutes after a programming session for side effects, including: autonomic effects (e.g., facial flushing, facial muscle contractions, or increased heart rate), hypomania, increased disease symptoms, and sensations such as tingling, smell, or taste. For obsessive-compulsive disorder, during treatment, patients should be monitored closely for increased depression, anxiety, suicidality, and worsening of obsessive-compulsive symptoms.

Patients should avoid activities that may put undue stress on the implanted components of the neurostimulation system. Activities that include sudden, excessive or repetitive bending, twisting, or stretching can cause component fracture or dislodgement that may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component. Patients should avoid manipulating the implanted system components or burr hole site as this can result in component damage, lead dislodgement, skin erosion, or stimulation at the implant site. Patients should not dive below 10 meters (33 feet) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA) as this could damage the neurostimulation system, before diving or using a hyperbaric chamber, patients should discuss the effects of high pressure with their clinician.

Patients using a rechargeable neurostimulator for Parkinson's disease, essential tremor, dystonia, or epilepsy must not place the recharger over a medical device with which it is not compatible (eg, other neurostimulators, pacemaker, defibrillator, insulin pump). The recharger could accidentally change the operation of the medical device, which could result in a medical emergency. Patients should not use the recharger on an unhealed wound as the recharger system is not sterile and contact with the wound may cause an infection.

WARNING for Obsessive-Compulsive Disorder:

Electroconvulsive Therapy (ECT) – The safety of ECT in patients who have an implanted deep brain stimulation (DBS) system has not been established. Induced electrical currents may interfere with the intended stimulation or damage the neurostimulation system components resulting in loss of therapeutic effect, clinically significant undesirable stimulation effects, additional surgery for system explantation and replacement, or neurological injury.

PRECAUTIONS: Loss of coordination in activities such as swimming may occur. For obsessive-compulsive disorder, the safety of somatic psychiatric therapies using equipment that generates electromagnetic interference (e.g., vagus nerve stimulation) has not been established. Patients using a rechargeable neurostimulator for Parkinson's disease, essential tremor, dystonia, or epilepsy should check for skin irritation or redness near the neurostimulator during or after recharging, and contact their physician if symptoms persist.

ADVERSE EVENTS: Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy, and weight gain or loss.

For Parkinson's disease or essential tremor, safety and effectiveness has not been established for patients with neurological disease other than idiopathic Parkinson's disease or essential tremor, previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression, patients who are pregnant, or patients under 18 years. For essential tremor, safety and effectiveness has not been established for bilateral stimulation or for patients over 80 years of age. For dystonia, safety of this device for use in the treatment of dystonia with or without other accompanying conditions (e.g., previous surgical ablation procedure, dementia, coagulopathies, or moderate to severe depression, or for patient who are pregnant) has not been established. Age of implant is suggested to be that at which brain growth is approximately 90% complete or above. For epilepsy, the safety and effectiveness of this therapy has not been established for patients without partial-onset seizures, patients who are pregnant or nursing, patients under the age of 18 years, patients with coagulopathies, and patients older than 65 years. For obsessive-compulsive disorder, the safety and probable benefit of this therapy has not been established for patients with: Tourette's syndrome, OCD with a subclassification of hoarding, previous surgical ablation (e.g., capsulotomy), dementia, coagulopathies or who are on anticoagulant therapy, neurological disorders, and other serious medical illness including cardiovascular disease, renal or hepatic failure, and diabetes mellitus. In addition, the safety and probable benefit has not been established for these patients: those whose diagnosis of OCD is documented to be less than five years duration or whose YBOCS score is less than 30, who have not completed a minimum of three adequate trials of first and/or second line medications with augmentation, who have not attempted to complete an adequate trial of cognitive behavior therapy (CBT), who are pregnant, who are under the age of 18 years, and who do not have comorbid depression and anxiety. Physicians should carefully consider the potential risks of implanting the Reclaim DBS System in patients with comorbid psychiatric disorders (e.g., bipolar, body dysmorphic, psychotic) as the Reclaim DBS System may aggravate the symptoms.

*** Humanitarian Device:** Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated. Authorized by Federal law for use as an adjunct to medications and as alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs). The effectiveness of the devices for this use has not been demonstrated.

USA Rx only Rev 09/22

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