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Engineering the extraordinary

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 health care professionals interested in brain sensing and focuses on two objectives.

The first objective is to summarize published literature reporting on the use of the Percept™ PC device with BrainSense™ technology* and to provide published examples and guidance for those interested to incorporate BrainSense™ technology into their practice.

The second objective is to provide a scientific overview of the research that has been conducted to investigate and understand local field potentials (LFPs). Years of published literature has 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 neurostimulator with BrainSense™ technology captures 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 system is intended for use in patients receiving DBS where chronically-recorded bioelectric data may provide useful, objective information regarding patient clinical status. Signal may not be present or measurable in all patients. Clinical benefits of brain sensing have not been established.

**Medtronic's DBS Therapy is approved for 4 indications: Parkinson's disease, essential tremor, dystonia, and epilepsy. Device indications vary, refer to product labeling.

Disclaimers

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.
- 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.
- This document contains sensing research conducted with an implanted Activa™ PC+S neurostimulation system that is for investigational use only.
- 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.

Table of contents

Featured articles

SECTION 1:

Basics of LFPs

Related articles

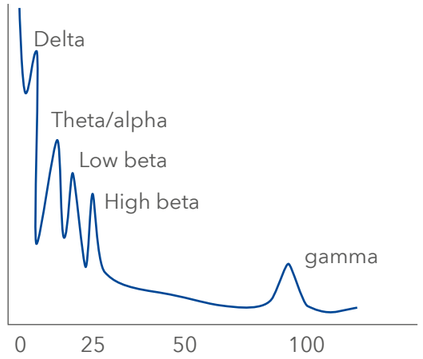
1. Brown and Williams. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol. 2005;116(11):2510-9. https://www.ncbi.nlm.nih.gov/pubmed/?term=16029963
2. Rosa M., Marceglia S., Barbieri S., Priori A. Local Field Potential and Deep Brain Stimulation (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
3. 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
4. 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/
5. 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/
6. 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. doi: 10.1016/j.nbd.2021.105372.
7. 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.
8. 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.
9. 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.
10. Brittain JS, Brown P. Oscillations and the basal ganglia: motor control and beyond. Neuroimage. 2014;85 Pt 2:637-47.

What is an LFP?

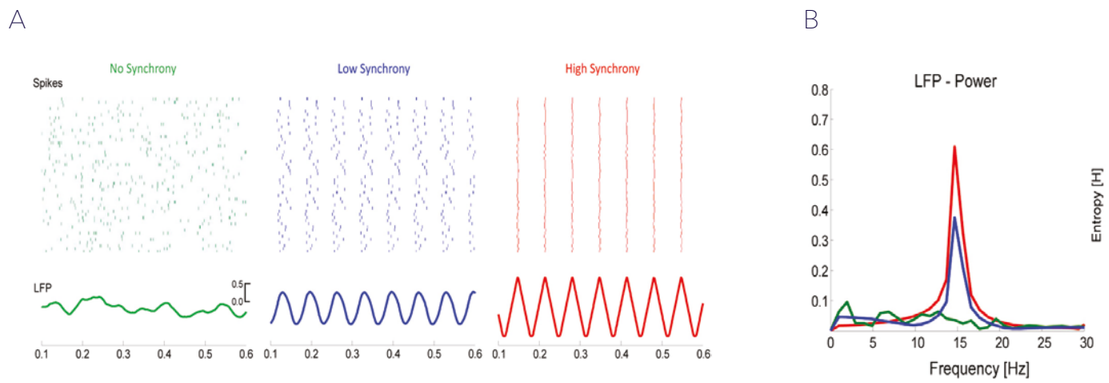
LFPs represent the summed electrical activity from local neuronal transmembrane currents around an electrode. Important factors that contribute to the LFP include the cellular and synaptic cellular architecture and the synchrony of the current sources.

LFPs have been characterized into frequency bands (approximate range, Hz): delta (0-3), theta (4-7), alpha (8-12), beta (13-30), gamma (31-200) and high frequency (> 200), 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."[1-10]

Characterization of LFP bands



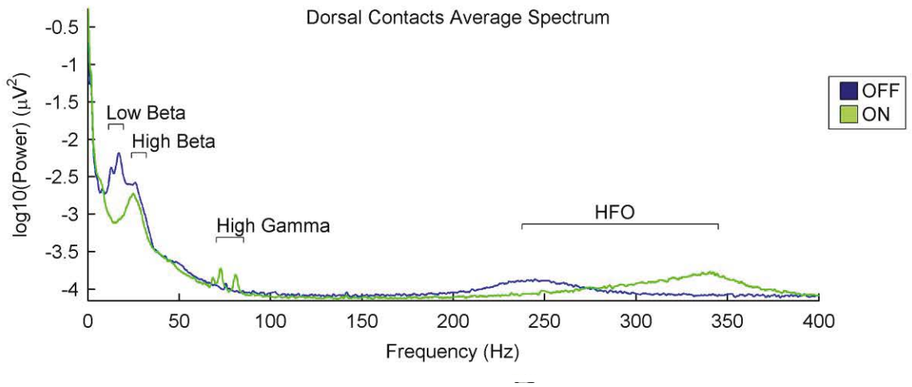
LFPs represent synchronized neural activity



Schematic showing the synchronization of neuronal spiking behavior into oscillatory behavior (A), representing frequency bands of different power strengths (B). Synchronization may promote interaction between neuronal populations.

Modified from Figure 6 in: Hanslmayr S., Staudig T., Fellner M.-C. Oscillatory power decreases and long-term memory: The information via desynchronization hypothesis. Front Hum Neurosci. 2012;6(74): 1–12. Use is covered under a Creative Commons license: https://creativecommons.org/licenses/by/4.0/. The image was modified from the original.

In Parkinson's disease, frequency spectra tend to show peaks in the beta range



Frequency spectrum during rest in a cohort of patients (n = 14) with PD in medication ON and medication OFF states. With medication ON, there is a reduction in low frequency beta power, but not high beta power. Peaks can also be seen in the theta/alpha, gamma, and high frequency (250-350 Hz) bands. The small change in gamma was attributable to 3 out of 15 subjects.

HFO = High-Frequency Oscillations

López-Azcárate J, Tainta M, Rodríguez-Oroz MC, et al. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. J Neurosci. 2010;30(19):6667-77. Used with permission from the Journal of Neuroscience.

SECTION 2:

LFP and disease state overview

LFPs in disease states: overview

LFPs have been associated with normal physiological brain function as well as pathological brain function and disease states. The majority of research on LFPs in subcortical brain 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 strong signal of interest. The relationship of LFP frequency bands to symptoms in other indications is still emerging, although the data that does exist generally supports an association of the theta/alpha band with tremor and low frequency bands with dystonia. The following tables overview the current perspective of LFPs across movement disorder indications for DBS.

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			●	●	●
PD: Tremor symptoms		●			●
Essential Tremor		●	●	●	
Dystonia (tonic)	●		●		● (60-90 Hz)
Dystonia (phasic)		●	●		● (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**

Based on: 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.

For information on **LFPs and Epilepsy go to Section 4**

Typical LFP frequency bands in movement disorders

Movement disorder	Local field potential (frequency peak)	
	Increased synchronization or power	**Reduced synchronization or power**
Parkinson's disease: Untreated symptoms of akinetic-rigidity	Low > high beta (13-20 Hz; longer bursts) Gamma‡ (35-250 Hz; at lower frequencies in this range)	Gamma (35-250 Hz; shifts to higher frequency in this range)
Parkinson's disease: Treated symptoms of akinetic-rigidity	High frequency‡ (250-350 Hz) Gamma‡ (35-250 Hz; at higher frequencies in this range)	Low > high beta‡ (13-20 Hz; shorter bursts)
Parkinson's disease: Untreated symptoms of tremor	Theta/alpha (4-13 Hz) Gamma‡ (35-250 Hz; at higher frequencies in this range) High frequency (250-350 Hz; at higher frequencies in this range)	Beta‡ (13-35 Hz)
Parkinson's disease: **Treated symptoms of tremor**	----------	Gamma (35-250 Hz; at lower frequencies in this range) High-frequency (250-350 Hz; at lower frequencies in this range)
Essential rremor	Theta/alpha (4-13 Hz) Beta‡ (13-35 Hz)	----------
Levodopa-induced dyskinesia	Theta/alpha (4-13 Hz) Gamma‡ (60-90 Hz)	Beta‡ (13-35 Hz)
Dystonia‡ (tonic)	Delta (0-4 Hz) Low beta (13-20 Hz; shorter bursts) Gamma (60-90 Hz)	----------
Dystonia‡ (phasic)	Theta/alpha (4-13 Hz) Low beta (13-20 Hz; shorter bursts) Gamma (60-90 Hz)	----------

‡ also associated with initiation and facilitation of normal voluntary movements

Adapted from: 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.

For information on **LFPs and epilepsy go to Section 4**

SECTION 3:

Use of BrainSense™ technology

Opportunities for brain sensing in clinical practice

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

Neurophysiologic correlates of disease

- Using sensing to gain familiarity with LFP relationship to factors such as electrode placement, medication states, stimulation, disease characteristics, and clinical symptoms.[1]

Objective approach to medical management

- Using LFP signals to inform therapy changes to stimulation and treatment strategy.[2,3,5]

More efficient contact selection

- Using "sensing maps" as additional data to inform stimulation programming; contacts with high beta power tend to be clinically effective contacts.[2,4]

Personalized patient treatment

- Using symptom-specific brain activity patterns and their response to therapies to manage symptom fluctuations over time.[2,3]
- Using BrainSense™ Streaming to help determine stimulation amplitude for best beta-band power reduction[2] and determine therapeutic stimulation threshold.[5]
- Investigating symptoms that may be related to other bands, such as gamma.[2,3]
- Potentially offering a more meaningful approach programming therapies for patients with delayed responses, such as dystonia.[2,6]

Monitoring patient events

- Adjustment of stimulation informed by unique signals present during various events, including on/off stimulation or medication and side effects.[3]
- Using Event markers for monitoring of specific symptom manifestations in a real-life environment which is ideal for slow-changing dynamics (minutes to hours), such as off periods, medication-induced dyskinesias, or sleep.[2]

Limitations

- The use of sensing to inform clinical decision-making remains unestablished.[1]
- Sensing and stimulation contacts are restricted to predefined combinations; in order to sense, stimulation is limited to the middle contacts.[1,2] 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™ directional 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 or freezing) 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]

Featured Percept™ PC articles

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. https://www.tandfonline.com/doi/full/10.1080/17434440.2021.1909471

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).

3 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.

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 Feldmann LK, Neumann WJ, Krause P, et al. Subthalamic beta band suppression reflects effective neuromodulation in chronic recordings. Eur J Neurol PMID: 33675144 PMID: 33675144. 2021.

6 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.

BrainSense™ features: purpose and use

Feature	Potential clinical relevance
BrainSense™ setup	
In order to use all features of BrainSense™ technology (with the exception of BrainSense™ survey), the user must first setup LFP sensing using BrainSense™ setup and select a frequency band of interest (approx. 5Hz wide) to track while the patient is out of office. **Use:** In-clinic, with approx. 90 seconds measurement for setup.	This is the first step in setting up BrainSense™ technology for chronic tracking of an LFP signal and checking for any impact of artifact on that signal.
BrainSense™ survey	
In Broad spatial overview of LFP signals measurable from both hemispheres of the patient with stimulation off. **Use:** In-clinic, with approximately 40 sec measurement duration for each grouping of electrode level pairs chosen to survey and approximately 70 sec measurement duration for each grouping of segment electrode pairs chosen to survey.	Check to confirm LFP activity is present at that visit and further sensing feature work is viable. View whole spectrum frequency domain (0-96.68 Hz). Check LFP signals between segmented pairs of contacts.
BrainSense™ timeline‡	
Once BrainSense™ setup has been completed, the Timeline can be used to analyze the out of-office data when the patient returns to the clinic. This is used to assess the data for changes in LFP activity (approx. 5Hz wide) that may occur over the course of a day(s). **Use:** Outside-clinic	This feature records a single LFP signal of interest data (ie, the power of a specific frequency band in the LFP signal) chronically for follow-up data analysis in-clinic via the Timeline view. View fluctuation of selected frequency band.
BrainSense™ events‡	
Once BrainSense™ setup has been completed, BrainSense™ events (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 (eg, 'symptom' or 'medication intake') 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 approx. 30 sec after patient marking an event.	• Allows LFP signal over a broad spectrum to be recorded at the time of a marked patient event. • View whole spectrum frequency domain. • A previously configured sensing group must be the active therapy group in order to collect LFP Snapshots.
BrainSense™ streaming‡ψ	
Once BrainSense™ setup has been completed, the user can view the LFP power in a selected frequency band in real-time, by streaming the data to the clinician tablet. This is used to observe changes in the LFP during active stimulation programming or while instructing and observing the patient performing activities. Moreover, streaming can be used to collect time domain data from the selected channel(s) for offline analysis and signal processing. **Use:** In-clinic, with no limit on streaming measurement duration, with or without stimulation.	Allows the physician to view the quantitative impact of stimulation or other events (such as medication) on LFP power. View selected frequency band.

‡ The system eligibility and battery longevity (Manual Document Number: M929534A122 REV. A) states that passive sensing influences battery longevity. The impact of continuous passive sensing is shown according to overall battery longevity estimates in the table below.

Table 3 [of the manual]: Influence of continuous passive sensing on battery longevity (All values are approximate)

Estimated battery longevity	11 years	5 years	2.5 years
Longevity reduction per month of continuous passive sensing	11.7 days	5.4 days	2.9 days

ψ Long clinician telemetry sessions with the Percept™ PC INS do have a small impact on the INS longevity. 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.

Selected publications using BrainSense™ technology with patients

Koeglsperger T, Mehrkens JH, Botzel K. Bilateral double beta peaks in a PD patient with STN electrodes. Acta Neurochir (Wien). 2021. 163(1):205-209.

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.

Feldmann LK, Neumann WJ, Krause P, et al. Subthalamic beta band suppression reflects effective neuromodulation in chronic recordings. Eur J Neurol. 2021. Jul;28(7):2372-2377.

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 band activity was suppressed in response to stimulation while bradykinesia improved.

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.

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.

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.

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. Apr 19;8(1):44.

https://www.nature.com/articles/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.

BrainSense™ survey

Determines if a signal is detectable between two contact pairs.

May provide objective information for contact selection.

Shows signals in the theta, alpha, beta, and gamma ranges (0 to 96.68 Hz).

Factors that may impact LFP signals and help explain variability include:

1. Medications suppressing beta
2. Tremor suppressing beta
3. Lead location
4. Voluntary movement impacting beta

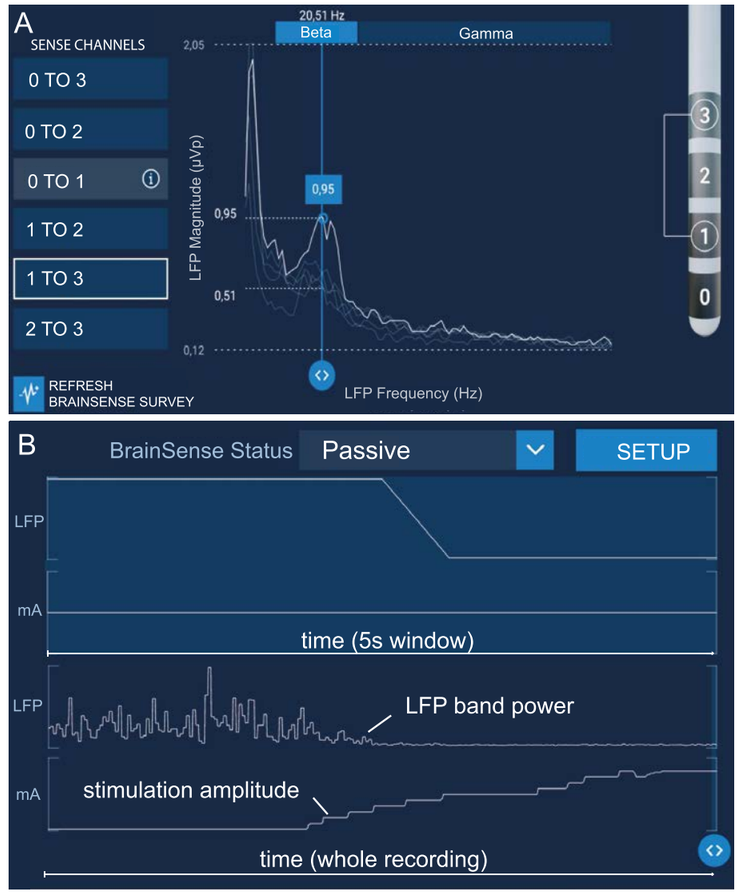
BrainSense™ streaming

View the quantitative impact of stimulation or other events (such as medication) on LFP power in a chosen frequency band.

May provide objective information for titration of stimulation amplitude and prevention of unnecessary overstimulation.

May support programming decisions by identifying signals related to the appearance of stimulation-induced side effects.

Example of BrainSense™ survey and streaming

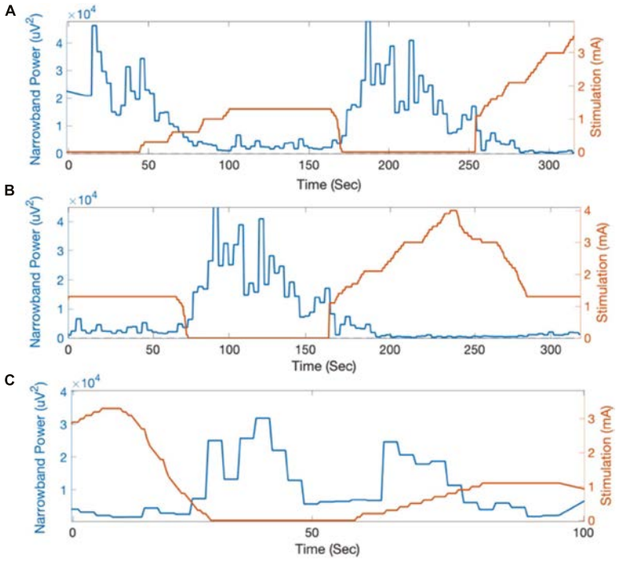


A) Screenshot of the BrainSense™ survey recording from a patient with Parkinson's disease in a Med OFF condition. The tablet displays the LFP magnitude (µ volts peak, µvp) vs frequency (Hz) (about 21 s of data for each pair). The highest beta power was seen when recording between contacts 1 and 3. Monopolar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

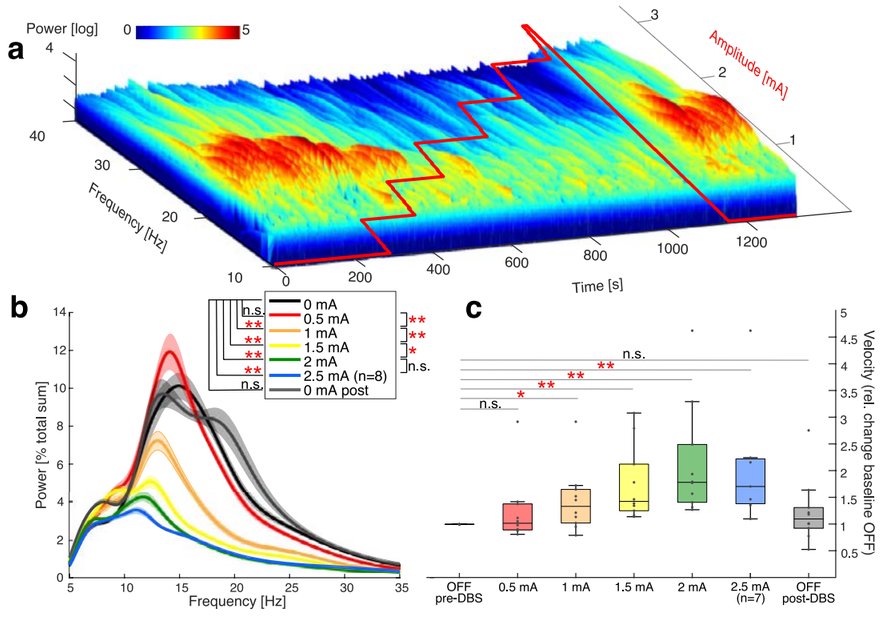
B) Power in a selected frequency band was tracked in BrainSense™ streaming mode in a patient with Parkinson's disease. With this feature, the tablet displays the selected power and stimulation amplitude in real time and over the entire recording. Increasing stimulation amplitude resulted in a decrease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

BrainSense™ Streaming: beta power versus stimulation amplitude

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 postimplant.



Movement velocity increases with stimulation and correlates to suppression of beta LFPs 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).

BrainSense™ timeline

Provides a chronic longitudinal map of a single LFP signal of interest data.

May help identify daily fluctuations in symptoms or isolate events that appear to change the LFP profile.

Upper and lower threshold can be set to identify the desired LFP levels, with one representing no/acceptable symptoms and the other indicating no side effects.

BrainSense™ event markers

Up to 4 patient event names can be programmed to collect information on when and how often a patient is experiencing an event. Separately, each event can be programmed to capture an LFP snapshot at the time of the button press to provide sensing information.

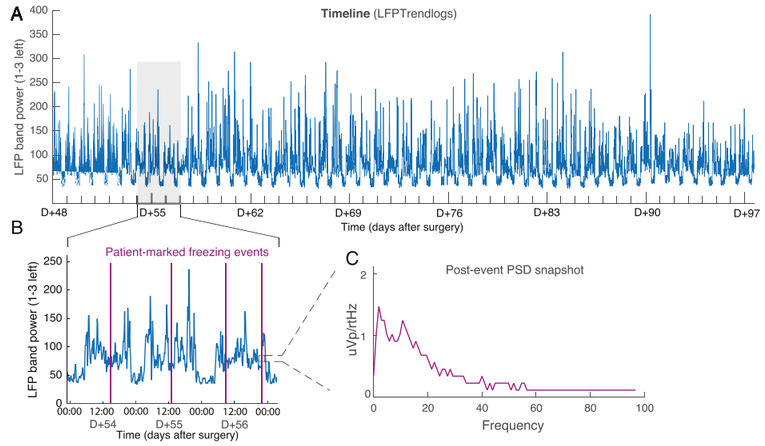
Example event markers for movement disorders:

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

Example event markers for mpilepsy:

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

Example of BrainSense™ timeline and event markers



A) Example of a patient with Parkinson's disease with a beta peak at 23.39 Hz. BrainSense™ timeline was used to record the power in this peak while the patient was at home. Stimulation was on contact 2 (2.9 to 3.2 mA), with recording from contacts 1-3. Data is shown between day 48 and day 97 after surgery.

B) A close-up of 3 days of recording is shown. Daily fluctuations in power are apparent, as well as circadian-related power oscillations with a decrease in beta power at night. The patient used the Events option on their programmer to manually log events related to freezing of gait* (B, purple lines).

C) Each logged event can capture a power spectrum density (PSD) snapshot starting at the time of the button press; a PSD related to one freezing event logged by the patient is shown in Panel C. Limitations of this function were discussed in the related paper: only one predefined power band can be tracked, power in the LFP recordings is averaged over 10 min, LFP Event snapshots may miss short episodic events, and recording of events requires patient compliance.

*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.

Publications using event markers

Citation	Indication and target	Events	Results
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	• 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.
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	• Freezing of gait*	• 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 might not be PSD modulation related to freezing, or 3) the device could not capture existing modulations.
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.	Epilepsy ANT	• Absence seizure** • Focal/partial seizure • Generalized seizure** • Took medication	• The PSD generated by the event marker showed a peak at 2.93 Hz for absence and 8.79 Hz for focal seizures. • The PSD helped to identify the frequencies of interest to track with Timeline. • Events could not be captured during the generalized seizures due to the severity of these episodes. • No peak was apparent during the medication event.

*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.

**Medtronic DBS Therapy for Epilepsy is not approved for the treatment of absence seizures or primary generalized seizures.

FEATURED ARTICLE:

Beta location and frequency distribution

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: STN

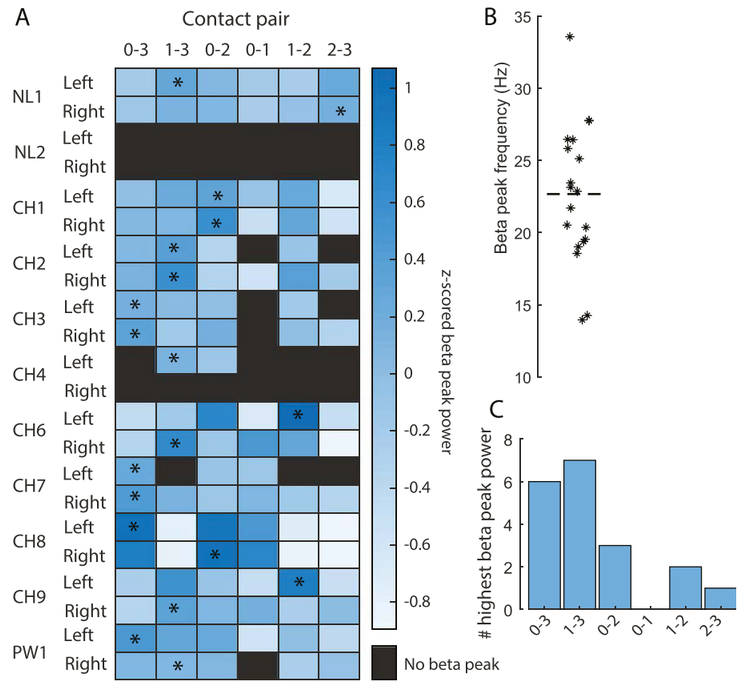
Design: BrainSense™ technology features were used to record LFPs in clinic and during at-home device use.

Results

- BrainSense™ survey identified a beta peak in 19 of 22 STNs with an average frequency of 22.6 Hz (SD, 4.9 Hz). No peak could be identified in 3 STNs.
- Location of the maximum peak varied, but most peaks were seen either on contact pairs 1-3 or pair 0–3.
- 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 STNs.
- Modulation of beta power due to medication, DBS, and movement could be captured with the device.

Notes

The authors did not report on complications.



A) A total of 22 STNs were observed in 11 patients using Percept™ PC with BrainSense™ survey and BrainSense™ streaming. Beta peak power (13-35 Hz) was normalized by STN; black indicates that no beta peak was identified. The contact pair with the maximum beta peak is indicated by a star.

B) The range of peak beta frequencies across the 19 STNs with beta identified on at least one contact pair; the horizontal dashed line indicates the average frequency.

C) Number of times each of the contact pairs was identified as one with maximum beta power across the 19 STNs with a beta peak.

Directional sensing

Several articles have reported sensing from directional leads in an intraoperative setting or in a postoperative setting with externalized leads and an external bench sensing system. The use of these signals for contact selection continues to be investigated.

Directional signals from the STN and their relationship to clinical outcomes were demonstrated by Tinkhauser et al (2018). In their analysis, one of the 2 contacts with the highest beta was also the most clinically effective contact in 84% of cases. Telkes et al (2020) observed directional LFPs in patients with PD (n = 8) during intraoperative recording. Positive trends with bradykinesia/rigidity and LFPs in the dorsoanterior direction (p = 0.087) and with axial scores in the dorsomedial direction (p = 0.072) were observed. Aman et al (2020) showed that directional signals can also be recorded from the internal globus pallidus in patients with PD (n = 3).

In the future, algorithms that consider LFP power across the full spectrum may add predictive value for clinical management and programming. For example, Shah et al (2022) studied whether a spectrum of LFP recordings conducted at rest and during movement could help define contact selection and predict outcomes (n = 17). They suggested that combining imaging with electrophysiological markers maybe a way to create more efficient approach to clinical practice and DBS programming.

Disclaimer: These studies did not use the SenSight™ directional DBS leads or BrainSense™ technology.

Sensing with 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.

Telkes I, Sabourin S, Durphy J, et al. Functional Use of Directional Local Field Potentials in the Subthalamic Nucleus Deep Brain Stimulation. Front Hum Neurosci. 2020 Apr 28;14:145.

Aman JE, Johnson LA, Sanabria DE, et al. Directional deep brain stimulation leads reveal spatially distinct oscillatory activity in the globus pallidus internus of Parkinson's disease patients. Neurobiol Dis. 2020;139:104819.

Shah A, Nguyen TK, Peterman K, et al. Combining Multimodal Biomarkers to Guide Deep Brain Stimulation Programming in Parkinson Disease. Neuromodulation. 2022 Feb 23:S1094-7159(22)00038-1.

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 postimplant 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.

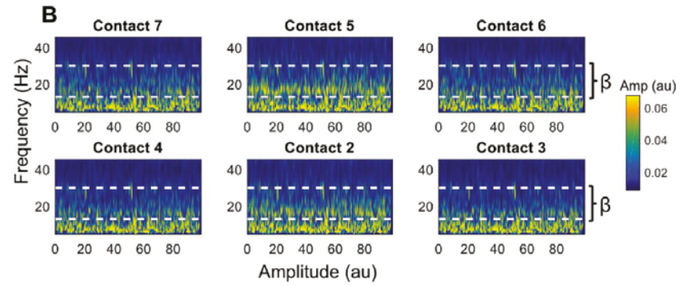
Notes

The authors did not report on complications.

FEATURED ARTICLE:

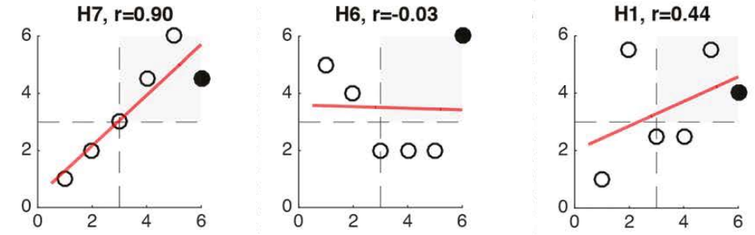
Sensing on directional leads *continued*

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.



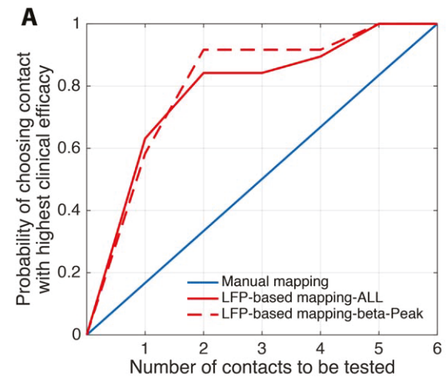
Tinkhauser G, Pogosyan A, Debove I, et al. Directional local field potentials: A tool to optimize deep brain stimulation. Mov Disord. 2018 Jan;33(1):159-164. Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). Only panel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

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.

Disclaimer: These studies did not use the SenSight™ directional DBS leads or BrainSense™ technology.

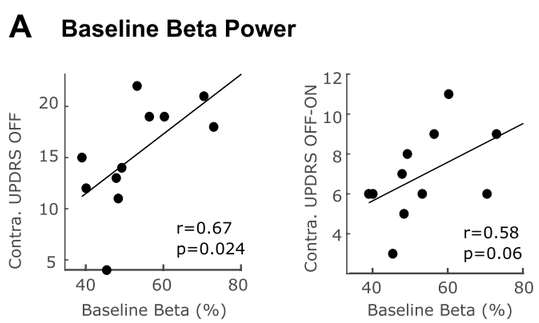
SECTION 4:

A historical look at LFPs in Parkinson's disease

How do LFPs relate to the symptoms of Parkinson's disease?

Literature is fairly consistent in supporting an association between the presence of the beta band and the symptoms of bradykinesia and rigidity. Exaggerated beta band activity has been shown to decrease following antiparkinsonian medication and in a voltage-dependent manner with DBS. A reduction in persistent beta band activity has also been associated with improvements in UPDRS-III scores after DBS implant. Conversely, an increase in beta band has been observed with increased presence of bradykinesia. The presence of the beta band in patients with tremor dominant symptoms has been less clear. Other frequency bands, including activity around the tremor frequency (e.g. 4-5 Hz) and high frequency activity (e.g. 35-55 Hz), have had some association with rest tremor. Beta energy is lower during movement such as walking.

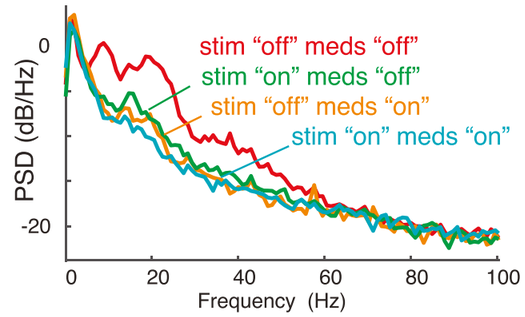
Beta correlation with symptoms



Baseline beta correlated with the contralateral UPDRS part III motor hemibody score in the OFF state (panel A. left) and the differences between the OFF vs ON state (panel A, right).

Wiest C, Tinkhauser G, Pogosyan A, et al. Local field potential activity dynamics in response to deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neurobiol Dis. 2020 Sep;143:105019. Image used under a Creative Commons Attribution 4.0 International License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/). The figure was modified to show only Panels A and B.

Beta LFPs are attenuated with medication and stimulation



LFP recordings from the Percept™ PC device in a patient with Parkinson's disease. LFPs were recorded under 4 conditions: 1) Med OFF, Med ON only, Stim ON only, and combined Med and Stim ON. Suppression of beta power shows a cumulative effect with both Med and Stim ON.

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/). Only panel A of the figure is shown; no modifications were made to the image in panel A.

Related 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.

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 sffects

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]

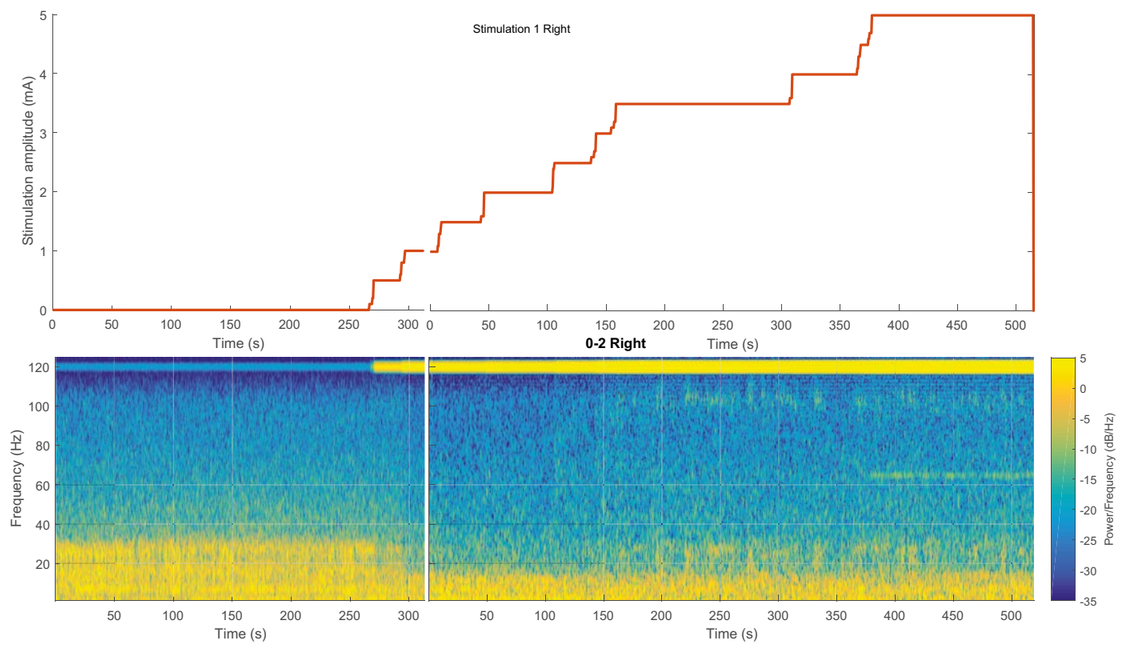
Current perspective of LFPs in Parkinson's disease

	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.

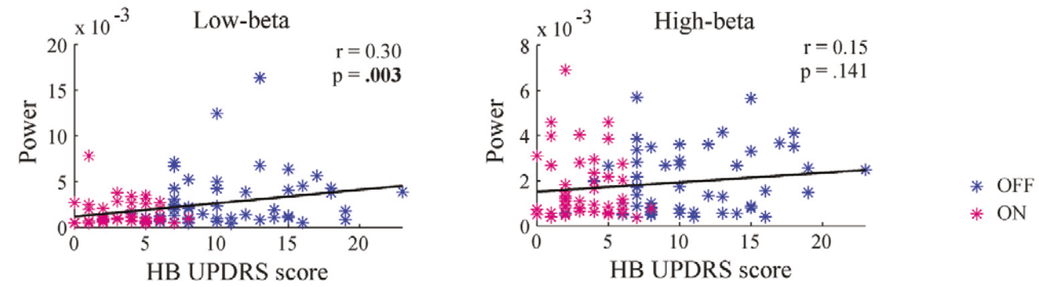
Higher stimulation amplitude decreases beta power but may induce gamma oscillations



Data recorded using the Percept™ PC device with BrainSense™ technology shows that power in the beta frequency range (ed, 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.

Symptom improvement correlates with changes in beta power



Regression analyses between hemibody bradykinesia/rigidity UPDRS scores and mean beta power in 33 patients with Parkinson's disease showed a significant correlation with low beta but not high beta. OFF medication state data are depicted in blue; ON state in pink. Note that OFF and ON states were combined in the computation of the regression coefficients. Correlation coefficients and p-values are indicated for each plot with significant relations in bold.

van Wijk BC, Beudel M, Jha A, Oswal A, Foltynie T, Hariz MI, Limousin P, Zrinzo L, Aziz TZ, Green AL, Brown P, Litvak V. Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. Clin Neurophysiol. 2016 Apr;127(4):2010-9. 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.

The persistence of LFPs over time in patients with Parkinson's disease.

Several studies have investigated the persistence of beta band LFPs over time in patients with Parkinson's disease. While LFP magnitude and peak frequency often differ between patients while at rest, beta activity in individual study patients has been generally consistent when recorded 1 year or more after lead implant. However, variability has also been described, with beta LFPs decreasing or increasing in magnitude from baseline measurements.

Related articles

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. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8382799/

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/

Hanrahan SJ, Nedrud JJ, Davidson BS, et al. Long-Term Task- and Dopamine- Dependent Dynamics of Subthalamic Local Field Potentials in Parkinson's Disease. Brain Sci. 2016;6(4):E57. http://dx.doi.org/10.3390/brainsci6040057

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

Giannicola G, Rosa M, Servello D, et al. Subthalamic local field potentials after seven-year deep brain stimulation in Parkinson's disease. Exp Neurol. 2012;237(2):312-7. https://www.ncbi.nlm.nih.gov/pubmed/22735488

Abosch A, Lanctin D, Onaran I, et al. Long-term recordings of local field potentials from implanted deep brain stimulation electrodes. Neurosurgery. 2012;71(4):804-14. https://www.ncbi.nlm.nih.gov/pubmed/?term=22791039

FEATURED ARTICLE:

Long-term beta

Anderson RW, Wilkins KB, Parker JE, et al. Lack of progression of beta dynamics after long-term subthalamic neurostimulation. Ann Clin Transl Neurol. 2021 Oct 11.

Link: 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

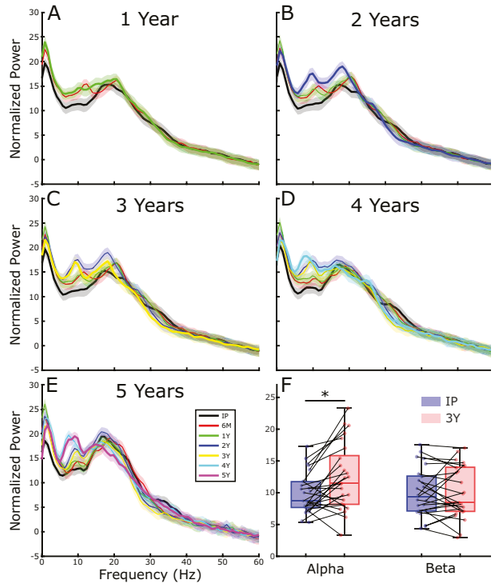
Conditions: Med OFF, DBS OFF

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.

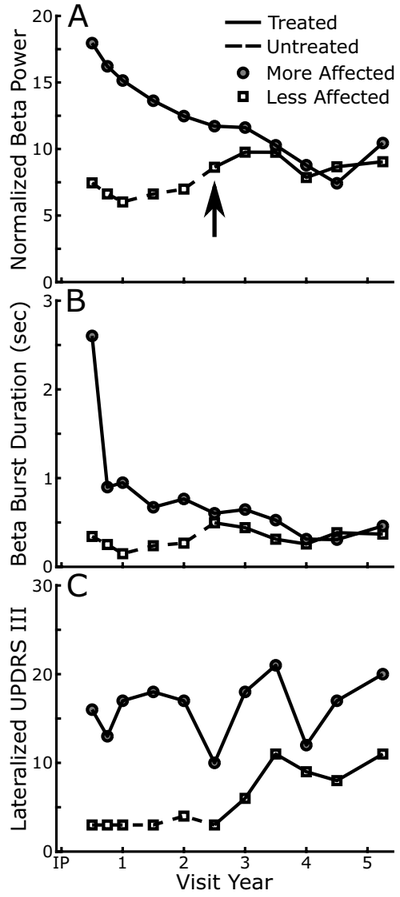
Notes and complications

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.



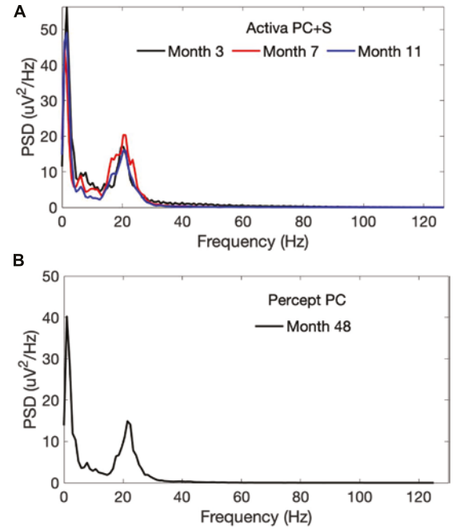
Off therapy average STN LFP power spectral density analysis before and after DBS. A) 33 STN recordings conducted at initial programming (IP), and 6- and 12-months postimplant. B) 25 STN recordings at 2 years. C) 25 STN recordings at 3 years. D) 16 STN recordings at 4 years. E) 6 STN recordings at 5 years. 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.

Case example: beta progression in an untreated hemisphere



Case example of one patient with bilateral STN leads, but activation of DBS only for the most affected side. Beta power on the treated side tended to decrease over time. After about 2 years, beta power began to increase in the less affected STN (arrow) and burst durations began to increase. When DBS was activated on the less affected side (solid line), beta continued to increase, but then stabilized.

Case example: beta continuity switching from Activa™ PC+S to Percept™ PC



Case example of LFPs in an individual patient initially implanted with the Activa™ PC+S device (Panel A) which was replaced with a Percept™ PC neurostimulator (Panel B). Dates indicate recording time from initial lead implantation. A beta peak at approximately 20 Hz was seen consistently in this patient.

Potential prevalence of LFP signals in patients with Parkinson's disease.

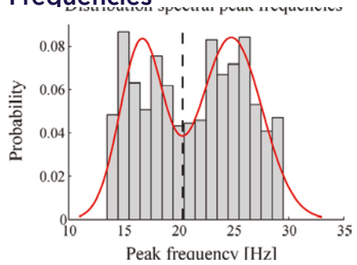
The ability to visualize LFP signals in patients may be dependent on several factors: the disease state, the physiology and anatomy of the patient, the activity state of the patient, the recording capabilities of the sensing system, and the signal-to-noise ratio capabilities of the system. Several studies have evaluated the occurrence of beta signals after standard lead implant procedures using microelectrode recording and symptom assessment. In one study, signals were identified in more than 99% of leads (129 of 130 leads), but varied in their peak frequency (from 8 to 35 Hz) and were more prevalent in the dominant hemisphere. A multicenter retrospective analysis found sufficient detectable beta signal in approximately 80% of patients.

Citation	Number of patients	Prevalence of beta	Additional information
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)	> 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%)
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 (13 to 35 Hz) with sufficient power for detection (0.8 µV/rtHz)	approximately 80% of patients	Limitations: • Conference presentation, not peer-reviewed. • Potential patient selection bias
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)	86% (19 of 22) 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).

Characterizing beta LFP frequency and location in patients with Parkinson's disease.

The fact that beta characteristics are unique to each patient is becoming more and more clear with additional research. Interesting observations include the variability in the peak beta frequencies between patients, ranging between about 15 to 30 Hz, and the finding that some patients have a "double beta peak." Interestingly, these double beta peaks may respond differently to medication, stimulation, and voluntary movement.

Distribution of Spectral Peak Frequencies



Histogram of peak and subpeak frequencies for 33 subjects with Parkinson's disease, on and off medication, showing a bimodal pattern. The red overlay is the optimal fit of a mixture of two normal distributions. The first distribution had its mean at 16.6 Hz; the second distribution at 24.79 Hz.

van Wijk BC, Beudel M, Jha A, Oswal A, Foltynie T, Hariz MI, Limousin P, Zrinzo L, Aziz TZ, Green AL, Brown P, Litvak V. Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. Clin Neurophysiol. 2016 Apr;127(4):2010-9. 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 image.

FEATURED ARTICLE:

Multiple beta peaks

Plate A, Hell F, Mehrkens JH, et al. Peaks in the beta band of the human subthalamic nucleus: a case for low beta and high beta activity. J Neurosurg. 2021 Sep 24:1-9.

Objective

To characterize the beta band peaks in patients with PD and study the effect of different types of movement and DBS on these peaks.

Methods

Patients (N): 38

Recording: externalized leads

Target: STN

Conditions: rest, hand opening/closing

Patients (N): 10

Recording: Activa™ PC+S

Target: STN

Conditions: stim OFF, 50% stimulation, 100% stimulation; standing, slow walking, fast walking

Results

Characterization of the beta peak found that the majority of STNs had a single beta peak (n = 51), several had 2 peaks (n = 8), and a total of 17 did not have a peak. A majority of patients (n = 24) had a peak in both hemispheres.

Peaks clustered around 2 frequencies, a low beta frequency around 15 Hz and a high beta frequency around 27 Hz.

Hand motion did not influence the magnitude of the beta power in any frequency range; however, walking reduced power in the high beta peaks. DBS decreased power in both beta peaks.

The location of contacts with low and high beta power did not differ.

Group	Number
All STNs (n = 76)	
No peak	17
One peak	51
Two peaks	8

Group	Number
All Subjects (n = 38)	
No peak	3
Peak on one side	11
Peak on both sides	24

Notes

Recordings were conducted with Meds OFF or after withdrawal of dopamine agonists.

The authors did not report on complications.

FEATURED ARTICLE:

Case report of double beta peaks

Koeglsperger T, Mehrkens JH, Bötzel K. Bilateral double beta peaks in a PD patient with STN electrodes. Acta Neurochir (Wien). 2021 Jan;163(1):205-209.

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7778623/

Objective

To report on continuous LFP recording using the Percept™ PC neurostimulator and the impact of different motor and stimulation states on signals within the beta-frequency range.

Methods

Case Report

Recording: Percept™ PC

Target: STN

Conditions: rest, walking

Results

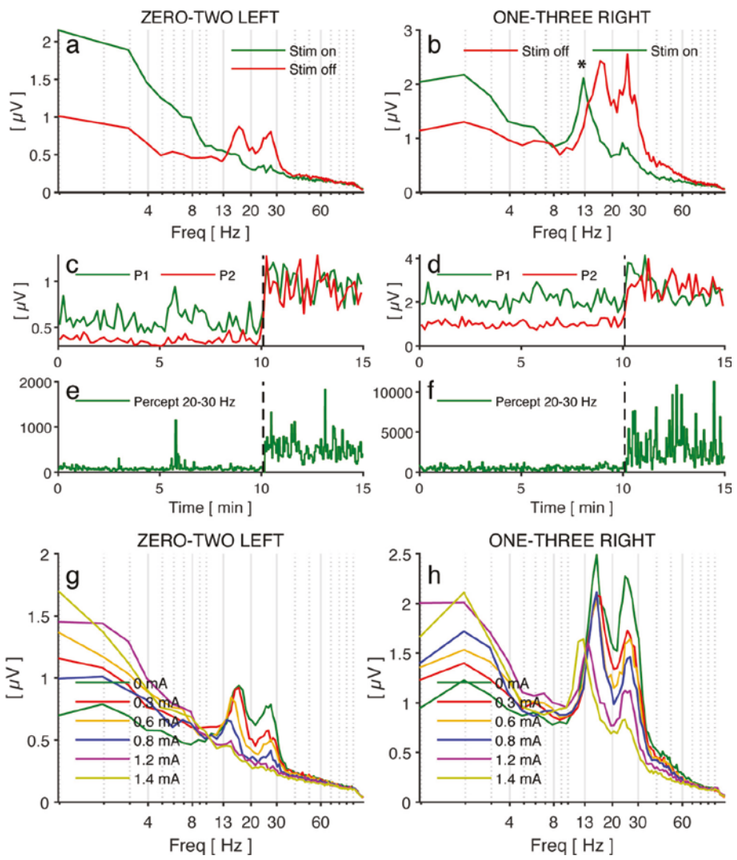
The LFP spectra showed a double-beta peak (at 15 Hz and 25 Hz) in both hemispheres (a, b). With stimulation, the peaks decreased, but a new peak emerged on the right side (b). LFP power gradually decreased with increasing DBS amplitudes (g, h). On the right side, while the 25 Hz-peak showed a gradual decrease, the 15 Hz peak shifted to a 13-Hz peak with increasing current (between 0.8 mA and 1.2 mA).

Beta peaks on the left side were suppressed with DBS ON and during walking. Beta on the right side was partially suppressed with walking and the 13 Hz peak reappeared with DBS ON during walking. Therefore, walking movement had suppressive effect on beta peaks on the right side with DBS ON, but it was incomplete.

Notes

The authors did not report on complications.

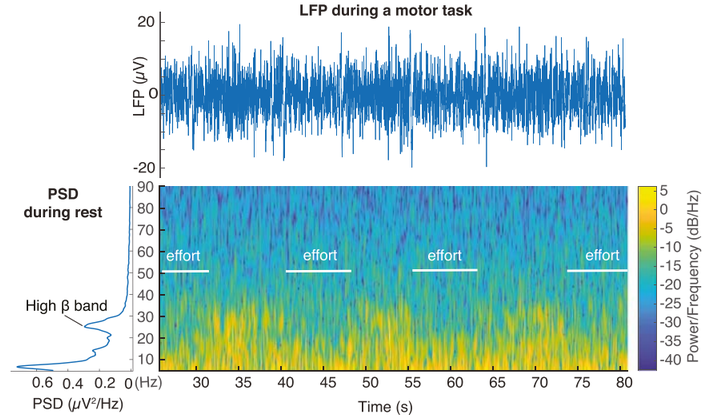
Limitation: this is a single-patient case report and the findings may not be representative of all patients.



Case report featuring a patient with double beta peaks recorded with the Percept™ PC device. Frequency spectrograms from the left (a) and right (b) hemisphere with stim ON and stim OFF. Recordings analyzed in Matlab display the amplitude of a 15 Hz band (P1) and a 25 Hz band (P2) over time (c and d). When stimulation was turned off (dashed line) peaks increased in power. A band between 20 and 30 Hz was also recorded form the Percept™ PC device (e and f). Power in this frequency band is suppressed until the stimulation is turned off (dashed line). Gradually increasing stimulation intensity caused power in the beta bands to decrease (g and h). Power in the left lead gradually reduced with stimulation. In the right hemisphere, power in the 25 Hz peak decreased with stimulation while the 15 Hz peak tended to remain and shift to 13 Hz.

Changes in beta during a motor task

Example of movement-related changes in beta power in a patient with STN DBS for Parkinson's disease. BrainSense™ streaming was used to collect raw LFP signals at rest and during knee extensions with medication OFF and stimulation OFF. Signals were processed into PSD estimates which showed expected changes in movement-related beta power (indicated by the "effort" labels).



Changes in beta related to circadian rhythms

More evidence is supporting the finding that beta power tends to fluctuate in a circadian pattern. See the figure highlighting **BrainSense™ timeline** for an example (page 17).

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

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.

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:

Low gamma and movement

Wiest C, Tinkhauser G, Pogosyan A, et al. Local field potential activity dynamics in response to deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neurobiol Dis. 2020;143:105019.

Objective

To investigate how STN LFP activity changes over time following the onset and offset of DBS.

Methods

Patients (N): 14 PD

Recording: externalized leads/Bench recording, 2 to 5 days postimplant

PD target: STN

Design: recordings conducted with patients at rest with blocks of 130 Hz DBS. Evoked resonant neural activity (ERNA) was evaluated.

Results

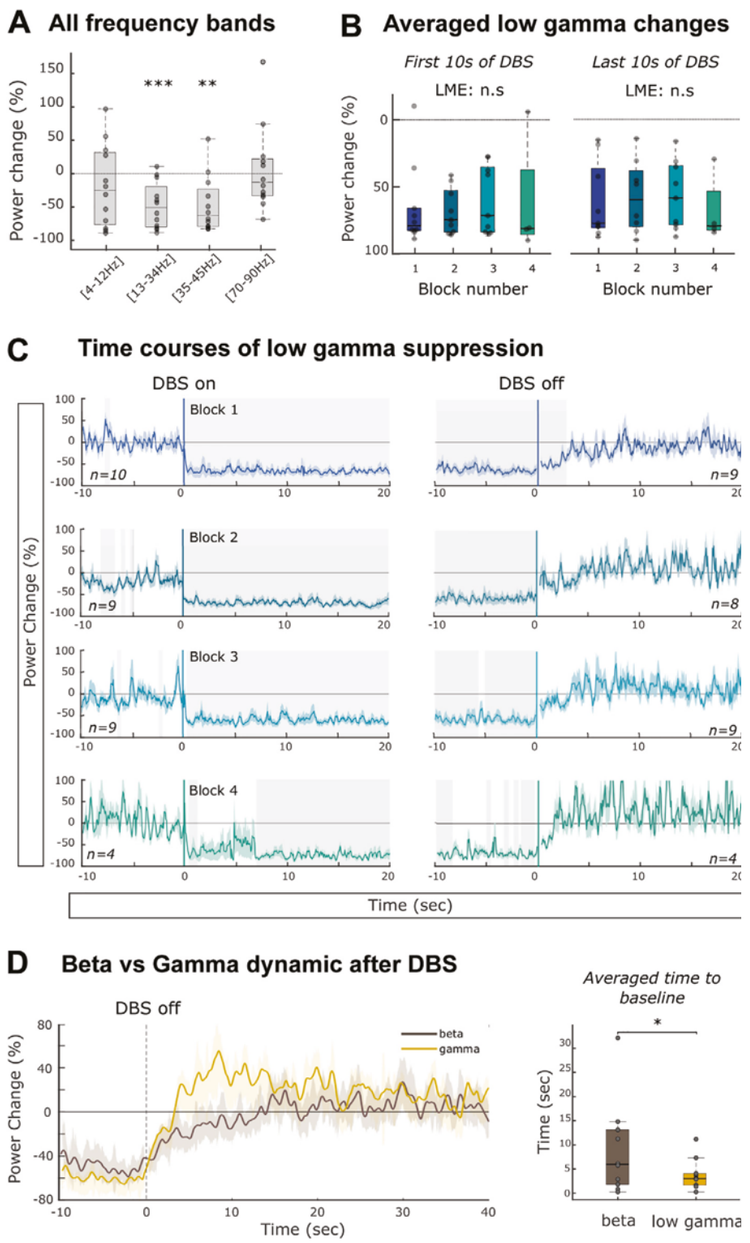
- Beta band activity was suppressed within 0.5 s of DBS onset.
- Spontaneous low gamma band (35-45 Hz) activity was also suppressed with DBS.
- Baseline beta power correlated with the contralateral UPDRS motor hemibody score OFF medication (r = 0.67, p = .024).
- Baseline beta power and the UPDRS difference between OFF-ON medication showed a trend toward correlation (r = 0.58, p = .06).

Notes

Low gamma activity is thought to be involved in coding voluntary movement. Its suppression by DBS may point to non-specificity of stimulation and perhaps is connected to DBS-related motor side effects.

The results of this small study may have been confounded by postoperative stun effects.

The authors did not report on high gamma activity.



Similar to the DBS-induced suppression of beta activity, power in the low gamma band (35-45 Hz) decreased with DBS.

A) Average power in 4 frequency bands showed a significant decrease in beta and low gamma power (** $p < 0.01$; ***$p<0.001$).

B) Averaged low gamma power changes in the first and last 10 seconds of DBS. Power was similar across all stimulation blocks.

C) When signals were aligned to the start of the stimulation, an abrupt reduction in low gamma power was observed, starting after 125 to 375 ms across the four stimulation blocks and maintained throughout the entire stimulation. Gray shading indicated the periods during which low gamma was significantly different from zero.

D) After DBS is stopped, gamma power returned to baseline more quickly than beta power (* $p < 0.05$).

FEATURED ARTICLE:

FTG in DBS with Meds OFF

Wiest C, Tinkhauser G, Pogosyan A, et al. Subthalamic deep brain stimulation induces finely-tuned gamma oscillations in the absence of levodopa. Neurobiol Dis. 2021 May;152:105287.

Objective

To investigate whether finely tuned gamma (FTG) in the 60 to 90 Hz range shows similar characteristics during DBS with Meds OFF as previously reported with Med ON.

Methods

Patients (N): 14 PD

Recording: externalized leads/ Bench recording, 2 to 5 days postimplant

PD target: STN

Design: medication was withdrawn overnight. Recordings were conducted with patients at rest during multiple blocks of stimulation.

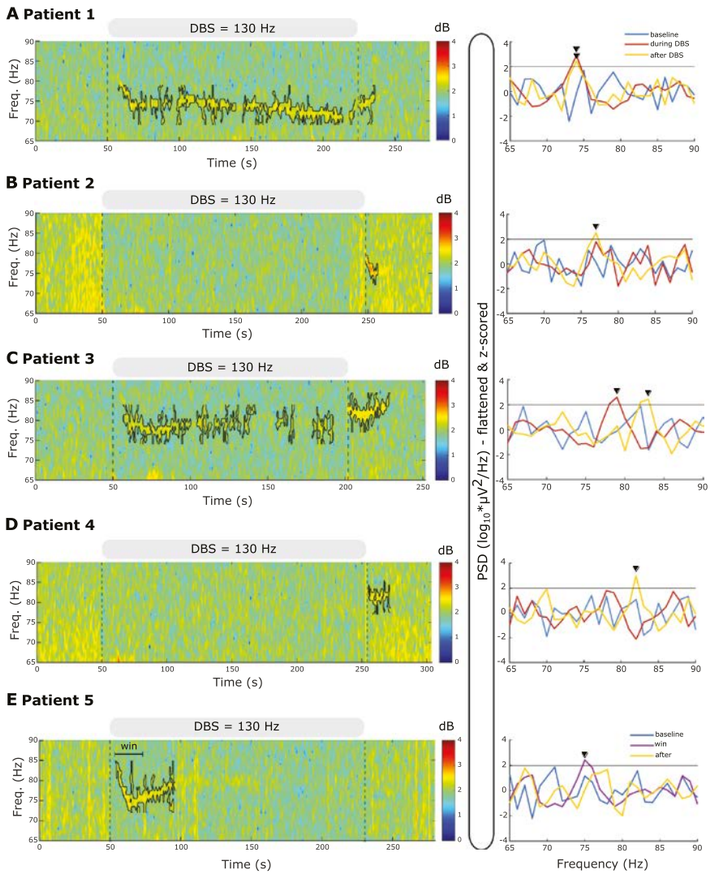
Results

- In 5 of the 14 patients, FTG was induced de-novo by DBS in the absence of dyskinesias.
- In some cases, FTG remained after stimulation stopped or began only after DBS ceased.
- FTG frequencies did not shift with changing stimulation frequency while off medication.
- FTG seen with Meds OFF is not likely due to simple entrainment by DBS.

Notes

The authors conclude that FTG is a network phenomenon behaving differently in the off-medication state. In this study, dyskinesias were not seen with the appearance of FTG; the authors hypothesize that "the FTG induced by stimulation in the off medication state may be a trait marker of the propensity for dyskinesias" at best.

The results of this small study may have been confounded by postoperative stun effects. Only a minority of patients showed an FTG signal.



Finely-tuned gamma oscillations were induced de-novo by DBS (130 Hz) in the absence of dyskinesias in a third of the cohort. Three patients displayed FTG during DBS (patients 1, 3, and 5), slightly delayed from stimulation onset. FTG outlasted DBS in two patients (patients 1 and 3), and in two other cases FTG started only after the cessation of DBS (patients 2 and 4). A broad, low gamma rebound was also seen in 4 of 5 patients with FTG (data not shown).

A-E (left): time-frequency spectrograms displaying response to blocks of DBS (gray bar at the top of the trace).

A-E (right): Power spectral densities (PSD) before DBS, during the DBS block, and after cessation of DBS. Peaks above the threshold (set at 2 standard deviations above average baseline) were considered significant (black arrowheads).

Characterizing LFPs in the GPi of patients with Parkinson's disease.

Pallidal recordings, while less well-studied, tend to show the same LFP characteristics as those found in the STN.[1]

Related articles

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

Eisinger RS, Cagle JN, Opri E, et al. Parkinsonian Beta Dynamics during Rest and Movement in the Dorsal Pallidum and Subthalamic Nucleus. J Neurosci. 2020;40(14):2859-2867.

Lofredi R, Neumann WJ, Brucke C, et al. Pallidal beta bursts in Parkinson's disease and dystonia. Mov Disord. 2019;34(3):420-424

Wang DD, de Hemptinne C, Miocinovic S, et al. Pallidal Deep-Brain Stimulation Disrupts Pallidal Beta Oscillations and Coherence with Primary Motor Cortex in Parkinson's Disease. J Neurosci. 2018;38(19):4556-4568.

AuYong N, Malekmohammadi M, Ricks-Oddie J, et al. Movement-Modulation of Local Power and Phase Amplitude Coupling in Bilateral Globus Pallidus Interna in Parkinson Disease. Front Hum Neurosci. 2018;12:270.

Location of LFPs in the STN, Informing DBS therapy

The possibility of beta LFPs informing DBS lead placement and programming strategy continues to be investigated in the literature.[1] Studies recording from microelectrodes and DBS leads have supported the localization of beta oscillations in the STN, and in particular, the sensorimotor aspect of the STN.[2-5] Use of beta is emerging as an objective signal providing additional information during lead placement, although recent studies suggest information from multiple LFP frequencies and features may provide more predictive input.[6]

Furthermore, the use of beta as a signal of interest for programming DBS therapy continues to be investigated, with several articles showing correlations between contacts with high beta LFPs and contacts selected for clinical therapy.[7-9] Similar to lead targeting, research is investigating the use of multiple LFP frequencies and features to guide programming strategies.[10] The use of beta may also inform programming for segmented leads. Several pilot studies have observed that LFPs may be spatially distributed around segmented contacts, with beta power correlating with clinical severity and therapeutic contacts in the STN[8,11] and globus pallidus internus (GPi).[12]*

*These studies did not use the SenSight™ directional DBS leads or BrainSense™ technology.

Beta localization in the STN

1. 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
2. Horn A, Neumann W, Degen K, et al. Toward an electrophysiological "sweet spot" for deep brain stimulation in the subthalamic nucleus. Hum Brain Mapp. 2017;38(7):3377-3390.
3. Pogosyan A, Yoshida F, Chen CC, et al. Parkinsonian impairment correlates with spatially extensive subthalamic oscillatory synchronization. Neuroscience. 2010;171(1):245-57.
4. Trottenberg T, Kupsch A, Schneider GH, et al. Frequency-dependent distribution of local field potential activity within the subthalamic nucleus in Parkinson's disease . Exp Neurol 2007; 205: 287– 291.
5. Chen CC, Pogosyan A, Zrinzo LU, et al. Intra-operative recordings of local field potentials can help localize the subthalamic nucleus in Parkinson's disease surgery. Exp Neurol 2006; 198: 214–221.
6. Rao AT, Lu CW, Askari A, et al. Clinically-derived oscillatory biomarker predicts optimal subthalamic stimulation for Parkinson's disease. J Neural Eng. 2022 Mar 28;19(2).

Beta and therapeutic contacts

7. 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). (n = 11 patients; LFPs evaluated in 22 STN; clinical contact associated with highest beta (on or between) in all but 3 STNs).
8. 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. (n = 12 patients; 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.)
9. Yoshida F, Martinez-Torres I, Pogosyan A et al. Value of subthalamic nucleus local field potentials recordings in predicting stimulation parameters for deep brain stimulation in Parkinson's disease . J Neurol Neurosurg Psychiatry. 2010; 81: 885–889. (n = 31 patients; LFPs evaluated in 54/57 STN; optimal contact evaluated > 6 months postimplant)
10. Shah A, Nguyen TK, Peterman K, et al. Combining Multimodal Biomarkers to Guide Deep Brain Stimulation Programming in Parkinson Disease. Neuromodulation. 2022 Feb 23:S1094-7159(22)00038-1.
11. Telkes I, Sabourin S, Durphy J, et al. Functional Use of Directional Local Field Potentials in the Subthalamic Nucleus Deep Brain Stimulation. Front Hum Neurosci. 2020 Apr 28;14:145. (n = 8 patients; beta power tended to localize to anterior direction, but was not significant; bradykinesia/rigidity in dorsoanterior direction tended to align with beta power [p = 0.087])
12. Aman JE, Johnson LA, Sanabria DE, et al. Directional deep brain stimulation leads reveal spatially distinct oscillatory activity in the globus pallidus internus of Parkinson's disease patients. Neurobiol Dis. 2020 Jun;139:104819. (n = 3 patients; power in the 5 to 35 Hz corresponded to clinical symptoms and clinical contact).

SECTION 5:

Essential tremor, dystonia, and epilepsy

Essential tremor

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

FEATURED ARTICLE:

Case report of tremor peak

Buijink A.W.G, Piña-Fuentes D.A., Stam M.J. et al. Thalamic local field potentials recorded using the deep brain stimulation pulse generator. Clinical Neurophysiology Practice 2022, 103–106.

Objective

To assess the feasibility of extracting usable neurophysiological biomarkers, recorded by Percept™ PC from a patient with Essential Tremor's Vim nucleus.

Methods

Case Report

Recording: Percept™ PC

Target: Vim nucleus

Conditions: Stimulation OFF, Stimulation ON

Results

TIn the OFF-stimulation condition, a peak tremor frequency of 3.8 Hz was identified from the left Vim nucleus during tremor evoking movements. No activity in the tremor frequency range was observed from the right Vim nucleus.

In the ON-stimulation condition (right Vim: 1.4mA – left Vim: 1.2mA), no activity in the tremor frequency range was observed in the LFPs of both the left and right Vim nucleus.

Notes

This is the first report of recorded tremor-related thalamic activity using the electrodes and pulse generator of an implanted DBS system.

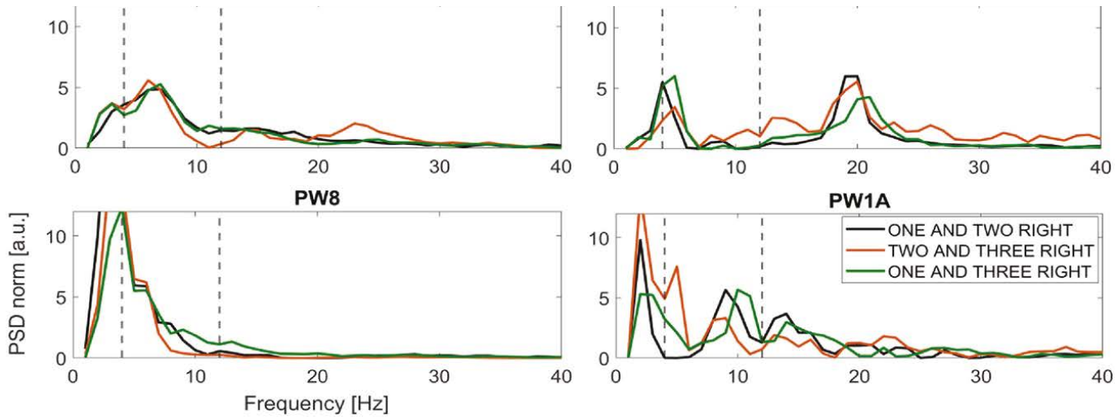
The signal recorded from the right Vim was contaminated with ECG-artifacts.

Dystonia

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

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



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.

FEATURED ARTICLE:

Theta-alpha location and frequency distribution

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

Target for dystonia: GPi

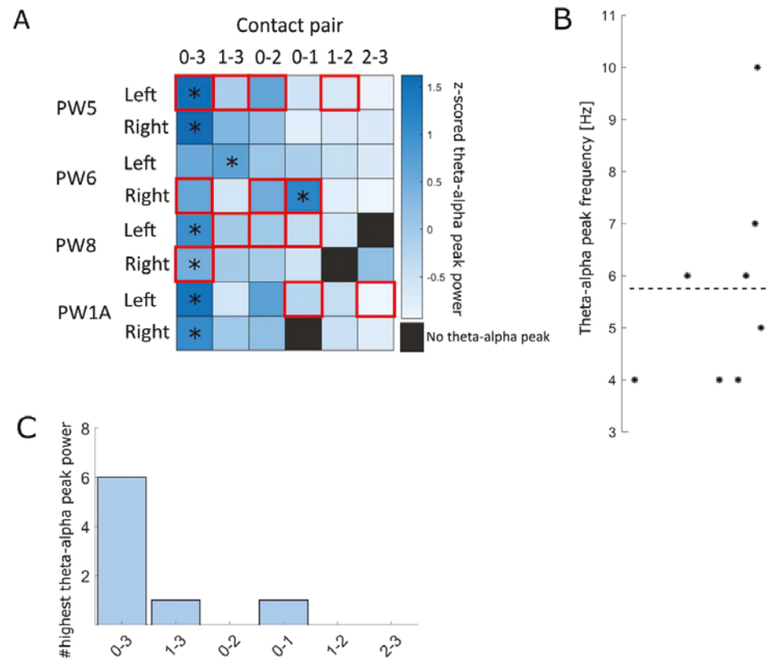
Design: BrainSense™ technology features were used to record LFPs in clinic and during at-home device use.

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 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.

Epilepsy

Epilepsy	
Common frequencies identified with Percept™ PC associated with seizures	4 to 11 Hz[1,2†] ~26 Hz[3,4]

1 Fasano A, Gorodetsky C, Paul D, et al. Local Field Potential-Based Programming: A Proof-of-Concept Pilot Study. Neuromodulation. 2021. The authors stated "Interictally, the most common epileptiform discharges were in the form of bisynchronous high amplitude theta/delta semi-rhythmic runs or bursts lasting up to 3 sec without clinical correlates."

2 Rego R, Lopes E, Santos A, et al. Simultaneous recording of thalamic local field potentials and long term video-EEG in a focal epilepsy patient: first insights. International Conference on DBS; November 20-21, 2020; Virtual.

3 Gielen F, Colon AJ, Van Dijk JP, et al. Comparison of intra-cranial recordings simultaneous with video-EEG recordings in a DBS for epilepsy patient. International Conference on DBS; November 20-21, 2020; Virtual.

4 Colon AJ, van Dijk JP, Gielen F, et al. Comparison of intra-cranial recordings simultaneous with Video-EEG recordings in a DBS for epilepsy patient. International Conference on Deep Brain Stimulation; Nov 20-21, 2020; Virtual.

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

FEATURED ARTICLE:

Case report, Percept™ PC 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.

*Medtronic DBS Therapy for Epilepsy is not approved for the treatment of absence seizures or primary generalized seizures.

SECTION 6:

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 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 are 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.

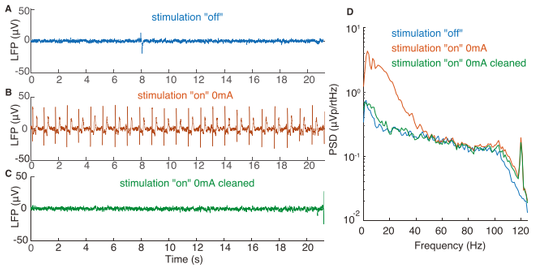
The ECG artifact may partially mask the information in the LFP in the frequency band between 0 to 40 Hz.

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 but not to symptoms fluctuation states. 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 the 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).

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.

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.

* 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 understand the patient, their symptoms, and rely on programming that is most beneficial for the patient.

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.

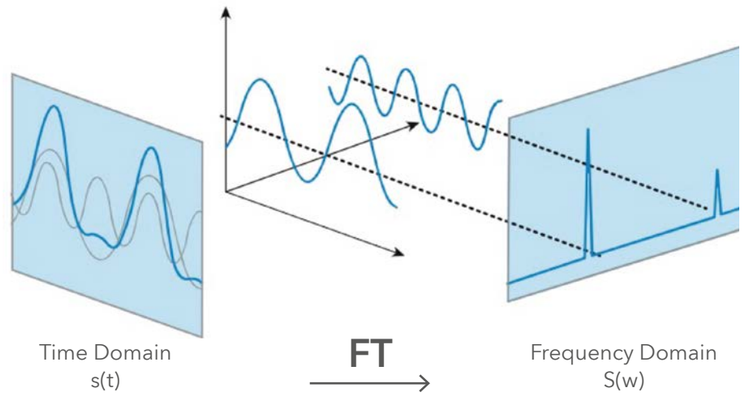
SECTION 7:

Glossary

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 fj. When the data and sinusoids "match," the power at frequency fj is large, whereas when the data and sinusoids do not match, the power at frequency fj 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: DBS BrainSense™ technology whitepaper FY20. 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.

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Brief Statement:

See the device manual for detailed information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative and/or consult the Medtronic website at www.medtronic.eu.

For applicable products, consult instructions for use on manuals.medtronic.com. Manuals can be viewed using a current version of any major internet browser. For best results, use Adobe Acrobat® Reader with the browser.

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