Medtronic

Scientific compendium

BrainSense™ Adaptive Deep Brain Stimulation (aDBS)†

Research on sensing-enabled, adaptive deep brain stimulation with BrainSense™ technology‡

† aDBS is only approved for patients with Parkinson's disease.

‡ The sensing feature of the Percept™ PC system and Percept™ RC system is intended for use in patients receiving DBS where chronically-recorded bioelectric data may provide useful, objective information regarding patient clinical status.

Introduction

This scientific compilation of published literature is intended as an educational resource for health care professionals interested in adaptive deep brain stimulation (aDBS) in patients with Parkinson's disease.

This resource begins by demonstrating the association between local field potential (LFP) signals sensed from the brain and the symptoms of Parkinson's disease. These signals can be sensed using the Percept™ PC and Percept™ RC devices with BrainSense™ technology. The following sections provide published examples of LFP recordings and guidance for incorporation of BrainSense™ technology into clinical practice. LFPs 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.

Years of published literature have helped to set a foundation for brain sensing and the use of LFPs as a control signal for closed-loop stimulation (i.e., aDBS) in Parkinson's disease.

The Percept™ PC and Percept™ RC neurostimulators with BrainSense™ technology capture brain signals (i.e., LFPs) using an implanted DBS lead(s). BrainSense™ aDBS, uses this data to automatically increase or decrease stimulation when a patient's brain signal (i.e., alpha or beta LFP power) is high or low (outside of a clinician-defined range), respectively. These adjustments aim to tailor stimulation amplitude to the patient's needs throughout the day.

Single and dual-threshold BrainSense™ aDBS algorithms have been tested in a pivotal trial. The final section of this resource provides an overview of the ADAPT-PD trial and associated outcomes.

Limitations

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

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

- The articles may be helpful for navigating through the science of brain sensing and aDBS. There is still much to learn regarding the optimal signal of interest to drive adaptive, closed-loop therapies and most effective algorithms for varying disease states and symptomology.
- Interpretation of early aDBS feasibility studies are often limited due to short-term, in-clinic, externalized testing or small sample sizes.
- Articles were selected as fair and balanced examples of "state of the art" for sensing and aDBS research. This document does not represent an exhaustive list of aDBS literature.
- Physicians should use their own clinical judgement when implementing the use of BrainSense™ technology and deciding how to treat patients with DBS therapy.
- The BrainSense™ features have several limitations themselves:
  - BrainSense™ aDBS is limited to two modes or algorithms (i.e., Single Threshold and Dual Threshold) and to control signals within the alpha-beta frequency range (8-30 Hz).
  - Sensing and stimulation contacts are restricted to predefined combinations; in order to sense, stimulation is limited to the middle contacts. Segmented contacts and surgical planning may help work around this limitation.[2]
  - Cardiac artifact, if present, overlaps with the beta frequency range.[2] Implant location (ie, right side)[2] and leads developed for sensing, such as the SenSight™ lead help reduce artifact noise.
  - Timeline recordings are restricted to a narrow band around a predefined frequency and could miss frequency shifts or the appearance of new bands.[1,2]
  - LFP signals related to a rapidly-occurring event (ie, a fall or freezing of gait) may be difficult to capture due to the delay between the event occurrence and marking with the patient programmer.[2]
  - High frequency oscillations, which may also carry information content regarding patient disease state or treatment, are beyond the recording capabilities of the device.[1]

Disclaimers

- Some of the articles describe acute postoperative research investigating aDBS 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.
- BrainSense™ aDBS and research summarized in this document are for Parkinson's disease indication only. Signals may not be present in all patients.

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

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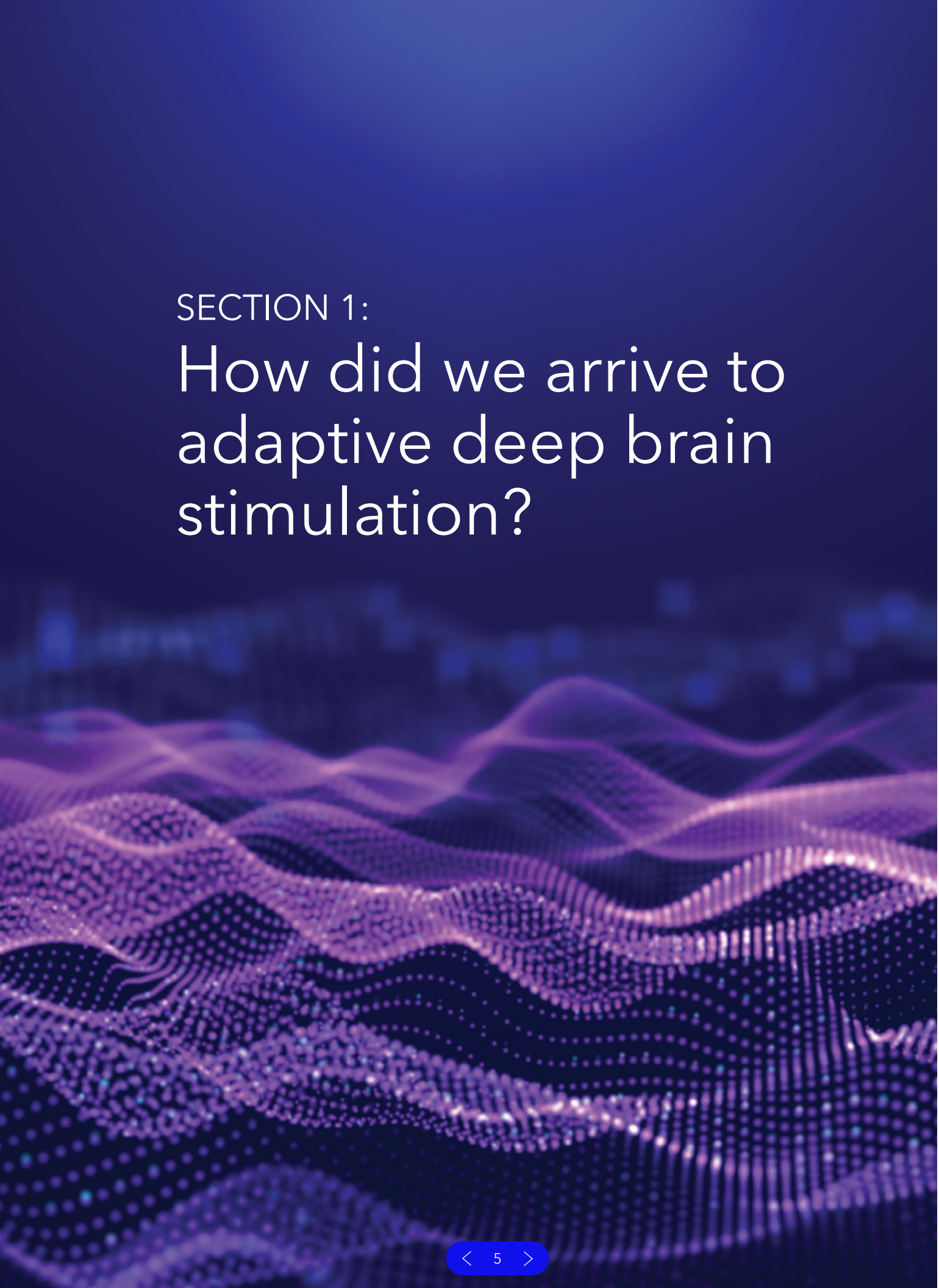


SECTION 1:

How did we arrive to adaptive deep brain stimulation?

A framework for Sensing-Enabled Deep Brain Stimulation: From sensing to adaptive deep brain stimulation (aDBS)

BrainSense™ technology: Trust, Select, Optimize and Maximize LFP Signals

The realization of sensing-enabled DBS, powered by BrainSense™ technology, relies on trust of the signal of interest's relevance to a specific context of use. BrainSense™ technology equips clinicians with tools to identify relevant LFP measures, including the ability to sense biomarkers of bradykinesia and rigidity in patients with PD.† This utility offers valuable and objective data to inform clinical-decision making. First, the detection of LFP peaks can contribute information for contact selection. Next, new and existing programming parameters may be optimized by examining LFP responses to stimulation. Finally, LFP monitoring features of BrainSense™ technology enables clinicians to adjust therapy through personalized insights.

Ultimately, the combined features of LFP characteristics and BrainSense™ technology capabilities provide the ability to adapt deep brain stimulation e.g., (aDBS) in response to patient-specific neurophysiology.

Select
(Contacts)

BrainSense™ Electrode Identifier

Personalized and focused mapping of alpha-beta activity in real-time to provide insights into "sweet spot" proximity

BrainSense™ Electrode Survey

Provides decision-making support to select a contact or directionally shift stimulation in monopolar review or follow up programming

Optimize
(Therapy configurations)

BrainSense™ Streaming

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

BrainSense™ Thresholds

Assess the time spent with or without symptoms when outside the clinic

Maximize ‡
(Therapeutic results)

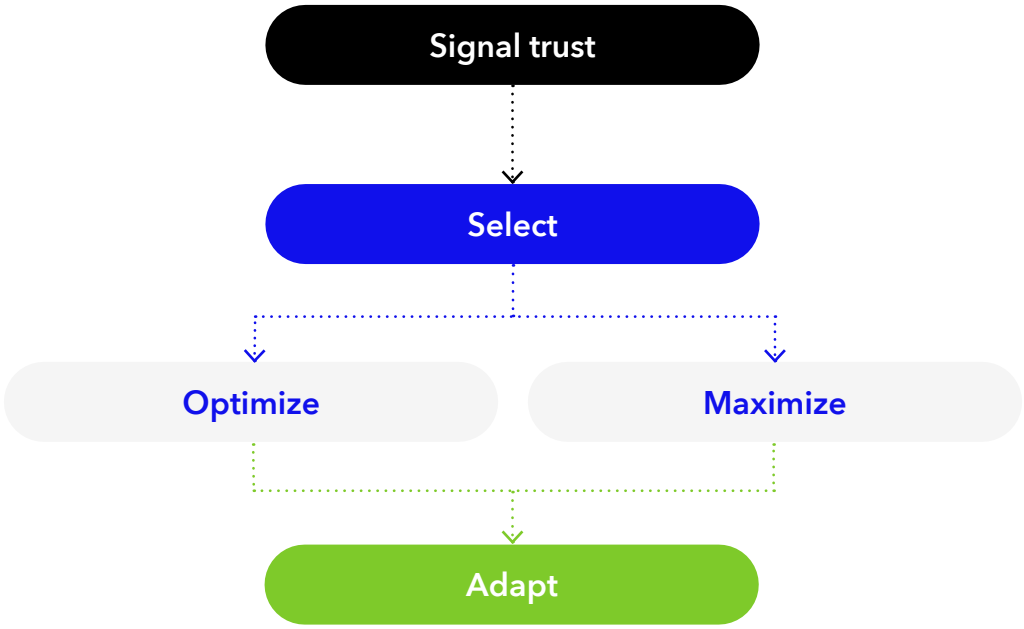
BrainSense™ aDBS

aDBS offers personalized, automatic stimulation amplitude adjustments in response to patient-specific neurophysiology

†Biomarker in this context refers to local field potentials from the subthalamic nucleus in the alpha-beta frequency range which correlate to bradykinesia and rigidity symptoms in patients with Parkinson's disease.

‡ Improved motor symptom control results were based on post hoc analysis averaging overall patient aDBS on time results compared to cDBS. Results presented for dual threshold aDBS. N=40. Based on results from an open-label comparison.

Sensing-enabled DBS framework



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

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

† Improved motor symptom control results were based on post hoc analysis averaging overall patient aDBS on time results compared to cDBS. Results presented for dual threshold aDBS. N=40. Based on results from an open-label comparison.

Local field potential characteristics conducive to support adaptive deep brain stimulation in patients with Parkinson's disease

Local field potential peaks are detectable in the majority of patients with PD and primarily fall within the alpha-beta range.

LFP peak and band power measures are correlated with Parkinsonian symptom states (e.g., UPDRS-III total score and bradykinesia/rigidity subscores).

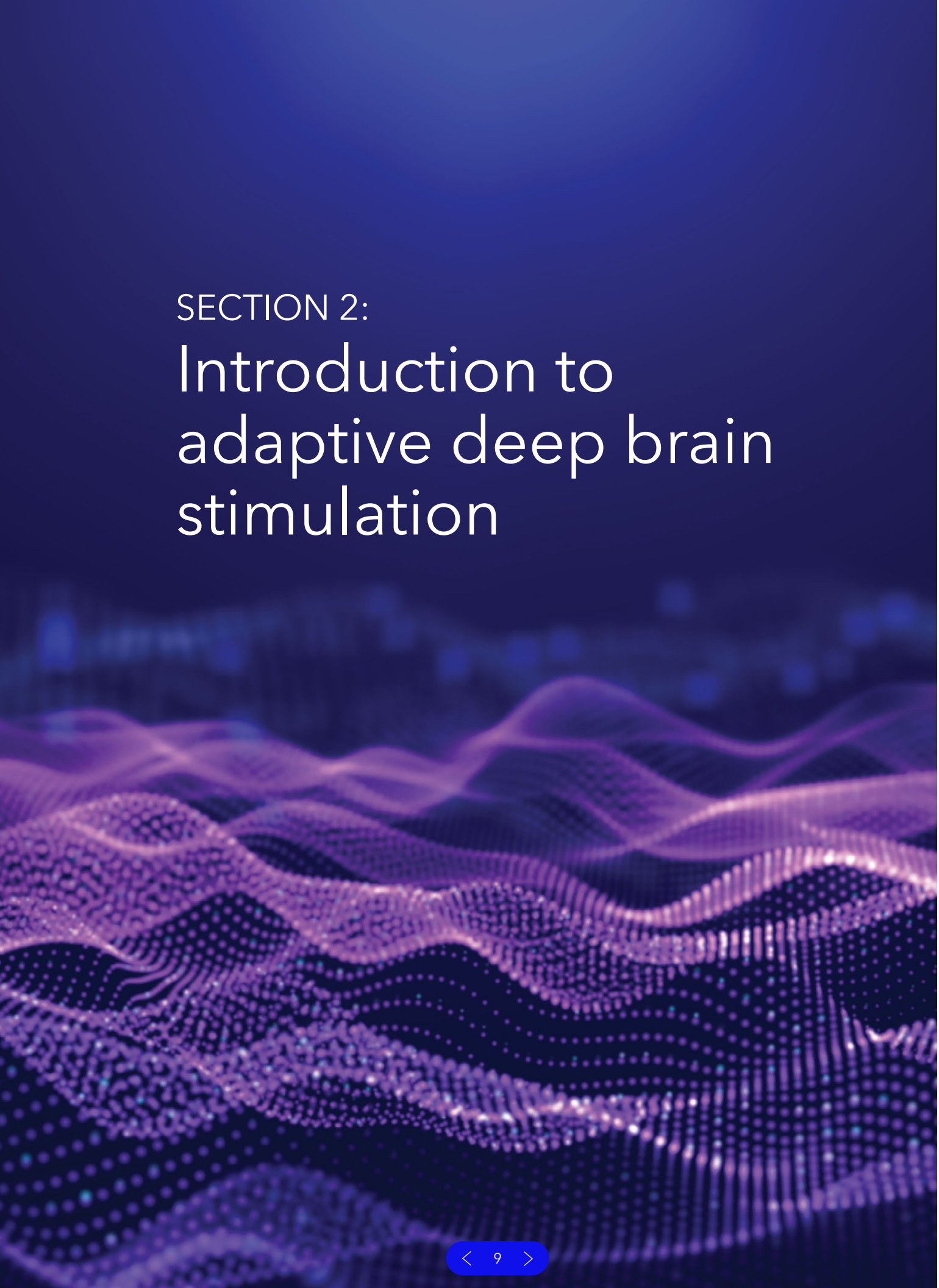
Beta power is suppressed by dopaminergic medications and DBS and can fluctuate with circadian rhythm. The magnitude of power suppression can reflect therapeutic responses to therapy.

Over the past decade, extensive research on local field potentials (LFP) from the subthalamic nucleus (STN) and globus pallidus internus (GPi) in patients with Parkinson's disease (PD) has revealed the diverse applications of these signals in gaining insights into pathophysiology and their potential clinical applications.[1] One key finding from LFP research in PD is the role of beta band (13-30 Hz) hyper-oscillatory activity in the clinical manifestation of motor impairments, principally bradykinesia and rigidity.[2,3] This hyper-oscillatory activity, manifesting as a LFP peak, is present in the majority of patients with PD.[4] Additionally, the response of beta measures to antiparkinsonian medication and DBS is noteworthy; elevated beta activity typically diminishes with treatment, leading to subsequent improvements in UPDRS-III scores.[4] Taken together, these findings provide substantive evidence to support a closed-loop, adaptive, DBS system based on patient STN and GPi LFP data.

1. Yin Z, Zhu G, Zhao B, et al. Local field potentials in Parkinson's disease: A frequency-based review. *Neurobiology of Disease*. 2021;155:105372.
2. Morelli N, Summers RLS. Association of subthalamic beta frequency sub-bands to symptom severity in patients with Parkinson's disease: A systematic review. *Parkinsonism & Related Disorders*. 2023;110.
3. van Wijk BCM, de Bie RMA, Beudel M. A systematic review of local field potential physiomarkers in Parkinson's disease: from clinical correlations to adaptive deep brain stimulation algorithms. *Journal of Neurology*. 2023;270(2):1162-1177.
4. Darcy N, Lofredi R, Al-Fatly B, et al. Spectral and spatial distribution of subthalamic beta peak activity in Parkinson's disease patients. *Experimental Neurology*. 2022:114150.

SECTION 2:

Introduction to adaptive deep brain stimulation



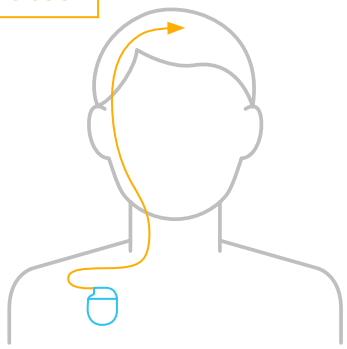
What is adaptive deep brain stimulation?

BrainSense™ technology's capacity to record local field potentials (LFP) provides opportunities to personalize DBS in a closed-loop, or adaptive (aDBS), system of therapy delivery. Given the association of alpha-beta power to medication and motor states, aDBS automatically adjusts stimulation in response to fluctuations of alpha-beta power.

Tonic Stimulation

Continuous DBS

- Tonic stimulation
- Stimulation parameters adjusted manually by physician

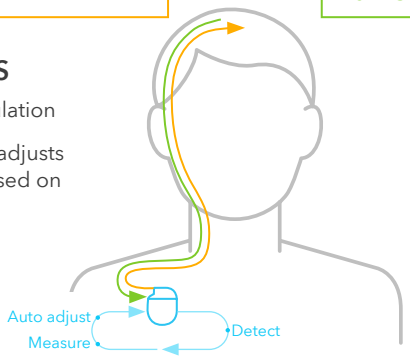


Dynamic Stimulation

Brain Signals

Adaptive DBS

- Dynamic stimulation
- Automatically adjusts stimulation based on brain signals



Why aDBS?

Continuous or classic DBS systems were not designed to respond to changes in patient state or medication regimen, ultimately requiring the patient or caregiver to manually adjust stimulation amplitude throughout the day to optimize symptom control.

Adaptive deep brain stimulation (aDBS) was developed to automatically adjust DBS amplitude in response to fluctuation in neural activity or behavior, in order to provide more stable symptom control, reduce side effects, and maximize neurostimulator battery longevity.[1-4]

1. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol* 2013;74(3):449–57.
2. Little S, Tripoliti E, Beudel M, et al. Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. *J Neurol Neurosurg Psychiatry* 2016;87(12):1388–9.
3. Rosa M, Arlotti M, Marceglia S, et al. Adaptive deep brain stimulation controls levodopa-induced side effects in Parkinsonian patients. *Mov Disord* 2017;32(4):628–9.
4. Pina-Fuentes D, Dijk JMC van, Zijl JC van, et al. Acute effects of adaptive Deep Brain Stimulation in Parkinson's disease. *Brain Stimul* 2020;13(6):1507–16.

Introduction to aDBS Modes

Two aDBS modes are available for use with Percept™ PC and Percept™ RC, including Single Threshold and Dual Threshold.

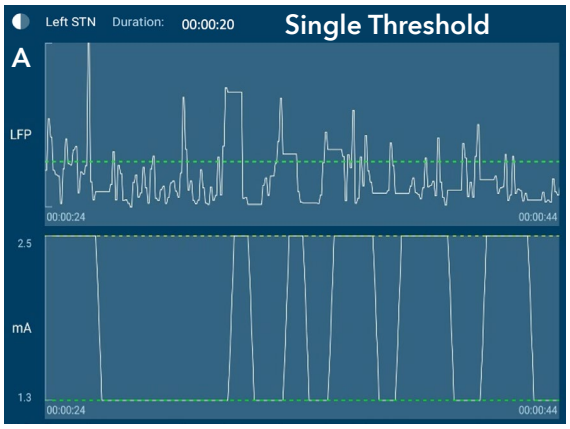
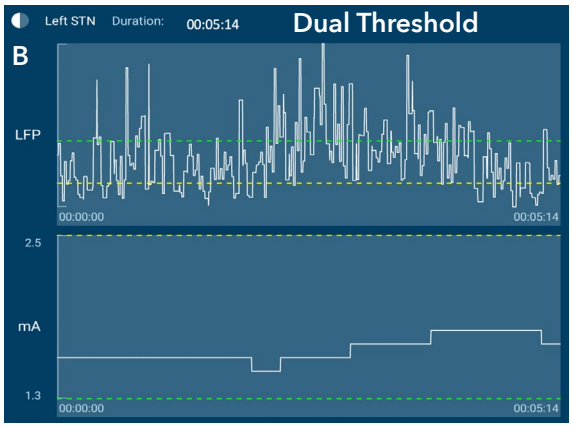
Mode	Single Threshold	Dual Threshold
Function	Single Threshold mode rapidly (milliseconds) adjusts stimulation amplitude between lower and upper limits within 250 milliseconds based on LFP power. Single threshold aDBS is designed to rapidly respond to long duration and high amplitude alpha-beta LFP power, which are associated with PD symptom states, while allowing for short elevations in alpha-beta LFP power associated with normal physiologic function.	Dual Threshold mode slowly (minutes) adjusts stimulation amplitude based on changes in LFP power, taking 2.5 minutes to increase and 5 minutes to decrease the amplitude. Dual threshold aDBS aims to provide more consistent symptom management by automatically adjusting stimulation amplitude in response to alpha-beta power fluctuations that may be caused by medication or daily activities.
Tablet view	 20 seconds	 ~5 minutes

Image adapted from Stanslaski et al. 2024. https://doi.org/10.1038/s41531-024-00772-5.

SECTION 3:

Adaptive deep brain stimulation feasibility research

Adaptive deep brain stimulation feasibility research

Technological advancements in LFP sensing have made it possible to personalize stimulation through adaptive deep brain stimulation (aDBS) for patients with Parkinson's disease (PD). As such, several small safety and feasibility studies have explored the use of aDBS to address a number of cardinal motor symptoms of PD. These early studies, leveraging alpha-beta control signals, have found bradykinetic and tremor symptoms are responsive to aDBS, potentially alongside reduced stimulation time and total electrical energy delivery compared to traditional continuous DBS. Together, these data highlighted the early feasibility of implementing aDBS in patients with PD.

Summary of aDBS feasibility studies

Clinical implications

- Feasible
- Safe
- Less total electrical energy delivery

Limitations

- Short-term exposure
- No studies for GPi or with directional stimulation
- One mode of aDBS at a time, no directional aDBS
- Limited to in-clinic and acute studies with few reports of real-world or chronic performance

Prior aDBS Publications

- Little, S., Pogosyan, A., Neal, S., Zavala, B., Zrinzo, L., Hariz, M., et al. (2013). Adaptive deep brain stimulation in advanced Parkinson disease. Ann. *Neurol*. 74, 449–457. doi: 10.1002/ana.23951
- Tinkhauser G, Pogosyan A, Little S, Beudel M, Herz DM, Tan H, et al. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. *Brain*. 2017; 140:1053–67.
- Little S, Beudel M, Zrinzo L, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2016;87(7):717
- Piña-Fuentes D, van Dijk JMC, van Zijl JC, et al. Acute effects of adaptive Deep Brain Stimulation in Parkinson's disease. *Brain Stimul*. 2020;13(6):1507-1516
- Nakajima A, Shimo Y, Fuse A, et al. Case Report: Chronic Adaptive Deep Brain Stimulation Personalizing Therapy Based on Parkinsonian State. *Front Hum Neurosci*. 2021;15:702961.
- Velisar A, Syrkin-Nikolau J, Blumenfeld Z, et al. Dual threshold neural closed loop deep brain stimulation in Parkinson disease patients. *Brain Stimul*. 2019;12(4):868-876

SECTION 4:

ADAPT-PD trial overview

Background and objectives

- The culmination of aDBS studies in PD indicate that aDBS may provide an effective therapy and energy savings compared to cDBS. However, these studies were predominantly of small sample size and consisted of short bedside evaluation, only tested one mode of aDBS (i.e., single or dual threshold), and mainly focus on one target for DBS (i.e., the STN).
- While the feasibility of aDBS in a naturalistic environment has been demonstrated,[5] aDBS had not yet been validated as safe and effective.
- The ADAPT-PD clinical trial was designed to address these gaps in understanding and make the adaptive feature clinically available.

Methods

Study design

- Multicenter, prospective, randomized single-blind crossover (between dual and single threshold modes of aDBS) with open-label comparison between aDBS and cDBS. All patients were implanted with Medtronic Percept™ PC.

Study purpose

- To demonstrate the safety and effectiveness of chronic dual and single threshold aDBS in patients with PD.

Notable inclusion criteria

- Stable STN or GPi DBS and medication therapy for PD.
- Patient is responsive to DBS.
- LFP peak power amplitude ≥1.2 µVp in the alpha-beta band on left and/or right DBS leads. (This peak amplitude is recommended for aDBS.)

ADAPT-PD study design

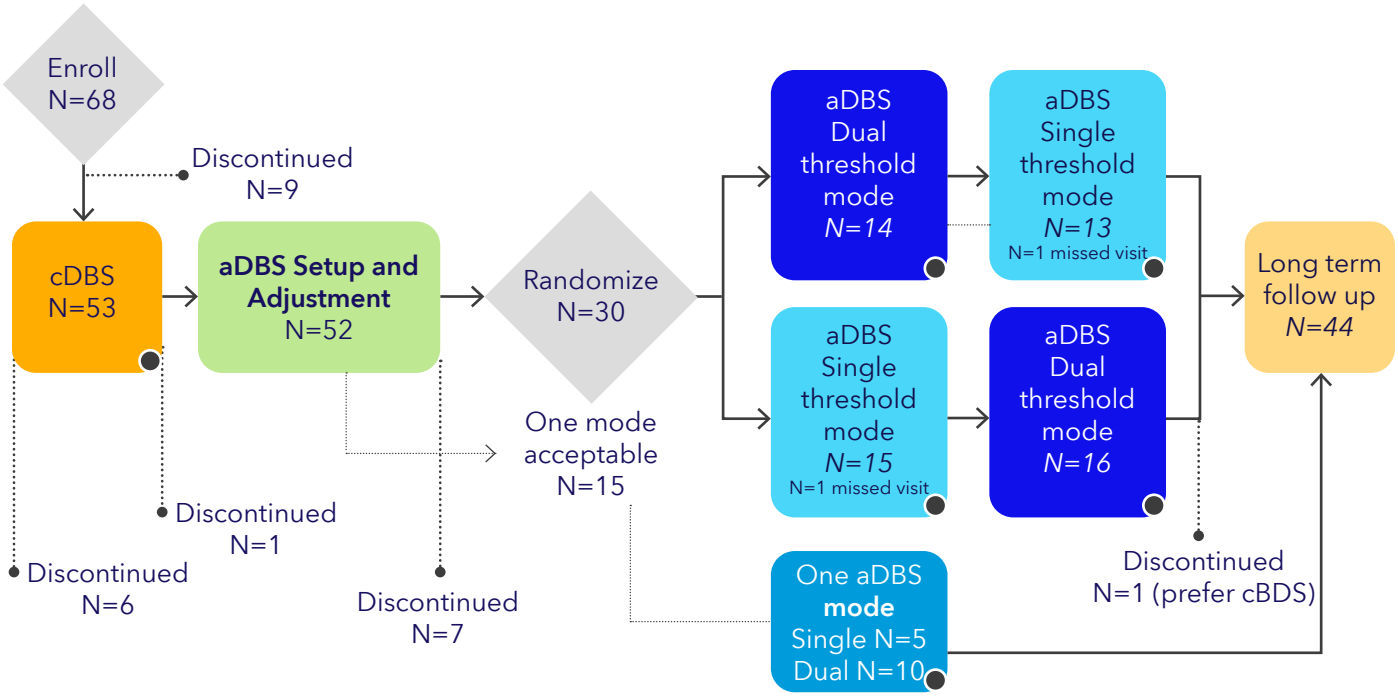


Figure adapted from Stanslaski et al. 2024. https://doi.org/10.1038/s41531-024-00772-5.

ADAPT-PD study phases

1. **cDBS baseline phase (gold):** 30-day evaluation on stable cDBS settings
2. **aDBS setup and adjustment phase (green):** up to 60-day programming on both modes
3. **aDBS evaluation phase (blue):** 30-day evaluation in one or both aDBS modes (if both deemed acceptable)
4. **Long-term follow-up phase (yellow):** ~10 months of aDBS in the mode selected by the patient

Primary objective

To meet the primary objective, at least 50% of participants were to meet a success criteria endpoint: no worse than -2 hours less "On" time without troublesome dyskinesia during aDBS evaluation compared to their stable cDBS evaluation, for each aDBS mode. "On" time was based on a self-reported motor diary completed by participants every 30 minutes over 24 hours on at least 3 consecutive days prior to the evalution visit.

Secondary endpoint: energy delivered

To demonstrate reduced total electrical energy delivered (TEED) during aDBS compared to cDBS.

Safety and additional objectives

Stimulation-related AEs, AEs, and device deficiencies. Wearable device data, Voice Handicap Index, MDS-UPDRS, EQ-5D-5L, PDSS-2, PDQ-39, and patient preference and satisfaction.

For more details regarding ADAPT-PD methodology and full endpoint descriptions, please see the published protocol: https://doi.org/10.1038/s41531-024-00772-5

Results

Participants

68 participants enrolled in the trial with 45 entering the aDBS evaluation phase (30 randomized to both aDBS modes). After the evaluation phase 44/45 participants chose to remain on aDBS and entered the long-term follow-up phase.

Baseline characteristics of study population

Characteristic	Mean ± standard deviation
Age - yr (n = 66) (range)	62.2 ± 8.4 (36-75)
PD duration - yr (n = 64)	13.5 ± 6.8
Dyskinesia - yr (n = 37)	6.9 ± 4.8
Motor fluctuations - yr (n = 46)	7.6 ± 4.6
Duration of levodopa treatment – yr (n = 60)	10.7 ± 6.1
Levodopa equivalent daily dose - mg	561.9 ± 568.3
Sex - no. (%)	
Male	48 (70.6%)
Female	20 (29.4%)
Target site by participant - no. (%)	
STN	51 (75.0%)
GPi	17 (25.0%)
Years from the lead implant to consent	3.4 ± 3.3
MDS-UPDRS part III (Off stim/Off meds) (n = 58)	45.7 (14.9)
Tremor	8.8 (6.4)
Rigidity	8.3 (3.6)
Bradykinesia	22.9 (8.3)
Axial	5.6 (3.0)
Primary Cohort Consented N = 68. On and off medication examination completed at enrollment and screening visits.	

aDBS is feasible and tolerable

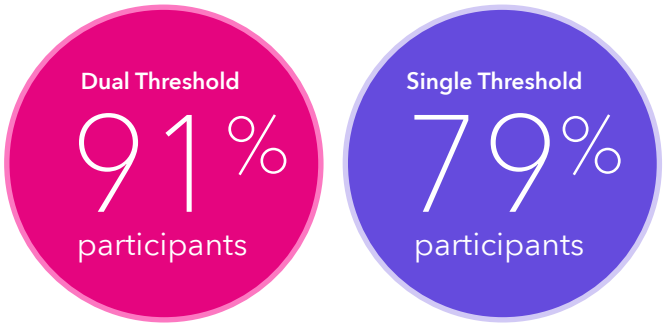
- ✓ LFP signal present to set up aDBS in 85% (57/68) of patients at enrollment
- ✓ aDBS is tolerable and successfully set up in 87% (45/52) of patients

aDBS is effective

Primary objective met: Effectiveness

The majority of patients met the success criteria. Dual Threshold aDBS proportion of success was 91% (N = 40); and Single Threshold aDBS proportion of success was 78.9% (N = 35).

Primary endpoint success criteria: no worse than -2 hour loss of "On" time without troublesome dyskinesia during aDBS relative to cDBS

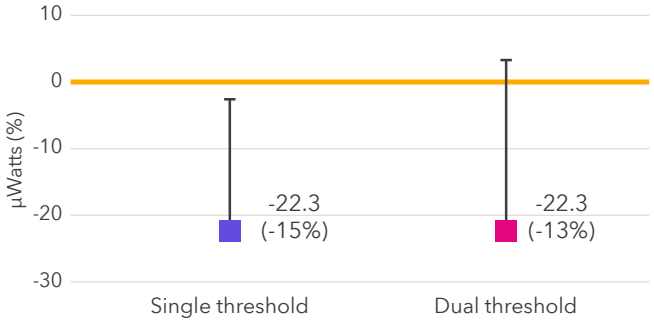


aDBS impact on energy and battery

Secondary objective met: Total electrical energy delivered (TEED)

Total energy delivered aDBS demonstrated a mean decrease of 22.3 (SE: 8.37) µWatts during Single Threshold aDBS and 22.3 (SE: 10.98) µWatts during Dual Threshold aDBS.

Change in TEED



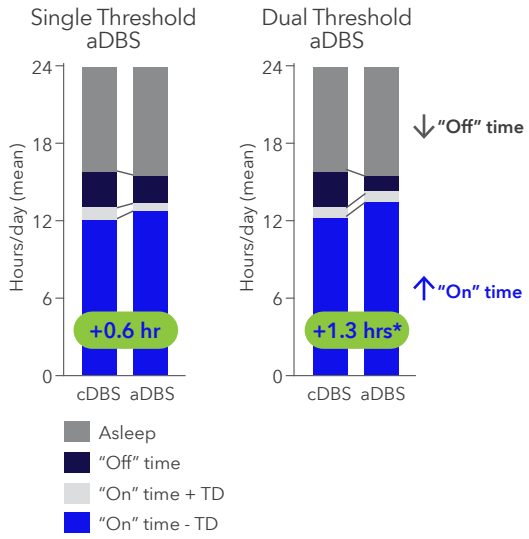
- Patients programmed in Dual Threshold mode showed a median aDBS longevity improvement of 5%/year vs cDBS.
- Patients programmed in Single Threshold mode showed a median aDBS longevity reduction of -4%/year vs cDBS.

Exploratory motor diary data

Changes in motor diary:

Dual Threshold (N = 40) aDBS resulted in a clinically significant improvement in "On" time without troublesome dyskinesia (+1.3 hrs/day) and reduced Off time (-1.6 hrs/day) compared to cDBS.[1,2] Single Threshold aDBS demonstrated a modest increase in "On" time without troublesome dyskinesia (+0.6 hrs/day) and reduction in Off time (-0.7 hrs/day).

Change in motor diary



Motor diary data at baseline continuous deep brain stimulation (cDBS) and adaptive deep brain stimulation (aDBS). Change in "On" time listed by hour change from baseline for group average. Note*: changes > 1 hour are clinically meaningful.[1,2] TD = troublesome dyskinesia

Single Threshold

+0.6 hours/day **"On" time without troublesome dyskinesia** relative to cDBS (single threshold)

-0.7 hours/day of **"Off" time** relative to cDBS (single threshold)

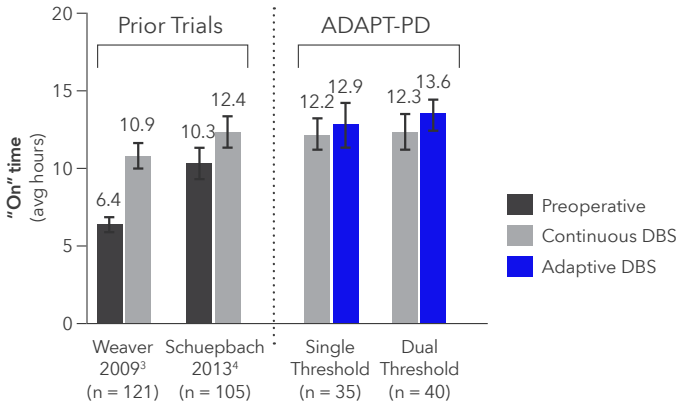
Dual Threshold

+1.3 hours/day **"On" time without troublesome dyskinesia** relative to cDBS (dual threshold)

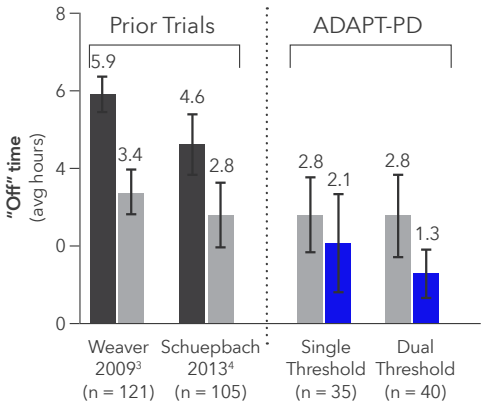
-1.6 hours/day **"Off" time** relative to cDBS (dual threshold)

Historical DBS "On" and "Off" time compared to ADAPT-PD study cohort. Average "On" and "Off" time after therapeutic intervention extracted from two prior studies establishing the effectiveness of cDBS for Parkinson's disease and in the ADAPT-PD trial. Note: Weaver et al., 2009 (N = 121) and Schuepbach et al, 2013 (N = 105) compared best medical therapy to cDBS at 6 months and 24 months follow-up postoperative, respectively.

"On" Time



"Off" Time



1. Hauser RA, Auinger P, Group on behalf of the PS. Determination of minimal clinically important change in early and advanced Parkinson's disease. *Mov Disord* (2011) 26:813–818. doi: 10.1002/mds.23638
2. Papapetropoulos S (Spyros). Patient Diaries As a Clinical Endpoint in Parkinson's Disease Clinical Trials. *CNS Neurosci Ther* (2012) 18:380–387. doi: 10.1111/j.1755-5949.2011.00253.x
3. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009;301(1):63-73. doi:10.1001/jama.2008.929
4. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013;368(7):610-622. doi:10.1056/NEJMoa1205158
5. Oehrn, C.R., Cernera, S., Hammer, L.H. et al. Chronic adaptive deep brain stimulation versus conventional stimulation in Parkinson's disease: a blinded randomized feasibility trial. *Nat Med* 30, 3345–3356 (2024). https://doi.org/10.1038/s41591-024-03196-z

aDBS is safe

The safety profile observed with aDBS is consistent with cDBS

- Of all adverse events collected during the ADAPT-PD trial, 30% (155 events) were related to aDBS.
- Falls were commonly reported, but 93% deemed unrelated to aDBS and determined to be related to Parkinson's disease as rates matched published literature.

As with initial cDBS programming, stimulation-related adverse events are expected during aDBS initial setup.

- In the ADAPT-PD trial, stimulation-related adverse events occurred during the aDBS Set-up and Adjustment phase, with most events categorized as worsening of PD cardinal symptoms (35% of events), as would be expected when modifying DBS settings.

Stimulation-related events are expected to resolve with reprogramming and it's important to ensure patients have regular follow up visits to optimize programming. aDBS is an optional programming feature and may not work for everyone.

- In the ADAPT-PD trial, all but one stimulation-related event resolved with reprogramming during the aDBS Set-up and Adjustment phase.

Stimulation-related events (subjects, % of subjects)

Study phase	Enrollment through cDBS baseline phase (N = 85, ~1mo)	aDBS setup and adjustment phase (N = 70, ~2mo)	aDBS evaluation phase (N = 60, 1mo)	Long-term follow-up phase (N = 59, 10mo)	Extended access phase (N = 54, 5.5mo)
All events (155)	4 (4, 4.7%)	75 (39, 55.7%)	23 (17, 28.3%)	24 (17, 28.8%)	29 (15, 27.8%)
#Subjects with event/month	4	19.5	17	1.7	2.7

aDBS Setup and adjustment phase

All but one stimulation-related adverse event resolved with reprogramming.

Enrollment through long-term follow-up

No serious adverse device events (N = 44)

BrainSense™ aDBS means patients living with Parkinson's have more ways to manage their symptoms

98% preferred BrainSense™ Adaptive DBS over traditional DBS after using for 30 days†

Common reasons for preferring aDBS

66%
Address symptom fluctuations

63%
Improving motor symptoms

45%
Manage side effects

While aDBS was preferred over cDBS, no clear preference for one mode was reported by patients: Among the 30 subjects randomized to both modes, 28 provided aDBS mode preference information. 11 (39.3%) preferred Dual Threshold mode, 10 (35.7%) preferred Single Threshold mode, 6 (21.4%) had no preference, and one 'didn't know'.

† Data from 45 patients who were previously stable on traditional DBS (cDBS).

Key takeaways

Summary of findings

Clinical outcomes

- Gain, on average, "On" time relative to stable cDBS
- +1.3hrs/day represents a clinically meaningful gain (Dual Threshold)

Patient preference

- Patients would recommend aDBS, were satisfied with therapy, and preferred to continue with aDBS at long-term follow-up

Technical

- Both modes are safe and feasible
- 87% of patients were able to be setup on aDBS (45/52)

Safety

- Safety profile aligned with current labeling for DBS
- All but 1 stim-related AEs resolved with reprogramming during aDBS setup and adjustment

Trial novelty

- First chronic aDBS study (>1 year)
- First aDBS in STN & GPi
- First to compare two aDBS modes
- First aDBS with directional stimulation

Commercial workflow insights

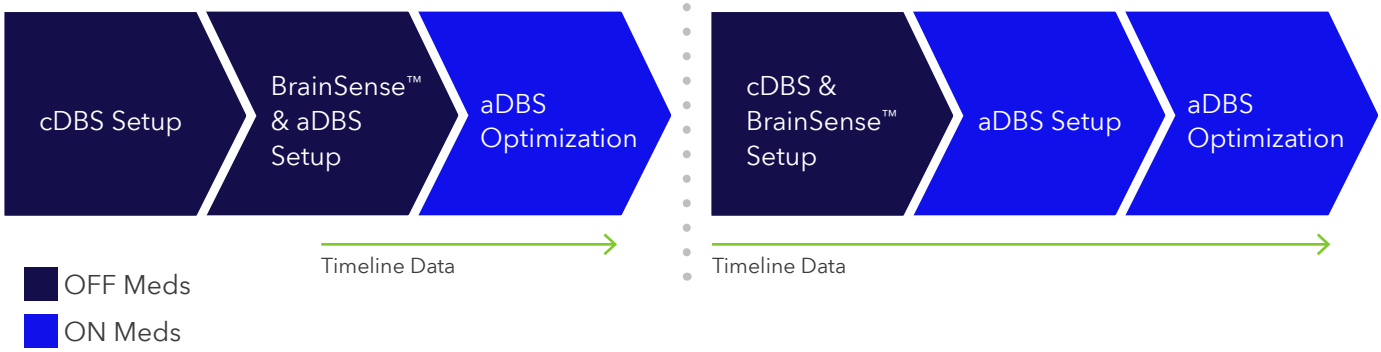
The ADAPT-PD clinical trial provided valuable insights into how to drive the efficient and successful set-up and optimization of adaptive DBS that also fits within the normal clinical workflow.

ADAPT-PD

- aDBS Setup was **based primarily on in-office exam**.
- The study protocol required deviation from the typical DBS programming workflow adding time, visits, and necessity to go 'OFF' Medication.
- The average number of visits to program BOTH aDBS modes was 4.1 +/- 2.2 visits (Visits include setting up aDBS modes and follow-up visits).[1]

Commercial workflow

- aDBS can be set up **based on both in-clinic and chronic data** from the start (as it was in the adjustment phases of the study)
- No extra 'OFF' Med visits beyond standard-of-care initial programming visit are needed for aDBS Setup.



1. Data on file, Medtronic.

SECTION 5:

Appendix: Primary and directional aDBS cohorts

Primary and directional cohorts

A subset of patients enrolled in the ADAPT-PD trial, with SenSight™ leads, underwent directional aDBS where 1 or 2 segments had amplitudes that were different than the others (directional steering on 1 or 2 segments).

ADAPT-PD Protocol and Enrollment

Primary Cohort (PC) and Directional Stimulation (DS) Cohorts

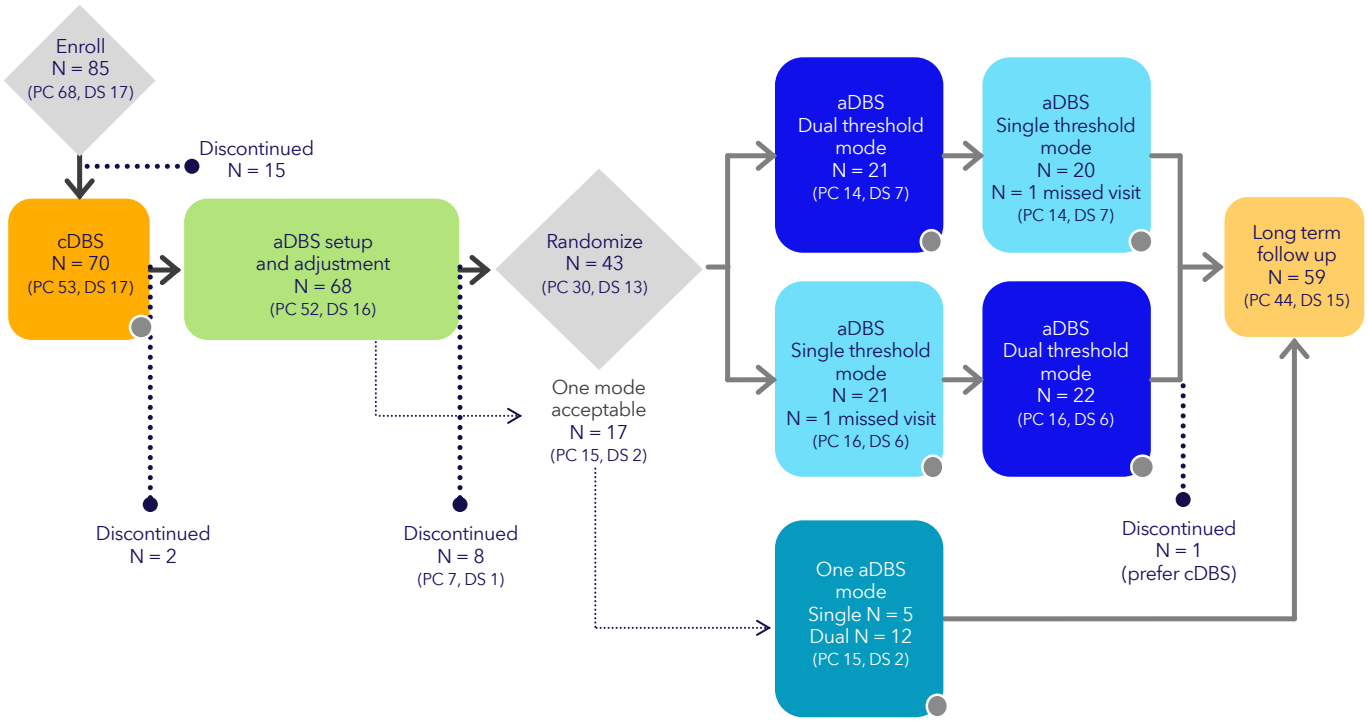


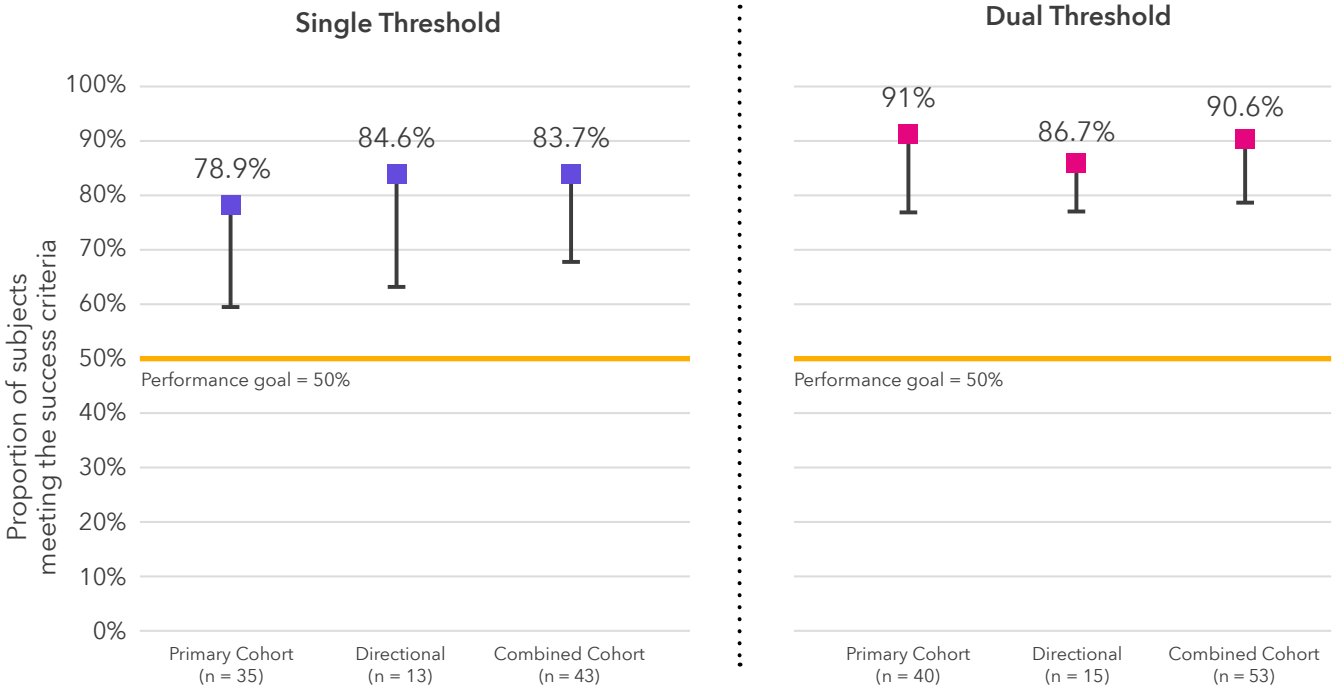
Figure adapted from Stanslaski et al. 2024. https://doi.org/10.1038/s41531-024-00772-5.

Primary and secondary endpoints and motor diaries

Of the 15 subjects included in Directional Stimulation Cohort,[1] 13 were included in Single Threshold evaluation and 15 in Dual Threshold evaluation.

Primary Endpoint

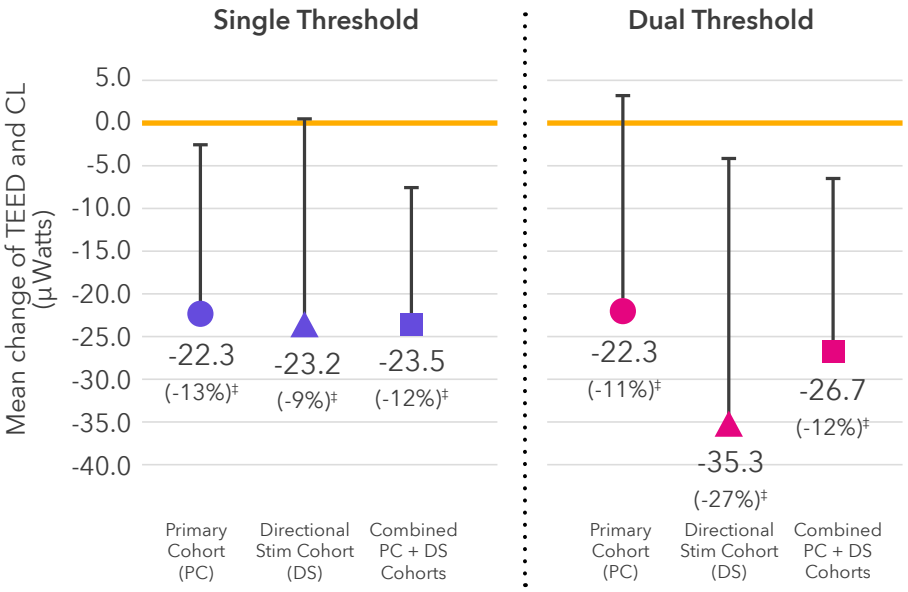
At least 50% of participants for each aDBS must meet the success criterion: no worse than -2 hour loss of "On" time without troublesome dyskinesia during aDBS relative to cDBS.



1. Data on file, Medtronic.

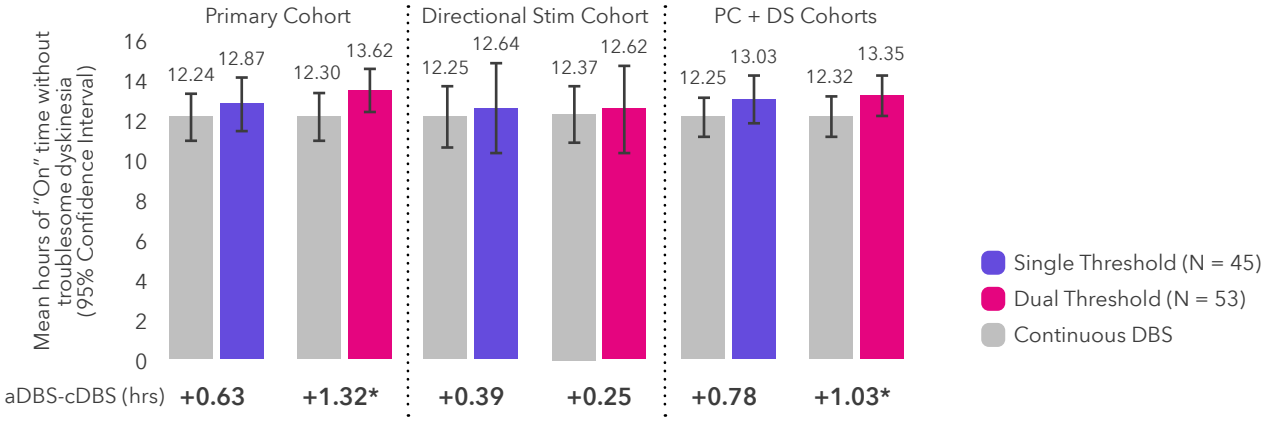
Secondary Endpoint

Reduced total electrical energy with aDBS



‡Median percent reduction TEED

Average "On" time without troublesome dyskinesia



Change in "On" time listed by hour change from baseline for group average.
Note*: changes > 1 hour are clinically meaningful.

Brief Statement: Medtronic DBS Therapy for Parkinson's Disease

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

INDICATIONS:

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

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

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

Patients should avoid activities that may put undue stress on the implanted components of the neurostimulation system. Activities that include sudden, excessive or repetitive bending, twisting, or stretching can cause component fracture or dislodgement that may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component. Patients should avoid manipulating the implanted system components or burr hole site as this can result in component damage, lead dislodgement, skin erosion, or stimulation at the implant site. Patients should not dive below 10 meters (33 feet) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA) as this could damage the neurostimulation system, before diving or using a hyperbaric chamber, patients should discuss the effects of high pressure with their clinician. Patients using a rechargeable neurostimulator must not place the recharger over a medical device with which it is not compatible (eg, other neurostimulators, pacemaker, defibrillator, insulin pump). The recharger could accidentally change the operation of the medical device, which could result in a medical emergency. Patients should not use the recharger on an unhealed wound as the recharger system is not sterile and contact with the wound may cause an infection.

PRECAUTIONS: Loss of coordination in activities such as swimming may occur. Patients using a rechargeable neurostimulator for Parkinson's disease should check for skin irritation or redness near the neurostimulator during or after recharging, and contact their physician if symptoms persist.

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

Safety and effectiveness has not been established for patients with neurological disease other than idiopathic Parkinson's disease, previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression, patients who are pregnant, or patients under 18 years.

USA Rx only Rev 10/24

Medtronic

710 Medtronic Parkway
Minneapolis, MN 55432-5604
USA
Tel: (763) 514-4000

medtronic.com