THERAPEUTIC ADVANCES in
Neurological Disorders

Case Report

Anterior nucleus of thalamus deep brain stimulation for medication refractory epilepsy modulates theta and low-frequency gamma activity: a case study

Ther Adv Neurol Disord

2025, Vol. 18: 1–13

DOI: 10.1177/17562864251323052

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***Abstract*:** A 35-year-old gentleman with a traumatic brain injury was diagnosed with refractory epilepsy with electroencephalogram and imaging findings supporting a broad seizure onset pattern in bilateral frontotemporal regions. He therefore received a Medtronic Percept PC Deep Brain Stimulator (DBS) placed bilaterally in the anterior nucleus of the thalamus (ANT). While most refractory epilepsy patients' stimulation parameters use the SANTE trial standard clinical settings of 145 Hz, 90 μs, with cycling 1-min stimulation on and 5 min stimulation off, this participant underwent 7 different stimulation parameter tests at home following testing in the clinic of 24 different stimulation parameters across 12 neurologist visits. This device allows for simultaneous stimulation of the ANT while recording the ANT local field potential (LFP) response under different stimulation parameters. Slepian multitaper analysis, modified Fitting Oscillations, and One Over F method for detrending the aperiodic component were performed to analyze neural oscillations in the frequency domain captured in the clinic. This participant was participating in a clinical study examining the effectiveness of nonstandard DBS settings to minimize broadband neural activity in the ANT. Statistically significant neuromodulatory suppression of gamma oscillations was observed in the clinic under multiple stimulation settings. We compared the ability of these research stimulation parameters to suppress at-home ANT neural activity against the standard clinical settings and examined the effects of both sets of parameters on LFP power nonstationarity. At home, theta/alpha LFP power suppression was statistically significantly reduced under the 125 Hz, 50 μs setting as opposed to the clinical setting of 145 Hz, 90 μs. The participant has achieved greater than 50% seizure reduction for over 1 year since the last neurology visit. Suppression of gamma in the clinic in the right hemisphere and suppression of theta at home in the left hemisphere show promise as quantitative feedback biomarkers for ANT-DBS. Understanding the local and network relationships of theta and slow gamma oscillations in the thalamus would further explain how these modulated oscillations may relate to the onset and propagation of seizures.

Keywords: ANT, anterior nucleus of thalamus, biomarkers, closed-loop, deep brain stimulation, epilepsy, gamma, Medtronic, multitaper, neuromodulation, percept, refractory epilepsy, SANTE, seizure frequency, seizures, slow gamma, theta

Received: 13 September 2024; revised manuscript accepted: 5 February 2025.

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Introduction

Deep brain stimulation (DBS) is an FDA-approved invasive neuromodulation therapy for the treatment of drug-resistant epilepsy.[1,2] The SANTE trial[3–5] demonstrated the anterior nucleus of the thalamus (ANT) as an efficacious brain target for the therapy with participants experiencing fewer seizures over time. As a well-established

surgical procedure, DBS offers a safe and effective therapy for many participants who would otherwise not be eligible for epilepsy surgery, but few patients achieve seizure freedom. The settings chosen for the SANTE trial were based on prior human and animal research[6–8] and were found to be effective in the overall group. Some modern implantable pulse generators now allow for local field potential (LFP) recordings which can inform clinicians about the participant's current neural activity state at the location of the implant during therapy delivery. Using LFP recordings to examine the impact of DBS therapy delivery over time offers the possibility to deliver individualized settings that may improve seizure outcomes beyond the standardized approach used in the SANTE trial. The main difficulty in moving toward an individualized approach is there are currently no prominent quantitative biomarkers of the therapy's effectiveness.

While a quantitative biomarker of response to ANT-DBS for refractory epilepsy is still under investigation, prior studies have observed neural oscillations within networks that interact with the ANT. Specifically, theta (4–8 Hz), alpha (10–12 Hz), and slow gamma (20–50 Hz) oscillations have shown utility in determining functional connectivity within the mesiotemporal network.[9] One proposed mechanism of epilepsy is the imbalance of excitation and inhibition.[10] Since gamma oscillations and the interaction between theta and gamma oscillations have been shown to play an important role in network dynamics, especially perisomatic inhibition,[11,12] modulation of theta and gamma may work to restore the balance between excitation and inhibition. Within the SANTE trial, 60% of enrolled participants had temporal lobe epilepsy and there is some evidence that patients with frontotemporal epilepsy have improved outcomes compared to other anatomic locations, presumably due to network changes within the circuit of Papez.

Changes in neuronal oscillatory activity have been observed during ANT-DBS. Mirski and Fisher[13] demonstrated that high-frequency ANT-DBS desynchronized rhythmic mammillary nuclei electroencephalogram (EEG) leading to a lowered cortical risk for pentylenetetrazol-induced seizures in rats.[8] It was also shown in an 11-patient study that bilateral high-frequency ANT-DBS in refractory epilepsy patients suppressed gamma (30–100 Hz) scalp EEG LFP activity at the left frontal (F3), left temporal (T3&5), middle central, and occipital (Cz and Oz), and right frontal pole (Fp2) contacts.[14] However, it is not clear which neural oscillations are most impacted or observable during ANT-DBS and if particular stimulation parameters have different effects on different oscillations within the ANT.

The LFP data presented here was captured as part of an ongoing Institutional Review Board-approved clinical trial (ClinicalTrials.gov identifier: #NCT05493722) protocol at the University of Minnesota. This study is investigating whether stimulation parameters can be optimized to effectively minimize broadband ANT neural activity in participants by examining the response of in-clinic recorded LFP to different stimulation parameters. We hypothesize that ANT LFP power can be effectively controlled with different stimulation parameters. This may lead to improvement in therapy outcomes and toward a personalized, closed-loop approach where stimulation is tailored to the individual, as opposed to a universal effective setting for all implanted epilepsy patients. Here we describe a case study in which different stimulation settings were tested as we monitored in-clinic LFP, at-home LFP power, and seizure frequency over time.

Case

This is a 35-year-old right-handed man who had a traumatic brain injury when he was 14 years old resulting in a prolonged hospitalization, from which he recovered with some cognitive deficits. Major regions of injury were in the bilateral frontotemporal regions, specifically the left frontal lobe. His resulting cognitive deficits included very slow responses on speeded, timed tasks, especially those requiring visual attention or rapid word retrieval. Verbal abstract thinking and reasoning were impacted, demonstrating below-average word knowledge and auditory attention span. However, mathematical reasoning and concentration, as well as visuospatial processing, are above average. Executive abilities have been impaired with slow but accurate division of attention. Lastly, verbal associative fluency and nonverbal planning were below expectation, demonstrating difficulty in word list learning

exercises and long-term retention. However, immediate recall of story passage exercises and inductive reasoning were intact.

At 21 years old, he had his first generalized tonic-clonic (GTC) seizure and started taking anti-seizure medications (ASMs). He has three seizure types currently: (1) focal aware (FA) where he speaks incoherent statements but is aware of his surroundings, (2) FA progressing to focal unaware (FU), where he loses awareness and his eyes deviates to the right, and (3) FA which progresses to FU seizures which then progress to tonic-clonic seizures. The tonic-clonic seizures generally last between 2 and 7 min. His parents are usually able to administer Diazepam immediately at the onset of FU seizures.

In the few years prior to DBS, his parents recounted roughly 4–8 seizures per month, often observing clustering of seizures if experiencing closer to 8 events in a given month. He has rarely experienced a seizure-free period greater than 2 months. The participant's ASMs at the time of DBS placement included oxcarbazepine 300 mg tablets, 2 taken in the morning and 2 taken in the evening for a total daily dose of 1200 mg, and phenytoin 100 mg capsules, 2 taken twice a day for a total of 400 mg/day. Past ASMs have included valproate, levetiracetam, and perampanel. Those past ASMs were discontinued due to side effects or lack of efficacy.

The participant's surface EEG and imaging suggest frontotemporal regions were most affected. Surface EEGs have shown seizure onset in the left frontotemporal region, but more widespread interictal activity has also been observed involving the right temporal regions. In addition, there is extensive slow-wave activity. EEGs have shown abnormal activity in the central temporal region and an independent seizure focus on the left temporal region. Two recorded seizures had left frontotemporal onset. MRI shows a large area of encephalomalacia and gliosis in the left frontal lobe with smaller regions in the right posterior inferior temporal and bilateral anterolateral occipital lobes. PET scans have demonstrated reduced radiotracer uptake in the region of encephalomalacia in the left frontal lobe and mildly reduced radiotracer uptake in the medial left parahippocampal gyrus.

Neuropsychological testing was done at age 23 (98 verbal score and 87 performance score) which showed residual multi-focal cerebral dysfunction, related to left frontal and right mesiotemporal functioning. Testing again at age 30 showed an overall worsening of cognition with the most severe findings related to left frontal functioning as well as a verbal memory decline. WADA tests demonstrated the left hemisphere was dominant for speech.

Based on his history, EEG, imaging findings, the refractory nature of his epilepsy, and that the frontotemporal regions were most affected, the participant was deemed a good candidate for a bilateral ANT-DBS implant.[3,6,15,16] A Medtronic Percept PC DBS device was placed at age 33 without complication.

Methods

Multiple stimulation parameters were selected around the clinical setting 145 Hz, 90 μs based on Percept parameter locks[17] to minimize recording artifacts while simultaneously stimulating. The clinical amplitude was titrated by the neurologist over the first 4–6 weeks for initial therapy tuning based on participant feedback. Research stimulation parameter current amplitudes were then adjusted accordingly to mimic the total electrical energy delivered (TEED)[18] by the clinical setting. After each neurologist follow-up visit (schedule shown in Figure 1), a research setting was selected based on the minimum ANT broadband response compared across all settings tested within the visit. The selected setting was programmed as an alternative setting in addition to the clinical setting. The participant would then trial the clinical or research stimulation setting by switching between settings using the Medtronic patient programmer.

In the clinic, LFP data is captured using Percept's BrainSense Streaming feature, which allows for simultaneous stimulation at a range of settings and recording at 250 Hz within the implanted region, the ANT. At home, the device can capture 144 samples per day of 10-min average LFP

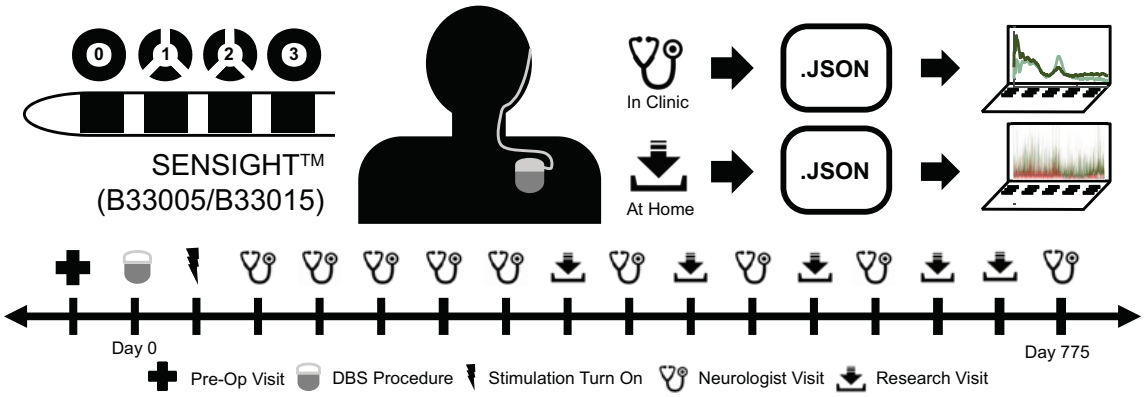

Figure 1. Participant device and timeline.
The participant underwent surgery with bilateral implantation of Medtronic Sensight™ (B33005/B33015) segmented leads and Percept PC on Day 0. Different stimulation settings were tested during in-clinic visits with the participant's neurologist. The IPG has a 60-day running buffer, after which at-home data gets overwritten. Therefore, data download visits were conducted between the neurologist's follow-up visits for uninterrupted at-home LFP recordings. Gaps in the data represent times when the team could not obtain data downloads from the participant. Data included in this study covers nearly 2 years of recordings.
IPG, implantable pulse generator; LFP, local field potential.

power measurements in a predefined 5 Hz wide frequency band.

LFP recordings in the clinic are transformed into the frequency domain through a Slepian multitaper analysis[19,20] which allows for optimal variance and frequency resolution of the power spectral density (PSD).[21] To better isolate different Berger frequency bands of interest for visualization, the $1/f$ aperiodic environmental neural noise PSD component is detrended using a modified "Fitting Oscillations & One Over F" FOOOF method.[22] The FOOOF method is based on modeling the aperiodic component as follows:

$$\text{aperiodic component} = -1 * \log 10(k + \text{freq} \wedge x) + b$$

Where b is the broadband offset, x is the frequency exponent, K is the PSD knee parameter, and F is the frequency vector based on the resolution of the sampling rate and Fourier transform. The aperiodic component represents a broader natural phenomenon of neural environment pink noise. Observable neural oscillations will "ride" on this aperiodic component because it represents the environment noise floor at each frequency. So, to not over-detrend the data and unintentionally remove some area under periodic Berger band components, the minimum points along the PSD were used for the detrended fit to keep all data above the aperiodic component. This results in a less detrended PSD but aims to keep all useful observed frequency oscillations. The baseline "stim off" aperiodic fit immediately prior to the tested stimulation setting was used to detrend the baseline and stimulation PSD for each setting. Because we hypothesized a reduction in activity, a non-parametric right single-tail Wilcoxon signed-rank test was used to compare the effect of stimulation suppression on right mean gamma LFP power.

The participant's seizure diary was kept by their caretaker, noting within their diary the date, time of day, and seizure type for each event. Total seizure frequency was recorded at every in-clinic follow-up visit and averaged over 30.43 days (the average number of days in a month). The initial seizure frequency prior to DBS for normalization was approximated at 6 seizures per month to average the estimated 4–8 seizures per month, as stated by the participant and family. The Medtronic patient programmer handheld was often used by the participant's caretaker to track seizures, though not every diary-tracked seizure was reported with the patient programmer.

The at-home Percept recorded LFP power data was concatenated across files and converted to decibels for further analysis. We used a Kwiatkowski-Phillips-Schmidt-Shin (KPSS) test to assess the stationarity of the signal across time. We then performed a one-tailed Wilcoxon rank sum test on the at-home LFP power recordings

Table 1. Stimulation settings.

Setting	Freq (Hz)	Pulse width (μs)	Stim Amp (mA)	Cycling (min)	Stim (TEED) $mA^2 \times Hz \times \mu s$	Days since implant	Days on setting	At home F_c (Hz)	Seiz. count	Participant subjective reports
C1	145	90	2	1 on/5 off	52,200	38.4	125.9	9.77	2.01	Indifferent
R1	145	120	1.5	1 on/5 off	39,150	265.4	60.0	7.81	3.68	Indifferent
C2	145	90	3	1 on/5 off	117,450	325.5	32.2	7.81	4.10	Increased amplitude
R2	110	60	5	None	165,000	357.7	19.9	7.81	0	Seizure free
C2	145	90	3	None	117,450	377.6	15.4	7.81	1.56	Indifferent
R2	110	60	5	None	165,000	392.9	23.4	7.81		Few seizures
C2	145	90	3	None	117,450	416.4	35.5	7.81	2.06	Indifferent
R3	145	60	4.5	None	176,175	451.9	0.4	7.81		Disliked, migraines
C2	145	90	3	None	117,450	452.4	23.0	7.81		Less seizures
R4	110	60	4.2	None	116,424	475.5	17.9	7.81	0	Seizure free
R5	125	50	4.3	None	115,563	494.6	30.1	7.81	2.4	Few seizures
C2	145	90	3	None	117,450	524.7	6.8	7.81		Less seizures
R5	125	50	4.3	None	115,563	531.5	52.9	7.81	1.72	Few seizures
C2	145	90	3	None	117,450	584.5	31.0	7.81	2.94	Less seizures
R5	125	50	4.3	None	115,563	615.5	27.9	7.81	2.17	Less seizures
R5	125	50	4.3	None	115,563	643.5	23.9	35.16	1.27	Few seizures
R4	110	60	4.2	None	116,424	667.5	7.9	35.16	0	Seizure free
R5	125	50	4.3	None	115,563	675.5	98.0	35.16	0.93	Few seizures

TEED, total electrical energy delivered.

within each hemisphere to assess whether there was a significant power reduction under any research stimulation settings compared to the clinical stimulation setting.

Results

Clinical summary

After implantation, the participant was seen approximately 1 month post-operatively to turn the device stimulation on. At this visit, the DBS stimulation parameters were set to the standard SANTE-defined clinical settings with a lower amplitude and it was planned to ramp the stimulation up over time. The stimulation settings tested over time are shown in Table 1.

Each setting is labeled with a "C" (clinical) or "R" (research) and number. Stimulation frequency, pulse width, amplitude, cycling, and TEED provide details for each setting. Days on the setting, time since implant when the setting was tested, at-home LFP power center frequency, and participant subjective feedback are also provided to give additional detail on activity that was qualitatively and quantitatively monitored throughout therapy tuning. Stimulation setting labels provide a reference for Figure 3.

At the last follow-up, the participant presented on research setting R5 and had experienced roughly 1 seizure per month. The participant has noted throughout the last few months of follow-up, just prior to the 2-year postoperative visit, that he

subjectively felt he was doing well compared to pre-operatively. More specifically, he was adamant to share that he felt his seizures were less severe and shorter lasting than similar events experienced prior to DBS. ASMs were not adjusted throughout the DBS follow-up. The semiology of the seizures has not changed; however, subjective feedback shows an improvement in seizure severity, duration, and recovery. Over this time-period, 773 days since implant, the participant tested seven different stimulation parameter configurations at home, of which five settings had unique frequency and pulse width combinations.

LFP analysis

LFP response in the ANT across the five at-home tested settings was analyzed over multiple in-clinic visits as shown in Figure 2. In the in-clinic right hemisphere ANT PSD, a slow gamma oscillation peak is observed between 30 and 45 Hz, which can be modulated under multiple stimulation parameters. The mean left and right ANT gamma LFP baseline activity prior to stimulation (stim off) and during stimulation (stim on) for each setting over every in-clinic visit in which the setting was tested is shown. Almost all stimulation settings (145 Hz/90 µs $p < 0.0001$, 145 Hz/60 µs $p < 0.0008$, 145 Hz/120 µs $p < 0.0046$, 125 Hz/50 µs $p < 0.2743$, and 110 Hz/60 µs $p < 0.0130$) statistically significantly reduced slow gamma power (Wilcoxon rank sum test). The baseline and stimulation $1/f$ detrended PSD under the standard SANTE trial clinical parameters are shown in Figure 2(e). While amplitude and cycling were different across visits shown in this figure, baseline slow gamma morphology decreased over time.

Participant seizure frequency was recorded over follow-up visits and shown in Figure 3(a). The participant experienced seizure reduction greater than 50% within the first year, for about 6 months relapsed to ~30% seizure reduction, and then once again achieved greater than 50% seizure reduction.

Approximately 2 years of 10-min averaged LFP power from both hemispheres are shown in Figure 3(b). Because of health and transportation difficulties early on, some data was lost given that the Percept PC has a 60-day running memory buffer. We found that the standard clinical setting (C2: 145 Hz, 90 µs, 2 mA) across at-home recordings showed significant nonstationarity ($p < 0.01$, KPSS test). We used C2 as the clinical reference for comparison to all research settings. Using a one-tailed Wilcoxon rank sum test, we found a significant difference when comparing R5 (125 Hz, 50 µs, 4.3 mA) to C2 in both hemispheres' theta/alpha (5.3–10.3 Hz) LFP power ($F_c = 7.81$ Hz; Left: $p < 0.001$, $z = -149.89$; Right: $p < 0.001$, $z = -18.76$) and R1 to C2 but only in the right hemisphere ($p < 0.001$, $z = -16.08$). These results are consistent with the CDF shift of LFP in the left hemisphere under R5 in Figure 3(d), indicating that some research settings reduced LFP power significantly compared to the clinical setting. To characterize the effect size, we measured Cohen's d between the power measured in the two stimulation conditions. The effect size, when comparing R5 to C2 in the left hemisphere was $d = -1.97$. In the right hemisphere, we did not observe a large effect size when comparing R1 to C2 ($d = -0.15$) or R5 to C2 ($d = -0.13$), suggesting that setting R5 was more effective in reducing the LFP power in the left hemisphere than in the right hemisphere.

The average daily cycle was extrapolated from 425 days of theta/alpha ($f_c = 7.81$ Hz) LFP power and 215 days of low-frequency slow gamma ($f_c = 35.16$) LFP power at-home recordings. The theta/alpha and slow gamma LFP power level in the right hemisphere was much greater than in the left hemisphere. In addition, higher theta/alpha activity was observed at night during the hours of ~10 pm–6 am while slow gamma was the reverse with higher activity observed during the day, as shown in Figure 4(a). Individual and clustering GTC seizure events were tracked by the participant over the course of follow-up through the patient programmer. The participant was not able to track every event they noted within their seizure diary, however, single and clustering events were noted while recording theta/alpha and slow gamma at-home LFP power. Prominent LFP power peaks can be observed time-locked to the participant's reported single and clustering GTCs, as shown in Figure 4(b)–(d). Additionally, during multiple clustering GTCs, the participant labeled 2 or more prominent inflections in at-home theta/alpha LFP power. The majority of GTC events were reported during the night between midnight and 6 am, which is consistent with the participant's tendency of nocturnal seizures.

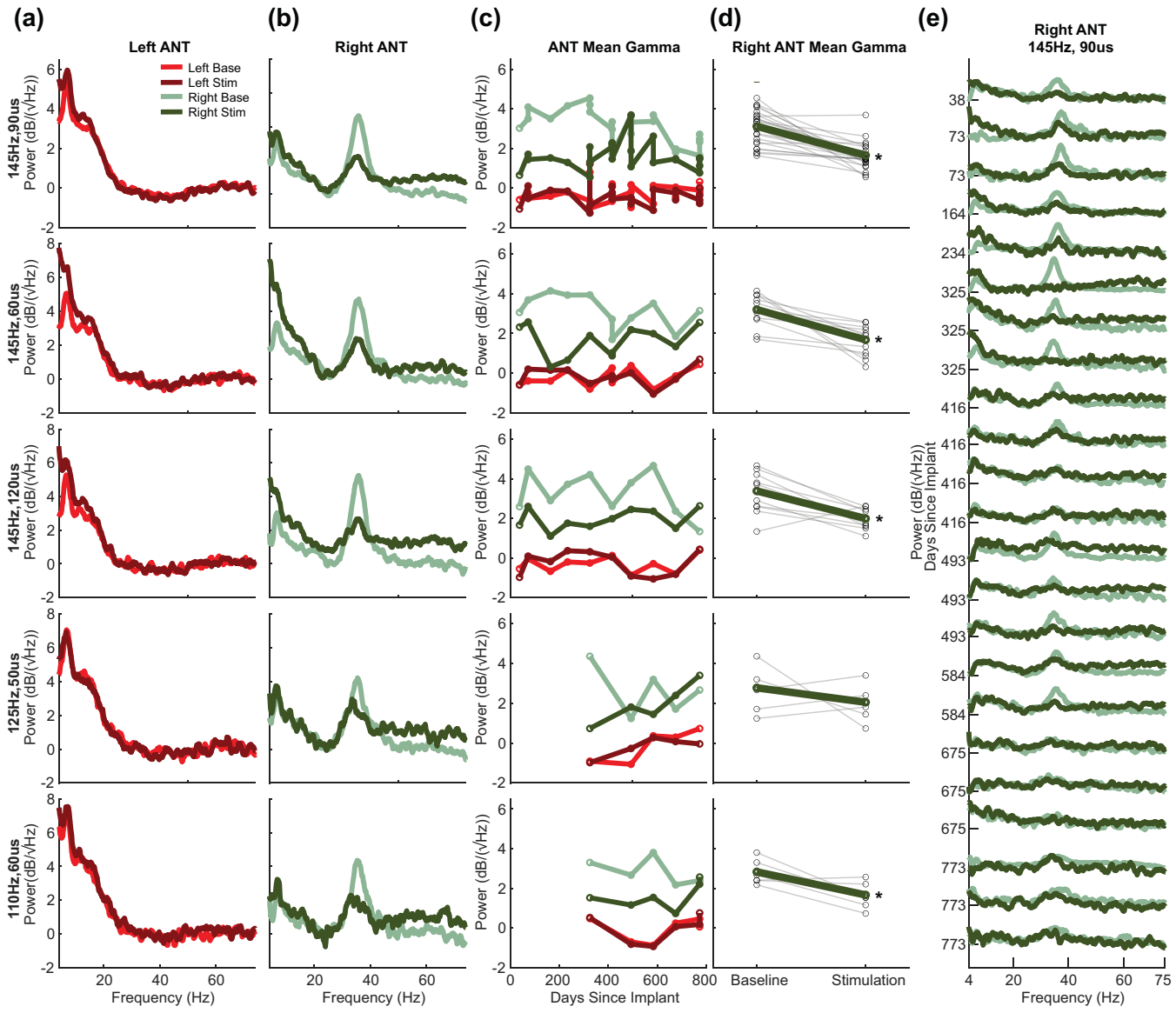

Figure 2. In-clinic ANT local field potential response to stimulation settings. Left (a) and right (b) hemisphere average ANT 1/*f* detrended PSD response during 1 min of baseline immediately prior to 1 min of stimulation across visits where each stimulation setting was tested. (c) For each setting tested at each corresponding visit, left and right ANT mean gamma power in dB between 30 and 45 Hz is shown versus days since implant. (d) Right mean gamma power response in baseline and stimulation on conditions are shown for each visit in gray and averaged across visits shown in green for each setting. All settings shown, except 125 Hz and 50 μs, statistically significantly reduced gamma power (*$p < 0.013$). (e) 1/*f* detrended right ANT PSD under baseline and standard clinical setting stimulation on conditions over the course of the therapy tuning to show PSD morphology change over time.
ANT, anterior nucleus of the thalamus; dB, decibels; PSD, power spectral density.

Discussion

In-clinic bilateral ANT recordings exhibited low-frequency "slow" gamma oscillations that could be observed over multiple visits in the "stim off" conditions that were subsequently suppressed with multiple stimulation parameters. This suppression of slow gamma activity was observed immediately after stimulation was turned on when comparing 1 min of preceding baseline activity ("stim off") to 1 min of specific stimulation parameters ("stim on"). In addition, when testing parameters in the clinic, cycling was disabled to test multiple stimulation parameters and minimize recording artifacts. Thus, this effect in

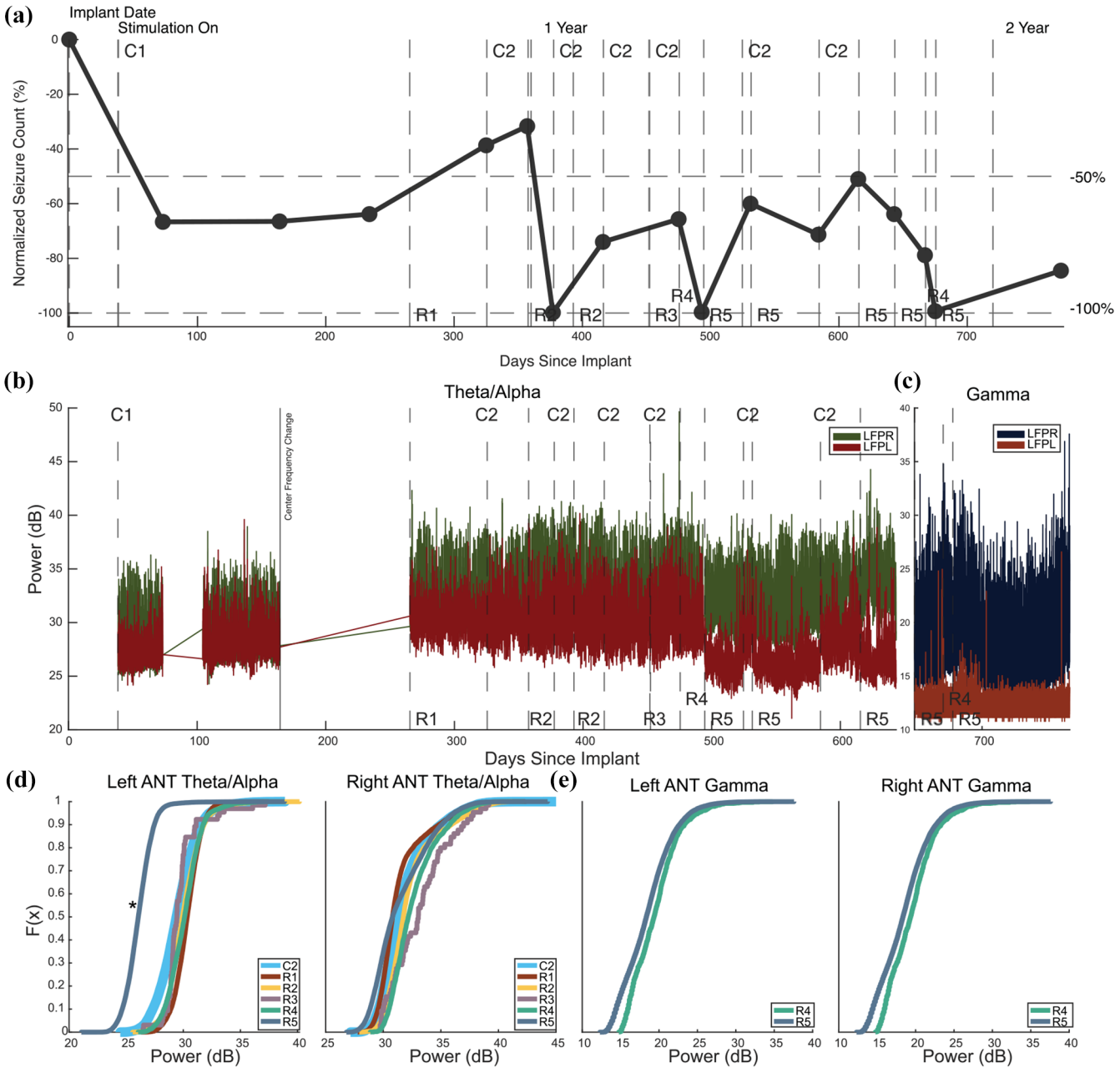

Figure 3. At-home ANT theta/alpha and gamma LFP power response to stimulation settings. (a) Seizure count in percent reduction per month normalized by pre-DBS seizure frequency measured across follow-up visits. The –50% dashed line represents the greater than 50% seizure reduction under ANT-DBS responder criteria used in the SANTE trial.[4] (b) Left and right hemisphere 10-min average LFP power from at-home recordings. Stimulation setting changes are marked with a vertical line and corresponding setting label from Table 1. Notable power reduction in the left ANT theta/alpha was observed when the participant was on setting R5 (red—left hemisphere; green—right hemisphere). (c) Slow gamma recordings in both hemispheres (f_c = 35.16) showed less relative power than alpha/theta recordings (note: *y*-axis scale differences, orange—left hemisphere; blue—right hemisphere). (d) CDF plot of theta/alpha LFP power of each stimulation setting (*$p < 0.01$, indicates a significant difference between distribution and control C2). (e) CDF plot of gamma LFP power of each stimulation setting.
ANT, anterior nucleus of the thalamus; CDF, cumulative distribution function; DBS, deep brain stimulator; LFP, local field potential.

the clinic appears to be entirely independent of a specific cycling regimen. Cycling was disabled for this participant on day 358. Although this is only a single participant, it is interesting to note that

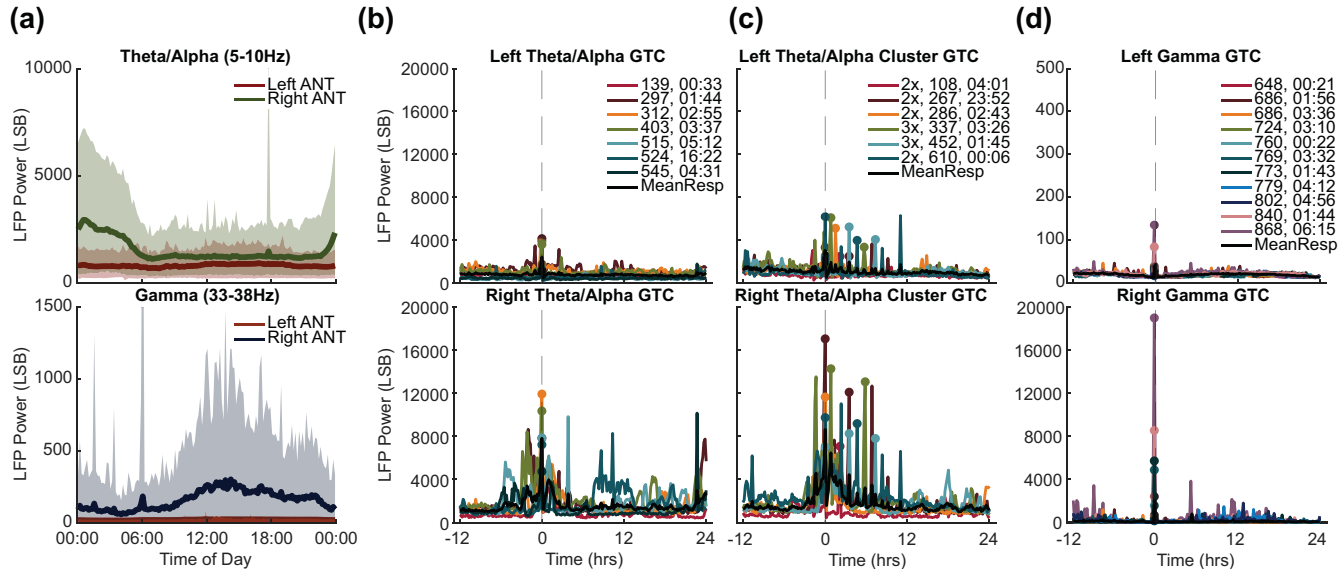

Figure 4. At-home ANT LFP power changes and seizure reporting. (a) Theta/alpha (f_c = 7.81 Hz) and low-frequency slow gamma (f_c = 35.16) at-home mean LFP power throughout the day in the left and right ANT is shown as a solid line. The shaded region indicates the LFP power from the minimum to the mean + 2 standard deviations. In right panels (b–d), LFP power around patient-reported seizures is shown with 12 h leading and 24 h following the events. (b) All single GTC seizure events were reported by the participant during theta/alpha recordings. A dot marker signifies the reported timestamp logged by the participant through the Medtronic patient programmer event feature. (c) All clustered GTC seizure events were reported by the participant during theta/alpha recordings. Multiple dots in the same color demonstrate the participant marking multiple events within the same day indicating a clustered event. In the legend, days since implant of the event and the time of the event are shown. In the legend, 2× represents a 2-event cluster and 3× represents a 3-event cluster reported by the participant. The mean LFP power response across all particular events is shown in black. (d) All single GTC seizure events reported by the participant during low-frequency gamma recordings (note: *y*-axis scales between theta/alpha and slow gamma have been adjusted for visualization if needed).
ANT, anterior nucleus of the thalamus; GTC, generalized tonic-clonic; LFP, local field potential.

these low-frequency gamma oscillations gradually disappeared over time with chronic stimulation. Future studies should examine whether this activity could represent a biomarker for the long-term improvement in DBS efficacy described in the open-label follow-up studies to the SANTE trial.

Shifts in low-frequency in-clinic PSD aperiodic components were observed in the left hemisphere and high-frequency PSD aperiodic component shifts were observed in the right hemisphere. While theta modulation may be observable in the in-clinic PSD, we believe this is an aperiodic shift rather than specific frequency band modulation. These shifts observed during stimulation may demonstrate population-level dynamical changes as shown by others and should be further explored.[23]

Fluctuations in the theta/alpha (5.3–10.3 Hz) band LFP power were distinct in both hemispheres at home. Statistically significant theta/alpha LFP power suppression was observed under one specific research setting (125 Hz, 50 µs) compared to other settings tested at home. This level of theta suppression was not observed in the clinic and therefore may require extended stimulation exposure to develop this suppressive effect. Additional effects may exist in different bands that cannot be observed by the Percept at-home recording feature. This is especially important to further investigate as nonstationary time domain signals could manifest as different neural oscillations when shown as a PSD. Some research groups have explored the dual-band coupling between theta and gamma[24–26] and perhaps observing modulation of theta and gamma under different stimulation settings could show different coupling between these neural oscillations at home.

The participant reported over 20 GTC events, of which 6 were clustering GTCs, where the participant was aware of 2 or 3 events within the cluster.

These reported seizure timestamps often coincided with large temporary increases in the at-home measurements of the 10-min average LFP power. We suspect this increase in power is not a frequency-specific increase but rather reflects a broadband increase in activity due to an epileptic event. Further investigation using high-resolution sEEG recordings of interictal and ictal ANT LFPs is necessary to confirm how ictal ANT LFP time domain data manifests in the frequency domain. In addition, scalp EEG and/or wearable devices may provide improved seizure tracking to determine whether unmarked large at-home LFP power measurements are physiological events, undocumented perceivable seizure events, or electrographic epileptic events not perceivable by the participant.

In the right ANT, theta/alpha LFP power showed large amplitude reported events riding on lower amplitude activity likely due to changes in sleep cycles. While no polysomnography was conducted to monitor sleep stages, varying amplitudes and durations of a 90-min cycle could be observed in the alpha/theta activity. The majority of seizures reported were nocturnal, often occurring between midnight and 6 am, which appeared to be at random phases of this cycle. However, the average of all these seizures indicates that perhaps nocturnal seizures have the highest probability of occurrence in the middle of the total sleep cycles over the night (Figure 4(c)).

Furthermore, slow gamma was most observable during the day opposite to theta/alpha activity. Better characterization of the functional connectivity of the ANT would clarify whether slow gamma activity is a local ANT signal, a network oscillation, or some epileptic network pathology. Given the known anatomy of the circuit of Papez and recent findings in connectivity showing strong projections between the ANT and the frontotemporal lobe,[9,27] searching for low-frequency slow gamma oscillations within scalp or stereo EEG recordings may shed light on slow gamma origination in the ANT and potentially associated lobes.

While the participant was bilaterally implanted in the ANT, slow gamma "stim off" LFP activity and subsequent suppression were only observed in the right hemisphere and theta/alpha (5.3–10.3 Hz) LFP power at-home suppression was best achieved using a research setting in the left hemisphere. Without the ability to record multiple frequency bands or continuous time domain data, it is hard to account for the chronic effects of stimulation on theta/alpha and gamma activity at home. In this specific case, the participant's predominantly left frontal lobe injury may have interfered with or affected gamma activity generation in the left hemisphere. Why theta/alpha activity in his left hemisphere was more affected or able to be more suppressed in the at-home data is unclear. Understanding the relationship between hemispheres may shed light on these unilateral effects we observed.

Limitations

Our study is limited by several factors. Clinically, seizure diaries are known to be relatively unreliable as an objective measure of seizure frequency. We have begun to add wearable sensor data such as heart rate, respiratory rate, and skin conductance from smartwatches designed for seizure detection to improve accuracy in seizure counts. Moreover, as our participant described, the quality of seizures can change as well, in terms of intensity, length, and other factors such as postictal fatigue or confusion. These are not well captured by current methods of seizure reporting. Developing systematic ways to track seizure type, frequency, intensity, postictal recovery, and change in symptoms would allow for a more accurate evaluation of therapy success. Improvements can also be seen in psychiatric comorbidities, cognition, and other aspects of health related to epilepsy but not necessarily to seizure count. Further investigation and reporting of these factors should be used when investigating chronic effects of stimulation as a function of time with therapy.

In epilepsy studies, the effect of DBS may take a long time to fully manifest, unlike other applications, such as Parkinson's disease, where the effects of stimulation can be observed in a short time frame. The benefit of Percept is that it allows for long-term at-home recordings to measure potential changes. We originally proposed to record for 1 month in the clinical setting and 1 month in the research setting given the 60-day at-home LFP memory buffer of Percept and repeat this for up to a year. However, as evidence accumulates showing that the patient performs better under one setting than another, it becomes difficult to justify balancing the use of the

two settings for comparisons. Additionally, if an effective setting is known and a new setting is potentially not as effective, it leaves the subject at greater risk of more GTC events which in turn could increase the risk of sudden unanticipated death in epilepsy. Nevertheless, clinicians have equipoise when making these decisions as there is currently no data to guide them in this process and a new setting could potentially be more effective rather than less. Thus, the only way this issue can be settled in the future is a prospective, blinded, randomized clinical trial in which patients are randomized to varying time periods using the standard clinical setting or a set of "optimized settings" based on a biomarker of choice.

Another challenge of interpreting the at-home ANT LFP power over time is the confound between the effects of chronic stimulation and changes in drug regimen. LFP signals recorded at higher resolution at home or in multiple frequency bands may provide additional detail which can help quantify the long-term response to stimulation. A study utilizing higher-resolution at-home recordings in parallel with ASM blood concentration tracking may reveal the dynamics of stimulation and ASM medication interactions as a combined therapy.

While this device has provided new recording capabilities, Percept PC can only capture LFPs at 250 samples per second with an inter-sample interval of 4 ms. Different neuronal populations have unique action potential characteristics on the order of 1–10 ms so a higher sampling rate could provide higher resolution time domain activity of the ANT neuronal population. Understanding aperiodic component shifts in the frequency domain will likely require higher sampling rates in the time domain. At home, the resolution is also limited, with a 60-day memory buffer of a 10-min average LFP power in a 5 Hz defined frequency band starting at 7.81 Hz. The center frequency was set to the lowest value of 7.81 Hz to capture as much theta as possible, but observing frequency bands below 5.31 Hz like delta is not possible with the current device options. Monitoring both theta and slow gamma at home while testing multiple settings will be crucial to better understand how these neural oscillations change over time, especially as chronic effects of stimulation and hemisphere-specific epilepsy dynamics take effect.

Lastly, this case study is limited by its single-participant design, which restricts the generalizability of its findings. Although this study highlights the successful intervention in a unique patient scenario, it cannot account for the broad variability across the heterogeneous epilepsy population. Caution should be exercised when extending these results to other patient groups or clinical contexts.

Conclusion

This patient participated in a clinical study examining the ability to minimize broadband ANT activity using standard and nonstandard DBS settings with a novel device that allows for the recording of LFPs. Clinically, the participant tolerated the research settings and did not appear to subjectively rate the research settings any differently than the clinical settings. Objectively, the participant spent the majority of the 2 years with greater than 50% reduction in seizures, which is typical for responding patients undergoing ANT-DBS. The participant also subjectively shared that he felt his seizures were less severe in intensity, shorter compared to his preoperative baseline seizure events, and often his post-ictal recovery was much quicker. Suppression of slow gamma activity in the clinic in the right hemisphere and suppression of theta at home in the left hemisphere show promise as quantitative feedback biomarkers for ANT-DBS in this specific participant. Understanding the local and network relationships of theta and low-frequency "slow" gamma oscillations in the thalamus would further explain how these modulated oscillations may relate to the onset and propagation of seizures. Future studies involving more participants could help determine whether theta and gamma modulation can prove useful as quantitative biomarkers of seizure suppression for use in closed-loop stimulation paradigms.

Declarations

Ethics approval and consent to participate

The experimental protocols were approved by the Institutional Review Board (IRB) of the University of Minnesota (No. STUDY00011863) on March 26, 2021. All research activities complied with ethical regulations and were performed in accordance with the regulations of each hospital. Informed consent to use participant data for

research purposes was obtained from all patients prior to involvement in the study. They were given the option to refuse to participate by opting out. Consent to participate: All participants provided written informed consent prior to participating.

Consent for publication

Consent to publish the participant's data was obtained through the IRB-approved informed consent form.

Author contributions

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Acknowledgements

A special thank you to the participant for contributing their data.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work has been supported by the National Institute of Neurological Disorders and Stroke (U01NS 124616). Zachary T. Sanger is a 2024–2025 MnDrive Brain Conditions Fellow and his time conducting research reported in this publication was supported by the University of Minnesota's MnDRIVE (Minnesota's Discovery, Research and Innovation Economy) initiative.

Competing interests

Financial conflict of interest: Z.T.S. is a paid graduate student intern contractor with Medtronic. All research conducted in this paper was not in collaboration with Medtronic or related to the contract work Z.T.S. has conducted through the contract role. All other author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Data can be made available upon reasonable request sent to the corresponding author.

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