

Evoked Resonant Neural Activity Supports Physiology-Guided Asleep Deep Brain Stimulation

Nuri Ince

Ince.Nuri@mayo.edu

Mayo Clinic <https://orcid.org/0000-0003-4985-4528>

Luciano R F. Branco

University of Houston

Hossein Heydari

Mayo Clinic

Chandra Prakash Swamy

Mayo Clinic

Nora Vanegas-Arroyave

Baylor College of Medicine

Arjun Tarakad

Baylor College of Medicine

Lisa Taneff

Baylor College of Medicine

Steven Bellows

Baylor College of Medicine

Charennya Anandan

Baylor College of Medicine

Sandhya Palit

Baylor College of Medicine

Emily Ruether

Mayo Clinic

Rushna Ali

Mayo Clinic

Kai J. Miller

Mayo Clinic <https://orcid.org/0000-0002-6687-6422>

Bryan Klassen

Mayo Clinic

Ashwin Viswanathan

Baylor College of Medicine

Article

Keywords: ERNA, PD, STN, GPi, Anesthesia, electrophysiology

Posted Date: August 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10483928/v1>

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Additional Declarations: There is **NO** Competing Interest.

Abstract

General anesthesia increasingly facilitates asleep deep brain stimulation (DBS) surgery but suppresses spontaneous electrophysiological signals used to guide lead placement. Here, we investigated whether evoked resonant neural activity (ERNA), a stimulation-evoked biomarker of basal ganglia circuitry, remains informative during asleep DBS. We analyzed intraoperative recordings from a multisite cohort of 45 patients (86 hemispheres) undergoing subthalamic nucleus or globus pallidus internus DBS under awake and anesthetized conditions. Anesthesia markedly attenuated spontaneous beta and high-frequency oscillatory activity. Although ERNA amplitude was reduced at matched stimulation intensities, increasing stimulation current restored high-amplitude, spatially localized responses while preserving anatomical specificity. Across both targets, ERNA spatial distributions remained stable across awake and anesthetized states, co-localized with established motor-network biomarkers, and retrospectively identified electrode levels associated with the greatest postoperative therapeutic window. These retrospective findings position stimulation-evoked circuit interrogation as a complement to imaging for physiology-guided asleep DBS and as a candidate signal for contact prioritization. Prospective studies are warranted to determine whether ERNA-guided decisions improve placement, programming efficiency and clinical outcomes.

Introduction

Over the last three decades, deep brain stimulation (DBS) has emerged as a highly effective treatment for a growing number of neurological conditions, including Parkinson's disease (PD).^{1–5} High-frequency DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPi) has demonstrated robust efficacy in managing the motor symptoms and complications in levodopa-resistant patients with PD.^{6–8} Clinical outcomes following DBS are strongly dependent on accurate electrode placement, with suboptimal targeting being associated with reduced therapeutic benefit and an increased incidence of stimulation-induced side effects.^{6,9–12} Both the STN and GPi occupy relatively small volumes within the tightly packed basal ganglia (Fig. 1a, b). The therapeutic target for DBS is the motor subterritories within the STN and GPi, narrow regions only a few millimetres wide, comparable in size to standard DBS contacts (~ 1–1.5 mm in height and ~ 1.3 mm in diameter), highlighting the challenge of precise lead placement.^{13–15} Accurate lead placement is further complicated by intraoperative brain shift, image-registration inaccuracies, stereotactic targeting error, and individual anatomical variability.^{16–19} Collectively, these factors emphasize that achieving effective electrode placement within structures of this scale remains inherently challenging.

DBS provides a unique opportunity to examine the oscillatory neural dynamics of motor networks in individuals with PD. Excessive beta-band (13–30 Hz) activity in local field potentials (LFPs) has long been recognized as a hallmark of PD pathophysiology, diminishing with DBS and dopaminergic medication.^{20–22} High-frequency oscillations (HFOs, 200–450 Hz) and their nonlinear coupling with beta oscillations have also emerged as important signatures in PD electrophysiology.^{23–28} These

spontaneous (“passive”) LFP features serve strategically in electrophysiological targeting during awake DBS procedures.^{29,30}

However, asleep DBS performed under general anesthesia (GA) has gained increasing adoption owing to improved patient comfort and more streamlined surgical workflow while reducing patient fatigue and vulnerability associated with remaining awake during surgery.^{31,32} Although asleep and awake DBS achieve broadly comparable motor outcomes at the group level,^{32,33} individual lead placement may still be affected by distorted anatomy, limited visualization of relevant landmarks, intraoperative brain shift, or mismatch between the anatomically defined and clinically optimal target.^{34,16,35,36} Electrophysiology can therefore provide complementary functional confirmation of lead location. GA, however, substantially limits the utility of passive electrophysiological biomarkers commonly used for targeting. In particular, single-unit firing rates^{37,38} and spontaneous LFP features such as beta activity and HFOs are markedly attenuated, limiting their utility for physiology-guided targeting.^{39,40} At the same time, reliance on imaging-based targeting alone has important limitations. Several studies have shown that anatomy-guided approaches can miss the intended STN sensorimotor territory in approximately one in five cases,^{41,42} suggesting that anatomical targeting alone may not reliably ensure optimal lead placement in all patients. Together, these observations highlight a critical need for alternative physiological markers or active probing strategies that can support accurate targeting during asleep DBS procedures.^{41,42}

Evoked Resonant Neural Activity (ERNA)⁴³ has emerged as a promising candidate. As the name suggests, ERNA is a dampened resonant response elicited by DBS and characterized by amplitudes in the hundreds of microvolts, substantially exceeding those of beta oscillations or HFOs, which typically fall in the tens and single-digit microvolt ranges, respectively.^{39,44} This high signal-to-noise ratio (SNR) enables reliable detection and underscores ERNA’s strong translational potential, which is further strengthened by its anatomical specificity. In prior intraoperative work including awake patients, our group demonstrated that ERNA is selectively evoked when stimulation is delivered within the STN, whereas stimulation superior to the nucleus produces a non-resonant response.⁴⁵ These properties make ERNA uniquely suited for electrophysiology-guided targeting during asleep DBS procedures, where spontaneous biomarkers are markedly attenuated and cannot reliably support surgical decision-making.

Building on these observations, we tested the hypothesis that ERNA can serve as a reliable and robust neurobiomarker for DBS electrode targeting under both awake and GA conditions. We systematically characterized ERNA across a large multisite cohort of patients undergoing bilateral lead placement in either the STN or GPi during awake and asleep DBS surgery (Fig. 1a-b). Using bursts of 130 Hz monopolar and biphasic stimulation delivered through chronic directional DBS leads (Fig. 1c-e), we addressed two primary questions: How does ERNA differ between STN and GPi targets under awake and GA conditions? How does the spatial topography of ERNA compare with that of passive PD biomarkers such as beta oscillations and HFOs?

By answering these questions, we aimed to clarify ERNA's relationship to established LFP neurophysiological markers and evaluate its utility as an additional biomarker to guide asleep DBS surgery and ultimately improve targeting accuracy and therapeutic outcomes.

Methods

Patient demographics

Forty-five patients (18 females) with refractory PD were recruited for this study, who had been recommended for bilateral STN (27 patients) or bilateral GPi-DBS (18 patients) by the movement disorders team (Fig. 1a, b). Patients' ages ranged between 44 to 83 (66 ± 10 years). Thirty-two patients were implanted with Boston Scientific Vercise Directional leads (Marlborough, MA, USA), 10 patients with Medtronic Directional lead model B33005 (Medtronic, Ireland) and 3 patients with Abbot Directional lead model 6172. Thirty-nine patients were implanted at Baylor St. Luke's Medical Center, Houston, TX, USA, and 6 patients were implanted at Mayo Clinic, Rochester, MN, USA. The study protocol was approved by the Institutional Review Boards of Baylor College of Medicine, Mayo Clinic, and University of Houston. All patients provided written informed consent.

Data collection and signal processing

We recorded LFPs from all 45 patients intraoperatively during bilateral DBS surgery after leads were secured at their final position (Fig. 1a). Four hemispheres were excluded due to technical issues leading to failed recordings, yielding 86 hemispheres with eight-channel ERNA recordings (Fig. 1g). General anesthesia was maintained intravenously with propofol and remifentanyl, supplemented by a bupivacaine scalp block. Anesthetic infusions were paused and patients were awakened for awake-state recordings, before re-establishing anesthetic depth for surgical closure.

The cohort included patients recorded exclusively awake, exclusively under GA, and a subset with recordings obtained in both conditions, when the same patient was fully awake and later under GA (Fig. 1g). All electrophysiological recordings and stimulation were performed using the Summit Macro+Stim amplifier (Ripple Neuro, Salt Lake City, UT). Local field potentials were acquired at a 15 kHz sampling rate with 24-bit resolution for an average duration of 123 ± 42 s in the awake state and 112 ± 37 s under GA. Raw signals were visually inspected for artifacts, and noise was attenuated using a previously validated source separation approach⁴⁶ to remove common activity across contacts. Unless otherwise stated, beta and HFO band comparisons between hemispheres used the contact with the largest root-mean-square (RMS) amplitude in the respective band for each electrode, whereas spatial distribution analyses included all recorded contacts.

Evoked potentials were elicited using bursts of unilateral, monopolar, biphasic, charge-balanced stimulation delivered separately to the most ventral and most dorsal contacts of each electrode (Fig. 1c), resulting in four stimulation sites per patient. In the awake state, stimulation amplitudes were titrated by

the attending neurologist within a 0.5 to 5 mA range based on each patient's therapeutic window (TW) and side-effect thresholds and were not routinely escalated to the maximum amplitude in order to ensure patient comfort. Under GA, stimulation was delivered from 0.5 to 5 mA in 0.5 mA increments. For each hemisphere, the stimulation amplitude that elicited the maximal ERNA response was selected for subsequent analysis. Each stimulation was repeated for a total of 9 non-consecutive trials, in a randomized order of amplitudes between 0.5 to 5 mA. A standard stimulation frequency of 130 Hz, 100 μ s pulse width was used for all patients. Each stimulation was delivered in bursts of 20 pulses followed by a 150-200 ms gap during which ERNA could be observed across the electrode (Fig. 1e) and allowed to dissipate before the next trial. This stimulation paradigm was selected to mimic clinically relevant DBS parameters (i.e. frequency, pulse width, amplitude) while allowing the evoked resonant response to emerge during the post stimulation interval. To provide additional time for the network to return to baseline, bursts were not delivered on the same site consecutively. Instead, an alternating pattern was implemented (Fig. 1c), selecting the contralateral hemisphere after each stimulation, followed by the ipsilateral hemisphere at the alternate top or bottom contact, then the contralateral hemisphere again, and finally returning to the initial contact approximately 1.3 second after the initial stimulation ended.

To avoid large stimulation artifacts, trial selection started 2 ms after termination of the stimulation burst, thereby excluding the peak artifact. To deal with amplifier settling transient, each trial was baseline corrected by modeling and subtracting residual exponential decay components using a third-order Savitzky–Golay filter with a 5 ms window. A subsequent third-order Savitzky–Golay filter with a 1 ms window was applied to attenuate high-frequency residual noise prior to analysis. This preprocessing pipeline was implemented to ensure stability of the early post-stimulation segment and to mitigate hardware-induced transients associated with charge-balanced stimulation, thereby preserving the integrity of the evoked neural response. As previously demonstrated, this preprocessing retains the ERNA morphology.⁴⁵

ERNA features were then calculated from preprocessed waveforms, including peak to peak (P2P, taken from the first positive deflection, P1, to the subsequent trough, N1), RMS values in a 50 ms window starting from first zero-crossing after N1, latency from last DBS pulse until P1, and frequency calculated as the inverse period between P1 and P2 (Fig. 1f). Given the greater robustness of RMS to waveform morphology and noise compared to P2P, most analyses focused on ERNA RMS. Unless otherwise noted, electrode contacts reliably capturing the strongest ERNA signal given by largest RMS value are selected for each hemisphere for the group analyses. To observe the spectral dynamics of ERNA, we calculated time-frequency maps (TFMs) from the preprocessed waveforms using Thompson's multi-taper method using 2 Slepian windows for each 20 ms of data with 19 ms overlap.

We assessed spatial correspondence between awake and GA signals, and between biomarkers using two complementary approaches. First, rank-based confusion matrices were constructed by ranking contacts according to biomarker features in each biomarker/condition and then aggregating these ranks across hemispheres. Second, cosine similarity was used to evaluate the angular similarity between the 8-dimensional amplitude vectors, capturing the spatial configuration of signals along the lead. For both

analyses, we derived biomarker features from all 8 contacts, using beta and HFO band power and ERNA RMS amplitudes.

Therapeutic benefit was assessed independently for each hemisphere by experienced movement disorder neurologists through systematic postoperative programming across electrode levels (Lv1–Lv4). At each level, stimulation amplitude was gradually increased to determine the entry point, defined as the lowest current producing a clinically meaningful improvement in Parkinsonian motor symptoms, and the exit point, defined as the current at which stimulation-induced adverse effects first emerged. The TW was calculated as the difference between the exit and entry amplitudes, representing the range of stimulation amplitudes that provide clinical benefit without intolerable side effects. Electrode levels with larger TW are generally considered to offer greater programming flexibility and superior clinical utility. Accordingly, the best levels were defined as those with the largest TW, lower entry amplitudes, and higher side-effect thresholds, whereas the worst levels exhibited absent or minimal therapeutic benefit (no identifiable entry point), narrow TW, lower side-effect thresholds, and higher stimulation amplitudes required to achieve benefit.

To align electrophysiological measures with the level-wise clinical programming assessment, biomarker measures from the eight directional contacts were consolidated into four electrode levels by averaging directional segments (A, B, and C) at levels 2 and 3, followed by within-electrode normalization (z-score). The relationship between electrophysiological biomarkers and clinical efficacy was then evaluated by comparing biomarker amplitudes at the electrode levels associated with the best and worst TW.

3D Electrode Reconstruction and Anatomical Validation

For a subset of patients (26 STN patients and 16 GPi patients; 84 hemispheres in total) with complete preoperative MRI and postoperative CT imaging, a 3D model of the electrode positions was created using Lead-DBS.³⁴ Specifically, MRI to MRI and MRI to CT images were linearly coregistered using Advanced Neuroimaging Tools (ANTs)⁴⁷ and SPM⁴⁸, respectively. All volumes were normalized to MNI152NLin2009bAsym⁴⁹ space using ANTs⁵⁰ with the preset “effective: low variance default + subcortical refinement”. DBS electrode trajectories were constructed using PaCER⁵¹ and manually refined afterwards. To examine the anatomical distribution of electrophysiological biomarkers, biomarker amplitudes were first normalized (z-score) within each hemisphere. For each biomarker (ERNA, beta, and HFO), the contacts exhibiting the strongest and weakest responses were identified and projected into standard MNI space together with their reconstructed electrode locations. This enabled visualization of the spatial distribution of biomarker maxima and minima relative to each STN and GPi.

To quantify anatomical specificity, receiver operating characteristic (ROC) analysis was performed using contact distance to the target structure to distinguish biomarker maxima from minima. Because stronger biomarker responses were expected to occur closer to the target, distance was used directly in the ROC estimation, with smaller distances indicating a higher likelihood of classification as a biomarker

maximum. The optimal distance threshold was selected from the ROC curve using Youden's index⁵² and subsequently applied to categorize contacts as inside or outside the target structures. Confusion matrices were generated by comparing these distance-based classifications against the biomarker-defined strongest and weakest contacts, and overall accuracy was calculated as the proportion of maxima classified as In and minima classified as Out. Hemispheres in which all channels were located outside the target structure were excluded from the inside-versus-outside confusion matrix analysis (7 STN and 1 GPi hemispheres; Fig. 6).

Statistical analysis

Unless otherwise stated, comparative statistical analyses between matched two groups were conducted using paired *t*-tests, while comparisons between independent groups were performed using unpaired *t*-tests (Welch correction for unequal variances where appropriate). The threshold level to determine significance was 0.05. In the boxplots, the central mark denotes the median, while the bottom and top edges represent the interquartile range (IQR; 25th and 75th percentiles), respectively. Whiskers extend to 1.5xIQR, with outliers depicted individually using a red "x" symbol. The Watson-Williams⁵³ test was used to compare circular mean directions in the angular similarity analyses. Surrogate null distributions were generated by repeatedly randomizing the observed data structure: for each iteration, vectors were randomly sampled from the empirical distribution, and their elements were shuffled to disrupt the original angular correspondence while preserving the distribution of observed values.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The raw data are not publicly available as the data might contain potentially identifying or sensitive information that could compromise the privacy of the research participants.

Results

Figure 1 summarizes the experimental protocol, representative ERNA waveforms, and the patient cohort. Among patients with available follow up data, DBS was associated with a significant improvement in OFF medication MDS UPDRS motor scores at 6 months (paired *t*-test, ****p* < 0.001; Fig. 1h). These clinical outcomes provide therapeutic context for the study and confirm effective engagement of the targeted motor circuits, thereby supporting the interpretation of the electrophysiological analyses.

General anesthesia suppresses beta and HFO activity

We first examined whether spontaneous electrophysiological biomarkers commonly used during awake surgery remain informative under GA. Baseline LFP recordings from final STN and GPi lead positions

revealed marked attenuation of spontaneous activity under GA, including reductions in both beta-band and HFO signals (Fig. 2a–f). Group-level spectral analysis confirmed significant suppression in both bands across targets ($***p < 0.001$, unpaired t -test), reflected by substantial reductions in median band-limited RMS amplitude in STN (beta: 6.8 to 1.1 μV ; HFO: 2.6 to 1.2 μV) and GPi (beta: 7.2 to 3.0 μV ; HFO: 2.2 to 1.0 μV).

Higher stimulation current restores ERNA under anesthesia

We next evaluated whether ERNA remains clinically informative under GA despite the suppression of spontaneous electrophysiological biomarkers. Because stimulation amplitudes were intentionally limited during awake recordings to maintain patient comfort but could be systematically increased under GA, we compared the maximal ERNA response obtained from each hemisphere in each condition. Under this framework, ERNA RMS amplitude remained comparable between awake and GA recordings in both STN and GPi (Fig. 3a, b), although significantly higher stimulation currents were required under GA to evoke these maximal responses (Fig. 3c). When recordings were compared at matched stimulation intensity (2 mA), ERNA amplitude was significantly reduced under GA (Fig. S1), indicating that anesthesia attenuates, but does not abolish, the underlying network response.

Grand average ERNA waveforms had comparable waveform morphology across awake and GA conditions, with median RMS amplitudes of 49.2 and 35.2 μV in STN and 9.2 and 6.8 μV in GPi, respectively. In agreement with the RMS analysis, peak-to-peak amplitudes were not significantly different between conditions (Fig. S2a; n.s., $p > 0.05$, unpaired t -test; STN: 414.9 vs. 347.5 μV ; GPi: 76.6 vs. 80.0 μV), and RMS and P2P measures were strongly correlated (Fig. S2b). Between targets, ERNA RMS was significantly higher in STN compared to GPi (Fig. 3b, $***p < 0.001$, unpaired t -test). To contextualize anesthesia effects across electrophysiological features, we computed the GA-to-awake magnitude ratio for each hemisphere with recordings in both conditions (Fig. 3d). ERNA exhibited the ratio closest to unity (1.07), consistent with minimal suppression relative to beta and HFO bands.

Although ERNA amplitude was preserved under GA, its center frequency was significantly reduced in both targets (Fig. 3e–h). In STN, the center frequency shifted from 352 to 322 Hz (Fig. 3f, $***p < 0.001$); GPi showed a similar reduction (center frequency 352 to 322 Hz; Fig. 3h, $***p < 0.001$). Illustrative ERNA waveforms recorded in the same hemispheres during awake and GA conditions (Fig. 3e, g) demonstrate inter-peak prolongation under GA, consistent with the observed frequency reduction. In addition to this effect, latency analysis (Fig. S3) revealed a modest but significant prolongation in STN under GA (3.6 ms in awake vs. 3.8 ms under GA; $*p < 0.05$, Fig. S3b), whereas GPi latency remained largely unchanged (n.s., Fig. S3d). Importantly, the matched-amplitude data (Fig. S2) reproduced the same GA-associated frequency slowing, indicating this effect is not driven by stimulation intensity.

ERNA spatial localization is preserved under anesthesia

To determine whether anesthesia alters the spatial localization of ERNA along the DBS lead, we compared the distribution of amplitudes across all eight contacts in hemispheres recorded during both awake and GA conditions (Fig. 4). Clinically, preservation of the same maximal ERNA contact across physiological states would indicate that ERNA remains a reliable marker of the optimal recording location despite anesthesia.

ERNA demonstrated remarkable spatial stability across anesthetic states. In the STN, the contact exhibiting the largest ERNA response during awake recordings was identical to that observed under GA in every hemisphere studied (12/12), indicating complete preservation of the physiologically dominant recording site (Fig. 4a). In contrast, beta and HFO showed substantially lower spatial agreement (Fig. 4b-c), reflecting the greater susceptibility of passive biomarkers to anesthesia. In the GPi, first-ranked agreement was more variable, but the complete ERNA spatial profile remained more stable across states, with smaller subspace angles than beta (33° versus 61° ; Fig. 4d-f). Surrogate analyses further confirmed significant awake–GA spatial correspondence for ERNA in both targets, whereas neither beta nor HFO exceeded chance-level correspondence.

ERNA spatially aligns with beta and HFO in awake DBS

Because beta oscillations and HFOs are established electrophysiological signatures of the Parkinsonian motor network, we next examined whether ERNA localizes to the same functional territories along the DBS lead. Demonstrating spatial agreement would indicate that ERNA captures the same clinically relevant motor circuitry while offering the practical advantage of remaining measurable under GA. In a representative STN hemisphere (Fig. 5a-c), the contact yielding the largest ERNA amplitude (Lv2c), coincided with the largest power in HFO and second largest power in beta bands. The distribution across the whole electrode is illustrated in the ERNA traces (Fig. 5a) and power spectral density plots of beta (Fig. 5b) and HFO (Fig. 5c), along with their normalized amplitude distributions which are used for subsequent

spatial analysis. Insets displaying the biomarker spatial agreement for this hemisphere are also shown as confusion matrices and polar plots highlighting the similarity between ERNA, beta, and HFO spatial distributions. This analysis was then extended to all hemispheres recorded in the awake state, and spatial agreement between biomarker pair was quantified using the same concordance framework described in methods, incorporating rank-based comparisons and cosine similarity across the leads.

Spatial profiles of ERNA closely paralleled those of beta and HFO, with rank-based analyses showing strong diagonal agreement (Fig. 5d) and subspace comparisons demonstrating angle distributions significantly different from surrogate null distributions (Fig. 5f). Comparison of agreement rates between the top four ERNA channels and each beta/HFO rank position demonstrates high specificity between ERNA and passive oscillatory biomarkers (Fig. 5e). The strongest beta and HFO channels co-localized with the highest-amplitude ERNA contacts in approximately 88% of hemispheres (53/60). Agreement remained high for the second-ranked beta and HFO channels (86% and 78%, respectively)

and was still substantial for the third-ranked channels, reaching 71% for both beta and HFO. Moreover, average cosine similarity was 0.67 for ERNA–beta, 0.68 for ERNA–HFO, and 0.75 for beta–HFO (Fig. 5f, g).

Anatomical localization of ERNA

We next investigated whether ERNA preferentially localizes to the dorsolateral STN and posteroventral lateral GPi, the sensorimotor subregions routinely targeted during DBS implantation to maximize motor benefit. For this purpose, each electrode and hemisphere were 3D-reconstructed and mapped to a normalized atlas space (see *Methods*), enabling anatomical visualization of biomarker maxima and minima within each target (Fig. 6b, f).

In the STN, the largest ERNA, beta, and HFO responses were localized towards the middle portion of the nucleus, whereas superior sites outside the nucleus displayed the weakest amplitudes (Fig. 6b). The accompanying confusion matrices summarize the ROC-derived distance classification, quantifying how often biomarker maxima were classified as IN and biomarker minima as OUT relative to the target. ERNA showed the strongest anatomical confinement, with 97% classification accuracy during awake recordings and 95% under GA. Awake HFO exhibited slightly lower specificity at 92%, whereas beta was more diffusely distributed, with 88% overall accuracy. By contrast, passive biomarkers under GA performed worse than GA ERNA with 77% accuracy for beta and 80% for HFO (Fig. S5a).

In the GPi, maximal biomarker activity was localized to posteroventral lateral territories (Fig. 6f). ROC-derived In/Out classification again showed strong spatial confinement of ERNA within the GPi boundaries, with 86% accuracy during awake recordings and 83% under GA. Awake beta and HFO showed accuracies of 81% and 86%, respectively (Fig. 6f) with GA counterparts at 50% and 77%, respectively (Fig. S5b).

Importantly, ROC analyses confirmed that ERNA provided the strongest spatial discrimination across targets and anesthetic states. In the STN, ERNA achieved the highest AUC during awake recordings (0.979) and remained highly discriminative under GA (0.959), exceeding awake beta (0.864), awake HFO (0.927), and GA passive biomarkers (beta: 0.705; HFO: 0.777; Fig. 6b and Fig. S5a). Although ERNA discrimination was slightly lower in GPi than STN, awake and GA ERNA still showed the highest AUCs in GPi (0.914 and 0.898), outperforming awake beta (0.780), awake HFO (0.891), and GA passive biomarkers (beta: 0.333; HFO: 0.818; Fig. 6f and Fig. S5b).

As an additional analysis, we examined the spatial distribution of ERNA, beta, and HFO across DBS electrode levels in both STN and GPi by combining directional contacts into their respective levels (Fig. S4a-c). Across targets, biomarker amplitudes showed a clear depth-dependent organization (Fig. S4). In the STN, ERNA, beta, and HFO most frequently peaked at level 2, whereas superior levels, which are typically positioned above the nucleus, rarely captured peak activity. A similar pattern was observed in the GPi, where ERNA and HFO most often peaked at level 2, while beta was more frequently maximal at

level 1. The weakest amplitudes were generally recorded at superior levels, particularly level 4, across biomarkers and targets. These findings reinforce the anatomical analyses by demonstrating that biomarker maxima consistently occur at electrode levels most likely to engage therapeutic motor territories. The preservation of this depth-dependent organization under general anesthesia further supports the potential utility of ERNA for intraoperative contact selection and physiology-guided targeting.

ERNA predicts clinically effective stimulation contact levels

Anatomical localization alone does not necessarily indicate clinical utility. We therefore asked whether biomarker amplitude predicts the electrode levels associated with the greatest long-term TW following postoperative programming (Fig. 6d, h). The relationship between electrophysiological biomarkers and postoperative programming efficacy was evaluated by comparing biomarker amplitudes at the electrode levels associated with the greatest and smallest TW. In both STN and GPi and for awake and GA recordings, ERNA RMS was significantly higher at contacts associated with the greatest therapeutic benefit compared to those with the poorest benefit ($***p < 0.001$), indicating strong alignment between ERNA amplitude and clinically optimal stimulation sites. In contrast under GA, beta band and HFO band power did not differ between best and worst clinically relevant levels (n.s., Fig. S5c, d).

Discussion

General anesthesia is increasingly used for asleep DBS implantation but suppresses spontaneous electrophysiological biomarkers traditionally used for physiological guidance. In this multisite study, we demonstrate that ERNA remains functionally informative during awake and anesthetized conditions. ERNA showed spatial correspondence with putative therapeutic motor territories, accurately identified contacts associated with the greatest long-term TW, and consistently outperformed conventional passive LFP biomarkers^{21,22} under GA. These findings establish ERNA as a reproducible, high SNR physiological feedback signal that complements anatomical imaging and provides a foundation for future neuromodulation systems integrating stimulation and sensing for physiology-guided targeting, streamlined programming, and adaptive DBS.

ERNA was present in both STN and GPi, although amplitudes were consistently larger in STN. This target-dependent difference may reflect circuit-level, anatomical, and microstructural factors, including differences in pallido-subthalamic connectivity, nucleus size, electrode–tissue geometry, and myelinated fiber content.^{14,54–57} Despite these amplitude differences, ERNA in both targets supports the concept that this response reflects resonance within the broader pallido-subthalamic network rather than a single-nucleus source. This interpretation is consistent with prior reports of related evoked potentials in GPe and models assigning GPe a central role in ERNA generation.^{54,55,58} Collectively, these observations further support the network-level nature of ERNA and its potential relevance to DBS mechanisms.

A key finding of the present study is that, unlike spontaneous beta oscillations and HFOs, ERNA remains functionally informative under general anesthesia. Consistent with previous studies, anesthetic agents suppress spontaneous basal ganglia activity and attenuate passive biomarkers.^{37,38,40,59} In contrast, ERNA is generated through controlled electrical interrogation rather than passive observation of ongoing neural activity. This distinction should, however, be interpreted in the context of stimulation conditions. Awake recordings are constrained by patient comfort and therapeutic-window limits on stimulation amplitude, whereas general anesthesia permits systematic exploration of higher stimulation currents while remaining within established charge-density safety limits. Accordingly, when stimulation intensity is matched, ERNA amplitude is reduced under GA (Fig. S1), consistent with Sinclair et al.,³⁹ indicating that anesthetic agents attenuate, rather than abolish, the underlying network response. Increasing stimulation current under GA restores large, spatially localized ERNA responses while preserving their anatomical specificity.

In addition to amplitude effects, GA produced a consistent downward shift in ERNA center frequency in both targets (Fig. 3e, g). This is compatible with circuit level models attributing ERNA to resonant interactions within the STN-GPe-GPi network.^{54,55} Anesthetic induced reductions in cortical input and changes in inhibitory excitatory balance are expected to increase effective synaptic delays within these loops.^{60,61} A lengthening of these delays would be predicted to slow synaptic dynamics and reduce the resonant frequency of the evoked response. Consistent with this interpretation, supplementary latency analysis (Fig. S3) revealed a modest but significant prolongation in STN under GA, whereas GPi latency remained largely unchanged.

Beyond demonstrating robustness across physiological states, ERNA also exhibited spatial properties that closely align with established DBS motor territories. In both awake and GA recordings, ERNA amplitude maxima were predominantly localized to the middle portion of the nucleus along the dorsoventral axis for STN and to the posteroventral lateral GPi, regions widely recognized as optimal therapeutic targets for Parkinson disease.^{62–66} ROC analyses further supported this anatomical specificity, with ERNA showing the highest AUCs across biomarkers in both targets. ERNA spatial patterns also correlated with beta-band activity and HFOs, suggesting complementary manifestations of a common functional subnetwork within the basal ganglia motor circuit. Importantly, ERNA maintained its spatial distribution under GA even when spontaneous biomarkers were suppressed and lost spatial specificity (Fig. 4), providing a practical advantage for asleep DBS procedures. Although the present study was not designed to directly evaluate ERNA guided clinical outcomes, our results provide strong within-electrode evidence linking ERNA amplitude to therapeutic efficacy. Levels associated with larger TW consistently exhibited higher ERNA amplitudes than those with minimal or absent benefit in both STN and GPi in awake and GA recordings (Fig. 6d, h). This extends prior 4-contact electrode findings showing that ERNA-based ranking identifies clinically optimal contacts in STN and GPi.^{43,67} In contrast, beta band and HFO activity did not significantly differentiate between best and worst contacts under GA (Fig. S5 c, d).

These findings have important implications for both asleep DBS implantation and postoperative programming. Intraoperatively, ERNA provides a rapid, high SNR physiological biomarker that remains informative when spontaneous beta oscillations and HFOs are suppressed by GA, thereby complementing anatomical imaging with real-time confirmation of local circuit engagement. In the postoperative setting, ERNA-based contact ranking has been shown to closely approximate the distribution of clinical benefit across electrode contacts,^{43,67} suggesting that ERNA could streamline initial programming by prioritizing contacts most likely to provide broad TW while reducing programming time and complexity. Moreover, ERNA has been shown to vary systematically with stimulation amplitude,⁴³ stimulation frequency,⁴⁵ medication state,³⁹ and stimulation mode,⁶⁸ indicating that it may ultimately support optimization of stimulation parameters in addition to contact selection. Importantly, ERNA is not intended to replace contemporary image-guided DBS workflows but rather to complement them with functional information unavailable from anatomical imaging alone. Modern MRI and stereotactic planning localize anatomical targets but do not directly assess motor-circuitry engagement or account for functional variability, brain shift, or image-registration error. By measuring circuit engagement at the implanted lead, ERNA offers an independent source of functional information that may improve confidence in lead placement and facilitate selection of clinically effective stimulation contacts.

Several limitations should be considered. First, the study was designed to characterize ERNA physiology rather than to evaluate ERNA guided targeting or programming strategies. Although ERNA demonstrated strong spatial agreement with established biomarkers, anatomical motor territories, and therapeutic benefit, the present data does not directly demonstrate that ERNA guided electrode placement or stimulation parameter selection improves clinical outcomes. Prospective studies incorporating ERNA based targeting strategies and longitudinal clinical follow up are required to establish its therapeutic utility. Second, anatomical classification depends on atlas segmentation, and boundary definitions may influence classifications and ROC metrics, particularly for electrodes located near anatomical borders. However, ERNA remained spatially informative under GA and showed stronger discrimination than passive biomarkers.

In summary, ERNA represents a stimulation-evoked signature of basal ganglia circuitry that remains informative across physiological states and DBS targets. In this multisite cohort, ERNA preserved its spatial correspondence with established motor territories and conventional electrophysiological biomarkers despite anesthesia-induced suppression of spontaneous activity. These findings suggest that ERNA provides functional information that complements anatomical imaging during asleep DBS, supporting physiology-guided targeting and postoperative programming. Prospective studies integrating ERNA-guided targeting with longitudinal clinical outcomes will be essential to determine whether ERNA-based approaches improve targeting precision, programming efficiency, and clinical outcomes.

Declarations

Funding

This work was primarily supported by National Institutes of Health, Grant R01NS124650.

Competing interests

The authors of this manuscript report no competing interests.

Supplementary material

Supplementary information accompanying this article is provided in the Supplementary Information file.

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Figures

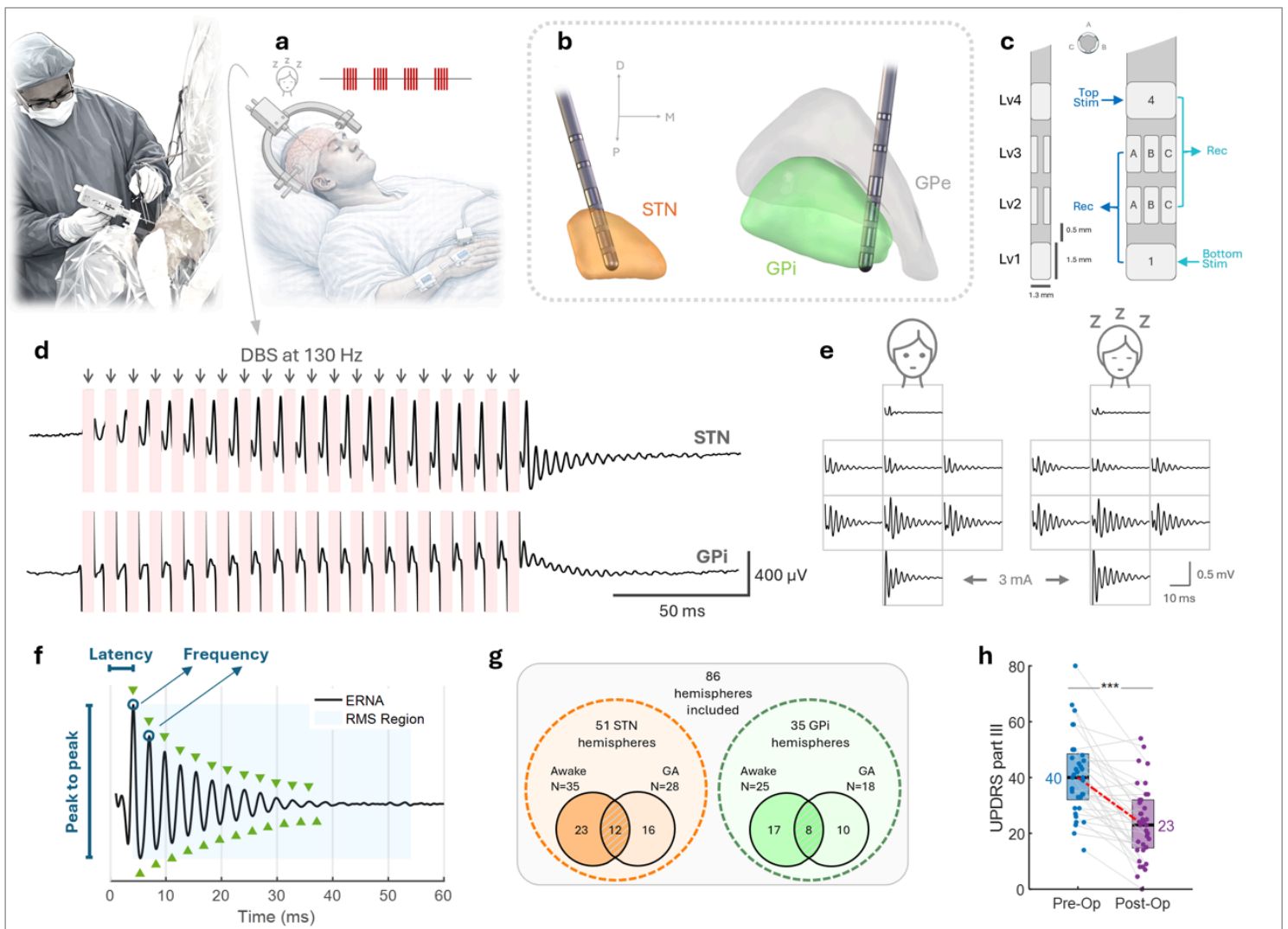


Figure 1

Experimental setup, representative target structures/ERNA waveforms, and clinical efficacy. (a) Illustration of surgical setup for DBS. (b) DBS electrodes implanted in two representative patients, illustrating commonly targeted structures for patients with Parkinson's disease. From left to right, subthalamic nucleus (STN), globus pallidus interna (GPi), and globus pallidus externa (GPe; shown for anatomical reference). (c) Electrode configuration used for stimulation and recording. Monopolar stimulation was delivered from both the top and bottom contacts (Lv1 or Lv4), one at a time and responses recorded from the remaining 7 contacts at 15 kHz. To avoid cumulative effects, an alternating stimulation protocol was applied during intraoperative recordings. (d) Representative examples of evoked resonant neural activity (ERNA) in STN (top) and GPi (bottom) following a 3 mA, 130 Hz stimulation train. Red shading marks each DBS pulse and the subsequent recovery period. Both STN and GPi exhibit a clear damped resonant response following the stimulation train. (e) ERNA distribution in STN across the eight-channel DBS electrode of the same patient under awake (left) and GA (right) conditions following 3mA stimulation at Lv1. (f) Quantification of ERNA features, including initial peak latency, peak-to-peak amplitude, frequency (inter-peak interval), and root mean square (RMS) over a 50 ms following the first ERNA peak. The black trace represents the ERNA response. (g) Distribution of the

86 hemispheres analyzed, categorized by target (STN or GPi) and anesthetic condition (awake, under general anesthesia, or both). A total of 51 STN hemispheres (35 awake, 28 GA, 12 both) and 35 GPi hemispheres (25 awake, 18 GA, 8 both) were recorded. **(h)** Motor MDS-UPDRS scores (part III) were assessed in the OFF-medication state both before (Pre-Op) and 6 months after (Post-Op) DBS implantation. Gray lines connect individual patients, and red dashed line highlights each group median. Boxplots display median as the center mark and interquartile ranges (IQR; 25th-75th percentiles). Among patients for whom UPDRS motor scores were available (n=37 out of 45 patients), DBS was associated with a significant group-level reduction in motor symptoms (median reduction from 40 to 23, ***p < 0.001, paired t-test).

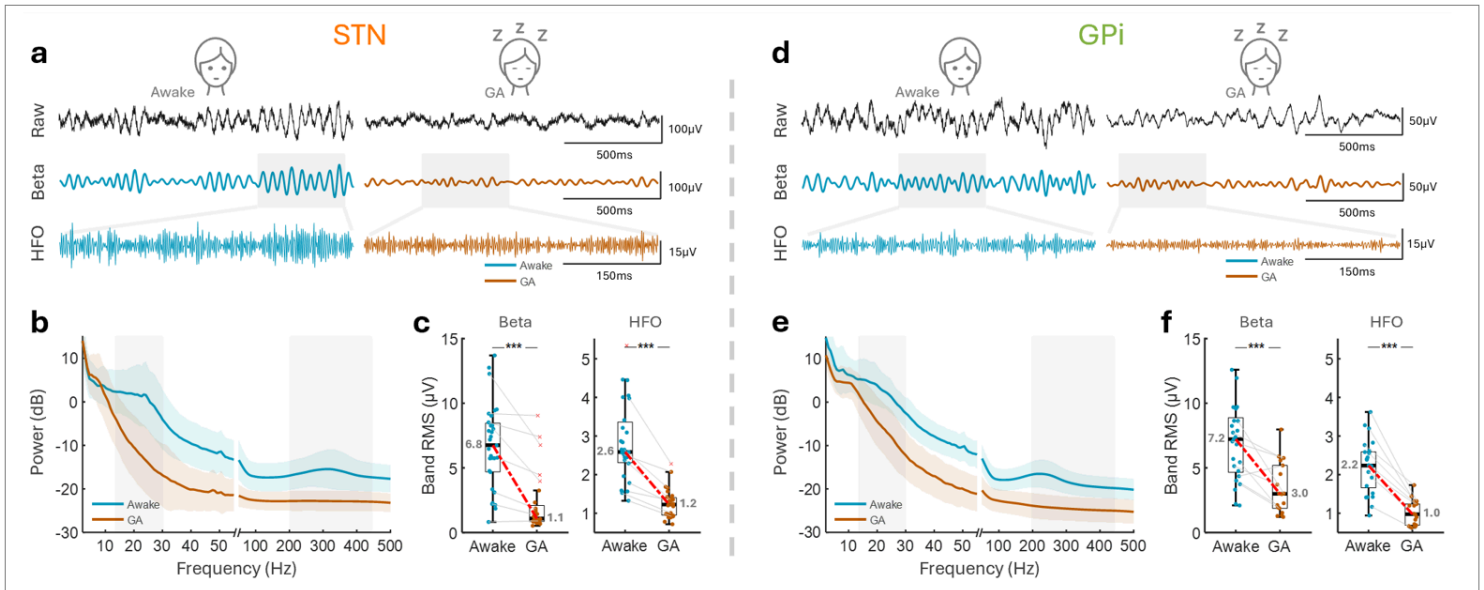


Figure 2

General anesthesia (GA) suppresses spontaneous oscillatory activity in both STN and GPi. (a)

Representative local field potential (LFP; black) traces from a single STN hemisphere recorded in the awake (blue) and general anesthesia (GA; orange) conditions. LFPs are filtered in the beta (13-30 Hz; *left*) and high-frequency oscillation (HFO; 200-450 Hz; *right*) bands. **(b)** Power spectral density (PSD) across all STN hemispheres, showing beta and HFO band power reduced from awake (n=35) to GA (n=28). **(c)** Quantification of STN band-limited RMS amplitudes demonstrates significant reductions under GA for both beta and HFO activity (***p < 0.001, unpaired t-test), with median values decreasing from 6.8 to 1.1 µV for beta and from 2.6 to 1.2 µV for HFO. **(d-f)** Same analyses performed for GPi recordings. **(d)** Example raw LFP traces from a representative GPi hemisphere. **(e)** PSDs across all GPi hemispheres show similar suppression of beta and HFO activity from awake (n=25) to GA (n=18). **(f)** Quantification of GPi band-limited RMS amplitudes confirms significant reductions under GA for both beta and HFO activity (***p < 0.001, unpaired t-test), with median values decreasing from 7.2 to 3.0 µV for beta and from 2.2 to 1.0 µV for HFO.

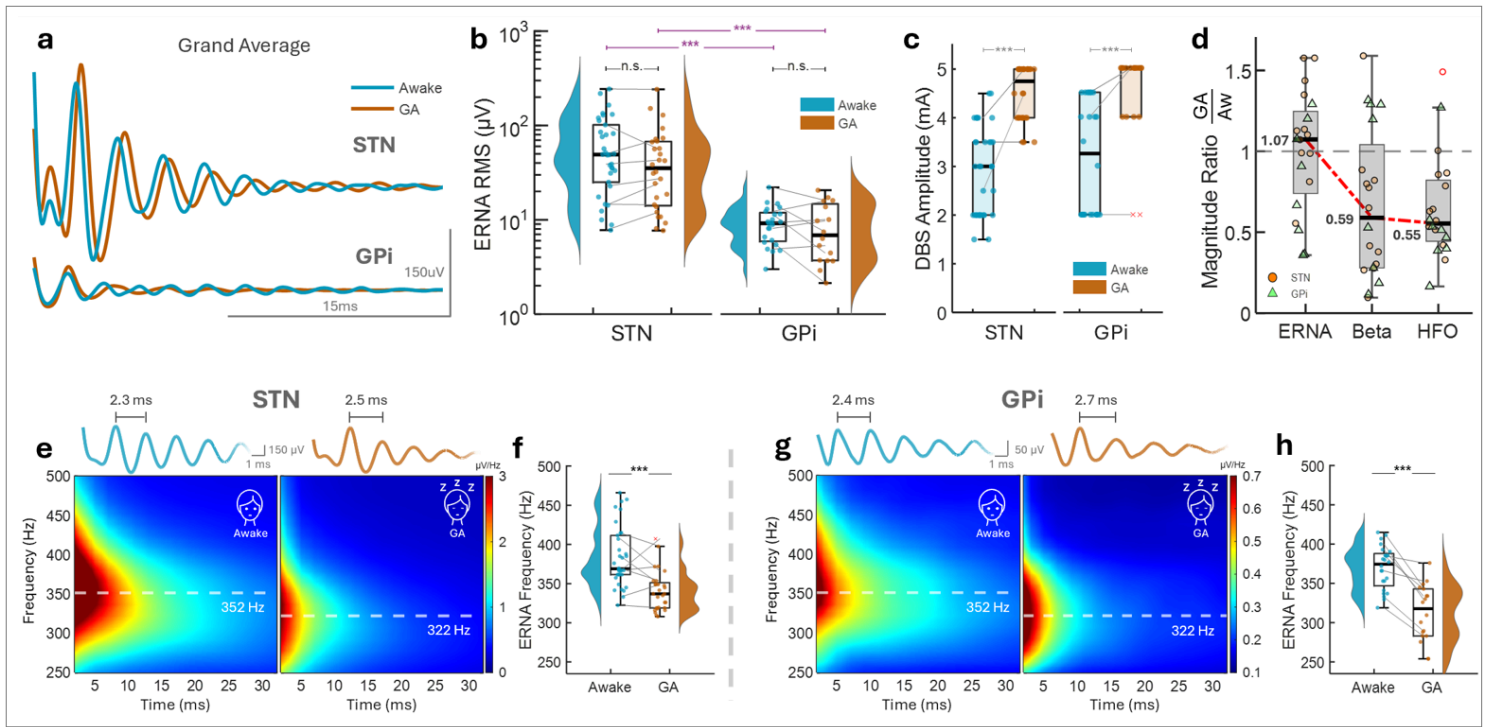


Figure 3

ERNA remains robust under GA but requires higher stimulation currents. For each hemisphere and condition, the waveform and RMS values shown were derived from the stimulation amplitude that produced the maximal ERNA response. In awake recordings, stimulation was limited to clinically tolerated therapeutic-window levels; under GA, stimulation was sampled from 0.5 to 5 mA. **(a)** Grand-average ERNA waveforms recorded during DBS stimulation in STN (top, $n=35$ in awake and $n=28$ under GA) and GPi (bottom, $n=25$ in awake and $n=18$ under GA). ERNA responses exhibit preserved morphology and amplitude under GA. **(b)** RMS amplitude differed significantly between STN and GPi (** $p < 0.001$, unpaired t-test, purple), whereas no significant difference was observed across states within either structure (n.s. > 0.05 , unpaired t-test, gray). Violin plots show the RMS distribution and points indicate individual hemispheres. **(c)** Boxplots displaying stimulation amplitude used in each hemisphere under awake and GA conditions (see Methods). In both targets, GA was associated with significantly higher stimulation amplitudes. **(d)** Magnitude ratio (GA/Awake) for ERNA, beta and HFO biomarkers in hemispheres recorded under both conditions. Beta and HFO values represent the band-limited RMS amplitudes from each hemisphere and ERNA values are RMS (see Methods). Ratios closer to 1 indicate preserved signal amplitude under GA. While beta and HFO amplitude ratios dropped notably under GA, ERNA remained the most stable across states. **(e, g)** Time-frequency maps (TFM) of ERNA averaged across hemispheres in STN (e) and GPi (g) during awake (left) and GA (right) conditions. Dashed white lines indicate the center frequency. In both STN and GPi, the center frequencies shifted from 352 Hz (awake) to 322 Hz (GA). Representative ERNA waveforms from hemispheres recorded in both states are shown above each TFM. Insets highlight prolonged inter-peak intervals under GA (STN: 2.3 ms awake vs. 2.5 ms GA; GPi: 2.4 ms vs. 2.7 ms GA), consistent with frequency slowing. **(f, h)** Quantification of ERNA center frequency in STN (f) and GPi (h). Median frequency was significantly reduced under GA in both

targets (STN: 369 Hz awake vs. 337 Hz GA; GPi: 374 Hz awake vs. 319 Hz GA; *** $p < 0.001$). Violin plots depict frequency distributions across hemispheres and points indicate individual hemispheres.

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Figure 4

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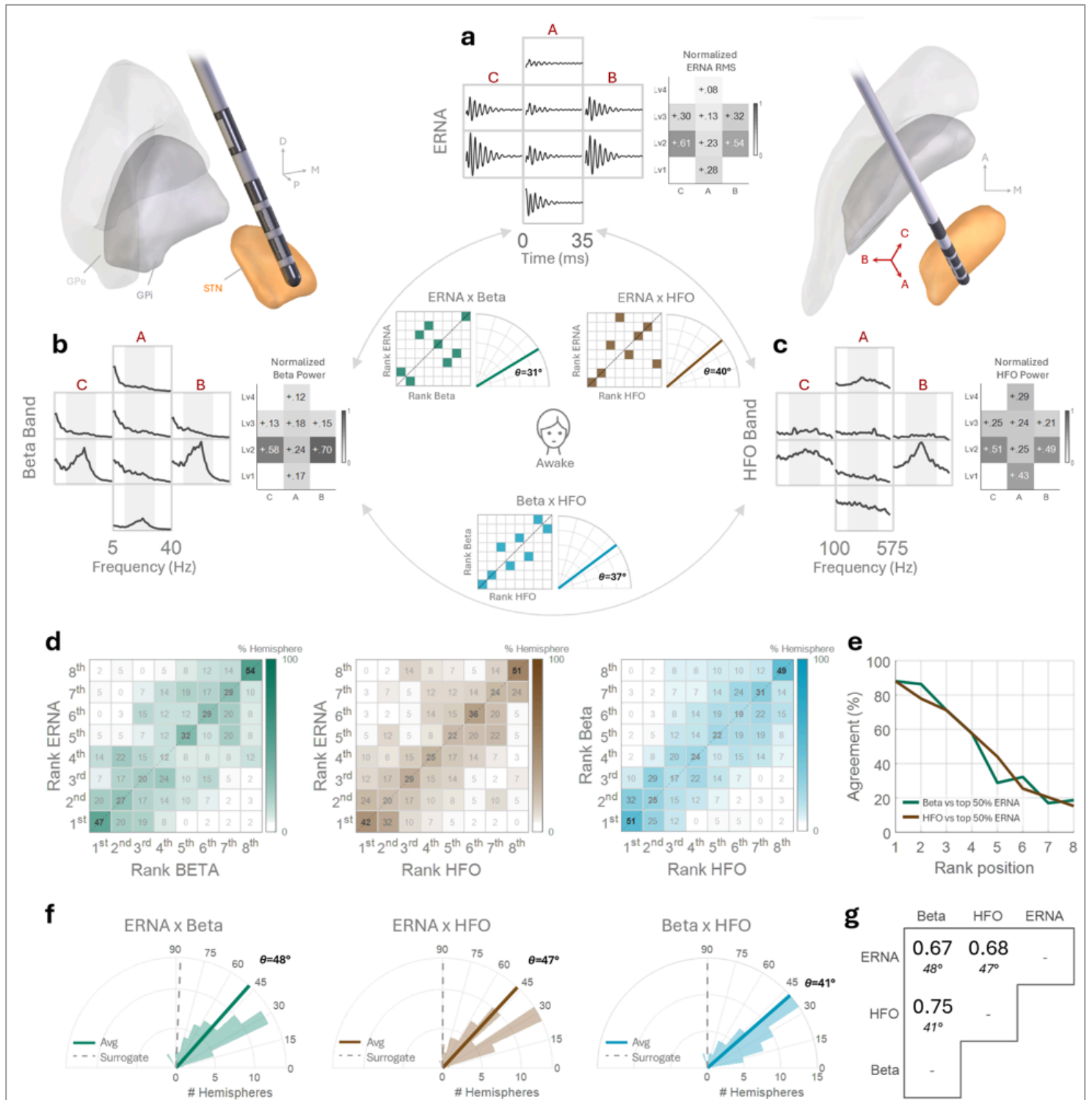


Figure 5

Spatial agreement between ERNA RMS, beta, and HFO bandpower across DBS electrode in STN and GPi.

(a-c) Imaging and electrophysiological data from a representative STN hemisphere. (a) Co-registered electrode positions illustrated (left; D, M and P denote dorsal, medial and posterior directions), and in an axial view (right; A and M denote anterior and medial directions), along with average ERNA waveforms (middle) shown as a distribution across the DBS lead. Red labels A, B, and C indicate the directions of the

implanted electrode. Contacts B and C are oriented toward the STN, while contact A points away, consistent with the spatial pattern observed in the electrophysiological recordings. **(b)** Power spectral density (PSD) profiles in the beta band (13–30 Hz, shaded region) and normalized beta power across the DBS electrode. **(c)** PSD profiles in the HFO range (200–450 Hz, shaded region) and normalized HFO power. For this subject, the contact exhibiting the largest ERNA amplitude aligned with the contact showing maximal HFO power and the second-highest beta power. Pairwise spatial agreement between biomarkers (ERNA–beta, ERNA–HFO, and beta–HFO) is summarized using rank-based confusion matrices and corresponding polar plots, illustrating the concordance of relative contact ordering within the lead. This panel serves as an illustrative example to contextualize the group-level analyses presented for the full cohort. **(d-g)** Group-level analysis of spatial agreement between biomarkers across all hemispheres recorded in the awake state. **(d)** Confusion matrices compare amplitude rankings across eight channels on the DBS electrode between ERNA and beta (*left*), ERNA and HFO (*middle*), HFO and beta (*right*). Gray dashed lines highlight the diagonal representing absolute agreement. **(e)** Comparing the top 50% ERNA channels to the ranked beta/HFO channels demonstrates strong spatial concordance at higher ranks, which gradually decreases at lower ranks. This pattern indicates preserved specificity between ERNA and passive oscillatory biomarkers. **(f)** Polar plots reflect spatial alignment between the 8-dimensional subspaces formed by each biomarker, namely ERNA vs. beta (*left*), ERNA vs. HFO (*middle*), and HFO vs. beta (*right*). Colored rectangles display polar histograms, solid line highlights the averages, and gray dashed lines indicate the surrogate null distribution. **(g)** Summarized confusion matrix of the cosines and angles formed in the polar plot analysis, with each quadrant displaying the average cosine similarity (*top*) and average angle (*bottom*).

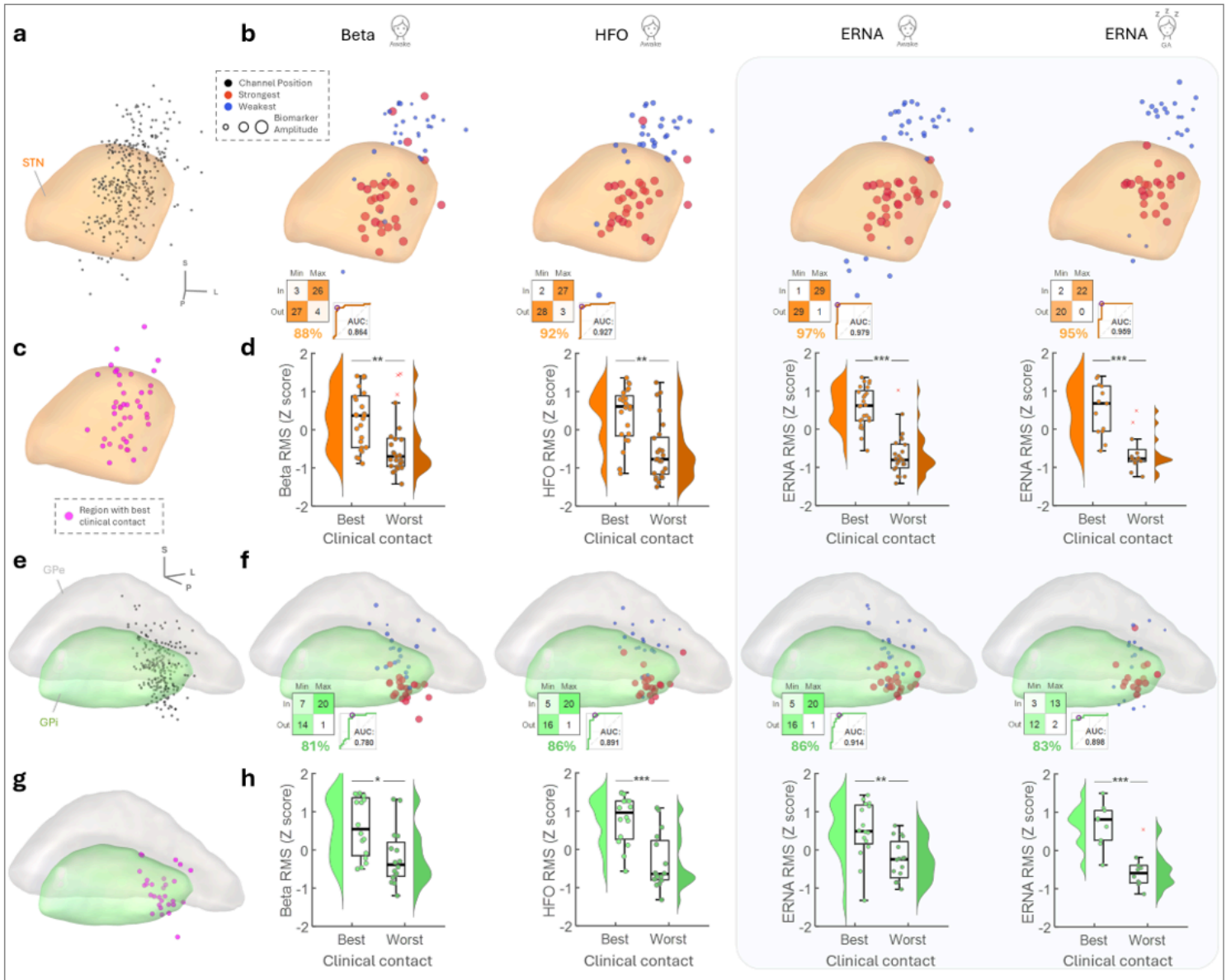


Figure 6

Spatial distribution between electrophysiological biomarkers and clinically effective DBS contacts in STN and GPi. (a) Distribution of recorded contact locations within the STN. Black points indicate channel positions projected into normalized imaging space. (b) Spatial distribution of contacts with the strongest and weakest biomarker intensity for awake beta power, awake HFO power, awake ERNA, and ERNA recorded under general anesthesia (GA). Red and blue points indicate the strongest and weakest contacts within each electrode, respectively, with point size scaled by biomarker intensity. Each hemisphere is z-score normalized. Insets show ROC curves evaluating whether channel distance to the target distinguishes strongest from weakest biomarker contacts. The optimal ROC-derived distance threshold was used to classify contacts as In or Out, and corresponding confusion matrices show the number of strongest and weakest contacts assigned to each category, together with overall accuracy. (c) Distribution of electrode levels associated with the greatest clinical benefit in STN. (d) Biomarker amplitude at contacts associated with the best versus worst therapeutic benefit in STN, after averaging

directional channels into levels and within-electrode Z-scoring. Across beta, HFO, awake ERNA, and ERNA under GA, signal amplitude was higher at clinically optimal contacts, with ERNA showing particularly robust separation between best and worst contacts. **(e)** Distribution of recorded contact locations within the GPi, with the GPe and GPi shown in gray and green, respectively. **(f)** Spatial distribution of strongest and weakest contacts for awake beta power, awake HFO power, awake ERNA, and ERNA under GA in GPi. **(g)** Distribution of contacts associated with the greatest clinical benefit in GPi. **(h)** Biomarker amplitude at contacts associated with the best versus worst therapeutic benefit in GPi, after within-electrode Z-scoring. Similar to STN, clinically optimal contacts showed higher biomarker amplitudes than clinically less effective contacts across modalities, including ERNA recorded under GA. Statistical comparisons were performed between best and worst clinical contacts; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

Supplementary Files

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