TOPICAL ISSUE REVIEW

Biomarkers for Epilepsy Deep Brain Stimulation

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Summary: Deep brain stimulation (DBS) of the anterior nucleus of the thalamus is an FDA-approved therapy for drug-resistant focal epilepsy. Recent advances in device technology, thalamic stereotactic-EEG, and chronic sensing have deepened our understanding of corticothalamic networks in epilepsy and identified promising biomarkers to guide and personalize DBS. In this review, we examine electrophysiological, imaging, and clinical biomarkers relevant to epilepsy DBS, with a focus on their potential to support seizure detection, target engagement, network excitability tracking, and seizure risk forecasting. We highlight emerging insights from thalamic sEEG, including both passive recordings and active stimulation protocols, which enable mapping and modulation of large-scale brain networks. The capabilities of clinical sensing-enabled DBS systems are reviewed. As device functionality and biomarker discovery evolve, concerted translational efforts are needed to realize a new paradigm of personalized DBS in epilepsy.

Key Words: Neuromodulation, Single pulse electrical stimulation, Chronic brain recordings, Adaptive stimulation, Thalamic sEEG.

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Anterior nucleus of the thalamus deep brain stimulation (ANT-DBS) is an FDA-approved adjunctive therapy for drug-resistant focal epilepsy and is a viable treatment option for patients who are poor surgical candidates. The pivotal ANT-DBS SANTE study[1,2] and long-term follow-up investigations have identified superior responses for patients with frontal and temporal seizure networks, compared with other regions,[1,2] leading to the "network theory" of ANT-DBS—that stimulating the ANT, a node in the Papez circuit, has greater therapeutic effects on seizure networks associated with this limbic network. Long-term follow tracking of the SANTE cohort has reported a median seizure frequency reduction of 56% at 2 years, increasing to 69% at 5 years and 75% at 7 years.[3]

Beyond stimulation of the ANT, other subcortical and thalamic structures have been identified and targeted for epilepsy DBS. Two common off-label thalamic targets, the centromedian (CM) nucleus and pulvinar, have been studied for generalized and posterior quadrant epilepsies, respectively, with some promising preliminary results.[4–6]

Despite proven efficacy, epilepsy DBS has notable limitations. Seizure freedom is rare, the latency to response is long, and DBS does not work for all patients.[7] One major challenge is the long latency and uncertain reliability of the clinical readout (patient reported seizure diaries), which is compounded by patient encounter intervals (roughly 3–6 months). This slow clinical response prevents efficient tuning of stimulation parameters, in contrast to DBS for conditions such as Parkinson disease, where parameters can be optimized during a single visit. Similarly, the use of generic targets means that the stimulated thalamic subfield may not optimally engage a patient's specific seizure network.

Advances in device technology, evolving clinical practices—including the growing interest in thalamic sEEG—and biomarker development may address these DBS limitations. The aim of this review was to summarize key biomarkers for DBS in epilepsy and propose biomarker-informed approaches to DBS for epilepsy.

NONINVASIVE SEIZURE NETWORK BIOMARKERS

Noninvasive biomarkers of seizure networks may improve the characterization of corticothalamic networks involved in epilepsy, informing patient candidacy and target selection for DBS. Scalp EEG remains a fundamental tool for epilepsy classification, distinguishing between focal and generalized epilepsy. Seizure onset networks identified by scalp EEG, combined with existing knowledge of thalamocortical circuits, can help with DBS target selection.[8,9] MRI plays a critical role in defining the anatomical extent of structural abnormalities in lesional epilepsy, while also assessing thalamic structures.[10] Functional and metabolic imaging may provide additional insights into the involvement of subcortical structures in seizure networks. For instance, interictal FDG-PET shows hypometabolism in the ANT in patients with temporal lobe epilepsy, indicating potential dysfunction in the corticothalamic pathways.[11–13] Similarly, interictal single-photon emission computed tomography has shown interictal hypoperfusion in the temporal lobe and ipsilateral thalamus in patients with refractory temporal lobe epilepsy[14] as well as in the thalamus of patients with frontal lobe epilepsy and motor seizure semiology.[15]

NETWORK-GUIDED DBS TARGET SELECTION

The ANT is the most thoroughly researched and only FDA-approved target for epilepsy DBS. The ANT is part of the thalamic anterior complex, a node of the Papez circuit, and

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a component of the limbic thalamus with strong efferent projections to mesial and anterior frontal, and temporal regions.[16,17] The network theory of ANT-DBS suggests that this target is best suited for frontotemporal seizure networks[18] and, in particular, for seizure networks with limbic system connectivity. Prior fMRI-based functional connectivity work has shown that ANT-DBS connectivity profiles differ between responders and nonresponders, with greater positive functional connectivity to the default mode network seen in responders.[19] Subsequently, a study fMRI-blood-oxygen-level–dependent (BOLD) signal during active ANT-DBS fMRI further demonstrated modulation of limbic and default mode network regions during high-frequency stimulation, further characterizing the networks engaged by ANT-DBS.[20]

The CM nucleus, an off-label thalamic target, exhibits strong connectivity with the basal ganglia and intrathalamic pathways, as well as diffuse cortical connections, particularly to the perirolandic sensorimotor cortex, premotor cortex, and anterior cingulate cortex.[21] Generalized epilepsy network mapping, derived from brain abnormalities in patients with idiopathic generalized epilepsy (IGE) and the human connectome, demonstrated that the CM nucleus has peak functional connectivity with the IGE network.[22] Several authors have demonstrated benefits of CM-DBS for patients with IGE[23] and Lennox–Gastaut syndrome.[24–26] In the stimulation group of the ESTEL trial, the primary outcome— patient-reported seizure diaries—did not reach statistical significance; however, a reduction in electrographic seizures on 24-hour ambulatory EEG was observed in the secondary outcome.[26] Network connectivity mapping, and EEG-fMRI comparing IGE and Lennox–Gastaut syndrome networks,[27] suggest that there may be syndrome specific targets for CM-DBS. Emerging computational imaging and field-modeling methods show promise network-guided neuromodulation to refine DBS—for example, a recent study combining deterministic tractography and a biophysical modeling framework to disambiguate DBS activation of neighboring fiber tracks was able to predict behavioral change in response to central thalamus DBS in nonhuman primates.[28]

Another off-label thalamic target, the pulvinar nucleus, has emerged as a potential target for treating posterior quadrant epilepsy.[6,29,30] The PULSE trial reported improvements in seizure severity and quality of life, alongside a nonsignificant trend toward seizure reduction.[6]

THALAMIC STEREOTACTIC-EEG

The thalamus plays a critical role in seizure generation and propagation,[31,32] and recent work using thalamic sEEG has delivered new insights into thalamic and subcortical ictal and interictal electrophysiological dynamics in epilepsy.[33–35] Research and clinical thalamic sampling during sEEG has rapidly grown, and best practices continue to evolve.[36,37] In a large series of thalamic sEEG, Pizzo et al.[32] found that in 86% of patients the thalamus was involved during their focal seizures whereas. In addition, other work has demonstrated variable thalamic nucleus propagation patterns across patients undergoing multisite thalamic sampling.[33] More work is needed to determine the predictive value of thalamic seizure characterization during sEEG for long-term response to thalamic DBS.

Unlike the cortex, the thalamus lacks a well-organized columnar and laminar structure,[38] which leads to lower amplitude local field potential (LFP) amplitudes, and so thalamic channels should be read at greater sensitivity compared with the cortex. To improve the interpretability of thalamic SEEG data, spectral analysis using Fast Fourier Transform (FFT) can be used. By comparing ictal spectral activity with epochs recorded during both wakefulness and sleep, we can better characterize the frequency bands during seizure activity. These spectral features can directly inform the ambulatory sensing parameters for clinical DBS systems. Prior work has demonstrated the feasibility of this method, using interictal and ictal thalamic sEEG spectral signatures to guide DBS sensing parameters for ambulatory seizure detection and lateralization.[39]

Stimulation during thalamic sEEG can provide important complementary information to passive recordings of spontaneously occurring activity. Single pulse electrical stimulation and the resulting thalamocortical-evoked potentials[40] provides a measurement of network effective connectivity (directed causal influence between neural populations). Prior work has demonstrated that effective connectivity between thalamic and cortical sites is not always reciprocal,[41] which has clear implications for DBS target selection (early or maximal ictal activity in a given thalamic nucleus does not necessarily indicate that stimulation of that nucleus provides optimal engagement of the seizure network). Thalamocortical-evoked potentials can be used to demonstrate seizure network engagement by thalamic stimulation. In addition, emerging work indicates that thalamocortical effective connectivity and trials of high-frequency thalamic DBS during sEEG can map seizure network engagement, suppress IEDs (Fig. 1), modulate network excitability, and perhaps predict response to chronic neuromodulation.[42–44]

DBS TARGETING AND LEAD LOCALIZATION

The ANT can be directly visualized on MRI imaging sequences, with particularly good visualization provided by white-matter–nulled imaging sequences, such as the fast gray matter acquisition T1 inversion recovery (FGATIR) sequence. The ANT receives afferent projections from the mammillary bodies through the mammillothalamic tract white matter bundle and is separated from neighboring thalamic nuclei by the internal medullary lamina, allowing for direct visualization of the mammillothalamic tract and ANT on FGATIR sequences.[45] Emerging techniques such as 3T quantitative susceptibility mapping also shows promise for direct ANT visualization.[46] Prior work suggests a DBS "sweet-spot" around the anterior third of the ANT and head of the mammillothalamic tract.[47–49]

Targeting the CM nucleus has been enhanced by high-contrast MRI sequences such as magnetization-prepared two rapid acquisition gradient-echo (MP2RAGE).[5] MP2RAGE at 3T yields uniform T1-weighted images with excellent gray–white matter differentiation. Warren et al.[5] demonstrated that the CM nucleus is distinctly hyperintense on MP2RAGE relative to adjacent nuclei—the pulvinar, mediodorsal, and parafascicular

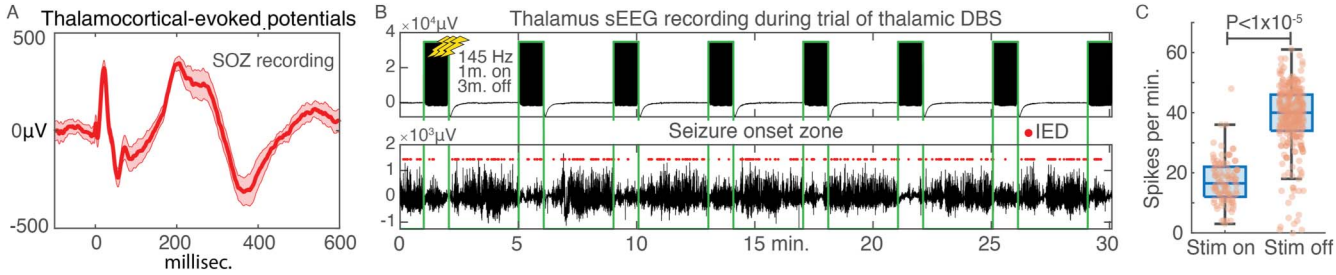

FIG. 1. Thalamic stimulation during sEEG. **A**, Single pules stimulation delivered to that thalamus and the resulting thalamocortical-evoked potentials can demonstrate if there is connectivity between the stimulation thalamic subfield and cortical regions of interest, such the seizure onset zone as shown in this plot. **B**, Trial of high-frequency duty-cycle stimulation can produce acute desynchronization of seizure network activity and suppression of IEDs during the on-phase of the duty cycle, as shown here, with on-phase marked by green lines. **C**, This stimulation trials resulted in significant suppression of the IED rate in the on-phase versus off-phase of duty-cycle stimulation.

nuclei. More recently, work has demonstrated the feasibility of direct visualization of the CM and parafascicular nuclei, using the edge-enhancing gradient echo with multi-image coregistration and averaging (EDGE-MICRA) imaging method.[50] The habenula, a small epithalamic nucleus, is posterior, superior, and medial relative to the CM nucleus and can assist with targeting.[51] As discussed above, CM-DBS targeting may be syndrome specific, with prior work identifying distinct sweet-spots for IGE[20] and Lennox–Gastaut syndrome.[52]

Advancements in MRI sequences (MP2RAGE and FGATIR) and ultra–high-field imaging have also enabled direct visualization of the pulvinar nucleus. Susceptibility-weighted imaging accentuates iron-rich regions and fibrous septa, with greater contrast at 7T, potentially delineating pulvinar subregions.[53] Pulvinar appears darker than the adjacent CM on MP2RAGE sequences, creating a visible interface.[5] Similarly, white-matter–nulled inversion recovery imaging (e.g., FGATIR) can highlight gray matter differences between nuclei.[53]

When direct MRI visualization is inadequate, atlas-based techniques can aid DBS targeting.[5] Automated thalamus segmentation methods[54] and digital thalamic atlases can be nonlinearly warped into a patient's MRI space, as described previously.[5,23,55]

In addition, postoperative imaging is crucial to localize DBS leads and select stimulation contacts. Typically, a postoperative high-resolution CT coregistered to preoperative MRI can help to identify contact proximity to target, for targets that can be directly visualized.[56] In addition, clinical and research packages[57] are available that provide automated imaging coregistration, lead localization, and thalamic atlas normalization tools to enhance contact-target localization.

BIOMARKERS FOR DBS WITH SENSING

Clinical DBS Recording Capabilities

The clinical Medtronic Percept DBS system offers constrained chronic ambulatory brain recordings, with additional functionality that is accessible by the physician programming tablet during in-person visits. This Percept system provides chronic ambulatory bipolar recordings (one recording channel per lead) of LFP power within a physician-selected 5-Hz wide frequency band, saved in 10-minute averaged increments. Data storage capacity ranges between 40 (Percept RC) and 60 days (Percept PC), with overwriting of earlier data for extended recording durations. These recordings require a sense-friendly configuration, with bipolar sensing contacts bracketing one or two monopolar stimulation contacts, allowing for common-mode artifact rejection. Sense-friendly stimulation frequencies range from 50 to 185 Hz, with stimulation rates at least 10 Hz higher than the frequency band of interest. Events of interest can be marked by the patient or caregiver using a patient programmer, which saves an event timestamp to the device, and records a full-spectrum FFT measurement (calculated over 30 seconds following event mark; 100 event snapshot per lead storage capacity) when the patient is in a sensing configured stimulation program. Up to four distinct event types can be configured. Patient-marked events will also trigger resumption of stimulation if an event is marked during the off phase of duty-cycle stimulation. Recorded data are accessible by the physician programming tablet during in-person visits.

During in-person encounters, the physician programming tablet can acquire time-series recordings, sampled at 250 Hz, from three bipolar pairs per lead when stimulation is off, or from a single bipolar pair during sense-friendly stimulation.[58] Fast Fourier Transform frequency spectra can be acquired from each bipolar pair across levels (6 per lead), as well as from directional segments.

Chronic Ambulatory Seizure Detection

Previous work has shown that chronic LFP spectral trends—such as those captured by the clinical Percept DBS system—can detect and lateralize seizures in some individuals with drug-resistant focal epilepsy. In a study using the investigational Medtronic Summit RC+S system in patients with drug-resistant mesial temporal lobe epilepsy implanted with bilateral ANT and hippocampal electrodes capable of 250 Hz time-series recordings, our group found that optimal seizure detection occurred using Percept-like power-in-band features centered at 7.8 Hz (with 5 Hz bandwidth). Shorter-duration epochs outperformed 10-minute averaged epochs. Notably, LFP power-in-band consistently lateralized seizure onset, with maximal power

in the thalamic lead ipsilateral to the hippocampal seizure focus.[57]

Subsequent work extended those findings from the investigational system to the clinical Percept DBS system, demonstrating the feasibility of seizure detection and lateralization by the clinical system[39] (Fig. 2). In that case, nurse identified clinical seizures during inpatient DBS recording were precisely coincident with peaks in the LFP power-in-band trends (again, 7.8 Hz center frequency), and this ictal peak in LFP power was maximal ipsilateral to the patient's prior identified seizure network.[39] Work is ongoing to establish optimal protocols and identify spectral signatures for epilepsy tracking by DBS with sensing systems.[59–62] Aperiodic changes in thalamic LFPs, such as a steeper 1/f slope, has been identified to differentiate ictal from interictal states,[62] and thalamic DBS recordings may enable seizure forecasting.[63]

Patient-reported seizure diaries are often unreliable,[64] and digitally marking events with the patient programmer, with associated FFT snapshot, and LFP spectral trends may improve event tracking. Furthermore, patient event tracking, coincident FFT spectral snapshot, and LFP trends, and be leveraged to guide adaptive DBS, as evident in recent studies of adaptive DBS for Parkinson disease.[65] This method improves accuracy by aligning stimulation adjustments with both electrophysiological signatures and reports of subjective symptoms.[66]

Interictal Recordings

Identifying contacts with abnormal electrophysiological activity, such as IEDs, may indicate that a thalamic subfield is involved in a pathological or seizure network. Identifying such activity in DBS contacts could inform stimulation contact and sensing channel selection, to best engage and track seizure networks. Prior work has demonstrated that IED amplitude differences between neighboring contacts and hemispheres are evident in DBS time-series recordings[39] (Fig. 3). More work is needed to establish how best to use interictal time series and spectral features to assess seizure network involvement, and track network excitability and seizure risk. Such biomarkers are needed for epilepsy—akin to Parkinson disease beta-band activity[65]—to guide adaptive neuromodulation for epilepsy.

FUTURE DIRECTIONS: ADAPTIVE DBS, BIOMARKER-TARGETED STIMULATION, SEIZURE RISK FORECASTING, AND MANAGEMENT OF COMORBIDITIES

The aim of adaptive DBS was to modulate epileptogenic networks and suppress seizures by adjusting stimulation parameters in real time based on physiological signals or biomarkers. Adaptive DBS is already an FDA-approved therapy for Parkinson disease—stimulation amplitude modulation directed by changes in beta-band power[65]—underscoring the need to establish biomarkers and stimulation protocols for adaptive DBS for epilepsy.

Candidate biomarkers include the rate of IEDs, spectral features, and evoked potential measures of excitability. Prior work has shown that thalamic high-frequency stimulation can acutely desynchronize seizure networks and modulate IED rates,[43] and modulate thalamocortical excitability.[42,69] Prior work has established the presence of circadian and multiday cycles of seizure risk,[69,70] with seizures occurring at a preferred phase in the fluctuating rate of IEDs, and may enable seizure risk forecasting. Importantly, studies have shown that ANT-DBS modulates these seizure risk cycles, adding complexity to the temporal dynamics of seizure risk.[71] In this context, understanding cycles in epilepsy will be crucial to track the impact of DBS

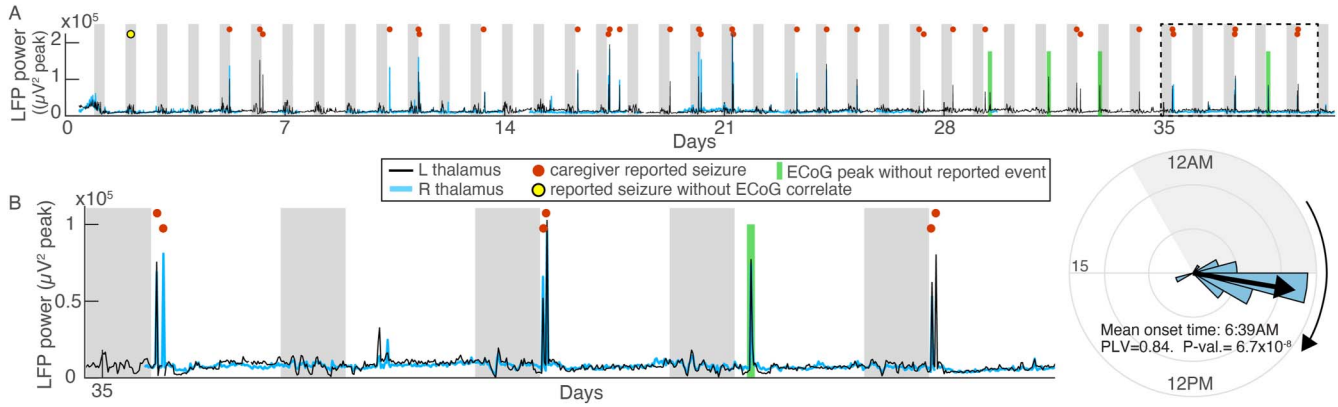

FIG. 2. Chronic ambulatory thalamic seizure detection by a clinical DBS system. The patient is a young man with a developmental and epileptic encephalopathy, drug-resistant epilepsy, and diffuse onset seizures, treated with bilateral centromedian nucleus DBS. **A**, Caregiver-recorded seizure times reliably correspond to relative peaks in the DBS LFP power-in-band trends (5.3-to-10.3 Hz frequency band). One event was captured without corresponding peak in LFP power, while four peaks in LFP power were without associated caregiver-reported events, which may represent true seizures that were missed by caregivers. Gray bars indicate evening hours (10 PM–6 AM). **B**, corresponds to marked inset from panel above. **C**, Significant circadian seizure phase locking is clearly evident in the 24-hour rose-plot. Gray arc corresponds to evening hours (10 PM–6 AM). *P*-value calculated by the omnibus test. DBS, deep brain stimulation; LFP, local field potential; PLV, phase-locking value, or R-value.

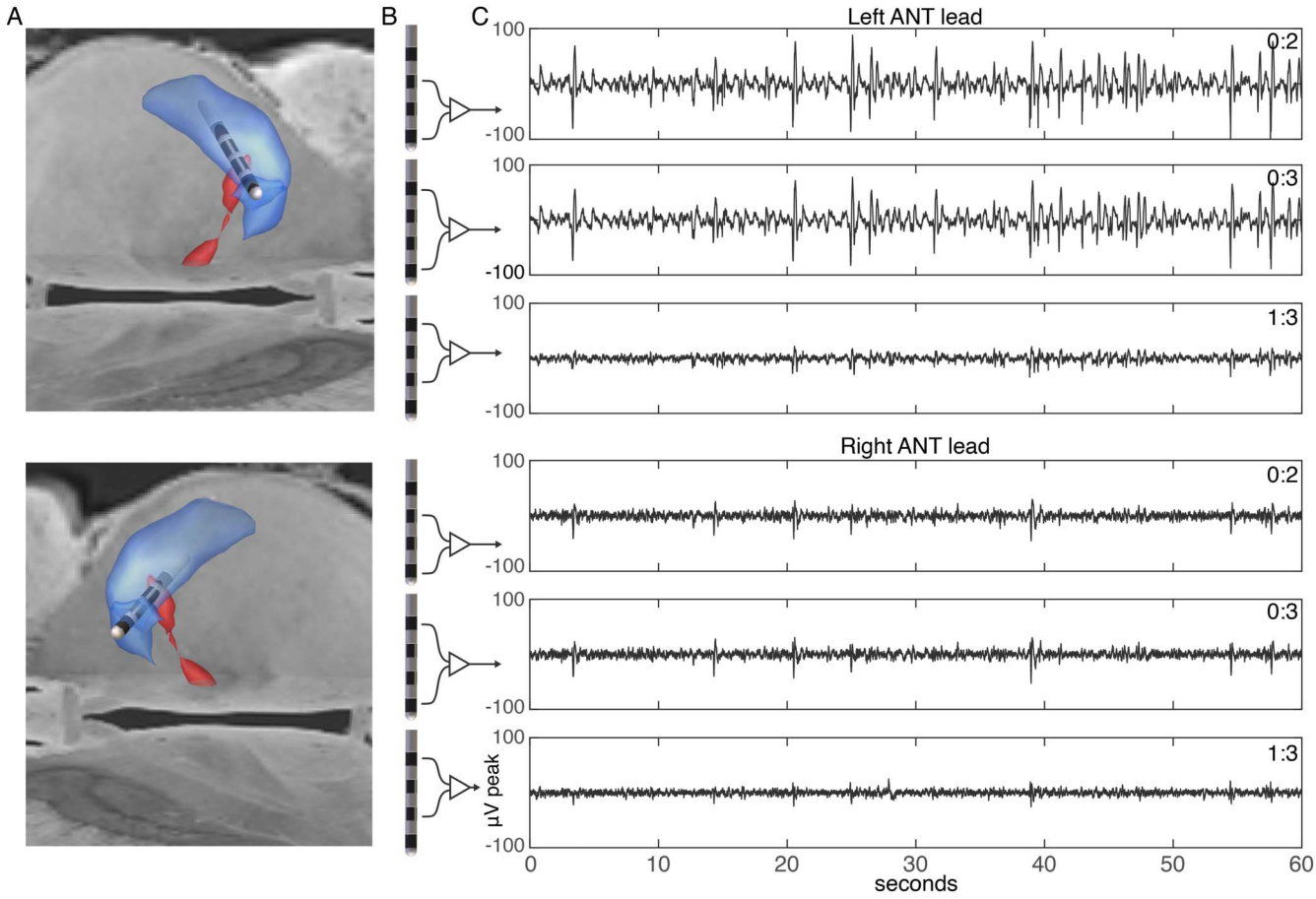

FIG. 3. Time-series recordings by a clinical DBS system. The patient is a young man with left frontotemporal regional epilepsy treated with ANT-DBS system. Data were acquired during a clinic visit by the physician programming tablet. **A**, Left and right ANT in blue and the mammillothalamic tract in red. Renderings were generated using the Lead-DBS imaging package.[67,68] Top panel right is anterior, left is posterior, up is superior; in bottom panel, the anterior–posterior axis is reversed. **B**, Model of implanted leads and the corresponding bipolar recording time series. DBS, deep brain stimulation.

and to adaptively tune stimulation to each patient's unique seizure dynamics.

Emerging platforms that link implanted neuromodulation system with brain sensing capabilities to a hand-held device with bidirectional connectivity to the cloud allow for new electrophysiological biomarker-triggered prompts to be given to patient by a handheld device, to assess cognitive faculties and mood. Continuous data streaming also allows for tracking of sleep. These behavioral data points are critical to characterize and track common epilepsy comorbidities—mood, memory, and sleep—and may provide new insights into epilepsy and therapeutic practice.[72]

CONCLUSION

Emerging DBS biomarkers—from thalamic sEEG, imaging, and chronic DBS sensing—offer new opportunities to guide target selection, optimize parameters, detect seizures, monitor network excitability, and enable adaptive stimulation. Continued efforts are needed to realize the potential of these advances for personalized DBS in epilepsy.

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