Stereoelectroencephalography of the Deep Brain: Basal Ganglia and Thalami

Sandipan Pati,* Shruti Agashe,† Ammar Kheder,‡ Kristen Riley,§ Jay Gavvala,* Robert McGovern,|| Surya Suresh,* Ganne Chaitanya,* and Stephen Thompson¶

*Texas Comprehensive Epilepsy Program, Department of Neurology, The University of Texas Health Science Center at Houston, Texas, U.S.A.; †Department of Neurology, Duke Comprehensive Epilepsy Center, Duke University, Durham, North Carolina, U.S.A.; ‡Department of Neurology, Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia, U.S.A.; §Department of Neurosurgery, Heersink School of Medicine, University of Alabama at Birmingham, Alabama, U.S.A.; ||Department of Neurosurgery, University of Minnesota, Minnesota, U.S.A.; and ¶Neurology Division of the Department of Medicine, Hamilton Health Sciences and McMaster University, Canada.

Summary: Stereoelectroencephalography (SEEG) has emerged as a transformative tool in epilepsy surgery, shedding light on the complex network dynamics involved in focal epilepsy. This review explores the role of SEEG in elucidating the role of deep brain structures, namely the basal ganglia and thalamus, in epilepsy. SEEG advances understanding of their contribution to seizure generation, propagation, and control by permitting precise and minimally invasive sampling of these brain regions. The basal ganglia, comprising the subthalamic nucleus, globus pallidus, substantia nigra, and striatum, have gained recognition for their involvement in both focal and generalized epilepsy. Electrophysiological recordings reveal hyperexcitability and increased synchrony within these structures, reinforcing their role as critical nodes within the epileptic network. Furthermore, low-frequency and high-frequency stimulation of the basal ganglia have demonstrated potential in modulating epileptogenic networks. Concurrently, the thalamus, a key relay center, has garnered prominence in epilepsy research. Disrupted thalamocortical connectivity in focal epilepsy underscores its significance in seizure maintenance. The thalamic subnuclei, including the anterior nucleus, centromedian, and medial pulvinar, present promising neuromodulatory targets, suggesting pathways for personalized epilepsy therapies. The prospect of multithalamic SEEG and thalamic SEEG stimulation trials has the potential to revolutionize epilepsy management, offering tailored solutions for challenging cases. SEEG's ability to unveil the dynamics of deep brain structures in epilepsy promises enhanced and personalized epilepsy care in our new era of precision medicine. Until deep brain SEEG is accepted as a standard of care, a rigorous informed consent process remains paramount for patients for whom such an exploration is proposed.

Key Words: Thalamus, Stereo-EEG, Focal epilepsy.

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The advent of stereoelectroencephalography (SEEG) has not only revolutionized the field of epilepsy surgery but also represents a paradigm shift in our understanding of focal epilepsy as a dynamic network disorder. With a minimally invasive approach, SEEG enables precise and accurate localization of the epileptogenic zone, providing a high-resolution understanding of the underlying network dynamics often crucial for successful surgical outcomes.[1] Furthermore, SEEG can potentially serve as a tool in selecting neuromodulatory targets by identifying the critical nodes within the seizure network.[2] As our understanding of the underlying mechanisms of ictogenesis evolves, there is increasing interest in the SEEG sampling of novel subcortical structures. This review explores explicitly the role of the basal ganglia and thalami in focal epilepsy, emphasizing the importance of SEEG sampling of these structures in patients with drug-resistant epilepsies. The data suggest innovative surgical and neuromodulation techniques previously inconceivable to yield tailored and more effective therapies.

EXPLORING THE HIDDEN SUBCORTICAL HUBS OF FOCAL EPILEPSY

Hughlings Jackson conceptualized a seizure as a discharging cortical focus accompanied by clinical manifestations, thus founding the idea of cerebral localization of an ictus.[3,4] Building upon this foundation, Hayashi conducted seminal studies in 1952[5] using chemicals to induce clonic motor seizures in dogs. His work demonstrated the critical pathways of subcortical spread, explicitly highlighting the involvement of the thalamus and basal ganglia in the propagation of motor seizures. Since then, evidence has confirmed that these subcortical structures are crucial hubs within the epileptic network. They contribute significantly to seizure dynamics, including regulation of onset, propagation, and termination.

The involvement of subcortical structures such as the thalamus[6–9] and basal ganglia[10,11] in focal epilepsy has gained increasing recognition. These hidden regions harbor intricate networks and connections that underlie the complex interplay of epileptic activity. To comprehensively understand and effectively treat focal epilepsy, exploring and sampling these deep brain

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Address correspondence and reprint requests to Sandipan Pati, MD, Texas Institute of Restorative Neurotechnologies, Room 440C, 1133 John Freeman Boulevard, Houston, TX 77030, U.S.A.; e-mail: patilabuab@gmail.com.

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structures may be required. Specifically, the thalamus and basal ganglia participate in the seizures of focal epilepsy. SEEG of these structures yields high-resolution temporal and spatial data that offer insights into these deep brain structures' intricate dynamics and functional contributions to the epileptic network.

SEEG OF THE BASAL GANGLIA

The basal ganglia—consisting of the subthalamic nucleus, globus pallidus, substantia nigra, and striatum—have been implicated in the pathophysiology of focal and generalized epilepsy.[10–13] In the 1950s, Stoll et al.[14] conducted experiments that demonstrated the recruitment of the caudate nucleus, globus pallidus, substantia nigra, and subthalamic nucleus following chemically or electrically induced seizures originating from the temporal pole in cats.

It has been hypothesized that the basal ganglia are involved in the propagation and termination of focal onset seizures originating in the frontal and temporal lobes.[15,16] However, the precise mechanisms and neural pathways involved in this process have been a subject of ongoing debate.[17–19]

Imaging studies have proposed a role for the basal ganglia in epilepsy. Volumetric magnetic resonance imaging (MRI) studies show a decrease in putamen volume after temporal lobectomy.[20] Fluorodeoxyglucose-18-positron emission tomography (FDG-PET) may show hypometabolism in basal ganglia ipsilateral to the seizure focus, and single-photon emission computed tomography (SPECT) studies show hyperperfusion in basal ganglia when temporal lobe seizures involve limb dystonia.[21–23] Interictal resting-state functional MRI (fMRI) studies have shown consistent changes in functional connectivity in the caudate, putamen, and substantia nigra in temporal as well as extratemporal epilepsies.[24]

Electrophysiological recordings of various structures in the basal ganglia exhibit hyperexcitability and increased synchrony in patients with epilepsy, and this increased activity can contribute to the generation and propagation of seizures.[13,25] In the study by Pizzo et al.,[12] recordings from the caudate nucleus showed rhythmic spiking, low-voltage fast activity, or theta activity during ictal recordings in 14 of 22 samples. A high epileptogenicity index in the caudate nucleus was found in two cases, one with temporal lobe epilepsy and another with opercular epilepsy. The basal ganglia were not recruited when ictal activity was restricted to the mesial temporal structures. However, propagation and generalization of those focal seizures showed slowing in the basal ganglia contralateral and ipsilateral to the seizure onset zones.[25] Preclinical studies on the subthalamic nucleus and globus pallidus externa in focal motor seizures show synchronous activity with the cortex at ictal onset compared with the putamen, which may be involved toward the end of the ictal activity.[13] Given the electrophysiological data displaying the involvement of the basal ganglia in various types of epilepsy, it is reasonable to hypothesize that deep brain stimulation (DBS) of basal ganglia has the potential to modulate epileptogenic networks. Early studies with low-frequency stimulation of the caudate nucleus interrupted both interictal and ictal activity.[26,27] In a study by Chabardes et al.,[28] high-frequency stimulation of the subthalamic nucleus in three patients with central epilepsy resulted in a 67% to 80% seizure reduction.

SEEG OF THE THALAMUS

The thalamus is a critical hub in focal epilepsy, playing a crucial role in the propagation of seizures. As a key relay for information between cortical and subcortical regions, the thalamus bridges various brain networks, making it a prime candidate for seizure maintenance. Studies have shown that thalamic connectivity is disrupted in focal epilepsy, with alterations in both structural and functional connectivity, and the persistence of this aberrant thalamocortical connectivity post-resection can sustain seizure recurrence and drive suboptimal surgical outcomes.[29–32] Targeting the thalamus with therapeutic interventions, such as DBS, may, therefore, be an effective strategy for controlling seizures in patients with focal epilepsy.[33]

The thalamus is not a unitary structure but a conglomeration of subnuclei, each with diverse reciprocal connectivity and functions. Distinct thalamic subnuclei (i.e., anterior nucleus [ANT], centromedian [CM], medial pulvinar [PuM]) have been targeted for neuromodulation in drug-resistant multifocal epilepsies (Fig. 1).

Anterior Nucleus of the Thalamus

The ANT, an integral part of the Papez circuit, serves as a central hub for information flow. It receives inputs from the hippocampus through the fornix and communicates with the mammillary bodies through the mammillothalamic tract.[34] This connectivity sets the stage for rapid seizure propagation to the ANT, whether directly from the seizure onset zone within the limbic network or indirectly through regions with connections to the ANT. The ANT's role in facilitating seizure propagation has been a topic of significant interest and debate.[35–37] Chronic neuromodulation of the ANT has demonstrated improved seizure control in patients with temporal (mesial and lateral), frontal, and parietal regions.[33,38,39] Figures 1A and 1B are diagrammatic illustrations of a common surgical approach to the ANT for SEEG.

Compelling evidence supporting the involvement of the ANT in seizures has emerged from preclinical studies. These studies have shown that chemical or electrical modulation of the ANT can disrupt the progression of limbic seizures, firmly establishing its causal role in the early organization of seizures.[37,40–42] Furthermore, limited electrophysiological investigations conducted in patients with focal epilepsy have corroborated these findings by demonstrating the early recruitment of the ANT during seizures.[43–45]

Given its role in the propagation of seizures, the ANT has become a prime target in the treatment of patients with multifocal epilepsies. Notably, Food and Drug Administration (FDA)-approved ANT DBS has been employed to provide chronic open-loop stimulation during the interictal state.[33,38,39] However, it is worth noting that while this intervention has shown promise, it typically results in only a modest reduction in seizure frequency.[33,39] The mechanism by which thalamic modulation perturbs seizures remains a subject of ongoing investigation, with

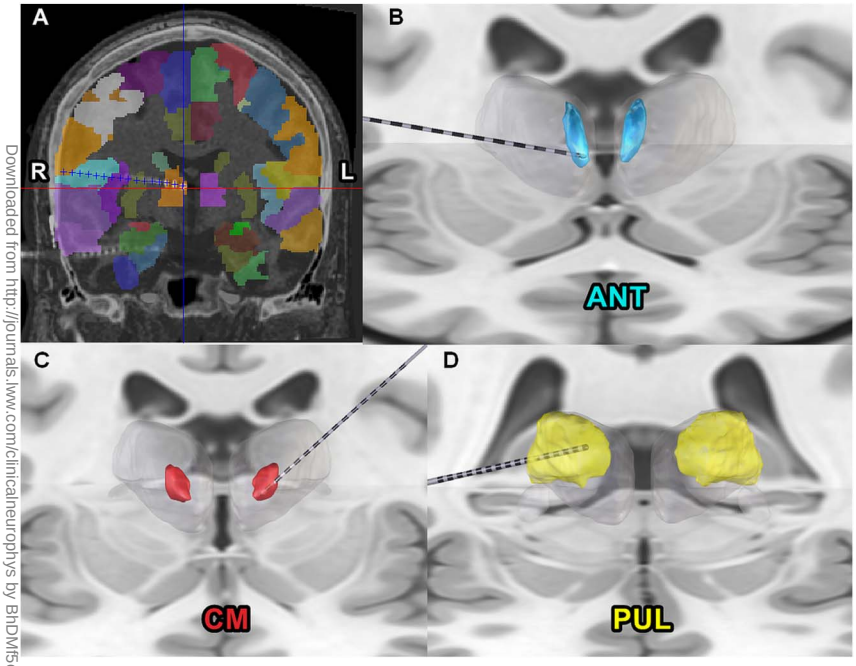

FIG. 1. Anatomical localization of SEEG electrodes targeting thalamic nuclei. **A**, Postimplant CT was co-registered with the preimplant MRI, and SEEG electrode trajectories were extracted (blue cross hairs). Trajectory of the electrode targeting the ANT: entry through precentral gyrus, traversing frontal operculum, insula, and putamen to reach the anterior ventral segment of the anterior nucleus of the thalamus—ANT. **B**, SEEG electrodes reconstructed in 3D using LeadDBS,[64] with the cyan ROI representing the ANT. **C**, SEEG electrode ending in the CM (red ROI). **D**, SEEG electrode targeting the pulvinar thalamus (yellow ROI) that tracks through the lateral pulvinar to end in the medial pulvinar. CM, centromedian thalamus; CT, computerized tomography; MRI, magnetic resonance imaging; ROI, region of interest; SEEG, stereoelectroencephalography.

changes in synchronization emerging as one proposed candidate mechanism.[46] Particularly noteworthy is the observation of increased coherence at 5 to 20 Hz (theta and beta bands) between the ANT and the hippocampus at the onset of induced seizures in experimental models of limbic epilepsy.[37,42]

In summary, as a key player in the Papez circuit, the ANT stands at the crossroads of early organization and bihemispheric propagation of limbic seizures. Its connections and active involvement in seizures make it a focal point of interest in the study and treatment of epilepsy. During SEEG investigations, the ANT can be effectively sampled by extending one of the clinical electrodes originally positioned to sample cortical structures, such as the insula or frontal region[47] (Fig. 1). This approach eliminates the need for additional electrodes dedicated solely to thalamic sampling, thereby reducing the associated risks of hemorrhage. The strategic sampling of the ANT within the clinical SEEG procedure can potentially inform the selection of neuromodulation. It becomes particularly relevant in cases of patients suspected of having bitemporal or temporal plus epilepsies, where determining the optimal treatment strategy, whether it be thalamocortical responsive neurostimulation (RNS) or thalamic DBS, is a subject of debate. Incorporating ANT sampling into clinical SEEG can inform the selection of effective neuromodulatory approaches.

Centromedian Thalamus and the Medial Pulvinar

The CM resides in the posterior part of the intralaminar thalamus and exhibits extensive connections with various brain regions, including the basal ganglia, sensorimotor areas, amygdala, hippocampus, anterior cingulate cortex, insula, and lateral temporal cortex. Notably, the CM plays a significant role in regulating arousal and sensory-motor processing.[48] In the realm of epilepsy, neuromodulation of the CM has been explored as a therapeutic approach for both generalized[49] and focal seizures,[50,51] particularly those originating in the frontal lobe. A preclinical study[52] revealed that during limbic seizures, neuronal firing rates in the parafascicular complex decreased initially but later increased toward seizure termination. Similarly, Feng et al.[53] reported decreased neuronal firing rates, this time in the central lateral thalamus, accompanied by a transition to a bursting firing pattern, often associated with slow-wave sleep and reduced consciousness. These insights into CM DBS shed light on potential mechanisms underlying seizure modulation and consciousness dynamics.

The pulvinar nucleus, accounting for 40% of the thalamic volume, is the largest among its thalamic counterparts. Its prominence in the brain's architecture is mirrored by its intricate network of connections. Specifically, the pulvinar acts as a central hub, receiving input from the visual, auditory, and somatosensory cortices.[54] Moreover, this heteromodal association nucleus fosters reciprocal connections with critical regions, including the mesial and lateral temporal areas, cingulate cortex, inferior parietal, and dorsolateral prefrontal regions. The connectivity of the lateral pulvinar with the visual cortex and inferior parietal regions underscores its multifaceted role in information integration. The pulvinar's extensive connectivity and ability to modulate corticocortical interactions and thalamocortical synchrony position it as a promising target for neuromodulation.[55–59] SEEG studies have validated its involvement in temporal lobe seizures, affirming the recruitment of the medial pulvinar.[56,59,60] Evoked potential studies have further elucidated the connectivity of the medial pulvinar with both mesial and lateral temporal regions.[55] Investigations employing closed-loop stimulation of the pulvinar and cortex have yielded encouraging outcomes,[57] demonstrating a reduction in the incidence of onset seizures originating from the posterior quadrant. In light of these findings, pulvinar neuromodulation emerges as a compelling avenue of

research and a potential therapeutic option for patients with bilateral mesial temporal and temporal plus epilepsies, where traditional resection is not viable.

In clinical SEEG, the pulvinar and CM's strategic sampling holds relevance, particularly in complex cases (Figs. 1C and 1D). Sampling the pulvinar for posterior quadrant epilepsies, bitemporal epilepsies, and temporal plus epilepsies is informative if neuromodulation strategies to target the pulvinar are considered. Demonstration of early seizure propagation in the pulvinar can impact decisions regarding corticopulvinar RNS or DBS in cases where resection is nonviable or previous epilepsy surgeries have been unsuccessful.[57,58]

On the other hand, the surgical outcomes of frontal lobe epilepsies, particularly in nonlesional cases, are often the least favorable among all surgical epilepsies. CM sampling may be considered in other specific challenging situations, such as in extensive multilobar encephalomalacia or dysplasia and in nonlesional patients where lateralization and localization prove difficult (Figs. 2 and 3). CM sampling in such contexts may help in the selection of neuromodulatory targets. In addition, early ictal electrophysiological changes in the CM may favor CM neuromodulation over ANT DBS.

SAFETY AND ETHICS

While stereotactic placement of DBS electrodes in the thalamus has been conducted in numerous cases for both epilepsy and movement disorders, implantation of thalamic subnuclei during SEEG is not a routine practice in epilepsy surgery. Meta-analyses of SEEG studies have indicated that the risk of bleeding increases by approximately 0.2% with each additional depth electrode implanted.[61] It is noteworthy that most bleeding events associated with SEEG are asymptomatic and typically occur near the cortical entry site, manifesting as subarachnoid hemorrhage, subdural hematoma, or trace intraparenchymal hemorrhage.

A viable strategy to mitigate these risks would involve modifying the trajectory of clinically indicated depth SEEG electrodes (Fig. 1).[47] Regardless, it is essential to ensure that patients are well informed about the potential benefits and risks of thalamic sampling before surgery and that the investigators comply with their local Institutional Review Board directives.

FUTURE PROSPECTS

Multithalamic SEEG

The sampling of multiple thalamic subnuclei during a single SEEG implant was recently reported.[62] The advantage of sampling multiple subnuclei lies in comparing thalamic recruitment patterns of cortical onset seizures within the same individual. Thus, although ANT is the FDA-approved target, different thalamic subnuclei specific to the patient's epileptogenic network may provide superior seizure control than ANT. It is important to note that clinical data supporting this hypothesis is lacking as of the current writing. Still, it is anticipated that such data will become available shortly. Corticothalamic RNS has been used in multifocal epilepsies,[57] and clinical trials are

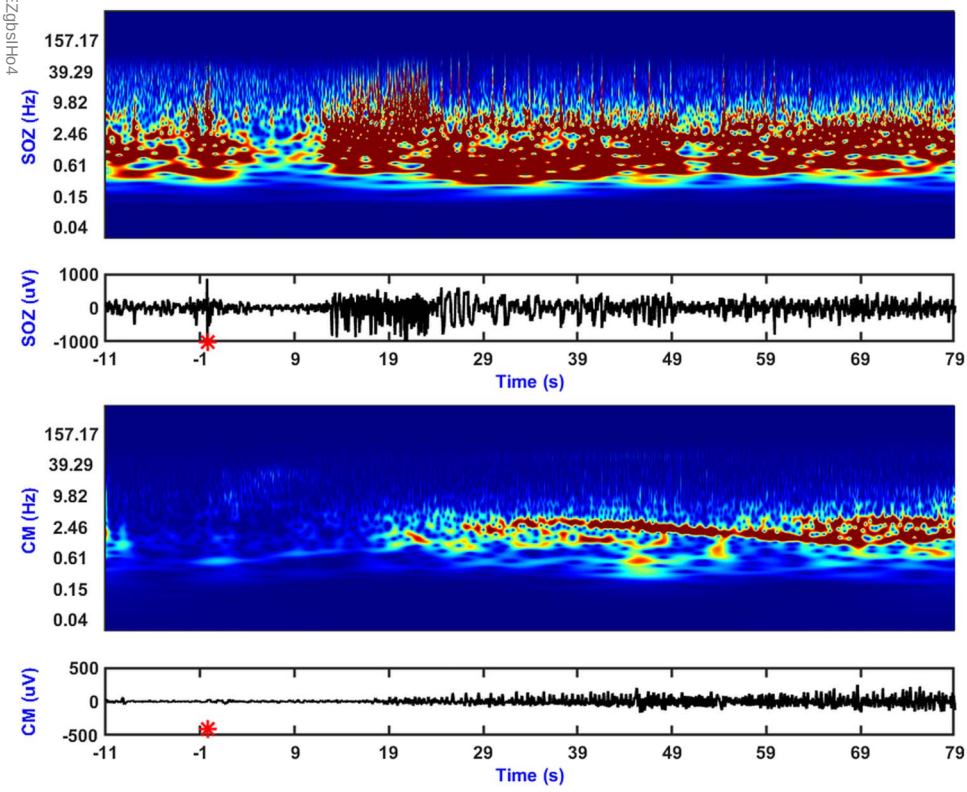

FIG. 2. Thalamic spectral changes in a patient with hippocampal onset seizures. A burst of high amplitude spike followed by LVFA was observed at seizure onset (time −1 on x-axis) in the hippocampus. Note the pronounced increased power in activity in the CM at time = 19. CM, centromedian thalamus; LVFA, low-voltage fast activity.

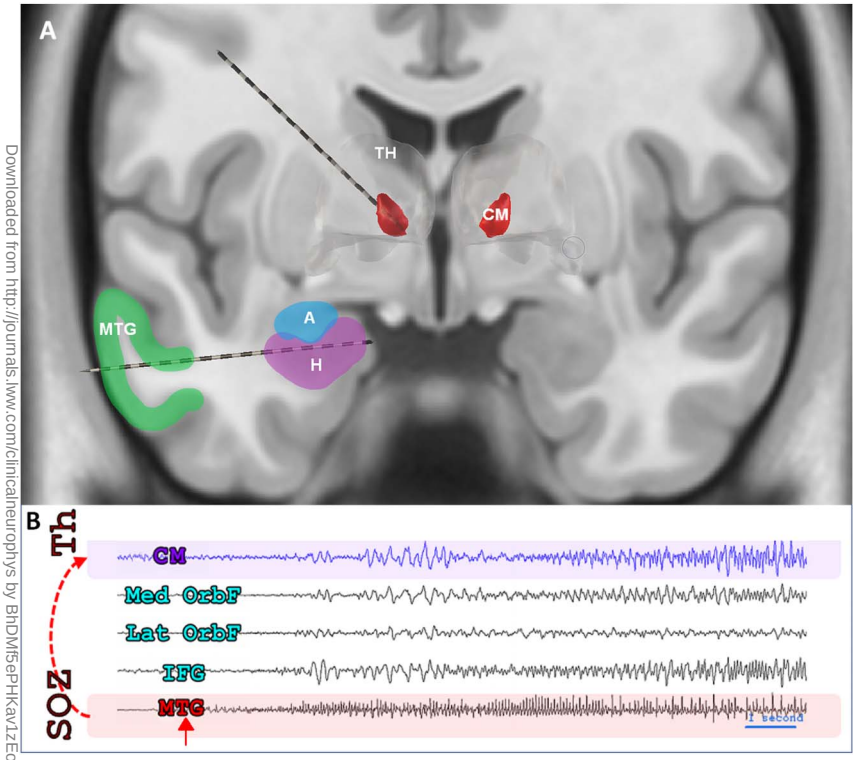

FIG. 3. Simultaneous sampling of the hippocampus and centromedian thalamus. The hippocampal electrode enters the MTG (green) and ends in the medial hippocampus (purple; H), inferior to the amygdala (blue ROI). The red ROI marks the CM of the TH. **B**, Seizure onset in the MTG (red arrow), quickly recruits the CM thalamus. CM, centromedian nucleus; IFG, inferior frontal gyrus; Lat OrbF, lateral orbitofrontal; Med OrbF, medial orbitofrontal; MTG, middle temporal gyrus; SOZ, seizure onset zone; TH, thalamus.

underway evaluating the CM RNS in generalized epilepsy (Clinical trials.gov identifier NCT05147571) and cortical-CM RNS in Lennox-Gastaut Syndrome (Clinical trials.gov identifier NCT05339126).

Thalamic SEEG Stimulation Trials

A further development in the field is the exploration of acute stimulation trials during SEEG evaluation of the thalamus. These trials aim to assess whether acute thalamic stimulation can effectively reduce the epileptiform burden, which is quantified by various measures, including changes in epileptiform spikes, power spectra, synchrony, high-frequency oscillations, and seizure duration recorded through cortical SEEG.[59,63] Typically lasting between 1 and 6 hours, these trials are frequently conducted toward the end of the SEEG evaluation process. In addition, patient-reported side effects induced by stimulation are assessed during these trials. However, it remains uncertain whether the outcomes of acute, short-term stimulation trials can serve as predictive indicators for long-term, chronic stimulation efficacy, making this an area of research interest.

CONCLUSION

SEEG has ushered in a new era in epilepsy surgery, allowing for the safe and reliable sampling of deep brain structures. The basal ganglia and thalamus, previously hidden from traditional diagnostic methods, have emerged as critical and multifaceted players in focal epilepsy. They hold the potential to serve as neuromodulatory targets, offering hope for more tailored therapies for individuals with drug-resistant epilepsies. The distinct thalamic subnuclei, the ANT, CM, and PuM present exciting avenues for personalized treatments. Multithalamic SEEG and thalamic SEEG stimulation are newer and promising developments. SEEG's ability to provide high-resolution insight into the dynamics of deep brain structures may yield more effective and individualized therapies for the most challenging situations. A rigorous informed consent process is essential when SEEG of the deep brain is proposed to patients.

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