Robot-assisted stereoelectroencephalography exploration of the limbic thalamus in human focal epilepsy: implantation technique and complications in the first 24 patients

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OBJECTIVE Despite numerous imaging studies highlighting the importance of the thalamus in a patient's surgical prognosis, human electrophysiological studies involving the limbic thalamic nuclei are limited. The objective of this study was to evaluate the safety and accuracy of robot-assisted stereotactic electrode placement in the limbic thalamic nuclei of patients with suspected temporal lobe epilepsy (TLE).

METHODS After providing informed consent, 24 adults with drug-resistant, suspected TLE undergoing evaluation with stereoelectroencephalography (SEEG) were enrolled in the prospective study. The trajectory of one electrode planned for clinical sampling of the operculoincisor cortex was modified to extend it to the thalamus, thereby preventing the need for additional electrode placement for research. The anterior nucleus of the thalamus (ANT) ($n = 13$) and the medial group of thalamic nuclei (MED) ($n = 11$), including the mediodorsal and centromedian nuclei, were targeted. The postimplantation CT scan was coregistered to the preoperative MR image, and Morel's thalamic atlas was used to confirm the accuracy of implantation.

RESULTS Ten (77%) of 13 patients in the ANT group and 10 (91%) of 11 patients in the MED group had electrodes accurately placed in the thalamic nuclei. None of the patients had a thalamic hemorrhage. However, trace asymptomatic hemorrhages at the cortical-level entry site were noted in 20.8% of patients, who did not require additional surgical intervention. SEEG data from all the patients were interpretable and analyzable. The trajectories for the ANT implant differed slightly from those of the MED group at the entry point—i.e., the precentral gyrus in the former and the postcentral gyrus in the latter.

CONCLUSIONS Using judiciously planned robot-assisted SEEG, the authors demonstrate the safety of electrophysiological sampling from various thalamic nuclei for research recordings, presenting a technique that avoids implanting additional depth electrodes or compromising clinical care. With these results, we propose that if patients are fully informed of the risks involved, there are potential benefits of gaining mechanistic insights to seizure genesis, which may help to develop neuromodulation therapies.

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KEYWORDS temporal lobe epilepsy; thalamus; stereotactic electroencephalography; anterior nucleus of the thalamus; mediodorsal nucleus; centromedian nucleus

ABBREVIATIONS ANT = anterior nucleus of the thalamus; CeM = centromedian nucleus of the thalamus; DBS = deep brain stimulation; EZ = epileptogenic zone; MED = medial group of thalamic nuclei; SEEG = stereoelectroencephalography; TLE = temporal lobe epilepsy.

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ACCURATE localization of the epileptogenic zone (EZ) in temporal lobe epilepsy (TLE) is paramount to optimizing outcomes following resection or ablation.⁴⁴ However, despite significant technological advancements in imaging and surgical tools, seizure-freedom outcomes have plateaued at 45%–65% over the last decade, necessitating a continued investigation of how distributed brain regions interact to cause seizures.³⁹ Growing evidence suggests that networks of functionally and structurally connected areas, both within and outside of mesial temporal structures, contribute to EZs.^{4,10,19,32} Among extratemporal structures implicated in seizure inception, increased thalamotemporal structural and functional connectivity independently predicts poor surgical outcomes.¹⁷ Experimental studies in preclinical models of limbic epilepsy support the hypothesis that the thalamus can regulate limbic seizures, and the stage at which ictogenesis is regulated (i.e., initiation, propagation, or termination) depends on the functional connectivity of the thalamic nuclei with limbic structures.^{6,9,36} Furthermore, modulation of the “limbic” thalamic nuclei (i.e., the anterior, midline and mediodorsal, and intralaminar centro-median [CeM] nuclei) through chemical, optogenetic, or electrical perturbation can interrupt focal seizures.^{6,16,25,37} However, despite numerous preclinical and imaging studies highlighting the importance of the thalamus in surgical prognosis,¹⁷ there are very limited human electrophysiological studies targeting the limbic thalamus.

Over the last decade, clinicians have implanted subdural grids, hybrid macro-micro depth electrodes, and laminar electrodes for high-density intracranial recordings from both the superficial and deep cortexes.^{41,43} Although the thalamus is likely a rich source of data about seizure regulation, propagation, and sleep dysfunction,^{12,15} progress in this area is relatively slow due to ethical and safety concerns. However, future therapeutic developments may

be highly informed by understanding thalamotemporal causal interactions during seizures. Here, we present the technical nuances, safety details, and accuracy data from stereoelectroencephalography (SEEG) implantation of electrodes into the limbic thalamus during the presurgical evaluation of patients with suspected TLE.

Methods

Patient Selection

Enrolled patients included those deemed eligible for SEEG after consensus recommendation from a multidisciplinary epilepsy conference consisting of neurologists, neurosurgeons, neuropsychologists, and nurses. Adults with drug-resistant, suspected TLE undergoing SEEG evaluation were eligible to participate in the study. Surgeons modified the trajectory of one electrode planned for clinical sampling to extend to the thalamus, obviating the need to implant an additional electrode for thalamic sampling. A 5-stage evaluation process helped streamline the process of recruiting considerably homogeneous groups of patients with suspected TLE (mesial and/or temporal plus) who would receive the thalamic implant (Fig. 1). The investigators approached the potential candidates for thalamic SEEG at the outpatient follow-up clinic visit, and written informed consent was obtained in accordance with protocols approved by the University of Alabama at Birmingham Institutional Review Board.

Thalamic Trajectory

In this study, the limbic thalamic nuclei that were targeted were as follows: 1) anterior nucleus of the thalamus (ANT), including anterior ventral, anterior dorsal, and anterior medial subnuclei; and 2) medial group of thalamic nuclei (MED), including mediodorsal and CeM subnuclei. Neurosurgeons planned trajectories using T1-weighted

FIG. 1. Patient selection and SEEG implantation: a multistage process to obtain informed consent from eligible patients scheduled to undergo SEEG investigation for localization of epilepsy. EMU = epilepsy monitoring unit.

MRI sequences with gadolinium contrast using robotic stereotactic planning software (ROSA; Medtech). MRI scans were acquired using the epilepsy protocol in a Philips Achieva 1.5T scanner (matrix size 384×384 mm/ 32×432 mm, slice thickness 1.2 mm, TR 7 msec, TE 3 msec, interslice gap 1.2 mm, flip angle 8°), Philips Achieva 3T scanner (matrix size 256×256 mm/ 528×528 mm, slice thickness 1 mm/ 1.2 mm, TR 6 msec, TE 3 msec/ 4 msec, interslice gap 1 mm/ 1.2 mm, flip angle $8^\circ/9^\circ$), Philips Ingenia 1.5T scanner (matrix size 512×512 mm/ 432×432 mm, slice thickness 1 mm, TR 7 msec, TE 3 msec, interslice gap 1 mm, flip angle 8°), Philips Ingenia 3T scanner (matrix size 528×528 mm/ 432×432 mm, slice thickness 1.2 mm, TR 7 msec, TE 3 msec, interslice gap 1.2 mm, flip angle 9°), or SIEMENS Skyra 3T scanner (matrix size 256×256 mm, slice thickness 0.9 mm, TR 7 msec, TE 3 msec, interslice gap 0 mm, flip angle 8°).

Based on a visual reference to Morel's thalamic atlas, the nuclei were determined to be located in relation to the following landmarks²¹ while planning the trajectory. The ANT was identified by its close relationship to the foramen of Monro and the venous angle formed by the confluence of thalamostriate and septal veins lying immediately posterior and lateral (Fig. 2). Extending a trajectory that incorporated the frontal operculum and insula, the thalamic region of interest was targeted without requiring an additional electrode. For the MED group of thalamic nuclei, neurosurgeons targeted the ventral midline thalamus near the massa intermedia, providing recordings from the centromedial or mediodorsal nuclei. The broadest midline nuclear segment was anterior and ventral to the massa intermedia, where the reunions and central median nuclei are located.³³ The massa intermedia could be visualized in 5 of the 8 MED thalamic groups of patients. When not distinct, the anteroposterior midpoint at the level of the anterior commissure–posterior commissure plane was chosen.⁵ The inferior and nearly parallel relationship with the ANT provided further anatomical confirmation.

Following SEEG implantation, patients were initially monitored in the neurosurgical ICU for 24 hours. High-resolution postimplantation head CT scans were obtained within 24 hours. Subsequently, the patients were transferred to the epilepsy monitoring unit for seizure localization and mapping.

Measuring Accuracy

Postimplantation CT scans were acquired using Philips Brilliance64 and Brilliance16P scanners (matrix size 512×512 mm, slice thickness 1 mm, 120 kVp [peak kilovoltage], interslice gap 1 mm, exposure time 1550 sec/727 sec). The CT scans were coregistered to the preoperative MR images using Advanced Normalization Tools (Fig. 3).³ Electrodes were localized using Lead-DBS software (www.lead-dbs.org), and trajectories were mapped using iElectrodes software.^{7,18} Coregistered images were normalized to ICBM152–2009b nonlinear asymmetrical atlases using nonlinear diffeomorphic normalization algorithms, and brain shift corrections were performed using Schönecker normalizations, providing refined registration of subcortical structures.³⁵ Registrations were checked manually for errors in 3D Slicer. The data were

FIG. 2. Landmarks for targeting the thalamic nuclei. The foramen of Monro as the anteromedial extent (A), the massa intermedia as the medial extent (B), the midpoint (red dot) of the anteroposterior length (yellow line) of the third ventricle in axial view as the inferior extent (C) (measured at the level of the superior colliculus and the venous angle as the anteromedial extent), and the confluence of the anterior septal vein, thalamostriate vein, and internal cerebral vein (D) were the major landmarks used while targeting the electrodes. Green crosshairs in A, B, and D indicate the coordinates of the aforementioned landmarks. E and F: The probable extents of ANT as per Morel's atlas. G and H: The probable extents of MED (CeM + mediodorsal subnuclei) as per Morel's atlas. The yellow brackets indicate the anteroposterior extent of nuclei in E and G and the medial to lateral extent in F and H. The red dots indicate the farthest extent of the thalamic nucleus in any given direction. The blue brackets indicate the superoinferior extent of the nuclei. A = anterior; I = inferior; L = lateral; M = medial; P = posterior; S = superior.

FIG. 3. Coregistration strategy. **A:** The postimplantation CT scan was coregistered onto the preoperative MR image to determine the postoperative target of the thalamic targets using Advanced Normalization Tools in Lead-DBS. **B:** Following coregistration, a manual verification of the anatomical landmarks and the overlap of the inner and outer tables of the MR image and CT scan were used to ensure accurate coregistration. In particular, the most probable location of the thalamic electrode was confirmed. **C:** The coregistered MR image and CT scan were then normalized to the MNI (Montreal Neurological Institute) space. The coregistered images were then resolved for finer registration and brain shifts using the Schöneck normalization algorithm to improve the registration of the subcortical structure (3D Slicer).

then visualized using Morel's atlas.²¹ To map the trajectories, the coregistered and normalized CT and MRI scans were imported along with the corresponding CT mask into iElectrodes and registered with the AAL2 atlas to identify their cortical-subcortical locations.^{28,40} As a final step in establishing the accuracy of the implant strategy from our experience, we estimated the postimplantation

accurate location of the thalamic target as well as the linear component distances along the x, y, and z axes and the Euclidean distances from the landmarks. Postexplantation CT scans were also obtained to look for postoperative hemorrhage or edema. If found, hemorrhage was graded using McGovern's SEEG hemorrhage grading system.²³

TABLE 1. Clinical presentation of the 24 participants and summary of post-SEEG localization of the seizure pathology and the treatment strategy

Thalamic Nucleus & Participant No.	Sex	Age (yrs)	Age at Epilepsy Onset (yrs)	Duration of Epilepsy (yrs)	No. of Failed AEDs	Preimplant MRI	No. of Electrodes	Laterality of Thalamic Electrode	Post-SEEG EZ	Treatment
ANT										
1	F	42	38	3.5	5	HS+	9	Lt	Lt TLE subtype*	Pt deferred surgical therapy
2	M	24	6	18.5	2	N	14	Rt	Rt MTLE	Rt ATL
3	F	47	41	6.2	7	N	14	Rt	Bilat TLE	Bilat HG RNS
4	M	37	29	8.0	4	EH	10	Rt	Rt TLE plus†	Rt HG & OrbF RNS
5	F	57	53	4.2	9	N	13	Rt	Rt TLE: Tp subtype	Rt ATL
6	F	51	40	11.0	3	N	11	Rt	Rt TLE plus†	Rt ATL extended to Ins & OperG
7	F	59	16	43.2	10	EH	14	Rt	Multifocal: rt TLE, parietal	Palliative rt HG LiTT
8	M	34	10	23.9	11	EH	20	Rt	Multifocal: rt TLE, frontal	Palliative rt ATL
9	M	46	6	39.9	4	HS+	15	Rt	Rt MTLE	Rt ATL
10	F	36	31	4.5	6	N	16	Lt	Lt TLE plus,† rt MTLE	Bilat HG RNS
11	M	29	8	20.6	4	N	12	Lt	Lt TLE plus†	Mesial OrbF, ACingG resected, planned HG RNS
12	F	48	41	7.5	5	HS+	14	Rt	Rt TLE plus†	Rt ATL extended to Ins
13	M	61	40	21.4	6	N	20	Rt	Rt MTLE	Rt LiTT HG
MED										
14	F	43	39	3.9	4	N	15	Lt	Lt MTLE	Scheduled for lt HG RNS
15	M	30	11	18.6	8	EH	15	Lt	Nonlocalized	Offered DBS (failed VNS)
16	F	23	13	9.5	5	N	8	Lt	Lt MTLE	Lt HG, subtemporal RNS
17	F	40	14	25.7	7	N	8	Rt	Rt MTLE	Rt ATL
18	F	42	8	34.0	12	HS+	18	Lt	Lt TLE plus,† rt MTLE	Palliative lt HG LiTT
19	M	46	41	4.7	3	HS	16	Rt	Rt TLE: Tp subtype	Rt ATL
20	M	27	13	13.6	5	HS	14	Lt	Lt MTLE	Lt ATL
21	M	34	20	13.9	5	EH	15	Rt	Rt lat TLE	Rt lat resection
22	F	40	8	32.0	8	HS	16	Lt	Lt TLE plus†	Scheduled palliative lt HG LiTT
23	M	24	16	8.1	3	HS+	15	Rt	Bilat TLE	Bilat HG RNS
24	F	44	33	11.0	8	HS+	13	Lt	Lt TLE plus†	Scheduled palliative lt HG LiTT

ACingG = anterior cingulate gyrus; AEDs = antiepileptic drugs; ATL = anterior temporal lobectomy; EH = extrahippocampal pathology; EZ = epileptogenic zone; HG = hippocampal gyrus; HS = hippocampal sclerosis; HS+ = hippocampal sclerosis along with additional temporal lobe pathology; Ins = insula; LiTT = laser interstitial thermal therapy; MTLE = mesial TLE; N = normal; OperG = opercular gyrus; OrbF = orbitofrontal; pt = patient; RNS = responsive neuronal stimulation; Tp = temporopolar; VNS = vagal nerve stimulation.

* Mesial to lateral temporal subtype of TLE.

† "TLE plus" indicates multiple seizure onset sites including the temporal lobe.

Results

Patient Demographics

Details regarding patient demographics are shown in Table 1. A total of 24 patients underwent thalamic SEEG implantation. The ANT was targeted in 13 patients

(54.2%), and the MED group nuclei were targeted in 11 patients (45.8%) (male/female ratio 11:13, mean age at implantation 40 ± 11 years). Brain MR images were negative for any epileptogenic lesions in 10 patients (41.7%), while 4 patients (16.7%) had hippocampal sclerosis, 5 (20.8%)

FIG. 4. Thalamic implant and complication rates. **A:** Pie chart showing the number of patients receiving ANT or MED thalamic implants. **B:** Pie chart demonstrating the number of patients who had postoperative complications in terms of asymptomatic vasogenic edema and asymptomatic hemorrhages in the proximity of the entry site of the electrodes. **C:** Postexplantation CT scan showing asymptomatic vasogenic edema (arrow) in the right temporal lobe. **D:** Postexplantation CT scan demonstrating an asymptomatic left temporal intracranial hematoma (arrow). **E:** Postexplantation CT scan showing an asymptomatic right frontal extradural hematoma (arrow).

had hippocampal sclerosis with additional extrahippocampal pathology, and the remaining 5 (20.8%) had extrahippocampal pathology only.

SEEG Implantation and Complications

On average, each patient received a median of 172 contacts (range 102–274 contacts). SEEG implantation and outcome data are presented in Table 1. None of the patients had thalamic hemorrhage or edema. Asymptomatic subarachnoid, subdural, and intracranial hemorrhages were noted close to the entry site of the electrodes in 5 (21%) of 24 patients (Fig. 4B). All hemorrhages were grade 1–2 according to McGovern's SEEG hemorrhage grading²³ (consisting of a small intracranial bleed, either close to or away from eloquent cortex); these were low-grade hemorrhages with a lower probability of being symptomatic. On evaluating the 3 major risk factors as identified by McGovern et al.,

we found no significant difference in sex, age, or number of electrode implants for patients with and without hemorrhage (male/female ratio 4:1, $t = 3.8$, $p = 0.051$; age of patients in the hemorrhage group 42.7 ± 7 years and age of patients in the no-hemorrhage group 39.4 ± 11 years, $t = 0.58$, $p = 0.56$; number of electrodes in the hemorrhage group 14 ± 4 and number of electrodes in the no-hemorrhage group 14 ± 3 , $t = 0.34$, $p = 0.73$). Asymptomatic vasogenic edema in the temporal or parietal lobe was noted in 3 of the 24 patients. Overall, 34% of patients had asymptomatic hemorrhage or edema shown on the postexplantation CT scans. Follow-up CT scans showed resolution of these findings. None of the patients had any symptomatic hemorrhage or required any surgical interventions to treat hemorrhage.

Targeting Accuracy

Of the 13 patients who underwent planned ANT im-

TABLE 2. Measurements of electrode targets to anatomical landmarks

	Target (mm)			FM (mm)			MI (mm)			TV (mm)		
	X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z
ANT												
Location												
Lt (n = 1)	-5	-5	8	-4	1	5	0	-12	10	0	-12	-4
Rt (n = 9)	2 ± 5	-6 ± 2	6 ± 7	2 ± 1	0 ± 1	3 ± 2	0 ± 0	-11 ± 2	2 ± 5	0 ± 0	-12 ± 1	-4.1 ± 1
	Target to FM			Target to MI			Target to TV					
Linear component distance												
Lt	1	6	3	5	7	2	5	7	12			
Rt	3 ± 4	6 ± 2	6 ± 3	5 ± 2	5 ± 2	7 ± 5	5 ± 2	7 ± 2	11 ± 5			
	to FM	to MI	to TV									
Euclidian distance												
Lt	7	9	15									
Rt	10 ± 3	11 ± 3	15 ± 2									
	Target (mm)			FM (mm)			MI (mm)			TV (mm)		
	X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z
MED												
Location												
Lt (n = 8)	-3 ± 1	-10 ± 3	2 ± 4	-3 ± 1	-1 ± 1	2 ± 2	0 ± 0	-10 ± 2	2 ± 5	0 ± 0	-12 ± 1	-4 ± 1
Rt (n = 2)	5 ± 3	-12 ± 1	1 ± 4	2 ± 1	0 ± 2	3 ± 4	0 ± 0	-10 ± 1	-2 ± 1	0 ± 0	-13 ± 2	-51
	Target to FM			Target to MI			Target to TV					
Linear component distance												
Lt	0 ± 1	9 ± 3	4 ± 2	2 ± 1	2 ± 3	2 ± 3	2 ± 1	3 ± 3	7 ± 3			
Rt	4 ± 3	12 ± 2	3 ± 2	5 ± 3	2 ± 1	3 ± 3	5 ± 3	1 ± 2	6 ± 5			
	to FM	to MI	to TV									
Euclidian distance												
Lt	10 ± 2	5 ± 3	8 ± 4									
Rt	13 ± 2	7 ± 2	9 ± 3									

FM = foramen of Monro; MI = massa intermedia; TV = anteroposterior midpoint of third ventricle.

The measurements (in mm) between the electrode target and the anatomical landmarks are provided in terms of actual 3D coordinates of the electrodes, their linear components vectorized on the x, y, and z axes, and, finally, the 3D euclidean distance in space between the target tip and the anatomical landmark. Values are presented as mean ± SD.

plantation, 10 (77%) had confirmed localization in the ANT (Fig. 4A). In one of the patients, the electrode passed through the ipsilateral ANT and crossed the midline to the contralateral thalamus, traversing through the mediodorsal nucleus. In another patient, the electrode target stopped short by 4 mm and was situated in the ventral lateral nucleus of the thalamus. In the third patient, the electrode target was situated 3 mm anterior to the ANT in the anterior fornix.

For the 11 patients who underwent MED implantation, the massa intermedia was used for localization. Ten electrodes (91%) were situated in the MED (CeM and mediodorsal). In one patient, the electrode target stopped short by 8 mm from the midline and was situated in the ventromedial thalamic nucleus.

Postimplantation accuracies on the x, y, and z axes and euclidean errors are presented in Table 2. The trajectories for the ANT group differed slightly from those of the

MED group at the entry point, which was in the precentral gyrus in the former and in the postcentral gyrus in the latter (Fig. 5).

Once the implantation process was completed, SEEG data were recorded continuously. The thalamic SEEG signals in all patients were interpretable and comparable to those of the cortical channels. However, the local field potentials of the thalamus were of a lower amplitude than those of the cortical channels (Fig. 6). The electrophysiological data thus obtained were analyzed and published previously, addressing key clinical questions.^{26,27,29,40}

Discussion

Stereotactic procedures targeting the thalamus date back to the mid-20th century when Spiegel and Wycis reported on thalamotomy for several psychiatric indications,³³ and these authors were also the first to record sei-

FIG. 5. Implant registration accuracy: Lead-DBS was used to reconstruct the target location of the thalamic electrodes, while the trajectories were reconstructed, and the cortical contacts were identified using iElectrodes. **A:** ANT implantation followed the trajectory of the precentral gyrus, pars opercularis frontalis, insula, putamen, and thalamus. **B and C:** MED group implantation followed a similar trajectory except that the entry point was the postcentral gyrus. **D and E:** The group implants showing the trajectories of all ANT and MED group implants, respectively.

zure activity from this location.³⁸ Since then, numerous thalamic stereotactic procedures have been performed for a wide variety of indications. However, by far the most significant experience in thalamic stereotaxy has been the implantation of deep brain stimulation (DBS) electrodes in the ventral intermediate thalamus for the management of essential tremor. The published complication rates of these DBS procedures mirror those of SEEG overall (range 1%–1.3%).^{8,11,14} In one pivotal study, McGovern et al. reported an overall hemorrhage rate of 19.1%,²³ while in our study the hemorrhage rate was 20.8%, with all hemorrhages occurring at the entry site of the electrodes. Contrary to the common belief that thalamic implantation is associated with a high bleed rate, in our study we noted no thalamic bleeds. In the pivotal trial for ANT DBS, 4.5% of the 110 patients had incidental asymptomatic intracerebral hemorrhage, but it is unclear if these bleeds were around the entry site of the DBS electrodes or if they were thalamic.^{13,34} Overall, SEEG requires an increased number of brain penetrations compared to DBS; however, the electrodes are smaller, and the procedure is very well tolerated, with a reported hemorrhage rate of 1%–4%.^{8,11,14,24} The higher complication rate reported in the study may be due to differences in reporting. Prior SEEG studies have reported hemorrhage rates based on evaluating postimplantation brain CT scans, while in the present study, postexplantation CT scans were used to estimate complications, similar

to what was done by McGovern et al. An electrophysiological sampling of the thalamus during SEEG investigation has been reported, but complications were not studied in detail.^{1,12,15,30,31}

Although the thalamus is successfully and safely targeted in DBS, SEEG requires quite different trajectory planning and implantation techniques. In contrast to DBS, where there is considerable flexibility in choosing the entry point, SEEG entry points and the target, as well as the structures along the path to the target, are frequently constrained by MRI abnormalities, magnetoencephalography or PET findings, intervening sulci, and vasculature. Also, thalamic DBS affords the opportunity, in many cases, to fully visualize the cortex if the dura is opened fully, whereas SEEG electrodes are placed via a small craniostomy in which direct visualization is not possible. Furthermore, a rigid cannula is passed either to the target or just shy of the target to guide placement of DBS electrodes, whereas SEEG electrodes are placed without a cannula and are more prone to deviations. Finally, SEEG surgical planning requires achieving adequate coverage of the putative epileptogenic areas with a limited number of electrodes. In suspected TLE, anatomical sampling with SEEG often includes extratemporal structures—including the insular operculum and the orbitofrontal, parietal, and cingulate regions—to rule out a lesion mimicking TLE.^{2,20} Numerous stereotactic techniques have been described for depth

FIG. 6. Seizure recording from the thalamus. A depiction of seizures recorded in the thalamus. The identification of the unequivocal electrographic onset was done by the clinician in the seizure onset channels (SOZ). Subsequent review of the thalamic channel showed that shortly after the seizure was noted in the SOZ, there was an evolving ictal rhythm noted in the thalamic channels. This EEG activity change was of a lower amplitude compared to that of the cortical channels and had a different morphology. **A:** An evolving ictal rhythm in a thalamic channel recording from ANT during a focal seizure originating in the ipsilateral hippocampus. **B:** Similar ictal activity recorded from the CeM nucleus during a focal seizure originating from the ipsilateral hippocampus.

electrode placement, including frame-based, frameless, and robotic methods, each with its own relative advantages and disadvantages. Many surgeons have recently gravitated toward robotic methods due to the precision and speed offered. We do not endorse any particular technique; in fact, we believe thalamic depth electrode implantation is likely safe when using any modern stereotactic system that has an accuracy error of approximately 1 mm or less. We maintain that safety is more a factor of careful trajectory planning, taking care to avoid cortical, sulcal, or deep vasculature and to ensure accurate image registration and cautious surgical technique that avoids common complications, such as drill skiving, drill plunging, and human measurement errors. These fundamentals are critical for the safety of all stereotactic procedures. We utilized a single technique and therefore cannot directly address the safety or accuracy differences of the various stereotactic methods.

Despite these myriad technical constraints, here our results demonstrate that it is safe to extend clinically indicated trajectories, specifically those through the frontal operculum or insula, for accurate targeting of the limbic thalamus. The overall complication rates are low and comparable to those of electrodes placed in any other location. With these results, we propose that if patients are fully informed of the risks involved, there are significant benefits to obtaining robust signals from thalamic nuclei involved in seizure networks, which may help guide future therapies.^{26,27,29} Some of the early studies by our group have shown the following: 1) periictal electrophysiological changes occurring in the thalamus during the seizures, 2) cortical responsiveness to thalamic stimulation, and 3) a temporal predictive model to determine ictal and interictal thalamic states in TLE. In concordance with the growing evidence from various centers around the world, there is a possibility to envisage a more patient-oriented closed-loop

DBS system. Systematic evaluation of complex thalamocortical interactions will eventually help in the development of such neuromodulation interventions in patients with drug-resistant epilepsies. Current thalamic DBS strategies are based mostly on a one-size-fits-all model without knowledge of the thalamocortical interactions specific to a given patient. Estimating patient-specific inherent thalamocortical frequency interactions can help in tailoring the stimulation parameters and developing DBS systems to optimize clinical response, which could significantly improve their clinical outcomes.

Limitations

From our collective experience, we highlight some of the challenges and future perspectives about thalamic sampling during SEEG investigation. First, target selection was performed directly on a 3T standard T1-weighted gadolinium-enhanced MRI sequence, which is challenging since both the ANT and MED are not well visualized. While used as an external visual reference, Morel's thalamic atlas overlay or its coordinate system²¹ has not, to date, been integrated into the robotic navigation systems, and we did not use specialized MRI sequences to visualize landmarks such as the mammillothalamic tract on an FGATIR (fast gray matter acquisition T1 inversion recovery) sequence. With experience and with potential incorporation of deformable atlases, we anticipate that our targeting process will become more precise. Second, although no hemorrhagic or focal neurological complications were noted, detailed neuropsychiatric examinations were not performed to assess whether the routine placement of electrodes produces damage that results in cognitive decline.⁴² A randomized trial of ANT DBS did not find any cognitive decline associated with the placement of the ANT DBS system. However, the transventricular

trajectory utilized in that study is different from the lateral trajectory used in the current study, making direct comparison difficult. Variable neuropsychological changes have been reported following ventral intermediate DBS that, when present, are thought to be primarily stimulation related and not the result of a lesion.^{22,45}

Conclusions

The therapeutic potential and prognostic role of the thalamus in focal epilepsy are well established in pre-clinical and clinical imaging studies. However, the lack of electrophysiological studies limits our knowledge of its involvement and may potentially hinder the development of therapies. Using robot-assisted SEEG, we have demonstrated the safety of electrophysiological sampling from various thalamic nuclei for research recordings and have presented a technique that avoids implanting additional depth electrodes or compromising clinical care. We state with utmost caution that the current results should not be mistaken for a safety blanket; instead, safe deep brain structure implantation should be judiciously performed only after the development of meticulous anatomical target strategies and robotic planning to avoid untoward complications during the SEEG procedure.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Pati, Chaitanya, Romeo, Riley. Acquisition of data: Pati, Romeo, Ilyas, Irannejad, Elsayed, Bentley, Riley. Analysis and interpretation of data: Pati, Chaitanya, Irannejad, Toth. Drafting the article: Pati, Chaitanya, Romeo, Ilyas. Critically revising the article: Pati, Chaitanya, Romeo, Bentley, Riley. Reviewed submitted version of manuscript: Chaitanya, Toth. Approved the final version of the manuscript on behalf of all authors: Pati. Study supervision: Pati.

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