BRAIN
ORIGINAL ARTICLE

Multisite thalamic recordings to characterize seizure propagation in the human brain

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See Bernabei et al. (https://doi.org/10.1093/brain/awad178) for a scientific commentary on this article.

Neuromodulation of the anterior nuclei of the thalamus (ANT) has shown to be efficacious in a subset of patients with refractory focal epilepsy. One important uncertainty is to what extent thalamic subregions other than the ANT could be recruited more prominently in the propagation of focal onset seizures. We designed the current study to simultaneously monitor the engagement of the ANT, mediodorsal (MD) and pulvinar (PUL) nuclei during seizures in patients who could be candidates for thalamic neuromodulation.

We studied 11 patients with clinical manifestations of presumed temporal lobe epilepsy (TLE) undergoing invasive stereo-encephalography (sEEG) monitoring to confirm the source of their seizures. We extended cortical electrodes to reach the ANT, MD and PUL nuclei of the thalamus. More than one thalamic subdivision was simultaneously interrogated in nine patients. We recorded seizures with implanted electrodes across various regions of the brain and documented seizure onset zones (SOZ) in each recorded seizure. We visually identified the first thalamic subregion to be involved in seizure propagation. Additionally, in eight patients, we applied repeated single pulse electrical stimulation in each SOZ and recorded the time and prominence of evoked responses across the implanted thalamic regions.

Our approach for multisite thalamic sampling was safe and caused no adverse events. Intracranial EEG recordings confirmed SOZ in medial temporal lobe, insula, orbitofrontal and temporal neocortical sites, highlighting the importance of invasive monitoring for accurate localization of SOZs. In all patients, seizures with the same propagation network and originating from the same SOZ involved the same thalamic subregion, with a stereotyped thalamic EEG signature. Qualitative visual reviews of ictal EEGs were largely consistent with the quantitative analysis of the corticothalamic evoked potentials, and both documented that thalamic nuclei other than ANT could have the earliest participation in seizure propagation. Specifically, pulvinar nuclei were involved earlier and more prominently than ANT in more than half of the patients. However, which specific thalamic subregion first demonstrated ictal activity could not be reliably predicted based on clinical semiology or lobar localization of SOZs.

Our findings document the feasibility and safety of bilateral multisite sampling from the human thalamus. This may allow more personalized thalamic targets to be identified for neuromodulation. Future studies are needed to determine if a personalized thalamic neuromodulation leads to greater improvements in clinical outcome.

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Received December 07, 2022. Revised February 22, 2023. Accepted March 23, 2023. Advance access publication May 4, 2023

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Keywords: epilepsy; multisite thalamic recordings; stereo-encephalography; corticothalamic interaction; evoked potentials; neuromodulation

Introduction

Understanding the precise nature of corticothalamic interactions has become increasingly relevant, since thalamic neuromodulation has shown recent promise in the treatment of patients with drug resistant epilepsies.[1] For instance, bilateral stimulation of the human thalamus in patients with drug resistant epilepsies has been shown to reduce seizures with favourable long-term efficacy and safety profiles, but the response to this mode of treatment has shown marked variability with localization of seizure foci.[2,3] A recent study found significant improvement of seizures originating from posterior cortical regions in three patients when the posterior thalamic region (pulvinar, PUL) was the target of responsive neurostimulation.[4]

To date, our understanding of thalamic involvement in the early phase of seizure propagation in the human brain has been limited to only a few studies where single thalamic site within each individual has been explored. In a seminal work with temporal lobe epilepsy (TLE) patients, Guye and colleagues[5] obtained single-site thalamic recordings from the medial PUL group or the posterior part of the mediodorsal (MD) nucleus and documented thalamic involvement in the early phase of seizure propagation in ~86% of patients. This was in keeping with studies showing that the field potentials recorded from rodent thalamus follow the cortical onset of seizures by <2 s.[6] Romeo and colleagues[7] studied three patients with a single additional depth electrode targeting the midline thalamus and confirmed that the thalamic recording site was recruited at varying points in seizure initiation ranging from 0 to 13 s. Chaitanya and colleagues[8] extended one single cortical electrode to reach either the anterior nuclei of the thalamus (ANT) or the MD and centromedian (CM) nuclei and reported correct placement in ~77% of ANT and 91% of MD/CM cases and their early recruitment during seizures. A different view was presented in a study[9] showing that thalamic ictal onset preceded scalp onset by about 0.5–2 s with electrodes recording from either ANT (in two patients) or CM sites (one patient), using a chronically implanted deep brain stimulation (DBS) device. While these studies have unanimously documented the involvement of the thalamus during early phases of seizure propagation, they have highlighted the need for a systematic observation of multiple thalamic sites during seizure propagation in the human brain—at the individual patient level.

To address this gap in knowledge, we designed the current study to characterize the involvement of the anterior (ANT), midthalamus (MD) and posterior (PUL) subdivisions during seizure onset in patients with drug resistant focal TLE. Inspired by the methodology used in prior studies,[6-8,10-12] we followed a surgical procedure for multi-thalamic sampling that utilized an orthogonal trajectory extending frontal and temporal opercular or insular electrodes to the three specific thalamic nuclear subgroups desired on a per patient basis. Uniquely, we pioneered a single trajectory that traveled through the massa intermedia to combine recordings from bilateral MD nuclei into one electrode. Doing so enabled us to achieve bilateral coverage across three distinct sites of the thalamus with fewer penetrations in order to not compromise the safety of our approach. We employed conventional visual review of EEGs during ictal events and validated our findings using repeated single pulse electrical stimulation approach. Our observations offer novel insights about the mode of involvement of different thalamic subregions during seizure propagation when monitored simultaneously and bilaterally in a group of patients with similar peri-ictal clinical signs.

Materials and methods

Patient selection

We recruited 11 patients who were considered clinically to have TLE of uncertain laterality and precise anatomical origin. Per routine clinical protocols in our institution, and research procedures and consents approved by the Stanford institutional review board, these patients underwent bilateral stereo-EEG (sEEG) recordings. Prior to the time of the sEEG recordings, all patients completed a comprehensive set of evaluations, including detailed clinical history, neurological examination, neuropsychological assessment, structural MRI and scalp EEG monitoring. The majority of patients completed additional imaging and neurophysiological studies as needed for pre-surgical planning, including functional MRI for language mapping, fluorodeoxyglucose (FDG) PET study and high-density electrical source imaging.

Anatomic electrode targets

Approximate locations and number of electrodes, along with their trajectories, were planned in a multidisciplinary surgical epilepsy conference with detailed review of presurgical data leading to the clinical hypotheses of most likely seizure onset zones (SOZ). Thalamic monitoring was achieved through extension of electrodes covering planned cortical zones; hence, no additional implantations were necessary. Thalamic recordings were derived from the most internal leads of the single multi-contact electrode clinically required to explore the superior temporal gyrus, posterior temporo-operculo-insular or frontal regions. Thalamic subdivisions that were monitored included the ANT, MD and PUL nuclei on either side. Given clinical limitations, the final number of thalamic electrodes ranged from 1–5 to monitor 1–6 thalamic nuclei. We did not implant in the CM thalamic nucleus in this series because its location was not within the trajectory of most other targets, and because it may be more involved with non-temporal lobe epilepsies.[13-16]

Electrode trajectory planning

High resolution T_1, fast grey matter acquisition T_1 inversion recovery (FGATIR), and T_1 post-contrast imaging were used for planning. All patients required frontal and temporal opercular and/or insular coverage. Trajectories were planned to traverse in an orthogonal plane to capture cortical frontal or temporal operculum, insula,

and then extended into specific nuclei of interest in the thalamus. The priority for all trajectories was safety and avoidance of middle cerebral sulcal and pial perforating blood vessels. At the highest density, we implemented a novel five-electrode multi-thalamic sampling approach. The first trajectory extended from frontal or anterior temporal operculum to anterior insula to anterior thalamic nucleus. A second trajectory extended from posterior temporal operculum, temporoparietal junction or supramarginal gyrus to the posterior insula to the PUL nucleus. These two trajectories were replicated bilaterally. The fifth and final electrode started in mid superior temporal gyrus or pars opercularis, traversed mid-insula and extended to the MD nucleus and through the massa intermedia to terminate approximately 1 cm into the contralateral mediodorsal nucleus. In this highest density montage, we captured six thalamic regions (anterior, middle, and posterior nuclear groups bilaterally) with five electrodes that also had coverage of desired cortical and insular regions superficially. We used only reduced diameter (0.86 mm) electrodes (Ad-Tech Medical) to help ensure minimal disruption to tissue. Trajectories were optimized by avoiding middle cerebral vessels as well as minimizing the distance traveled through the sylvian fissure. This was to minimize risk of deflection as the reduced diameter obturating stylet and electrodes passed through the two pial boundaries. Figure 1 shows the electrode trajectories across all subjects in our cohort.

Intraoperative workflow

The patients were brought to the operating room where general endotracheal anaesthetic was induced. Five bone fiducials were placed. A volumetric intraoperative O-arm® (Medtronic Inc.) CT scan was obtained with the fiducials. The image data set was then merged with the preoperative CT and T_1 pre- and post-contrast MRI scans. The patient was placed in a Leksell head holder and positioned supine. The ROSA™ robot (Zimmer Biomet) was then attached to the Leksell adapter and registered to the patient's head using the bone fiducials. Registration was accepted once <0.5 mm accuracy was achieved. The head was then prepped in the usual fashion. For each percutaneous trajectory, the ROSA robot was positioned coaxially. A small vertical stab incision was made with a #15 blade. A 2.4 mm drill bit was then introduced through the ROSA drill guide, and the drill guide lowered coaxially all the way down to the scalp. Once through the inner table of the skull, a bolt (bone anchor) was placed. A reduced diameter (0.8 mm) obturating stylet was passed slowly to create the trajectory. This was a critical step due to the need for precise targeting and passing through sylvian fissure. Once the stylet was passed to depth, a reduced diameter (0.86 mm) electrode was passed to target depth, inner stylet removed, and tightened into the bolt cap. The trans-massa thalamic trajectory was always performed first, to ensure highest degree of accuracy prior to the chance for subtle brain shift. At the end of the procedure, a 3–0 chromic gut buddy stitch was secured around each anchor bolt, to close the small stab incision upon bedside removal of the electrodes and bolts.

Co-localization of electrodes

A thin-cut CT-Head was obtained after electrode implantation to confirm absence of intracranial haemorrhage. Additionally, the CT images were co-registered to MRI data for verification of the trajectory. Precise electrode positioning in the FreeSurfer surface space, voxel space and Montreal Neurological Institute (MNI) space was automatically extracted by the iElVis toolbox.[17] A T_1-weighted MRI scan was used to generate 3D cortical volume and subcortical segmentation using the recon-all command in Freesurfer v6.0.0.[18] The post-implant CT scan was aligned to the pre-implant MRI using the *flirt* function from the Oxford Centre for Functional MRI of the Brain Software Library[19,20] or using *bbregister* from Freesurfer[21] to get the best results. We then manually labelled each electrode on the T_1-registered CT image using BioImage Suite.[22] The electrode coordinates in the native anatomical space were carefully inspected for every single electrode contact and manually labelled by a neurologist and anatomist (J.P.) based on the individual brain's morphology and landmarks.

Thalamic parcellation

The individual contact centre of mass was defined in native T_1 space for each subject. Centre of mass of each contact was converted into a scalar X, Y, Z coordinate in MNI space. A widely used MNI thalamic atlas developed by our colleagues, Thalamus Optimized Multi Altas Segmentation (THOMAS),[23] was utilized to parcellate the nuclear location of each contact within the thalamus. In order to do this, a 1 mm cubic voxel region was created around each contact centre of mass (contact neighbourhood). For each contact neighbourhood, the fraction of voxels that overlapped with each thalamic nucleus in the THOMAS atlas was calculated.

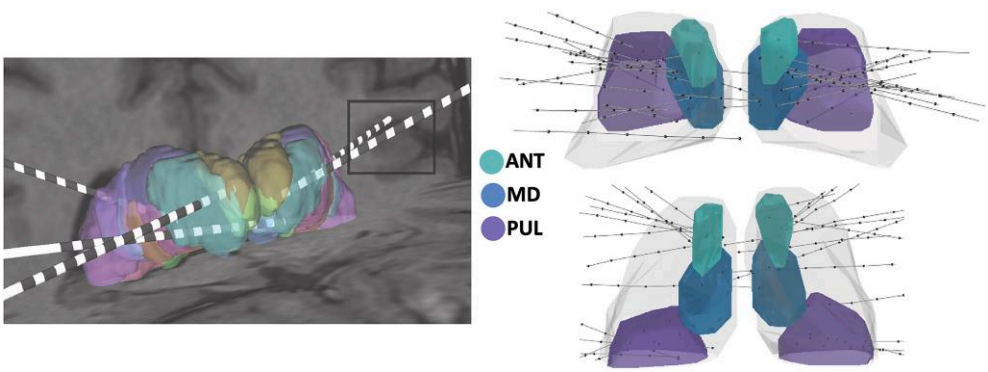

Figure 1 Thalamic electrode parcellation across subjects. The trajectories pass through opercular and insular structures which were desired by the clinical sampling strategy (boxed area on the *right*) and are simply extended into the thalamus. *Right*: Coronal and axial views of an MNI space representation of all thalamic electrode trajectories are shown across 10 subjects. Each line is one electrode shaft with dots denoting the individual recording contacts. The location and relative size of ANT, MD and PUL nuclei can be appreciated in the anterior to posterior order within the boundaries of the thalamus (outer shape model). Images were reconstructed using the THOMAS atlas.[23]

Contact neighbourhoods that fell solely within a single THOMAS nuclear mask would have a value of 1 for that specific nucleus, while contact neighbourhoods that had no overlapping voxels with a given nuclear mask would have a value assigned to 0 for that specific nucleus. Thus, for every contact neighbourhood anatomically inside the thalamus, the fractional overlap with each THOMAS nuclear mask was calculated. Then for each THOMAS thalamic nucleus, this within-subject fractional overlap was summed across subjects across all thalamic contacts to generate overall contact neighbourhood fractional overlap values. Lastly, each THOMAS nucleus was segregated based on the most common trajectory used to obtain that nuclear coverage (between anterior versus mid versus posterior thalamic electrode trajectories).

Intracranial recording

Signals were collected from multiple contact depth electrodes with centre-to-centre contact spacing of 3 mm. Continuous ECG signal was acquired with a digital Nihon-Kohden EEG machine at a sampling rate of 1000 Hz, in combination with continuous video recording. High frequency filter, time-constant, as well as voltage sensitivity settings, were adjusted to optimize visual detection of high-frequency oscillations (typically at 300 Hz high-frequency filter, 0.001 s time-constant, 10 μV sensitivity) and thalamic signals (best seen at 300 Hz, 0.1 s, 10 μV). A sEEG bipolar montage including all channels was used for signal detection. Channels with excessive artifacts obscuring EEG signals were excluded from the analysis.

Identification of ictal patterns

All seizures captured were reviewed for onset zones. The cortical seizure onset zones were determined by visual analysis by the primary inpatient epilepsy team. The thalamic onset was determined by visual analysis of the sEEGs. Cortical and thalamic ictal onset signals were inclusive of various morphologies, such as pathologic high frequency oscillations, evolving fast activity, rhythmic spikes or rhythmic spike-waves. Two epilepsy fellows and a senior attending, blinded to the diagnosed cortical seizure onset zones, reviewed the EEG tracings of seizures and answered three specific questions: (i) Is the seizure propagated to the thalamus; (ii) which subregion of the thalamus is involved first; and (iii) which other thalamic sites are engaged next and in which temporal order. The raters were given randomly selected seizures from each individual patient. If a patient had more than one seizure type during their inpatient monitoring, we randomly selected three seizures from each seizure pattern. In selecting seizures from each individual patient, we relied on the clinical notes available in the electronic medical records prepared by the original clinical team caring for the patient during inpatient sEEG monitoring. Only 1–2 seizures were included if fewer than three seizures were captured for a specific seizure pattern. After completion of the ratings, we measured the interrater reliability of the three readers' assessments of thalamic involvement and assessed (i) agreement on whether the thalamus was involved during ictal propagation; and (ii) agreement on which thalamic nucleus was first involved at or following cortical onset. For the first assessment, Cohen's Kappa was calculated based on the first two reviewers' impressions. For the second assessment, consensus was determined with at least 2/3 agreement by independent review, as well as with group review and discussion.

We would like to highlight that Reviewers 1 and 2 were senior EEG fellows. Despite their extensive EEG training, this may be a limitation of our method, given that thalamic recordings and the precise onset of ictal patterns can be challenging even for experienced EEG readers. While we report a reasonably high Kappa (0.79) between two of the reviewers, one could imagine that the dynamics between a senior attending (Reviewer 3) and the two trainees might not be conducive to each reviewer having an equal voice in the final adjudication. The design of future studies may need to take this potential limitation into account.

Study of cortico-thalamic evoked potentials

To obtain an independent measure of effective connectivity between SOZs and each thalamic site, we used the well-known method of repeated single electrical pulses as described previously.[24] Single pulse stimulations ($n = 45$) were performed with a bipolar setup using a cortical stimulator while the subjects were awake and resting. Single pulses of electrical current (5 mA, biphasic, 500 μs/phase) were injected between pairs of all adjacent intracranial electrodes at a frequency of 0.5 Hz (in total 90 s for each pair of electrodes). Electrical potentials were simultaneously measured in all other electrodes with a sampling rate of 1000 Hz. As we were interested in only the cortico-thalamic networks, electrodes in the white matter were excluded from the analysis. Specifically, we kept only electrodes which contained at least 1 grey matter voxel within a 2 mm sphere centred on the electrode. To minimize volume conduction effects, we also discarded data recorded from electrodes on the same electrode shaft as the stimulated electrode.

Table 1 Patient characteristics

Patient No.	Age	Gender	Handedness	IQ percentile	Epilepsy duration (years)	Lesional (Y/N)	Pathology
1	37	F	R	82	2	N	n/a
2	23	F	L	55	3	N	n/a
3	23	M	R	23	19	Y	Ganglioglioma, WHO Grade 1
4	40	M	R	75	24	N	n/a
5	52	M	R	82	35	N	n/a
6	47	M	R	–	17	Y	Non-specific reactive changes
7	31	F	R	79	8	N	n/a
8	29	M	R	75	19	Y	Grey matter heterotopia
9	28	M	R	88	19	Y	Focal dysplasia versus prior injury
10	34	F	R	47	3	N[a]	n/a
11	19	M	R	61	4	N[b]	n/a

WHO = World Health Organization.
[a]There was a left temporal encephalocele, which was not seizure focus.
[b]There were grey matter periventricular nodular heterotopia present, which were not seizure foci.

Two groups performed the analysis of evoked thalamic responses independently from each other to ensure validity of findings. Often changing parameters of the analysis of evoked responses may yield different results. To examine this possibility and ensure validity of our findings despite changes in the cortico-thalamic evoked potentials (CCTP) approach, we employed two different analysis approaches (i.e. CTEP Pipeline 1[25] and CTEP Pipeline 2[26]). These approaches were different in some important details (Supplementary Table 1).

Thalamic nuclei channels which did not show a significant response were discarded from the analysis. The order of occurrence and prominence of the post-stimulus peaks were compared between different thalamic nuclei. We were specifically interested in the latency of the first evoked peak in the recordings from the thalamus. Pipeline 1 identified the earliest responding thalamic channel in each seizure pattern; Pipeline 2 identified the thalamic channel that has the earliest and most prominent response in each seizure pattern.

Data availability

The data that support the findings of this study (clinical EEGs and CTEP data) are available on reasonable request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of patient participants.

Results

Patient characteristics

Eleven patients (seven males and four females) were included in this study, with an age range of 19–52 years. The mean interquartile (IQ) percentile was 66.7 (range 23–88, SD 19.2). The mean epilepsy duration was 14 years (range 2–35, SD 10.2). Six cases were non-lesional. For the five lesional cases, structural and pathological findings revealed a ganglioglioma (WHO Grade 1), grey matter heterotopia, focal dysplasia versus prior injury, focal herniation through a skull base defect and non-specific reactive changes (Table 1). The mean number of electrodes placed per patient was 15 (range 10–21, SD 3.5), which included contacts extending to monitor 1–6 thalamic subdivisions (anterior, mid and posterior on each side). Detailed presurgical data are summarized in Supplementary Table 2.

Anatomical coverage

The pattern of thalamic coverage was not identical across all subjects, because the thalamic electrodes were simply meant to be

Table 2 Engagement of different thalamic subregions during seizure propagation

Pt	No. of electrodes	No. of recording sites	Thalamic sites monitored	Seizure pattern	No. of seizures	SOZ	Thalamic site first engaged
1	18	176	R: ANT	A	2	R anterior hippocampus	R ANT
				B	8	R middle temporal gyrus	R ANT
				C	2	L orbital frontal	–
2	13	168	R: ANT, PUL	A	6	R posterior insula	R PUL
3	17	186	R: ANT, MD, PUL L: ANT, MD	A	21	R peri-lesional, fusiform/inferior occipital gyrus	R ANT
4	10	116	R: MD	A	4	L collateral sulcus, inferior temporal sulcus	L PUL
			L: ANT, MD, PUL	B	4	L inferior temporal sulcus, broad lateral temporal	L PUL
5	21	252	R: ANT, MD, PUL L: ANT, MD, PUL	A	13	R orbital frontal + widespread R frontal and temporal	R PUL
				B	15	L collateral sulcus	L ANT and PUL
6	14	174	R: MD L: ANT, MD	A	17	L temporal pole, anterior insula, anterior hippocampus, posterior hippocampus	L MD
7	12	152	R: MD	A	1	L anterior hippocampus	L MD
			L: ANT, MD, PUL	B	1	L amygdala	L PUL
8	11	156	L: MD, PUL	A	15	L periventricular heterotopia—posterior portion of temporal horn of lateral ventricle	L PUL
				B	2	L insula + transverse temporal gyrus, supra marginal gyrus	L PUL
				C	1	L anterior hippocampus, L hippocampus heterotopia	L PUL
				D	1	L periventricular heterotopia- frontal horn of lateral ventricle	–
9	20	252	R: ANT, MD, PUL L: ANT, MD, PUL	A	15	L anterior collateral sulcus	L PUL
				B	1	R PHG, mid hippocampus	R ANT
10	13	156	L: ANT	A	11	L anterior hippocampus	L ANT
				B	1	L anterior, mid, posterior hippocampus	L ANT
11	14	168	R: ANT, PUL L: ANT, PUL	A	1	L anterior hippocampus	L ANT
				B	3	R anterior, posterior hippocampus	R ANT

Please note that 'Thalamic Site First Engaged' and 'Concordance between visual analysis and CTEPs' in Patient 1 and Patient 10 are not valid terms, since only one thalamic nucleus was recorded in these subjects. The data from these patients were included in the study because their data served towards other conclusions of the study, including feasibility and safety of the procedure, as well as the thalamic engagement during seizure propagation.
L = left; R = right; Pt = patient; PHG = parahippocampal gyrus.

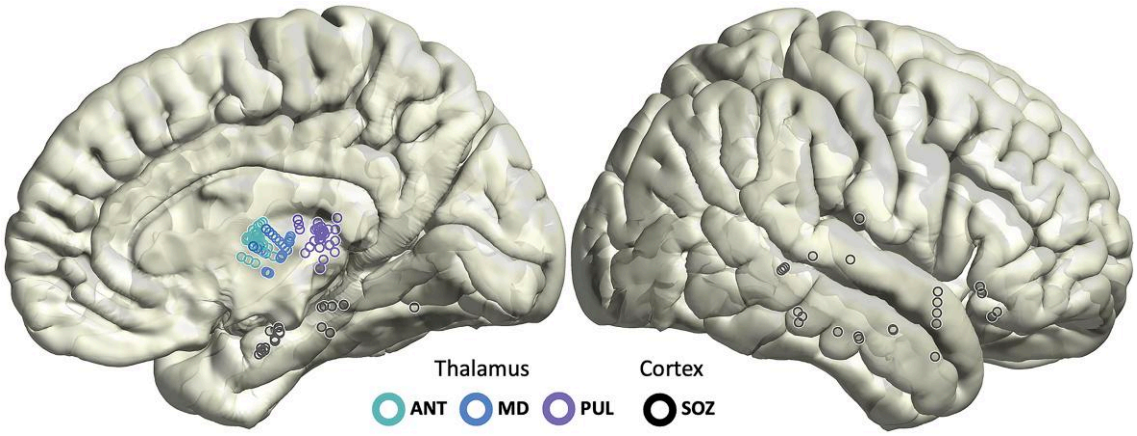

Figure 2 Electrode coverage. Electrodes in the thalamus and SOZs for all recorded seizures are shown on the right hemisphere. See Table 2 for additional details about SOZs. Each patient was implanted with many more electrodes throughout the brain, not shown here. Also, note that the electrodes are projected to the surface for 3D visualization.

extensions of the appropriate cortical electrodes. Table 2 shows the details of thalamic coverage in each case. In 9 of 11 patients, more than one thalamic nuclear subdivision was interrogated. In 7 of these 9 patients, both ANT and PUL territories were covered simultaneously. In 8 of 11 patients, we were able to perform the CTEP procedure. Figure 2 demonstrates the MNI space locations of the electrodes, including overall 53 channels in the SOZ areas, as well as 33, 24 and 30 channels in the anterior, mid and posterior thalamic regions. It is worth mentioning that all electrode locations have been superimposed in the right hemisphere for the visualization. The Supplementary material provides a discussion of how the nuclear coordinates of the recording sites should be taken with caution since the coordinates of the sites were transferred from the native space onto a standard atlas space.

Safety of thalamic implantation

There were no complications during or after implantation. There were no haemorrhages identified on the post-operative CT and no other complications were noted. All patients woke up neurologically intact (or at their preoperative baseline) following the implantation procedure. During the epilepsy monitoring unit admission, all patients were able to participate fully in the clinical testing that was required. After explantation, minor pneumocephalus was a uniform finding across all patients. There were no clinical complications that occurred due to explantation. Patients were able to be discharged within 12–24 h of explantation as desired.

Seizure onset zones

A total of 145 seizures were captured and visually analyzed (2–28 seizures per patient). The seizures were grouped into 22 distinct patterns. Within each pattern, the seizures had the same onset zone and propagation pathway based on electrode sampling. Of the seizure patterns, cortical onset was noted to be on the left in 15 and on the right in 7. Six seizure patterns (from five patients), which consisted of 41 captured seizures, had broad regions of onset (>1 identified cortical origin), where the exact onset location was unclear. The cortical onset zones were predominantly of temporal origin, including orbitofrontal, amygdalar, hippocampal, parahippocampal, insular, inferior temporal and temporoparietal regions (Table 2).

Thalamic propagation of seizures based on visual EEG review

There was substantial agreement on whether the monitored thalamic nuclei were involved during seizures (percentage agreement was 98.0, Cohen's Kappa between Reviewers 1 and 2 was 0.79). To determine the level of agreement on which thalamic nucleus was first to be involved at seizure onset, a total of 37 seizures with more than one thalamic site monitored were included. Unanimous (i.e. 3/3 reviewers) agreement was reached only in 20/37 cases (54%), underscoring the need for more objective computational analysis methods in the future. However, in 34/37 seizures (92.0%), there was at least 2/3 majority agreement. In the remaining 3/37 seizures (all of which belonged to the same seizure pattern), one reviewer called the ANT to be first involved, one called the PUL and the third called the ANT and PUL to be simultaneously affected. A group review was then conducted, with consensus achieved for anterior and posterior simultaneous involvement (see the 'Materials and methods' section for details). The thalamic onset with majority agreement was used for subsequent analysis. Table 2 lists the first thalamic nucleus involved in each seizure pattern identified by the visual analysis.

CTEP and visual review comparisons

A summary of the results is provided in Table 3, which includes data from eight patients (a total of 13 seizure patterns), with relevant cortico-thalamic evoked potential data. Subsequent comparisons of the CTEP-identified thalamic response using two independent pipelines and the visual analysis method revealed agreement in 11/13 seizure patterns. There were two seizure patterns with discrepant results. The first case (Patient 1, seizure pattern C) had the cortical seizure onset zone in the left hemisphere, while the implanted thalamic electrode was on the right—both CTEP Pipeline 1 and visual review did not appreciate an early thalamic signal, whereas Pipeline 2 detected signal in the right anterior thalamus, albeit at prolonged latency of >200 ms. In the second case (Patient 3, seizure pattern A), the cortical seizure onset zone was in the right peri-lesional inferior posterior temporal region; however, CTEP Pipeline 1 did not appreciate a significant thalamic signal, whereas Pipeline 2 detected response in the posterior thalamus and visual review in the anterior thalamus. It should be noted

that in the patient (Patient 6) with CTEP recording who was not included in the table, there were no sufficient electrode contact pairs in the thalamic nucleus of interest to produce accurate CTEP comparisons. In this patient, visual analysis identified left MD to be the first thalamic nucleus involved. However, there was only one channel contact in the left MD (the pair of contacts spread between left and right MD nuclei). Hence, according to this CTEP analysis, the earliest peaks were detected in the left ANT and bilateral MD. Additionally, in Patient 3 with SOZ in the inferior temporal cortex, based on the Pipeline 1 approach, the injected current to the lesion cavity did not induce any evoked potential in the recorded channels in the thalamic nuclei. According to the data from eight patients with valid relevant cortico-thalamic evoked potential data, the earliest significant peak in the recorded voltage occurred in the thalamic divisions which were initially identified as the first thalamic nuclei involved during a seizure (Table 3).

Cortical and thalamic onset comparisons

Of all the seizures captured, ictal propagation was visually detected in the thalamus, following cortical onset, in 20/22 seizure patterns. None of the seizure started in the thalamus prior to cortical onset. In the 20 seizure patterns with thalamic propagation, the earliest thalamic signals occurred ipsilateral to cortical ictal onset zones. In the two seizure patterns without visually detected thalamic spread, one had a cortical onset zone in the contralateral hemisphere from the implanted thalamic electrodes, and the seizures remained focal within the contralateral hemisphere; one began and remained distinctly in grey matter heterotopia without further spread.

We next explored the relationship between the anatomy of the cortical seizure onset location and the subregion of the thalamus to first become involved. This was examined only in seizures with detected thalamic spread and with more than one thalamic nuclei monitored. Seizures originating from a periventricular heterotopia also were excluded. Fifteen seizure patterns with a total of 105 captured seizures met this criteria. Of these, six seizure patterns with 41 seizures had broad regions of onset (>1 identified cortical origin), while nine seizure patterns with 64 seizures had captured a narrow, potentially surgically targetable, cortical region of onset on intracranial monitoring (Table 4). In seizures with narrow or broad regions captured at onset, the cortical geography was not predictable of which thalamic subdivision, whether anterior, mid or posterior, became first involved in seizure propagation. For instance, of 51 seizures with onset in the inferior temporal cortex, 21 propagated first to the anterior thalamus, 15 to the posterior thalamus and 15 to the anterior and posterior thalamus simultaneously. Additionally, 23/41 (56.1%) of the seizures with broad regions of onset, which included frontal and temporal regions, propagated to the posterior thalamus first. Hence, despite their well-known networks, the anatomic location of cortical origins did not predict first thalamic subdivision involvement.

Thalamic 'ictal signature'

While individual seizures within each seizure pattern carried a stereotyped electrographic morphology and cortical spread, thalamic ictal signal also appeared to be highly stereotyped. The first thalamic nucleus involved in every seizure within a seizure pattern remained consistent. Additionally, while the morphology of the thalamic ictal signal differed between seizure patterns, it remained nearly identical between seizures within a seizure pattern. Figure 3 displays examples of stereotyped thalamic onset in two distinct seizure patterns.

Table 3 Concordance between CTEP findings and visual EEG reviews

Pt	Seizure pattern	CTEP			Clinical visual EEG finding
		Seed	First prominent thalamic target		Thalamic site
			CTEP Pipeline 1	CTEP Pipeline 2	
1	A	R anterior hippocampus	R ANT	R ANT	R ANT
	B	R middle temporal gyrus	R ANT	R ANT	R ANT
	C	L orbitofrontal	–	R ANT	–
2	A	R posterior insula	R PUL	R PUL	R PUL
3	A	R peri-lesional	–	R PUL	R ANT
4	A	L inferior temporal sulcus	L PUL	L PUL + L MD	L PUL
	B	L inferior temporal sulcus	L PUL	L PUL + L MD	L PUL
5	A	Orbitofrontal cortex	R PUL	R PUL	R PUL
	B[a]	–	–	–	–
9	A	L anterior collateral sulcus	L PUL	L PUL	L PUL
	B[a]	–	–	–	–
10	A	Anterior hippocampus	L ANT	L ANT	L ANT
	B	Posterior hippocampus	L ANT	L ANT	L ANT
11	A	L anterior hippocampus	L ANT	L ANT	L ANT
	B	R posterior hippocampus	R ANT	R ANT	R ANT

Included are comparisons of results from two independent analyses, from Pipeline 1 and Pipeline 2, as well as results from visual method. Highlighted are two seizure patterns with discrepancy between the three results. Please note, Patients 1 and 10 only had one thalamic nucleus recorded. The data from these patients were included in the study because their data served towards other conclusions of the study, including feasibility and safety of the procedure, as well as the thalamic engagement during seizure propagation observed in both visual review and CTEP analysis.

L = left; R = right; Pt = patient.

[a]No cortico-thalamic evoked potential data were available.

Table 4 Thalamic initial engagement during focal versus broad onset seizures

Brain SOZs	Number of seizures (Patients)	Thalamic onset			
		ANT	MD	PUL	ANT + PUL
Focal seizure onset					
Hippocampus	7 (4)	5	1	1	–
Amygdala	1 (1)	–	–	1	–
Posterior Insula	6 (1)	–	–	6	–
Inferior or ventral temporal cortex	51 (3)	21	–	15	15
Broad seizure onset					
Frontal and temporal	13 (1)	–	–	13	–
Temporal + insular	17 (1)	–	17	–	–
Insular + supramarginal gyrus	2 (1)	–	–	–	2
Collateral sulcus + ITG	4 (1)	–	–	–	4
ITS + broad LTL	4 (1)	–	–	–	4

Included are seizures in patients with >1 thalamic region monitored. ITG = inferior temporal gyrus; LTL = leucocyte telomere length.

Discussion

We recruited 11 patients with presumed TLE and documented SOZs in not only the medial temporal lobe structures but also in the anterior and posterior insula, orbitofrontal cortex and temporal neocortical sites, highlighting the importance of intracranial monitoring for increased accuracy of seizure origin. We used conventional visual review of EEG by clinicians and documented the involvement of different thalamic sites in most of our patients with multisite thalamic electrodes. To assess the validity of the visual review method in determining thalamic involvement, we measured the level of agreement amongst three independent clinician reviewers, and compared visual results with CTEP, using the repeated single pulse electrical stimulation approach.

Our results provide proof-of-concept evidence for feasibility and safety of multisite thalamic sampling in individuals. We implanted patients using an orthogonal approach for sampling frontal or temporal operculum, followed by anterior, mid or posterior insula. With these trajectories, we extended the cortical probes into various desired regions of the thalamus without adding to the total number of implanted electrodes—as pioneering studies had shown to be possible with single electrodes.[5,8] For bilateral mid-thalamic coverage, a single mid thalamic electrode trajectory was performed through a novel trans-massa intermedia approach, thus decreasing the overall surgical risk by obviating the need for one additional trans-sylvian electrode. With this surgical approach, we observed no complications, no thalamic haemorrhage or oedema and no neurological symptoms post-operatively.

In the current study, we emphasized the use of conventional visual review of ictal EEGs (instead of relying on computerized quantitative analyses) to determine thalamic subregion with earliest seizure propagation. Our use of the CTEP method was merely to verify the reliability of the findings obtained by the visual review. In essence, the rationale for not using a purely computational approach was to examine the utility of multisite sampling of the thalamus in routine clinical practice. Currently, in the practice of intracranial monitoring, clinicians rely largely on visual inspection of EEGs, rather than sophisticated quantitative analyses. Hence, we aimed to prove that multisite sampling of the thalamus could be practically feasible without relying on sophisticated quantitative algorithms. It is noteworthy that we observed substantial agreement between the visual analyses of different reviewers. Importantly, we also observed a substantial agreement between clinical visual EEG and CTEP analyses. Therefore, from a practical standpoint, we postulate that the expert visual identification of the thalamic site with the earliest and most salient involvement during seizures can be used as a relatively reliable method in today's clinical setting to direct management strategies. However, in the future practice of epileptology, we hope unbiased and more reliable automated computational methods will empower clinicians to determine the profile of thalamic involvement in seizure propagation in a more precise and less time-consuming manner.

Overall, our results agree with the extant literature, where thalamic participation in the epileptogenic networks of focal epilepsies in the human brain has been well documented.[1,5,7,8,10,27,28] Our findings with simultaneous recordings across multiple sites of the thalamus extend the existing evidence further and document important new observations that deserve attention and replication.

Our simultaneous multisite thalamic sampling documented that the earliest and most prominent thalamic involvement in a patient with presumed TLE could be a thalamic site other than ANT. Our cohort included patients who had been through several lines of presurgical diagnostic workup, including 3 T MRI, multiday inpatient observations with video EEG and neuropsychological exams. On the basis of these diagnostic measures, the clinical diagnosis in majority of these patients was 'likely temporal lobe epilepsy'. As such, all of these patients would have been candidates for ANT neuromodulation. However, as we report here, in a large proportion of these patients, nuclei other than ANT were engaged first during seizures. While stimulation of the ANT is currently proven to be a useful remedy for controlling seizures in patients with various kinds of medication-resistant epilepsies,[3] the neuromodulation of ANT only benefits about two-thirds of these patients.[2,29] Our observation raises an important question of whether neuromodulation of the thalamus ought to be personalized to each patient, and whether a personalized approach may yield better outcomes.

It is presumed that patients with seizures originating from brain structures such as the hippocampus and medial temporal lobe—that are known from animal studies to communicate with and through ANT[30] to be the ones who benefit most from neuromodulation of the anterior thalamus. Our findings add to the evidence from prior intracranial studies and suggest that the anatomy of thalamic involvement may not be entirely predictable based on the clinical semiology or lobar localization of seizures. In our study, location of SOZ was evidently not entirely predictive of which thalamic subdivision was to be involved first and prominently during seizures. For instance, some seizures of hippocampal, amygdalar and insular origin were observed to first propagate to the PUL nucleus rather than ANT. Additionally, a notable number of seizures without a clear focal origin first propagated to the MD or PUL, including those with a broad frontal and temporal onset. This again highlights the possible additional clinical benefit of personalizing the target of thalamic neuromodulation based on intracranial monitoring.

It is worth highlighting that, similar to prior observations,[10] we also noted a stereotyped 'thalamic signature' in seizures of the same cortical origin and propagation pattern. In other words, in a patient with thalamic recordings, capturing different thalamic ictal footprint may indicate that that the patient's seizures may be originating from different sources and involve distinct ictal networks. In the future, and with additional evidence from a larger patient cohort, one may be able to compile an atlas of thalamic ictal footprints which will help identify the source of seizures or propagation

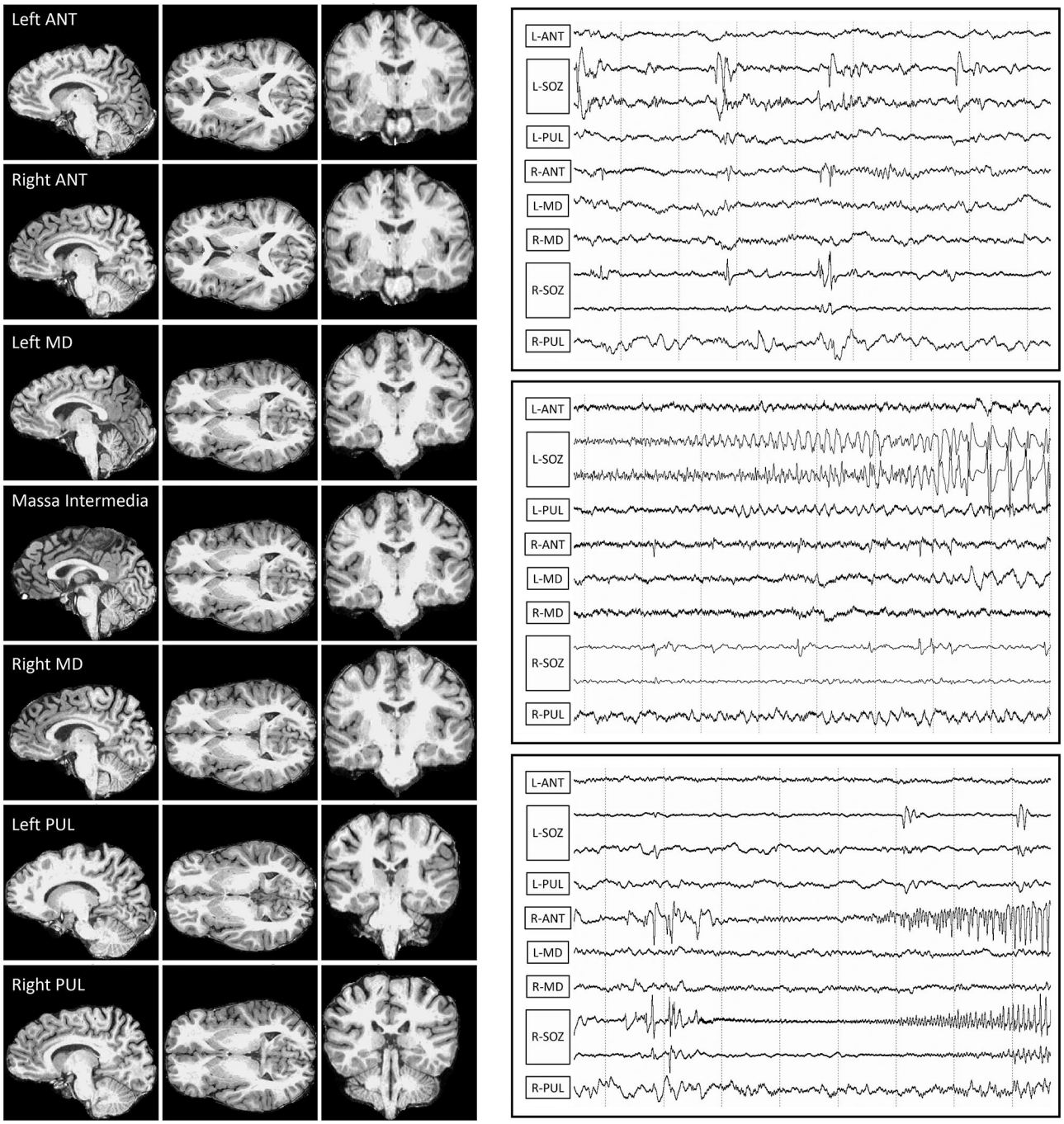

Figure 3 Electrophysiological thalamic ictal signature. *Left*: The location of electrodes in three subregions of the thalamus bilaterally (ANT, MD and PUL) in a single subject (Patient 9). Note the single electrode targeting the MD traverses across the massa intermedia. *Right*: A selection of EEG tracings from two SOZs and the thalamic subregions in the left (L) and right (R) hemispheres during interictal (*top*) and two types of seizures (*middle* and *bottom*). In this patient, we found two types of seizures with two different SOZs. The left SOZ was located in the neocortical inferior temporal region and the right SOZ was in the hippocampus. Note the relationship between the hippocampus (R-SOZ) and the ANT during inter-ictal and ictal conditions, and the relationship between the left inferior temporal cortex (R-SOZ) and the ipsilateral PUL.

pathways involving various brain regions. Such an atlas might usefully be correlated with data available from the Human Connectome Project. As such, knowing the exact thalamic circuitry involved in seizure propagation may yield clinically important information about the source of seizures and the networks of brain structures involved. For instance, a thalamic onset prior to observed onset in implanted cortical sites, or a surprising and unexpected thalamic nucleus being recruited during a patient's seizures, may indicate that the real SOZ is being missed, and hence further exploration may be needed. For instance, in one of our cases (Patient 7, Seizure B, missing CTEP data), the clinical review of EEGs determined the SOZ (i.e. the first captured ictal signs among the implanted recording sites) to be in the amygdala but the first thalamic sign of the seizure was seen in the PUL site. One might argue that the thalamic observation in this patient suggests that additional data should be collected. If for instance CTEP in this patient had

shown a thalamic site other than PUL to be connected with the amygdala, one could deduce that the real SOZ (directly connected with PUL) in this patient was being missed.

Our study has several limitations. First, the seizures analyzed are from a small number of patients included during the study period, which may not be representative of the overall patient population undergoing surgical considerations. As noted, only nine patients had more than one thalamic subdivision interrogated and CTEP study was performed in only eight. Second, the captured seizures in our study are of temporal onset, which do represent the most common seizure types but are not representative of all focal onset locations. Third, sEEG studies with depth electrodes are inherently bound to sampling very limited regions in the brain, as ethical concerns limited electrode placements to only regions hypothesized to yield useful clinical information for the patient. Despite a clinician's best planning for where to place electrodes based on comprehensive presurgical data, there remains the possibility of missing the actual cortical onset zone due to lack of sampling in that region. This may be the case in particular for the seizures with captured broad regions at onset, and in effect the complete seizure network may not be accurately characterized by the intracranial recording. Furthermore, we intended to avoid sophisticated computational tools for the analysis of thalamic engagement during seizures to ensure that our results are practically feasible and ecologically valid, but we cannot assess to what extent such observer-dependent methods are affected by the observer's inexperience or bias. We are, however, hopeful that objective computational tools will eventually become widely available in our everyday clinical practice of epileptology and will be taken into use to allay concerns about reviewer inexperience or bias. Finally, it remains to be determined if an early propagation site necessarily qualifies as the optimal location for neuromodulation.

Our study highlights the unmet need for future investigations of the thalamus in human epilepsy. For instance, capturing information about the speed of first propagation to thalamic targets may provide valuable prognostic information as previously suggested.[5] Latency of seizure propagation to the thalamus and intra-thalamic spread patterns are also worth further investigations, as this may yield significant prognostic information for resective, ablative surgical or neuromodulatory approaches in the treatment of refractory epilepsies. Also, studies in the future may be able to confirm if multisite sampling from the thalamus could replace widespread cortical implantations if the presurgical workup already suggests neuromodulation rather than resection. Future studies can also determine if added information from thalamic multisite recordings can help optimize seizure localization and thus better surgical outcomes in cases where the SOZ can be resected. Lastly, future studies can clarify if MD or PUL rather than ANT neuromodulation may produce better clinical benefits in patients with broad onset of seizures. One of the meaningful findings of our study pertains to cases in which the epileptic network was found to be more distributed than initially hypothesized on the basis of pre-operative evidence. In these cases, a significant number of seizures propagated to the MD and PUL as the earliest and most prominent sites. This pattern of engagement might either indicate that the actual seizure onset zone was more posterior than hypothesized, or that the ictal onsets in these cases were simply broad.

In closing, we argue that multisite thalamic monitoring may be helpful in elucidating the optimal thalamic target for personalized neuromodulation since knowing cortical seizure onset zone may not entirely predict which thalamic nucleus will be most involved at onset. Additionally, with future studies, thalamic ictal patterns may help direct cortical SOZ localizations, narrowing the target regions for potential surgical interventions.

Acknowledgements

We wish to thank clinical EEG technologists providing support during the intracranial EEG recordings and other members of the laboratory of Behavioral and Cognitive Neuroscience (LBCN) for assistance with data collection and technical support.

Funding

This work was supported by R21NS113024 from the National Institutes of Health (PI: J.P.).

Supplementary material

Supplementary material is available at *Brain* online.

Competing interests

The authors report no competing interests.

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