communications medicine
A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-025-00920-9

Inter-seizure variability in thalamic recruitment and its implications for precision thalamic neuromodulation

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Abstract

Background Thalamic stimulation is a promising approach to controlling seizures in patients with intractable epilepsy. It does not, however, provide good control for everyone. A big issue is that the role of the thalamus in seizure organization and propagation is unclear. When using responsive stimulation devices, they must detect seizure activity before sending stimulation. So, it's important to know which parts of the thalamus are involved in different seizures.
Methods To better choose thalamic targets for stimulation, we studied how different seizures spread to each stimulation target. Expert reviews and automated tools were used to identify seizure spread recorded from invasive recordings. We categorized seizures based on how they start and spread, and determined whether seizures reached thalamic areas early or late. We used generalized linear models (GLM) to evaluate which seizure properties are predictive of time of spread to the thalamus, testing effect significance using Wald tests.
Results We show that seizures with <2 Hz synchronized-spiking patterns do not spread early to the thalamus, while seizures starting with faster activity (<20 Hz) spread early to all thalamic areas. Most importantly, seizures that begin broadly across the brain quickly recruit the centromedian and pulvinar areas, suggesting these may be better stimulation targets in such cases. Alternatively, seizures that start deep in the temporal lobe tend to involve the anterior part of the thalamus, meaning the centromedian might not be the best choice for those seizures.
Conclusions Our results suggest that by analyzing electrical activity during seizures, we can better predict which parts of the thalamus are involved. This could lead to more effective stimulation treatments for people with epilepsy.

Plain language summary

Some people with epilepsy don't get relief from standard treatments and may need brain stimulation to help control their seizures. The thalamus, a deep brain structure, is a promising area for this kind of therapy, but clinicians still don't know exactly which people with epilepsy will benefit most. In our study, we found that certain brainwave patterns during seizures can help identify which part of the thalamus is most involved. This could lead to more personalized and effective brain stimulation treatments for different types of epilepsy.

Antiseizure medications are employed as the primary therapeutic option for epileptic disorders, but as many as 30% of patients either do not benefit from their use or suffer significant side effects[1]. Traditional surgical resection of epileptic foci can lead to seizure freedom in some patients, but, unfortunately, despite advances in diagnostic techniques, as few as 50% of patients undergoing surgery are seizure-free long-term[2,3]. In addition, resection is not always feasible due to the overlap of the epileptic region with eloquent cortex or because the epileptic region is too widespread or diffuse[4,5].

Neuromodulation via intracranial direct electrical stimulation is increasingly being employed as a viable option to afford patients greater control over their seizures[6–10]. Stimulation can target either the seizure onset area(s) (when a clear onset area is identified) or specific nuclei of the

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thalamus[5,11–13]. Open-loop neurostimulation (through deep brain stimulation; DBS) and, more recently, closed-loop neurostimulation (responsive neurostimulation, RNS) devices targeting the thalamus have been shown to lead to an improvement in some patients, reducing their seizure frequency by more than 50%[9,10,12,14–17]. Despite these encouraging outcomes, however, not all patients receiving thalamic neurostimulation benefit from such treatment, and those that do benefit may still not become completely seizure-free. Recent studies have sought to understand how neurostimulation within the thalamus may control seizures and who may benefit from such treatment, but the results are inconclusive[6,10,18–22]. This is likely due to the fact that not all seizures may recruit the targeted thalamic nuclei in their network[23,24]. Indeed, recent registry data suggest that DBS of the anterior nucleus is not efficacious in treating seizures outside of temporal-frontal networks[9,25].

When considering the structure of the thalamus, the unpredictability of efficacy in thalamic neurostimulation is perhaps unsurprising. Far from being homogenous, the thalamus consists of many nuclei, with each thought to play a different role in overall brain function[26–29] and in epilepsy in particular[30–33]. For instance, Ilyas et al.[34] recently proposed that the anterior nucleus of the thalamus (ANT) may facilitate seizure propagation[34], while, the centromedian (CM) nucleus may be more involved in seizure termination[34], a role that was also suggested for the pulvinar (PLV) in temporal lobe epilepsy[35]. The involvement of these nuclei in seizures is complex, differing from patient to patient and even from one seizure to another[34,36,37].

Beyond the functional differences between thalamic nuclei, seizures themselves have different properties. One factor that makes epilepsy challenging is that it can manifest from so many different conditions. While inroads have been made in understanding some of these functional differences[38–45], the extent to which those differences are reflected in propagation and involvement of subcortical regions including the thalamus is largely unknown. First, the onset dynamics of seizures are suggestive of different pathophysiological processes[38], and it is unclear how this relates to thalamic involvement. Second, the thalamus makes widespread connections throughout the brain via its various nuclei[32], and different regions of the brain have different connections to these nuclei but the consequences of this variation are not fully understood. Finally, the extent to which seizures propagate to other regions after onset may also influence thalamic recruitment. It stands to reason that many factors need to be considered when evaluating which thalamic nucleus may be the best candidate for seizure detection and/or stimulation in a given patient with epilepsy.

Seizure propagation to the thalamus, specifically, has important implications for the use of RNS as a neuromodulation device. In particular, there is evidence that the specific signature of neural activity required by the device for detection may not be present in the targeted thalamic nuclei for all seizures, leading to lower treatment efficacy[46]. For the RNS to be effective, seizures first need to be detected by the device[8,12,47–53], but this requires determining thalamic involvement during intracranial monitoring, when not all nuclei can be targeted simultaneously[54]. Indeed, a recent paradigm shift is the evolution of stereo-electroencephalography (sEEG) to inform the potential use of thalamic nuclei in RNS therapy[55].

Therefore, we sought to define seizures propagation to the thalamus based on clinically accessible categorization of the seizures themselves. We investigated whether there are specific seizure types that are more likely to propagate to main stimulation-targeting nuclei of the thalamus (CM, ANT, and PLV) by evaluating seizures recorded during presurgical evaluation of patients with refractory epilepsy[18,21].

Our findings suggest that electrographic seizure features, including seizure onset region and spread, are predictive of the thalamic nuclei involved in the network of specific seizures. Seizures with broader onset arising from multiple regions are more likely to spread early to CM and PLV, while seizures with mesial temporal onset have an earlier spread to the ANT. Seizures with sharp patterns at their onset are more likely to spread to any of the nuclei, whereas seizures with hypersynchronous activity characterized by spiking at their onset are the least likely to spread to any nucleus. We propose that this information can empower clinicians in selecting the most reliable targets for thalamic neuromodulation.

Methods

Data acquisition and seizure classification

The seizures analyzed in this study were recorded from 44 patients (21 female; mean age = 31.5 years; range = 8–65 years) with medication-refractory epilepsy (Supplementary Data 1) who underwent a clinical monitoring procedure to locate their seizure onset zone at Massachusetts General Hospital (MGH) from 2020 to 2023 and at the University of Alabama at Birmingham (UAB) Hospital in 2018. Only patients who received at least one electrode implant in the centromedian nuclei of the thalamus (CM), anterior nucleus of the thalamus (ANT), or pulvinar (PLV) as part of the procedure were selected for this study. At MGH, electrode placement was designed by the clinical team to evaluate the involvement of the thalamus in hypothesized seizure networks, in order to inform decisions regarding the potential use of RNS[56], independent of this study. At UAB, patients were enrolled in an IRB-approved research study specific to the ANT[57]. Data from both MGH and UAB were recorded using Natus Quantum (Natus Medical Incorporated, Pleasanton, CA) with a sampling rate of 1024 Hz or 2048 Hz. Data acquisition for each electrode was performed relative to a reference contact. All participants provided informed consent, and all data acquisition and analyses in this study were approved by the Institutional Review Board (IRB) at Mass General Brigham (IRB 2007P000165) and the Institutional Review Board of the University of Alabama (IRB-170323005) at Birmingham (UAB, Birmingham).

Recorded seizures were reviewed visually (bipolar montage) in MATLAB (R2020a; MathWorks) using the FieldTrip browser[58] and classified into different types based on (1) their regions of onset, (2) the electrographic pattern at their onset, and (3) the pattern of their spread.

Electrographic patterns at seizure onset

Seizure onset times and patterns were identified by two experienced reviewers and discussed until an agreement was reached. Only the seizure onset contacts (bipolar montage), initially identified by clinicians, were visually analyzed for seizure onset time annotation and pattern classification (Fig. 1)[38]. The two reviewers visually identified six distinct electrographic patterns in the dataset, similar to the previously reported onset patterns[38,40,41]. The hypersynchronous (HYP; Fig. 1b) pattern was characterized by high amplitude spikes with a frequency of ~2 Hz at seizure onset. The second two patterns (spike LVF and LVF) feature a low-voltage fast (LVF; Fig. 1d) activity which is characterized by an increase in power at frequencies greater than 20 Hz at the onset that may (in the case of spike LVF) or may not be preceded by a poly spike or a sentinel spike time-locked to seizure onset. Spike sharp and sharp (Fig. 1f) patterns were identified as an increase in oscillatory activity at seizure onset that was less than 20 Hz. This activity could precede a poly spike or a sentinel spike (in the case of spike sharp). The final pattern (spike and wave; Fig. 1h) was characterized by spike and wave activity at the seizure onset (for more examples, see ref. 38).

Region of seizure onset

We identified the anatomical location of all bipolar contacts using a combined volumetric and surface registration approach. Electrode coordinates were manually determined from the CT and placed into each patient's native space[59,60]. Then, brain regions were identified using FreeSurfer and an electrode labeling algorithm (ELA) was used to map electrodes to brain regions in the DKT atlas[60–65]. Channels from different regions were classified into five distinct groups for both left and right hemispheres based on proximity and structural similarity: Region 1) mesial temporal structures (including hippocampus, amygdala, subiculum); Region 2) lateral temporal areas (including inferior, middle and superior temporal and insula); Region 3) Centroparietal areas (including pre-central, post-central, superior and inferior parietal and posterior cingulate); Region 4) Frontal areas (including frontal areas, orbitofrontal, and anterior cingulate) and Region 5) occipital structures (including occipital area, cuneus, and lingual).

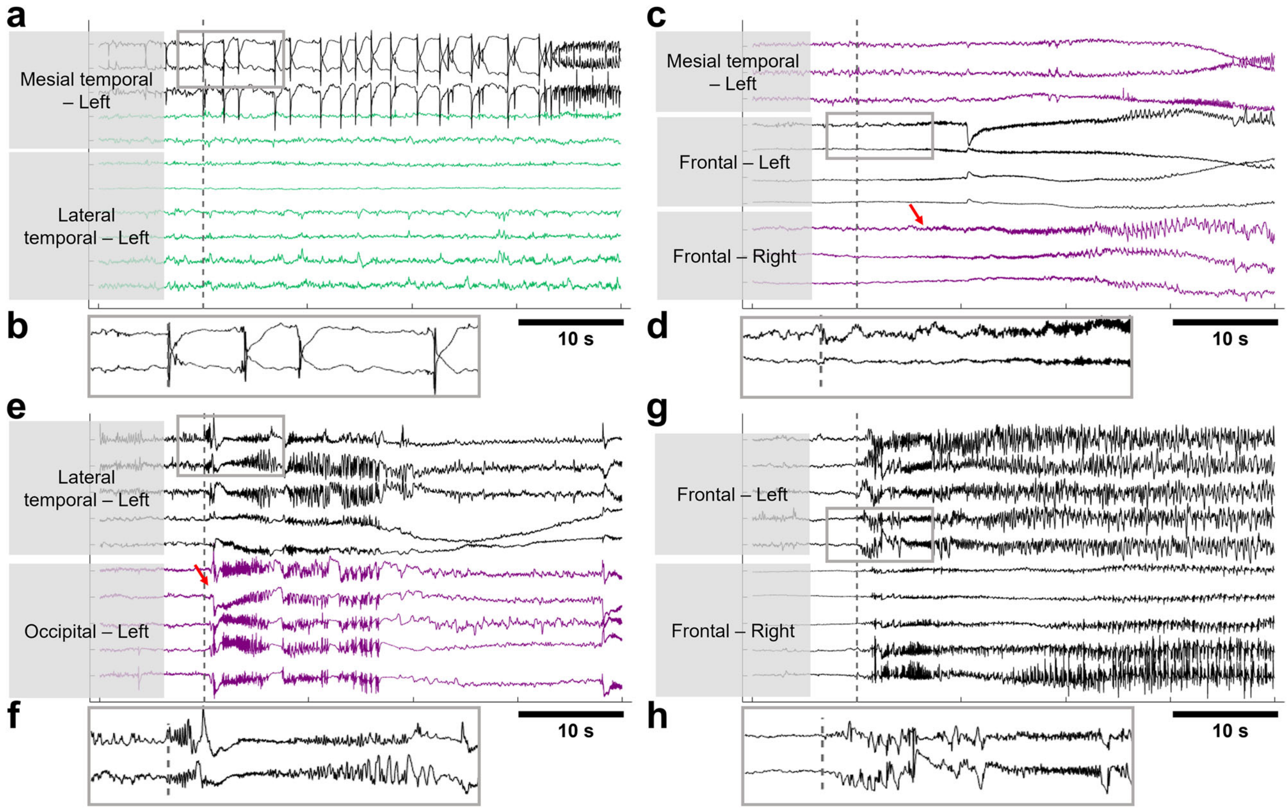


Fig. 1 | Examples of seizures with different onset and spread patterns. **a** A seizure recorded from patient 24 with an onset in left mesial temporal region, with no spread to other regions (FF seizure). **b** The expanded trace of the selected gray rectangle in **a** shows a hypersynchronous (HYP) spike pattern at the onset of the seizure. **c** A low voltage fast (LVF) activity at a seizure from patient 18 with a left frontal onset that propagates (red arrow) after a few seconds to other areas such as right frontal and left mesial temporal regions. **d** The expanded trace shows LVF activity at the onset of the seizure. **e** A seizure recorded from patient 9 with a sharp (**f**) onset in left lateral temporal area that spreads within milliseconds (red arrow) to other areas such as left occipital. **g** A spike-wave (**h**) broad seizure started simultaneously in left and right frontal regions of patient 16. Black traces indicate the contacts that show seizure activity simultaneously at the onset. Purple traces are the contacts with seizure spread. Green traces are the contacts with no ictal activity during the seizure.

All the electrodes that simultaneously showed activity at seizure onset were labeled as seizure onset contacts. Then, a region label was assigned to each seizure based on its onset region from the ELA. If contacts in more than one region were part of the onset, the seizure was labeled as a "multi-region" onset.

Identifying the location of the electrodes within the thalamus

Localizing electrode contacts to the thalamus involved the electrode volume labeling (EVL) approach[60]. The thalamic segmentations was performed after the brain and subcortical labeling of brain regions[61,62] were produced in FreeSurfer[66]. We exported the results of thalamic segmentation as volumes and imported them into MATLAB (MATLAB 2020b) where enclosed volumes were generated per brain region label. Then for each electrode, the region within which it was located was identified. Relative to the original thalamic nucleus segmentation in FreeSurfer[66] we identified the three target nuclei as: CM: Centromedian, AV: Anterior Nucleus, and PuM: Pulvinar (Fig. 2). The electrodes located within these nuclei were selected. For bipolar pairs of electrodes, we classified the pair as within the nucleus if one contact of the pair is contained in the nucleus.

Seizure pattern of spread

Finally, seizures were classified into four groups based on the extent of their spread. Seizures with focal onset which did not propagate to other regions were classified as starting and staying focal (FF; Fig. 1a). Seizures that propagated only after more than 500 milliseconds to other areas in the same hemisphere or between the hemispheres were classified as focal with slow spread (FSS; Fig. 1c). Seizures that spread in 500 milliseconds or less to other regions were labeled as focal with fast spread (FFS; Fig. 1e). Finally, seizures with simultaneous activity in more than one region, either within one hemisphere or in both, were labeled as broad onset (BO; Fig. 1g). These classifications were determined using all recorded contacts (excluding the activity in the contacts within the thalamus) but are limited by the spatial sampling of the sEEG recordings.

Identifying the delay of seizure spread to the thalamus

During the seizure monitoring of patients with sEEG implants, clinicians rely on visual detection of seizure activity and annotate the time of seizure start and spread based on the visually identifiable changes in different signals. In this study, we identified the time of spread to the thalamus using two different methods: (1) an automated method to capture the spread of ictal activity, and (2) a visual method, carried out by an epileptologist to complement the detections of the automated method.

Automated method. We used traditional signal analysis techniques to identify the time at which a seizure spreads to the thalamic nuclei of interest. We used seven signal processing measures, quantifying their changes over time from 30 s before the seizure onset to 30 s after the seizure onset[12,48,49,67]. The seven measures are line length, area under the curve, standard deviation of the voltage traces and spectral power in theta, alpha, beta, and gamma frequency bands (Fig. 2). The value for each measure was calculated for every 1 s period in a 60 s window around seizure onset (30 s before to 30 s after the onset). The values for each measure were then normalized by subtracting the mean and dividing by the standard deviation of the first 15 s (reference period: −30 s to −15 s from the beginning, green line Fig. 2a, b). The bottom traces of Fig. 2a, b show changes in these measures over time. We determined that the

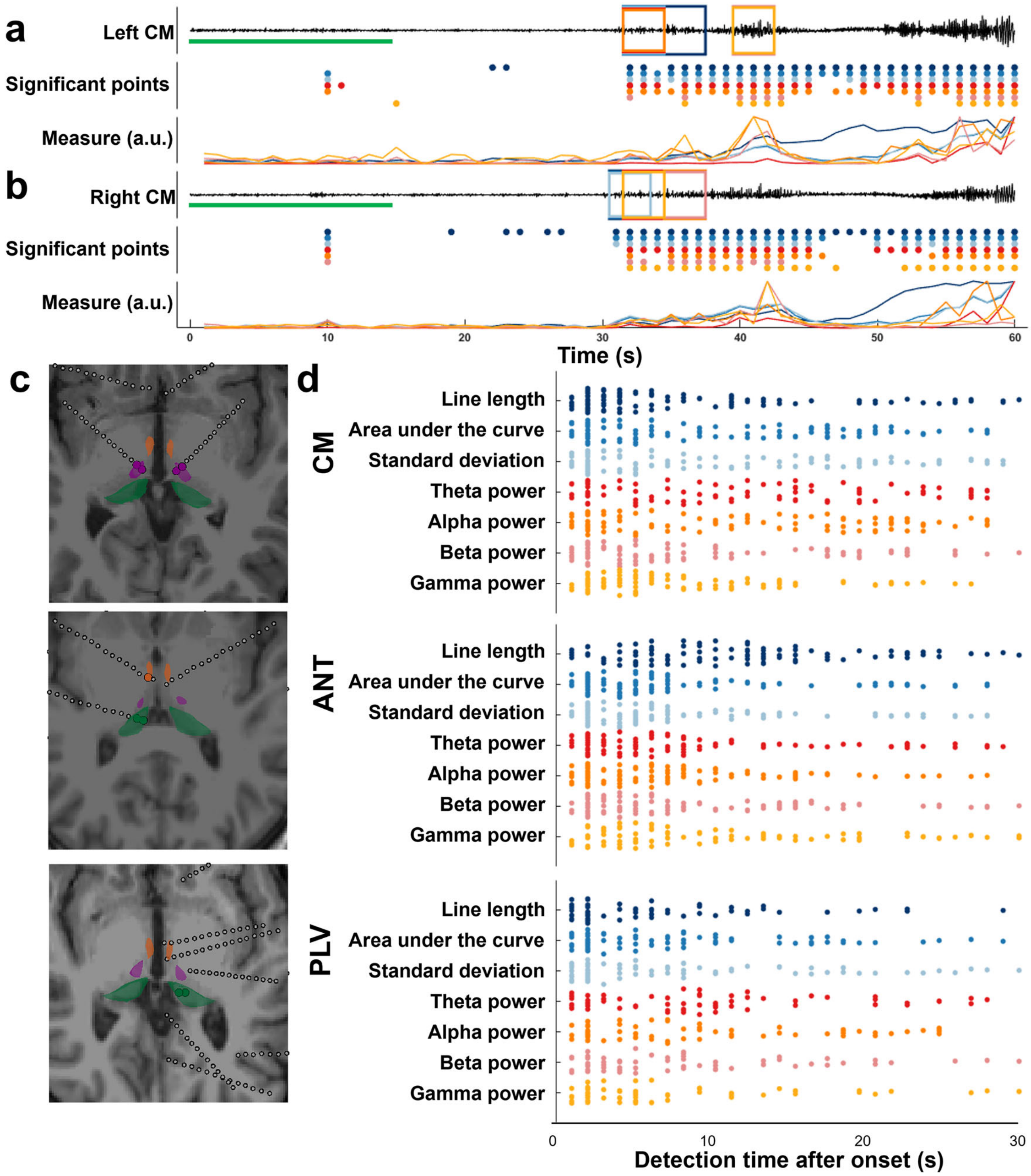


Fig. 2 | Detecting seizure spread in the thalamus with different measures. **a**, **b** (bottom traces) Changes in the measures over time. **a**, **b** (middle traces) The time at which these measures were significant (i.e., exceeded twice the standard deviation of the reference period (green line)). **a**, **b** (top traces) A recorded signal from left and right CM, where colored rectangles signify detecting a spread of activity by a specific measure. The time at which the 3 s significant increase from the background has started is identified as the time of the spread for that specific measure, ranging from 1–30 s. **c** Example of the anatomical location of the electrodes (dotted lines) within CM (purple), ANT (orange), and PLV (green). **d** Swarm chart showing the time of detected spread by any of the measures to CM ($n = 190$ seizures), ANT ($n = 126$ seizures), and PLV ($n = 97$ seizures). Line length and gamma power measure could detect a spread of activity within the CM faster than other measures, but this was only significant in comparison to detection by theta and alpha power (Kruskal–Wallis $p = 0.002$). Within the ANT line length detected the spread later than all measures other than gamma power (Kruskal–Wallis $p = 0.0004$). Otherwise, these distributions were broadly similar across other measures and across all measures within PLV. (CM Centromedian, ANT anterior nucleus of thalamus, PLV pulvinar, a.u. arbitrary unit, s second).

measure was significantly different from the reference period when its value exceeded twice the standard deviation of the reference period (Fig. 2a, b, middle traces). For each channel within the thalamic nuclei of interest, for each measure, if the measure was significant for at least three consecutive seconds within the 30 s period after the seizure onset, the seizure was determined to have spread and the time of spread was marked for that channel (colored rectangles in Fig. 2a, b, top traces).

Visual method. An epileptologist reviewed the seizure spread to all recorded thalamic nuclei by visually inspecting only the thalamic channels of a 120 s long signal around the seizure onset (with ±10 s jitter). The reviewer was blind to the thalamic location, the seizure category at onset (i.e., pattern at onset, region of onset, and pattern of spread), the seizure onset channels, and the seizure onset times. The reviewer was asked to mark the time at which they see the first seizure activity on the thalamic channels.

Automated and visual methods comparison. Since we are interested in determining the thalamic involvement around the seizure's initiation, only the first 30 s after the seizure onset was subject to evaluation. The time of spread to the thalamus was classified into three different categories: early (1–6 s), late (7–30 s), and no-spread, the latter for cases where no spread could be detected in the thalamus within the first 30 s after the seizure onset. The time of early spread (1–6 s) was chosen based on our experience and more importantly based on preliminary data we captured from patients who responded well to thalamic stimulation within the CM (Supplementary Fig. 1). The seizures captured during intracranial recordings of four patients who received CM stimulation were analyzed and the time of spread of ictal activity to the CM was detected with the seven measures. We found that the detected time of spread for the seizures of patients who had favorable outcomes (Engel I and II) were mostly distributed within 1–6 s after the seizure onset. On average, seizures were detected after 5.48 ± 6.21 s in patients with favorable outcomes, compared to 14.51 ± 6.96 s in patients with unfavorable outcomes (Engel IV).

Generalized linear model

To evaluate the effect of each seizure type (onset pattern, onset regions, and pattern of spread) on the propagation into different thalamic nuclei, we fit the data to a generalized linear model (GLM; statsmodels in Python). A binomial response GLM was used to evaluate the effect of each categorical feature on the early response (early spread (<6 s) versus not-early or no-spread). A GLM was fitted to each of these responses, for each nucleus (CM, ANT, and PLV) and each category type (onset pattern, onset regions, and pattern of spread).

The categorical labels assigned to each seizure (onset pattern, onset regions, and pattern of spread) were one-hot encoded to create dummy variables x_k, such that each GLM took the form:

$$\beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p \sim y \quad (1)$$

Statistics and reproducibility

To evaluate differences in each measure's detected time of spread within the thalamic nuclei of interest, the Kruskal–Wallis test was used, followed by the Tukey–Kramer method for multiple comparisons with the level of significance set at $p = 0.05$.

To evaluate whether a predictor (seizure feature) affects the response variable (time of spread to the thalamus), we used Wald test (Python "statsmodels" library). This test assesses whether the null hypothesis that a predictor coefficient is equal to zero is true. If the null hypothesis is rejected ($p < 0.05$), we determine that the predictor (seizure feature) affects the response variable. Wilcoxon rank-sum test was employed to compare the time of spread to different nuclei when more than one nucleus was recorded in a patient. Fisher's Exact test was used to evaluate the differences between the prevalence of events (comparing the prevalence of early detection in multiple nuclei and comparing the prevalence of agreement between visual and automated methods), with the level of significance set at $p = 0.05$. To evaluate whether the differences between group counts are significant we used one-tailed binomial test for proportions, with the level of significance set at $p = 0.05$ (Fig. 5d).

Results in the text are reported as mean ± standard error of the dataset across patients or seizures. Numerical values displayed in heat map cells (Supplementary Figs. 2–4) are the mean for each group.

Results

Patients were selected if they had received at least one electrode in either the centromedian (CM) nucleus, anterior nucleus (ANT), or the pulvinar (PLV). A total of 717 seizures from 44 patients were reviewed (Supplementary Data 1). Seizures were visually analyzed by two reviewers and classified into multiple categories based on three classification criteria: electrographic onset pattern, seizure onset region, and seizure pattern of spread. Only seizures that lasted more than 15 s and whose onset times and regions could be agreed upon by the reviewers were selected for further evaluation. To account for seizure count variability across patients, for patients with many seizures of one type (based on their electrographic pattern, region of onset, and pattern of spread), only five seizures of each type with the best recordings were selected. This resulted in 308 seizures for analysis across all patients (7 ± 0.6 seizures per patient).

Time of the ictal spread to the thalamus

Thalamic contacts within the CM/ANT/PLV were identified for each patient (Supplementary Data 1 and Fig. 2c). The number of seizures selected for analysis in patients with recordings in the CM was 190, with an ANT electrode was 126, and 97 for PLV. In addition to these three planned targeted nuclei, depending on the electrode trajectory, some other nuclei were sampled by the same electrodes. The most commonly recorded additional nucleus mediodorsal nucleus (MD). We identified 71 seizures from 11 patients with MD electrodes. The time of seizure spread to these contacts, which we term thalamic spread, was determined on each CM, ANT, or PLV contact using the seven different measures for automated method and by an expert reviewer (see "Methods").

When bilateral thalamic recordings were available, the thalamic contacts were separated into ipsilateral and contralateral contacts where the ipsilateral thalamus matched the side of the seizure origin. Seizures were excluded from analysis when they originated from a side with no thalamic implant within the nuclei of interest. In seizures with broad onset, where the seizures started in both hemispheres simultaneously, the earliest detected time of spread across both hemispheres was assigned to be the time of spread to the ipsilateral thalamus for each specific measure. The distribution of time of spread in the ipsilateral CM, ANT, and PLV for each measure for all seizures is shown in Fig. 2d. Line length and gamma power measure could detect a spread of activity within the CM faster than other measures, but this was only significant in comparison to detection by theta and alpha power (Kruskal–Wallis $p = 0.002$). Within the ANT line length detected the spread later than all measures other than gamma power (Kruskal–Wallis $p = 0.0004$). Otherwise, these distributions were broadly similar across other measures and across all measures within PLV (Fig. 2d).

Propagation time to the CM, ANT, and PLV varies across seizures

For each seizure, the time of thalamic spread identified by each measure in the ipsilateral CM (Supplementary Fig. 2), ipsilateral ANT (Supplementary Fig. 3), and ipsilateral PLV (Supplementary Fig. 4) was averaged across different groups in different categories (onset pattern, onset region, and pattern of spread). We compared the spread using two metrics: (1) the average time of thalamic spread by any of the measures in each category (Supplementary Figs. 2–4ai, bi, ci), and (2) the percentage of seizures with detectable spread by each measure in each category (Supplementary Figs. 2–4aii, bii, cii).

Certain types of seizures exhibited a faster thalamic spread to CM (Supplementary Fig. 2). In particular, spike-wave and sharp seizures, as well as multi-region onset and broad-onset seizures were detected by most of the measures in CM within 10 s of onset (Supplementary Fig. 2i) across the majority of seizures (>75%; Supplementary Fig. 1ii). Other seizure types (e.g., spike sharp, lateral temporal) also have a relatively fast spread to CM (Supplementary Figs. 2ai, 1bi), but only for a subset of measures. Within the ANT (Supplementary Fig. 3), many seizure types propagated to this nucleus, but seizures within mesial temporal regions have faster detected spread by most of the measures. Notably, the majority of seizures with hypersynchronous patterns (HYP) and seizures with focal onset that stayed focal (FF) did not have any spread to ANT (Supplementary Fig. 3aii, cii), with the caveat that only $n = 2$ seizures were classified as FF in our sample where ANT was also recorded. Looking at the spread of seizures to PLV (Supplementary Fig. 4), we found that seizures with spike followed by low-voltage fast activity (spike LVF) and spike-wave patterns showed a faster spread to PLV (Supplementary Fig. 4ai, aii). Seizures with an onset in the lateral

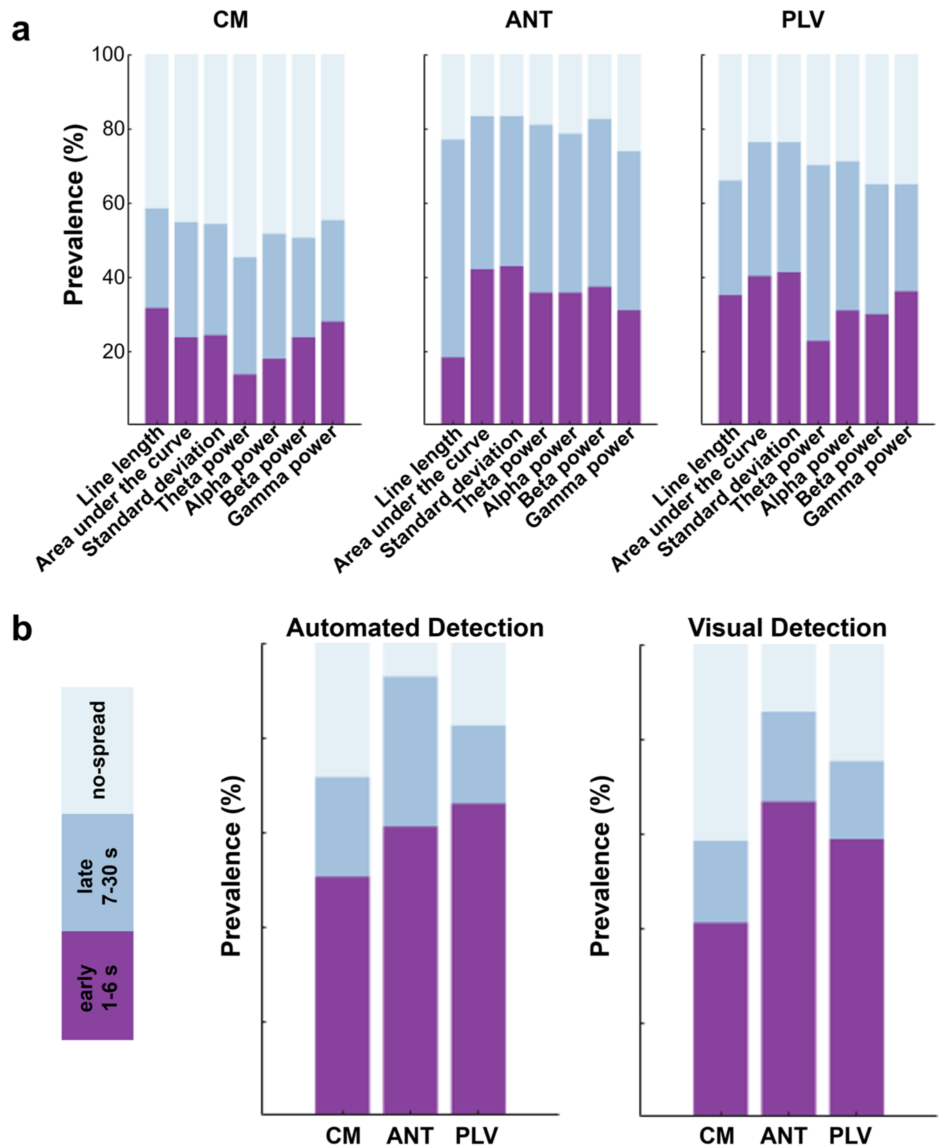


Fig. 3 | Distribution of spread to different thalamic nuclei. **a** The prevalence of early, late, and no-spread as detected by each measure. For example, line length detected more early spread in the CM cohort while missing most of the spread in ANT. **b** Automated and visual detection performed similarly in identifying the seizure spread, with the automated method detecting higher early spread only within the CM cohort. Around 75% of seizures spread to CM (purple and steel blue), with around 50% of seizures having an early spread (purple). Seizure spread (purple and steel blue) to ANT is prominent, however this spread is early (purple) for ~60% of seizures. Around 60% of seizures have an early spread to PLV. Comparing **a** and **b**, it is clear that while each single measure may only detect an early spread in less than 40% of seizures, using a combination of the measures can help identify spread of more seizures.

temporal areas or those arising from broader regions also exhibited faster spread to PLV (Supplementary Fig. 4bi, bii, ci, cii).

Classifying propagation time for seizure comparison

We showed that the average time of spread to different thalamic nuclei (CM, ANT, and PLV) is faster in some seizure types than others. To assess whether seizure type can be predictive of whether a seizure may spread to the thalamic nucleus of interest, we categorized the detection time into different delay categories: Early (1–6 s), Late (7–30 s), and no-spread (where no spread could be detected in the thalamus within the first 30 s after the seizure onset; Fig. 3).

Some seizure types appear to spread to specific nuclei with different timings (Fig. 3a). To assign a single time of spread label to each seizure detected by the automated method, we needed to consolidate the time of spread across all measures. There are some aspects of this analysis that make comparison between seizure types difficult. For one, the time of spread varies from one measure to the next. In some cases, the spread may be identified by only one measure—such cases are more likely to be false positives. We labeled seizures as “no-spread” if their spread to the thalamus was not detected, or only detected by one measure. Within the remaining seizures, the earliest detection time across all measures was considered as the time of spread, and seizures were labeled as “early” or “late” in the same way as before. Around two-thirds of seizures had spread to the CM within 30 s after the onset (Fig. 3b CM), but only ~50% of seizures had an early spread (within 6 s) to the CM. While more than 75% of seizures spread to the ANT in the first 30 s after the onset, only ~60% of seizures had early spread to ANT (Fig. 3b ANT). Around 80% of seizures spread to the PLV, with more than 60% having an early spread (Fig. 3b PLV).

We found that the automated and visual methods agreed on more than 75% of early/not early spread times. The prevalence of early spread times determined by the two methods differed only in CM (Fisher’s exact, $p = 0.02$), with no significant difference between the two methods in ANT or PLV (Fig. 3b).

Features predictive of early spread to the thalamus

Next, we evaluated whether seizure type can be informative for the time of spread to any of the thalamic nuclei. Looking closer at different classes of seizures (Fig. 4), it appears that some seizures spread more frequently to certain nuclei. We quantified these differences between seizure types using mathematical modeling. As mentioned earlier, a single time of spread label was assigned to each seizure by consolidating the time of spread across all measures. We fitted binomial GLMs to the data using seizure types as predictors and “early-or-not” spread time (as determined by the automated method) as the binary response variable. The

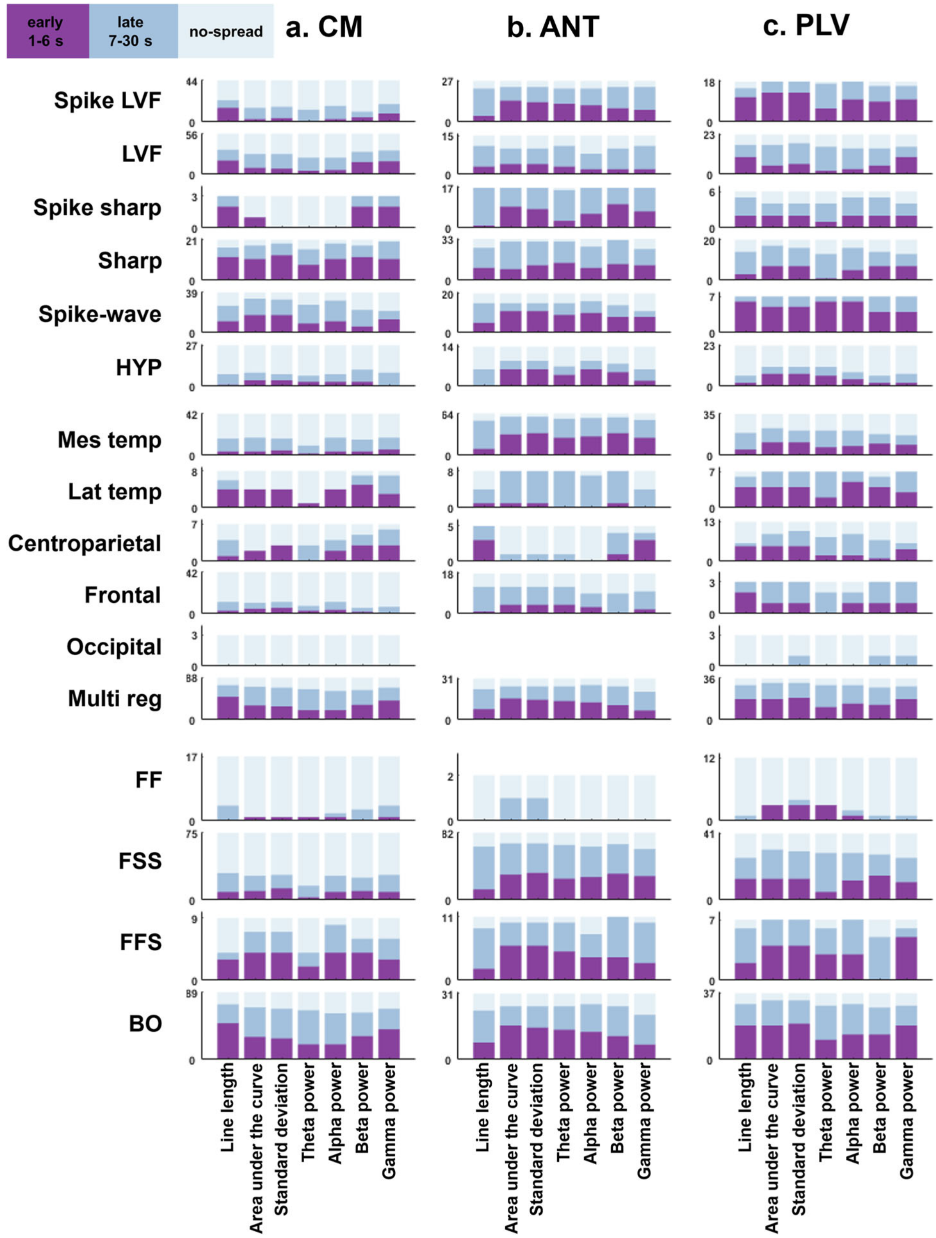


Fig. 4 | Distribution of different categories of spread to different thalamic nuclei. **a** Most seizures with sharp and spike-wave patterns spread to CM. Seizures with a broad onset in multi regions often spread to CM. **b** Most seizures with an onset in mesial temporal areas, or with a spread (non-FF seizures) may have an early or late spread to the ANT. **c** Seizures with spike LVF and spike-wave patterns, lateral temporal seizures or seizures with an onset in multiple regions may have an early (purple) spread to PLV. (LVF low-voltage fast, HYP hypersynchronous, Mes temp mesial temporal, Lat temp lateral temporal, FF focal onset remaining focal, FSS focal onset with slow spread, FFS focal onset with fast spread, BO broad onset, s second).

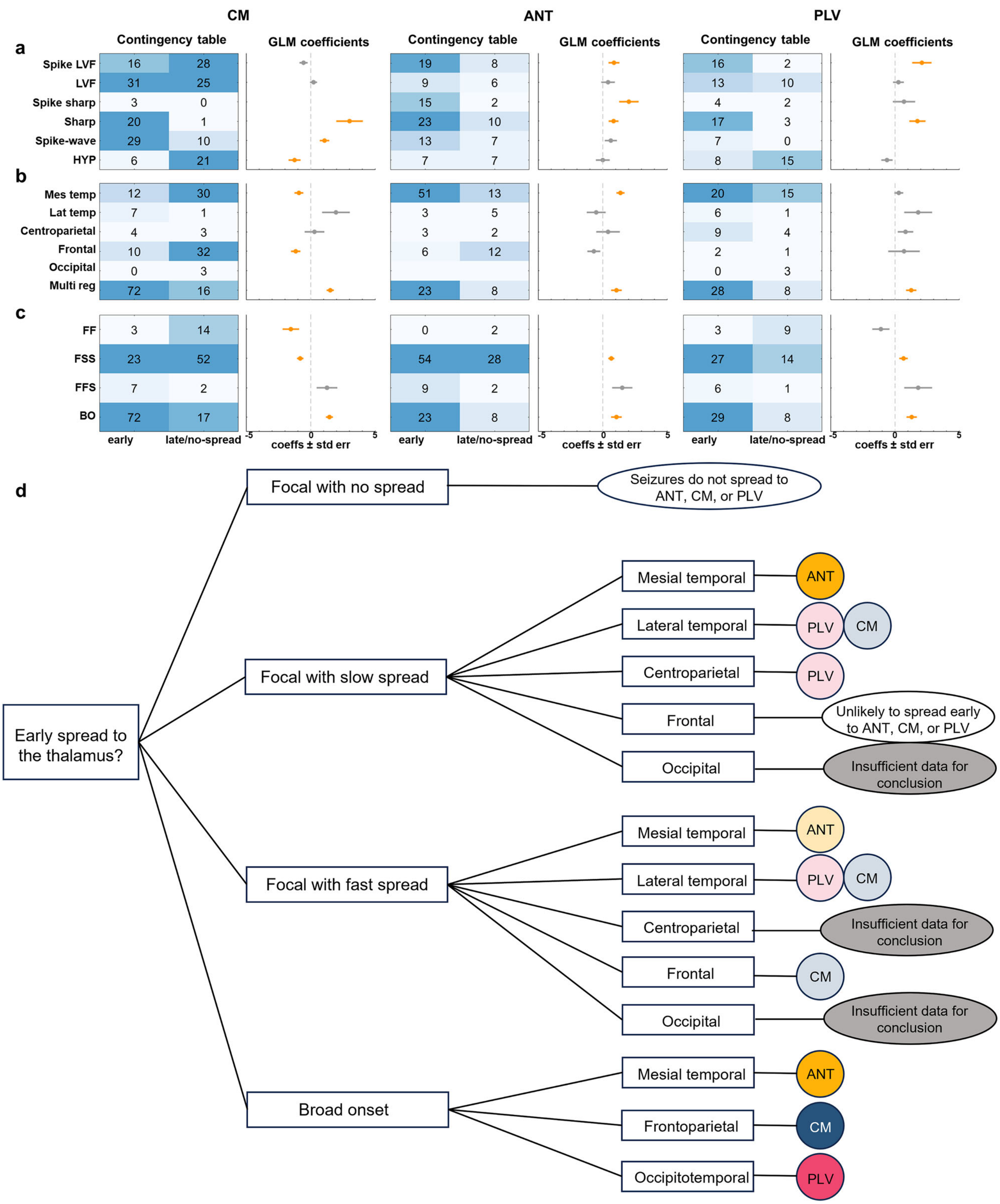
coefficients of the GLMs are plotted for each seizure type (predictor) (Fig. 5).

Seizures with a sharp onset pattern almost always spread to the CM, and this spread was early ($z = 2.924$, $p = 0.003$ for early spread), while HYP seizures had late or no-spread to CM (Fig. 5a CM; $z = -2.706$, $p = 0.007$ for early spread). The most important factors for predicting an early spread to CM are whether the seizures are (1) broad onset ($z = 5.353$, $p < 0.001$) or (2) originate from multiple regions ($z = 5.442$, $p < 0.001$; Fig. 5b CM and 5c CM). Perhaps surprisingly, seizures that originate from frontal areas are not predictive of spread to CM (Fig. 5b CM) since these seizures are likely to have a late spread ($z = -3.211$, $p = 0.001$) to this nucleus, along with seizures originating from the mesial temporal areas ($z = -2.683$, $p = 0.007$). The occurrence of seizures from occipital regions in patients with an implant in the CM was rare in our data set, making it harder to draw a meaningful conclusion for such seizures. However, none of the occipital seizures showed any spread to the CM, which is consistent with expectations from the anatomy of thalamic connectivity.

Sharp (with and without spike) and spike LVF pattern seizures frequently spread early to ANT (Fig. 5a ANT). We found the most predictive factor of any spread to ANT to be whether the seizure originated from the mesial temporal lobe or had a multi-region broad onset (Fig. 5b ANT). The most predictive factor of an early spread specific to ANT is, however, seizures originating from mesial temporal areas ($z = 4.399$, $p < 0.001$).

As is the case for the other nuclei, seizures with a sharp pattern at their onset are significantly likely to spread early to PLV ($z = 2.778$, $p = 0.006$), and seizures with HYP patterns may not spread early to this nucleus. All seizures with spike-wave patterns spread to PLV. Seizures with broad onset arising from multi-regions were more likely to have an early spread to PLV ($z = 3.225$, $p = 0.001$; Fig. 5b PLV and 5c PLV). While most seizures with lateral temporal onsets tended to have an early spread to PLV, the number of such seizures was limited in our dataset and did not reach significance. We further, separated seizures into subgroups based on spread, onset regions, and pattern using a decision tree (Fig. 5d). This figure shows the thalamic nucleus to which seizures of each category may spread early, with darker coloring indicating significant differences (binomial test for proportions; $p < 0.05$).

We performed the same analysis for patients whose MD nucleus was recorded by chance and found that seizures originating from mesial



temporal or frontal areas were unlikely to spread early to MD ($z = -2.405$, $p = 0.016$; $z = -2.604$, $p = 009$, respectively), while broad seizures originating from multiple regions were more likely to have an early spread to MD ($z = 3.023$, $p = 0.003$; Supplementary Fig. 5).

We also fitted binomial GLMs to the data using the spread times identified visually by an expert. These results are reported in Supplementary Fig. 6 and, in the majority of cases, were in agreement with the reported results detected by the automated method. More specifically, 85% of model coefficients matched in sign.

When recording from multiple nuclei simultaneously, the prevalence of early spread to PLV is similar to that of CM and ANT

We recorded from 44 patients with implants in thalamic nuclei, out of which 15 patients had implants in more than one nucleus (Supplementary Data 1).

Fig. 5 | Evaluating the effect of each seizure type on the time of spread to different thalamic nuclei. Seizures are classified based on their onset pattern (**c**), onset region (**b**), and pattern of spread (**c**). **a**–**c** Contingency tables showing the number of seizures with early and late/no-spread in each category. The shades of blue indicate higher (dark blue) or lower (light blue) number of occurrences. The plots show the coefficients of GLMs with an "early-or-not-early" response variable. Markers show the coefficients ± standard errors for each category predictor (seizure type). For each category, positive (negative) coefficients suggest a positive (negative) association with the occurrence of the response variable. The coefficients highlighted in yellow indicate that the specific predictor significantly affects the response variable ($p < 0.05$; the exact p values can be found in Supplementary Table 1). The missing coefficients correspond to variables where their response is invariant (always 0 or 1; e.g., Spike sharp in CM group). Therefore, no meaningful coefficient could explain the relationship between the predictor and response variable. **d** Decision tree showing possible nuclei to which seizures may have an early spread. Darker coloring indicates significance (binomial test; dark shades p values from top to bottom: 0.000108, 0.0016, 2.82×10^{-9}, 7.53×10^{-6}). We note that in groups with lighter coloring, while at least 60% of seizures show early spread to selected nuclei, there are not enough seizures (<10) to perform a meaningful statistical analysis. (CM centromedian, ANT anterior nucleus of the thalamus, PLV pulvinar, LVF low-voltage fast, HYP hypersynchronous, Mes temp mesial temporal, Lat temp lateral temporal, FF focal onset remaining focal, FSS focal onset with slow spread, FFS focal onset with fast spread, BO broad onset).

In this subgroup, we investigated the simultaneous seizure spread to these multiple nuclei for relevant seizure types.

An example seizure recorded from Pt 22 shows a seizure with a broad/multi-regional onset with a spike-wave pattern (Fig. 6a). Automated (orange rectangle) and visual (green rectangle) methods of spread detection agree on the time of spread to the right ANT and right CM. In the patients where both CM and ANT were recorded, the two nuclei had similar times of spread, except in cases where seizures had broad onset from multi-regions (Fig. 6b). In these seizures, CM showed significantly more prevalence of early spread than ANT (Fisher's Exact $p = 0.02$), and the average times of spread after the onset to CM (2.4 s) was significantly faster than those of ANT (6.3 s; ranksum test, $p = 0.01$), confirming our previous results of the high likelihood of early spread of broad seizures to the CM.

In Fig. 7a, an example seizure recorded from Pt 23 shows a seizure with a sharp onset in the right centroparietal region that spreads to the rest of the brain after a few seconds. The time of spread to ipsilateral CM and PLV are identified by both automated (orange rectangle) and visual (green rectangle) methods. In this example, both methods determined that seizure spread to PLV was slightly earlier than spread to CM. In general, seizures recorded from patients with both CM and PLV implants tended to spread faster to PLV, especially the seizures with spike LVF patterns and onset within mesial temporal regions, but this did not reach significance, as the number of seizures in these categories is small within this cohort (Fig.7b).

A sharp onset seizure rising from right mesial temporal regions recorded from Pt 13 with identifiable spreads to both ANT and PLV nuclei is shown in Fig. 8a. Comparing the spread of different seizure types to ANT and PLV, we found that there are no significant differences between the time of spread between these nuclei (Fig. 8b). It is important to mention that most of the patients with electrodes within both these nuclei had seizures rising from mesial temporal areas, and we did not identify any differences in spread to mesial temporal areas in this cohort.

Discussion

We sought to better understand the physiology of thalamocortical interactions in seizures and use this information to develop a principled, objective, and quantitative method for determining which thalamic nuclei are involved in the network of different seizure types. We found that some seizure types are more likely to spread to certain thalamic nuclei. Specifically, (1) seizures arising from multiple regions with a broad onset are very likely to spread early to CM and PLV; (2) seizures with an onset in mesial temporal regions were more likely to spread early to ANT; (3) focal seizures that remained focal were the least likely to spread to any of the thalamic nuclei; (4) sharp onset seizures had the highest likelihood of spreading to any of the nuclei, while HYP seizures were the least likely to spread to any nucleus; (5) seizures with onset in lateral temporal areas tend to have an early spread to PLV or CM; (6) comparing multiple nuclei, broad seizures have significantly earlier spread to CM compared to ANT; (7) the prevalence of early seizure spread to PLV is high; and (8) there is no difference between PLV and other nuclei when recording from multiple nuclei simultaneously.

We have validated our automated seizure spread detection method with visual detection. The automated method classification of seizure spread to the thalamus into early/not early agreed in 75% of the seizures with the visual method. While we reported the results of both detections, we relied on the automated method for reporting the main results. We did this because unlike the results of visual inspection, which can vary significantly between experts, the use of an automated method allows for the same criteria for detection across all seizures. The utilized measures did not perform similarly in the detection of seizure spread; some measures were able to detect certain seizure types faster and more reliably than other measures (as is the case clinically as well). When seizure detection is necessary (e.g., with the RNS), it is important to identify which metrics should be used for different seizure types and different regions. For instance, the line length measure could detect an early spread of broad seizures to CM, but performed poorly in detecting the spread to ANT. In the future, it will be crucial to evaluate how off-line detection methods compare to RNS (or, eventually, other systems) detection algorithms. Detecting seizures in closed-loop devices is critical; determining which measures can more reliably detect specific seizure types is likely to increase the efficacy of closed-loop neuromodulatory treatment.

Our results align with those of previous studies showing that in the case of multi-region epilepsy, including cases that affect frontotemporal areas, CM preceded ANT during seizures[24,68]. Unless the seizures are coming from a broader area or both hemispheres, our results did not find CM to be involved early in frontal or mesial temporal seizures. These findings may explain why CM may not be the ideal target for treatment of frontal or mesial temporal epilepsies[69]. These findings also apply to MD since only seizures with broad onset are more likely to spread to MD. However, MD was not part of the planned targeted nuclei in our cohort, and there are fewer patients with recordings from this nucleus compared to those for other nuclei. More studies are needed to address the seizure spread to this nucleus.

Although previous work has shown that ANT stimulation leads to inconsistent seizure management for temporal epilepsy[9,70], this nucleus remains a popular target for this kind of epilepsy. Here we show that, similar to previously reported results[30], seizures with mesial temporal onset are more likely to spread quickly to ANT. We observed, however, eight seizures with an onset in lateral temporal areas while recording from ANT, and most of these (five) had a delayed or no spread to ANT. On the other hand, our data suggest that lateral temporal seizures spread early to PLV (in 86% of our recorded seizures). This agrees with previous work that found seizure spread to PLV in 80% of recorded temporal lobe seizures, suggesting its involvement in their propagation[71]. Comparing ANT and PLV in patients with recordings from both sites, we did not identify any differences between PLV and ANT. These findings suggest that PLV is involved in the network of seizures originating from more lateral temporal areas and thus it might be reasonable to be targeted for these seizures especially in situations in which seizure onset includes both mesial and lateral temporal regions.

Even though stimulating PLV has not been common among patients, there is evidence that this nucleus has high global connectivity and may be involved rather early in a majority of seizures[35,71,72], and other studied nuclei here (CM, ANT) may not get involved before PLV. The effect of PLV stimulation has also shown promising results[73,74], where recently, Ikegaya et al.[74] studied the effect of stimulation of various nuclei on a patient with multifocal bilateral temporoparieto-occipital epilepsy and showed PLV stimulation results in a higher reduction of interictal discharges in occipital and parietal lobes. Interestingly, this reduction is

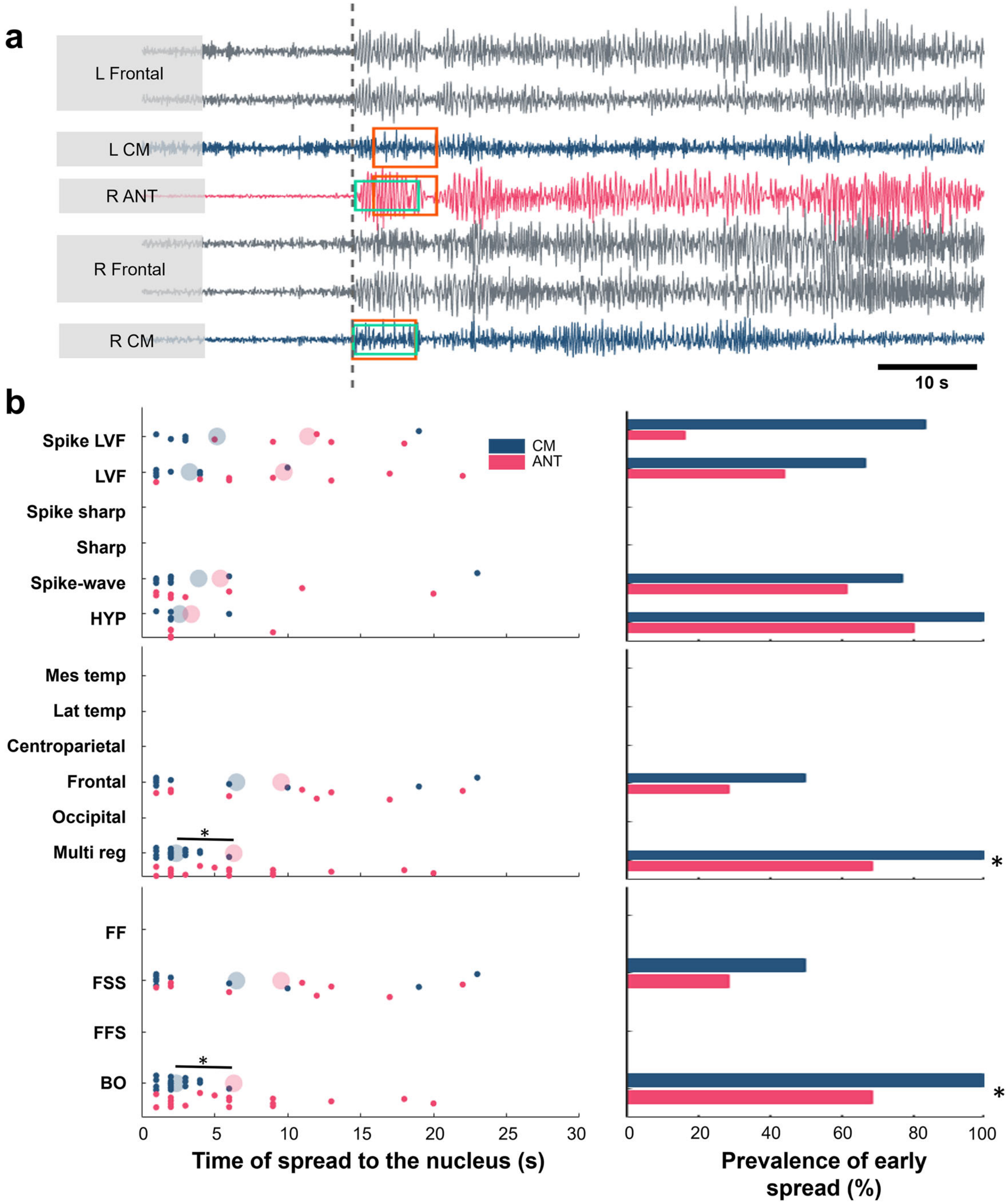


Fig. 6 | Seizure spread to centromedian (CM) and anterior nucleus of the thalamus (ANT). a A seizure recorded from Pt 22 with a broad multi-regional spike-wave pattern at the onset (example recordings of right and left frontal region onsets are shown here). Automated (orange rectangle) and visual (green rectangle) methods of spread detection agree on the time of spread to the right ANT and right CM. **b** Time of spread to the CM and ANT in different seizure types. The small solid circles indicate the time of spread for each seizure. The larger circles with light shading indicate the average time of spread for each category. There are no significant differences between the two nuclei for the times of spread of seizures in most of the cases, except for the seizures with broad onset from multi-regions where seizures spread significantly earlier to CM than ANT ($p = 0.01$), and the early spread occurs in significantly larger number of seizures ($p = 0.02$). (LVF low-voltage fast, HYP hypersynchronous, Mes temp mesial temporal, Lat temp lateral temporal, FF focal onset remaining focal, FSS focal onset with slow spread, FFS focal onset with fast spread, BO broad onset).

seen in both hemispheres (ipsi- and contra-lateral) only following the PLV stimulation[74]. Our results support an early involvement of PLV in a majority of the recorded seizures. This calls for more investigation to evaluate the efficacy of stimulation within this area in seizure treatment. It is worthwhile to note that, in this study, we included pulvinar medial (PuM in FreeSurfer[66]) structure as part of the analysis, and we did not have enough patients with recordings from other parts of pulvinar to evaluate their involvement in seizures. More studies are needed to differentiate between the involvement and role of various parts of pulvinar in seizures.

Admittedly, the core limitation of our study concerns the lack of available recordings from multiple nuclei simultaneously. This results in an uneven distribution of seizures per group—especially for groups based on onset region. In the ANT group, for example, most seizures arise from mesial temporal areas. Two factors contribute to this particular discrepancy: (1) temporal lobe epilepsy is the most prevalent of the focal epilepsies[75], and

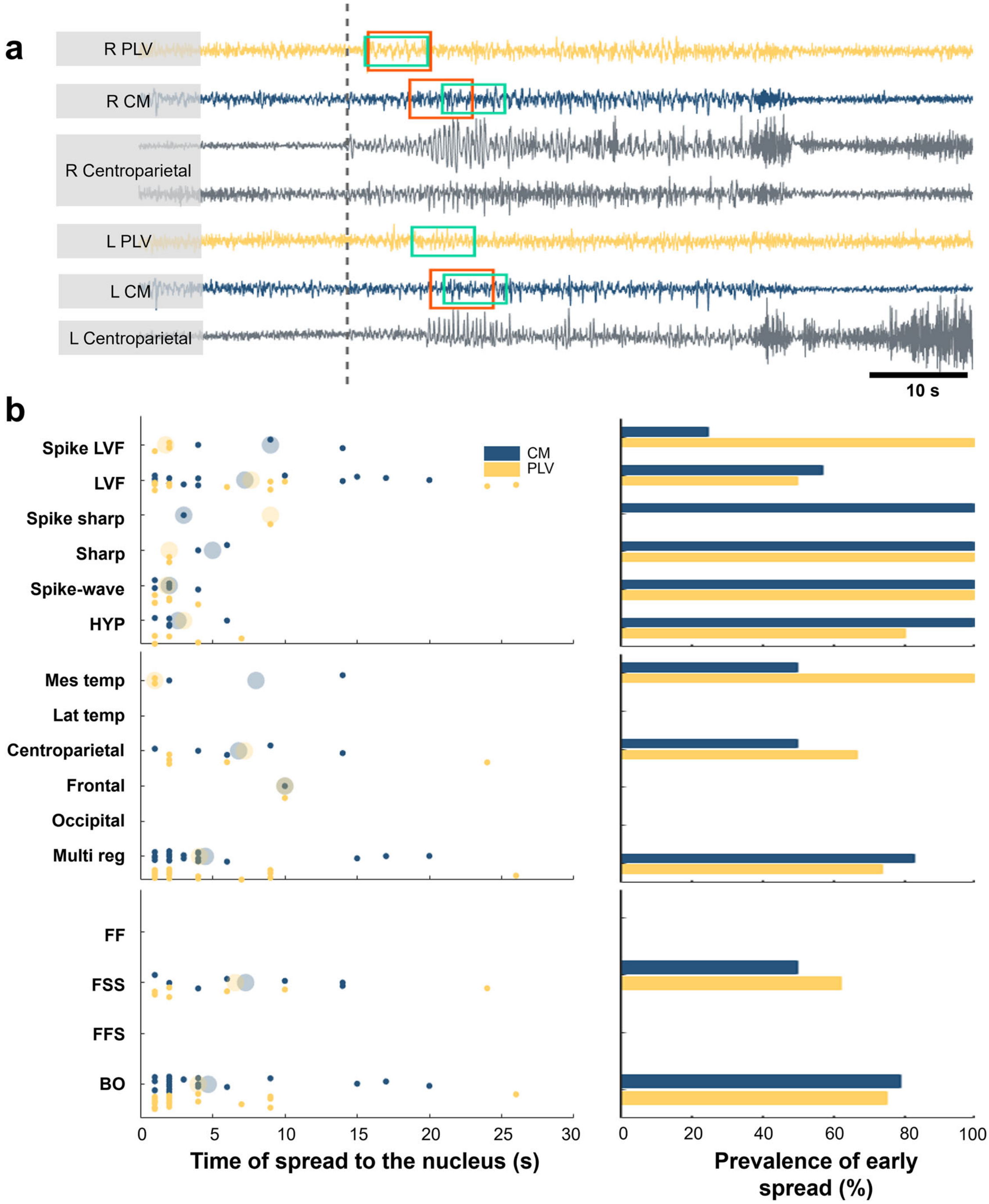


Fig. 7 | Seizure spread to centromedian (CM) and pulvinar (PLV). **a** A sharp onset seizure recorded from Pt 23 with an onset in the right centroparietal region that spreads to the rest of the brain after a few seconds. The time of spread to ipsilateral CM and PLV, identified by both automated (orange rectangle) and visual (green rectangle) methods, shows that the spread was detected slightly earlier in the PLV compared to CM. **b** The small solid circles indicate the time of spread for each seizure. The larger circles with light shading indicate the average time of spread for each category. Seizures recorded from patients with both CM and PLV implants tend to spread faster to PLV, especially the seizures with spike LVF patterns and onset within mesial temporal regions, but this did not reach significance, as the number of seizures in these categories is small within this cohort. (LVF low-voltage fast, HYP hypersynchronous, Mes temp mesial temporal, Lat temp lateral temporal, FF focal onset remaining focal, FSS focal onset with slow spread, FFS focal onset with fast spread, BO broad onset).

(2) historically, ANT was a common neurostimulation target for this population when other therapies were not feasible. While we cannot firmly evaluate the spread of other seizure types to ANT, our data support an early spread (within 6 s) to ANT in seizures with a mesial temporal origin. Since HYP seizures do not show an early spread to ANT, it is important to mention that, reportedly, mesial temporal seizures have a high rate of HYP patterns[41,76]. However, we did not find this in our cohort. In our studies, we have noticed a lower number of HYP patterns in our patients with mesial temporal onset[38]. This pattern is mostly associated with mesial temporal sclerosis (MTS)[41], and since patients with this specific pathology may be determined and become surgical candidates before intracranial investigation, we have fewer patients with MTS pathology and, therefore, fewer seizures with HYP patterns in mesial temporal areas. More specifically, out of 64 seizures arising from mesial temporal structures in the ANT cohort, only nine seizures had HYP patterns, and most of the rest had sharp or spike sharp patterns.

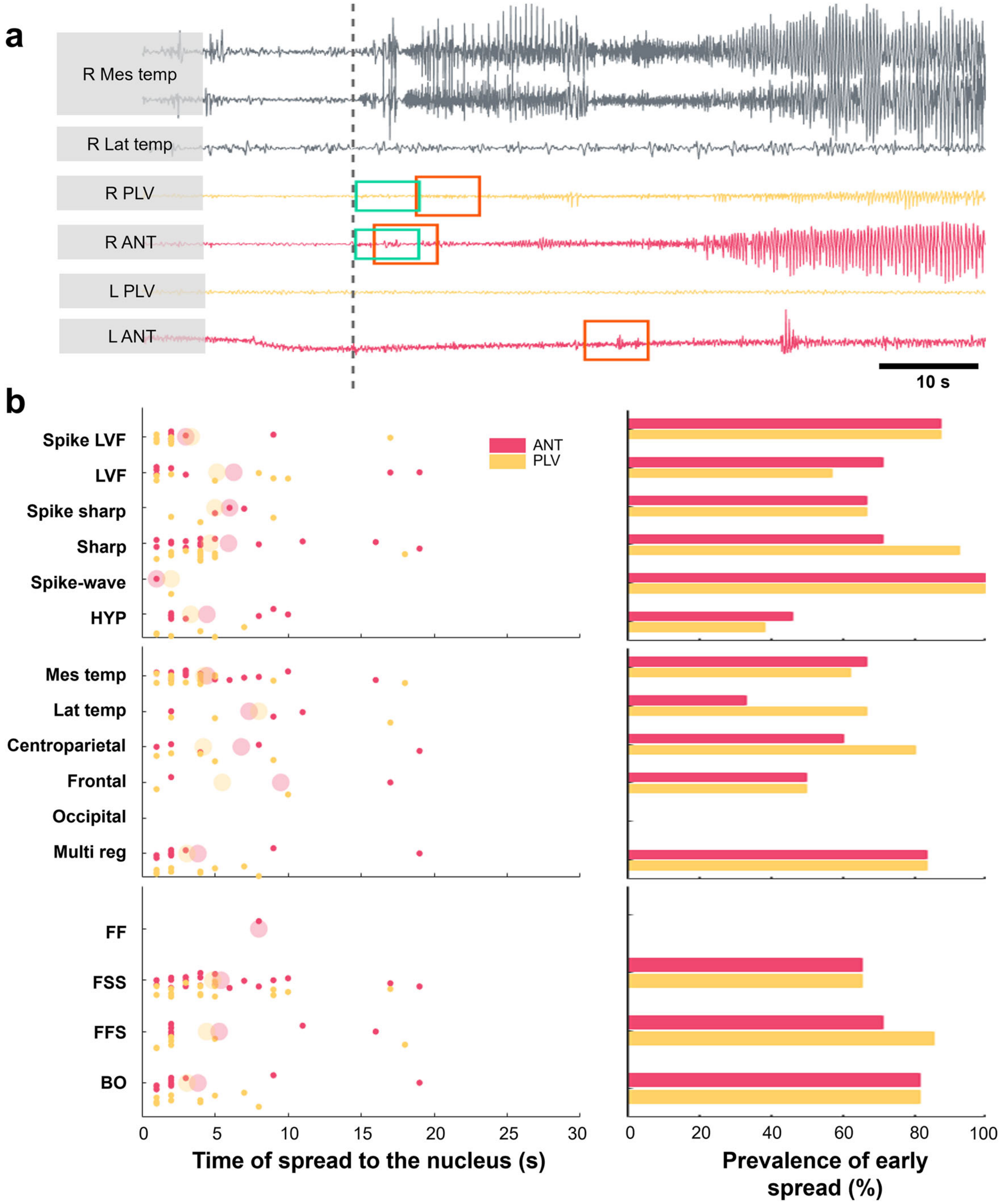


Fig. 8 | Seizure spread to anterior nucleus of the thalamus (ANT) and pulvinar (PLV). a A seizure with a sharp mesial temporal onset recorded from Pt 13 with identifiable spreads to both ANT and PLV (orange: automated detection; green: visual detection). **b** The small solid circles indicate the time of spread for each seizure. The larger circles with light shading indicate the average time of spread for each category. No significant differences were found between the time of spread of different seizures to ANT and PLV. Note that most of the patients with electrodes within both these nuclei had seizures rising from mesial temporal areas. We showed that mesial temporal seizures have a high likelihood of spreading early to ANT, and when comparing simultaneously, these seizures may equally have an early spread to PLV. (LVF low-voltage fast, HYP hypersynchronous, Mes temp mesial temporal, Lat temp lateral temporal, FF focal onset remaining focal, FSS focal onset with slow spread, FFS focal onset with fast spread, BO broad onset).

To compensate for this data limitation, we have had to adapt our classification schemes for multi-region and broad onset seizures. In particular, all seizures with multi-region onsets have been grouped together, although this class includes a broad spectrum of seizure onset regions (e.g., grouping seizures with both centroparietal and frontal onsets together with seizures that originate in mesial and lateral temporal regions). In addition, some seizures involved only two regions and were still labeled as broad onset, while in other cases, seizures originated from more than five different regions. Sampling from different brain regions in each patient also places constraints on how we devise our classification scheme. For instance, if a seizure had an onset or spread in an unsampled brain region, the seizures could have been misclassified. Future studies with more data should address these limitations. It would be interesting to pursue these investigations for specific types of region involvement at seizure onset in future studies where more data are available for analysis.

Moreover, the thalamus is comprised of many more nuclei than those examined in this work[32,77]. For example, other structures, such as the midline nuclear of the thalamus, have also been the subject of studies in epilepsy[11,70,78–80], showing involvement in seizures originating from mesial temporal areas[79]. The main targeted nuclei in this study were CM, ANT, and PLV. Depending on the trajectory, other thalamic nuclei were recorded by chance. Among these, only MD was recorded in enough patients to be included in the analysis. It stands to reason that other thalamic nuclei may show different involvement during seizures, which may be indicative of more effective targets for neurostimulation.

In spite of these limitations, our results are the first to indicate that seizure characteristics may be predictive of spread to different thalamic nuclei. Interestingly, Wu et al.[81] investigated the spread of seizures to the thalamus in temporal lobe seizures and reported that none of the seizure onset regions could be predictive of a spread to any specific thalamic nuclei[81]. We note that their study involved only a limited number of patients ($n = 11$), all with temporal lobe epilepsy, with identification of seizure spread performed visually. In contrast, our study involves recordings from $n = 44$ patients with a wide range of epilepsies, where seizure spread was determined using both automated and visual methods and quantified using multiple signal processing measures. Under our proposed classification scheme, we demonstrated that it is possible to predict an early spread of seizures to CM, ANT, and PLV based on specific seizure characteristics. Above all, our results demonstrate that regional differences are just one factor that may impact the spread to the thalamus and that other aspects, such as the degree of spread and the dynamics of initiation, need to be considered. Indeed, in a recent study, we evaluated the connectivity between different thalamic nuclei and the rest of the brain[82], finding that even though some functional connectivity between various brain areas and the thalamus can be predicted by structural connectivity, the epileptogenesis process induces changes in the brain that may impact this connection. It is, therefore, possible that seizure features such as the pattern at onset and the pattern of spread can account for this variability. These features, in turn, may end up being informative of the thalamocortical connectivity profile in epilepsy.

Our findings may be informative to clinicians who are looking to determine the most appropriate stimulation target for thalamic neurostimulation candidates as part of their seizure management. As discussed, certain seizure types are more likely to have certain patterns of spread to the thalamus (e.g., multi-region broad onset spreads quickly to CM), and in turn, the nucleus to which they spread may serve as a more viable target for neuromodulatory treatment. On the other hand, seizures that have no or late spread (e.g., HYP seizures) to the thalamus may be more difficult to modulate through thalamic stimulation. Eventually, with access to a large enough dataset, we will be able to predict the involvement of the thalamus in specific patients. For instance, if imaging findings and scalp EEG recordings of a patient are suggestive of seizures with broad onset, we may be able to predict that CM and PLV are involved in their seizures. This information can further be used to identify a reliable target for thalamic stimulation without further intracranial investigation. In contrast, if a patient is found to have very focal seizures within eloquent cortex with no spread (based on the scalp recording and imaging data), our findings suggest that thalamic nuclei may not be involved during the seizures and that consequently, thalamic neuromodulation may not be effective.

As more becomes known about the role of the thalamus in seizure propagation and how this is influenced by neurostimulation, we are likely to discover novel biomarkers that are informative of treatment efficacy for specific seizure types. This knowledge, in turn, may also help us to better understand how other factors, such as the stimulus waveform or the timing of stimulation relative to seizure onset are likely to impact clinical findings[83–85]. We anticipate that future studies building from our work will facilitate the development of a principled approach towards clinical decision-making that ultimately results in more effective neuromodulatory therapies—an approach that will be further enhanced as even more understanding is reached and biomarkers discovered.

Data availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. The source data for Figs. 2–8 is in Supplementary Data 2. This includes the detected time of spread by each measure (Figs. 2d and 3a), the time of spread identified by visual and automated methods (Fig. 3b), the seizure categories and detected spread time by each measure (Fig. 4), the identified time of spread to each nuclei and seizure categories (Fig. 5), the time of spread to each nuclei pair for each seizure (Figs. 6–8). The raw EEG data of this study are available upon reasonable request from the corresponding author.

Received: 4 January 2025; Accepted: 15 May 2025;
Published online: 22 May 2025

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Acknowledgements

The authors wish to thank Giovanna Aiello, Nikola Bolt, Brian Coughlin, Rina Zelmann for their contributions towards early drafts of this manuscript and to Jessica Chang for helping with data collection. We are also grateful to the clinical team, epilepsy monitoring unit technicians, and our patients. This study was supported by Department of Defense CDMRP FY21 Epilepsy Research Program W81XWH-22-1-0315 (P.S.), Fondation Fyssen research grant and the Fulbright (Monahan grant) (P.B.), The Executive Committee on Research (ECOR) of Massachusetts General Hospital (S.S.C., A.C.P., D.J.S.), National Institutes of Health grant R01 NS079533 (S.S.C., A.C.P., D.J.S.), National Institutes of Health grant R01 NS062092 (S.S.C., A.C.P., D.J.S.), National Institutes of Health grant R01 NS072023 (S.S.C., A.C.P., D.J.S.), National Institutes of Health grant K24-NS088568 (S.S.C., A.C.P., D.J.S.), National Institutes of Health grant R25 NS065743 (P.N.H.).

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Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-025-00920-9.

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Peer review information *Communications Medicine* thanks Liankun Ren and Naotaka Usui for their contribution to the peer review of this work. A peer review file is available.