

# Thalamo-cortical synchrony shapes seizure expression in human temporal lobe epilepsy

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In drug-resistant temporal lobe epilepsy (DR-TLE), some seizures are clinically symptomatic while others remain electrographic despite arising from the same seizure-onset zone (SOZ), suggesting that clinical expression reflects network dynamics beyond seizure origin. We examined whether thalamo-cortical network engagement differs between clinical (CS) and non-clinical seizures (NCS). We analyzed 286 seizures from 62 DR-TLE patients recorded using stereoelectroencephalography with pulvinar and/or anterior thalamic group coverage. Thalamo-cortical synchrony during the first 20 seconds of seizure onset was quantified as correlation between SEEG-derived time-frequency patterns in thalamic nuclei and the cortical SOZ. Synchrony was significantly stronger during CS than NCS ( $p < 0.0001$ , Cliff's  $\delta > 0.6$ ), including within-subject analyses, and was independent of other clinical variables, including postsurgical outcome. Linear mixed-effects modeling identified seizure type as the sole independent predictor of synchrony ( $p = 0.0069$ ). These findings identify thalamo-cortical synchrony as a network-level feature associated with clinical seizure expression in DR-TLE.

Temporal lobe epilepsy (TLE), the most common form of focal drug-resistant epilepsy (DRE), is frequently treated with anterior temporal lobectomy or laser ablation, particularly in mesial temporal sclerosis (MTS)<sup>1</sup>. However, despite comprehensive presurgical evaluation, 20–40% of patients, including those with MTS, experience recurrent seizures postoperatively<sup>1–3</sup>. This limitation has shifted the field toward viewing epilepsy as a disorder of distributed brain networks rather than an isolated cortical phenomenon<sup>4–6</sup>. Stereo-electroencephalography (SEEG) has been instrumental in this shift, revealing that subcortical

structures, particularly the pulvinar (Pul) and the anterior thalamic nuclei, are active participants in seizure generation and modulation in TLE<sup>5,7–16</sup>.

Thalamo-cortical interactions are not unique to epilepsy; across neurological disorders, they shape the expression of symptoms, from motor network dysregulation in movement disorders to functional deficits following stroke<sup>17,18</sup>. Although debate over the relative roles of the thalamus and cortex in seizure pathogenesis dates back to the 1800s<sup>19,20</sup>, evidence from imaging and SEEG neurophysiology studies

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highlights that the thalamus is not a passive relay but an active hub influencing seizure propagation, termination, and clinical manifestation, and it may contribute to surgical failure<sup>8,10,12,13,15,21</sup>. Increasingly, the thalamus is recognized as a critical therapeutic target, particularly for patients with bilateral seizure onset or unresectable networks, where neuromodulation offers the next step beyond resection<sup>9,22–24</sup>.

In DR-TLE, clinical seizures (CS) are epileptic discharges associated with overt subjective symptoms or objectively observable clinical manifestations and are associated with reduced quality of life. With widespread SEEG use, non-clinical seizures (NCS), electrographic seizures without observable symptoms, are increasingly recognized alongside clinical seizures<sup>25–28</sup>. Although CS and NCS may originate from the same epileptogenic zone (EZ) in a given patient, the mechanisms underlying their divergent clinical expression remain poorly understood. A substantial body of literature has attempted to explain this dissociation through mechanisms outside a cortico-thalamic synchrony framework, focusing instead on cortical network features such as seizure onset patterns, neuronal recruitment, spatial extent, propagation, and large-scale synchronization<sup>27,29–32</sup>, as well as the prevalence, localization, and surgical relevance of non-clinical seizures identified with intracranial recordings<sup>33,34</sup>.

Although variability in thalamic recruitment during seizures has been reported including variability related to ictal frequency content and spatial extent<sup>11,35</sup>, its specific relationship to clinical versus non-clinical seizure expression has not been systematically examined. In particular, no study has systematically evaluated how thalamo-temporal dynamics differ across clinical subtypes, focal preserved consciousness (FPC), focal impaired consciousness (FIC), and focal to bilateral tonic-clonic (FBTC), or how these patterns relate to postoperative seizure outcomes. Understanding why some seizures produce symptoms while others remain silent remains a central challenge, hindered by the lack of a reproducible network-level biomarker. Addressing this gap is essential for advancing mechanistic understanding of seizure semiology and for guiding neuromodulatory strategies for nonresectable DR-TLE.

We hypothesized that thalamo-cortical synchrony, particularly involving the Pul and anterior thalamic group (ATG), contributes to clinical seizure expression in DR-TLE. Specifically, we predicted that CS would exhibit stronger thalamo-temporal coupling than NCS. We further examined whether this coupling differs across seizure subtypes (FPC, FIC, FBTC) and whether it relates to post-surgical outcomes. Using SEEG-based time–frequency (TF) analysis in a multicenter cohort with targeted thalamic coverage, we quantified thalamo-temporal spectral correlation to examine its association with seizure semiology and surgical prognosis.

Results

Patient demographics

A total of 62 consecutive patients with DR-TLE (286 seizures: 224 clinical seizures (CS), 62 non-clinical seizures (NCS)) were included. The average seizure duration was 158 s for CS and 67 s for NCS. Across all analyzed seizures ( $n=286$ ; 224 CS and 62 NCS), seizure duration differed significantly between CS and NCS ( $p<0.001$ ;  $\delta=0.31$ ). The median age at SEEG evaluation was  $37\pm13.6$  years (range: 16–68), and median epilepsy duration was  $11.5\pm11.2$  years (range: 1–43.5). Most were right-handed males with non-lesional MRI; 10 had prior resective surgery or laser ablation (Table 1). During SEEG monitoring, 66.1% of the patients ( $n=41$ ) had only CS, 32.3% ( $n=20$ ) had both CS and NCS, and 1.6% ( $n=1$ ) had only NCS. Mesial temporal lobe epilepsy (mTLE) was diagnosed in 51.5% ( $n=32$ ), including five with bilateral onset. Thalamic coverage included Pul only ( $n=48$ ), both Pul and ATG ( $n=11$ ), and ATG only ( $n=3$ ). Surgical intervention was performed in 77.4% ( $n=48$ , 46 surgical resections, 2 laser ablations, Table 2). Of the 46 patients who underwent resection, 38 (178 seizures: 138 CS, 40 NCS) had  $\geq 1$  year of follow-up (mean: 21.4 months; range: 12–63), with 50% ( $n=19$ ) achieving seizure

**Table 1 | Detailed demographics and clinical information of the patient population**

|                                                                       |                                |
|-----------------------------------------------------------------------|--------------------------------|
| Age at the time of SEEG recording (median, mean $\pm$ SD) (range) (y) | 37.0, 38.4 $\pm$ 13.6 (16–68)  |
| Age at time of seizure onset (median, mean $\pm$ SD) (range) (y)      | 24.0, 24.6 $\pm$ 15.0 (0–65)   |
| Duration of epilepsy (median, mean $\pm$ SD) (range) (y)              | 11.5, 13.6 $\pm$ 11.2 (1–43.5) |
| Handedness                                                            |                                |
| – Right                                                               | 53 (85.5%)                     |
| – Left                                                                | 8 (12.9%)                      |
| – Ambidextrous                                                        | 1 (1.6%)                       |
| Male (%)                                                              | 39 (62.9%)                     |
| MRI finding                                                           |                                |
| – None                                                                | 30 (48.4%)                     |
| – Prior resection or laser ablation                                   | 10 (16.1%)                     |
| – Mesial temporal sclerosis                                           | 8 (12.9%)                      |
| – Temporal lobe encephalomalacia and temporal encephalocele           | 7 (11.3%)                      |
| – Nonspecific changes (cortical flair changes)                        | 5 (8.1%)                       |
| – Cavernoma                                                           | 2 (3.25%)                      |
| SEEG implantation scheme                                              |                                |
| – Unilateral                                                          | 43 (69.4%)                     |
| • Left                                                                | 33/43                          |
| • Right                                                               | 10/43                          |
| – Bilateral                                                           | 19 (30.6%)                     |
| Thalamus Implantation                                                 |                                |
| – Only Pulvinar                                                       | 48 (77.4%)                     |
| – Only Anterior thalamus Group                                        | 3 (4.8%)                       |
| – Both Pulvinar and Anterior thalamus Group                           | 11 (17.7%)                     |
| Seizure semiology captured during SEEG evaluation                     |                                |
| – Only Clinical (FPC, FIC and FBTC) seizures                          | 41 (64.5%)                     |
| – Only Nonclinical seizures                                           | 1 (1.6%)                       |
| – Both Clinical Nonclinical Seizures                                  | 20 (33.9%)                     |
| Location of the confirmed epileptogenic zone <sup>a</sup>             |                                |
| – Mesial temporal                                                     | 32 (51.6%)                     |
| • Unilateral                                                          | 30/32                          |
| • Bilateral <sup>b</sup>                                              | 5/32                           |
| – Mesial and lateral temporal                                         | 11 (17.7%)                     |
| • Unilateral                                                          | 10/11                          |
| • Bilateral                                                           | 1/11                           |
| – Lateral temporal <sup>a</sup>                                       | 19 (30.6%)                     |
| Surgical Intervention                                                 |                                |
| – Resection                                                           | 46 (74.2%)                     |
| • Corticectomy                                                        | 9                              |
| • Temporal lobectomy                                                  | 37                             |
| – Laser ablation                                                      | 2 (3.2%)                       |
| – RNS                                                                 | 6 (9.7%)                       |
| – No intervention or waiting for surgical intervention <sup>c</sup>   | 8 (12.9%)                      |

<sup>a</sup>*N* number, *SD* standard deviation, *y* year, *m* month, % percentage, *FPC* focal preserved consciousness, *FIC* focal impaired consciousness, *FBTC* Focal to bilateral tonic clonic seizure.  
<sup>b</sup>Out of 18 patients, one patient had ipsilateral lateral temporal lobe epilepsy and contralateral mesial temporal lobe epilepsy in relation to the SEEG thalamus electrode analyzed.  
<sup>c</sup>Out of 5 patients, one patient had ipsilateral mesial temporal and contralateral lateral temporal epilepsy in relation to the SEEG thalamus electrode analyzed.  
<sup>d</sup>Including recent SEEG waiting for intervention.

freedom (Engel IA). Among them, 30 had Pul-only coverage, 6 had both Pul and ATG, and 2 had ATG only.

**Thalamo-temporal spectral synchrony correlation analysis**  
Descriptive statistics (median, mean  $\pm$  SD, IQR) and subgroup comparisons are presented in Supplementary Tables 1–18 and Fig. 1. Among the 62 patients analyzed, 11 had SEEG coverage of both the Pul and ATG. For these patients, 61 seizures (51 CS, 10 NCS) were analyzed

**Table 2 | Postoperative outcomes and pathological findings in patients with  $\geq 12$  months follow-up ( $N = 38$ )**

|                                                                                                             |                             |
|-------------------------------------------------------------------------------------------------------------|-----------------------------|
| The outcome of 38 patients who underwent resective or laser ablation surgery with at least 1 year follow-up |                             |
| – Engel IA outcome                                                                                          | 19 (50%)                    |
| – Other Engel 1 outcome                                                                                     | 6 (15.8%)                   |
| – Engel II–IV outcome                                                                                       | 13 (34.2%)                  |
| Follow-up duration of all 38 patients who underwent resective surgery (median, mean $\pm$ SD) (range) (m)   | 32, 32.4 $\pm$ 17.4 (12–63) |
| Pathology of all 38 patients                                                                                |                             |
| – Reactive gliosis                                                                                          | 26 (68.4%)                  |
| – Hippocampal sclerosis                                                                                     | 5 (13.1%)                   |
| – FCD type IIB, and III                                                                                     | 3 (7.9%)                    |
| – No pathology due to laser ablation                                                                        | 2 (5.3%)                    |
| – Lesion (cavernoma, AVM)                                                                                   | 2 (5.3%)                    |

$N$  number,  $SD$  standard deviation,  $y$  year,  $m$  month, % percentage.

twice, once per thalamic nucleus, resulting in a total of 347 seizure entries (275 CS, 72 NCS). Additionally, 20 patients with both CS and NCS contributed 82 paired within-subject comparisons.

Across all seizures, thalamo–temporal spectral correlation values were significantly lower in NCS ( $n = 72$ ) compared to CS ( $n = 275$ ) (Wilcoxon rank-sum test,  $p < 0.0001$ ,  $\delta = 0.63$ ; Supplementary Table 1, Fig. 1A(i)). This pattern persisted across temporal epilepsy subtypes correlations in NCS were significantly lower than in CS for mesial temporal (Wilcoxon rank-sum test,  $p < 0.0001$ ,  $\delta = 0.67$ ), lateral temporal (Wilcoxon rank-sum test,  $p = 0.0003$ ,  $\delta = 0.60$ ), and mesiolateral subtypes (Wilcoxon rank-sum test,  $p = 0.0032$ ,  $\delta = 0.66$ ) (Supplementary Table 2). When stratifying CS into FPC ( $n = 83$ ), FIC ( $n = 140$ ), and FBTC ( $n = 52$ ), no significant differences were found (Supplementary Table 3, Fig. 1A(ii)). Within the sampled thalamo–temporal network, synchrony strength reliably distinguished clinical from non-clinical seizures. However, the ability to assess additional modulation by awareness level (FPC vs FIC) or secondary generalization (FBTC) was limited by the spatial extent of SEEG coverage. In the subset of 38 patients with  $\geq 1$  year of surgical follow-up (250 seizure entries), CS again demonstrated significantly higher thalamo–temporal correlation than NCS (Wilcoxon rank-sum test,  $p < 0.0001$ ,  $\delta = 0.72$ ; Supplementary Table 4, Fig. 1A(iii)). No overall difference was observed between seizure free (SF) and non-seizure free (NSF) groups (Wilcoxon rank-sum test,  $p = 0.7514$ , Supplementary Table 5); however, when stratified into four subgroups (SF-CS, SF-NCS, NSF-CS, NSF-NCS), significant differences emerged (Kruskal–Wallis test,  $p < 0.0001$ ; Supplementary Table 6, Fig. 1A(iv)). Notably, SF-CS showed significantly higher correlation than SF-NCS and NSF-NCS (post hoc comparisons,  $p < 0.0001$ ), while NSF-CS also exceeded NSF-NCS (post hoc comparisons,  $p = 0.0007$ ) (Supplementary Table 6, Fig. 1A(iv)).

When analyzed separately by vigilance state (wakefulness vs sleep), no significant differences in thalamo–temporal correlation were observed between wakefulness and sleep for either CS (Wilcoxon rank-sum test,  $p = 0.2525$ ) or NCS (Wilcoxon rank-sum test,  $p = 0.4999$ ) (Supplementary Fig. 1).

To account for clustering of multiple seizures within individuals, a linear mixed-effects model was fitted with subject included as a random intercept. Thalamo–temporal spectral coupling was modeled as a function of seizure type (clinical vs. non-clinical), with thalamic region, TLE subtype, seizure duration, vigilance state, and post-surgical seizure outcome included as covariates. In this model (347 seizures from 62 patients), seizure type remained a significant independent predictor of thalamo–temporal coupling, with non-clinical seizures showing significantly lower synchrony than clinical seizures ( $\beta = -0.074$ ,  $SE = 0.027$ ,  $p = 0.0069$ , 95% CI  $[-0.128, -0.020]$ ). None of the additional covariates,

including thalamic region, epilepsy subtype, seizure duration, vigilance state, or surgical outcome, were significantly associated with coupling strength (all  $p > 0.05$ ). The inclusion of a subject-level random intercept accounted for substantial inter-individual variability, indicating that the observed effect of seizure type was not driven by subjects contributing a higher number of seizures (Table 3).

**Within-subject comparisons.** Intra-subject analyses were performed to confirm these findings. In 20 patients with both CS and NCS, correlation remained higher in CS (Wilcoxon signed-rank test,  $p = 0.0003$ ,  $\delta = 0.37$ ; Supplementary Table 7, Fig. 1B(i)), with a stronger difference in the subset with  $\geq 1$  year of outcome data (Wilcoxon signed-rank test,  $p < 0.0001$ ,  $\delta = 0.52$ ; Supplementary Table 8, Fig. 1B(ii)). Subject-level paired box plots demonstrate that this effect was consistently observed across individuals (Wilcoxon signed-rank test,  $p = 0.0169$ ,  $\delta = 0.48$ ; Supplementary Fig. 2). Figure 2A, B illustrates two representative patients with both clinical and non-clinical seizure types, where thalamic involvement was observed only during CS, despite identical EZ.

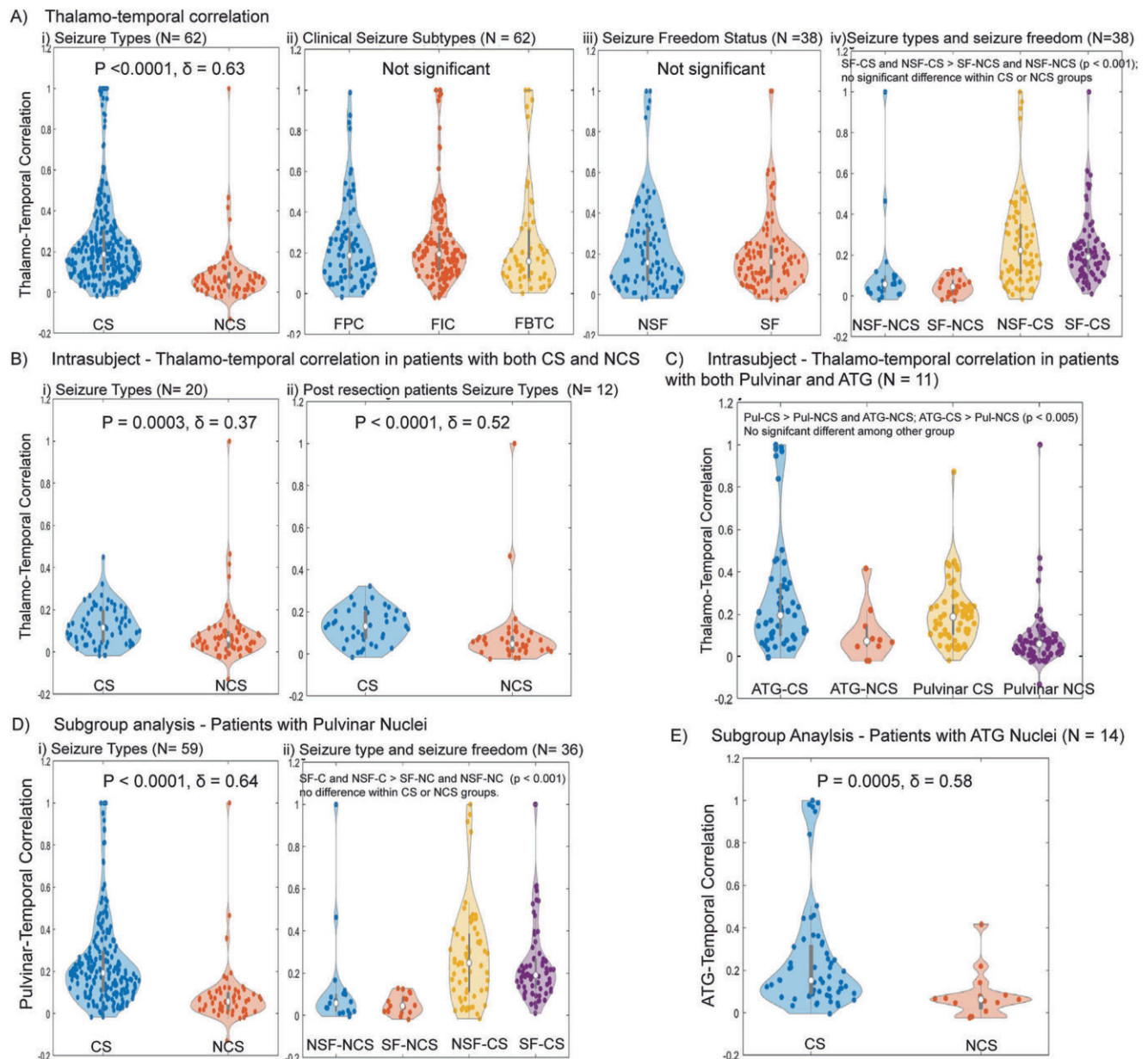
To access whether thalamo–cortical synchrony reflects selective network engagement rather than a purely local effect, we compared thalamic synchrony with SOZ and propagation zone (PZ) during the first 20 s of ictal activity in 20 patients with both CS and NCS (Fig. 3, Supplementary Table 9). During NCS, synchrony did not differ between SOZ and PZ (post hoc comparisons,  $p = 0.1717$ ). In contrast, during CS, thalamo–SOZ synchrony exceeded thalamo–PZ synchrony (post hoc comparisons,  $p = 0.0096$ ,  $\delta = 0.26$ ), although this finding should be interpreted in the context of multiple comparisons. Direct seizure-type comparisons showed higher SOZ–thalamus synchrony in CS than NCS (post hoc comparisons,  $p = 0.0004$ ,  $\delta = 0.36$ ), while clinical and non-clinical PZ–thalamus synchrony differed modestly (post hoc comparisons,  $p = 0.0078$ ,  $\delta = 0.27$ ).

When analyses were restricted to CS, thalamo–cortical synchrony differed across SOZ and PZ regions (Wilcoxon signed-rank test,  $p = 0.0244$ , Supplementary Table 10, Supplementary Fig. 3), with higher SOZ–thalamus than PZ–thalamus synchrony (post hoc comparisons,  $p = 0.0096$ ,  $\delta = 0.26$ ). Thalamo–SOZ synchrony did not differ from SOZ–PZ cortico–cortical synchrony (Wilcoxon signed-rank test,  $p = 0.4451$ ), and thalamo–PZ synchrony likewise did not differ from SOZ–PZ synchrony (Wilcoxon signed-rank test,  $p = 0.0511$ ).

Linear mixed-effects modeling confirmed seizure type as an independent predictor of thalamo–temporal synchrony after adjustment for propagation strength and other covariates ( $\beta = -0.033$ ,  $SE = 0.011$ ,  $p = 0.0027$ , 95% CI  $[-0.055, -0.012]$ ; Table 4). In addition, propagation–thalamus correlation was strongly associated with synchrony ( $\beta = 0.865$ ,  $SE = 0.047$ ,  $p < 0.001$ , 95% CI  $[0.771, 0.958]$ ), whereas thalamic region, epilepsy subtype, seizure freedom, vigilance state, and seizure duration were not.

In the 11 patients with both Pul and ATG coverage, Pul-CS showed the highest correlation values, significantly exceeding Pul-NCS (post hoc comparison,  $p = 0.0006$ ) and ATG-NCS (post hoc comparison,  $p = 0.005$ ). No difference was found between Pul-CS and ATG-CS (Supplementary Table 11, Fig. 1C). Figure 4A, B highlights two patients with mesial and lateral temporal epilepsy showing bilateral thalamic coupling during CS.

**Thalamic subregion analysis.** The pulvinar group (273 seizures (216 CS, 57 NCS) from 59 patients) mirrored the global findings: CS had significantly stronger pulvinar–temporal synchrony than NCS (Wilcoxon rank-sum test,  $p < 0.0001$ ,  $\delta = 0.64$ ; Supplementary Table 12, Fig. 1D (i)), regardless of clinical subtype (FPC, FIC and FBTC) (Supplementary Table 13) or surgical outcome (SF vs NSF). Stratified analysis again showed that SF-CS had higher coupling than all other subgroups (Kruskal–Wallis test,  $p < 0.0001$ ; Supplementary Table 14, Fig. 1D (ii)) and no differences were found in comparisons between SF-C and NSF-C (post hoc comparison,  $p = 0.408$ ) and between SF-NC and



**Fig. 1 | Thalamo-temporal spectral correlation across seizure types and outcomes (combined pulvinar (Pul) and anterior thalamic group (ATG)).** **A** (i) Across all 62 patients, correlation was higher in clinical seizures (CS) than non-clinical seizures (NCS) (Wilcoxon rank-sum,  $p < 0.0001$ ) and (ii) No differences across seizure subtypes (FPC, FIC, FBTC; Kruskal-Wallis,  $p = 0.4266$ ). (iii) This effect persisted in 38 patients with  $\geq 1$ -year follow-up (Wilcoxon rank-sum,  $p < 0.0001$ ) and (iv) Stratified groups with seizure free (SF) and nonseizure free (NSF) (SF-CS, SF-NCS, NSF-CS, NSF-NCS) differed overall (Kruskal-Wallis,  $p < 0.0001$ ), driven by higher correlation in CS than NCS within both outcome groups. **B** (i) In 20 patients with both seizure types, CS > NCS (Wilcoxon signed-rank,  $p = 0.0003$ ). (ii) Findings were consistent in 12 patients with  $\geq 1$ -year follow-up (Wilcoxon signed-rank,  $p < 0.0001$ ). **C** In 11 patients with Pul and ATG coverage, groups differed overall

(Kruskal-Wallis,  $p < 0.0001$ ; Bonferroni-adjusted  $p < 0.0083$ ), with higher correlation in CS relative to NCS conditions. **D** (i) In 59 patients with Pul subgroup; CS > NCS (Wilcoxon rank-sum,  $p < 0.0001$ ) and (ii) In 36 patients with  $\geq 1$ -year follow-up, stratified groups differed overall (Kruskal-Wallis,  $p < 0.0001$ ), with CS > NCS in both SF and NSF. **E** ATG subgroup ( $n = 14$ ): CS > NCS (Wilcoxon rank-sum,  $p = 0.0005$ ). Violin plots represent kernel density estimates of the data distribution, with width corresponding to relative data density and extending to the minimum and maximum values. The y-axis represents synchrony values, defined as spectral correlation coefficients (unitless). The overlaid white circle indicates the median, and the dark line represents the interquartile range. All statistical tests were two-sided. Bonferroni correction was applied where appropriate. Effect sizes are reported as Cliff's  $\delta$ . Source data is provided.

NSF-NC (post hoc comparison,  $p = 0.568$ ). Figure 4C illustrates three mTLE patients with the Pul involvement during CS.

ATG-specific analysis (74 seizures (59 CS, 15 NCS) from 14 patients) similarly showed a higher correlation in CS than NCS (Wilcoxon rank-sum test,  $p = 0.0005$ ,  $\delta = 0.58$ ; Supplementary Table 15), with no differences across FPC, FIC, and FBTC (Supplementary Table 16). Eight patients underwent resective surgery (mean follow-up = 33.3 months), contributing 36 seizures (29 CS, 7 NCS). NCS again

showed lower correlation than CS (Wilcoxon rank-sum test,  $p = 0.0001$ ,  $\delta = 0.94$ , Supplementary Table 17), but no significant difference was observed between SF and NSF groups (Wilcoxon rank-sum test,  $p = 0.8868$ , Supplementary Table 18).

### Epileptogenicity index and surgical outcome

EI values were analyzed in 38 patients with  $\geq 12$  months of post-operative follow-up (Supplementary Table 19). Of these, 37 patients

**Table 3 | Linear mixed-effects model predicting thalamo–temporal correlation values, adjusted for propagation, seizure type, thalamic region, epilepsy subtype, seizure freedom, vigilance state, and seizure duration, with subject-level random intercepts in 20 patients who had both clinical and non-clinical seizures**

| Predictor                                          | $\beta$ (Estimate)    | SE                   | 95% CI                                        | t     | p-value  |
|----------------------------------------------------|-----------------------|----------------------|-----------------------------------------------|-------|----------|
| Intercept                                          | 0.112                 | 0.033                | 0.047 to 0.177                                | 3.42  | 0.0009   |
| Seizure type (NCS vs CS)                           | −0.033                | 0.011                | −0.055 to −0.012                              | −3.06 | 0.0027** |
| Propagation-thalamus correlation value             | 0.865                 | 0.047                | 0.771 to 0.958                                | 18.27 | <0.001** |
| Thalamic region (ATG vs pulvinar)                  | 0.016                 | 0.017                | −0.018 to 0.050                               | 0.91  | 0.365    |
| Epilepsy subtype (lateral vs mesial)               | −0.030                | 0.025                | −0.079 to 0.020                               | −1.19 | 0.236    |
| Epilepsy subtype (mesiolateral vs mesial)          | 0.004                 | 0.030                | −0.056 to 0.064                               | 0.14  | 0.892    |
| Seizure freedom (seizure free vs non-seizure free) | −0.029                | 0.032                | −0.092 to 0.034                               | −0.92 | 0.361    |
| Vigilance state (asleep vs awake)                  | −0.022                | 0.012                | −0.046 to 0.003                               | −1.77 | 0.079    |
| Seizure duration (seconds)                         | $-2.1 \times 10^{-5}$ | $1.6 \times 10^{-5}$ | $-5.3 \times 10^{-5}$ to $1.2 \times 10^{-5}$ | −1.27 | 0.206    |

Fixed-effects coefficients ( $\beta$ ), standard errors (SE), 95% confidence intervals (CI), and *p*-values are reported. Seizure type was coded as 0 = clinical and 1 = non-clinical; thalamic region as 0 = pulvinar and 1 = anterior thalamic group (ATG); epilepsy subtype as 1 = mesial, 2 = lateral, and 3 = mesiolateral; clinical subtype as 0 = focal perceptual cognitive (FPC), 1 = focal impaired consciousness (FIC), and 2 = focal to bilateral tonic-clonic (FBTC); seizure freedom as 0 = not seizure-free and 1 = seizure-free; and vigilance state as 0 = awake and 1 = asleep. Subject was included as a random intercept to account for repeated seizures within individuals.

Random effects: Subject-level random intercept SD = 0.037 (95% CI 0.023–0.059).

Residual SD = 0.059 (95% CI 0.051–0.067).

Model fit: AIC = AIC = −328.41; BIC = −293.72.

Ordinary  $R^2$  = 0.7880; Adjusted  $R^2$  = 0.7725.

Significant *p*-values (*p* < 0.05) are indicated by\*\*.

had at least one clinical seizure subtype, and one patient had only NCS. Using a threshold of EI > 0.3 based on previously suggested threshold in the Pul, 5.3% (*n* = 2) patients were classified as high EI, one was seizure-free. Of the 36 with EI ≤ 0.3, 23 (63.9%) achieved SF, suggesting that limited thalamic recruitment at seizure onset may be associated with a higher likelihood of postoperative seizure control.

## Discussion

By leveraging simultaneous thalamic and temporal SEEG recordings in DR-TLE, we demonstrate that thalamo-temporal spectral synchrony within the first 20 s of ictal activity reliably distinguishes CS from NCS within the sampled network. Across the cohort, thalamo-temporal synchrony was consistently higher during CS than during NCS, independent of seizure duration, seizure subtype, epilepsy subtype, thalamic nucleus, vigilance state, or surgical outcome. These differences were robust across within-subject analyses and models accounting for repeated seizures, indicating that seizure type (CS versus NCS) is the primary factor associated with thalamo-cortical coupling strength. Importantly, these findings do not imply that thalamic involvement alone determines clinical seizure expression. Rather, they demonstrate that CS and NCS differ systematically in network-level synchrony within the sampled thalamo-temporal circuitry, highlighting the thalamus as a key relay within clinically expressive seizures.

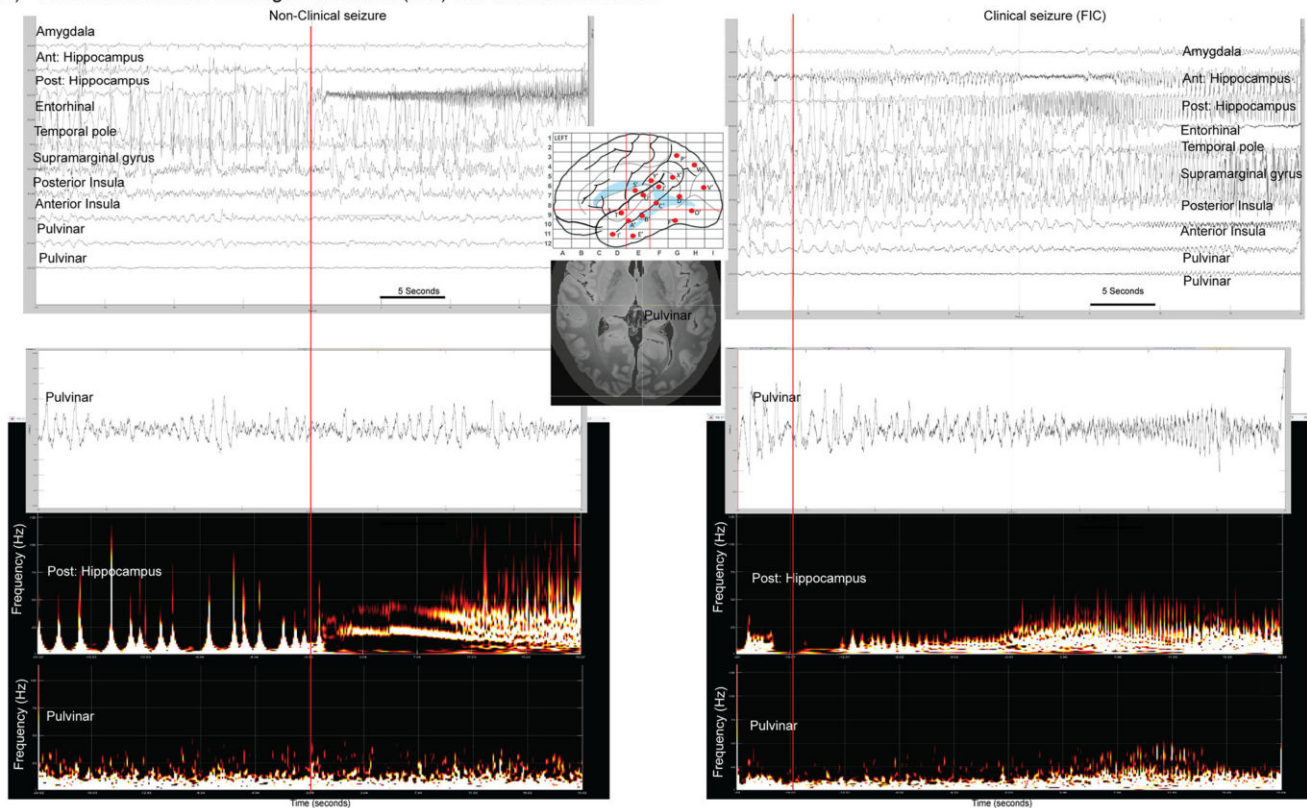
A critical insight emerged from the subset of patients who exhibited both CS and NCS, which provided a unique opportunity to examine state-dependent variability within a shared anatomical network. In these individuals, thalamo-cortical synchrony varied across seizures despite stable electrode coverage, demonstrating that clinical expression is not a fixed property of network anatomy but reflects dynamic network engagement. Within this shared network context, clinically expressive seizures were characterized by stronger thalamo-cortical coupling, within the first 20 s of ictal activity, than NCS, independent of total seizure duration. Although thalamic coupling during CS tended to be greater with the SOZ than with propagated regions, this effect was modest, suggesting relatively greater SOZ engagement rather than definitive selective anchoring. Even within the same individual and with comparable onset features, thalamic synchrony was prominent during CS and attenuated during NCS, supporting a state-dependent model of thalamo-cortical network engagement rather than nonspecific propagation or fixed anatomical pathways.

Recent work has shown that seizure onset characteristics, such as spatial extent or dominant frequency, influence the timing of thalamic recruitment<sup>35</sup>. Our results are broadly consistent with this framework but extend it by demonstrating that early thalamic engagement is contingent on clinical expression rather than onset features alone. In our cohort, both mesial and lateral temporal seizures exhibited early thalamic involvement only when seizures became clinically manifest, suggesting that thalamic recruitment reflects behavioral expression rather than propagation mechanics per se. In this framework, thalamo-cortical spectral synchrony emerges as a network-level correlate of seizure semiology, capturing functional engagement beyond seizure onset patterns or spatial spread.

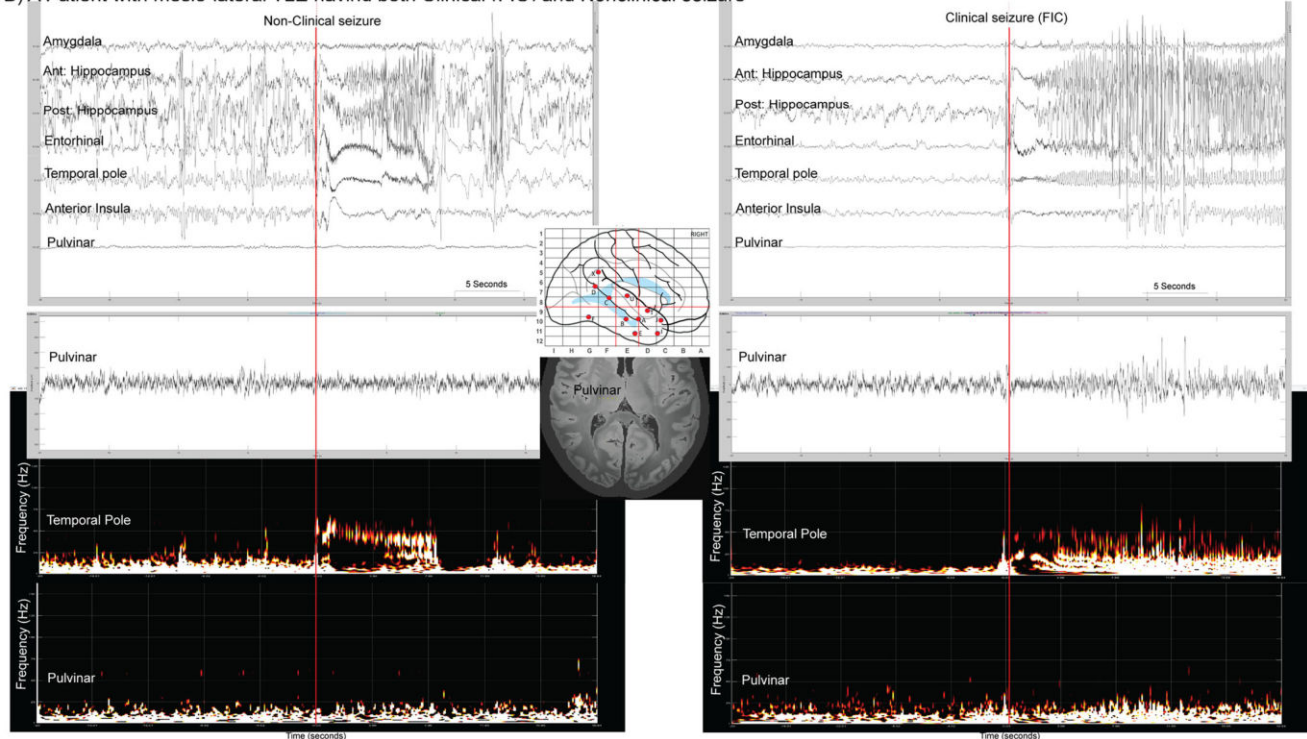
From a translational perspective, this framework is consistent with emerging neuromodulatory approaches targeting thalamic circuits. Early-phase studies of anterior thalamic interventions, including focused ultrasound ablation of the anterior nucleus of the thalamus, have demonstrated feasibility, safety, and substantial seizure reduction in small pilot cohorts<sup>36</sup>, supporting further investigation of thalamic pathways as potential modulators of clinically expressive seizures. Importantly, the absence of NCS in patients should not be interpreted as evidence of fixed network states; rather, it likely reflects inter-individual variability in the range of network configurations sampled during monitoring. This heterogeneity highlights the importance of considering seizure semiology and network state when interpreting thalamic involvement, particularly for neuromodulatory strategies that aim to influence pathological network dynamics rather than eliminate seizure generation outright.

Over the past several decades, SEEG has fundamentally reshaped our understanding of epilepsy, shifting the paradigm from a focal disorder localized to discrete cortical regions to a dynamic network disease involving both cortical and subcortical structures, particularly the thalamus<sup>5,7</sup>. Although subcortical involvement is a known mechanistic process in generalized epilepsy<sup>37</sup>, its role in focal epilepsy, particularly DR-TLE, continues to evolve. Increasing attention has concentrated on specific thalamic subregions, such as the Pul and the ANT, both of which have been implicated in TLE pathophysiology and seizure propagation<sup>9–11</sup>. Visual SEEG analyses have suggested heterogeneous recruitment across thalamic nuclei, including earlier or more prominent pulvinar involvement in some patients<sup>11,38</sup>; however, visual inspection alone is insufficient to reliably characterize thalamic

## A) A Patient with mTLE having both Clinical (FIC) and Nonclinical seizure



## B) A Patient with mesio-lateral TLE having both Clinical (FIC) and Nonclinical seizure



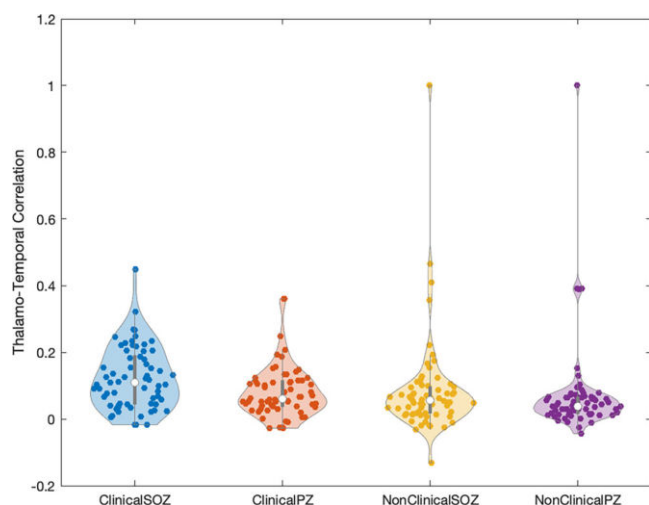
engagement given the complexity and variability of ictal signals, limitations also encountered in our dataset.

Using quantitative spectral correlation analysis, our findings extend prior work<sup>10,11,13,15,16,38</sup> by demonstrating that thalamo-cortical synchrony generalizes across temporal epilepsy subtypes, vigilance states, and thalamic nuclei, rather than being restricted to specific seizure or epilepsy subtypes. This observation aligns with a prior

report<sup>39</sup> showing preserved seizure network organization across sleep-wake states and supports the view that thalamic involvement accompanies clinically expressive seizures within a distributed epileptic network. Previous studies have reported increased thalamo-cortical synchrony or thalamic power during seizures associated with impaired awareness<sup>10,15,40</sup> or secondary generalization<sup>15</sup>, although these studies varied in thalamic targets<sup>10,15,40,41</sup> and did not systematically compare

**Fig. 2 | Representative cases of pulvinar–temporal spectral synchrony in patients with pulvinar SEEG coverage showing pulvinar–temporal spectral correlation across seizure types and onset regions. A, B** Patient-level examples illustrating thalamic involvement differences in seizure times series followed by corresponding time frequency analysis of the same SEEG time series between two seizure types (clinical and non-clinical seizures) in the same patients. **A** In a patient with mesial temporal lobe epilepsy (with Engel 1A outcome with 51 months follow up after temporal lobectomy), the pulvinar exhibits strong thalamo–temporal spectral correlation (with focus time series of the pulvinar SEEG contact U1-2) during a clinical seizure (right panel) compared to the non-clinical seizure (left

panel), closely mirroring hippocampal seizure onset dynamics seen in the clinical seizure but not in the non-clinical seizures even with fast onset in cortical regions. **B** In a patient with lateral temporal epilepsy (with Engel 1D outcome with 51 months follow up after temporal lobe lobectomy), the non-clinical seizure (right panel) shows minimal pulvinar involvement, despite a broader cortical onset. In contrast, the clinical seizure (left panel) displays strong pulvinar engagement (with focus time series of the pulvinar SEEG contact U1-2), with time–frequency patterns that closely align with cortical seizure onset dynamics. Time zero indicates seizure onset and highlighted with red solid line.



**Fig. 3 | Thalamo-cortical synchrony in seizure onset zone (SOZ) and propagation zones (PZ) during clinical and non-clinical seizures.** Thalamo–cortical synchrony was compared between the seizure onset zone (SOZ) and propagation zone (PZ) within the first 20 seconds of ictal activity in patients exhibiting both clinical seizures (CS) and non-clinical seizures (NCS; total number of patient ( $n$ ) = 20; total number of CS = 65 seizures, total number of NCS = 68 seizures). During NCS, thalamo–cortical synchrony did not differ between SOZ and PZ regions (Wilcoxon signed-rank test,  $p = 0.1717$ ,  $\delta = 0.14$ ). In contrast, during CS, synchrony differed significantly between SOZ and PZ (Wilcoxon signed-rank test,  $p = 0.0096$ ,  $\delta = 0.26$ ), although the effect size was small. Violin plots represent kernel density estimates of the data distribution, with width corresponding to the relative data density and extending to the minimum and maximum values. The y-axis represents synchrony values, defined as spectral correlation coefficients (unitless). The overlaid white circle indicates the median, and the dark line represents the interquartile range. All statistical tests were two-sided. Bonferroni correction was applied for multiple comparisons where appropriate. Effect sizes are reported as Cliff's  $\delta$ . Effect sizes were classified as negligible ( $\delta < 0.147$ ), small ( $0.147–0.33$ ), medium ( $0.33–0.474$ ), or large ( $\geq 0.474$ ). Source data is provided.

CS and NCS within individuals. Other work has reported that preictal functional connectivity variability within the cortical SOZ was greater for CS than NCS in TLE<sup>27</sup>, albeit without thalamic recordings. Supporting a potential mechanistic role, a proof-of-concept stimulation of the medial pulvinar during hippocampal seizures has been shown to improve consciousness, possibly suggesting that modulation of thalamic activity can influence behavioral expression<sup>42</sup>.

Building on this literature, our results demonstrate that thalamo–temporal spectral synchrony within the first 20 s of ictal activity reflects a state-dependent network signature of clinical seizure expression across seizure subtypes, epilepsy subtypes, vigilance states, and thalamic nuclei. The absence of synchrony differences across seizure subtypes or epilepsy subtypes reinforces its association with clinical seizure state rather than specific semiological categories. Together, these findings position thalamo–temporal spectral synchrony as a physiological correlate of seizure semiology that complements conventional markers such as cortical onset patterns or EEG morphology.

Thalamic involvement has been proposed as a prognostic marker in TLE, with imaging studies linking pulvinar atrophy and disrupted thalamo-temporal connectivity to poor surgical outcomes, even after adequate cortical resection<sup>2,43</sup>. Some reports have associated higher thalamic epileptogenicity ( $EI > 0.3$ )<sup>15</sup> or early thalamic synchronization<sup>10</sup> with poor surgical failure, while others found that delayed thalamic recruitment predicted poor surgical outcomes<sup>35</sup>. These discrepancies raise questions about whether thalamic involvement is causative, compensatory, or epiphenomenal. Our findings provide a complementary perspective, showing that thalamic spectral synchrony was strongly associated with seizure semiology but not with surgical outcome. Coupling strength was significantly higher in CS than NCS, regardless of postoperative seizure freedom. This suggests that thalamo-cortical synchrony reflects downstream network engagement rather than the primary epileptogenic substrate targeted by resection. Focusing on synchrony strength, as opposed to timing alone<sup>10,35</sup>, may help reconcile previous discrepancies and better capture the functional relevance of thalamic dynamics in TLE.

In summary, our findings identify thalamo–temporal spectral synchrony as a robust physiological marker of clinical seizure expression in DR-TLE. Within the sampled network, synchrony reliably distinguished clinical from non-clinical seizures and was independent of seizure onset zone or surgical outcome. By prioritizing seizure semiology and network state, this work supports a network-based framework in which thalamo–cortical dynamics accompany the translation of electrographic seizures into clinical symptoms, while remaining agnostic regarding causality. Future prospective studies will be required to determine whether these network signatures are permissive, epiphenomenal, or modifiable, and how they should be interpreted in the context of neuromodulatory interventions.

## Limitations and future directions

Although our study provides important insights, several limitations should be acknowledged. First, electrode implantation was clinically determined and therefore heterogeneous, and not all patients had coverage of both the pulvinar and anterior thalamic group, limiting subregional comparisons. Only a subset of patients (20 of 62) exhibited both CS and NCS, constraining within-subject analyses; nonetheless, paired analyses within this group consistently demonstrated reduced thalamo–cortical synchrony during NCS.

Second, our time–frequency correlation approach quantified functional synchrony but did not assess causality or directionality. Accordingly, thalamo–cortical synchrony should be interpreted as a network-level correlate of clinical seizure expression rather than evidence of a driving or initiating role of the thalamus. Future studies incorporating causal or directional metrics together with prospective designs and higher seizure sampling per patient will be required to clarify underlying mechanisms. Importantly, robust directional inference will require prospective designs with precise time-locking of electrophysiological changes to behavioral assessment, higher seizure counts per patient, and longer ictal coverage than was available in the present study. In addition, although prior studies have emphasized the prognostic relevance of thalamic propagation timing, our study was not designed to systematically evaluate propagation latency as a

**Table 4 | Linear mixed-effects model predicting thalamo-temporal correlation values, adjusted for, seizure type, thalamic region, epilepsy subtype, seizure freedom, vigilance state, and seizure duration, with subject-level random intercepts in 62 patients**

| Predictor                                          | $\beta$ (Estimate)    | SE                   | 95% CI                                        | t     | p-value  |
|----------------------------------------------------|-----------------------|----------------------|-----------------------------------------------|-------|----------|
| Intercept                                          | 0.320                 | 0.048                | 0.226 to 0.415                                | 6.69  | <0.001   |
| Seizure type (NCS vs CS)                           | -0.074                | 0.027                | -0.128 to -0.020                              | -2.72 | 0.0069** |
| Thalamic region (ATG vs Pul)                       | 0.007                 | 0.027                | -0.047 to 0.060                               | 0.24  | 0.809    |
| Epilepsy subtype (lateral vs mesial)               | -0.079                | 0.044                | -0.165 to 0.007                               | -1.80 | 0.072    |
| Epilepsy subtype (mesiolateral vs mesial)          | 0.001                 | 0.054                | -0.105 to 0.108                               | 0.02  | 0.982    |
| Seizure freedom (seizure-free vs non-seizure free) | -0.065                | 0.052                | -0.167 to 0.037                               | -1.26 | 0.209    |
| Vigilance state (asleep vs awake)                  | -0.015                | 0.022                | -0.058 to 0.029                               | -0.68 | 0.500    |
| Seizure duration (seconds)                         | $-6.5 \times 10^{-6}$ | $1.1 \times 10^{-5}$ | $-2.8 \times 10^{-5}$ to $1.5 \times 10^{-5}$ | -0.59 | 0.556    |

Fixed-effects coefficients ( $\beta$ ), standard errors (SE), 95% confidence intervals (CI), and *p*-values are reported. Seizure type was coded as 0 = clinical and 1 = non-clinical; thalamic region as 0 = pulvinar and 1 = anterior thalamic group (ATG); epilepsy subtype as 1 = mesial, 2 = lateral, and 3 = mesiolateral; clinical subtype as 0 = focal perceptual cognitive (FPC), 1 = focal impaired consciousness (FIC), and 2 = focal to bilateral tonic-clonic (FBTC); seizure freedom as 0 = not seizure-free and 1 = seizure-free; and vigilance state as 0 = awake and 1 = asleep. Subject was included as a random intercept to account for repeated seizures within individuals.  
Random effects: Subject-level random intercept SD = 0.127 (95% CI 0.100–0.162).  
Residual SD = 0.163 (95% CI 0.150–0.176).  
Model fit: AIC = -167.78; BIC = -125.44; Log-likelihood = 94.89.  
Ordinary  $R^2$  = 0.454; Adjusted  $R^2$  = 0.441.  
Significant *p*-values (*p* < 0.05) are indicated by\*\*.

predictor of surgical outcome, which therefore remains an important area for future investigation.

Third, our analysis focused on the first 20 s of ictal electrophysiological activity, which may limit interpretation of how clinical semiology evolves, particularly for motor features or progression to FBTC seizures. In addition, behavioral testing used to classify seizures as clinical or non-clinical was not uniformly time-locked to electrographic seizure onset, as onset was identified retrospectively from SEEG recordings. Future studies should examine the full duration of seizures, including ictal evolution, to better characterize how thalamo-cortical dynamics shape the emergence and progression of clinical symptoms. This approach may help differentiate synchrony patterns among distinct clinical seizure subtypes, such as FPC, FIC, and FBTC.

Formal sleep staging according to American Academy of Sleep Medicine criteria<sup>44</sup> was not possible due to the absence of EOG and EMG channels, which are necessary to reliably distinguish wakefulness from REM sleep. To mitigate this limitation, synchronized video review was used to classify seizures as occurring during sleep or wakefulness based on behavioral correlates. Importantly, the absence of overt clinical symptoms during non-clinical seizures should not be interpreted as absence of functional impact. Recurrent non-clinical seizures may still contribute to cumulative network or cognitive effects, which will require longitudinal investigation. Despite these limitations, the consistency of our findings supports thalamo-cortical synchrony as a marker of symptomatogenic network engagement in focal DR-TLE.

Methods

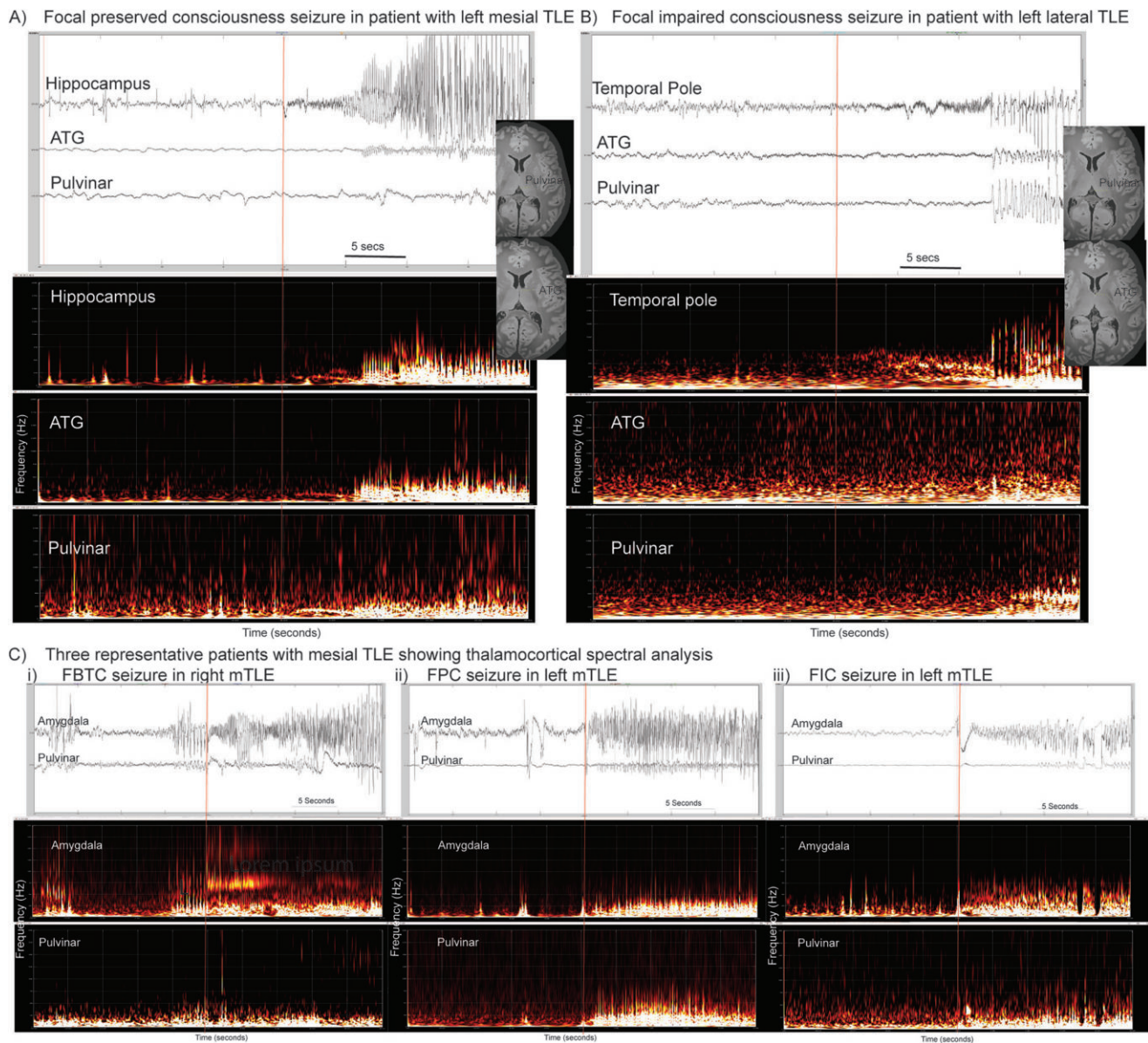
**Patient selection, demographic data, and seizure classification**  
The study was approved by the institutional review board at the University of Pittsburgh (January 2020 to June 2025) and the Duke University Hospital (June 2023 to June 2025). The requirement for informed consent was waived by both institutional review boards because this study used retrospectively collected data obtained as part of routine clinical care. Participants did not receive compensation for participation. Consecutive patients ( $\geq 16$  years) with focal DR-TLE from both centers were included if intracranial exploration covered temporal and thalamic regions with at least one SEEG electrode contact in ATG, Pul, or both. Only patients who experienced at least one spontaneous habitual seizure during SEEG monitoring were eligible. Patients whose EZ extended beyond or was outside the temporal lobe were excluded to maintain a homogeneous temporal lobe epilepsy cohort for network-level analyses (Supplementary Fig. 4).

Demographic and clinical data, including age, biological sex, epilepsy onset, duration, MRI findings, SOZ, electrode placement, outcome, and follow-up duration, were collected from medical records. Biological sex was determined based on medical records. Gender identity was not assessed. Sex-based analyses were not performed because the study was not designed or powered to assess sex-specific effects. Race, ethnicity, and other socially relevant demographic variables were not systematically collected or analyzed in this study.

Anatomical and electrophysiological data on each patient’s SOZ were obtained from the multidisciplinary patient management conferences held after SEEG evaluation. Two experienced epileptologists (T.A., T.T.) independently reviewed and confirmed the SOZ localization. Additionally, all recorded seizures were retrospectively reviewed and classified as clinical or non-clinical by the same two epileptologists (T.A., T.T.). In cases of disagreement, seizures were jointly re-reviewed, and if consensus could not be reached, those seizures were excluded.

Seizures were classified into two seizure types (NCS and CS). Seizures were defined as non-clinical when no observable behavioral changes and no patient-reported symptoms were identified on synchronized video review. Data were collected as part of routine clinical care, and bedside behavioral testing was performed by trained clinical staff as soon as seizures were recognized. Testing included verbal commands (e.g., orientation questions or name recall), simple motor tasks (e.g., hand squeeze or arm raise on request), and direct questioning regarding subjective symptoms and awareness, including verbal report or button press when prompted. Because electrographic seizure onset was determined retrospectively from SEEG recordings, the timing of behavioral testing relative to EEG onset varied across seizures. Seizures were classified as non-clinical only when testing performed during the ictal or immediate postictal period revealed neither subjective symptoms nor observable behavioral changes. Seizures without behavioral testing or with indeterminate findings on video review were excluded.

Seizures were *clinical* if patients reported subjective symptoms, or observable signs were present and further categorized using the updated ILAE classification<sup>45</sup> as FPC, FIC, or FBTC (seizure subtypes). FPC was defined as seizures with retained awareness and responsiveness; FIC as seizures with altered awareness or responsiveness; and FBTC as focal seizures that secondarily generalized to bilateral tonic-clonic activity. A maximum of four seizures per category (FPC, FIC, FBTC, and non-clinical) were analyzed per patient. For patients exhibiting multiple seizure types, up to four seizures from each type



**Fig. 4 | Representative cases of thalamo-temporal spectral synchrony in patients with both pulvinar and ATG SEEG coverage.** **A, B** Patient-level examples illustrating Time-frequency correlation analysis from two patients with SEEG contacts in both the pulvinar (Pul) and anterior thalamic group (ATG), illustrating distinct thalamo-cortical synchrony patterns during clinical seizures. **A** Patient with mesial temporal lobe epilepsy showing strong thalamo-temporal spectral synchrony in both Pul and ATG during a clinical seizure. The hippocampus exhibits low-voltage fast activity at seizure onset (time zero), with near-perfect correlation between hippocampal seizure onset zone electrode contacts and both thalamic

regions. **B** Patient with lateral temporal lobe epilepsy demonstrating weaker thalamo-temporal correlation during a clinical seizure. Seizure activity begins with fast intrusion in the temporal pole around 5 s, evolving into rhythmic delta/theta activity by 13 s, with involvement of Pul and ATG. **C** Three representative patients with mesial temporal lobe epilepsy and clinical seizures. Time-frequency analysis shows that pulvinar SEEG contacts display spectral patterns that closely track and align with cortical seizure onset activity, indicating temporally and spectrally coordinated thalamo-cortical involvement. Time zero indicates seizure onset and highlighted with red solid line.

were included. Epilepsy subtypes were classified based on seizure onset zone. mTLE was defined as seizures arising from the mesial limbic network, including the hippocampus, amygdala, entorhinal cortex, and mesial temporal pole, defined anatomically as cortex medial to the collateral sulcus. Mesio-lateral TLE involved both mesial and lateral temporal regions. Lateral TLE was defined as seizures originating exclusively from the lateral or basal temporal neocortex, including fusiform and inferior-temporal regions lateral to the collateral sulcus, without evidence of mesial involvement<sup>46</sup>.

The PZ was defined as all other cortical regions outside the SOZ and thalamic regions that demonstrated a clear ictal pattern change within the first 20 s following seizure onset. Consistent with

established visual SEEG criteria<sup>47</sup>, ictal propagation was identified by the emergence of sustained rhythmic activity, evolving frequency content, or a clear increase in signal amplitude consistent with seizure spread. The 20-s window was chosen a priori to ensure consistency with the thalamo-cortical synchrony analyses and to focus on early ictal network organization. Cortical regions without an ictal pattern change within this time window were not included in the PZ. For SOZ and PZ analyses, the number of bipolar SEEG channel pairs contributing to each region was recorded for each subject to characterize relative spatial sampling.

For patients who underwent resective surgery or neurostimulation, follow-up duration was calculated from the date of surgery to the

most recent clinic visit. Seizure outcomes were classified using the Engel system<sup>48</sup>. Patients were considered SF only if they achieved Engel Class IA at 12 months or later following surgery, based on the most recent available follow-up beyond the 1-year time point. Patients without at least one year of follow-up were excluded from outcome analyses.

### Electrode localization

Electrode contacts were localized by co-registering post-implantation thin-sliced CT with preoperative 1 mm T1-weighted MRI using Statistical Parametric Mapping<sup>49</sup> (SPM12, revision 7765, Wellcome Centre for Human Neuroimaging, University College London, UK) (Fig. 5A). Electrode positions were mapped in subject space using a 0.4 mm radius sphere and the Automated Anatomical Labeling atlas version 3 (AAL3)<sup>50</sup>. T1 MRIs were then nonlinearly registered to the ICBM2023b MNI template<sup>51</sup> to obtain MNI coordinates for all the implanted electrodes. Pulvinar group contacts included any subnucleus within the pulvinar complex (e.g., PuA, PuM, PuL, PuI). ATG contacts included those labeled as ventral anterior (VA), anteroventral (AV), or ventral lateral anterior (VLa) per AAL3 (Supplementary Table 20). Figure 5B shows electrode trajectories from all patients overlaid on the ICBM2023b cortical surfaces, with pulvinar and ATG contacts visualized using AAL3 surface-rendered thalamic segmentation (Fig. 5C) and ultra-high resolution 7 Tesla ex vivo brain scans in MNI space (Fig. 5D)<sup>52</sup>. For cortical regions, only SEEG contacts localized to cortical or subcortical gray matter regions based on the AAL3 atlas were retained for analysis; contacts assigned to white matter were excluded (Supplementary Tables 21, 22).

### Data selection, time-frequency decomposition, synchrony correlation analysis and epileptogenicity index

SEEG signals were sampled at 2048 Hz at both institutions. For each seizure, 40 s of SEEG data were extracted, comprising 20 s before and 20 s after electrographic seizure onset (Fig. 5A). Additionally, a 40-s baseline epoch was obtained at least two minutes prior to seizure onset. Data were preprocessed in Brainstorm version 3.26<sup>53</sup> and imported to the Epileptogenic Zone Fingerprint software<sup>54</sup> for the following TF analyses. Both ictal and baseline TF decomposition was performed using the Morlet wavelets (1–200 Hz, 1 Hz steps; 3-s time resolution). Seizure TF maps were normalized against the corresponding baseline maps across all frequencies, following our previously published methodology<sup>55,56</sup>. All analyses were performed using bipolar montages.

To reduce artifacts, a complex independent component analysis was applied to the TF plots to identify and remove artifacts common across channels (e.g., muscle activity). Channels with channel-specific artifacts, including those located outside the brain or within the ventricular system, were excluded. Seizures containing artifacts in SOZ or thalamic contacts were excluded. In patients with bilateral thalamic implantation, analyses were restricted to ipsilateral thalamic contacts and ipsilateral mesial temporal SOZ electrodes, because only a small number of patients had bilateral thalamic coverage, precluding reliable and unbiased contralateral analyses.

A Spectral Synchrony Correlation was applied to quantify frequency-specific thalamo-cortical SOZ coupling, i.e., thalamo-cortical synchrony. Synchrony was computed using SEEG data from the first 20 s following electrographic seizure onset. To minimize confounding by seizure duration, late propagation, or termination dynamics, all thalamo-cortical synchrony analyses were restricted to the first 20 s following electrographic seizure onset, consistent with prior time-frequency-based seizure fingerprinting frameworks<sup>55,56</sup>. TF decomposition was performed using a continuous wavelet transform, and Pearson correlation coefficients were calculated between normalized power envelopes across sliding windows, generating frequency-correlation profiles.

All thalamo-temporal synchrony analyses were conducted at the seizure level, with each seizure contributing a single median synchrony value computed across all SOZ–thalamus bipolar pairs (Fig. 5A). For each anatomical region, only one representative bipolar pair was included per seizure to minimize bias from unequal electrode density across patients. The number of bipolar SOZ–thalamus pairs varied across patients depending on individual implantation schemes. Summarizing synchrony using the median per seizure prevented over-weighting patients with denser electrode coverage and accounted for unequal numbers of bipolar pairs across subjects. A seizure-level analytic approach was used because approximately one third of the patients exhibited both CS and NCS ( $n = 20$ ), and some had electrodes sampling multiple thalamic nuclei ( $n = 11$ ). Repeated seizures within individuals were addressed using mixed-effects modeling, with complementary within-subject paired analyses performed in patients who exhibited both CS and NCS.

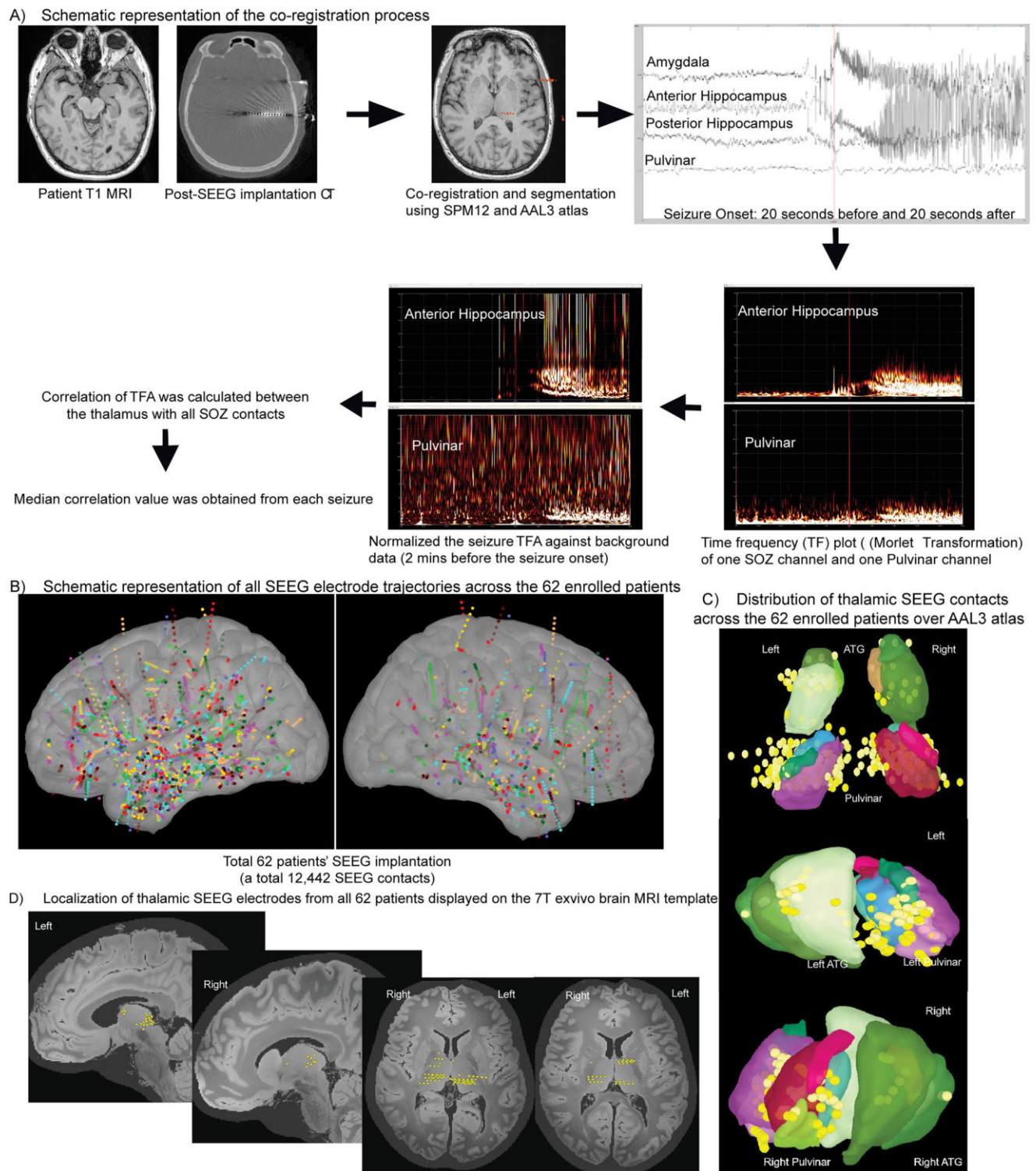
Vigilance state was classified using visual inspection of SEEG tracings and synchronized video review. Wakefulness was defined by visually low delta power on SEEG together with behavioral signs of alertness on video, including eyes open, spontaneous movements, purposeful interaction with the environment (e.g., speaking or responding to staff), or active engagement with electronic devices at seizure onset. Sleep was inferred from visually increased delta activity on SEEG in conjunction with video evidence of sleep.

In patients who underwent resection, one habitual stereotypic seizure, preferably clinical, per patient was additionally used to compute the epileptogenicity index (EI) following Bartolomei et al.<sup>57</sup>, using a 20-s window from ictal onset, to assess thalamic involvement in seizure initiation. By measuring the abruptness and magnitude of ictal power changes relative to interictal baseline, EI offers a standardized, quantitative assessment of a structure's role in the early propagation of epileptic activity. Applying an EI threshold of  $>0.3^{15}$ , as previously suggested for the pulvinar, allowed classification of patients into high- and low-EI groups, enabling direct comparison with postoperative seizure outcomes. EI was not applied to define cortical SOZ or PZ.

### Statistical analysis

Due to non-normal distribution of thalamo-temporal correlation values, non-parametric tests were used. Exact sample sizes (numbers of patients and seizures) for each comparison were reported in the Results and corresponding tables and figure legends. Analyses were performed at the seizure level; non-independence arising from repeated seizures within patients and occasional sampling of multiple thalamic nuclei was addressed using within-subject analyses and linear mixed-effects modeling. All statistical tests were two-sided.

Group-level comparisons between CS and NCS were performed using the Wilcoxon rank-sum (Mann–Whitney U) test, both overall and after stratification by vigilance state (wakefulness vs. sleep). The same test was used to compare SF (Engel IA) and NSF (Engel IB–IV) outcome groups. For seizure subtypes (FPC, FIC, FBTC), the Kruskal–Wallis test was followed by Bonferroni-adjusted pairwise tests ( $p < 0.0167$ ). For combined outcome/semiology groups (SF-CS, SF-NCS, NSF-CS, NSF-NCS), six comparisons were tested with a threshold of  $p < 0.0083$ . The same threshold was applied to intra-subject comparisons involving thalamic region and seizure type (Pul-CS, ATG-CS, Pul-NCS, ATG-NCS) and outcome/semiology groups (SF-CS, SF-NCS, NSF-CS, NSF-NCS), and SOZ/PZ groups (CS-SOZ, CS-PZ, NCS-SOZ, and NCS-PZ). For comparisons among clinical seizure correlations between SOZ–thalamus, PZ–thalamus, and SOZ–PZ, Bonferroni-adjusted pairwise tests ( $p < 0.0167$ ) were applied. Effect size was estimated using Cliff's delta ( $\delta$ ). Effect sizes were classified as negligible ( $\delta < 0.147$ ), small ( $0.147–0.33$ ), medium ( $0.33–0.474$ ), or large ( $\geq 0.474$ ). In patients who exhibited both CS and NCS, with identical SEEG implantation, within-subject paired comparisons were performed using the Wilcoxon



**Fig. 5 | Thalamic SEEG electrode localization and seizure-related cortico-thalamic correlation analysis framework.** **A** Schematic representation of the co-registration process, in which each patient's pre-implantation T1-weighted MRI (1 mm resolution) was co-registered with the post-implantation MRI or CT to localize electrode contacts within the thalamus. Thalamic contacts in the pulvinar (Pul) and anterior thalamic group (ATG) were identified using the AAL3 atlas. For each seizure, 40 s of SEEG data (20 s before and after seizure onset) were extracted and transformed into time-frequency representations (TFA) using bipolar

derivations. Seizure TFA was normalized to baseline (pre-ictal) TFA, and correlation analyses were performed between the thalamic contacts and all seizure onset zone (SOZ) contacts. The median correlation value per seizure was then computed.

**B** Schematic showing the SEEG electrode trajectories for all 62 implanted patients. **C** AAL3 thalamic atlas<sup>30</sup> overlay showing the location, divided into ATG (ventral anterior (VA), anteroventral (AV), or ventral lateral anterior (VLa)) and Pulvinar groups (Pul\_A, Pul\_Med, Pul\_Inf, Pul\_Lat). **D** Localization of thalamic electrodes from all 62 patients displayed on the 7 T MRI ex vivo brain MNI template<sup>32</sup>.

signed-rank test. To account for unequal seizure counts, one CS and one NCS were randomly selected per patient to ensure balanced within-subject comparisons and minimize bias from unequal sampling, and paired differences were visualized using paired box plots.

To account for clustering of multiple seizures within individuals, linear mixed-effects models were used to assess independent predictors of thalamo-temporal coupling. Seizure type (clinical vs. non-clinical) was specified as the primary fixed effect, with thalamic region, TLE subtype, seizure duration, vigilance state, and surgical outcome included as covariates. In patients who had both CS and NCS, PZ-thalamus correlation was additionally included as a covariate in the models. Subject was included as a random intercept to model within-subject correlation across seizures. Model inference focused on fixed-effect estimates and their statistical significance. Model fit was evaluated using likelihood-based criteria (AIC/BIC), and when applicable, marginal and conditional  $R^2$  values were computed to estimate variance explained by fixed effects alone and by the full model, respectively. Analyses were conducted in MATLAB (version R2023b, The MathWorks Inc., Natick, MA, USA).

### Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

### Data availability

Source data supporting the main findings of this study are provided with this paper. The intracranial EEG data and associated clinical metadata are not publicly available due to patient privacy considerations and institutional review board (IRB) restrictions governing the use of retrospectively collected clinical data. Access to de-identified data may be granted to qualified researchers for non-commercial academic purposes, subject to IRB approval and execution of a data use agreement. Data sharing is subject to institutional policies at the University of Pittsburgh and Duke University. The raw intracranial EEG data are protected and are not publicly available due to data privacy regulations. The processed data supporting the findings of this study are provided in the Source Data file. Requests for access should be directed to the corresponding author. Requests will be reviewed within 4–6 weeks, and access will be provided for a defined period in accordance with institutional policies. The code used for time–frequency analysis in this study is publicly available as the Epileptogenic Zone Fingerprint (EFZ) framework at [https://silencer1127.github.io/software/EZ\\_Fingerprint/efz\\_main](https://silencer1127.github.io/software/EZ_Fingerprint/efz_main). Reference Source data are provided with this paper.

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## Author contributions

Thandar Aung (T.A.) contributed to the conception and design of the study, data analysis, data interpretation, and drafting of the manuscript. Jian Li (J.L.), Prachi Parikh (P.P.), Derek Southwell (D.S.), Muhammad Zafar (M.Z.), Tipakorn Tummark (T.T.), and Chandana Belly (C.B.) contributed to data analysis, interpretation, and data collection. John Thomas (J.T.) and Kassem Jaber (K.J.) contributed to data collection. Patrick Chauvel (P.C.), Birgit Frauscher (B.F.), and Jorge Gonzalez-Martinez (J.G.M.) contributed to study conception and design and critically revised the manuscript. All authors contributed to data interpretation, revised the manuscript for important intellectual content, approved the final version of the manuscript, and agreed to be accountable for the work.

## Competing interests

D.S. reports consulting relationships with NeuroOne, NeuroPace, and Alpha Omega, and J.G.M. serves as a consultant for DIXI Medical. These activities are unrelated to the present study. All other authors declare no competing interests.

## Additional information

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