Neurotherapeutics 23 (2026) e00967

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics

Current Perspectives

Corticothalamic loops and cellular networks: Implications for thalamic neuromodulation in epilepsy☆

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ARTICLE INFO

Keywords:
Epilepsy
Thalamus
Seizure propagation
Thalamocortical networks

ABSTRACT

Thalamic neuromodulation has emerged as a promising therapy to reduce seizures in patients with drug-resistant epilepsy who are not candidates for resective or ablative surgical treatments. This advance creates therapeutic opportunities for patients with seizure foci that are generalized, poorly localized, multifocal, or in eloquent cortex. However, optimal treatment requires improved understanding of the thalamocortical circuits and cellular mechanisms that support seizure initiation, propagation, and termination. With its dense, nucleus-specific reciprocal connectivity with cortical and limbic regions and intrinsic oscillatory properties, the thalamus is well-constructed and well-positioned to influence epileptic activity. Importantly, distinct thalamic nuclei exhibit differing engagement depending on seizure type and propagation patterns. Here, we review current knowledge of thalamocortical anatomy and function, cellular mechanisms of ictal propagation, and the role of the thalamus in generalized and focal seizures, with emphasis on human studies. We further examine how these anatomical and mechanistic insights inform neuromodulatory interventions aimed at improving seizure control.

Introduction

Thalamic neuromodulation has ushered in a new era of treatment for patients with drug-resistant epilepsy, especially in those whose seizure focus is within eloquent cortex or cannot be localized [1]. Deep brain stimulation targeting the anterior nucleus of the thalamus reduces seizure frequency in patients with focal and multifocal epilepsy [2,3], while responsive neuromodulation targeting the centromedian nucleus of the thalamus has shown promising seizure reduction in children and adults with generalized epilepsy [4–6]. These advances underscore the need to reexamine the thalamus' roles in seizure dynamics and the optimal nuclei to target for seizure control across diverse patient populations.

The critical role that the thalamus plays in initiating and maintaining generalized absence seizures has been well characterized for decades [7,8]. Despite early pioneering work that highlighted thalamic involvement during focal seizures in both human [9] and animal studies [10–12], modern models of focal seizures have mainly delineated multiple mechanisms of cortico-cortical spread [13–16]. Subcortical network hubs, however, also play a critical role in seizure propagation [17–19]. The thalamus is uniquely designed and anatomically positioned to function as such a hub, due to its dense reciprocal connectivity with nearly all cortical regions and its intrinsic capacity for oscillatory activity [20].

Indeed, recent human intracranial recordings and neuroimaging studies have demonstrated that thalamic involvement is common during focal seizures [18,21–26], and may mediate secondary generalization and impaired consciousness [17,27,28]. The thalamus has even been shown to be integral to the development and maintenance of seizures in a rodent model of remote cortical stroke [29]. Recent work in humans

This article is part of a special issue on <SI name (fetch from PTS item description)> published in Neurotherapeutics
☆ Invited review: **Neuromodulation in Epilepsy**.
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https://doi.org/10.1016/j.neurot.2026.e00967
Received 10 April 2026; Received in revised form 30 June 2026; Accepted 3 July 2026

highlights that thalamocortical circuits contribute not only to seizures but also cognitive and mood comorbidities in epilepsy [30–32].

Neuromodulatory devices that stimulate specific thalamic nuclei have created both a therapeutic opportunity [2] and imperative to define which corticothalamic and thalamocortical pathways are recruited during seizures, and which nuclei are best positioned to modulate the relevant epileptic network. Because the thalamus is not functionally homogeneous, with distinct nuclei participating in partially overlapping cortical and limbic circuits, thalamic recruitment has been linked to seizure type, cortical onset zone, and propagation pattern [33–35]. In this review, we first outline the structural and functional organization of corticothalamic loops, then consider cellular mechanisms by which ictal activity propagates through those loops. We next review human evidence for nucleus-specific thalamic recruitment during seizures and finally discuss how these observations may inform thalamic neuromodulation strategies.

Corticothalamic and thalamocortical structure

The inputs and outputs of the electrical activity performed across approximately 1800 cm^2 of human cortex are funneled through the ~15 cm^3 thalamus [36,37], resulting in both a dense anatomical network for electrical activity to propagate among and a concentrated target for wide-ranging neuromodulatory impact. The thalamus itself can be broadly separated into different clusters of neuronal cell bodies forming distinct thalamic nuclei. The majority of these function as "relay" nuclei, which produce regional excitatory innervation across broad cortical regions, though with some overlap between nuclei. Because these tracts are comprised of myelinated axons, the latency from thalamus to cortical cell is rapid—on the order of milliseconds [31,38]—and faster than adjacent or local corticocortical spread [39]. These dense and rapid thalamocortical information highways could enable rapid ictal jumps between non-contiguous cortex and rapid generalization.

The most widely adopted modern atlas of human thalamus uses *ex vivo* MRI and histology to identify 26 distinct nuclei [40]. These nuclei and cortical connectivity patterns are organized along a medial-lateral gradient [41]. Connectivity maps can help define the hodological networks through which pathological seizure activity is expected to propagate in non-lesional epilepsy patients (Fig. 1). For example, the anterior nucleus of the thalamus is preferentially connected to limbic regions across the Papez circuit. The centromedian nucleus of the thalamus has dense connections to motor networks across the frontal and sensorimotor cortex. The mediodorsal nucleus strongly innervates prefrontal and orbitofrontal cortex, anterior cingulate, and mesial temporal structures. The medial pulvinar has broad connections across temporo-parieto-occipital cortex, posterior hippocampus, and orbitofrontal cortex. Using non-invasive tractography, the connectivity maps across each thalamic nucleus can be inferred (Supplementary Fig. 1). Importantly, these thalamocortical anatomical networks are phylogenetically conserved and evident by the second trimester in humans [41], and therefore expected to be preserved across most humans. However, they may be macroscopically or microscopically altered in epilepsy

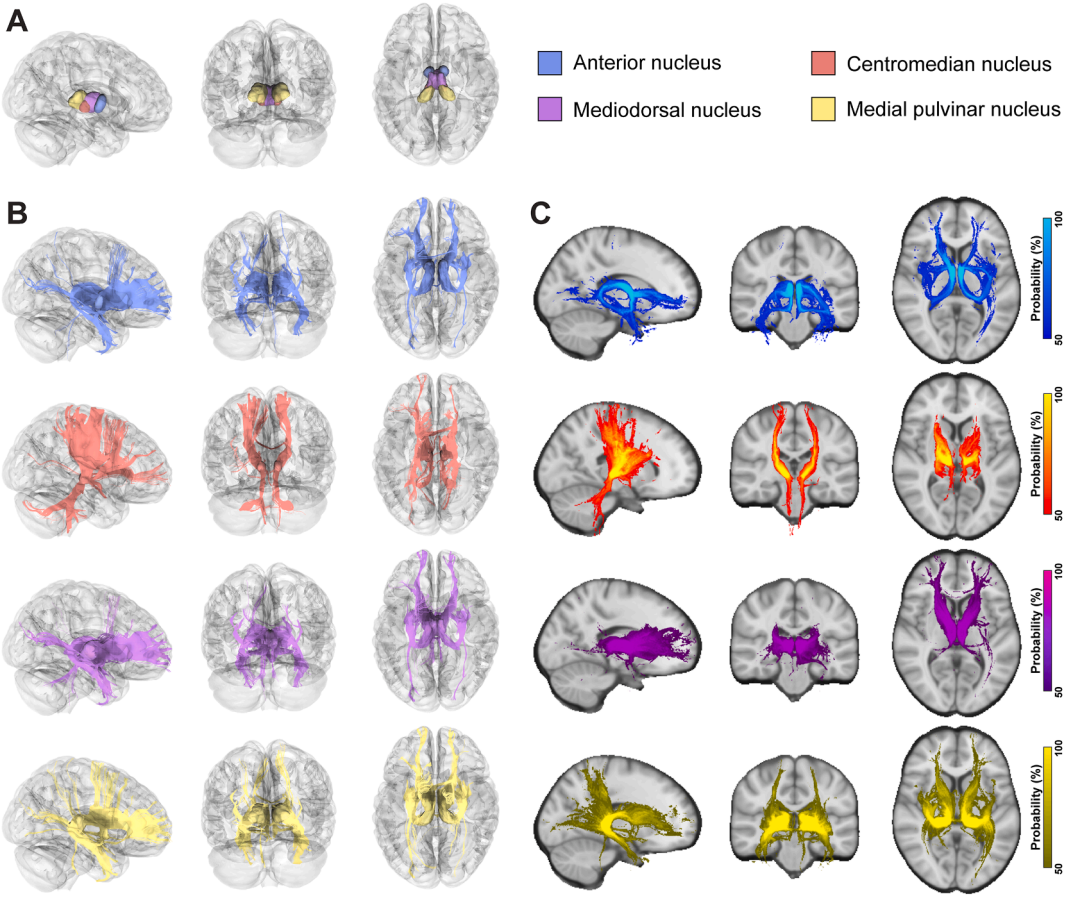

Fig. 1. Regional thalamocortical circuits inferred from probabilistic tractography. (A) Labeled thalamic nuclei detected using a probabilistic atlas based on anatomical definitions (FreeSurfer) in a 10-year-old healthy child. **(B)** Probabilistic diffusion tractography in the same subject as A, computed via seeding 10,000 streamlines from each of the highlighted nuclei, demonstrating varying cortical connectivity patterns for each thalamic nucleus. **(C)** Common thalamocortical connectivity patterns across 5 subjects (ages 7–18 years), including one child with non-lesional focal epilepsy. In each subject, 10,000 streamlines were seeded from each nucleus and voxels containing fewer than 20 streamlines were excluded. The proportion of voxels with streamlines present in at least 3 subjects is shown per nucleus; see colorbar.

patients, particularly those with known malformations of cortical development.

Corticothalamic cellular mechanisms underlying ictal propagation

The thalamus is not merely a routing station for information to and from cortex but also exhibits rich cellular dynamics that can modulate cortical activity (Fig. 2A) [42]. Excitatory hodologic thalamocortical connections arising from each nucleus primarily innervate layer 4 in neocortex (though with some variation across thalamocortical cell types and neocortical regions) and the molecular layer of CA1 in the hippocampus. Reciprocal corticothalamic fibers can be differentiated largely between modulatory feedback fibers, originating in cortical layer 6, and feedforward fibers, originating in cortical layer 5. The former of these, comprised of relatively thinner fibers, regulate thalamic gain, while the latter, with coarser fibers and projections to higher order thalamic relay nuclei, are capable of entraining thalamic firing [43]. At both the cortical and thalamic end of these reciprocal connections, the excitatory neurons also synapse directly onto adjacent and nearby inhibitory interneurons [44–46], providing a mechanism for powerful feedforward inhibition. Importantly, some corticothalamic projections are unique to specific cortical regions, for example layer 5 monosynaptic projections are unique to the frontal cortex in mice [47], highlighting that thalamic activity during seizures could vary greatly depending on cortical origin.

Thalamic relay neurons have intrinsic membrane properties that support rhythmic burst firing and synchronization, via low-threshold calcium currents. Moreover, inhibitory neurons in the reticular thalamus and excitatory thalamocortical neurons synapse onto one another, producing a circuit with a resonant oscillatory output: bursts of activity in reticular thalamus restrain thalamocortical neurons, which fire a volley of action potentials upon release from this restraint, which in turn produces firing in reticular thalamus once more to re-start the cycle [48–50]. Together, these mechanisms allow the thalamus not only to route information but also to take part in both gating cortical activity and producing intrinsic oscillations that entrain cortical regions.

At the network level, ictal propagation is constrained and guided by structural and functional connectivity. Recruitment of local and distant circuits, mediated by cortical laminar organization, short- and long-range white matter tracts, and subcortical circuits—including thalamocortical loops—determine whether seizures remain focal or spread (Fig. 2B) [51–53]. Recent structural and functional connectivity studies have highlighted the thalamus as a central hub within these circuits [54–57], with disrupted maturation of both structural and functional thalamocortical connectivity observed in pediatric epilepsies [58–60]. Within this network, initial seizure spread from a focal origin can occur when excitatory neurons produce intense glutamatergic barrages onto postsynaptic cells, promoting recruitment of these downstream neurons into the ictal discharge [61,62]. Importantly, these postsynaptic cells may be adjacent, such as across cortical columns, or at some distance, as in the case of corticothalamic projections. In corticocortical propagation, excitatory projections similarly synapse onto local interneurons, which, at least transiently, are capable of restraining ictal propagation into the surrounding tissue due to their inhibitory control of the downstream excitatory cells [63–67]. Given that corticothalamic neurons also directly innervate inhibitory interneurons in the thalamus, similar initial feedforward inhibition might also be expected in the thalamus.

Outside of synaptic mechanisms of ictal propagation, ictal propagation via non-synaptic mechanisms becomes increasingly relevant during intense, hypersynchronous firing. Ephaptic interactions, mediated by extracellular electric fields generated during population discharges, can directly modulate neuronal membrane potentials and synchronize firing over short distances, even when synaptic transmission is reduced or blocked [68,69]. In parallel, electrical coupling via gap junctions supports rapid synchronization and may contribute to high-frequency oscillations associated with the ictal core [70,71]. Astrocytic gap junction networks further influence extracellular potassium and glutamate dynamics, indirectly shaping neuronal excitability and the spatial extent of seizure propagation [72,73]. Seizures may spread locally within the thalamus via these mechanisms if thalamic nuclei are successfully recruited into the seizure.

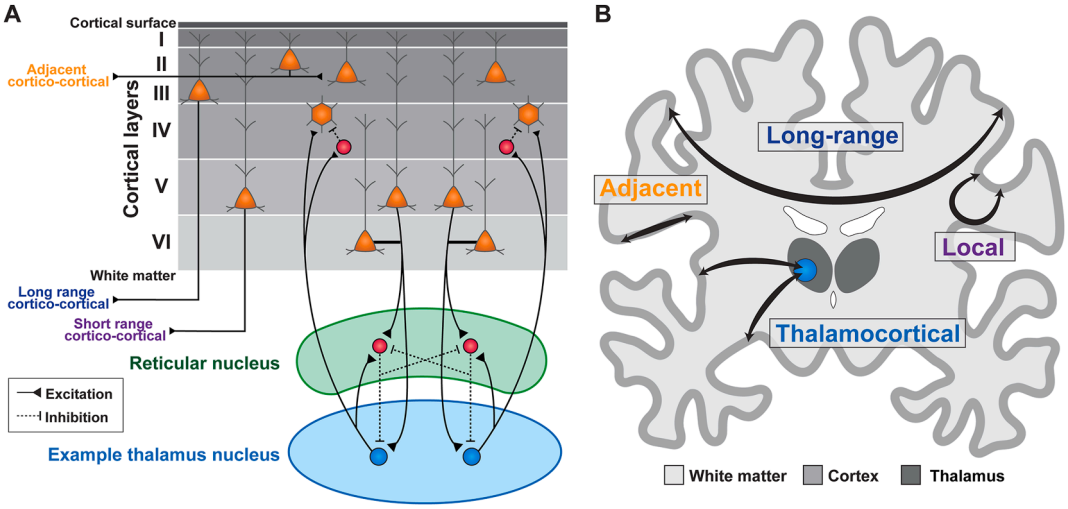

Fig. 2. Schematic of major thalamocortical, corticothalamic, and corticocortical neuronal circuits. (A) Excitatory corticothalamic projections arise from both layer 5 and 6, which provide initial drive and subsequent modulation to the thalamus respectively. Thalamocortical projections in turn primarily target neocortical layer 4. Both thalamocortical and corticothalamic excitatory neurons synapse not only onto excitatory cells, but onto local inhibitory neurons that also innervate the same postsynaptic excitatory cell. In the neocortex these inhibitory neurons target the cell body of the excitatory cell while the thalamocortical cells target the dendrites, resulting in a powerful feedforward inhibition in response to thalamocortical drive. Similarly powerful feedforward inhibition may occur in thalamus due to the targeting of proximal and distal dendrites from the reticular nucleus and neocortex respectively. Simultaneously, a range of corticocortical connections provide innervation between local and distal regions of neocortex. **(B)** The same regional connections highlighted in A, shown at the macroscale. Seizure propagation may occur along or within any of these connections.

The ictal thalamus

The reciprocal and highly interconnected multitude of thalamocortical circuits provide anatomical highways and oscillatory networks that can be hijacked to enable, amplify, and even sustain seizures. The thalamus's role in generating spike-and-wave discharges was highlighted as far back as the 1940s when Hunter and Jasper [74] showed that electrical stimulation in the intralaminar nuclei of the thalamus could elicit 3 Hz spike and wave discharges in the cortex and thalamus in unanesthetized cats. Later experiments revealed that disinhibition in cortex was sufficient to produce local spike wave discharges, suggesting that seizures initiated in the cortex but were amplified by the regional thalamocortical circuits [75]. In the case of absence seizures, evidence supports that the spike wave discharges arise from the cortex [76] but require both cortical and thalamic activity to sustain and organize [77,78]. In the 1970s, Gutnick and colleagues showed that both focal application of penicillin and focal electrical stimulation in somatosensory cortex *in vivo* recruited the ventral posterolateral nucleus into the seizure in cats [11,12]. Once recruited, the ventral posterolateral nucleus was capable of sustaining after-discharges independently of cortical input.

The inclusion of electrodes targeting the thalamus during stereo-EEG recordings in patients undergoing intracranial monitoring has provided compelling evidence that thalamic nuclei are frequently recruited during seizures in humans. Given the known neuroanatomy, generalized seizures involving broad bilateral cortical regions are expected to engage broad thalamic nuclei. Indeed, stereo-EEG recordings from patients sampling from cortex and bilateral centromedian, anterior nucleus, and pulvinar thalamic nuclei suggest the ubiquity of ictal electrographic changes diffusely through sampled thalamus simultaneous with the onset of generalized seizures (Fig. 3A). In contrast, focal seizures follow distinct propagation patterns along regional thalamocortical circuits, where thalamic involvement can be near-instantaneous or delayed relative to the first observed cortical onset (Fig. 3B).

Increasing observations across multiple cohorts demonstrate that focal seizures engage distinct thalamocortical networks [33], where the patterns reported remain consistent with known neuroanatomy. Recordings from the medial pulvinar nucleus during temporal lobe seizures demonstrate ictal thalamic involvement in approximately 80% of seizures, typically occurring seconds after cortical onset, with thalamic low voltage fast activity more frequently observed in seizures of neocortical origin and rhythmic spiking or slow waves in those originating in mesial temporal structures [22,79]. Similarly, both anterior [80] and ventral midline thalamic nuclei [81] have shown ictal activity during temporal lobe seizures. The ventral midline thalamus (including the reuniens and rhomboid nuclei) showed unequivocal ictal activity in all three patients in a study of mesial temporal lobe epilepsy, in whom thalamic stimulation was able to induce seizures similar to those occurring spontaneously [81]. In one cohort of 44 patients undergoing intracranial monitoring, seizures with broad onset rapidly recruit the centromedian and pulvinar nuclei, while those originating in the mesial temporal lobe predominantly involve the anterior nucleus [35].

The timing and pattern of thalamic recruitment may be a critical determinant of seizure propagation [34]. Recent analyses categorizing thalamic spread as early or late relative to seizure onset demonstrate that early thalamic involvement—within seconds of cortical onset—is associated with more widespread subsequent spread [35]. Hypersynchronous activity may serve as an early indicator of seizure onset, potentially playing a role in the initial synchronization of thalamocortical networks. Meanwhile low voltage fast activity may indicate or enable rapid and diffuse ictal propagation. Ictal baseline shifts and suppression, meanwhile, appear to contribute to transitions between seizure phases. Notably, suppression was seen diffusely throughout the thalamus while baseline shifts were only observed in medial or ventral thalamus in the cohort studied [34].

While many clinical reports detail ictal thalamic propagation in human seizures, evidence for this at the neuronal level has not been shown. Importantly, the voltage activity seen in clinical electrophysiology

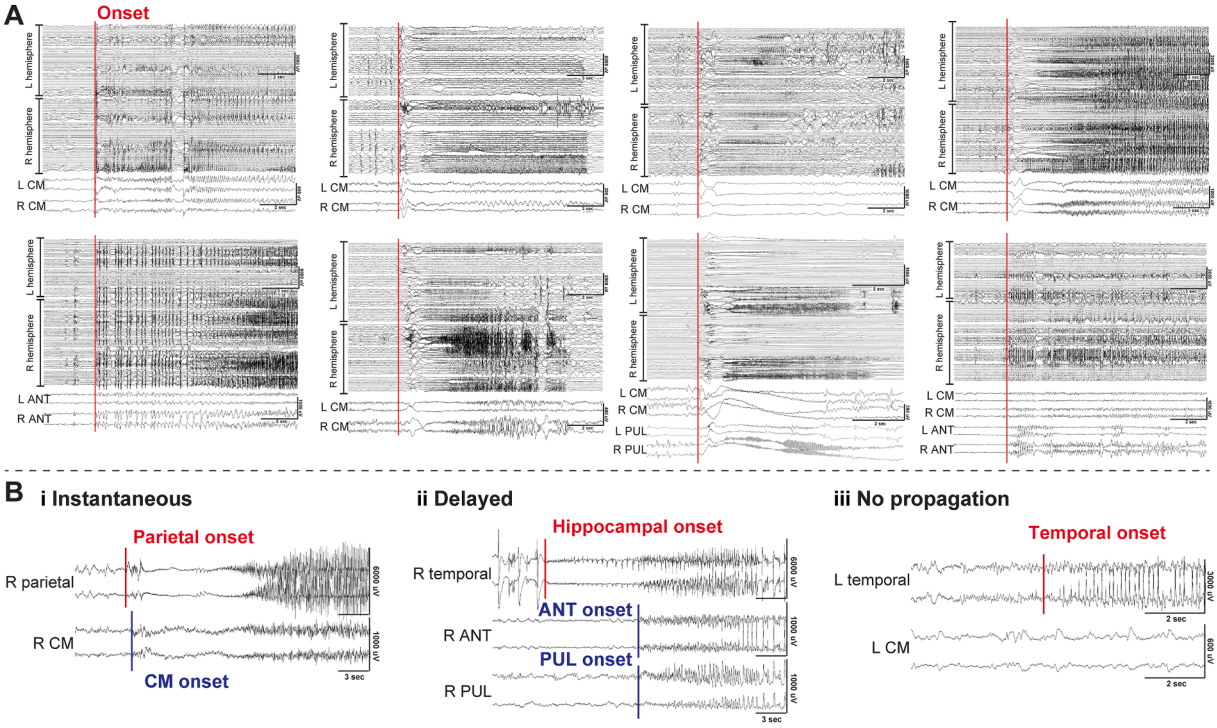

Fig. 3. Example thalamic recruitment patterns across seizure types. (A) Example generalized seizures consistently show instantaneous recruitment of bilateral thalamic nuclei, including in centromedian (CM), anterior (ANT) and pulvinar (PUL) nuclei (abbreviations maintained throughout). **(B)** Example focal seizures show heterogeneous patterns of thalamic recruitment ranging from instantaneous **(i)**, to delayed **(ii)**, to no clear involvement during the seizure **(iii)**.

recordings is primarily the local synaptic activity reflecting the input to the tissue being recorded [82]. As a result, the clinical EEG gives information about the synaptic barrages received at that location, but little information about the local neuronal firing, which constitutes the output of that tissue. In neocortex this has highlighted how the spread of ictal patterns on intracranial EEG reflects efforts to recruit local tissue, not necessarily that the tissue has become involved in generating these pathological ictal discharges [83]. The thalamus similarly exhibits feedforward inhibitory connections, however whether this may result in a similar disconnect between EEG signals and actual recruitment to the pathology is still unknown.

Considering both micro- and macro-structural connectivity, corticothalamic ictal propagation likely emerges from a combination of cellular excitability, local coupling mechanisms, and activity across large-scale networks. In this context, whether or not an ictal EEG signature can be observed in the thalamus and when may depend less on the cortical electrographic pattern itself than on the cortical location and volume of the seizure onset zone that is driving inputs to the thalamus, the thalamic nucleus sampled, and the underlying thalamocortical connectivity. Seizure propagation via the thalamus could occur by recruitment of larger cortical regions and subsequent further thalamic nuclei, or potentially within the thalamus itself mediated by the reticular nucleus of the thalamus or via local ephaptic mechanisms.

Neuromodulation targeting the thalamocortical loop

Chronic responsive neuromodulation targeting the thalamus has now been reported to improve seizure control in case series across diverse epilepsy cohorts, including focal and generalized seizures, in children and adults [4,5,84–88]. Similarly, chronic "open loop" stimulation—which does not rely on detection of seizures but instead delivers stimulation continuously or at set intervals—of the anterior and pulvinar nuclei has also been shown to reduce seizure frequency [89,90]. Thalamic neuromodulation has even been shown to abort seizures acutely in cases of super-refractory status epilepticus [91–96].

The mechanisms through which thalamocortical interactions modulate and terminate seizures remain poorly understood. Although improved seizure control can also be obtained using responsive cortical stimulation [97], thalamocortical cellular and anatomical circuits are uniquely designed to support the increased spatial and temporal neural synchronization that is observed prior to seizure termination [98]. Indeed, in one cohort of 10 patients, Evangelista et al. found that synchronization of medial dorsal and pulvinar thalamic nuclei to mesial temporal structures increased at the end of seizures and correlated with shorter seizure duration [99]. These observations suggest that thalamocortical oscillations may actively contribute to seizure termination by enhancing cortical synchronization, which could be leveraged in future stimulation paradigms that seek to deliver appropriately timed pulses at thalamic nuclei that would entrain the relevant cortical regions.

Using simultaneous recordings from the nucleus reuniens, hippocampus, and entorhinal cortex, a progressive increase in thalamocortical coupling was found as seizure-like events developed in a guinea pig brain model [100]. In this model, early pathological bursts in the hippocampus preceded progressive entrainment of thalamic activity. However, towards the end of the seizure-like events, the thalamus led the bursting activity, highlighting the potential role of the midline thalamus in synchronizing seizures across limbic structures and facilitating seizure termination. Additionally, as the thalamus directly influences regional cortical circuits, thalamic stimulation enables modulation of broader or multifocal networks without requiring as precise anatomical targeting as direct cortical stimulation.

Many open questions remain regarding which thalamic nuclei to target to optimize seizure control. It may be a reasonable assumption that pathological activity simply follows anatomical routes, in which case knowledge of connections between specific cortical areas and specific thalamic nuclei will be sufficient to predict pathological spread routes and chokepoints to target with therapeutics. However, ictal propagation mechanisms—which represent highly pathological activity—may not strictly adhere to anatomical pathways. Further, the expected anatomical pathways may be subtly or grossly disrupted in focal cortical dysplasias or major malformations of cortical development. Patient-specific anatomical differences are expected even in the absence of overt anatomical alterations related to epilepsy. For example, in healthy subjects the interthalamic adhesion—tissue that connects the two sides of the thalamus and thus could have implications for focal to bilateral seizures—shows marked variability across individuals, including being completely absent in roughly 1 in 8 people [101]. Highlighting this variability, Wu et al. showed that the first location of thalamic involvement was not reliably predicted based on either clinical semiology or neocortical onset location [102]. Future research evaluating the consistency of ictal propagation patterns across different epilepsy etiologies or combining thalamic and cortical stereo-EEG recordings with diffusion tensor imaging (DTI) within the same patients may help to answer both whether pathological activity is restricted to anatomical pathways and whether those anatomical pathways are consistent across patients.

As these details remain uncertain, empirical evidence from personalized thalamic stereo-EEG recordings can validate hypothesized targets prior to permanent device placement. With careful planning thalamic sampling can be achieved without implantation of additional depth electrodes [103], and with few complications [104]. Given the reciprocal cellular architecture linking specific cortical and thalamic networks, observation of ictal input from a cortical seizure onset zone to a particular thalamic nucleus implicates that nucleus as connected to the seizure network. Although the clinical stereo-EEG recordings do not clarify whether the thalamus is propagating the seizure or simply receiving ictal inputs, any thalamic location that is impacted by the seizure should in turn innervate the tissue that is producing the pathological discharges upstream, providing an attractive potential node for neuromodulation. This expectation can readily be confirmed via evoked potentials during clinical mapping in patients undergoing surgical monitoring.

In addition to ictal propagation patterns, early observations suggest that interictal epileptiform discharges may help map connectivity and predict the optimal thalamic location for stimulation, and improve seizure response rate, enabling patient-specific targeting informed by thalamic stereo-EEG recordings [105]. Alternatively, single pulse stimulation can be used to map electrophysiological connectivity between cortical or limbic and thalamic nuclei [79,106].

While potentially critical to inform neuromodulatory targets in focal or multifocal epilepsies, thalamic stereo-EEG sampling is less useful in generalized epilepsy. Given the diffuse cortical involvement in generalized seizures, broad thalamic involvement is both expected and has been observed in generalized seizures. Rather, determining which thalamic nuclei to target for electrical stimulation in generalized epilepsy may be best dictated by which thalamocortical network one aims to modulate. For example, stimulation of the centromedian nucleus may mitigate tonic clonic activity driven by sensorimotor cortex [4]. In contrast, stimulation of the medial pulvinar or dorsomedial nucleus may represent a promising approach to preserve consciousness during seizures, for example [18,90,107–109].

In addition to anatomical targeting, the optimal electrical stimulation parameters to drive seizure reduction via thalamic neuromodulation remain poorly understood. In clinical practice, a range of stimulation parameters, such as frequency, amplitude, and duration have been reported with varying levels of response across patients [110–112]. Moreover, electrical stimulation can have both local and distal effects. For example, single pulse stimulation can produce a local increase in activity within around 40 mm while distal stimulation produces a suppression of firing [113]. While some studies report effective

seizure control using higher stimulation currents and longer stimulation durations [4,5], these settings also drive earlier battery failure and can increase stimulation side effects. Low frequency stimulation may offset both of these concerns [112]. Studies that quantify the tissue responses across these parameter spaces—stimulation frequency and amplitude, as well as distance from stimulation—likely will open up a clinically relevant toolbox.

Taken together, these observations support a model in which thalamic neuromodulation is most likely to succeed when it is guided by the specific thalamocortical network recruited in an individual patient. In focal and multifocal epilepsies, this may require integrating anatomy with patient-specific physiological data from thalamic stereo-EEG, interictal discharges, or single-pulse stimulation to identify the nucleus most tightly linked to seizure propagation. In generalized epilepsies, target selection may instead be driven by the cortical network and clinical feature one aims to modulate. Beyond target selection, defining the stimulation parameters that most effectively disrupt pathological synchronization remains a major unmet need.

Conclusions

Building on earlier basic research, the past two decades have yielded substantial new evidence defining the role of the thalamus in modulating spontaneous human seizures. This progress has been driven in part by the widespread use of stereo-EEG in presurgical evaluation and by chronic neuromodulation devices that stimulate the thalamus. Available evidence supports a model in which thalamic nuclei are not passive bystanders but network-specific participants in seizure propagation, synchronization, and termination. This makes the thalamus an attractive neuromodulation target, particularly in diffuse, multifocal, or eloquent-cortex epilepsies not amenable to resection.

Combined cortical and thalamic recordings have shown that focal-onset seizures frequently recruit the thalamus, often in a nucleus-specific manner. Given their extensive anatomical connectivity, these thalamic nuclei likely serve as network hubs that support rapid propagation of ictal activity across distributed cortical regions, providing a plausible mechanism for abrupt noncontiguous seizure spread on EEG, secondary generalization, and impaired consciousness. Because thalamic nuclei are reciprocally connected with specific cortical regions, patterns of seizure spread should indicate the thalamic targets most likely to modulate the cortical networks involved.

Although thalamic neuromodulation can reduce seizures across focal, multifocal, and generalized epilepsies, many factors that determine treatment success remain incompletely understood. The optimal nucleus and stimulation parameters likely depend on the specific thalamocortical network involved in each patient. Integrating thalamocortical neuroanatomy, cellular mechanisms, and ictal physiology will help move thalamic neuromodulation toward a patient-specific, principled, network-guided therapy.

Author contributions

Conceptualization: EMM, MAK and CJC; literature review: EMM and PW; writing—original draft preparation: EMM; writing—review and editing: EMM, HK, PW, MAK and CJC; figure creation: EMM and HK. All authors have read and agreed to the final version of the manuscript.

Declaration of competing interest

Catherine J Chu reports the following relationships: Biogen (consulting, funding); Novartis (consulting, funding); Ovid Therapeutics Inc (consulting); Ionis Pharmaceuticals Inc (consulting). Mark A Kramer reports the following relationships: Ionis Pharmaceuticals Inc (consulting); Biogen (consulting). The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by National Institute of Neurological Disorders and Stroke (R01NS139524, R01NS115868, and R01NS119483). The authors would like to thank Katie Walsh for assistance in the creation of Fig. 3.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2026.e00967.

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