Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

Thalamic Neuromodulation in Epilepsy: A Primer for Emerging Circuit-Based Therapies

Bryan Zheng, David D. Liu, Brian B Theyel, Hael Abdulrazeq, Anna R. Kimata, Peter M Lauro & Wael F. Asaad

To cite this article: Bryan Zheng, David D. Liu, Brian B Theyel, Hael Abdulrazeq, Anna R. Kimata, Peter M Lauro & Wael F. Asaad (2023): Thalamic Neuromodulation in Epilepsy: A Primer for Emerging Circuit-Based Therapies, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2023.2176752

To link to this article: https://doi.org/10.1080/14737175.2023.2176752

Accepted author version posted online: 02 Feb 2023.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Neurotherapeutics*

DOI: 10.1080/14737175.2023.2176752

Title: Thalamic Neuromodulation in Epilepsy: A Primer for Emerging Circuit-Based Therapies

Authors: Bryan Zheng BS[1, 3], David D. Liu BS[1], Brian B Theyel MD PhD[2, 4], Hael Abdulrazeq MD[3], Anna R. Kimata[1, 3], Peter M Lauro PhD[1,4], Wael F. Asaad MD PhD[3, 4, 5, 6]

Affiliations
[1]The Warren Alpert Medical School of Brown University, Providence, RI, USA
[2]Department of Psychiatry, Rhode Island Hospital, Providence, RI, USA
[3]Department of Neurosurgery, Rhode Island Hospital, Providence, RI, USA
[4]Department of Neuroscience, Brown University, Providence, RI, USA
[5]The Carney Institute for Brain Science, Brown University, Providence, RI, USA
[6]The Norman Prince Neurosciences Institute, Rhode Island Hospital, Providence, RI, USA

Corresponding Author: Bryan Zheng (bryan_zheng@brown.edu)
Element Counts
Abstract Word Count: 193
Text Word Count: 6999
Expert Opinion Word Count: 1063
Figures: 5
Tables: 0
References: 240

Disclosures: None
Funding: None
Note: This paper has not been previously presented or published in any form.

Thalamic Neuromodulation in Epilepsy: A Primer for Emerging Circuit-Based Therapies

Bryan Zheng[1, 3], David D. Liu[1], Brian B Theyel[2, 4], Hael Abdulrazeq[3], Anna R. Kimata[1, 3], Peter M Lauro[1,4], Wael F. Asaad[3, 4, 5, 6]

Affiliations
[1]The Warren Alpert Medical School of Brown University, Providence, RI, USA
[2]Department of Psychiatry, Rhode Island Hospital, Providence, RI, USA
[3]Department of Neurosurgery, Rhode Island Hospital, Providence, RI, USA
[4]Department of Neuroscience, Brown University, Providence, RI, USA
[5]The Carney Institute for Brain Science, Brown University, Providence, RI, USA
[6]The Norman Prince Neurosciences Institute, Rhode Island Hospital, Providence, RI, USA

Corresponding Author: Bryan Zheng (bryan_zheng@brown.edu)

Abstract

Introduction: Epilepsy is a common, often debilitating disease of hyperexcitable neural networks. While medically intractable cases may benefit from surgery, there may be no single, well-localized focus for resection or ablation. In such cases, approaching the disease from a network-based perspective may be beneficial.

Areas covered: Herein, the authors provide a narrative review of normal thalamic anatomy and physiology and propose general strategies for preventing and/or aborting seizures by modulating this structure. Additionally, they make specific recommendations for targeting the thalamus within different contexts, motivated by a more detailed discussion of its distinct nuclei and their respective connectivity. By describing important principles governing thalamic function and its involvement in seizure networks, the authors aim to provide a primer for those now entering this fast-growing field of thalamic neuromodulation for epilepsy.

Expert opinion: The thalamus is critically involved with the function of many cortical and subcortical areas, suggesting it may serve as a compelling node for preventing or aborting seizures, and so it has increasingly been targeted for the surgical treatment of epilepsy. As various thalamic neuromodulation strategies for seizure control are developed, there is a need to ground such interventions in a mechanistic, circuit-based framework.

Keywords

Thalamus, neuromodulation, seizures, epilepsy, anterior nucleus, centromedian nucleus, pulvinar nucleus, microcircuits, neurosurgery

Article highlights

- Epilepsy affects more than 45 million people worldwide and is conservatively estimated to cost over 10 billion dollars each year in the United States alone.
- The thalamus acts as a control point for brain-wide information processing, neural synchronization, and cortical state via thalamocortical microcircuits.
- There is extensive evidence that the thalamus is involved, both as a passive node and active participant, in seizure onset and propagation in animal models of epilepsy.
- Clinical trials have thus far highlighted stimulation of the anterior and centromedian nuclei of the thalamus as compelling therapies for temporal lobe and generalized epilepsies, respectively.
- The thalamus is likely to become a critical and routinely utilized target for network-based seizure treatment.

1. Introduction

Epilepsy is a disease of hyperexcitable neural networks that affects more than 45 million people worldwide and is conservatively estimated to cost over 10 billion dollars each year in just the United States[1,2]. Improved knowledge of the structural and functional connectivity of brain networks has produced insights regarding seizure onset, propagation, and maintenance[3]. Until recently, clinical therapy was limited largely to anti-seizure medications (ASMs) or surgical resection. While the rate of seizure control in persons with epilepsy has been approximately 70% for ASMs, surgical intervention may be an option for those who do not adequately respond to medication[4-6]. Those with primary generalized seizures, seizures arising from "eloquent" cortical areas, or with multifocal epilepsy, were not typically neurosurgical candidates. Now, however, the advent of neuromodulatory approaches means that some or perhaps many of those who did not previously have a surgical option are now eligible for operative intervention.

Both open-loop (deep brain stimulation) and closed-loop (responsive neurostimulation) neuromodulation devices are now available to treat epilepsy. Each approach has relative benefits and disadvantages, but both have opened the door to a more network-centric approach to seizures and their treatment. Increasingly, epileptologists and epilepsy surgeons speak of addressing networks of interconnected brain structures rather than fixate on a putative single seizure focus[7-10]. In contrast to a seizure "focus" that might traditionally be regarded as simply the initial point of seizure activity, a "seizure network" is a collection of brain areas whose coordinated excitatory and inhibitory interactions yield increasing synchronization that promotes seizure onset in one or more components of that network. Even the mechanisms behind vagal nerve stimulation (VNS), a longstanding but poorly understood neuromodulatory therapy, has

recently been re-examined in the context of thalamic functional networks[11-13]. This framework provided impetus for the neuromodulatory approach to epilepsy because electrical stimulation may propagate broadly to more effectively treat the networks that give rise to seizures[14], and may regulate these circuits in a chronic fashion to reduce seizure likelihood[15]. Additionally, as opposed to ASMs, neuromodulatory approaches can provide the opportunity to both observe and influence circuits that may be lateralized to either hemisphere[16,17]. As neuromodulation is better understood and optimized, it may one day become a primary rather than a palliative treatment for epilepsy.

Within this context of new neuromodulation therapies for epilepsy, the thalamus has garnered increasing attention in large part because its broad and highly robust connectivity with cortex makes it an intuitively attractive target for modulation. Though formerly viewed as a subcortical-cortical relay node with some modulatory influence on the transmitted information, the thalamus is now understood to play a substantial and critical role in processing information as it travels to, from, and between cortical areas. Its modular, canonical thalamocortical (TC) and corticothalamic (CT) projections are widely appreciated, but the thalamus also makes extensive connections with additional deep structures such as the hippocampus, amygdala, piriform lobule, and basal ganglia[18]. Nonetheless, our clinical models have yet to fully incorporate the improved understanding of thalamic anatomy, physiology, and pathology that has resulted from technical advances such as precise intracellular recordings, high-resolution imaging, and optogenetics.

Here, we provide a comprehensive overview of progress in the study of thalamic circuits implicated in the pathogenesis of epilepsy. Our goal is to translate a body of basic, pre-clinical neuroanatomical and neurophysiological research for application by clinicians and clinical researchers developing and testing novel therapies for epilepsy. We also qualitatively review clinical evidence supporting a thalamic approach to epilepsy treatment and propose some general principles for neuromodulation of the thalamus in epilepsy.

2. Thalamic Structure and Function

The thalamus is a cluster of nuclei that are grouped based on shared patterns of connectivity with cortical and subcortical areas and are enveloped within the shell-like thalamic reticular nucleus (TRN). Topographically organized thalamocortical and corticothalamic projections are the basic, modular elements around which more elaborate thalamic circuits are built. The surrounding TRN is a major source of feedforward and feedback inhibition. Meanwhile, in contrast to the principal nuclei that connect to relatively circumscribed areas of cortex, intralaminar nuclei are more diffuse structures with correspondingly broader cortical interactions. Further, the borders between principal nuclei are not always distinct and the anatomical and functional perspectives do not consistently map directly onto one another. As such, alternative classification schemes based on thalamocortical circuitry may more clearly lay the framework for therapeutic thalamic neuromodulation.

2.1. Gross Anatomy and Connectivity

The thalami are paired structures abutting the midline and connected by a small strip of grey matter forming the inter-thalamic adhesion. Clusters of thalamic neurons have been grouped by

several properties, including: the particular cortical regions with which they interact, whether they receive primary (sensory inputs from the periphery) versus secondary (cortical) inputs, or based on local anatomy and circuitry. The classic framework organizes the thalamus into various nuclei based on histological and anatomical features. Within the classical framework, nuclei are apportioned into lateral, medial, anterior, and midline groups, localized in reference to an intralaminar group and surrounded by the TRN (**Figure 1**)[18]. Among several further subdivisions, the lateral group of nuclei is segregated into ventral and dorsal tiers[19]. These nuclear subdivisions are almost universally accepted and broadly inform function. However, increasing evidence suggests that most nuclei do not have a single, neatly-circumscribed role. For example, the posteriorly-located pulvinar is classically associated with visual-attentional processing[20,21], but has also been implicated in other cognitive functions such as emotional processing[22], working memory[23], and decision-making[23]. Even despite further divisions of the primate pulvinar into distinct anatomical subgroups (e.g., lateral, inferior, and medial; PuL, PuI and PuM), there is evidence that these smaller areas nevertheless have multimodal functions[24,25].

Because classification schemes based primarily on local anatomy and histology do not capture the functional heterogeneity of individual thalamic nuclei, some modern thalamic classification systems are based on circuit topology[26]. Distinctions have been made based on (i) the characteristics of thalamocortical output – core versus matrix nuclei[27], (ii) input – first- versus higher-order nuclei[28], or (iii) both input and output[29]. For example (of [i]), the anterior nucleus of the thalamus (ANT) has been defined as a core nucleus because it provides focal projections as a node in the medial limbic circuit. The pulvinar nucleus, specifically the PuM,

also possesses “core-like” properties based on its distinct circuits involving the temporal lobe[24]. In contrast, matrix nuclei like the centromedian nucleus of the thalamus (CMT) are characterized by markedly more diffuse cortical projections[30]. Meanwhile, within the framework of the first- and higher-order nuclear scheme (ii): first-order nuclei receive “driver” inputs from subcortical sites carrying primary sensory information (e.g., lateral geniculate nucleus [LGN] receives visual input from the retina), while higher-order nuclei (e.g., the pulvinar) receive driver inputs from cortical layer V and primarily participate in transthalamic cortico-cortical circuits[28]. This classification scheme is useful in that it highlights how the thalamus continues to be involved in information processing between areas of cortex in addition to modulating and relaying primary sensory information.

The data used to develop these functional frameworks suggest that defining an area within the thalamus based on anatomical location alone neglects rich functional diversity. Overlap between somatosensory, motor, and auditory afferents and efferents illustrate the difficulty in defining clean nucleus-based distinctions. For example: the central lateral (CL), mediodorsal (MD), and pulvinar nuclei have all been shown to have extensive cortical projections with overlapping modalities consistent with multisensory interplay at the thalamic level[31,32]. Indeed, the roles of these and multiple other nuclei may most aptly be characterized by multidomain integrations rather than modality-specific computations with specific inputs or outputs[33-35]. This intertwining of networks and the heterogeneity of nuclei may be relevant to thalamus-based clinical therapy, particularly deep brain stimulation and responsive neurostimulation, and encourages this “functional perspective” that may be partially independent of traditional nuclear boundaries. Presently, few clinical studies directly leverage functional attributes related to the

core/matrix or first/higher-order perspectives, as the anatomically-based organization provides a simpler framework to evaluate and target particular thalamic nuclei. To underscore the benefit of a functional perspective, however, one might consider the intralaminar and midline groups of nuclei: this set of nuclei, which includes the CMT, are often grouped based on their canonical association with arousal and attention and their connections with the brainstem reticular activating system (RAS) versus their anatomical borders[36]. Thus, thalamic recordings from these nuclei in multiple animal models have demonstrated relatively high sensitivity to changes in arousal[37-39]. There has been the suggestion, therefore, that targeting these nuclei might have preferential effects on the loss of awareness that often accompanies seizures.

2.2. Microcircuits and Proposed Functions

2.2.1. First- and Higher-Order Microcircuits

The canonical thalamocortical circuit is well-conserved across cortical domains yet supports diverse aspects of cortical processing[40,41]. In general, thalamocortical projections, particularly from core nuclei, synapse onto cortical layer IV (**Figure 2**), and to a somewhat lesser extent layer VI[42-44]. Information is broadcasted to superficial layers, integrated/processed, and then sent back down to the deep cortical layers. From there, the cortex sends (i) projections from layer VI to the thalamus and TRN as a dense feedback projection, and (ii) feed-forward cortical output from layer V to the "next" processing stage in the thalamus before it is relayed to a subsequent cortical area, in parallel to direct cortico-cortical projections[45-47]. This motif is modular, such that primary inputs can be processed and handed-off to downstream thalamocortical loops involving neurons in higher-order nuclei. Importantly, synapses on thalamic relay cells are numerically dominated by modulators (i) rather than their "driving" inputs (ii), suggesting rich

complexity of intrathalamic processing that has rendered the earliest notions of the thalamus as a mere waystation obsolete[48]. Indeed, the organization of this canonical circuit inspired several co-existing theories of thalamocortical function that each have accrued evidence in their favor.

Two fundamental functions of the thalamus may be to both modulate and mediate the transfer of information between cortical areas[49-54]. In fact, thalamocortical projections may be just as important to information transfer between cortical areas as direct cortico-cortical projections[55]. For example, chemically silencing the thalamus can prevent the propagation of activity from primary to secondary somatosensory cortices, suggesting the cortico-thalamo-cortical (transthalamic) route is critical in this process[56]. In other words, different cortical areas may have difficulty "speaking" to each other without the mediating functions of the thalamus. Further, the concept of a thalamic mediator for cortico-cortical information processing points to a broader functional role of the thalamus as an enabler of "communication through coherence"[57]. The basic idea here is that the spiking activity from upstream regions (e.g., from both thalamus and cortex) should be synchronized to promote post-synaptic summation and activation of neurons at the next stage of processing, so thalamic circuits may help entrain activity across those upstream sites to coherent rhythms. In addition, downstream regions may be more receptive to that information at particular phases within an oscillatory cycle so, in similar fashion, the thalamus may promote coherence across efferent and afferent cortical areas to facilitate their direct interactions[58,59]. Another function of the thalamus may be to serve as a gate for subcortical and cortical information processing. This role is supported by observations in nuclei such as the LGN, which appears to minimally alter its input (from the retina, in this case) before passing that information along to cortex (here, visual cortex)[60], and whose inputs are

blocked from cortical access during particular states such as sleep[61,62]. Thalamic gating of information may also play a role during awake states: for example, thalamocortically-induced suppression in the neocortex can focus the receptive fields of sensory neurons[63,64]. None of these functions are mutually exclusive, and the extent to which different thalamic regions or circuit components contribute to each is a subject of ongoing investigation.

2.2.2. Intralaminar and Midline Microcircuits

The thalamus is likely key to the implementation of state transitions between levels or types of cortical arousal and can maintain those states through broad, course regulation of cortical activity[65-69]. This function is evident in various sleep stages and their distinct thalamocortical signatures. For example, the synchronous transition to "down" states across multiple cortical regions during slow-wave sleep is likely mediated by the midline thalamus[70]. Here, the thalamus appears to be the critical link between brainstem regions involved in arousal, primarily the ascending reticular activating system (RAS), and the cortex. This network serves as a synchronous, broad modulator of cortical processing, and a potential regulator of sleep, alertness, and consciousness[71-73]. So, in addition to being the gatekeeper for specific information trying to gain access to cortex, modulatory projections via the thalamus enforce cortical compliance with brainstem-derived state signals.

2.2.3. TRN Microcircuits

Thalamocortical functions reflect a complex interplay of excitatory and inhibitory feedback and feedforward interactions, and our understanding of these dynamics continues to evolve. Central to this interplay is the TRN, which dynamically modulates the gain of thalamic neuronal activity

in addition to regulating oscillations[74]. Trans-reticular circuits are generally topographically[75] and functionally[61] distinct, forming recurrent networks between regions of the TRN and the thalamic subdivisions they modulate, and connected cortical areas[76]. A key underlying feature of this circuit is the ability of TRN cells to adopt distinct tonic and burst firing modes. Rhythmic tonic spiking, which occurs when neurons are depolarized, is typically the dominant state during wakeful and attentive states. In contrast, hyperpolarized reticular neurons fire in bursts, a pattern characteristic of sleep. The switching of thalamocortical cells in the TRN between tonic and burst modes is mediated by T-type calcium channels that are inactivated at resting membrane potentials and dependent on relatively long periods of hyperpolarization to de-inactivate[77]. The frequency of these cycles possesses notable clinical interest, because their duration (approximately 300 ms) matches the periodicity characteristic of absence seizures and other epilepsies with stereotyped spike-wave discharges[78].

In the context of the proposed roles for the thalamus in directing cortical states that are largely defined by oscillatory patterns, the TRN plays a critical role in the synchronization of thalamic and cortical neurons[79]. Reticular neurons generate inhibitory post-synaptic potentials in TC cells, which can prime these relay neurons for post-inhibitory rebound spikes. TC neurons, when in “burst mode” following sustained periods of inhibition, can fire periodic volleys that synchronize to delta frequencies (1-4 Hz), while TC-TRN circuits generate spindle oscillations (7-14 Hz) in the cortical regions onto which they project[80-84]. These rhythmic bursts of output feed back to the TRN, causing recurrent activation that sustains oscillations in physiologic states and is aberrant in pathologic ones[85,86]. Specifically, a higher degree of coherence between TRN and cortex results in the emergence of characteristic 3-Hz spike-wave oscillations rather

than normal spindles, suggesting a potential functional target for suppressing the spread of these discharges[87]. Indeed, suppression of spike-wave activity in a genetic rat model of absence epilepsy disrupted cortico-reticular synchrony, while firing patterns of thalamic relay neurons were unaffected[88].

2.2.4. Thalamic Triads

Recent work has highlighted an important local thalamic circuit component for non-TRN-mediated inhibition within thalamic nuclei consisting of local GABAergic interneurons that inhibit relay cells. The motif at these synapses has been dubbed a thalamic "triad", stemming from the unique functional and structural arrangement of interneuron dendrites, TC dendrites, and incoming axonal input (**Figure 3**)[89]. These interneurons comprise around 20% of the total neuronal population in the rodent dorsal thalamus and around 35-40% in that of humans[90], suggesting a more prominent role in thalamic processing in humans. In the triad a local feedback circuit is triggered by glutamate release onto AMPA receptors present on interneuron dendrites, which then release GABA onto TC relay cell dendrites, inhibiting the same segments of those TC dendrites receptive to incoming glutamatergic activation by the thalamic inputs[91].

Interestingly, stimulation of the optic tract can produce synaptic responses in these interneurons without corresponding activity in "classic" relay neurons, suggesting a unique and critical role regulating thalamic circuit dynamics[92]. Their role within thalamic circuits is likely modulatory, and they may contribute to functions such as gain control via dynamic conductance regulation[91]. However, despite being perhaps as critical to network regulation as the TRN[93], these intrinsic interneurons have only recently been appreciated. They are thus less-well studied

than their principal neuron counterparts, so their specific function and recruitment during thalamic stimulation are only just beginning to be explored[94].

2.2.5. Functional Implications of Thalamocortical Interconnectivity

Beyond its modulatory influence, the thalamus likely contributes to cortical processing at a finer scale as well. The feedforward CT projection from layer V may provide an "efference" copy of upstream cortical information to a downstream cortical target via the transthalamic route, thereby supporting predictive coding[28,95,96] in which ongoing experience is compared to learned expectations. In this and other ways, the thalamus may be critical for a variety of routine cortical processing and may enable higher-order cognitive functions such as working memory[97], cognitive control[98], and behavioral flexibility[99]. In fact, atrophy of higher-order thalamic nuclei as well as functional alterations in MD-prefrontal connectivity have been implicated in neurodevelopmental disorders such as schizophrenia and may contribute to associated symptoms including motor dysfunction, psychotic behavior, and impaired memory[100].

These perspectives on thalamic function relate directly to the potential mechanisms by which thalamic modulation may influence seizures. If the thalamus acts as a gate for information access to the cortex via excitatory inputs, closing this gate may help normalize the balance of excitation and inhibition. If the thalamus regulates cortical state, perhaps altering or resetting that state using thalamic modulation (e.g., by targeting intralaminar or midline nuclei, selecting a stimulus protocol tuned to activate local thalamic interneurons, or broadly activating TRN) may interrupt seizures or at least engender a state that is less conducive to their sustenance. If the thalamus enables or facilitates cortico-cortical communication, then interrupting this communication may

interrupt the propagation of seizures. We will return to these themes when considering the evidence for the involvement of the thalamus in epilepsy.

2.3. Potential Thalamocortical Circuit Dynamics of Seizures

The synaptic and circuit properties of thalamocortical networks offer a plausible narrative to explain observations that stimulating the thalamus peri-ictally may be therapeutic[101,102]. Animal studies have demonstrated that thalamocortical relay cells exert more excitatory drive onto inhibitory neocortical interneurons than onto excitatory cells[103,104]. Thalamically-derived signals onto cortical synapses are also precisely tuned and synchronized[105], such that few inputs are required to drive those interneurons. Indeed, derangements of these dynamics could potentially be epileptogenic[106] and, conversely, harnessing these circuit dynamics could potentially offset the cortical hyperexcitability characteristic of seizures. Additionally, there is a calibrated counterplay between cortico-thalamo-cortical and cortico-cortical tracts[107]. The former, transthalamic pathway more effectively activates the feedforward inhibitory circuit than the latter "horizontal" one, suggesting that thalamic influences on cortical activity may be stronger than even direct cortical influences, again illustrating the likely significant modulatory utility of thalamocortical pathways.

TRN circuits offer another key node for controlling thalamocortical dynamics. Because the TRN provides widespread feedforward and feedback regulation of CT-TC pathways, activation of TRN cells can dramatically alter cortical activity and rhythms[108,109]. Moreover, the distinctive bimodal cellular dynamics of TRN activity, switching between tonic and burst firing modes, may be biased by electrical stimulation for immediate effects, and may produce longer-

term effects by influencing thalamocortical plasticity. Therefore, stimulation targeting core thalamic nuclei may also invoke TRN mechanisms for additional or more potent cortical effects.

3. Thalamic Influence in Epilepsy

Whether ictal activity is initiated, propagated, or merely reflected by the thalamus has been debated and studied ever since thalamic neural activity has been associated with seizure discharges[110-113]. Cortical network hyperexcitability associated with seizures may be contextualized within particular thalamocortical circuits and can even be mapped onto specific nuclei in some instances. So far, most attention has been focused on the anterior nucleus and centromedian nuclei. However, more recent work has begun to examine other nuclei such as the pulvinar group as well as the TRN, and has explored more precise mechanisms of seizure development in TC circuits.

3.1. Evidence for Thalamic Involvement in Seizures

3.1.1. Thalamic Involvement in Seizures: Temporal Lobe Epilepsy

Studies of macroscale volumetric changes in temporal lobe epilepsy (TLE) have shown that thalamic atrophy is the most common extratemporal structural abnormality[114,115]. Reduced diameter of a related medial limbic circuit component – the fornix, which provides input to the ANT via the mammillary bodies – is also commonly observed[116]. Atrophy of the fornix is a potential risk factor for persistent postoperative seizures[117], particularly within the subset of patients with mesial temporal sclerosis[118]. Likewise, bilateral thalamic atrophy, in addition to atrophy of the contralateral hippocampus, was associated with persistent postoperative seizures in subjects with medial TLE[119].

In addition to localized anatomical changes, seizures may also produce changes in functional connectivity. Neuroimaging measures of functional connectivity between thalamus and cortex have suggested correlations with epilepsy, though their clinical applicability is unclear. For example, relatively increased functional connectivity between the thalamus and hippocampus and decreased functional connectivity between the thalamus and entorhinal cortex has been proposed to localize seizures to the left and right hemisphere, respectively[120]. In addition, increased functional connectivity between the thalamus and brainstem RAS has been observed via fMRI in TLE, and was at least partially normalized after anterior temporal lobectomy or selective amygdalohippocampectomy[121].

Robust anatomical and neurophysiological data support the involvement of the ANT, which closes the medial limbic circuit via the mammillothalamic tract (**Figure 4**), in TLE. Indeed, among the earliest clues suggesting a link between the thalamus and epilepsy was the observation that lesions of the mammillothalamic tract protected guinea pigs from pentylenetetrazol(PTZ)-induced temporal lobe seizures[122,123]. A rodent model of electrical stimulation-induced focal limbic seizures demonstrated that the ANT may exhibit seizure activity prior to cortex with a high degree of accuracy and consistency[124]. Such an observation, if generalizable to human TLE, may motivate a more primary role for thalamic seizure detection and modulation in at least this form of epilepsy[125]. Other thalamic nuclei that connect with broader regions of the temporal lobe, particularly the PuM nucleus (**Figure 5**), have also been shown to be electrographically recruited by seizures, following initiation in cortex[126-129].

3.1.2. Thalamic Involvement in Seizures: Generalized Epilepsies

While thalamic involvement in focal epilepsies may be regarded as secondary to cortical pathology, the thalamus may in fact be a central node in primary generalized epilepsies. In contrast to relay or "core" nuclei, primary generalized epilepsies have uniquely implicated the intralaminar nuclei, particularly the CMT. Epileptiform activity in the CMT was observed during generalized seizures in adults and children with Lennox-Gastaut Syndrome (LGS)[130-132]. Intraoperative iEEG recordings from eight Lennox-Gastaut patients found 86% of generalized paroxysmal fast activity events were seen at both the site of cortical onset and the CMT. Furthermore, activity in multiple frequency bands appeared to propagate from cortex to thalamus during periods of ictal activity, implying propagation of seizures through the thalamus[132]. However, a recent case series suggested that the CMT may in fact lead ictogenic activity in cortex in generalized epilepsy and that the nucleus itself has independent ictal discharge[133].

The thalamus exhibits early epileptiform activity also in absence epilepsy[134,135]. A substantial body of research supports a cortico-reticular basis of SWDs characteristic of this form of epilepsy[136-138]. While still contested, the thalamus is more likely to be an early node in the spread of SWDs rather than their primary driver, which rather may be deep layers V and VI cortical neurons[139]. Nonetheless, although seizure activity may originate in those cortical circuits, immediate pathologic 3-8 Hz spike-wave discharges can be seen in the thalamus even before seizure activity generalizes to the rest of the cortex[138,140,141]. Additionally, rodent models of absence epilepsy have demonstrated that individual seizures could be forecasted by low-dimensional, pre-ictal neural dynamics in the higher-order thalamus, but not the cortex[142],

suggesting the thalamus may be critical to transform a local ictal signal into a generalized absence seizure.

TRN circuits have been studied extensively in animal models of generalized seizure pathogenesis. Without the GABAergic reticular nucleus, unconstrained excitatory activity in these loops would freely amplify, and so manipulation of TRN responses may be clinically relevant[143]. Because indirect cortico-thalamic inhibition via the TRN usually outweighs direct corticothalamic excitation, loss of normal neocortical activation of the TRN can result in downstream disinhibition of the dorsal thalamus[87]. Consistent with this, experimental models of generalized-absence epilepsy in mice revealed pathologic synchrony via corticothalamic transmission when normal TRN recruitment was weakened by altered ion channels (*Gria4*)[144]. Similarly, knockout of *Scn8a* sodium channels in TRN neurons caused seizures by impairing tonic firing and recurrent desynchronization mechanisms[145,146]. These observations suggest restoring or amplifying TRN-mediated inhibitory mechanisms could promote seizure control[147-149].

3.2. Preclinical Evidence for Seizure Control via Thalamic Stimulation

Preclinical work in animal models, mostly focusing on the ANT, has demonstrated the ability of thalamic modulation to potentially halt seizures. Several different animal models over the last three decades have investigated the efficacy of high-frequency stimulation (and lesioning) of the ANT in suppressing chemically-induced seizures. High frequency (100 Hz) stimulation of the ANT was shown to have an analogous effect to lesioning the mammillothalamic tract, protecting against PTZ-induced seizures, whereas low frequency (8 Hz) stimulation was

proconvulsant[150]. In a nonhuman primate model of MTL seizures, 40 Hz (as opposed to high-frequency 130 Hz) stimulation was successful at reducing the number of seizures, particularly when coherence between ANT and the hippocampus existed at lower frequencies[151]. These results parallel those of a pilocarpine model of secondary generalized seizures, where bilateral ANT thalamotomies completely suppressed seizures[152] and ANT stimulation had differing anticonvulsant effects depending on stimulation current and frequency[152,153]. Likewise, electrical stimulation of the ANT suppressed kainic-acid induced focal limbic[154] and cortical[155] seizures. To a first approximation, electrical stimulation (particularly at higher frequencies) has effects similar to lesions in the context of other disorders (e.g., Parkinson's Disease, Essential Tremor)[156-159], and so these results in the case of epilepsy fit within that general pattern.

Optogenetic studies that more precisely activate or inactivate particular cells have yielded more detailed information about how thalamic modulation might promote seizure control. For example, closed-loop optogenetic activation of principal relay cells in the rat ventrobasal nucleus (analogous to the human ventral posteromedial and posterolateral complex) effectively interrupted seizures following cortical injury (e.g., stroke)[148]. Meanwhile, optogenetic activation of the reticular nucleus suppressed cortical seizures, in keeping with the importance of the reticular nucleus in constraining activity in thalamocortical loops[160]. Notably, optogenetically switching TC neurons between phasic and tonic firing modes modulated absence seizure activity[101]. Specifically, the synchronous phasic state was required for seizure activity and switching to the tonic state quickly halted absence seizures.

Stimulation of the intralaminar nuclei may be particularly useful for modulating arousal, which may be impaired during or after seizures. In a mouse model, 40-100 Hz optogenetic stimulation of the intralaminar nuclei aroused animals from sleep into a waking state, with widespread activation of forebrain structures[161]. Similarly, in non-human primates, electrical stimulation of the intralaminar nuclei reversed propofol-induced unconsciousness, with concomitant reversal of electrophysiologic features of anesthesia[162]. These results suggest that, in addition to modulating seizures themselves, stimulation may be used palliatively to avert the debilitating loss of awareness in patients with seizures that impair consciousness[163].

4. Clinical Thalamic Neuromodulation for Epilepsy

4.1. Current Therapeutic Options

In recent years, neuromodulation for epilepsy has become increasingly routine. Two forms of neuromodulation are available: open-loop modulation via deep brain stimulation (DBS) and closed-loop, "responsive" neurostimulation (RNS). The former is built upon standard, pre-existing DBS devices to modulate seizure-related circuits in a continuous manner, whereas the latter uses a novel neurostimulator device intended to record and disrupt seizures when they occur. The efficacy of DBS for the treatment of DRE has been supported by several influential RCTs including, but not limited to, the thalamus[15,164-170], while the largest study providing Class I evidence of RNS efficacy was in the context of cortical stimulation for partial onset seizures in 2011[171]. Currently, there is only one commercially available closed-loop system for RNS in epilepsy[172,173]. Though there have been pivotal studies of responsive cortical stimulation[174,175], there have not yet been large clinical trials of RNS targeting the thalamus. Mechanistically, DBS is generally associated with chronic network disruption while RNS is

designed for real-time seizure detection and termination, although their precise physiologic effects and overall advantages are still debated.

4.2. Clinical Neuromodulation: Temporal Lobe Epilepsy

TLE is one of the most common forms of intractable epilepsy and the most common form of focal epilepsy[176]. Furthermore, the ANT, which is connected to medial-limbic cortex, has been definitively implicated in the pathogenesis of TLE seizures, as described above,[177] and was among the first brain structures to be stimulated for the treatment of epilepsy[178,179] (**Figure 2**). Since then, ANT stimulation in patients with predominantly temporal lobe seizures has been found to be more successful than for other seizure types[170].

Initially, multiple, relatively small case series (<5 subjects) of successful ANT DBS were presented in patients with partial-onset seizures both with and without secondary generalization[180-183]. The early clinical successes of ANT DBS for epilepsy culminated in the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial, which tested the therapeutic efficacy of bilateral ANT stimulation[164]. One month after implantation, patients were blindly assigned to sham stimulation or active stimulation groups for three months, followed by nine months of open-label active stimulation for all subjects[170]. Both groups experienced implantation-related improvement at one month, with a 20% reduction in seizures. However, after one month of stimulation, the active stimulation group began to experience greater improvements in seizure reduction while the sham stimulation group plateaued. There was no statistically significant difference between these two groups until the third and final month of blinded stimulation. After initiation of stimulation in both groups at one year, the

SANTE investigators continued to track long-term outcomes. Nearly half of subjects reported an improvement in quality of life and 73% of subjects reported being satisfied with the therapy. The improvement in seizure frequency and quality of life, in addition to longer-term, post-trial data submitted the Food and Drug Administration (FDA), resulted in FDA approval for ANT DBS in 2018.

A few small series (<5 subjects) describe the use of RNS in ANT for the treatment of epilepsy, usually using cortical electrode grids for detection and thalamic depth electrodes for stimulation. Unilateral ANT RNS was reported as successful in each of three patients with multifocal epilepsy[184]. Further, there was a 90-95% reduction in seizures using RNS in a patient with childhood-onset genetic generalized epilepsy who had also received anterior callosotomy[185]. The literature on RNS stimulation specifically for pediatric patients is likewise limited to small case series of one or two subjects[186-188].

The PuM has been implicated in focal seizures in patients with motor-premotor epilepsy and temporal lobe epilepsy[126]. In an evoked potential study of patients undergoing depth electrode monitoring for epilepsy, 80% of temporal neocortical contacts responded to PuM stimulation while the response rate of the mesial temporal region was only 34%. This difference suggests that electrical neuromodulation of the PuM may preferentially target the spread of mesial TLE to neocortical sites, or may have second-order, indirect effects on mesial TLE itself[189]. Recent data have also suggested that stimulation of the PuM in patients with TLE who are not typically candidates for resection can help terminate seizures and reduce impairment in awareness[190,191]. Transient regional diffusion-weighted MRI hyperintensities have also

implicated the pulvinar in focal status epilepticus for various seizure types[192], including evidence that the medial pulvinar is a relay node specifically for temporal status epilepticus[193]. With the support of further clinical trials, PuM-targeted neuromodulation may eventually follow a similar trajectory as the ANT for the treatment of medically-intractable TLE.

"Insertion" effects such as transient edema or more durable micro-lesions may account for some fraction of these reported therapeutic benefits[194]. Frank lesions of the thalamus were investigated as a therapeutic option in patients with epilepsy as early as 1967[148,195]. More recently, when directly compared in non-randomized groups, both stereotactic anterior thalamotomy and ANT stimulation were found to be effective for seizure control in frontal and temporal lobe epilepsy[196]. Consistent with this, therapeutic insertion effects have been well-documented[180-182,197,198], though SANTE did eventually show a clear benefit of prolonged, active stimulation[164].

4.3. Clinical Neuromodulation: Generalized Epilepsies

Multiple studies have implicated the CMT as a nucleus that can be safely[168] and effectively targeted for the treatment of various types of primary- or secondary- generalized seizures **(Figure 4)**[168,199]. In an early series of five patients, CMT stimulation markedly decreased the frequency of generalized tonic-clonic seizures[200,201]. CMT spike-wave complexes were found even to precede cortical generalization in passive recordings[130]. In a more recent clinical trial, six patients with generalized epilepsy undergoing bilateral DBS at 60-130 Hz experienced >50% initial improvement in seizure frequency, with 5 of 6 patients being seizure

free or with 67-80% reduced seizures at long-term follow-up[202]. However, CMT stimulation was not effective for the five included subjects with frontal lobe epilepsy.

A potentially key role for the thalamus in Lennox-Gastaut syndrome (LGS) was suggested by rapid recruitment of the CMT in some patients[132]. Early evidence supported potentially effective control of atypical absence seizures characteristic of LGS by targeting the CMT, with reduction in seizure frequency of >87%[203]. As LGS is a uniquely complex disorder with high treatment-resistance and morbidity, these patients may stand to benefit substantially from thalamic neuromodulation. Thus, the recent ESTEL (Electrical Stimulation of Thalamus for Epilepsy of Lennox-Gastaut phenotype), a randomized clinical trial, demonstrated reduced electrographic seizures with bilateral CMT DBS in a cohort of 19 patients with LGS[204]. While outcomes were limited to three months, both diary-recorded and electrographic seizures were less frequent compared to controls.

4.4. Clinical Neuromodulation: Other Types of Epilepsy

Frontal lobe epilepsy, the second most common focal epilepsy, accounts for about one-quarter of medically refractory cases[205] and is often included in clinical trials such as SANTE. Yet evidence of abnormal frontothalamic correlates in epilepsy remain vague and inconclusive[206,207]. In the SANTE trial, ANT stimulation did not significantly reduce seizures from the frontal (as well as parietal and occipital) lobes[164]. Likewise, in a trial of CMT stimulation that included five patients with frontal lobe epilepsy, only one had clinically-reduced seizures[202]. A recent case report of a patient with bilateral frontotemporal epilepsy demonstrated a meaningful decrease in seizure frequency and intensity after RNS of the CMT

complex combined with VNS, though improved awareness during seizures was perhaps the more notable result[208]. Interestingly, the degree of thalamic involvement has been linked to poorer postsurgical outcomes in a stereo-electroencephalography (SEEG) study involving a diverse series of patients comprising multiple epilepsy categories (TLE, “temporal plus”, bitemporal, opercular, motor-premotor)[209]. These preliminary observations suggest there may be a role for thalamic neuromodulation in non-temporal focal epilepsies, but much work remains to be done.

Moreover, there is a paucity of laboratory and clinical studies investigating the thalamus in epilepsies of parietal, occipital, insular, and multifocal origin as well as in persistent seizures following trauma, infection, and stroke. Closed-loop CMT stimulation demonstrated clinical efficacy in seven patients with refractory focal epilepsy involving various neocortical regions[194]. That study showed an 80% mean reduction in disabling seizures and 67% reduction of all seizures. Stimulation was initiated in response to 3-5 Hz spike-wave thalamic discharges. In another trial, detection of seizure onset in the CMT by RNS was characterized by increasing amplitude alpha waves, and these electrographic signals correlated with clinical seizure presentation[210]. There were relatively few reported adverse events across studies, although careful selection of parameters was noted to be important for minimizing paresthesias. Interestingly, targeting the anterior ventrolateral CMT slightly more dorsally led to >50% reduction in 7 of 10 multilobar epilepsy patients[139]. That such slight changes in target might have dramatic therapeutic effects highlights both the promise and current peril of thalamic neuromodulation for epilepsy: while there are frequent reports of dramatic benefits, without the requisite attention to underlying seizure mechanisms and without sufficient knowledge of the relevant thalamic circuitry, inconsistent outcomes may be observed, potentially leading to failed

or inconclusive studies that dampen enthusiasm for this approach, or render it a poorly-reasoned "hit or miss" strategy much like VNS.

5. Future Directions

5.1. Improving Peri-Ictal States of Impaired Awareness

Prolonged periods of cognitive impairment and loss-of-awareness (LOA) during and after seizures are major sources of seizure-related morbidity and often significantly impair quality of life[211,212]. The key role of the thalamus linking cortex with brainstem arousal networks suggests leveraging thalamocortical circuitry to improve peri-ictal states of impaired consciousness is a reasonable goal, and animal studies (described above) provided early proof-of-concept. In humans, the presence of focal aware versus focal impaired seizures in TLE has been associated with constitutive changes in thalamic-related anatomy, functional connectivity, and electrophysiology[121,191], bolstering the case that thalamic-directed neuromodulation may have a role in counteracting peri-ictal LOA. In cases where seizures cannot be eliminated or substantially reduced, this potential benefit may nonetheless be of significant value and has motivated the ongoing Stimulation of the Thalamus for Arousal Restoration in Temporal Lobe Epilepsy (START) Trial (NCT04897776).

5.2. Responsive Neurostimulation in the Thalamus

From a graph theory perspective, the thalamus is likely to have the highest connectivity of any node in the seizure network due to its extensive inputs and outputs[210]. RNS systems typically detect ictal activity from electrocorticography (ECoG) strips or depth electrodes. Because seizures can originate in areas of cortex unsampled by ECoG or depth electrodes, thalamic

recordings may more reliably detect the onset of seizure activity due to the presence of a thalamic focus or propagation through convergent cortico-thalamic loops. However, while the thalamus may therefore be a useful "choke point" for seizure control, how that compares to direct stimulation of the seizure onset zone, which is typically regarded as the most effective neuromodulatory intervention[148,164], has yet to be established. Further, RNS provides a unique opportunity for chronic ambulatory recordings of seizures and potential network changes in "real-life" environments, especially if the volume of data that can be stored is expanded.

The mechanism by which RNS treats epilepsy stems not only from its unique capacity for closed-loop stimulation, but also from its chronic network related effects involving multiple nodes. As such, the thalamus is an intuitive target for both recording and stimulation due to its role in modulating cortico-cortical synchrony and coherence. An analysis of ECoG recordings from 11 RNS patients found no association between improved long-term clinical outcomes and direct interruption of pre-ictal or ictal activity but demonstrated significant relationships between those outcomes and indirect effects including spontaneous ictal inhibition, frequency modulation, and ictal duration modulation[213]. Moreover, a study across three large epilepsy centers showed that preoperative iEEG metrics of network synchronizability could predict the likelihood of successful RNS therapy, as this may index the "perturbability" of the epileptic network[214]. Notably, a large decrease in synchronizability at the time of seizure onset was found to be associated with poor RNS outcomes. This provides evidence that network stabilization in the long run is a primary mechanism of seizure palliation, and that thalamic neuromodulation may offer a scenario to fully leverage the advantages of RNS.

5.3. Novel Thalamic Circuit Targets

The ANT and CMT are thus far the most clinically relevant nuclei, followed by the pulvinar[215]. A few nuclei in the thalamus are sometimes designated as "limbic" nuclei, a group which most notably includes the ANT and sometimes the PuM[216,217]. While this grouping is somewhat fuzzy, these limbic nuclei may roughly be seen as directly participating in seizure hyperexcitability, particularly for TLE; while intralaminar nuclei may play the primary role in the seizure-associated sequelae and morbidity, especially following generalized seizures[124]. Evidence for the utility of other thalamic nuclei, so far, is dominated by animal studies with limited preliminary trials on the human ANT, CMT, and pulvinar. Nonetheless, due to the heterogeneity of seizure types, the door should remain open to a variety of potential thalamic control points and approaches. The specific targeting within these nuclei may have varying efficacy at treating each type of epilepsy, so there remains much to answer with regards to the ideal target that can provide the best outcomes. Additionally, to what degree of precision RNS will have in targeting specific regions of these nuclei, and what the parameters will provide the best seizure freedom with the least side effects are still uncharted.

5.4. "Other" Thalamic Nuclei

5.4.1. Central Lateral Nucleus

The central lateral (CL) nucleus appears to be a significant control point for improving postictal arousal states (see *START trial, NCT04897776*). DBS targeting the CL nucleus improved functional recovery after traumatic brain injury[218]. Further, CL stimulation-induced cortical slow-wave activity in rats was notably distinct from neuronal population in other thalamic nuclei[124]. Building on this work, the same group demonstrated that CL stimulation in the

postictal period prevented cortical slow waves and was associated with performance improvement in a shock-escape task[219].

5.4.2. Midline Nucleus Reuniens

Physiologic evidence of thalamic midline nucleus reuniens involvement in seizures was demonstrated in rat models of medial temporal lobe epilepsy[220]. Although relatively small, the midline nucleus reuniens mediates connections between specific hippocampal structures (CA1) and medial prefrontal cortex[216,221,222]. While limited in its conclusions, an SEEG study of three patients demonstrated recruitment of the midline thalamus in seizure initiation[223].

5.4.3. Mediodorsal Nucleus

While its role is not yet well-defined, the mediodorsal (MD) thalamic nucleus may be involved in performance on several cognitive tasks[224]. Decreased connectivity on fMRI between the MD nucleus and multiple cortical and subcortical structures was found in patients with idiopathic generalized epilepsy[225]. While evidence for CMT stimulation for treating IGE significantly exceeds that for the MD, the heterogeneity of generalized epilepsies suggests that increased knowledge of precise connectivity disturbances may yield more specialized targets[226].

5.4.4. Parafascicular Nucleus

The parafascicular (Pf) nucleus is inextricably linked to the CM nucleus. Focus on the Pf nucleus reveals a strong association with the basal ganglia and subcortical structures. Specifically, nigral projections to the rat Pf nucleus via layers of the superior colliculus were exploited in control of both genetic absence and temporal lobe epilepsy models[227,228]. While the precise

physiological effects may not have human parallels, such research provides a possible basis for neuromodulation of subcortical-cortical networks.

6. Conclusion

The thalamus has become an increasingly attractive target for neuromodulation for drug-resistant epilepsy, including for types of epilepsy that have not traditionally been surgically addressed. Ongoing studies revealing the structure and function of various thalamic nuclei and their responses to modulation provide an ever-growing foundation for well-informed interventions. The thalamus is likely to become a critical and routinely utilized target for network-based seizure treatment.

7. Expert Opinion

While there is increasing awareness of the potential value of thalamic neuromodulation for the treatment of epilepsy, and clinical trials are beginning to formally assess some specific strategies beyond established ANT DBS, such as START for maintenance of awareness through seizures and the ESTEL trial for LGS, the status of thalamic neuromodulation in routine surgical epilepsy practice is controversial. Formally, so long as the seizures are believed to be focal (with no more than 2 known foci), thalamic RNS is technically "on-label" in the U.S. Nonetheless, there is debate among clinicians about whether there are sufficient data to warrant thalamic implantation. Here, we briefly discuss a few increasingly utilized strategies we believe are representative of the current status of thalamic neuromodulation.

7.1. Augmentation of Cortical Neuromodulation with Thalamic Leads

In “traditional” RNS, the goal has been to place the lead(s) in or as near to the cortical seizure onset zone as possible. The success of that approach is implicitly tied to the accuracy of that localization and the breadth of the target. In situations where the onset zone is somewhat ambiguous or known to be broad, some groups may consider augmentation of a cortical RNS lead with a thalamic lead. The hope, here, is to address the cortical target in the typical direct fashion as well as indirectly via the thalamus. There are as yet no adequate clinical studies to determine the true value of this approach, but the premise is sound. The alternative would be to place a second cortical lead, but often there is no principled reason to choose a secondary cortical site, whereas a thalamic implantation can be grounded at least in the knowledge of corticothalamic anatomy and physiology. Therefore, unless there is a clearly more suitable secondary cortical target, the choice of an appropriate thalamic nucleus (e.g., ANT for temporal lobe epilepsy or CM for frontal lobe epilepsy) is likely technically and ethically justifiable.

7.2. Bilateral Thalamic Neuromodulation

7.2.1. Bilateral Bi-focal Epilepsy

Bilateral epilepsy with two known foci is best exemplified by the relatively common scenario of bilateral mesial temporal lobe epilepsy. Typically, clinicians may implant bilateral hippocampal RNS leads or bilateral ANT DBS leads. The choice between these two approaches derives primarily from the preferences and experiences of a center’s clinical team, because there is as yet no direct head-to-head comparison of these techniques. One could reasonably substitute bilateral ANT RNS for DBS, giving up the possible benefit of more continuous stimulation but gaining the benefit of objective seizure tracking. The value of objective seizure monitoring can be

significant, both for the tuning of stimulation parameters and for the adjustment of medications. Therefore, that strategy could be reasonably selected with a sufficient rationale.

7.2.2. Multi-focal Epilepsy

When there are more than two foci, RNS becomes technically "off-label" in the U.S. Here, as with any decision to pursue an off-label approach, the relatively unknown value must be weighed against a patient's need for seizure palliation. On the one hand, epilepsy can be debilitating and, under-treated, life-threatening. On the other, the implantation of deep leads into subcortical structures like and including the thalamus are routine in neurosurgical practice, and the potential risks are fairly well understood. Meanwhile, any cortical implantation strategy might be doomed to failure given a broad, multi-focal seizure pattern. Therefore, if the patient and clinical team are sufficiently motivated and informed, and given the increasing availability of data demonstrating the likely benefit of at least some forms of thalamic neuromodulation for seizure mitigation, this approach could also be considered reasonable and worthwhile.

7.3. Thalamic Neuromodulation for the Treatment of Generalized Epilepsy

Primary generalized epilepsies are not typically regarded as just an elaboration of a focal seizure pathology, but rather as a relatively distinct entity[229], and one that has not traditionally been subject to neurosurgical intervention. To the extent that one perceives generalized epilepsy as a fundamentally different disease, neurosurgical intervention may appear wholly novel and experimental. Conversely, the fact that generalized epilepsies may arise from a thalamic circuit mechanism, the rationale for thalamic neuromodulation would seem more intuitive and convincing. Early studies suggest there may be significant value of thalamic stimulation for

generalized epilepsy[188,230,231], but larger and more controlled studies are just getting underway. Again, a balanced treatment of a patient's need, the possible benefits, and the potential risks will guide different groups in different directions based upon their own experience and comfort with this and similar approaches. In cases where there is a decision to proceed, at least retrospective data collection, including objective pre-active-RNS and post-active-RNS records, would benefit the community broadly.

7.4. Local Field Potentials in Neuromodulation for Epilepsy

Reliable neurophysiologic biomarkers for detection of the myriad seizure types and networks have thus far remained elusive[232,233]. In comparison, the study of chronic local field potential (LFP) recordings for closed-loop DBS in Parkinson's disease (PD) has recently expanded dramatically and could potentially serve as a model paradigm[234]. Specifically, the study of LFPs in the context of PD has yielded information about what types of signals (e.g., beta-band synchronization) are most likely to be useful as control signals for closed-loop control of PD symptoms[235-238]. Analogously, neuromodulation devices for epilepsy with chronic recording ability may likewise allow us to examine LFPs for neural signatures of seizures and perhaps even their impending onset, to more effectively avert them[239,240]. Given the heterogeneity of seizure networks across individuals, these signatures may even be patient-specific, thus arguing for the importance of personalized closed-loop therapies.

7.5. Thalamic Recordings Prior to Permanent Stimulator Implant

The use of thalamic stereoencephalography (SEEG) to determine whether an individual's seizures can, in fact, be detected may be useful to determine whether thalamic neuromodulation

is potentially feasible. Furthermore, multiple thalamic SEEG leads may be used to determine where, precisely, seizure-related signals are most prominent and thereby guide implantation of a permanent DBS or RNS lead. One might even consider a trial run of test stimulation in the epilepsy monitoring unit, though the proper measure of its effect (e.g., electrographic versus clinical seizures) is unknown and the value of that approach in the short term is highly uncertain. We would argue that if a team's consensus is that an individual may benefit from a permanent thalamic lead for DBS or RNS, gathering additional information to maximize the value of that strategy can be worthwhile, though the potential risks associated with additional SEEG leads should be communicated.

Funding:

This manuscript has not been funded.

Declaration of Interest:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer Disclosures:

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Collaborators GBDE. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Apr;18(4):357-375.
2. Begley CE, Durgin TL. The direct cost of epilepsy in the United States: A systematic review of estimates. Epilepsia. 2015 Sep;56(9):1376-87.
3. Kramer MA, Cash SS. Epilepsy as a Disorder of Cortical Network Organization. The Neuroscientist. 2012;18(4):360-372.
4. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314-9.
5. Chen Z, Brodie MJ, Liew D, et al. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurol. 2018 Mar 1;75(3):279-286.
6. Perucca E, Brodie MJ, Kwan P, et al. 30 years of second-generation antiseizure medications: impact and future perspectives. Lancet Neurol. 2020 Jun;19(6):544-556.
7. Spencer SS. Neural Networks in Human Epilepsy: Evidence of and Implications for Treatment. Epilepsia. 2002;43(3):219-227.
8. van Diessen E, Zweiphenning WJEM, Jansen FE, et al. Brain Network Organization in Focal Epilepsy: A Systematic Review and Meta-Analysis. PLOS ONE. 2014;9(12):e114606.
9. Pittau F, Megevand P, Sheybani L, et al. Mapping epileptic activity: sources or networks for the clinicians? Front Neurol. 2014;5:218.
10. Amorim-Leite R, Remick M, Welch W, et al. History of the Network Approach in Epilepsy Surgery. Neurosurg Clin N Am. 2020 Jul;31(3):301-308.
11. Zhu J, Xu C, Zhang X, et al. The thalamus-precentral gyrus functional connectivity changes in epilepsy patients following vagal nerve stimulation. Neurosci Lett. 2021 Apr 23;751:135815.
12. Ryvlin P, Rheims S, Hirsch LJ, et al. Neuromodulation in epilepsy: state-of-the-art approved therapies. Lancet Neurol. 2021 Dec;20(12):1038-1047.
13. Carron R, Roncon P, Lagarde S, et al. Latest Views on the Mechanisms of Action of Surgically Implanted Cervical Vagal Nerve Stimulation in Epilepsy. Neuromodulation. 2022 Sep 1.
14. Yu T, Wang X, Li Y, et al. High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. Brain. 2018 Sep 1;141(9):2631-2643.
15. Fisher RS, Velasco AL. Electrical brain stimulation for epilepsy. Nature Reviews Neurology. 2014 2014/05/01;10(5):261-270.
16. Tripoliti E, Limousin P, Foltynie T, et al. Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. Mov Disord. 2014 Apr;29(4):532-8.
17. Lizarraga KJ, Gnanamanogaran B, Al-Ozzi TM, et al. Lateralized Subthalamic Stimulation for Axial Dysfunction in Parkinson's Disease: A Randomized Trial. Mov Disord. 2022 May;37(5):1079-1087.
18. Jones EG. The thalamus. Second edition. Cambridge, UK ; New York : Cambridge University Press, 2007.; 2007.

19. Mendoza JE, Foundas AL. The Thalamus. Clinical Neuroanatomy: A Neurobehavioral Approach. New York, NY: Springer New York; 2008. p. 195-211.
20. Zhou H, Schafer RJ, Desimone R. Pulvinar-Cortex Interactions in Vision and Attention. Neuron. 2016 Jan 6;89(1):209-20.
21. Benarroch EE. Pulvinar: associative role in cortical function and clinical correlations. Neurology. 2015 Feb 17;84(7):738-47.
22. Bertini C, Pietrelli M, Braghittoni D, et al. Pulvinar Lesions Disrupt Fear-Related Implicit Visual Processing in Hemianopic Patients. Front Psychol. 2018;9:2329.
23. Jaramillo J, Mejias JF, Wang XJ. Engagement of Pulvino-cortical Feedforward and Feedback Pathways in Cognitive Computations. Neuron. 2019 Jan 16;101(2):321-336 e9.
24. Homman-Ludiye J, Bourne JA. The medial pulvinar: function, origin and association with neurodevelopmental disorders. Journal of anatomy. 2019 Sep;235(3):507-520.
25. Homman-Ludiye J, Mundinano IC, Kwan WC, et al. Extensive Connectivity Between the Medial Pulvinar and the Cortex Revealed in the Marmoset Monkey. Cerebral cortex (New York, NY : 1991). 2020 Mar 14;30(3):1797-1812.
26. Rikhye RV, Wimmer RD, Halassa MM. Toward an Integrative Theory of Thalamic Function. Annual Review of Neuroscience. 2018;41(1):163-183.
27. Jones EG. The thalamic matrix and thalamocortical synchrony. Trends in Neurosciences. 2001;24(10):595-601.
28. Sherman SM. Thalamus plays a central role in ongoing cortical functioning. Nat Neurosci. 2016 Apr;19(4):533-41.
29. Halassa MM, Sherman SM. Thalamocortical Circuit Motifs: A General Framework. Neuron. 2019;103(5):762-770.
30. Muller EJ, Munn B, Hearne LJ, et al. Core and matrix thalamic sub-populations relate to spatio-temporal cortical connectivity gradients. Neuroimage. 2020 Nov 15;222:117224.
31. Cappe C, Morel A, Barone P, et al. The thalamocortical projection systems in primate: an anatomical support for multisensory and sensorimotor interplay. Cerebral cortex (New York, NY : 1991). 2009 Sep;19(9):2025-37.
32. Georgescu IA, Popa D, Zagrean L. The Anatomical and Functional Heterogeneity of the Mediodorsal Thalamus. Brain Sci. 2020 Sep 9;10(9).
33. Campi KL, Bales KL, Grunewald R, et al. Connections of auditory and visual cortex in the prairie vole (Microtus ochrogaster): evidence for multisensory processing in primary sensory areas. Cerebral cortex (New York, NY : 1991). 2010 Jan;20(1):89-108.
34. Tyll S, Budinger E, Noesselt T. Thalamic influences on multisensory integration. Commun Integr Biol. 2011 Jul;4(4):378-81.
35. Antunes FM, Malmierca MS. Corticothalamic Pathways in Auditory Processing: Recent Advances and Insights From Other Sensory Systems. Front Neural Circuits. 2021;15:721186.
36. Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain research reviews. 2002;39(2-3):107-140.
37. Llinas R, Ribary U, Contreras D, et al. The neuronal basis for consciousness. Philos Trans R Soc Lond B Biol Sci. 1998 Nov 29;353(1377):1841-9.
38. Baker R, Gent TC, Yang Q, et al. Altered activity in the central medial thalamus precedes changes in the neocortex during transitions into both sleep and propofol anesthesia. J Neurosci. 2014 Oct 1;34(40):13326-35.

39. Redinbaugh MJ, Phillips JM, Kambi NA, et al. Thalamus Modulates Consciousness via Layer-Specific Control of Cortex. Neuron. 2020 Apr 8;106(1):66-75 e12.
40. Pouchelon G, Gambino F, Bellone C, et al. Modality-specific thalamocortical inputs instruct the identity of postsynaptic L4 neurons. Nature. 2014 Jul 24;511(7510):471-4.
41. Alzu'bi A, Homman-Ludiye J, Bourne JA, et al. Thalamocortical Afferents Innervate the Cortical Subplate much Earlier in Development in Primate than in Rodent. Cerebral cortex (New York, NY : 1991). 2019 Apr 1;29(4):1706-1718.
42. Beierlein M, Connors BW. Short-term dynamics of thalamocortical and intracortical synapses onto layer 6 neurons in neocortex. J Neurophysiol. 2002 Oct;88(4):1924-32.
43. Zarrinpar A, Callaway EM. Local connections to specific types of layer 6 neurons in the rat visual cortex. J Neurophysiol. 2006 Mar;95(3):1751-61.
44. Crandall SR, Patrick SL, Cruikshank SJ, et al. Infrabarrels Are Layer 6 Circuit Modules in the Barrel Cortex that Link Long-Range Inputs and Outputs. Cell Rep. 2017 Dec 12;21(11):3065-3078.
45. Sherman SM, Guillery RW. The role of the thalamus in the flow of information to the cortex. Philos Trans R Soc Lond B Biol Sci. 2002 Dec 29;357(1428):1695-708.
46. Thomson AM. Neocortical layer 6, a review. Front Neuroanat. 2010;4:13.
47. Prasad JA, Carroll BJ, Sherman SM. Layer 5 Corticofugal Projections from Diverse Cortical Areas: Variations on a Pattern of Thalamic and Extrathalamic Targets. J Neurosci. 2020 Jul 22;40(30):5785-5796.
48. Guillery RW, Sherman SM. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron. 2002 Jan 17;33(2):163-75.
49. Kinomura S, Larsson J, Gulyas B, et al. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. Science. 1996 Jan 26;271(5248):512-5.
50. Poulet JF, Fernandez LM, Crochet S, et al. Thalamic control of cortical states. Nat Neurosci. 2012 Jan 22;15(3):370-2.
51. Nakajima M, Halassa MM. Thalamic control of functional cortical connectivity. Current opinion in neurobiology. 2017 Jun;44:127-131.
52. Schmitt LI, Wimmer RD, Nakajima M, et al. Thalamic amplification of cortical connectivity sustains attentional control. Nature. 2017 2017/05/01;545(7653):219-223.
53. Honjoh S, Sasai S, Schiereck SS, et al. Regulation of cortical activity and arousal by the matrix cells of the ventromedial thalamic nucleus. Nat Commun. 2018 May 29;9(1):2100.
54. Phillips JM, Kambi NA, Redinbaugh MJ, et al. Disentangling the influences of multiple thalamic nuclei on prefrontal cortex and cognitive control. Neurosci Biobehav Rev. 2021 Sep;128:487-510.
55. Reinhold K, Lien AD, Scanziani M. Distinct recurrent versus afferent dynamics in cortical visual processing. Nat Neurosci. 2015 Dec;18(12):1789-97.
56. Theyel BB, Llano DA, Sherman SM. The corticothalamocortical circuit drives higher-order cortex in the mouse. Nat Neurosci. 2010 Jan;13(1):84-8.
57. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci. 2005 Oct;9(10):474-80.
58. Saalmann YB, Pinsk MA, Wang L, et al. The pulvinar regulates information transmission between cortical areas based on attention demands. Science. 2012 Aug 10;337(6095):753-6.

59. Halassa MM, Kastner S. Thalamic functions in distributed cognitive control. Nat Neurosci. 2017 Dec;20(12):1669-1679.
60. Weyand TG. The multifunctional lateral geniculate nucleus. Rev Neurosci. 2016 Feb;27(2):135-57.
61. Halassa MM, Chen Z, Wimmer RD, et al. State-dependent architecture of thalamic reticular subnetworks. Cell. 2014 Aug 14;158(4):808-821.
62. Durkin JM, Aton SJ. How Sleep Shapes Thalamocortical Circuit Function in the Visual System. Annu Rev Vis Sci. 2019 Sep 15;5:295-315.
63. McAlonan K, Brown VJ, Bowman EM. Thalamic reticular nucleus activation reflects attentional gating during classical conditioning. J Neurosci. 2000 Dec 1;20(23):8897-901.
64. Castro-Alamancos MA. Role of thalamocortical sensory suppression during arousal: focusing sensory inputs in neocortex. J Neurosci. 2002 Nov 15;22(22):9651-5.
65. Lewis LD, Voigts J, Flores FJ, et al. Thalamic reticular nucleus induces fast and local modulation of arousal state. Elife. 2015 Oct 13;4:e08760.
66. Matyas F, Komlosi G, Babiczky A, et al. A highly collateralized thalamic cell type with arousal-predicting activity serves as a key hub for graded state transitions in the forebrain. Nat Neurosci. 2018 Nov;21(11):1551-1562.
67. Murata Y, Colonnese MT. Thalamus Controls Development and Expression of Arousal States in Visual Cortex. J Neurosci. 2018 Oct 10;38(41):8772-8786.
68. Martinez-Garcia RI, Voelcker B, Zaltsman JB, et al. Two dynamically distinct circuits drive inhibition in the sensory thalamus. Nature. 2020 Jul;583(7818):813-818.
69. Molnar B, Sere P, Borde S, et al. Cell Type-Specific Arousal-Dependent Modulation of Thalamic Activity in the Lateral Geniculate Nucleus. Cereb Cortex Commun. 2021;2(2):tgab020.
70. Hay YA, Deperrois N, Fuchsberger T, et al. Thalamus mediates neocortical Down state transition via GABAB-receptor-targeting interneurons. Neuron. 2021 Sep 1;109(17):2682-2690 e5.
71. Erro E, Lanciego JL, Gimenez-Amaya JM. Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. Exp Brain Res. 1999 Jul;127(2):162-70.
72. Krout KE, Belzer RE, Loewy AD. Brainstem projections to midline and intralaminar thalamic nuclei of the rat. The Journal of comparative neurology. 2002 Jun 17;448(1):53-101.
73. Fuller PM, Sherman D, Pedersen NP, et al. Reassessment of the structural basis of the ascending arousal system. The Journal of comparative neurology. 2011 Apr 1;519(5):933-56.
74. Houser CR, Vaughn JE, Barber RP, et al. GABA neurons are the major cell type of the nucleus reticularis thalami. Brain Res. 1980 Nov 3;200(2):341-54.
75. Halassa MM, Acsady L. Thalamic Inhibition: Diverse Sources, Diverse Scales. Trends Neurosci. 2016 Oct;39(10):680-693.
76. Lam YW, Sherman SM. Functional organization of the thalamic input to the thalamic reticular nucleus. J Neurosci. 2011 May 4;31(18):6791-9.
77. Huguenard JR, Prince DA. A novel T-type current underlies prolonged Ca(2+)-dependent burst firing in GABAergic neurons of rat thalamic reticular nucleus. J Neurosci. 1992 Oct;12(10):3804-17.

78. Ulrich D, Huguenard JR. Gamma-aminobutyric acid type B receptor-dependent burst-firing in thalamic neurons: a dynamic clamp study. Proc Natl Acad Sci U S A. 1996 Nov 12;93(23):13245-9.
79. Jones EG. Thalamic circuitry and thalamocortical synchrony. Philos Trans R Soc Lond B Biol Sci. 2002 Dec 29;357(1428):1659-73.
80. McCORMICK DA, Pape H-C. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. The Journal of physiology. 1990;431(1):291-318.
81. Nun A, Amzica F, Steriade M. Intrinsic and synaptically generated delta (1–4 Hz) rhythms in dorsal lateral geniculate neurons and their modulation by light-induced fast (30–70 Hz) events. Neuroscience. 1992;51(2):269-284.
82. Soltesz I, Lightowler S, Leresche N, et al. Two inward currents and the transformation of low-frequency oscillations of rat and cat thalamocortical cells. The Journal of physiology. 1991;441(1):175-197.
83. Morison R, Bassett D. Electrical activity of the thalamus and basal ganglia in decorticate cats. Journal of Neurophysiology. 1945;8(5):309-314.
84. Steriade M, Deschenes M, Domich L, et al. Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. Journal of neurophysiology. 1985;54(6):1473-1497.
85. Huguenard JR, McCormick DA. Thalamic synchrony and dynamic regulation of global forebrain oscillations. Trends Neurosci. 2007 Jul;30(7):350-6.
86. Rogala J, Waleszczyk WJ, Leski S, et al. Reciprocal inhibition and slow calcium decay in perigeniculate interneurons explain changes of spontaneous firing of thalamic cells caused by cortical inactivation. J Comput Neurosci. 2013 Jun;34(3):461-76.
87. Paz JT, Huguenard JR. Microcircuits and their interactions in epilepsy: is the focus out of focus? Nat Neurosci. 2015 Mar;18(3):351-9.
88. Ali I, Gandrathi A, Zheng T, et al. Neuropeptide Y affects thalamic reticular nucleus neuronal firing and network synchronization associated with suppression of spike-wave discharges. Epilepsia. 2018 Jul;59(7):1444-1454.
89. Wilson JR. Synaptic organization of individual neurons in the macaque lateral geniculate nucleus. J Neurosci. 1989 Aug;9(8):2931-53.
90. Arcelli P, Frassoni C, Regondi MC, et al. GABAergic neurons in mammalian thalamus: a marker of thalamic complexity? Brain Res Bull. 1997;42(1):27-37.
91. Sherman SM. Interneurons and triadic circuitry of the thalamus. Trends Neurosci. 2004 Nov;27(11):670-5.
92. Govindaiah, Cox CL. Synaptic activation of metabotropic glutamate receptors regulates dendritic outputs of thalamic interneurons. Neuron. 2004 Feb 19;41(4):611-23.
93. Simko J, Markram H. Morphology, physiology and synaptic connectivity of local interneurons in the mouse somatosensory thalamus. J Physiol. 2021 Nov;599(22):5085-5101.
94. Charalambakis NE, Govindaiah G, Campbell PW, et al. Developmental Remodeling of Thalamic Interneurons Requires Retinal Signaling. J Neurosci. 2019 May 15;39(20):3856-3866.
95. Sherman SM. Functioning of Circuits Connecting Thalamus and Cortex. Compr Physiol. 2017 Mar 16;7(2):713-739.

96. Zimmermann E, Ghio M, Pergola G, et al. Separate and overlapping functional roles for efference copies in the human thalamus. Neuropsychologia. 2020 Oct;147:107558.
97. Bolkan SS, Stujenske JM, Parnaudeau S, et al. Thalamic projections sustain prefrontal activity during working memory maintenance. Nature Neuroscience. 2017 2017/07/01;20(7):987-996.
98. Guo ZV, Inagaki HK, Daie K, et al. Maintenance of persistent activity in a frontal thalamocortical loop. Nature. 2017 2017/05/01;545(7653):181-186.
99. Rikhye RV, Gilra A, Halassa MM. Thalamic regulation of switching between cortical representations enables cognitive flexibility. Nature Neuroscience. 2018 2018/12/01;21(12):1753-1763.
100. Ouhaz Z, Fleming H, Mitchell AS. Cognitive Functions and Neurodevelopmental Disorders Involving the Prefrontal Cortex and Mediodorsal Thalamus. Front Neurosci. 2018;12:33.
101. Sorokin JM, Davidson TJ, Frechette E, et al. Bidirectional Control of Generalized Epilepsy Networks via Rapid Real-Time Switching of Firing Mode. Neuron. 2017;93(1):194-210.
102. Wicker E, Forcelli PA. Optogenetic activation of the reticular nucleus of the thalamus attenuates limbic seizures via inhibition of the midline thalamus. Epilepsia. 2021 Sep;62(9):2283-2296.
103. Cruikshank SJ, Lewis TJ, Connors BW. Synaptic basis for intense thalamocortical activation of feedforward inhibitory cells in neocortex. Nat Neurosci. 2007 Apr;10(4):462-8.
104. Gabernet L, Jadhav SP, Feldman DE, et al. Somatosensory integration controlled by dynamic thalamocortical feed-forward inhibition. Neuron. 2005 Oct 20;48(2):315-27.
105. Bruno RM, Sakmann B. Cortex is driven by weak but synchronously active thalamocortical synapses. Science. 2006 Jun 16;312(5780):1622-7.
106. Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. Nat Rev Neurosci. 2013 May;14(5):337-49.
107. Gil Z, Amitai Y. Properties of convergent thalamocortical and intracortical synaptic potentials in single neurons of neocortex. J Neurosci. 1996 Oct 15;16(20):6567-78.
108. Astori S, Luthi A. Synaptic plasticity at intrathalamic connections via CaV3.3 T-type Ca2+ channels and GluN2B-containing NMDA receptors. J Neurosci. 2013 Jan 9;33(2):624-30.
109. Fernandez LMJ, Pellegrini C, Vantomme G, et al. Cortical afferents onto the nucleus Reticularis thalami promote plasticity of low-threshold excitability through GluN2C-NMDARs. Sci Rep. 2017 Sep 25;7(1):12271.
110. Jasper HH, Droogleever-Fortuyn J. Experimental studies on the functional anatomy of petit mal epilepsy. Res Publ Ass nerv ment Dis. 1947;26:272-298.
111. Spiegel EA, Wycis HT. Thalamic recordings in man with special reference to seizure discharges. Electroencephalography and Clinical Neurophysiology. 1950 1950/01/01/;2(1):23-27.
112. Williams D. A study of thalamic and cortical rhythms in petit mal. Brain. 1953 Mar;76(1):50-69.
113. Blumenfeld H. The thalamus and seizures. Arch Neurol. 2002 Jan;59(1):135-7.

114. Natsume J, Bernasconi N, Andermann F, et al. MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. Neurology. 2003 Apr 22;60(8):1296-300.
115. Caciagli L, Allen LA, He X, et al. Thalamus and focal to bilateral seizures: A multiscale cognitive imaging study. Neurology. 2020 Oct 27;95(17):e2427-e2441.
116. Kuzniecky R, Bilir E, Gilliam F, et al. Quantitative MRI in temporal lobe epilepsy: evidence for fornix atrophy. Neurology. 1999 Aug 11;53(3):496-501.
117. Keller SS, Glenn GR, Weber B, et al. Preoperative automated fibre quantification predicts postoperative seizure outcome in temporal lobe epilepsy. Brain. 2017 Jan;140(1):68-82.
118. Concha L, Beaulieu C, Collins DL, et al. White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis. J Neurol Neurosurg Psychiatry. 2009 Mar;80(3):312-9.
119. Keller SS, Richardson MP, O'Muircheartaigh J, et al. Morphometric MRI alterations and postoperative seizure control in refractory temporal lobe epilepsy. Hum Brain Mapp. 2015 May;36(5):1637-47.
120. Barron DS, Fox PT, Pardoe H, et al. Thalamic functional connectivity predicts seizure laterality in individual TLE patients: application of a biomarker development strategy. Neuroimage Clin. 2015;7:273-80.
121. Gonzalez HFJ, Chakravorti S, Goodale SE, et al. Thalamic arousal network disturbances in temporal lobe epilepsy and improvement after surgery. J Neurol Neurosurg Psychiatry. 2019 Oct;90(10):1109-1116.
122. Mirski MA, Ferrendelli JA. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science. 1984 Oct 5;226(4670):72-4.
123. Mirski MA, Ferrendelli JA. Interruption of the connections of the mammillary bodies protects against generalized pentylenetetrazol seizures in guinea pigs. J Neurosci. 1987 Mar;7(3):662-70.
124. Feng L, Motelow JE, Ma C, et al. Seizures and Sleep in the Thalamus: Focal Limbic Seizures Show Divergent Activity Patterns in Different Thalamic Nuclei. J Neurosci. 2017 Nov 22;37(47):11441-11454.
125. Yang AC, Meng DW, Liu HG, et al. The ability of anterior thalamic signals to predict seizures in temporal lobe epilepsy in kainate-treated rats. Epilepsia. 2016 Sep;57(9):1369-76.
126. Rosenberg DS, Mauguiere F, Demarquay G, et al. Involvement of medial pulvinar thalamic nucleus in human temporal lobe seizures. Epilepsia. 2006 Jan;47(1):98-107.
127. Burton H, Jones EG. The posterior thalamic region and its cortical projection in New World and Old World monkeys. The Journal of comparative neurology. 1976 Jul 15;168(2):249-301.
128. Mauguiere F, Baleydier C. Topographical organization of medial pulvinar neurons sending fibres to Brodman's areas 7, 21 and 22 in the monkey. Exp Brain Res. 1978 Apr 14;31(4):605-7.
129. Baleydier C, Morel A. Segregated thalamocortical pathways to inferior parietal and inferotemporal cortex in macaque monkey. Visual neuroscience. 1992 May;8(5):391-405.
130. Velasco M, Velasco F, Velasco AL, et al. Epileptiform EEG activities of the centromedian thalamic nuclei in patients with intractable partial motor, complex partial, and generalized seizures. Epilepsia. 1989 May-Jun;30(3):295-306.

131. Velasco M, Velasco F, Alcala H, et al. Epileptiform EEG activity of the centromedian thalamic nuclei in children with intractable generalized seizures of the Lennox-Gastaut syndrome. Epilepsia. 1991 May-Jun;32(3):310-21.
132. Dalic LJ, Warren AEL, Young JC, et al. Cortex leads the thalamic centromedian nucleus in generalized epileptic discharges in Lennox-Gastaut syndrome. Epilepsia. 2020 Oct;61(10):2214-2223.
133. Martín-López D, Jiménez-Jiménez D, Cabañés-Martínez L, et al. The Role of Thalamus Versus Cortex in Epilepsy: Evidence from Human Ictal Centromedian Recordings in Patients Assessed for Deep Brain Stimulation. Int J Neural Syst. 2017 Nov;27(7):1750010.
134. Westmijse I, Ossenblok P, Gunning B, et al. Onset and propagation of spike and slow wave discharges in human absence epilepsy: a MEG study. Epilepsia. 2009;50(12):2538-2548.
135. Maheshwari A, Noebels JL. Monogenic models of absence epilepsy: windows into the complex balance between inhibition and excitation in thalamocortical microcircuits. Progress in brain research. 2014;213:223-252.
136. Gloor P, Fariello RG. Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. Trends Neurosci. 1988 Feb;11(2):63-8.
137. Wallace RH, Marini C, Petrou S, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. Nat Genet. 2001 May;28(1):49-52.
138. Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. Nature Reviews Neuroscience. 2002;3(5):371-382.
139. Polack PO, Guillemain I, Hu E, et al. Deep layer somatosensory cortical neurons initiate spike-and-wave discharges in a genetic model of absence seizures. J Neurosci. 2007 Jun 13;27(24):6590-9.
140. Noebels J, Avoli M, Rogawski M, et al. Jasper's basic mechanisms of the epilepsies. 2012.
141. Tenney JR, Fujiwara H, Horn PS, et al. Focal corticothalamic sources during generalized absence seizures: a MEG study. Epilepsy research. 2013;106(1-2):113-122.
142. Sorokin JM, Williams A, Ganguli S, et al. Thalamic activity patterns unfolding over multiple time scales predict seizure onset in absence epilepsy. bioRxiv. 2020:2020.03.04.976688.
143. Steriade M, McCormick D, Sejnowski T. Thalamocortical oscillations in the sleeping and aroused brain. Science. 1993;262(5134):679-685.
144. Paz JT, Bryant AS, Peng K, et al. A new mode of corticothalamic transmission revealed in the Gria4(-/-) model of absence epilepsy. Nat Neurosci. 2011 Aug 21;14(9):1167-73.
145. David F, Çarçak N, Furdan S, et al. Suppression of hyperpolarization-activated cyclic nucleotide-gated channel function in thalamocortical neurons prevents genetically determined and pharmacologically induced absence seizures. Journal of Neuroscience. 2018;38(30):6615-6627.
146. Makinson CD, Tanaka BS, Sorokin JM, et al. Regulation of thalamic and cortical network synchrony by Scn8a. Neuron. 2017;93(5):1165-1179. e6.
147. Tung JK, Berglund K, Gross RE. Optogenetic Approaches for Controlling Seizure Activity. Brain Stimul. 2016 Nov-Dec;9(6):801-810.
148. Paz JT, Davidson TJ, Frechette ES, et al. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. Nat Neurosci. 2013 Jan;16(1):64-70.

149. Malpass K. Epilepsy: shining a light on seizure control-optogenetic approach shows promise for treatment and prevention of epilepsies. Nat Rev Neurol. 2013 Jan;9(1):1.
150. Mirski MA, Rossell LA, Terry JB, et al. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res. 1997 Sep;28(2):89-100.
151. Sherdil A, Chabardès S, David O, et al. Coherence between the hippocampus and anterior thalamic nucleus as a tool to improve the effect of neurostimulation in temporal lobe epilepsy: An experimental study. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2020;13(6):1678-1686.
152. Hamani C, Ewerton FI, Bonilha SM, et al. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery. 2004 Jan;54(1):191-5; discussion 195-7.
153. Hamani C, Hodaie M, Chiang J, et al. Deep brain stimulation of the anterior nucleus of the thalamus: effects of electrical stimulation on pilocarpine-induced seizures and status epilepticus. Epilepsy Res. 2008 Feb;78(2-3):117-23.
154. Takebayashi S, Hashizume K, Tanaka T, et al. Anti-convulsant effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal limbic seizure in rats. Epilepsy Res. 2007 May;74(2-3):163-70.
155. Takebayashi S, Hashizume K, Tanaka T, et al. The effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal cortical seizure status in rats. Epilepsia. 2007 Feb;48(2):348-58.
156. Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol. 2016 Jan 1;115(1):19-38.
157. Dostrovsky JO, Levy R, Wu JP, et al. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol. 2000 Jul;84(1):570-4.
158. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology. 1998 Sep;51(3):850-5.
159. Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg. 1996 Feb;84(2):203-14.
160. Chang WJ, Chang WP, Shyu BC. Suppression of cortical seizures by optic stimulation of the reticular thalamus in PV-mhChR2-YFP BAC transgenic mice. Mol Brain. 2017 Sep 2;10(1):42.
161. Liu J, Lee HJ, Weitz AJ, et al. Frequency-selective control of cortical and subcortical networks by central thalamus. Elife. 2015;4:e09215.
162. Bastos AM, Donoghue JA, Brincat SL, et al. Neural effects of propofol-induced unconsciousness and its reversal using thalamic stimulation. bioRxiv. 2020:2020.07.07.190132.
163. Gummadavelli A, Kundishora AJ, Willie JT, et al. Neurostimulation to improve level of consciousness in patients with epilepsy. Neurosurgical Focus FOC. 2015 01 Jun. 2015;38(6):E10.
164. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51(5):899-908.
165. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. Epilepsia. 2018 Feb;59(2):273-290.

166. Laxpati NG, Kasoff WS, Gross RE. Deep Brain Stimulation for the Treatment of Epilepsy: Circuits, Targets, and Trials. Neurotherapeutics. 2014 2014/07/01;11(3):508-526.
167. Tellez-Zenteno JF, McLachlan RS, Parrent A, et al. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology. 2006 May 23;66(10):1490-4.
168. Fisher RS, Uematsu S, Krauss GL, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia. 1992 Sep-Oct;33(5):841-51.
169. Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry. 1984 Aug;47(8):769-74.
170. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015;84(10):1017-1025.
171. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77(13):1295-1304.
172. Skarpaas TL, Morrell MJ. Intracranial stimulation therapy for epilepsy. Neurotherapeutics. 2009 Apr;6(2):238-43.
173. Skarpaas TL, Jarosiewicz B, Morrell MJ. Brain-responsive neurostimulation for epilepsy (RNS((R)) System). Epilepsy Res. 2019 Jul;153:68-70.
174. Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011 Sep 27;77(13):1295-304.
175. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. 2020;95(9):e1244-e1256.
176. Blair RD. Temporal lobe epilepsy semiology. Epilepsy Res Treat. 2012;2012:751510.
177. Sherdil A, Coizet V, Pernet-Gallay K, et al. Implication of Anterior Nucleus of the Thalamus in Mesial Temporal Lobe Seizures. Neuroscience. 2019 2019/10/15/;418:279-290.
178. Heath RG. Electrical self-stimulation of the brain in man. American Journal of Psychiatry. 1963;120(6):571-577.
179. Upton AR, Cooper IS, Springman M, et al. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol. 1985;19-20:223-30.
180. Hodaie M, Wennberg RA, Dostrovsky JO, et al. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia. 2002 Jun;43(6):603-8.
181. Kerrigan JF, Litt B, Fisher RS, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia. 2004 Apr;45(4):346-54.
182. Lim SN, Lee ST, Tsai YT, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia. 2007 Feb;48(2):342-7.
183. Osorio I, Overman J, Giftakis J, et al. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia. 2007 Aug;48(8):1561-71.
184. Elder C, Friedman D, Devinsky O, et al. Responsive neurostimulation targeting the anterior nucleus of the thalamus in 3 patients with treatment-resistant multifocal epilepsy. Epilepsia Open. 2019;4(1):187-192.

185. Herlopian A, Cash SS, Eskandar EM, et al. Responsive neurostimulation targeting anterior thalamic nucleus in generalized epilepsy. Ann Clin Transl Neurol. 2019 Oct;6(10):2104-2109.
186. Kokoszka MA, Panov F, La Vega-Talbott M, et al. Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. J Neurosurg Pediatr. 2018 Apr;21(4):421-427.
187. Singhal NS, Numis AL, Lee MB, et al. Responsive neurostimulation for treatment of pediatric drug-resistant epilepsy. Epilepsy Behav Case Rep. 2018;10:21-24.
188. Welch WP, Hect JL, Abel TJ. Case Report: Responsive Neurostimulation of the Centromedian Thalamic Nucleus for the Detection and Treatment of Seizures in Pediatric Primary Generalized Epilepsy. Front Neurol. 2021;12:656585.
189. Rosenberg DS, Mauguière F, Catenoix H, et al. Reciprocal thalamocortical connectivity of the medial pulvinar: a depth stimulation and evoked potential study in human brain. Cerebral cortex (New York, NY : 1991). 2009 Jun;19(6):1462-73.
190. Filipescu C, Lagarde S, Lambert I, et al. The effect of medial pulvinar stimulation on temporal lobe seizures. Epilepsia. 2019 Apr;60(4):e25-e30.
191. Arthuis M, Valton L, Régis J, et al. Impaired consciousness during temporal lobe seizures is related to increased long-distance cortical-subcortical synchronization. Brain. 2009 Aug;132(Pt 8):2091-101.
192. Chatzikonstantinou A, Gass A, Forster A, et al. Features of acute DWI abnormalities related to status epilepticus. Epilepsy Res. 2011 Nov;97(1-2):45-51.
193. Capecchi F, Mothersill I, Imbach LL. The medial pulvinar as a subcortical relay in temporal lobe status epilepticus. Seizure. 2020 Oct;81:276-279.
194. Burdette DE, Haykal MA, Jarosiewicz B, et al. Brain-responsive corticothalamic stimulation in the centromedian nucleus for the treatment of regional neocortical epilepsy. Epilepsy Behav. 2020 Nov;112:107354.
195. Mullan S, Vailati G, Karasick J, et al. Thalamic lesions for the control of epilepsy. A study of nine cases. Arch Neurol. 1967 Mar;16(3):277-85.
196. Sitnikov AR, Grigoryan YA, Mishnyakova LP. Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of pharmacoresistant epilepsy. Surg Neurol Int. 2018;9:137.
197. Andrade DM, Zumsteg D, Hamani C, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology. 2006 May 23;66(10):1571-3.
198. Krishna V, King NK, Sammartino F, et al. Anterior Nucleus Deep Brain Stimulation for Refractory Epilepsy: Insights Into Patterns of Seizure Control and Efficacious Target. Neurosurgery. 2016 Jun;78(6):802-11.
199. Velasco M, Velasco F, Velasco AL, et al. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. Arch Med Res. 2000 May-Jun;31(3):304-15.
200. Velasco F, Velasco M, Ogarrio C, et al. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia. 1987 Jul-Aug;28(4):421-30.
201. Velasco F, Velasco M, Velasco AL, et al. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia. 1995 Jan;36(1):63-71.

202. Valentín A, García Navarrete E, Chelvarajah R, et al. Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia. 2013 Oct;54(10):1823-33.
203. Velasco AL, Velasco F, Jimenez F, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia. 2006 Jul;47(7):1203-12.
204. Dalic LJ, Warren AEL, Bulluss KJ, et al. DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). Ann Neurol. 2021 Dec 7.
205. Bagla R, Skidmore CT. Frontal lobe seizures. Neurologist. 2011 May;17(3):125-35.
206. Huang W, Lu G, Zhang Z, et al. Gray-matter volume reduction in the thalamus and frontal lobe in epileptic patients with generalized tonic-clonic seizures. J Neuroradiol. 2011 Dec;38(5):298-303.
207. Law N, Smith ML, Widjaja E. Thalamocortical Connections and Executive Function in Pediatric Temporal and Frontal Lobe Epilepsy. AJNR Am J Neuroradiol. 2018 Aug;39(8):1523-1529.
208. Phillips RK, Aghagoli G, Blum AS, et al. Bilateral thalamic responsive neurostimulation for multifocal, bilateral frontotemporal epilepsy: illustrative case. Journal of Neurosurgery: Case Lessons. 2022;3(12).
209. Pizzo F, Roehri N, Giusiano B, et al. The Ictal Signature of Thalamus and Basal Ganglia in Focal Epilepsy: A SEEG Study. Neurology. 2021 Jan 12;96(2):e280-e293.
210. Gummadavelli A, Zaveri HP, Spencer DD, et al. Expanding Brain–Computer Interfaces for Controlling Epilepsy Networks: Novel Thalamic Responsive Neurostimulation in Refractory Epilepsy [Hypothesis and Theory]. Frontiers in Neuroscience. 2018 2018-July-31;12(474).
211. Devinsky O, Spruill T, Thurman D, et al. Recognizing and preventing epilepsy-related mortality: A call for action. Neurology. 2016 Feb 23;86(8):779-86.
212. Blumenfeld H. Epilepsy and the consciousness system: transient vegetative state? Neurol Clin. 2011 Nov;29(4):801-23.
213. Kokkinos V, Sisterson ND, Wozny TA, et al. Association of Closed-Loop Brain Stimulation Neurophysiological Features With Seizure Control Among Patients With Focal Epilepsy. JAMA Neurology. 2019;76(7):800-808.
214. Scheid BH, Bernabei JM, Khambhati AN, et al. Synchronizability predicts effective responsive neurostimulation for epilepsy prior to treatment. medRxiv. 2021:2021.02.05.21250075.
215. Klinger N, Mittal S. Deep brain stimulation for seizure control in drug-resistant epilepsy. Neurosurg Focus. 2018 Aug;45(2):E4.
216. Vertes RP, Linley SB, Hoover WB. Limbic circuitry of the midline thalamus. Neurosci Biobehav Rev. 2015 Jul;54:89-107.
217. Taber KH, Wen C, Khan A, et al. The limbic thalamus. J Neuropsychiatry Clin Neurosci. 2004 Spring;16(2):127-32.
218. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007 Aug 2;448(7153):600-3.
219. Xu J, Galardi MM, Pok B, et al. Thalamic Stimulation Improves Postictal Cortical Arousal and Behavior. J Neurosci. 2020 Sep 16;40(38):7343-7354.
220. Bertram EH, Mangan PS, Zhang D, et al. The midline thalamus: alterations and a potential role in limbic epilepsy. Epilepsia. 2001 Aug;42(8):967-78.

221. Dolleman-van der Weel MJ, Witter MP. The thalamic midline nucleus reuniens: potential relevance for schizophrenia and epilepsy. Neurosci Biobehav Rev. 2020 Dec;119:422-439.
222. Sloan DM, Zhang D, Bertram EH, 3rd. Excitatory amplification through divergent-convergent circuits: the role of the midline thalamus in limbic seizures. Neurobiol Dis. 2011 Aug;43(2):435-45.
223. Romeo A, Issa Roach AT, Toth E, et al. Early ictal recruitment of midline thalamus in mesial temporal lobe epilepsy. Ann Clin Transl Neurol. 2019 Aug;6(8):1552-1558.
224. Pergola G, Danet L, Pitel AL, et al. The Regulatory Role of the Human Mediodorsal Thalamus. Trends Cogn Sci. 2018 Nov;22(11):1011-1025.
225. Wang Z, Zhang Z, Jiao Q, et al. Impairments of thalamic nuclei in idiopathic generalized epilepsy revealed by a study combining morphological and functional connectivity MRI. PLoS One. 2012;7(7):e39701.
226. Zhang CH, Sha Z, Mundahl J, et al. Thalamocortical relationship in epileptic patients with generalized spike and wave discharges--A multimodal neuroimaging study. Neuroimage Clin. 2015;9:117-27.
227. Nail-Boucherie K, Le-Pham BT, Gobaille S, et al. Evidence for a role of the parafascicular nucleus of the thalamus in the control of epileptic seizures by the superior colliculus. Epilepsia. 2005 Jan;46(1):141-5.
228. Chen B, Xu C, Wang Y, et al. A disinhibitory nigra-parafascicular pathway amplifies seizure in temporal lobe epilepsy. Nat Commun. 2020 Feb 17;11(1):923.
229. Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. Curr Neurol Neurosci Rep. 2017 Jun;17(6):48.
230. Zillgitt AJ, Haykal MA, Chehab A, et al. Centromedian thalamic neuromodulation for the treatment of idiopathic generalized epilepsy. Front Hum Neurosci. 2022;16:907716.
231. Sisterson ND, Kokkinos V, Urban A, et al. Responsive neurostimulation of the thalamus improves seizure control in idiopathic generalised epilepsy: initial case series. J Neurol Neurosurg Psychiatry. 2022 May;93(5):491-498.
232. Mormann F, Andrzejak RG, Elger CE, et al. Seizure prediction: the long and winding road. Brain. 2007;130(2):314-333.
233. Kuhlmann L, Lehnertz K, Richardson MP, et al. Seizure prediction — ready for a new era. Nature Reviews Neurology. 2018 2018/10/01;14(10):618-630.
234. Sirica D, Hewitt AL, Tarolli CG, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag. 2021 Aug;11(4):315-328.
235. Rowland NC, De Hemptinne C, Swann NC, et al. Task-related activity in sensorimotor cortex in Parkinson's disease and essential tremor: changes in beta and gamma bands. Front Hum Neurosci. 2015;9:512.
236. Cole SR, van der Meij R, Peterson EJ, et al. Nonsinusoidal Beta Oscillations Reflect Cortical Pathophysiology in Parkinson's Disease. J Neurosci. 2017 May 3;37(18):4830-4840.
237. Ahn M, Lee S, Lauro PM, et al. Rapid motor fluctuations reveal short-timescale neurophysiological biomarkers of Parkinson's disease. J Neural Eng. 2020 Aug 27;17(4):046042.

238. Lauro PM, Lee S, Amaya DE, et al. Decoding Dynamically Shifting States of Parkinson's Disease: Tremor, Bradykinesia, and Effective Motor Control. bioRxiv. 2022:2022.02.12.480213.
239. Scherer M, Milosevic L, Guggenberger R, et al. Desynchronization of temporal lobe theta-band activity during effective anterior thalamus deep brain stimulation in epilepsy. NeuroImage. 2020 2020/09/01/;218:116967.
240. Gadot R, Korst G, Shofty B, et al. Thalamic stereoelectroencephalography in epilepsy surgery: a scoping literature review. J Neurosurg. 2022 Mar 11:1-16.

Articles of High Interest

29. *Halassa MM, Sherman SM. Thalamocortical Circuit Motifs: A General Framework. Neuron. 2019;103(5):762-770.***
This review by Halassa and Sherman proposes a classification of thalamic neurons based on thalamocortical microcircuitry which provides a potential mechanistic basis for understanding thalamic neuromodulation for epilepsy.

164. *Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51(5):899-908.***
This article reports the primary results from the SANTE trial, which is the single most influential trial of thalamic neuromodulation for epilepsy.

204. *Dalic LJ, Warren AEL, Bulluss KJ, et al. DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). Ann Neurol. 2021 Dec 7.***
The ongoing ESTEL trial seems poised to similarly accomplish for the centromedian nucleus in Lennox-Gastaut Syndrome what the SANTE trial accomplished for the anterior nucleus in temporal lobe epilepsy.

Articles of Interest

15. *Fisher RS, Velasco AL. Electrical brain stimulation for epilepsy. Nature Reviews Neurology. 2014 2014/05/01;10(5):261-270.**
This review discusses neurostimulation for epilepsy more generally. It therefore offers useful insights that can either be applied more specifically to the thalamus or used as a jumping-off point for discussion of neuromodulation of seizures as a whole.

87. *Paz JT, Huguenard JR. Microcircuits and their interactions in epilepsy: is the focus out of focus? Nat Neurosci. 2015 Mar;18(3):351-9.**
Paz and Huguenard offer the most microscale analysis of the excitatory and inhibitory interactions and motifs that could potentially underlie seizure networks. The concepts in this paper complement the work by Halassa et al. above.

201. *Velasco F, Velasco M, Velasco AL, et al. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia. 1995 Jan;36(1):63-71.**
All of the many articles by the Velasco groups are of interest and have contributed extensively to the study of the centromedian nucleus in treating generalized epilepsies. This article synthesizes their work and likely informed ongoing as well as future clinical trials.

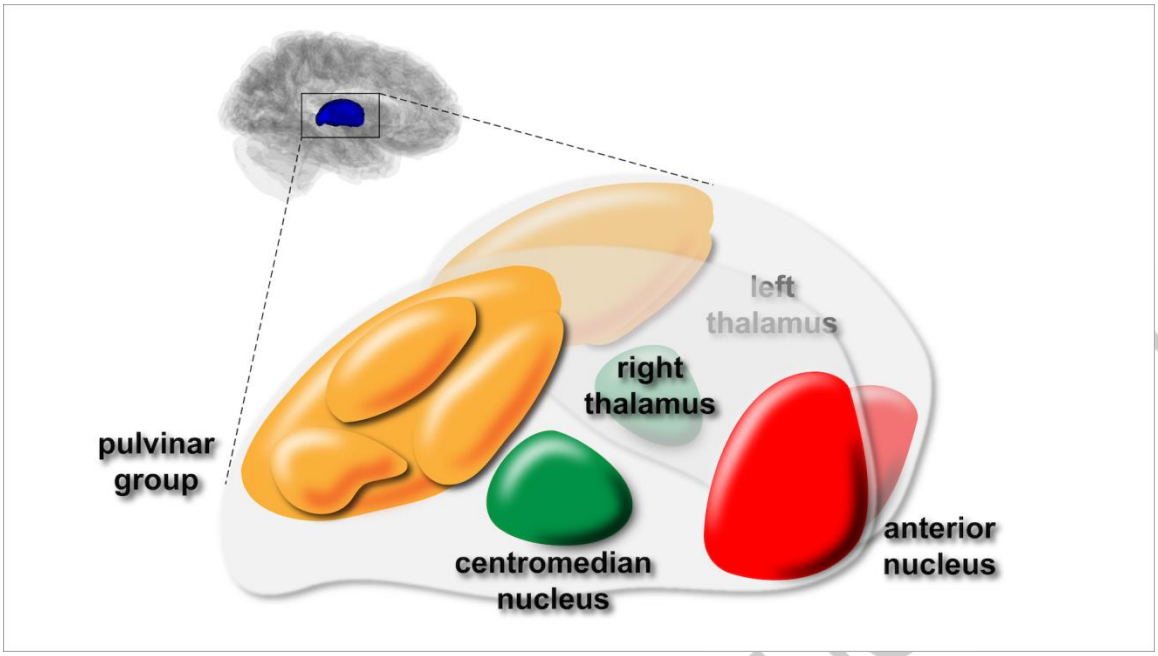

Figure 1

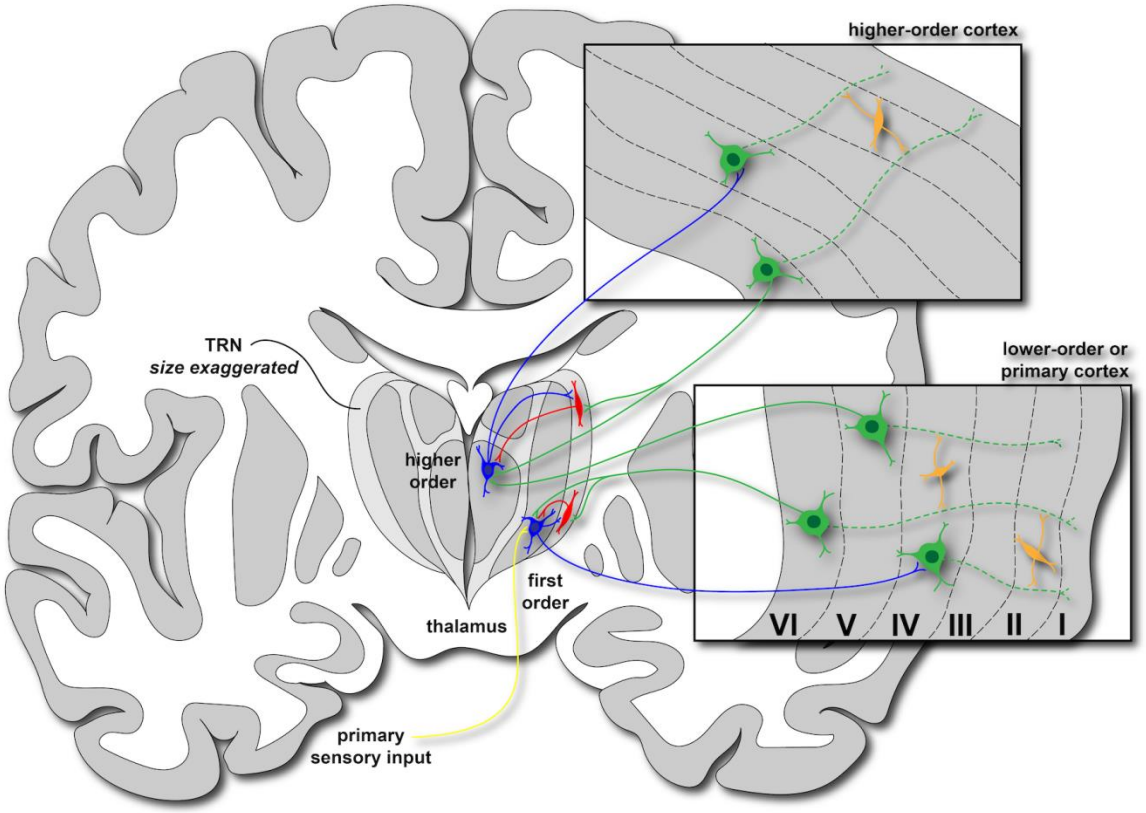

Figure 2

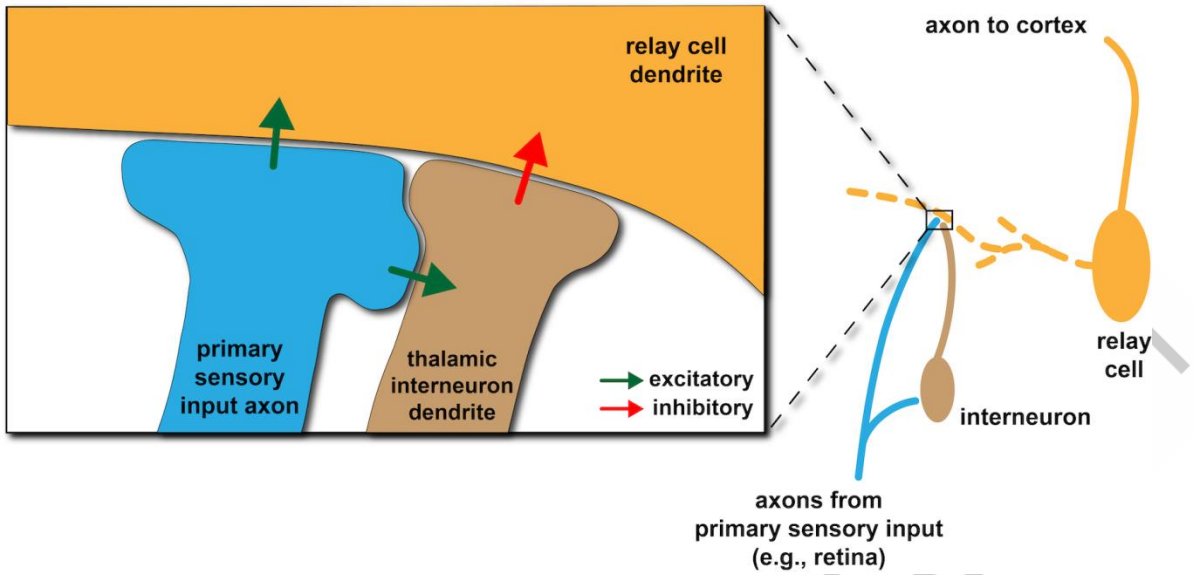

Figure 3

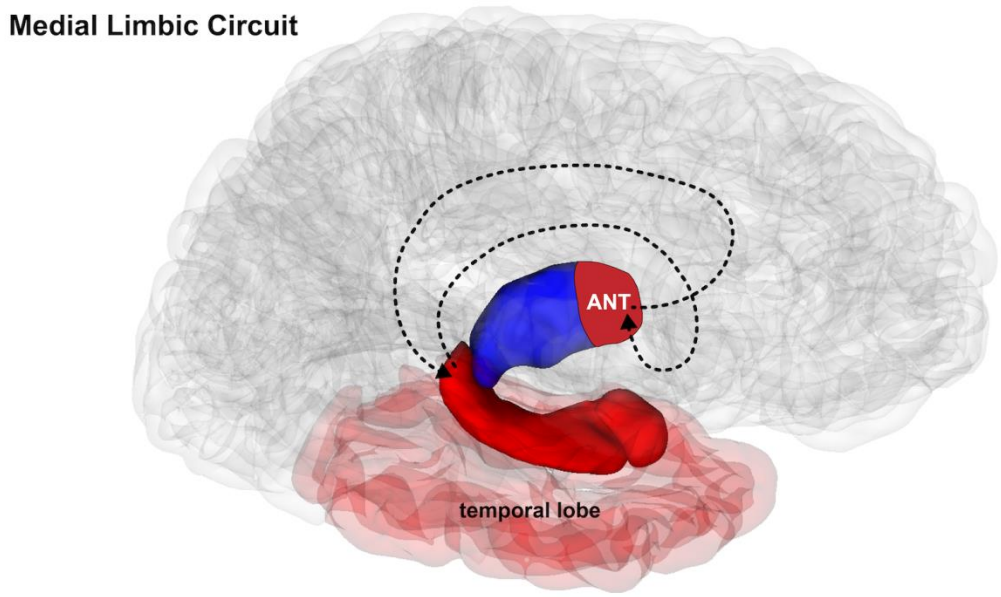

Figure 4

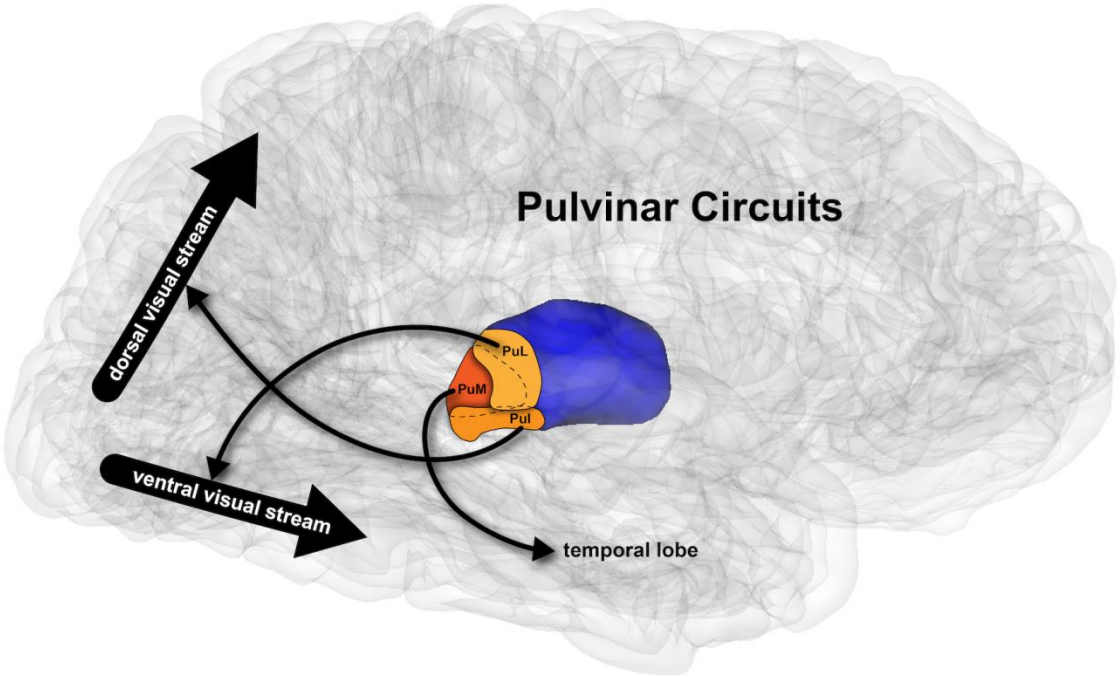

Figure 5