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Advancing the frontiers of thalamic neuromodulation: A review of emerging targets and paradigms

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ABSTRACT

The thalamus is a key structure that plays a crucial role in initiating and propagating seizures. Recent advancements in neuroimaging and neurophysiology have identified the thalamus as a promising target for neuromodulation in drug-resistant epilepsies. This review article presents the latest innovations in thalamic targets and neuromodulation paradigms being explored in pilot or pivotal clinical trials. Multifocal temporal plus or posterior quadrant epilepsies are evaluated with pulvinar thalamus neuromodulation, while centromedian thalamus is explored in generalized epilepsies and Lennox Gastaut syndrome. Multinodal thalamocortical neuromodulation with novel stimulation paradigms such as long bursting or low-frequency stimulation is being investigated to quench the epileptic network excitability. Beyond seizure control, thalamic neuromodulation to restore consciousness is being studied. This review highlights the promising potential of thalamic neuromodulation in epilepsy treatment, offering hope to patients who have not responded to conventional medical therapies. However, it also emphasizes the need for larger randomized controlled trials and personalized stimulation paradigms to improve patient outcomes further.

1. Introduction

Epilepsy is a chronic debilitating condition afflicting millions of people worldwide, with approximately 40% of individuals in the United States continuing to experience seizures despite available treatment options (Engel, 2016). Drug-resistant epilepsy (DRE) is a particularly challenging form of epilepsy, defined as the absence of sustained seizure freedom following appropriate trials of two well-tolerated antiseizure drugs (Kwan et al., 2010). DRE not only results in significant morbidity and mortality but also accounts for a large proportion of the costs associated with epilepsy. While newly diagnosed patients with epilepsy have a SUDEP (Sudden Unexpected Death in Epilepsy) rate of 1 in 10, 000, those with DRE have 90-fold higher rates of SUDEP, hence causing a major concern (Institute of Medicine (US) Committee on the Public Health Dimensions of the Epilepsies, 2012). In addition, cognitive and neuropsychiatric comorbidities, including poor memory, attention, and depression, are highly prevalent in persons with DRE. A higher seizure burden is a major driver of these comorbidities, highlighting the urgent need for innovative therapies to abort seizures in patients with DRE (Institute of Medicine (US) Committee on the Public Health Dimensions of the Epilepsies, 2012). Neuromodulation has emerged as a promising approach for those who are ineligible for resective surgery or have failed epilepsy surgery, offering a potential solution to this unmet need. Among the potential targets for neuromodulation, the thalami have garnered attention due to their extensive connectivity with the cortex and their ability to modulate neural excitability and seizure network. This review article will provide an overview of the current state of the art in thalamic neuromodulation for epilepsy, focusing on ongoing clinical trials and promising future directions for this field.

The thalamus has been well-known to play a role in epilepsy for a long time. In 1949, Hunter and Jasper demonstrated that stimulation of the thalamus induced spike-wave seizures. Further, in 1954, Penfield and Jasper illustrated the use of electrical stimulation caused abortion of seizures through animal models. They proposed that the ictogenesis of spike-wave seizures is mediated by a thalamocortical network (named centrencephalic theory) (Jasper et al., 1955; Roa et al., 2022). This work

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laid the groundwork for developing thalamic neuromodulatory therapies, including open-loop duty cycle (deep brain stimulation-DBS) and closed-loop responsive neurostimulation (RNS). Among the various thalamic targets, the anterior nucleus of the thalamus (ANT) and centromedian (CM) have emerged as promising candidates for modulating seizures in DRE (Ilyas et al., 2022; Zheng et al., 2023). While the efficacy of these thalamic neuromodulation therapies has been extensively reviewed (see references for an excellent review), this article will highlight novel thalamic targets and neuromodulation paradigms in the pilot (explorative or feasibility) or pivotal clinical trials or off-label use in clinical practice. We will provide a brief overview of ongoing and upcoming trials worldwide, emphasizing the exciting potential of thalamic neuromodulation in the treatment of epilepsy.

2. Novel thalamic targets for neuromodulation: Insights from ongoing clinical trials

2.1. Pulvinar nuclei of thalamus

While the ANT and CM have been extensively studied in the context of neuromodulation for DRE, the pulvinar nucleus has received comparatively little attention. The pulvinar is the largest of the thalamic nuclei, consisting of various subnuclei, including the anterior (PuA), medial (PuM), inferior (PuI), and lateral (PuL) pulvinar subnuclei. While the involvement of the PuL in visual processing and its strong connectivity to the occipital lobe is well-established, the role of PuM is not well-understood (Olszewski et al., 1952). However, recent research has shed new light on the potential of PuM as a target for neuromodulation in DRE. For example, Rosenberg et al. conducted a stereo EEG exploration of pulvinar connectivity in patients with DRE, identifying abundant reciprocal connections of PuM with the frontal eye field, prefrontal cortex, temporal neocortex, insula, temporoparietal junction, and the frontoparietal operculum (Rosenberg et al., 2009).

2.1.1. Rationale for Pulvinar neuromodulation

Studies have also demonstrated the recruitment of PuM in temporal lobe epilepsy (TLE). Rosenberg et al. recorded the electrophysiological activity of the PuM (Fig. 1A-B) during sEEG exploration of spontaneous TLE seizures, observing PuM ictal activity in 80% of analyzed 74 seizures. Rhythmic slow waves or rhythmic spikes occurred in seizures arising from mesiotemporal structures, and low voltage fast activity was observed in seizures from the neocortex (Rosenberg et al., 2006). Previous studies have demonstrated the synchrony of the thalamus and remote cortical structures during TLE seizures, particularly in the last phase. Guye et al. particularly explored the pulvinar nucleus of the thalamus in their study and demonstrated that the medial pulvinar nucleus of the thalamus, which has several connections with association cortex, may serve as a relay for spreading epileptic activity in MTLE. They also found a correlation between the degree of thalamocortical synchrony and the presence of an early loss of consciousness and also a better surgical prognosis in patients with low values of thalamocortical couplings at seizure onset (Guye et al., 2006). A recent retrospective analysis using diffusion-weighted MRI imaging demonstrated the involvement of PuM in the maintenance of ictal activity in temporal onset focal status epilepticus. They hence proposed the extensive reciprocal connections between the PuM and the temporoparietal associative areas providing a framework for seizure perpetuation (Capecchi et al., 2020). Based on this evidence, Filipescu et al. conducted a clinical trial to investigate the acute, short-term electroclinical effects of stimulating PuM in patients with TLE. The PuM was stimulated with high-frequency stimulation(130 Hz), 450-microsecond pulse width, and 3–7 s duration at 1–2 mA, immediately after the seizure onset. They observed that patients with pulvinar stimulation had a faster clinical recovery, and the stimulation prevented the progression of focal to bilateral tonic-clonic seizures. Consciousness changes assessed by the Consciousness seizure scale (CSS) were also found to be significantly less elevated in patients with pulvinar stimulation (Filipescu et al., 2019). A study by Evangelista et al. which mainly explored PuM demonstrated the potential role of thalamocortical synchrony in seizure termination in patients with drug-resistant MTLEs. Non-linear correlation analysis in these patients showed a significant increase in synchronization between the thalamus, neocortex, and mesial-temporal region($p < 0.0001$) during seizure termination as compared to the beginning. Hence, targeting thalamocortical synchrony may be a potential therapeutic approach for treating seizures (Evangelista et al., 2015).

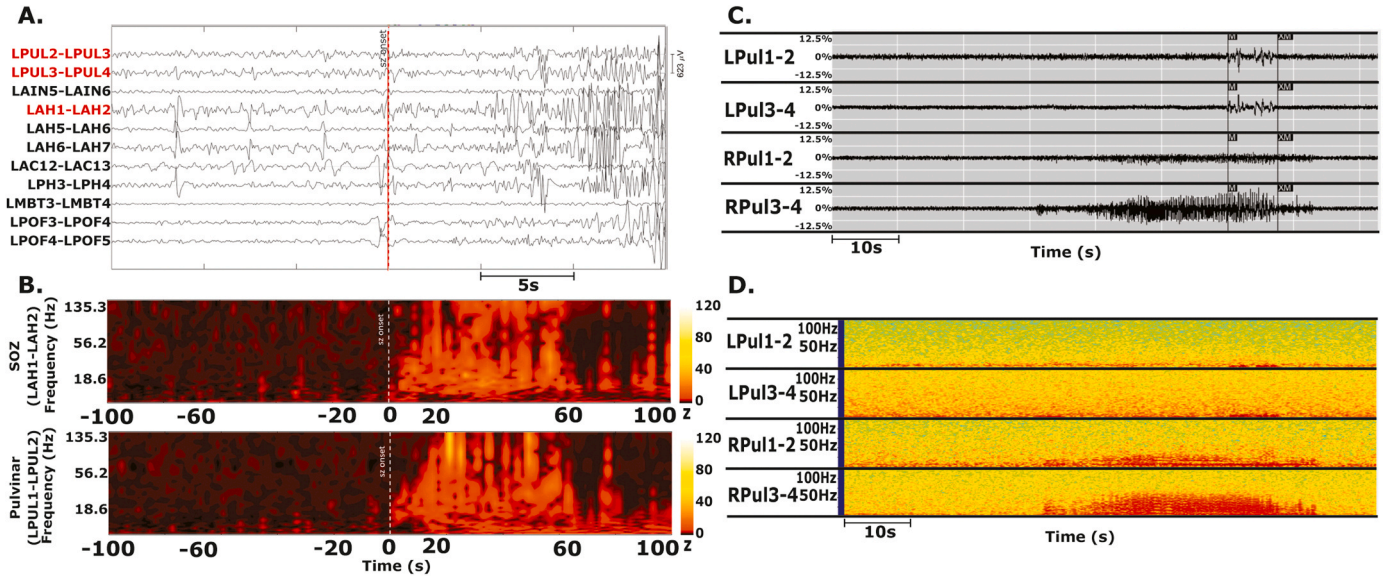


Fig. 1. A-B: Example of thalamocortical stereo EEG recording of a focal impaired awareness seizure (FIAS). Seizure onset was at the left anterior hippocampus (LAH 1–2) with rapid propagation to the left pulvinar (LPul 2–3, Lpul 3–4). Time-frequency decomposition of the seizure using continuous Morlet wavelet transform is depicted in B. The power intensities were z-score normalized with respect to means of pre-ictal power. The vertical white line indicates the seizure onset. C-D: Electrocorticographic (ECoG) recordings from the Responsive Neurostimulation device implanted in the left and right pulvinar nuclei (LPuL, RPul) showing focal seizure lateralized to the right pulvinar nucleus. Spectrographic representation of that seizure in D.

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2.1.2. PULSE study (NCT04692701)

The encouraging results of these studies propelled the investigators to propose an open-label clinical trial called Pulvinar Stimulation in Epilepsy (PULSE). In this pilot study, 18–60-year-old patients with focal or multifocal drug-resistant epilepsy who are inoperable or have failed epilepsy surgery or vagus nerve stimulation (VNS) since 2021 will be recruited for bilateral PuM duty-cycle DBS. This trial aims to measure the seizure reduction percentage, quality of life, and relationship with psychiatric and cognitive comorbidities at the end of 12 months (Assistance Publique Hopitaux De Marseille, 2022).

2.1.3. Pulvinar RNS

Recently, a single retrospective study evaluated the outcomes of PuM-cortical responsive neurostimulation (RNS) in posterior quadrant epilepsies, with all three patients responding positively. One cortical strip or depth electrode was placed at the putative seizure foci, and the second depth electrode was implanted in the PuM ipsilateral to the seizure foci. All three patients were responders with > /= 50% seizure reduction at one-year follow-up, and two patients had a 90% or greater seizure reduction. Thalamic RNS was chosen over DBS for the potential value of the electrographic data that allows ambulatory seizure monitoring (Fig. 1C-D). The other advantage of RNS is its ability to provide responsive, on-demand stimulation with the detection of an incipient seizure, although no clinical study has compared the effectiveness of open duty cycle vs. tailored responsive neurostimulation (Burdette et al., 2021).

Table 1
ONGOING/UPCOMING STUDIES ON THALAMIC NEUROMODULATION IN FOCAL EPILEPSY.

Name of the Study	Target nuclei	Age group	Aim of the study	Method	Primary and Secondary Outcomes
A Study to Evaluate fMRI of Active DBS Stimulation in Epilepsy (Withdrawn due to funding issue) (NCT04753983)	ANT DBS	18 and older	Using fMRI to help guide mapping of brain activity during DBS and also help optimize device settings to reduce seizure severity and number.	The subject will undergo alternating short periods of DBS in the "on" and "off" state with high and low-frequency settings to measure the changes in the brain and for mapping brain activity with DBS	The primary outcome measure will be to map the brain network activation with high and low-frequency ANT stimulation.
A Deep Brain Stimulation System in Epilepsy: Tracking Neural Excitability (NCT03465163)	ANT DBS	18 and older	Aims to use the brain's response to measure the level of seizure susceptibility after electrical stimulation. This measure can be used to provide efficient DBS in each patient for optimal seizure reduction.	B/L implantation of DBS device into the AN nucleus and the hippocampus. Stimulation will be conducted over five phases.	Primary outcome: Change in seizure rate recorded throughout the baseline and in the probe-calibrated DBS phase. Secondary outcome: -To determine if the probing responses provide a seizure susceptibility measure throughout the probing phase. -Change in brain excitability is assessed according to changes in probing response energy before and after stimulation therapy which is measured during the 3rd and 4th phases.
Network Neuro-modulation for Mesial Temporal Lobe Epilepsy (NCT05608408)	ANT DBS	18–65	We aim to show that epilepsy neuromodulation, utilizing low-frequency stimulation and informed by network architecture, is superior to no stimulation or standard high-frequency stimulation in patients with hippocampal epilepsy. This approach results in a considerable reduction in seizure frequency and severity, a decrease in EEG spike counts, and an improvement in memory function.	In a crossover manner, various types of stimulation will be given as follows: Four four-month periods of low-frequency DBS stimulation will take place, with stimulation at one of four sites [the anterior nucleus of the thalamus, entorhinal cortex, piriform cortex, and hippocampal fornix] during each period. The order in which participants receive the stimulation will differ.	Primary: Number of seizures as self-reported by participants at multiple time frames. -Number of seizures as assessed by EEG, number of seizures as assessed by the Percept PC, number of inter-ictal spikes as assessed by the Percept PC at 4 months compared to baseline Secondary: Verbal memory, quality of life
Stimulation of the Thalamus for Arousal Restoral in Temporal Lobe Epilepsy (START) (NCT04897776)	CL DBS	18–75	To understand how thalamic neuromodulation can help restore consciousness in patients whose seizures cannot be controlled.	The device stimulates the central lateral (CL) nuclei in the thalamus to improve conscious arousal and targets the hippocampus for seizure reduction in epilepsy. During the four-month post-implant period, the experimental group will receive hippocampal stimulation for all seizures, and thalamic stimulation at a therapeutic level for seizures lasting more than 5 s, based on physician evaluation. The sham group will receive hippocampal stimulation and sub-therapeutic thalamic stimulation as the control.	The primary outcome of this study is to measure the change in conscious awareness during and following seizures based on the brain responsiveness scale. Secondary outcomes are changes in seizure severity measured using the Liverpool seizure severity questionnaire and changes in the quality of life 20 months post-implant.
Pulvinar Stimulation in Epilepsy: a Pilot Study (PULSE) (NCT04692701)	PuM DBS	18–60	This study aims to understand the role of the pulvinar nucleus in seizure reduction, improvement in quality of life, and cognitive function.	This is an open-label study that involves patients who have focal or multifocal drug-resistant epilepsy not operable or failure of epilepsy surgery or VNS failure who will receive pulvinar stimulation.	The primary outcome measured would be the number of seizures recorded after 12 months of PuM stimulation. Secondary outcomes which would be measured are the score of depression, anxiety score, a score of quality of life, and a score of epilepsy severity.

Abbreviations: fMRI-Functional Magnetic Resonance Imaging, DBS-Deep Brain Stimulation, ANT: Anterior nucleus of thalamus, EEG: Electroencephalogram, CL: Central Lateral, PuM: Medial Pulvinar, VNS: Vagal Nerve Stimulation

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2.1.4. Chronic sensing of the pulvinar

The ability to continuously sense the local field potentials with the Medtronic Percept DBS has opened the possibilities of ambulatory seizure monitoring from the pulvinar DBS. A recent exploratory study demonstrated that temporal lobe seizures can be detected and monitored using a 12.15–17.15 Hz spectral band. The case study highlights the potential of developing an electronic seizure diary from thalamic DBS (Vakilna et al., 2023).

In conclusion, the pulvinar nucleus of the thalamus represents a promising target for neuromodulation in epilepsy, particularly in patients with drug-resistant multifocal epilepsy. Given the connectivity profile of pulvinar thalami, the target may be suitable in patients with posterior quadrant epilepsies and temporal plus epilepsies. With the growing interest in thalamic neuromodulation as a treatment for epilepsy, future studies exploring the role of the pulvinar nucleus in seizure control and cognitive function are warranted Tables 1 and 2.

2.2. Centromedian nucleus of the thalamus

The centromedian (CM) and the parafascicular (Pf) nuclei complex belongs to the intralaminar group of nuclei and is considered a prototypic thalamic projection system. The CM proper, or parvocellular area, and the magnocellular or central lateral nucleus are the two distinct cellular areas that make up the CM. Due to its extensive connections to various cortical and subcortical structures implicated in seizure onset (in generalized epilepsy) and propagation (in focal epilepsy) (Fig. 2A-B), the CM is a desirable target for neuromodulation in DRE. The CM receives input from a wide range of sources, including sensory and motor cranial nerves, cortical input from sensory-motor cortices, and subcortical projections to forebrain limbic and non-limbic sites. Additionally, the CM plays a significant role in controlling states of vigilance, including attention and arousal (Ilyas et al., 2019; Li et al., 2020; Velasco et al., 2021).

2.2.1. Rationale for CM neuromodulation

In 1987, Velasco et al. were the first to describe the benefit of electrical stimulation of centromedian nuclei to treat primary generalized or multifocal uncontrollable seizures and noted improvement in psychological performance (Velasco et al., 1987). They further continued to study CM stimulation in patients with intractable partial motor, complex partial, and generalized seizures. They found that CM participated little in the spread of complex partial or focal motor epileptic discharges but observed that CM had an important role in the initiation and propagation of generalized seizures (Velasco et al., 1989). Shortly after this, Velasco et al. conducted a pilot study to evaluate CM DBS in 13 patients with intractable epilepsy. They noted improvement for generalized tonic-clonic seizures and atypical absences and significant results for Lennox-Gastaut syndrome (LGS) but not for complex partial seizures or focal spikes in frontal regions (Velasco et al., 2000). Based on these preliminary data, there has been a growing interest in using the CM as a target for neuromodulation in the treatment of generalized onset seizures.

Table 2
ONGOING/UPCOMING STUDIES ON THALAMIC NEUROMODULATION IN GENERALIZED EPILEPSY.

Name of the Study	Target nuclei	Age group	Aim of the study	Method	Primary and Secondary Outcomes
RNS System NAUTILUS STUDY (NCT05147571)	CM RNS	12 years and older	To demonstrate the RNS system for thalamic stimulation is safe and effective in patients 12 years or older with drug-resistant IGE	RNS provides closed-loop stimulation if any abnormal activity has been detected neurostimulator delivers electrical stimulation to prevent seizure in the active group vs the system only records the abnormal activity but doesn't deliver electrical stimulation in the sham control group	The primary safety outcome is to monitor a 12-week post-implant serious device-related adverse event rate and the primary effective endpoint is the time to the patient's second GTC during the 9-month effectiveness evaluation period. The study's secondary endpoint is the percentage change in the monthly rate of generalized seizures during the 9-month period. The study also measures the annual rate of serious device-related adverse effects and other important adverse events over two years post-implant. Additionally, it compares pre-implant and post-implant affective status, neurophysiological functioning, sleep, health-related behaviors, and quality of life.
RNS System LGS FEASIBILITY STUDY (NCT05339126)	CM RNS	15 years or older for 1st cohort, 12 years or older for 2nd cohort	To provide early safety and preliminary evidence of effectiveness for brain-responsive neurostimulation of thalamocortical networks for the treatment of generalized seizures in patients with LGS.	Two neurostimulators (one on the left parieto-temporal and one on the right homologous region) and four leads (two in the CM nuclei, and two in the prefrontal cortex) will be placed. Patients will receive three randomly assigned treatment blocks (two active treatments with either high or low-frequency burst stimulation and sham stimulation). After the blinded period of three blocks, patients will transition to a one-year open-label trial, followed by a two-year long-term follow-up trial with appointments every three months.	The primary safety outcome measures are serious device-related adverse events at 12 and 24 months post-implant period and the primary effectiveness outcome is the blinded evaluation period responder rate 12 months post-implant. The secondary measured outcome is the 4-week post-implant rate of SAEs. Other measured outcomes include the rate of relevant SAEs 12 months post-implant, affective status, and cognitive function during the pre-implant, blinded evaluation period, and open-label period, median percent change in drop seizures and tonic-clonic seizures four years post-implant, quality of life, and caregiver burden four years post-implant.

Abbreviations: CM-Centromedian, RNS-Responsive Neurostimulation, IGE-Idiopathic generalized epilepsy, GTC-Generalized tonic clonic, LGS-Lennox Gastaut Syndrome, SAEs-Serious adverse events

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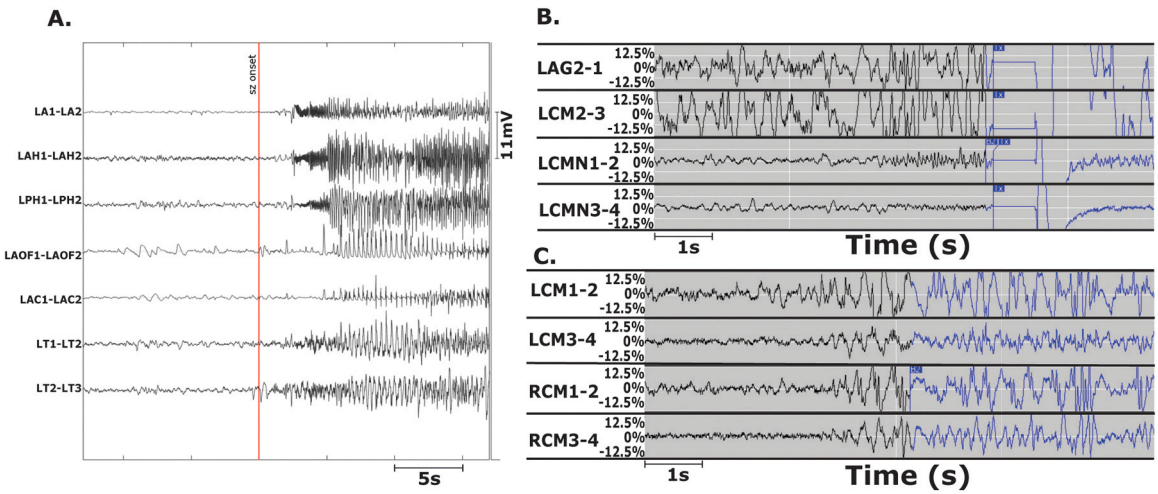


Fig. 2. A: Example of thalamocortical stereo EEG recording of a focal impaired awareness seizure (FIAS). Seizure onset was at the left anterior hippocampus (LAH 1–2) with rapid propagation to the left centromedian thalamus (LT1–2,2–3). B-C: Electrocorticographic (ECoG) recordings from the Responsive Neurostimulation device in multifocal epilepsy (B) and Primary Generalized Epilepsy (C). The neuromodulatory target for multifocal epilepsy was the left angular gyrus (LAG 1–2;3–4) and left centromedian thalamus (LCM1–2; 3–4), while for Generalized Epilepsy was bilateral centromedian thalamus (L/RCM 1–4). The blue line indicates RNS detection followed by a delivered therapy (Tx).

2.2.2. ESTEL trial

The first double-blind, randomized controlled trial to evaluate CM DBS in Lennox-Gastaut Syndrome (LGS) was conducted in Australia (ESTEL trial). Twenty participants (17–37 years) with LGS were enrolled and implanted with CM DBS, and a seizure diary was maintained throughout the study to collect daily seizure counts of each seizure type. Four 24-hour ambulatory EEGs were obtained during the four phases of the study. The stimulation was initiated at 1 V during the blinded phase and increased to 2.5 V bilaterally in two weeks. At the end of the blinded phase, there was a significant seizure reduction (≥50%) in diary-reported seizures in 50% of patients in the stimulation group compared to 22% in the control group. For the 24-hour EEG-recorded seizures, 89% of patients had a ≥ 50% reduction in seizure frequency compared to none in the control group. Patients showed no deterioration in cognitive function. The most common stimulation-related adverse events noted were ipsilateral hand and face/lips paresthesia, which resolved within a few hours to days. However, further studies are needed to identify optimal parameters of stimulation, including amplitude, frequency, and duration, to optimize the therapeutic benefits of CM DBS (Dalic et al., 2022a, 2022b).

2.2.3. CM RNS in Idiopathic Generalized Epilepsy "NAUTILUS STUDY" (NCT05147571)

There has been a growing interest in targeting CM with RNS (Fig. 2C) in drug-resistant Idiopathic Generalized Epilepsy (IGE). Although there are only a few case reports demonstrating the potential of CM RNS in IGE, a phase 3 clinical trial called the RNS System NAUTILUS study has recently started recruiting subjects. The NAUTILUS study, led by Neuropace, is a prospective, randomized, single-blind, sham-controlled study designed to demonstrate the safety and efficacy of the RNS system for thalamic stimulation in patients aged 12 years or older with drug-resistant IGE. The study will enroll 100 participants and follow them for up to 2 years, assessing outcomes such as safety, efficacy, affective status, neurophysiological functioning, sleep, health-affecting behaviors, and quality of life pre- and post-implantation. Positive outcomes from this study are likely to significantly impact clinical practice, potentially leading to approval for CM thalamic neuromodulation in drug-refractory IGE (NeuroPace, 2023a).

2.2.4. RNS system LGS feasibility study (NCT05339126)

The RNS System LGS Feasibility study is a phase 2 clinical trial that began recruiting subjects in 2022. This two-stage, single-blind, prospective, crossover study aims to assess the safety and preliminary effectiveness of responsive neurostimulation of thalamocortical networks in treating generalized onset seizures in patients aged 12 years and older with LGS. The primary safety outcomes for the study include serious device-related adverse events at 12- and 24-months post-implantation, while primary effectiveness is measured by the responder rate, which is defined as a reduction of > 35% in drop seizure frequency compared to baseline. The study will also report other outcomes such as affective status, cognitive function, quality of life, and caregiver burden before and after implantation. The clinical trial outcomes may position RNS as a feasible treatment alternative for individuals experiencing drug-resistant LGS (NeuroPace, 2023b).

2.3. Central lateral nucleus of the thalamus

The central lateral nucleus (CL) is a part of the anterior intralaminar nucleus of the thalamus. It is the most dorsal component and is situated towards the posterior and dorsal region relative to the paracentral nucleus. It receives afferents from the pontine, mesencephalic, and medullary reticular formation as well as from the median and dorsal raphae nuclei, tegmental and pretectal regions, medical and lateral supramammilary nuclei, and superior colliculus (Van der Werf et al., 2002). CL nucleus has gained interest due to its role in maintaining the level of consciousness and arousal in the brain. One possible mechanism by which the CL may modulate arousal and consciousness is through its connections to the reticular activating system (RAS), a group of brainstem nuclei that are critical for regulating wakefulness and attention. Studies have shown that the CL sends dense projections to the RAS and that these projections can modulate the activity of the RAS to regulate the level of arousal and consciousness in the brain (Sherman, 2016).

2.3.1. Rationale for CL neuromodulation

The role of CL in arousal and attention was described early on by Schiff et al. in patients with severe traumatic brain injury(TBI). They implanted DBS electrodes bilaterally in a 38-year-old male patient who had a severe TBI and remained in a minimally conscious state (MCS). Within 48 h after surgery they noted changes in arousal including increased heart rate, sustained eye-opening, and head-turning to voice. The titration phase of the study lasted 18 weeks and tested a range of different stimulation frequencies and intensities. Qualitative changes in

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behavior were observed during the DBS titration, which correlated with abrupt changes in the Coma Recovery Scale-Revised (CRS-R) subscale scores. After titration testing, a final set of stimulation parameters was chosen for each electrode, and the patient began the crossover phase. The study found that the patient's ability to execute functional limb movement sequences and to chew and swallow independently significantly improved with DBS ON state. There was no significant difference in object-naming ability. Improvements in arousal, motor control, and behavioral persistence may be a result of direct activation of the frontal cortical and basal ganglia systems by neurons within the anterior intralaminar and adjacent para laminar regions of thalamic association nuclei. These neurons serve as a key intermediary system and final pathway for brainstem arousal systems and frontal lobe regions, which control effort regulation, working memory, attention, and vigilance. Hence, they proposed the use of central thalamic DBS for arousal regulation in patients who are in a minimally conscious state (MCS) and have functionally connected but inconsistently active cerebral networks (Schiff et al., 2007).

Motelow et al. presented evidence that subcortical arousal circuits show decreased activity during partial limbic seizures, leading to a depressed cortex similar to deep sleep or coma. This suppression of subcortical arousal systems is consistent with the "network inhibition hypothesis" for loss of consciousness during complex partial temporal lobe seizures. He suggested that suppression of cholinergic and other subcortical arousal systems participate in the loss of consciousness during seizures (Motelow et al., 2015). In a study by Xu et al., thalamic CL DBS was delivered at 100 Hz during the postictal period in 21 female rats. They demonstrated decreased cortical slow wave activity and improved task performance in the postictal period. In patients with epilepsy, impaired consciousness can have a major negative impact on quality of life. In addition, impaired arousal in the postictal state can serve as a risk factor for SUDEP. Hence, it is important to convert seizures associated with impaired awareness to ones with preserved awareness, and CL neuromodulation can be used as a solution based on results from previous studies in TBI patients and animal studies for epilepsy (Xu et al., 2020). Encouraging findings from various studies above have led to clinical trials in humans to stimulate the central lateral nucleus of the thalamus to restore consciousness during focal temporal lobe seizures, known as the START trial.

2.3.2. START trial (NCT04897776)

Stimulation of the Thalamus for Arousal Restoral in Temporal Lobe Epilepsy (START) is a cutting-edge double-blind, randomized controlled study designed to restore consciousness in patients with temporal lobe epilepsy who suffer from FIAS (focal impaired awareness seizures), even if the seizures cannot be stopped. The START trial employs a novel approach that combines hippocampal and CL thalamic stimulation, targeting four specific areas of the brain with state-of-the-art neurostimulator devices (Medtronic Summit RC+S). To track seizures and measure arousal, patients are equipped with a handheld device (Epilepsy Personal Assistant Device, or EPAD) and a smartwatch (Automatic Responsiveness Testing in Epilepsy, or ARTiE), which asks questions during seizures to gauge the patient's level of responsiveness. The success of the START trial could revolutionize clinical practice, significantly improve patient outcomes, and enhance the overall quality of life (Blumenfeld, 2022).

2.4. Anterior nuclei of the thalamus

DBS of the anterior nucleus of the thalamus (ANT) has been approved for the treatment of multifocal epilepsies in Europe and North America. While ANT is not a novel target in this context, there are ongoing pilot clinical studies evaluating multinodal network neuromodulation, including the ANT. The ANT is located in the rostral part of the dorsomedial thalamus and is subdivided into three parts: anterodorsal, anteroventral, and anteromedial nuclei. It plays a crucial role in the Papez circuit, which has been extensively studied in the context of seizure propagation (O'Mara, 2013).

2.4.1. ANT as a target for limbic network neuromodulation

The rationale for using the ANT as a target for limbic network neuromodulation is its extensive connections to various limbic structures involved in seizure propagation (Fig. 3A). It receives dense inputs from the subiculum, retrosplenial cortex, hippocampus, mesial temporal cortex, and mammillary body, which are all involved in the limbic system. These inputs project diffusely to the thalamus through the mammillothalamic tract and also to the cerebral cortex, including the cingulate gyrus. As a key component of the Papez circuit, the ANT is involved in the generation and propagation of limbic seizures. Therefore, modulation of the ANT may provide a therapeutic approach to modulate the activity of the limbic system and reduce seizure frequency in patients with drug-resistant epilepsy (Moreira-Holguín et al., 2022; O'Mara, 2013).

Animal studies have demonstrated that ANTS-DBS can modulate hippocampal network excitability and synchronization. Stypulkowski et al. investigated the effects of hippocampal and thalamic stimulation on network activity in large animals (sheep). The results suggest that low-frequency stimulation generates synchronous activity within the circuit, while higher frequencies activate inhibitory mechanisms. High-frequency stimulation reduces excitability and induces a state of inhibitory network bias, suggesting a potential mechanism for the therapeutic use of brain stimulation for epilepsy (Stypulkowski et al., 2014). In a recent experimental study on primates by Sherdil et al., they aimed to improve the effectiveness of neurostimulation in treating TLE by targeting the coherence between the hippocampus and anterior thalamic nucleus. They found that low-frequency stimulation (40 Hz) had a stronger effect on the number of seizures and the total time spent in seizures) as compared to high-frequency stimulation (130 Hz) which had no effects. The coherence analysis showed significant oscillatory activity at around 40 Hz during seizures in both structures, which was not observed with 130 Hz. The best therapeutic effects were observed in the animal with the highest ictal coherence score in the low-frequency bands, hence coherence score can be used to predict the anti-epileptic effects of ANT stimulation (Sherdil et al., 2020). In rhesus monkeys, ANT-DBS showed remote inhibition of KA-induced excitatory hyperactivation (Bouwens van der Vlis et al., 2019).

These served as a basis for human studies where similar results were recorded. Yu et al. studied the mechanism of ANT neuromodulation in nine patients with refractory focal epilepsy using sEEG and demonstrated desynchronization as a potential mechanism of action for seizure reduction in patients with ANT-DBS. They demonstrated that high-frequency stimulation of the ANT (130 Hz) can reduce epileptic discharges and desynchronize brain activity, including in large-scale networks involving the hippocampus and cortex. The study found that frequencies between 15 and 45 Hz synchronized hippocampal activity, while higher frequencies (>45 Hz) desynchronized it. The study also demonstrated effective connectivity between the thalamus and hippocampus (Yu et al., 2018). Chaitanya et al. conducted a study to investigate dynamic changes in synchronization between the seizure onset zone and ANT during peri-ictal states in seven patients with drug-resistant epilepsy. They found that the ANT is coactivated at the onset of seizures using local field potentials (LFPs) and there was also an alteration in thalamocortical phase synchronization that was higher at seizure onset. The study also found that increased thalamic excitability paralleled increased thalamocortical coupling at seizure onset, while termination was characterized by decreased thalamic excitability and decoupling. The findings suggest a mechanism that integrates local and long-range thalamic subnuclei-specific neural interactions during seizures (Chaitanya et al., 2020a).

Stereo-EEG (sEEG) also has provided an opportunity to investigate the connectivity profile of ANT in an epileptogenic network (Fig. 3B). A study conducted by Chaitanya et al. demonstrated that patient-specific

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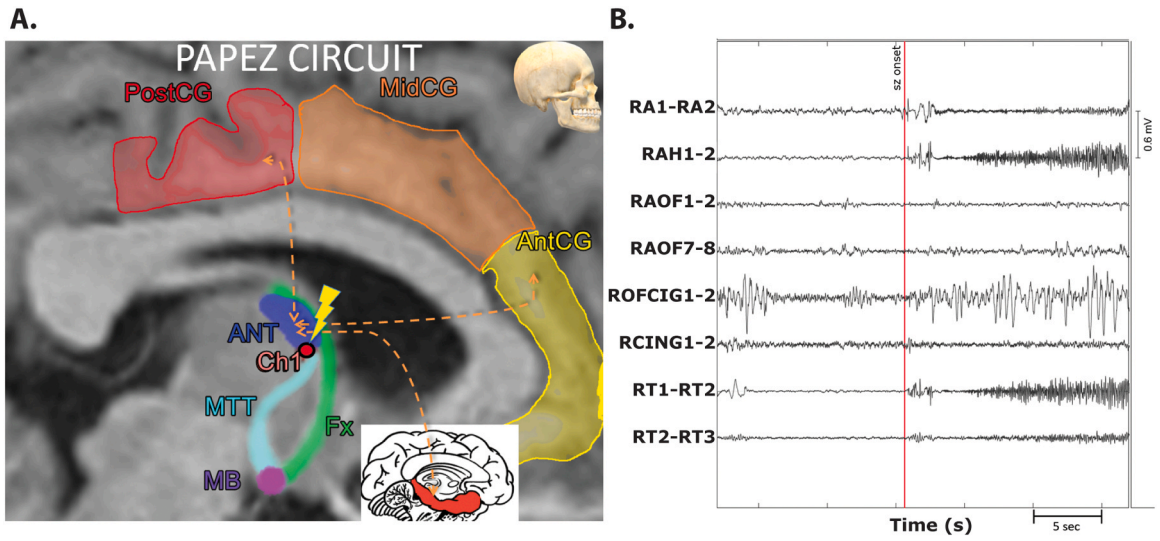


Fig. 3. A: Schematic illustration of the Papez circuit depicting the extensive connections of the Anterior Nucleus of the thalamus (ANT) with various limbic structures involved in seizure propagation. B: Example of thalamocortical stereo EEG recording of a focal impaired awareness seizure (FIAS). Seizure onset was at the right anterior hippocampus (RAH 1–2) with propagation to the right ANT (RT1–2,2–3).

engagement patterns during stimulation could be mapped with sEEG. They showed the local amplitude responses were increased with 10 Hz stimulation while were suppressed with 50 Hz stimulation. This shows that high-frequency ANT stimulation desynchronizes the epileptogenic network as compared to lower frequencies. They concluded that EEG markers like gamma-band response would allow monitoring of nodal responses and guide the selection of stimulation parameters (Chaitanya et al., 2020b).

2.4.2. A deep brain stimulation system in epilepsy: Tracking neural excitability (NCT03465163)

The study performed in Melbourne aimed to use the brain's response to single-pulse electrical stimulation to measure the level of seizure susceptibility, which can be used to program DBS for more effective therapy. Patients over 18 years of age with DRE underwent bilateral implantation of the DBS device into the ANT and the hippocampus. The experimental phase included three stages: 1) probing with continuous low-frequency (2 Hz) stimulation to the thalamus, 2) probe-calibrated DBS with 18 different parameter configurations used during two clinic visits lasting for two months, and 3) open DBS, during which the DBS parameters were optimized based on the probing responses. The primary outcome measured was the change in seizure rate recorded throughout the baseline and the probe-calibrated DBS phase, while the secondary outcome was to determine if the probing responses provide a seizure susceptibility measure throughout the probing phase and changes in brain excitability assessed according to changes in probing response energy before and after stimulation therapy. Studies like these can help determine optimal stimulation parameters for patients with ANT-DBS, leading to more effective and personalized treatment (Cook, 2020).

2.4.3. PRIME study (NCT05608408)

The study aims to investigate the safety and efficacy of low-frequency stimulation, informed by network architecture, in epilepsy patients aged 18–65 with hippocampal-related memory impairment. Four implanted depth electrodes will target distinct components of the seizure network. The team proposes to implant unilateral ANT in selected patients with presumed epilepsy in a precious hippocampus (EPH) that is undergoing Phase II (invasive monitoring with SEEG) targeting the mesial temporal network to localize their epilepsy. They will then stimulate the ANT, adjacent piriform cortex, entorhinal cortex, and hippocampus with low-frequency electrical stimulation to diminish excitability and restore normal network behavior. The study will use the Medtronic Percept PC Neurostimulator DBS System with BrainSense Technology to record and stimulate brain activity after SEEG electrode explantation. While the stimulation parameters will follow general principles across the group, they will be further refined (including target electrode pair and current intensity) based on the electrophysiology of individual epilepsy networks. Primary endpoints include a decrease in seizure frequency and spike frequency, while secondary endpoints include verbal memory and subjective wellness outcomes. This could provide unprecedented insights into the neurobiology of mesial temporal lobe epilepsy and determine which subtypes of this epilepsy are most favorable for neuromodulation. It hopes to provide novel insights into the neuromodulation of seizure networks and a therapeutic strategy for intractable seizures (Tandon, 2023).

3. Novel stimulation paradigms

3.1. Long bursting pattern of stimulation

A retrospective study conducted on ten patients with DRE (predominantly bitemporal mesial epilepsy) who were implanted with RNS, demonstrated low-frequency stimulation (LFS) when coupled with longer burst duration as an effective approach in seizure control. Stimulation frequency was set to < 10 Hz and burst duration to at least 1000 ms. LFS was associated with 76% mean seizure reduction (MSR) as compared to the baseline after a median of 19 months while high-frequency stimulation (HFS) only demonstrated 13% MSR. There were no adverse events related to LFS that were reported. Hence, LFS with long bursting can serve as an alternative treatment in patients who do not respond to standard HFS settings (Alcala-Zermeno et al., 2023).

Another case study has been reported on the use of long bursting in a 19-year-old female patient with drug-resistant juvenile myoclonic epilepsy since 13 along with several episodes of status epilepticus implanted with CM RNS. The stimulation parameters were 125 Hz, 160 μs, and 3.4 ms, and the burst duration was increased from 500 to 5000 ms for the first three bursts and 2000 ms for the last two. A decrease in the bilateral tonic-clonic (BiTC) seizure duration was noted by the parents. On reprogramming to 5000 ms for all bursts (Fig. 4) the patient reported resolution of BiTC and myoclonic seizures for a year along with improvement in mood and cognition. But the patient continued to have weekly absence seizures. Therefore, larger studies are needed to better understand the benefit of long bursting stimulations in patients with DRE (M et al., 2023).

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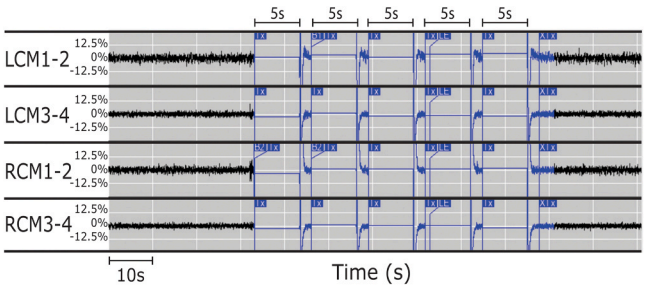


Fig. 4. Electrocorticographic (ECoG) recordings from the Responsive Neurostimulation device in Primary Generalized Epilepsy.The neuromodulatory target was bilateral centromedian thalami (L/RCM 1–4). The blue line indicates RNS detection followed by multiple 5 s bursts of responsive stimulation therapy (Tx) that terminated the seizure.

3.2. Thalamic responsive neurostimulation in multifocal epilepsies

The emerging case series (< 5 patients) has highlighted the feasibility of using ANT-RNS for the treatment of multifocal epilepsy, which differs from the chronic duty cycle high-frequency stimulation used in ANT-DBS. Elder et al. conducted a study on three patients with treatment-resistant multifocal epilepsy who were implanted with RNS in cortical epileptogenic zones and ANT. Two patients underwent B/L ANTS RNS, and one had U/L RNS. After a follow-up period of over 33 months, two patients had at least a 50% reduction in seizures, and one had a 50% reduction compared to baseline, with no observed adverse effects on mood, behavior, or memory (Elder et al., 2019).

3.3. Connectomic DBS

Functional MRI (fMRI) is a non-invasive tool that evaluates brain activity by measuring blood-oxygen-level-dependent (BOLD) signals fluctuations. BOLD signal coherence can be used to assess functional connectivity between distant brain regions and can help identify chances of responsiveness, correct any inaccuracies in targeting, and determine optimal stimulation parameters in a patient-specific manner. Sarica et al. and Middlebrook et al. both demonstrated changes in the pattern of BOLD response on thalamic stimulation in patients with ANT-DBS. They observed marked changes in the pattern of BOLD response on thalamic stimulation, which showed variability with the locus of active contact in each patient. Patients with stimulation that engaged at least 5% of ANT by volume showed changes in B/L putamen, thalamus, posterior cingulate cortex, ipsilateral middle cingulate cortex, precuneus, and contralateral medial prefrontal and anterior cingulate (Middlebrooks et al., 2020; Sarica et al., 2021). While these studies have limitations, further research into fMRI-based clinical programming of patients with DBS could pave the way for improved treatment outcomes. Additionally, research by Warren et al. and Torres et al. has shown that tailoring stimulation targets using functionally defined epileptic zones or networks (Fig. 5A and B) can lead to therapeutic benefits in patients with generalized epilepsy, indicating the potential for improved treatment outcomes with a personalized approach. The areas of the bilateral volume of tissue activated (VTA) structural connectivity with seizure reduction positively correlated with connectivity to the premotor cortex, frontal operculum, dorsoposterior putamen, globus pallidus, right hippocampal head, right inferoposterior cerebellum, locus coeruleus (Torres Diaz et al., 2021; Warren et al., 2019).

4. Conclusion

Thalamic neuromodulation is a breakthrough in treating drug-resistant epilepsy, backed by clinical studies demonstrating its efficacy in reducing seizures and improving cognitive function. However, identifying the optimal stimulation targets and parameters remains an ongoing challenge. Advanced neuroimaging techniques and closed-loop systems offer the potential to enhance the therapy's efficacy while reducing side effects. Targeting the pre-seizure state via neuromodulation may prevent seizures by diverting the network away from the seizure onset (Fig. 6). Understanding the therapy's long-term impact on quality of life, cognitive function, and psychiatric comorbidities is crucial. Overall, thalamic neuromodulation holds great promise for enhancing the lives of epilepsy patients, but more research is necessary to realize its full potential. The therapy may also offer new opportunities for precision medicine as we continue to expand our understanding of epilepsy's pathophysiology.

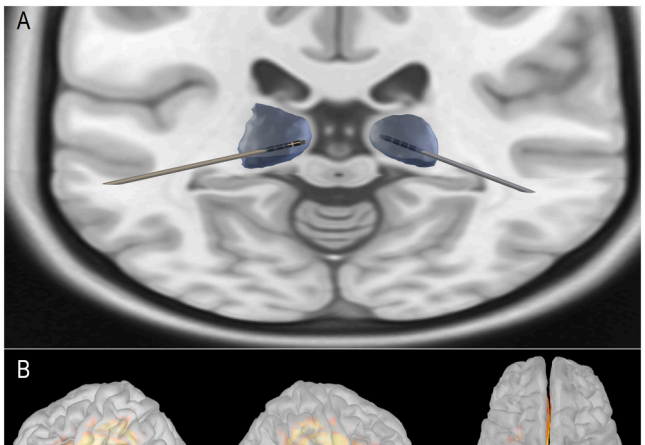


Fig. 5. A: DBS electrodes are reconstructed using LeadDBS. The electrodes are implanted in the pulvinar thalamus. Reconstruction was in the MNI space. The blue ROIs represent Pulvinar nuclei, as seen from the posterior aspect. The nucleus is based on Saranathan Atlas 2019. B: Spatial distribution of the pulvinar DBS stimulation source power computed using dynamical Statistical Parametric Mapping (dSPM). The stimulation parameter was 145 Hz, 90 microseconds pulse width, 2 mA with one minute On and one minute off.

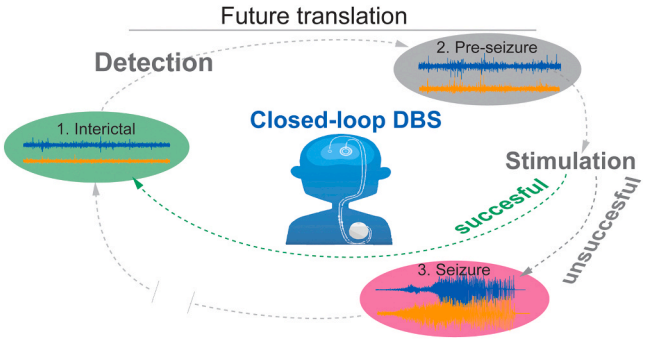


Fig. 6. Closed or adaptive neuromodulatory strategy targeting modulation of the pre-seizure state to disrupt the progression of seizure onset. Effective neuromodulation can drive the brain state from the pre-seizure state to the interictal state, thereby preventing the seizure. NOTE: Color to be added to all the six images.

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Declaration of Competing Interest

None.

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