REVIEW ARTICLE

Towards network-guided neuromodulation for epilepsy

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Abbreviations: ANT = anterior nucleus of the thalamus. CMT = centromedian nucleus of the thalamus. DBS = deep brain stimulation. DRE = drug-resistant epilepsy. fMRI = functional magnetic resonance imaging. iEEG = intracranial electroencephalography. LFP = local field potential. LGS = Lennox-Gastaut syndrome. PC = piriform cortex. RNS = responsive neurostimulation. SA = septal area. SOZ = seizure-onset zone. SEEG = stereo-encephalography. TLE = temporal lobe epilepsy

Abstract

Epilepsy is well-recognized as a disorder of brain networks. There is a growing body of research to identify critical nodes within dynamic epileptic networks with the aim to target therapies that halt the onset and propagation of seizures. In parallel, intracranial neuromodulation, including deep brain stimulation and responsive neurostimulation, are well-established and expanding as therapies to reduce seizures in adults with focal epilepsy; and there is emerging evidence for their efficacy in children and generalized seizure disorders. The convergence of these advancing fields is driving an era of '*network-guided neuromodulation*' for epilepsy. In this review we distil the current literature on network mechanisms underlying neurostimulation for epilepsy. We discuss the modulation of key *propagation points* in the epileptogenic network, focusing primarily on thalamic nuclei targeted in current clinical practice. These include (a) the anterior nucleus of thalamus, now a clinically approved and targeted site for open loop stimulation, and increasingly targeted for responsive neurostimulation; and (b) the centromedian nucleus of the thalamus, a target for both deep brain stimulation and responsive neurostimulation in generalized-onset epilepsies. We discuss briefly the networks associated with other emerging neuromodulation targets, such as the pulvinar of the thalamus, piriform cortex, septal area, subthalamic nucleus, cerebellum and others. We report synergistic findings garnered from multiple modalities of investigation that revealed structural and functional networks associated with these propagation points – including scalp and invasive electroencephalography, diffusion and functional magnetic resonance imaging. We also report on intracranial recordings from implanted devices which provide us data on the dynamic networks we are aiming to modulate. Finally, we review the continuing evolution of network-guided neurostimulation for epilepsy to accelerate progress towards two major goals: (1) to use pre-surgical network analyses to determine patient candidacy for neurostimulation for epilepsy by providing network biomarkers that predict efficacy; and (2) to deliver precise, personalized and effective antiepileptic stimulation to prevent and arrest seizures, limit seizure propagation through mapping and modulation of each patients' individual epileptogenic networks.

Introduction

We now understand that epilepsy is a neurological disorder that alters the normal connectivity of the brain [1–6]. Advances in brain connectivity ('network neuroscience' or 'connectomics') research over the last few decades [7,8] have driven the study of epilepsy as a network disorder. The propagation of abnormal brain activity both during (ictal) and between (inter-ictal) seizures alters widespread networks in generalized-onset epilepsy, but we also now understand that focal epilepsy subtypes have a wider implicated network than previously considered [9,10].

A persistent group of around 30% of patients with epilepsy will develop drug-resistant epilepsy (DRE) and require alternative forms of therapy [11]. Not all patients with DRE, however, are eligible for surgical resection of the seizure-onset zone (SOZ). Whilst traditional epilepsy surgical options – including resections and disconnections – have the potential to decouple the epileptogenic network from the normal networks of the brain [12,13], they are limited by their morbidity and irreversibility. Stimulation therapies provide a greater degree of control and reversibility while being minimally-invasive, potentially offering a more accurate and controllable treatment option. Intracranial neurostimulation interventions, such as deep brain stimulation (DBS) and responsive neurostimulation (RNS), have become effective and available treatment options to reduce seizure burden for selected patients with DRE [14–16]. Although not further discussed in this review, vagus nerve (extracranial) stimulation also delivers neuromodulation in order to reduce seizure frequency by altering brain networks via the afferent innervation of the vagus nerve [17].

The convergence of advances in brain network analyses and the fortuitous availability of data gathered from long-term implants in the human epileptic brain has enabled a cascade of research in the field of 'network-guided neuromodulation' [18–21]. Our understanding of how neurostimulation works on a network level has been made possible by studying and combining multiple complimentary methods such as diffusion and functional magnetic resonance imaging (fMRI) [22–25], scalp electroencephalography (EEG) and intracranial electroencephalography (iEEG) [26].

Whilst there have been recent reviews that have summarized the current availability and efficacy of intracranial neurostimulation therapies for epilepsy [14–16,27,28], we here approach

these therapies from a network neuroscience perspective. A network-guided neuromodulation framework for epilepsy allows us to ask questions that may advance the treatment options and efficacy that we can offer to patients. These include but are not limited to:

(1) What is the mechanism through which current neurostimulation therapies inhibit epileptic activity in brain networks?

(2) What are the network properties of the thalamic regions currently implanted with antiepileptic devices that make them useful targets for neurostimulation?

(3) Are there other potential stimulation targets and what are the network properties associated with these?

(4) Are there properties of epileptic networks (biomarkers) that predict their responsiveness to neurostimulation before device implantation?

(5) How do we optimize and personalize neurostimulation to maximize its efficacy?

This review of intracranial neuromodulation approaches these questions, draws on the latest research, and suggests future research that may help us to advance in this field.

The mechanistic role of network modulation in neurostimulation for epilepsy

From a connectivity perspective, all epilepsy surgery interventions are an attempt to sufficiently disrupt the epileptogenic network to prevent seizures and to prevent the alteration of 'healthy' brain networks [29]. Surgical resection and thermal ablation directly target and destroy the putative seizure-onset zone (SOZ) and hemispherotomy or corpus callosotomy surgeries structurally 'disconnect' the white matter bridging the epileptogenic and normal networks. DBS instead targets the most influential downstream *'propagation points'* within the epileptogenic network and aims to prevent onward spread of seizure activity. RNS aims to suppress seizure generation by stimulating the SOZ in *response* to epileptiform activity recorded at the SOZ. These concepts are illustrated in **Figure 1**.

This review does not attempt to describe all of the hypotheses that have been postulated to explain the efficacy of DBS and RNS. Other articles have specifically set out to summarize these approaches across multiple scales and modes[30–32]. These include, but are not limited to mechanisms of DBS at the local/target level; for example, high-frequency stimulation has been suggested to prevent onward propagation of seizures by either direct inhibition ('functional lesioning') of the target or activation disrupting pathological activity in circuits ('jamming theory'[33]. In addition, studies have suggested that DBS disrupts pathological oscillations as a therapeutic mechanism[34]. At the cellular level, for example, it has been suggested that thalamic stimulation causes glutamate[34,35] and adenosine[35] release that may reduce thalamic oscillations. Since these mechanisms have already been reviewed in detail, our review summarizes and questions the main contributions that intracranial neurostimulation may offer in terms of wider *network* modulation.

[1] Neurostimulation desynchronizes the epileptogenic network

Desynchronization of epileptogenic neural networks has been shown in multiple investigations as a responsible mechanism for the efficacy of neurostimulation, rather than a global reduction in excitability [36]. In 1954 Penfield and Jasper commented on the hyper-synchronization of brain activity occurring during epileptiform activity [37] and this observation remains corroborated in the literature [38–43]. For example, Stypulkowski et al's study in sheep compared the network alterations in the Papez circuit between ANT ('indirect') and hippocampal ('direct') stimulation[44]. Both indirect and direct high-frequency stimulation suppressed theta-band power of local field potentials in the hippocampus, but only direct stimulation caused a 'post-ictal suppression' (defined as a higher threshold to produce further discharges from the hippocampus following stimulation). A more recent in-human study by Yu et al investigated nine patients with temporal lobe epilepsy undergoing intracranial EEG through inclusion of an electrode in the ANT [42]. They showed that high-frequency stimulation of the ANT lead caused the broadband local field potentials measured in the ANT to become desynchronized with LFTs in the ipsilateral hippocampus and neocortex. A subsequent study by Scherer et al supported these findings of desynchronization in 14 patients with temporal lobe epilepsy with intermittent ANT DBS investigated with scalp EEG [41]. They found that stimulation caused desynchronization of scalp-recorded theta

and alpha band activity in responders, but not in non-responders, which supports this finding as an important therapeutic mechanism [41].

DBS therefore uses high-frequency stimulation to prevent so-called *propagation points* (stimulation targets, e.g. the thalamus) from allowing seizure activity from the SOZ to propagate to and synchronize with the unaffected networks of the brain (**Figure 1**). DBS may prevent seizure propagation by suppressing the local generation of seizure activity through common projections, for example along the Circuit of Papez (to be discussed) in the case of anterior nucleus of the thalamus (ANT) stimulation (**Figure 2**). In comparison, RNS offers a closed-loop system in which the receiving and delivering electrodes are both located in the SOZ, and RNS suppresses synchronization locally or regionally during the occurrence of ictal and inter-ictal epileptiform activity.

The concept of desynchronization is relatively straightforward to apply to focal-onset epilepsies (**Figure 1**) but more challenging to understand in generalized-onset or multifocal-onset epilepsies. Bilateral thalamic stimulation may desynchronize cortically driven epileptiform activity from the subcortical networks, as suggested by studies that have shown that Lennox-Gastaut syndrome (LGS) is a cortically-driven network disorder [45]. However, there is also evidence for the thalamus as primary source of seizures in idiopathic generalized epilepsy [46].

[2] Can neurostimulation normalize brain networks?

We question if electrically disrupting the epileptogenic network and restoring a more physiological functional connection allows restoration of normal cortical network functioning. This concept of 'neural hijacking' has been postulated before by Cheney et al who suggest that 'high-frequency stimulation eliminates and replaces natural activity'. However, whilst functional network normalization has been shown in resective epilepsy surgery [47], antiseizure medication therapy[48,49], and in DBS for other conditions such as Parkinson's disease [50], there remains a lack of evidence and need for investigation for this effect in neurostimulation for DRE.

There is an understandable focus within the current neurostimulation literature on seizure frequency reduction as the primary outcome measure for neurostimulation strategies. There have been a number of studies, however, that have investigated the neuropsychological improvement associated with neurostimulation for epilepsy, most comprehensively covered by Chan et al in their review [51]. Longer-term data at five [52] and nine years [53] following the SANTE trial of DBS for DRE showed patients gained neuropsychological improvement – including improvement in attention, executive function, mood (including depression, tension and anxiety) and subjective cognitive function. Similarly, a study that examined cognitive outcomes two-years following the RNS trial identified a small yet significant improvement in cognition [54]. Of significance, there has recently been a prospective clinical trial examining the cognitive effects of DBS of the anterior nucleus of the thalamus for epilepsy [55]. Heminghyt et al randomized eight adults to active stimulation and 10 adults to no stimulation for six-months following implantation but did not show any cognitive differences between the groups at the six-months endpoint. However, at one year (the open-label phase) there was a reduction in the proportion of patients experiencing executive dysfunction.

It may be, however, that a mechanism that allows these neuropsychological improvements is the relief from seizures or weaning of antiseizure medications, but some have argued that this may not be the only mechanism [56]. In addition, neurostimulation may allow neuropsychological improvements by normalizing brain networks. Regardless, neurostimulation may be of particular therapeutic value in the developing brains of children – in whom the comorbidities of epilepsy may be equally or more concerning than seizures. Data to shed light on pediatric outcomes is likely to soon become available owing to a recent increase in DBS and RNS studies in children [57–59].

Lastly, neurostimulation approaches must consider the risk of iatrogenic and negative implications to the normal brain network(s). Adverse events are not uncommon in neurostimulation therapies – for example, the SANTÉ trial of DBS reported that 18.2% of participants had a paresthesia and 16.4% withdrew due to adverse effects. Studies of diffusion MRI in patients undergoing DBS for movement disorders have demonstrated that it is possible to model optimal electrode positioning that allows for targeting efficacious white matter connections (tracts) but avoiding those associated with adverse effects [20]. Other adverse effects that remain uninvestigated from a network perspective include the potential effects of neurostimulation on cognition, mood and sleep [60].

[3] Neurostimulation alters temporally dynamic brain networks

As well as considering stationary (single time point) brain networks, there is a need to consider that brain networks are dynamic over time. Patients with epilepsy demonstrate temporally organized seizure occurrences that respect either circadian (in the course of a day), multidien (over multiple days) or circannual (over years) patterns [61,62]. The opportunity to study the longer-term data recorded from intracranial devices, such as patients undergoing intracranial EEG for pre-surgical assessment, has demonstrated changing 'seizure pathways' within the epileptogenic network of individual patients across time [63]. Whilst RNS is responsive to seizure activity in real-time, both DBS and RNS therapy may be refined by further *'adaptive'* stimulation regimes that account for cyclical seizure patterns.

The ability of RNS and more recent DBS technologies to detect local-field potentials (LFPs) within the epileptogenic network over time allows for further investigation of the neurophysiological impact of stimulation on the patient's epileptic network. There is a growing consensus that the efficacy of RNS is likely due to an long-term neuromodulatory effect on the epileptogenic network, rather than only arresting seizures [64]. Sisterson et al proposed this temporal effect to result from progressive disruption of epileptogenic network connectivity and reduction of the core synchronized population, rendering the clinical manifestation of seizures less severe [65], rather than RNS just being a 'defibrillator for the brain'. In a recent key in-human study, Khambhati et al used the long-term data from 51 patients with RNS (either mesial temporal or neocortical) to examine the dynamics in functional interictal epileptiform connectivity over time by constructing a network using device-recorded local field potentials. In patients with RNS electrodes in two seizure-onset zones the inter-electrode network was temporally plastic, meaning that they were able to detect alterations in functional connectivity (measured as 'phase locking values') between these electrodes over time, and particularly within the first year post-implantation. For patients with neocortical electrodes, they found that functional connectivity was decreased in alpha and beta bands but increased in gamma bands between seizure-onset zones in 'super' responders (>90% reduction in seizures) compared to poor responders (<50% reduction in seizures) [66]. This led the authors to propose a 'spark-on-kindling' hypothesis, suggesting that RNS desynchronizes the epileptogenic network ('kindling') and reduces the risk of a seizure generation caused by inter-ictal epileptiform discharges ('spark'). This may provide a

mechanistic explanation for the observations from both RNS and DBS long-term clinical studies showing that seizure frequency often gradually decreases over time [53,67]. This concept of stimulation-induced plasticity agrees with the observations from the literature on dystonia showing gradual improvement in symptoms with DBS over a number of months [30].

It is conceptually plausible that closed-loop RNS, with both sensing and stimulation electrodes in the SOZ, may induce plastic change in the SOZ and reduce the number of focal-onset seizures. However, it is intriguing to consider how this mechanism might occur during DBS to reduce the frequency of focal-onset seizures. This raises the question as to whether DBS also has a 'plastic' influence on the SOZ as well as working to isolate/desynchronize the SOZ from the rest of the brain's network. However, the data from Yu et al's aforementioned study[42], showed that ANT stimulation decreased the rate of inter-ictal epileptiform discharges and high-frequency oscillations, supporting the plasticity concept. A provisional longer-term study has been reported in one patient who first had RNS with receiving and stimulating leads in the seizure onset and who then went on to have ANT DBS[68]. In this patient, over 1.5 years, ANT DBS progressively suppressed hippocampal epileptiform activity. Overall, however, further research is required into the effects of stimulation on brain networks and their dynamics.

Propagation points within the epileptogenic network

In this section, we focus on network studies concerning the current clinical intracranial targets for neuromodulation for epilepsy. We have focused primarily on the regions of the thalamus – the anterior nucleus of the thalamus (ANT) and centromedian nucleus of the thalamus (CMT) that are DBS and RNS targets in current clinical practice. We also highlight hypothetical targets that either have previously been targeted or may bring future opportunities, including the pulvinar of the thalamus, piriform cortex, the septal area, subthalamic nucleus and cerebellum.

Thalamus

The notion that the thalamus is a critical hub in the propagation of seizures is not a new concept. Following the dawn of Penfield's 'Montreal Procedure' for epilepsy in 1930s,

during which patients with epilepsy undergoing awake craniotomy would have cortical stimulation followed by ablation, attention was turned to deeper structures [69]. The thalamus became a target of therapeutic neurostimulation in the animal studies by Penfield and Jasper as early as 1949 [37,70,71]. The thalamus is responsible for the mediation of reciprocal cortical to subcortical connections and thus defined as an 'integrative hub' for functional brain networks [72]. The thalamus has classically been implicated as a propagation point in generalized-onset seizures [73,74] and focal-onset seizures with secondary generalization on account of the onward bilateral cortical spread of epileptiform activity and connection to the brainstem. However, more recent evidence suggests that the thalamus also has a significant network role in focal-onset epilepsies without generalization. From a clinical perspective, in the landmark SANTÉ trial of DBS for adult DRE there was also significant improvement in seizure frequency seen in those patients with focal-onset epilepsy [75].

The role of the thalamus has been a particular focus in studying the epileptogenic network of TLE [40], partly due to the relative amenability to group studies owing to the homogeneity of the epileptic network in this condition. He et al demonstrated that patients who were not rendered seizure-free following temporal lobe resection surgery for TLE were more likely to have a higher functional connectivity of the thalami on preoperative resting-state fMRI, suggesting that patients with particular thalamic 'hubness' within their epileptogenic network were less likely to have seizure freedom after resective surgery [76].

The thalamus is a complex structure with nuclei that each have distinct connectivity profiles. The two common targets of DBS are the anterior nucleus (ANT) and centromedian nucleus (CMT) of the thalamus (shown in **Figure 2**). Of note, ANT stimulation remains the only Food and Drug Administration (USA) and National Institute for Health and Care Excellence (UK) approved stimulation target for adults with DRE. The pulvinar is another nucleus of the thalamus that has been shown to be a component in the epileptogenic network [77 78], but has been less well studied.

Anterior nucleus of the thalamus

The ANT has been a stimulation target for epilepsy for several decades. Early studies in humans include lesioning of the ANT in the 1960s [79] and a small cohort reported by Upton

and Cooper of six adults who underwent ANT stimulation in the 1980s [80]. The *SANTÉ trial* validated the efficacy of ANT stimulation, in which adults with focal-onset (TLE or extra-TLE) DRE underwent bilateral ANT DBS [75]. Despite this early success of clinical translation, subsequent and ongoing research continues in order to further understand the network mechanics that explain the efficacy of this therapy and to refine neurostimulation strategies.

The ANT has been described as a component of the 'extended hippocampal system' [81] as it receives inputs from the mamillary body (via the mammillothalamic tract), subicular and retrosplenial cortex, whilst it has outputs to the medial prefrontal cortex (detailed in **Figure 3**). These brain regions connected to the ANT are components of the so-called *Papez circuit* [82]. This network of cortical and subcortical structures gives a route of seizure propagation between the hippocampus and thalamus by connections through the mammillothalamic tract and the fornix. The ANT feeds back to the hippocampus via the cingulum to the parahippocampal gyrus and entorhinal cortex [83]. Neurostimulation that targets nodes (including the ANT) within the Papez circuit may desynchronize, or even recalibrate, this network.

The ANT is composed the anteroventral, anterodorsal and anteromedial subnuclei. There are ANT subnucleus-specific differences in connectivity [81,84], and studies have investigated the differences in lead placement between patients who have and have not responded to ANT DBS. Multiple retrospective studies have shown that stimulation of the anterior-ventral and anterior-medial ANT is more associated with responder status [85–88], but the wider network substrates that underpins this more efficacious target have not yet been demonstrated. A recent connectivity study by Schaper et al looked at 20 patients undergoing ANT DBS and found that responders (>50% seizure reduction) had a shorter distance of the contacts to the junction of the ANT and mammillothalamic tract [89].

Stereo-EEG has offered an opportunity to probe the mechanism of ANT in the epileptogenic network, as demonstrated in the aforementioned study by Yu et al[42]. Another interesting SEEG study by Chaitanya et al has examined 26 seizures in seven patients with drug-resistant TLE and investigated the dynamic changes in synchronization between the SOZ and ANT [90]. They showed that there was an increase in coupling between the amplitude of high gamma band in the SOZ and the phases of low-frequency oscillations (alpha, delta and theta) in the ANT. They also showed, however, that the synchronization between the ANT and the

epileptic network preceded seizure-onset, suggesting that the ANT has a key role in the ictogenesis as well as seizure propagation. A further study by Toth et al used an epileptogenicity index based on SEEG data and found that seizures that had an onset in the mesial temporal lobe (compared to other seizure-onset zones) had a higher and faster rate of ANT recruitment and that ANT recruitment preceded clinical onset. They also found that seizures that recruited the ANT lasted longer. The authors suggest that the ANT has a key role in the early organization and maintenance of seizure activity. Also, data from local-field potentials captured from DBS devices with sensing capabilities (e.g. the *Medtronic Percept*) are beginning to emerge that may provide further information on long-term network effects of ANT stimulation in DRE [91].

The synchronization of thalamo-cortical seizure activity and altered connectivity has been best studied in the TLE paradigm. The results from the SANTÉ trial suggest that patients with TLE are more likely to respond to DBS than extratemporal epilepsy or generalized epilepsy cases [75]. The SANTÉ trial showed that although patients with TLE had a median of 44% seizure frequency reduction from baseline, there was no significant difference in seizure frequency reduction in patients with seizures with onset in the frontal, parietal or occipital lobes. That said, the SANTE trial was not statistically powered to compare rates of efficacy according to different seizure-onset zones, and other studies have identified connectivity alterations that are suggestive of a role of the ANT in a wider cortical network. For example, in a study of five patients with epilepsy undergoing ANT DBS measured a transient reduction in intracortical inhibition within the motor cortex, determined by increases in motor thresholds during transcranial magnetic stimulation [92]. Additionally, in a study of five patients with either multifocal or generalized epilepsy undergoing ANT stimulation, time-locked cortical responses (estimated using scalp EEG and source modelling) during ANT stimulation were increased in ipsilateral cingulate gyrus, insular cortex and lateral temporal cortices [43]. Lastly, a study of 10 patients with idiopathic generalized epilepsy were studied with paired EEG-fMRI which showed that the ANT (as well as centromedian nucleus) was activated during spike-and-wave discharges [93], suggesting ANT synchrony with the generalized epileptogenic network and thus a potential propagation point.

RNS has been used to treat generalized epilepsy, with a receiving detector on the cortex and the stimulation contacts in the ANT [94]. Further studies are required to understand the network mechanisms by which extratemporal epileptogenic networks may benefit from ANT

stimulation. Lastly, further studies are also required in order to determine the potential for ANT stimulation to be of benefit in children with epilepsy [57,58,95].

Centromedian nucleus of the thalamus

The centromedian nucleus of the thalamus (CMT) (shown in **Figure 2**) is an intralaminar nucleus sited at the lateral wall of the third ventricle [96]. The CMT has been a neurostimulation target for 30-years, particularly for the treatment of generalized-onset epilepsies, namely LGS. The earlier works [97–103] identified the CMT as a potentially efficacious stimulation target, later confirmed by clinical trials [104] and recently (December 2021) by the DBS of thalamic centromedian nucleus for Lennox-Gastaut syndrome (the ESTEL trial) [105]. Although the CMT has been a target since at least the 1990s [102], corresponding in-vivo human studies investigating the network substrates of the CMT are only beginning to emerge.

A study by Torres Diaz et al used both diffusion and functional MRI acquired in 10 adults with generalized epilepsy undergoing CMT DBS [106]. Although the cohort was small, the clinical effect was striking – with 8/10 achieving at least 50% seizure frequency reduction. The structural (diffusion tractography) and functional (fMRI) networks of the CMT were determined using the lead contacts as seeds – *'volume of tissue activated'.* Improved outcomes were associated with increased connectivity between the volume of tissue activated and the reticular system, supporting the hypothesis that the brainstem is an important component of CMT network [107]. The functional connections of the CMT, derived from resting-state fMRI, involved the anterior cingulate, pre-frontal, pre-central, post-central, insular, medial temporal and occipital cortices. Similarly, results from simultaneous EEG-fMRI in young adults with Lennox-Gastaut syndrome in the ESTEL trial identified significant connectivity with the basal ganglia, brainstem, cerebellum, sensorimotor cortex, premotor cortex and limbic cortex [108]. The same group have published two other paired EEG-fMRI studies showing that, in both adults and children with Lennox-Gastaut syndrome, generalized paroxysmal fast activity starts in the cortex and involves the CMT only after a delay [109], perhaps propagating to the brainstem via cortico-reticular pathways first before involving the CMT afterwards [108]. A study by Kim et al, using both diffusion MRI and EEG and in a cohort of 10 patients undergoing DBS for either generalized or multifocal epilepsy,

also showed that the anterior cingulate gyrus and frontotemporal regions had significant connections with the CMT [110].

A recently published study, also from the ESTEL trial[105], used probabilistic mapping, structural connectivity (tractography) and functional connectivity (simultaneous EEG-fMRI) to refine the 'sweet spot' (the target of area of maximal efficacy) for CMT DBS in 20 young adults with Lennox-Gastaut syndrome[111]. The study identified that DBS lead localization in the anterior-inferior-lateral CMT border (the parvocellular region) was associated with patients with higher seizure frequency reduction. Structural connectivity profiles associated with greater seizure frequency reduction showed higher connectivity with the premotor cortex, frontal operculum, putamen, globus pallidus, hippocampus, cerebellum and brainstem. Posterior (parietal, occipital and temporal) cortical connectivity was, in contrast, associated with lesser seizure frequency reduction.

Lastly, so far, only a few reports exist of efficacy of RNS for the treatment of drug-resistant idiopathic generalized epilepsy. For example, a recent retrospective cohort of four patients with idiopathic generalized epilepsy treated with CMT RNS demonstrated seizure frequency reductions ranging between 75-99%, seizure duration reduction and quality of life improvements. Another group have reported that bilateral RNS was used to detect seizure activity from and deliver neurostimulation to the CMT in a 16-year-old boy with primary generalized epilepsy [112]. It will be intriguing to review the results from the upcoming RNS trial for patients with Lennox-Gastaut syndrome that detects seizure activity at the cortex and uses the CMT as the stimulation target [113].

Alternate and prospective stimulation targets

Whilst we will not discuss these in such detail as currently targeted propagation points, there are several other stimulation targets that have been or could be explored for the treatment of epilepsy. We have chosen to discuss also the piriform cortex and septal area, which may be emerging as potential therapeutic stimulation targets.

Pulvinar of the thalamus

The pulvinar of the thalamus has received lesser attention than ANT and CMT. The pulvinar is a large region of the thalamus that has distinct zones with differing connectivity profiles. The inferior and lateral subregions are considered the 'visual pulvinar' with strong connectivity to the occipital lobe[114] and has been a suggested stimulation target for patients with posterior quadrant seizure-onset zones[78].

The medial pulvinar has connections with the frontal and medial temporal lobes[115 116]. A study of eight patients with TLE undergoing SEEG showed that seizures triggered by hippocampal stimulation were rendered less severe with high-frequency medial pulvinar stimulation than those without[115]. This study noted that reduction in severity was noted to occur with an improvement of awareness during seizures. A follow-on study of the same data measured functional connectivity (correlation in broad band SEEG) between temporal and extratemporal regions and compared connectivity differences between (a) between stimulation on and stimulation off; and (b) responders and non-responders[117]. 'Synchrony' (i.e. connectivity) was found to be lower during stimulation in responders. The authors hypothesized that 'reducing global synchrony' caused by medial pulvinar stimulation may relate to improved awareness during TLE seizures.

Piriform cortex

The piriform cortex (PC) is a region of paleocortex that bridges the medial temporal and inferior frontal lobes superficial to the limen insulae (**Figure 4**). Whilst in health the PC is a primary olfactory cortex, the PC has been implicated as a key zone of seizure propagation and kindling for several decades now [118–120]. An early study in rats identified the 'deep prepiriform' cortex as a potent seizure zone [121], leading to a deep zone of the PC named as *'area tempestas'* (Latin for 'storm area') [122]. There has been a recent renewal of interest in the PC's role in epilepsy which has been made possible by the availability of non-invasive (scalp EEG, MRI & PET) and invasive (intracranial EEG) modalities to investigate the functional network of the human PC in-vivo [123]. The PC has been demonstrated as an important node within the epileptogenic network in independent cohort studies showing that extent of PC resection was associated with a higher rate of seizure freedom following anterior

temporal lobe resection [124,125]. This raises the question as to whether the PC is not only a seizure propagation zone, but, as previously thought, a site of epileptogenesis in TLE.

Laufs et al used simultaneous EEG-fMRI in adults with focal epilepsy to demonstrate increased activity of the frontal component of the PC ipsilateral to the putative SOZ was associated with interictal epileptiform discharges and using PET showed that $GABA_A$ binding was decreased in this region [126]. Another EEG-fMRI study in 27 patients with either TLE or ETE showed that the PC was a common connectivity node [127], supported also by a resting-state fMRI study in ETE by Pedersen [128]. The PC may, therefore, be implicated as a propagation point within the epileptogenic network of focal epilepsies and could thus serve as a stimulation target [118]. Again, it is interesting that the PC is a common node amongst multiple forms of epilepsies. The PC is a structural and functional connection between the temporal lobe and the limbic system [118]. As such, the PC is connected to the medial temporal lobe and its associated network – including the hippocampus, amygdala, entorhinal and perirhinal cortices [129], orbitofrontal cortex [130], and the circuit of *Papez*. Studies of olfaction using fMRI have shown functional connectivity between the PC and the mediodorsal thalamus [130]. The PC has also been implicated in generalized-onset epilepsies [118], but this has been less studied.

Focus now turns to how the piriform cortex may be modulated for the treatment of DRE, particularly within TLE which seems to be the most related epilepsy type thus far. Further studies to refine our understanding of the network of the PC are required [123], and movement towards ultra-high-field imaging (7-Tesla MRI) may facilitate studies of small structures such as the PC. As it stands, there is currently a shortage of network-based analyses analogous to those described above for other stimulation targets.

Septal area

The septal area (SA) (also termed the 'medial septum' or 'medial frontal zone') is a small region of the cortex at the most posterior and deep portion of the frontal lobe (**Figure 4**). Although less well explored, there has been an interest in the septal area as a neurostimulation zone for epilepsy [131].

The SA has been an area of particular interest in the context of TLE considering the septo-hippocampal structural and functional connectivity. There is coupling of epileptiform activity between the SA and hippocampus [132] and SA stimulation inhibits hippocampal neuronal activity [133]. An MRI study showed that patients with TLE (but without mesial temporal sclerosis) have higher volumes of the SA nuclei compared to patients with extratemporal epilepsy and controls [134]. The authors stated that this finding was 'evidence of neuroplasticity/augmentation of the septal-hippocampal system in TLE'.

As it stands, studies performing neurostimulation of the SA to treat epilepsy have been limited to animal models. A study by Takeuchi et al demonstrated that closed-loop stimulation of the medial septum was able to terminate seizures in Long-Evans rats with TLE [135]. A study by Izadi et al showed that continuous stimulation of the medial septum in Sprague-Dawley rats with pilocarpine-induced TLE was able to raise the seizure threshold and improve cognitive performance measured using the Barnes maze [136]. Further studies are required in order to determine the role of the SA in the epileptogenic network of both TLE and ETE and its potential as a propagation point and stimulation target.

The subthalamic nucleus

The subthalamic nucleus (STN), more typically a target for DBS in Parkinson's disease, has also been proposed as a stimulation target in epilepsy [137–139]. The STN has connections with the cortex, both directly and via the thalamus[140]. Following reports in animal models [141], Chabardès, Benabid and colleagues first performed STN DBS in a child with focal cortical dysplasia[142] followed by four other patients[143]. They hypothesized that stimulation of the STN acts on a 'cortico-subcortical network' by anti-dromic neuromodulation of the cortex[143], but data available in the study could not corroborate this and the network mechanism of STN stimulation in epilepsy remains unknown.

We found one study that used SEEG to investigate the role of the STN in seven patients with epilepsy undergoing presurgical evaluation and who had seizure-onset zone in the motor area[138]. The investigators reported a downstream propagation of epileptiform activity from the motor cortex to the ipsilateral STN. Furthermore, the study used trials of high-frequency stimulation to the STN to show reductions in interictal spiking and high-frequency

oscillations, leading to their conclusion that the STN is a key node / propagation point in the network for these patients and thus a potential stimulation target.

The cerebellum

In 1976, Cooper and colleagues published their results on using stimulation at the cerebellar cortex to inhibit seizures in 10 of 15 human subjects[144]. Whilst the results suggested that anterior cerebellar lobe stimulation was more efficacious than posterior cerebellar lobe stimulation, there was no further data to refine our network understanding of this clinical effect. A small number of further human studies [101,145,146] have not convincingly replicated the finding of seizure reduction with cerebellar stimulation[147] and subsequently the cerebellum has not been further explored like other targets have.

Others

Alternate targets include the central lateral thalamus [148,149], pontine nucleus oralis [149], hypothalamus [150] and caudate nucleus [151], as well as others [15,152]. Further pre-clinical (including network analyses) and clinical evidence are required to investigate these potential seizure propagation points.

Towards personalized, network-guided neurostimulation

This review has so far discussed the mechanisms by which network augmentation delivers therapeutic effect to patients with epilepsy, the network properties of particular propagation points within the epileptogenic network and how network differences are related to varying degrees of therapeutic benefit of neuromodulation (seizure frequency reduction). This section discusses how we may be able to employ pre-implantation network metrics to guide our clinical decision making in neurostimulation and personalize therapies to maximize the delivered clinical impact to our patients.

The next translational step in network-guided neuromodulation for epilepsy is to apply the patient's epileptogenic network to a candidacy algorithm – i.e. can we use preoperative

network data to predict which patients will benefit from neurostimulation? Studies have predicted postoperative seizure freedom based on preoperative multi-modal network data in patients undergoing resective surgery [153–158] and VNS implantation [159] for DRE. For example, a study by Li et al developed the network-based concept of *neural fragility* to predict surgical failure in 43 of 47 patients undergoing resective surgery for epilepsy [160]. Only recently a small number of published studies have reported the ability of pre-implantation networks to predict response to intracranial neurostimulation for epilepsy.

Whilst we await prospective studies of network-predicted DBS or RNS efficacy in epilepsy, a number of retrospective studies have been performed that speak to the ability of preoperative data to be associated with response to neurostimulation. For example, a study by Middlebrooks et al showed that, in six patients undergoing ANT DBS for DRE, the volume of tissue activated (by stimulation) in responders was hyperconnected to the default mode network (derived within a normative dataset from resting-state fMRI data) when compared to non-responders [161]. A recent study by Charlebois et al concluded that higher structural connectivity of the volume of tissue activated (VTA) was correlated with greater seizure reduction in patients treated with hippocampal RNS [162]. These studies raise the possibility that preoperative network measures may provide biomarkers to determine stimulation candidacy and tailor targeting to the individual patient's network. Furthermore, Scheid et al. used pre-RNS functional network data derived from 30 patients undergoing iEEG [26]. They tested the hypothesis that wide-scale networks (i.e. those that incorporate nodes beyond the SOZ) can be identified as a predictive marker of RNS responder rate. They found that, compared to non-responders, responders to RNS had a smaller decrease in the functional connectivity (high-γ band (95–105 Hz)) measured between iEEG contacts. iEEG could therefore be used as a pre-neurostimulation investigation, but there is still a need to determine whether predictive network signatures can be identified non-invasively.

As well as predicting patient responsiveness to neurostimulation and determining candidacy, a future objective of this field is to use preoperative measures of brain connectivity to deliver personalized and network-guided neurostimulation [106,163,164] (**Figure 5**). As one would expect, it has been clearly demonstrated that brain connectivity is to some degree individual in health [165], as well as in disease paradigms such as epilepsy, so stimulation targeting must be individualized which is at odds with the likely necessity of individualizing associated with epilepsies inherent heterogeneity. There has recently been a significant drive towards these

'precision' DBS approaches within the context of adult movement disorders such as Parkinson's disease [20], but epilepsy remains a step behind in terms of available evidence. There are moves to provide 'adaptive' neurostimulation, such as alteration of stimulation paradigms in response to temporally-variant neurophysiological (e.g. local field potentials in RNS) or manual programming based on clinical feedback (seizure frequency).

Although invasive, SEEG offers a clinically-viable opportunity for network-guided and individualized neuromodulation planning, and has already begun transitioning in routine clinical practice[18,42,166,167]. Richardson's review of paradigm shifts in closed-loop neuromodulation suggests that by augmenting the current '(seizure) focus-guided' decision-making framework with a 'network-orientated' framework, SEEG implantation that includes potential propagation points may identify both sites for seizure detection in RNS and sites for the delivery of neuromodulation (DBS or RNS) [18]. Similarly, the latest *DBS Think Tank* report describes 'reassessing the purpose of SEEG' by moving away from a 'node based philosophy' towards a 'network based philosophy' [168]. The authors challenge the notion that 'one size fits all' in thalamic stimulation and suggest that SEEG may allow quantitative determination of the optimal stimulation target per patient. A retrospective study of 74 patients undergoing thalamic SEEG supports an individualized and data-driven approach to thalamic connectivity – they revealed that thalamic epileptogenicity was different according to epilepsy localization and was correlate with the extent of the epileptogenic network [77]. Further retrospective studies claim that SEEG can be used to optimally place the receiving RNS lead [166] and that graph theory metrics can identify the most 'controllable' node(s) within the epileptogenic network [169]. However, further prospective evidence for the utility of SEEG-guided neuromodulation is required – including proof of concept for the network-guided placement of the stimulating RNS (or DBS) leads. Stimulation during SEEG investigation may also provide further inferences to the optimal stimulation target(s) [170].

The intent of network-guided neurostimulation for epilepsy would be to isolate an individual's unique epileptogenic network and to identify key locations responsible for generating seizures, perhaps the SOZ, and an optimal propagation point in order to normalize brain connectivity. As stated in the *DBS Think Tank* report, this would require integrating neuroimaging and network data to deliver 'precision DBS' [164]. Whilst many of the network-based neurostimulation studies in adult disorders outside of epilepsy predominantly use structural data, such as diffusion tractography, epilepsy would more than likely require a

more advanced and multi-modality approach that incorporates functional connectivity (inc. EEG and fMRI) in order to incorporate data describing the dynamic and temporal network properties. Seizure occurrences in epilepsy are not random, but hold a chronotype – a temporal variation that respects cyclical patterns and may eventually allow for seizure forecasting in some patients [61,171,172].

We suggest that existing data could be used to, at first, retrospectively test the idea that the preoperative and individual network can identify the patient's optimal stimulation target. Simulated lesioning (a.k.a. 'virtual resection') has been used in neuroimaging studies of patients with DRE in attempts to manipulate the preoperative epileptogenic network [154,173,174]. A small number of studies have similarly attempted 'virtual stimulation' experiments that computationally abate seizures[175–177] , but further clinical validation and prospective studies are required. As mentioned, the availability of network data following implantation and during stimulation would be a powerful addition to allow validation of these models' predictions in terms of network modulation and outcome. For example, the recording of local field potentials simultaneous to whole-brain connectivity measures, for example fMRI or scalp EEG, could further explain the network effects of neurostimulation at different targets or stimulation regimes [178,179].

The availability of normative datasets – for example structural normative networks in the Human Connectome Project[180] or epilepsy-specific data such as stereo-EEG datasets – may allow for the identification of key propagation points in the individual [181]. A recent example of applying normative data is in the study by Vetkas et al, who used the normative functional (fMRI) dataset from 1000 adults to derive the nodes that are common to the networks of three clinically-used neurostimulation targets – the ANT, CMT and hippocampus [152]. They used graph theory to show that the anterior cingulate and other regions of the default mode and salience networks were common nodes connected with these stimulation targets. The ultimate goal is to use the pre-operative and non-invasively derived network to identify the particular propagation point (stimulation target) where DBS would produce the greatest effect for an individual patient.

Lastly, unlike movement disorders where the effect of stimulation alteration can be measured quickly, the clinical effects of such augmentations on seizure patterns can take days to weeks

to become apparent. Whilst we have so far discussed pre-implantation investigations that could inform of DBS or RNS efficacy, another potential application of network analyses is to determine how alterations in stimulation regimes will affect seizure control. A catalyst in this regard could be the capability to perform neuroimaging studies with these implanted stimulation devices in-situ, to measures how stimulation alters network dynamics[178,179,182]. For example, Middlebrooks et al used fMRI during active ANT DBS to demonstrate the network differences of patients with high (145 Hz) versus low (35 Hz) stimulation frequency regimes. Provided safety risks can be managed [183,184], observations of acute and chronic effects of DBS modulation can substantially improve our understanding of their mechanism of action and ultimately clinical efficacy.

Conclusions

The convergence of the fields of network neuroscience and neurostimulation are leading towards an exciting opportunity for personalized, network-guided approaches to neurostimulation for patients with epilepsy. The opportunity to combine data derived from implanted neuromodulation devices and studies of whole-brain networks gives us the opportunity to work towards this goal. Further studies are required to (1) determine the mechanistic role of network modulation; (2) define the critical nodes within the epileptogenic network (at disease paradigm, syndrome and individual levels); and (3) to use preoperative network data to deliver precision neurostimulation to individual patients; and (4) validate markers and models with post-operative data including imaging. As always, we need prospective clinical trials of these technologies and philosophies in order to demonstrate their clinical utility. This will require a multi-site, international and coordinated effort.

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References

1. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522-530. doi:10.1111/epi.13670
2. Richardson MP. Large scale brain models of epilepsy: dynamics meets connectomics. *J Neurol Neurosurg Psychiatry*. 2012;83(12):1238-1248. doi:10.1136/jnnp-2011-301944
3. Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia*. 2002;43(3):219-227. http://www.ncbi.nlm.nih.gov/pubmed/11906505
4. Van Diessen E, Diederen SJHH, Braun KPJJ, Jansen FE, Stam CJ. Functional and structural brain networks in epilepsy: What have we learned? *Epilepsia*. 2013;54(11):1855-1865. doi:10.1111/epi.12350
5. Centeno M, Carmichael DW. Network Connectivity in Epilepsy: Resting State fMRI and EEG-fMRI Contributions. *Front Neurol*. 2014;5:93. doi:10.3389/fneur.2014.00093
6. Royer J, Bernhardt BC, Larivière S, et al. Epilepsy and brain network hubs. *Epilepsia*. 2022;63(3):537-550. doi:10.1111/epi.17171
7. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 2009;10(3):186-198. doi:10.1038/nrn2575
8. Bassett DS, Sporns O. Network neuroscience. *Nat Neurosci*. 2017;20(3):353-364. doi:10.1038/nn.4502
9. Larivière S, Bernasconi A, Bernasconi N, Bernhardt BC. Connectome biomarkers of drug-resistant epilepsy. *Epilepsia*. 2021;62(1):6-24. doi:10.1111/epi.16753
10. Laufs H. Functional imaging of seizures and epilepsy: evolution from zones to networks. *Curr Opin Neurol*. 2012;25(2):194-200. doi:10.1097/WCO.0b013e3283515db9
11. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342(5):314-319. doi:10.1056/NEJM200002033420503
12. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for Drug-Resistant Epilepsy in

Children. *N Engl J Med*. 2017;377(17):1639-1647. doi:10.1056/NEJMoa1615335

13. Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345(5):311-318. doi:10.1056/NEJM200108023450501
14. Fisher RS, Velasco AL. Electrical brain stimulation for epilepsy. *Nat Rev Neurol*. 2014;10(5):261-270. doi:10.1038/nrneurol.2014.59
15. Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. *Cochrane Database Syst Rev*. Published online July 18, 2017. doi:10.1002/14651858.CD008497.pub3
16. Ryvlin P, Rheims S, Hirsch LJ, Sokolov A, Jehi L. Neuromodulation in epilepsy: state-of-the-art approved therapies. *Lancet Neurol*. 2021;20(12):1038-1047. doi:10.1016/S1474-4422(21)00300-8
17. Hachem LD, Wong SM, Ibrahim GM. The vagus afferent network: emerging role in translational connectomics. *Neurosurg Focus*. 2018;45(3):E2. doi:10.3171/2018.6.FOCUS18216
18. Richardson RM. Closed-Loop Brain Stimulation and Paradigm Shifts in Epilepsy Surgery. *Neurol Clin*. 2022;40(2):355-373. doi:10.1016/j.ncl.2021.12.002
19. Horn A, Fox MD. Opportunities of connectomic neuromodulation. *Neuroimage*. 2020;221:117180. doi:10.1016/j.neuroimage.2020.117180
20. Hollunder B, Rajamani N, Siddiqi SH, et al. Toward personalized medicine in connectomic deep brain stimulation. *Prog Neurobiol*. 2021;(September 2021):102211. doi:10.1016/j.pneurobio.2021.102211
21. Denison T, Morrell MJ. Neuromodulation in 2035. *Neurology*. 2022;98(2):65-72. doi:10.1212/WNL.0000000000013061
22. Tavakol S, Royer J, Lowe AJ, et al. Neuroimaging and connectomics of drug-resistant epilepsy at multiple scales: From focal lesions to macroscale networks. *Epilepsia*. 2019;60(4):593-604. doi:10.1111/epi.14688
23. Middlebrooks EH, Domingo RA, Vivas-Buitrago T, et al. Neuroimaging advances in deep brain stimulation: Review of indications, anatomy, and brain connectomics. *Am J Neuroradiol*. 2020;41(9):1558-1568. doi:10.3174/ajnr.A6693
24. Foit NA, Bernasconi A, Ladbon-Bernasconi N. Contributions of Imaging to Neuromodulatory Treatment of Drug-Refractory Epilepsy. *Brain Sci*. 2020;10(10):700. doi:10.3390/brainsci10100700

25. Wu C, Ferreira F, Fox M, et al. Clinical applications of magnetic resonance imaging based functional and structural connectivity. *Neuroimage*. 2021;244:118649. doi:10.1016/j.neuroimage.2021.118649
26. Scheid BH, Bernabei JM, Khambhati AN, et al. Intracranial electroencephalographic biomarker predicts effective responsive neurostimulation for epilepsy prior to treatment. *Epilepsia*. Published online January 7, 2022. doi:10.1111/epi.17163
27. Starnes K, Miller K, Wong-Kisiel L, Lundstrom BN. A Review of Neurostimulation for Epilepsy in Pediatrics. *Brain Sci*. 2019;9(10):283. doi:10.3390/brainsci9100283
28. Touma L, Dansereau B, Chan AY, et al. Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis from the ILAE Surgical Therapies Commission. *Epilepsia*. Published online April 18, 2022:0-3. doi:10.1111/epi.17243
29. Chari A, Thornton RC, Tisdall MM, Scott RC. Microelectrode recordings in human epilepsy: a case for clinical translation. *Brain Commun*. 2020;2(2). doi:10.1093/braincomms/fcaa082
30. Ashkan K, Rogers P, Bergman H, Ughratdar I. Insights into the mechanisms of deep brain stimulation. *Nat Rev Neurol*. 2017;13(9):548-554. doi:10.1038/nrneurol.2017.105
31. Laxpati NG, Kasoff WS, Gross RE. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. *Neurotherapeutics*. 2014;11(3):508-526. doi:10.1007/s13311-014-0279-9
32. Lozano AM, Lipsman N, Bergman H, et al. Deep brain stimulation: current challenges and future directions. *Nat Rev Neurol*. 2019;15(3):148-160. doi:10.1038/s41582-018-0128-2
33. Carlson JD, Cleary DR, Cetas JS, Heinricher MM, Burchiel KJ. Deep Brain Stimulation Does Not Silence Neurons in Subthalamic Nucleus in Parkinson's Patients. *J Neurophysiol*. 2010;103(2):962-967. doi:10.1152/jn.00363.2009
34. Lee KH, Hitti FL, Chang S-Y, et al. High frequency stimulation abolishes thalamic network oscillations: an electrophysiological and computational analysis. *J Neural Eng*. 2011;8(4):046001. doi:10.1088/1741-2560/8/4/046001
35. Tawfik VL, Chang S-Y, Hitti FL, et al. Deep Brain Stimulation Results in Local Glutamate and Adenosine Release. *Neurosurgery*. 2010;67(2):367-375. doi:10.1227/01.NEU.0000371988.73620.4C
36. Medeiros D de C, Moraes MFD. Focus on desynchronization rather than excitability:

A new strategy for intraencephalic electrical stimulation. *Epilepsy Behav*. 2014;38:32-36. doi:10.1016/j.yebeh.2013.12.034

37. Penfield W, Jasper H. *Epilepsy and the Functional Anatomy of the Human Brain*.; 1954.

38. Kramer MA, Cash SS. Epilepsy as a Disorder of Cortical Network Organization. *Neurosci*. 2012;18(4):360-372. doi:10.1177/1073858411422754

39. Chaitanya G, Toth E, Pizarro D, et al. Anterior Nucleus of Thalamus Gates Progression of Mesial Temporal Seizures by Modulating Thalamocortical Corresponding. *bioRxiv*. 2020;132(4):100363. https://doi.org/10.1101/2020.09.17.301812

40. Guye M, Régis J, Tamura M, et al. The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain*. 2006;129(Pt 7):1917-1928. doi:10.1093/brain/awl151

41. 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;218:116967. doi:10.1016/j.neuroimage.2020.116967

42. Yu T, Wang X, Li Y, et al. High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. *Brain*. 2018;141(9):2631–2643. doi:10.1093/brain/awy187

43. Zumsteg D, Lozano AM, Wieser HG, Wennberg RA. Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. *Clin Neurophysiol*. 2006;117(1):192-207. doi:10.1016/j.clinph.2005.09.015

44. Stypulkowski PH, Stanslaski SR, Jensen RM, Denison TJ, Giftakis JE. Brain stimulation for epilepsy - Local and remote modulation of network excitability. *Brain Stimul*. 2014;7(3):350-358. doi:10.1016/j.brs.2014.02.002

45. Warren AEL, Simon Harvey A, Vogrin SJ, et al. The epileptic network of Lennox-Gastaut syndrome: Cortically driven and reproducible across age. *Neurology*. 2019;93(3):E215-E226. doi:10.1212/WNL.0000000000007775

46. Martín-López D, Jiménez-Jiménez D, Cabañés-Martínez L, Selway RP, Valentín A, Alarcón G. 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;27(7):1750010. doi:10.1142/S0129065717500101

47. Boerwinkle VL, Cediel EG, Mirea L, et al. Network-targeted approach and postoperative resting-state functional magnetic resonance imaging are associated with seizure outcome. *Ann Neurol*. 2019;86(3):344-356. doi:10.1002/ana.25547

48. Xiao F, Koepp MJ, Zhou D. Pharmaco-fMRI: A Tool to Predict the Response to Antiepileptic Drugs in Epilepsy. *Front Neurol*. 2019;10. doi:10.3389/fneur.2019.01203
49. Wandschneider B, Stretton J, Sidhu M, et al. Levetiracetam reduces abnormal network activations in temporal lobe epilepsy. *Neurology*. 2014;83(17):1508-1512. doi:10.1212/WNL.0000000000000910
50. Horn A, Wenzel G, Irmen F, et al. Deep brain stimulation induced normalization of the human functional connectome in Parkinson's disease. *Brain*. 2019;142(10):3129-3143. doi:10.1093/brain/awz239
51. Chan AY, Rolston JD, Rao VR, Chang EF. Effect of neurostimulation on cognition and mood in refractory epilepsy. *Epilepsia Open*. 2018;3(1):18-29. doi:10.1002/epi4.12100
52. 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. doi:10.1212/WNL.0000000000001334
53. 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. doi:10.1212/WNL.0000000000010154
54. Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia*. 2015;56(11):1836-1844. doi:10.1111/epi.13191
55. Heminghyt E, Herrman H, Skogan AH, et al. Cognitive change after DBS in refractory epilepsy: A randomized-controlled trial. *Acta Neurol Scand*. 2022;145(1):111-118. doi:10.1111/ane.13539
56. Spencer D. Responsive Neurostimulation and Cognition. *Epilepsy Curr*. 2016;16(2):98-100. doi:10.5698/1535-7511-16.2.98
57. Khan M, Paktiawal J, Piper RJ, Chari A, Tisdall MM. Intracranial neuromodulation with deep brain stimulation and responsive neurostimulation in children with drug-resistant epilepsy: a systematic review. *J Neurosurg Pediatr*. 2022;29(2):208-217. doi:10.3171/2021.8.PEDS21201
58. Nagahama Y, Zervos TM, Murata KK, et al. Real-World Preliminary Experience With Responsive Neurostimulation in Pediatric Epilepsy: A Multicenter Retrospective Observational Study. *Neurosurgery*. 2021;0(0):1-8. doi:10.1093/neuros/nyab343
59. Kerezoudis P, Gyftopoulos A, Alexander AY, et al. Safety and efficacy of responsive

neurostimulation in the pediatric population: Evidence from institutional review and patient-level meta-analysis. *Epilepsy Behav*. 2022;129:108646. doi:10.1016/j.yebeh.2022.108646

60. Voges BR, Schmitt FC, Hamel W, et al. Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. *Epilepsia*. 2015;56(8):e99-e103. doi:10.1111/epi.13045

61. Karoly PJ, Rao VR, Gregg NM, et al. Cycles in epilepsy. *Nat Rev Neurol*. 2021;17(5):267-284. doi:10.1038/s41582-021-00464-1

62. Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun*. 2018;9(1):1-10. doi:10.1038/s41467-017-02577-y

63. Schroeder GM, Diehl B, Chowdhury FA, et al. Seizure pathways change on circadian and slower timescales in individual patients with focal epilepsy. *Proc Natl Acad Sci*. 2020;117(20):11048-11058. doi:10.1073/pnas.1922084117

64. Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of Closed-Loop Brain Stimulation Neurophysiological Features With Seizure Control Among Patients With Focal Epilepsy. *JAMA Neurol*. 2019;76(7):800-808. doi:10.1001/jamaneurol.2019.0658

65. Sisterson ND, Wozny TA, Kokkinos V, Constantino A, Richardson RM. Closed-Loop Brain Stimulation for Drug-Resistant Epilepsy: Towards an Evidence-Based Approach to Personalized Medicine. *Neurotherapeutics*. 2019;16(1):119-127. doi:10.1007/s13311-018-00682-4

66. Khambhati AN, Shafi A, Rao VR, Chang EF. Long-term brain network reorganization predicts responsive neurostimulation outcomes for focal epilepsy. *Sci Transl Med*. 2021;13:6588. http://stm.sciencemag.org/

67. Salanova V, Sperling MR, Gross RE, et al. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. *Epilepsia*. 2021;62(6):1306-1317. doi:10.1111/epi.16895

68. Silva AB, Khambhati AN, Speidel BA, Chang EF, Rao VR. Effects of anterior thalamic nuclei stimulation on hippocampal activity: Chronic recording in a patient with drug-resistant focal epilepsy. *Epilepsy Behav Reports*. 2021;16:100467. doi:10.1016/j.ebr.2021.100467

69. Gardner J. A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools. *Soc Stud Sci*. 2013;43(5):707-728. doi:10.1177/0306312713483678

70. Jasper H, Naquet R, King EE. Thalamocortical recruiting responses in sensory receiving areas in the cat. *Electroencephalogr Clin Neurophysiol*. 1955;7(1):99-114. doi:10.1016/0013-4694(55)90063-8
71. Hunter J, Jasper HH. Effects of thalamic stimulation in unanaesthetised animals. *Electroencephalogr Clin Neurophysiol*. 1949;1(1-4):305-324. doi:10.1016/0013-4694(49)90196-0
72. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The Human Thalamus Is an Integrative Hub for Functional Brain Networks. *J Neurosci*. 2017;37(23):5594-5607. doi:10.1523/JNEUROSCI.0067-17.2017
73. Blumenfeld H. The thalamus and seizures. *Arch Neurol*. 2002;59(1):135-137. doi:10.1001/archneur.59.1.135
74. Norden AD, Blumenfeld H. The role of subcortical structures in human epilepsy. *Epilepsy Behav*. 2002;3(3):219-231. http://www.ncbi.nlm.nih.gov/pubmed/12662601
75. 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. doi:10.1111/j.1528-1167.2010.02536.x
76. He X, Doucet GE, Pustina D, Sperling MR, Sharan AD, Tracy JI. Presurgical thalamic "hubness" predicts surgical outcome in temporal lobe epilepsy. *Neurology*. 2017;88(24):2285-2293. doi:10.1212/WNL.0000000000004035
77. Pizzo F, Roehri N, Giusiano B, et al. The Ictal Signature of Thalamus and Basal Ganglia in Focal Epilepsy: A SEEG Study. *Neurology*. 2021;96(2):e280-e293. doi:10.1212/WNL.0000000000011003
78. Burdette D, Mirro EA, Lawrence M, Patra SE. Brain-responsive corticothalamic stimulation in the pulvinar nucleus for the treatment of regional neocortical epilepsy: A case series. *Epilepsia Open*. 2021;6(3):611-617. doi:10.1002/epi4.12524
79. Mullan S. Thalamic Lesions for the Control of Epilepsy. *Arch Neurol*. 1967;16(3):277. doi:10.1001/archneur.1967.00470210053006
80. Upton ARM, Amin I, GARNETT S, SPRINGMAN M, NAHMIAS C, COOPER IS. Evoked Metabolic Responses in the LimbicStriate System Produced by Stimulation of Anterior Thalamic Nucleus in Man. *Pacing Clin Electrophysiol*. 1987;10(1):217-225. doi:10.1111/j.1540-8159.1987.tb05952.x
81. Child ND, Benarroch EE. Anterior nucleus of the thalamus: functional organization and clinical implications. *Neurology*. 2013;81(21):1869-1876. doi:10.1212/01.wnl.0000436078.95856.56

82. Papez JW. A Proposed mechanism of emotion. *Arch Neurol Psychiatry*. 1937;38(4):725. doi:10.1001/archneurpsyc.1937.02260220069003
83. Li DH, Yang XF. Remote modulation of network excitability during deep brain stimulation for epilepsy. *Seizure*. 2017;47:42-50. doi:10.1016/j.seizure.2017.02.016
84. Aggleton JP, O'Mara SM. The anterior thalamic nuclei: core components of a tripartite episodic memory system. *Nat Rev Neurosci*. Published online April 27, 2022. doi:10.1038/s41583-022-00591-8
85. Krishna V, King NKK, Sammartino F, et al. Anterior Nucleus Deep Brain Stimulation for Refractory Epilepsy: Insights Into Patterns of Seizure Control and Efficacious Target. *Neurosurgery*. 2016;78(6):802-811. doi:10.1227/NEU.0000000000001197
86. Lehtimäki K, Möttönen T, Järventausta K, et al. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. *Brain Stimul*. 2016;9(2):268-275. doi:10.1016/j.brs.2015.09.014
87. Koeppen JA, Nahravani F, Kramer M, et al. Electrical Stimulation of the Anterior Thalamus for Epilepsy: Clinical Outcome and Analysis of Efficient Target. *Neuromodulation*. 2019;22(4):465-471. doi:10.1111/ner.12865
88. Gross RE, Fisher RS, Sperling MR, Giftakis JE, Stypulkowski PH. Analysis of Deep Brain Stimulation Lead Targeting in the Stimulation of Anterior Nucleus of the Thalamus for Epilepsy Clinical Trial. *Neurosurgery*. 2021;89(3):406-412. doi:10.1093/neuros/nyab186
89. Schaper FLWVJ, Plantinga BR, Colon AJ, et al. Deep Brain Stimulation in Epilepsy: A Role for Modulation of the Mammillothalamic Tract in Seizure Control? *Neurosurgery*. 2020;87(3):602-610. doi:10.1093/neuros/nyaa141
90. Chaitanya G, Toth E, Pizarro D, Irannejad A, Riley K, Pati S. Precision mapping of the epileptogenic network with low- and high-frequency stimulation of anterior nucleus of thalamus. *Clin Neurophysiol*. 2020;131(9):2158-2167. doi:10.1016/j.clinph.2020.05.036
91. Gregg NM, Marks VS, Sladky V, et al. Anterior nucleus of the thalamus seizure detection in ambulatory humans. *Epilepsia*. 2021;62(10). doi:10.1111/epi.17047
92. Molnar GF, Sailer A, Gunraj CA, et al. Changes in motor cortex excitability with stimulation of anterior thalamus in epilepsy. *Neurology*. 2006;66(4):566-571. doi:10.1212/01.wnl.0000198254.08581.6b
93. Tyvaert L, Chassagnon S, Sadikot A, LeVan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: an EEG-fMRI study. *Neurology*.

2009;73(23):2018-2022. doi:10.1212/WNL.0b013e3181c55d02

94. Herlopian A, Cash SS, Eskandar EM, Jennings T, Cole AJ. Responsive neurostimulation targeting anterior thalamic nucleus in generalized epilepsy. *Ann Clin Transl Neurol*. 2019;6(10):2104-2109. doi:10.1002/acn3.50858

95. Piper RJ, Tangwiriyasakul C, Shamshiri EA, et al. Functional Connectivity of the Anterior Nucleus of the Thalamus in Pediatric Focal Epilepsy. *Front Neurol*. 2021;12:670881. doi:10.3389/fneur.2021.670881

96. Warsi NM, Yan H, Suresh H, et al. The anterior and centromedian thalamus: Anatomy, function, and dysfunction in epilepsy. *Epilepsy Res*. 2022;182:106913. doi:10.1016/j.eplepsyres.2022.106913

97. Fisher RS, Uematsu S, Krauss GL, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia*. 1992;33(5):841-851. doi:10.1111/j.1528-1157.1992.tb02192.x

98. Velasco F, Velasco M, Jiménez F, et al. Predictors in the Treatment of Difficult-to-control Seizures by Electrical Stimulation of the Centromedian Thalamic Nucleus. *Neurosurgery*. 2000;47(2):295-305. doi:10.1097/00006123-200008000-00007

99. 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;47(7):1203-1212. doi:10.1111/j.1528-1167.2006.00593.x

100. Velasco M, Velasco F, Velasco AL, Jiménez F, Brito F, Márquez I. REVIEW ARTICLE Acute and Chronic Electrical Stimulation of the Centromedian Thalamic Nucleus. *Arch Med Res*. 2000;31(3):304-315. doi:10.1016/S0188-4409(00)00085-0

101. Velasco F, Carrillo-Ruiz JD, Brito F, et al. Double-blind, Randomized Controlled Pilot Study of Bilateral Cerebellar Stimulation for Treatment of Intractable Motor Seizures. *Epilepsia*. 2005;46(7):1071-1081. doi:10.1111/j.1528-1167.2005.70504.x

102. Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M. Electrical Stimulation of the Centromedian Thalamic Nucleus in Control of Seizures: Long-Term Studies. *Epilepsia*. 1995;36(1):63-71. doi:10.1111/j.1528-1157.1995.tb01667.x

103. Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical Stimulation of the Hippocampal Epileptic Foci for Seizure Control: A Double-Blind, Long-Term Follow-Up Study. *Epilepsia*. 2007;48(10):1895-1903. doi:10.1111/j.1528-1167.2007.01181.x

104. 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;54(10):1823-1833. doi:10.1111/epi.12352

105. Dalic LJ, Warren AEL, Bulluss KJ, et al. DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). *Ann Neurol*. 2022;91(2):253-267. doi:10.1002/ana.26280
106. Torres Diaz C V., González-Escamilla G, Ciolac D, et al. Network Substrates of Centromedian Nucleus Deep Brain Stimulation in Generalized Pharmacoresistant Epilepsy. *Neurotherapeutics*. 2021;18(3):1665-1677. doi:10.1007/s13311-021-01057-y
107. Warren AEL, Harvey AS, Vogrin SJ, et al. The epileptic network of Lennox-Gastaut syndrome. *Neurology*. 2019;93(3):e215-e226. doi:10.1212/WNL.0000000000007775
108. Warren AEL, Dalic LJ, Thevathasan W, Roten A, Bulluss KJ, Archer J. Targeting the centromedian thalamic nucleus for deep brain stimulation. *J Neurol Neurosurg Psychiatry*. 2020;91(4):339-349. doi:10.1136/jnnp-2019-322030
109. Dalic LJ, Warren AEL, Young JC, et al. Cortex leads the thalamic centromedian nucleus in generalized epileptic discharges in Lennox-Gastaut syndrome. *Epilepsia*. 2020;61(10):2214-2223. doi:10.1111/epi.16657
110. Kim SH, Lim SC, Yang DW, et al. Thalamo-cortical network underlying deep brain stimulation of centromedian thalamic nuclei in intractable epilepsy: a multimodal imaging analysis. *Neuropsychiatr Dis Treat*. 2017;13:2607-2619. doi:10.2147/NDT.S148617
111. Warren AE. L, Dalic LJ, Bulluss KJ, Roten A, Thevathasan W, Archer JS. The optimal target and connectivity for DBS in Lennox-Gastaut syndrome. *Ann Neurol*. Published online April 15, 2022. doi:10.1002/ana.26368
112. 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. doi:10.3389/fneur.2021.656585
113. NeuroPace. NeuroPace Awarded Five-Year NIH Grant Funding of More than $9M to Study RNS System in Patients with Lennox-Gastaut Syndrome. https://www.neuropace.com/. Published 2021. Accessed December 8, 2021. https://www.neuropace.com/neuropace-awarded-five-year-nih-grant-funding/
114. Bridge H, Leopold DA, Bourne JA. Adaptive Pulvinar Circuitry Supports Visual Cognition. *Trends Cogn Sci*. 2016;20(2):146-157. doi:10.1016/j.tics.2015.10.003

115. Filipescu C, Lagarde S, Lambert I, et al. The effect of medial pulvinar stimulation on temporal lobe seizures. *Epilepsia*. 2019;60(4):e25-e30. doi:10.1111/epi.14677
116. Homman-Ludiye J, Bourne JA. The medial pulvinar: function, origin and association with neurodevelopmental disorders. *J Anat*. 2019;235(3):507-520. doi:10.1111/joa.12932
117. Deutschová B, Pizzo F, Giusiano B, et al. Ictal connectivity changes induced by pulvinar stimulation correlate with improvement of awareness. *Brain Stimul*. 2021;14(2):344-346. doi:10.1016/j.brs.2021.01.021
118. Young JC, Vaughan DN, Paolini AG, Jackson GD. Electrical stimulation of the piriform cortex for the treatment of epilepsy: A review of the supporting evidence. *Epilepsy Behav*. 2018;88:152-161. doi:10.1016/j.yebeh.2018.09.004
119. Vaughan DN, Jackson GD. The piriform cortex and human focal epilepsy. *Front Neurol*. 2014;5:259. doi:10.3389/fneur.2014.00259
120. Löscher W, Ebert U. The role of the piriform cortex in kindling. *Prog Neurobiol*. 1996;50(5-6):427-481. doi:10.1016/s0301-0082(96)00036-6
121. Piredda S, Gale K. A crucial epileptogenic site in the deep prepiriform cortex. *Nature*. 1985;317(6038):623-625. doi:10.1038/317623a0
122. Gale K. Progression and generalization of seizure discharge: anatomical and neurochemical substrates. *Epilepsia*. 1988;29 Suppl 2:S15-34. doi:10.1111/j.1528-1157.1988.tb05795.x
123. Koepp M, Galovic M. Functional imaging of the piriform cortex in focal epilepsy. *Exp Neurol*. 2020;330:113305. doi:10.1016/j.expneurol.2020.113305
124. Borger V, Schneider M, Taube J, et al. Resection of piriform cortex predicts seizure freedom in temporal lobe epilepsy. *Ann Clin Transl Neurol*. 2021;8(1):177-189. doi:10.1002/acn3.51263
125. Galovic M, Baudracco I, Wright-Goff E, et al. Association of Piriform Cortex Resection With Surgical Outcomes in Patients With Temporal Lobe Epilepsy. *JAMA Neurol*. 2019;76(6):690. doi:10.1001/jamaneurol.2019.0204
126. Laufs H, Richardson MP, Salek-Haddadi A, et al. Converging PET and fMRI evidence for a common area involved in human focal epilepsies. *Neurology*. 2011;77(9):904-910. doi:10.1212/WNL.0b013e31822c90f2
127. Flanagan D, Badawy RAB, Jackson GD. EEG-fMRI in focal epilepsy: Local activation and regional networks. *Clin Neurophysiol*. 2014;125(1):21-31. doi:10.1016/j.clinph.2013.06.182

128. Pedersen M, Curwood EK, Vaughan DN, Omidvarnia AH, Jackson GD. Abnormal Brain Areas Common to the Focal Epilepsies: Multivariate Pattern Analysis of fMRI. *Brain Connect*. 2016;6(3):208-215. doi:10.1089/brain.2015.0367
129. Vismer MS, Forcelli PA, Skopin MD, Gale K, Koubeissi MZ. The piriform, perirhinal, and entorhinal cortex in seizure generation. *Front Neural Circuits*. 2015;9:27. doi:10.3389/fncir.2015.00027
130. Plailly J, Howard JD, Gitelman DR, Gottfried JA. Attention to Odor Modulates Thalamocortical Connectivity in the Human Brain. *J Neurosci*. 2008;28(20):5257-5267. doi:10.1523/JNEUROSCI.5607-07.2008
131. Fisher RS. Stimulation of the medial septum should benefit patients with temporal lobe epilepsy. *Med Hypotheses*. 2015;84(6):543-550. doi:10.1016/j.mehy.2015.02.016
132. Sinel'nikova V V, Popova IY, Kichigina VF. Correlational relationships between the hippocampus and medial septal area and their changes during epileptogenesis. *Neurosci Behav Physiol*. 2009;39(7):619-623. doi:10.1007/s11055-009-9189-4
133. Vinogradova OS, Brazhnik ES, Kitchigina VF, Stafekhina VS. Acetylcholine, theta-rhythm and activity of hippocampal neurons in the rabbit—IV. Sensory stimulation. *Neuroscience*. 1993;53(4):993-1007. doi:10.1016/0306-4522(93)90484-W
134. Butler T, Zaborszky L, Wang X, et al. Septal nuclei enlargement in human temporal lobe epilepsy without mesial temporal sclerosis. *Neurology*. 2013;80(5):487-491. doi:10.1212/WNL.0b013e31827f0ed7
135. Takeuchi Y, Harangozó M, Pedraza L, et al. Closed-loop stimulation of the medial septum terminates epileptic seizures. *Brain*. 2021;144(3):885-908. doi:10.1093/brain/awaa450
136. Izadi A, Pevzner A, Lee DJ, Ekstrom AD, Shahlaie K, Gurkoff GG. Medial septal stimulation increases seizure threshold and improves cognition in epileptic rats. *Brain Stimul*. 2019;12(3):735-742. doi:10.1016/j.brs.2019.01.005
137. Benabid AL, Koudsié A, Benazzouz A, et al. Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. *J Neurol*. 2001;248(S3):37-47. doi:10.1007/PL00007825
138. Ren L, Yu T, Wang D, et al. Subthalamic Nucleus Stimulation Modulates Motor Epileptic Activity in Humans. *Ann Neurol*. 2020;88(2):283-296. doi:10.1002/ana.25776
139. Handforth A, DeSalles AAF, Krahl SE. Deep Brain Stimulation of the Subthalamic

Nucleus as Adjunct Treatment for Refractory Epilepsy. *Epilepsia*. 2006;47(7):1239-1241. doi:10.1111/j.1528-1167.2006.00563.x

140. Benarroch EE. Subthalamic nucleus and its connections: Anatomic substrate for the network effects of deep brain stimulation. *Neurology*. 2008;70(21):1991-1995. doi:10.1212/01.wnl.0000313022.39329.65

141. Dybdal D, Gale K. Postural and Anticonvulsant Effects of Inhibition of the Rat Subthalamic Nucleus. *J Neurosci*. 2000;20(17):6728-6733. doi:10.1523/JNEUROSCI.20-17-06728.2000

142. Benabid AL, Minotti L, Koudsié A, de Saint Martin A, Hirsch E. Antiepileptic Effect of High-frequency Stimulation of the Subthalamic Nucleus (Corpus Luysi) in a Case of Medically Intractable Epilepsy Caused by Focal Dysplasia: A 30-month Follow-up: Technical Case Report. *Neurosurgery*. 2002;50(6):1385-1392. doi:10.1097/00006123-200206000-00037

143. Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid A-L. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord*. 2002;4 Suppl 3:S83-93. http://www.ncbi.nlm.nih.gov/pubmed/12495878

144. Cooper IS. Chronic Cerebellar Stimulation in Epilepsy. *Arch Neurol*. 1976;33(8):559. doi:10.1001/archneur.1976.00500080037006

145. Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. *J Neurosurg*. 1978;48(3):407-416. doi:10.3171/jns.1978.48.3.0407

146. 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;47(8):769-774. doi:10.1136/jnnp.47.8.769

147. Kellinghaus C, Loddenkemper T. Double-blind, Randomized Controlled Study of Bilateral Cerebellar Stimulation. *Epilepsia*. 2006;47(7):1247-1247. doi:10.1111/j.1528-1167.2006.00598_4.x

148. Redinbaugh MJ, Phillips JM, Kambi NA, et al. Thalamus Modulates Consciousness via Layer-Specific Control of Cortex. *Neuron*. 2020;106(1):66-75.e12. doi:10.1016/j.neuron.2020.01.005

149. Kundishora AJ, Gummadavelli A, Ma C, et al. Restoring Conscious Arousal During Focal Limbic Seizures with Deep Brain Stimulation. *Cereb Cortex*. 2017;27(3):1964-1975. doi:10.1093/cercor/bhw035

150. Benedetti-Isaac JC, Torres-Zambrano M, Vargas-Toscano A, et al. Seizure frequency

reduction after posteromedial hypothalamus deep brain stimulation in drug-resistant epilepsy associated with intractable aggressive behavior. *Epilepsia*. 2015;56(7):1152-1161. doi:10.1111/epi.13025

151. Šramka M, Chkhenkeli SA. Clinical Experience in Intraoperational Determination of Brain Inhibitory Structures and Application of Implanted Neurostimulators in Epilepsy. *Stereotact Funct Neurosurg*. 1990;54(1-8):56-59. doi:10.1159/000100190

152. Vetkas A, Germann J, Elias G, et al. Identifying the neural network for neuromodulation in epilepsy through connectomics and graphs. *Brain Commun*. 2022;4(3). doi:10.1093/braincomms/fcac092

153. Gleichgerrcht E, Munsell B, Bhatia S, et al. Deep learning applied to whole-brain connectome to determine seizure control after epilepsy surgery. *Epilepsia*. 2018;59(9):1643-1654. doi:10.1111/epi.14528

154. Kini LG, Bernabei JM, Mikhail F, et al. Virtual resection predicts surgical outcome for drug-resistant epilepsy. *Brain*. 2019;142(12):3892-3905. doi:10.1093/brain/awz303

155. Taylor PN, Sinha N, Wang Y, et al. The impact of epilepsy surgery on the structural connectome and its relation to outcome. *NeuroImage Clin*. 2018;18:202-214. doi:10.1016/j.nicl.2018.01.028

156. Hutchings F, Han CE, Keller SS, Weber B, Taylor PN, Kaiser M. Predicting Surgery Targets in Temporal Lobe Epilepsy through Structural Connectome Based Simulations. Sporns O, ed. *PLOS Comput Biol*. 2015;11(12):e1004642. doi:10.1371/journal.pcbi.1004642

157. Johnson GW, Cai LY, Narasimhan S, et al. Temporal lobe epilepsy lateralisation and surgical outcome prediction using diffusion imaging. *J Neurol Neurosurg Psychiatry*. Published online March 28, 2022. doi:10.1136/jnnp-2021-328185

158. Morgan VL, Sainburg LE, Johnson GW, et al. Presurgical temporal lobe epilepsy connectome fingerprint for seizure outcome prediction. *Brain Commun*. Published online May 17, 2022. doi:10.1093/braincomms/fcac128

159. Workewych AM, Arski ON, Mithani K, Ibrahim GM. Biomarkers of seizure response to vagus nerve stimulation: A scoping review. *Epilepsia*. 2020;61(10):2069-2085. doi:10.1111/epi.16661

160. Li A, Huynh C, Fitzgerald Z, et al. Neural fragility as an EEG marker of the seizure onset zone. *Nat Neurosci*. 2021;24(10):1465-1474. doi:10.1038/s41593-021-00901-w

161. Middlebrooks EH, Grewal SS, Stead M, Lundstrom BN, Worrell GA, Van Gompel JJ. Differences in functional connectivity profiles as a predictor of response to anterior

thalamic nucleus deep brain stimulation for epilepsy: a hypothesis for the mechanism of action and a potential biomarker for outcomes. *Neurosurg Focus*. 2018;45(2):E7. doi:10.3171/2018.5.FOCUS18151

162. Charlebois CM, Anderson DN, Johnson KA, et al. Patient-specific structural connectivity informs outcomes of responsive neurostimulation for temporal lobe epilepsy. *Epilepsia*. 2022;Online ahe. doi:10.1111/epi.17298

163. Denison T, Koubeissi M, Krook-Magnuson E, Mogul D, Worrell G, Schevon C. Stimulating Solutions for Intractable Epilepsy. *Epilepsy Curr*. 2021;21(5):315-319. doi:10.1177/15357597211012466

164. Vedam-Mai V, Deisseroth K, Giordano J, et al. Proceedings of the Eighth Annual Deep Brain Stimulation Think Tank: Advances in Optogenetics, Ethical Issues Affecting DBS Research, Neuromodulatory Approaches for Depression, Adaptive Neurostimulation, and Emerging DBS Technologies. *Front Hum Neurosci*. 2021;15. doi:10.3389/fnhum.2021.644593

165. Finn ES, Shen X, Scheinost D, et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. *Nat Neurosci*. 2015;18(11):1664-1671. doi:10.1038/nn.4135

166. Feldman L, Krishnan B, Alexopoulos A, Mackow M, Taylor K, Bulacio J. Brain-Responsive Neurostimulation Guided by Stereo-EEG. In: *American Epilepsy Society*. ; 2018.

167. Gadot R, Korst G, Shofty B, Gavvala JR, Sheth SA. Thalamic stereoelectroencephalography in epilepsy surgery: a scoping literature review. *J Neurosurg*. Published online March 1, 2022:1-16. doi:10.3171/2022.1.JNS212613

168. Wong JK, Deuschl G, Wolke R, et al. Proceedings of the Ninth Annual Deep Brain Stimulation Think Tank: Advances in Cutting Edge Technologies, Artificial Intelligence, Neuromodulation, Neuroethics, Pain, Interventional Psychiatry, Epilepsy, and Traumatic Brain Injury. *Front Hum Neurosci*. 2022;16. doi:10.3389/fnhum.2022.813387

169. Scheid BH, Ashourvan A, Stiso J, et al. Time-evolving controllability of effective connectivity networks during seizure progression. *Proc Natl Acad Sci*. 2021;118(5). doi:10.1073/pnas.2006436118

170. George DD, Ojemann SG, Drees C, Thompson JA. Stimulation Mapping Using Stereoelectroencephalography: Current and Future Directions. *Front Neurol*. 2020;11. doi:10.3389/fneur.2020.00320

171. Gregg NM, Nasseri M, Kremen V, et al. Circadian and multiday seizure periodicities, and seizure clusters in canine epilepsy. *Brain Commun*. 2020;2(1). doi:10.1093/braincomms/fcaa008
172. Toth R, Zamora M, Ottaway J, et al. DyNeuMo Mk-2: An Investigational Circadian-Locked Neuromodulator with Responsive Stimulation for Applied Chronobiology. *Conf proceedings IEEE Int Conf Syst Man, Cybern*. 2020;2020:3433-3440. doi:10.1109/SMC42975.2020.9283187
173. Chari A, Seunarine KK, He X, et al. Drug-resistant focal epilepsy in children is associated with increased modal controllability of the whole brain and epileptogenic regions. *Commun Biol*. 2022;5(1):394. doi:10.1038/s42003-022-03342-8
174. Khambhati AN, Davis KA, Lucas TH, Litt B, Bassett DS. Virtual Cortical Resection Reveals Push-Pull Network Control Preceding Seizure Evolution. *Neuron*. 2016;91(5):1170-1182. doi:10.1016/j.neuron.2016.07.039
175. Taylor PN, Thomas J, Sinha N, et al. Optimal control based seizure abatement using patient derived connectivity. *Front Neurosci*. 2015;9. doi:10.3389/fnins.2015.00202
176. Kramer MA, Lopour BA, Kirsch HE, Szeri AJ. Bifurcation control of a seizing human cortex. *Phys Rev E*. 2006;73(4):041928. doi:10.1103/PhysRevE.73.041928
177. Ashourvan A, Pequito S, Khambhati AN, et al. Model-based design for seizure control by stimulation. *J Neural Eng*. 2020;17(2):026009. doi:10.1088/1741-2552/ab7a4e
178. Middlebrooks EH, Jain A, Okromelidze L, et al. Acute Brain Activation Patterns of High- Versus Low-Frequency Stimulation of the Anterior Nucleus of the Thalamus During Deep Brain Stimulation for Epilepsy. *Neurosurgery*. 2021;89(5):901-908. doi:10.1093/neuros/nyab306
179. Middlebrooks EH, Lin C, Okromelidze L, et al. Functional Activation Patterns of Deep Brain Stimulation of the Anterior Nucleus of the Thalamus. *World Neurosurg*. 2020;136:357-363.e2. doi:10.1016/j.wneu.2020.01.108
180. Toga AW, Clark KA, Thompson PM, Shattuck DW, Van Horn JD. Mapping the Human Connectome. *Neurosurgery*. 2012;71(1):1-5. doi:10.1227/NEU.0b013e318258e9ff
181. Taylor PN, Papasavvas CA, Owen TW, et al. Normative brain mapping of interictal intracranial EEG to localize epileptogenic tissue. *Brain*. Published online January 24, 2022. doi:10.1093/brain/awab380
182. Saenger VM, Kahan J, Foltynie T, et al. Uncovering the underlying mechanisms and whole-brain dynamics of deep brain stimulation for Parkinson's disease. *Sci Rep*.

2017;7(1):9882. doi:10.1038/s41598-017-10003-y
183. Carmichael DW, Pinto S, Limousin-Dowsey P, et al. Functional MRI with active, fully implanted, deep brain stimulation systems: safety and experimental confounds. *Neuroimage*. 2007;37(2):508-517. doi:10.1016/j.neuroimage.2007.04.058
184. Carmichael DW, Thornton JS, Rodionov R, et al. Feasibility of simultaneous intracranial EEG-fMRI in humans: a safety study. *Neuroimage*. 2010;49(1):379-390. doi:10.1016/j.neuroimage.2009.07.062
185. Amunts K, Lepage C, Borgeat L, et al. BigBrain: An ultrahigh-resolution 3D human brain model. *Science (80-)*. 2013;340(6139):1472-1475. doi:10.1126/science.1235381
186. Horn A, Kühn AA. Lead-DBS: A toolbox for deep brain stimulation electrode localizations and visualizations. *Neuroimage*. 2015;107:127-135. doi:10.1016/j.neuroimage.2014.12.002
187. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. *Neuroimage*. 2019;184:293-316. doi:10.1016/j.neuroimage.2018.08.068
188. Su JH, Thomas FT, Kasoff WS, et al. Thalamus Optimized Multi Atlas Segmentation (THOMAS): fast, fully automated segmentation of thalamic nuclei from structural MRI. *Neuroimage*. 2019;194:272-282. doi:10.1016/j.neuroimage.2019.03.021
189. Saranathan M, Iglehart C, Monti M, Tourdias T, Rutt B. In vivo high-resolution structural MRI-based atlas of human thalamic nuclei. *Sci Data*. 2021;8(1):275. doi:10.1038/s41597-021-01062-y
190. Horn A, Kühn AA, Merkl A, Shih L, Alterman R, Fox M. Probabilistic conversion of neurosurgical DBS electrode coordinates into MNI space. *Neuroimage*. 2017;150:395-404. doi:10.1016/j.neuroimage.2017.02.004
191. Setsompop K, Kimmlingen R, Eberlein E, et al. Pushing the limits of in vivo diffusion MRI for the Human Connectome Project. *Neuroimage*. 2013;80:220-233. doi:10.1016/j.neuroimage.2013.05.078
192. Mai JK, Majtanik M, Paxinos G. *Atlas of the Human Brain*. 3rd ed.; 2015.
193. Ewert S, Plettig P, Li N, et al. Toward defining deep brain stimulation targets in MNI space: A subcortical atlas based on multimodal MRI, histology and structural connectivity. *Neuroimage*. 2018;170:271-282. doi:10.1016/j.neuroimage.2017.05.015

Figure legends

Figure 1 Potential network modulation mechanisms of resective surgery, deep brain stimulation (DBS) and responsive neurostimulation (RNS) using mesial temporal lobe epilepsy as an example of a focal epileptogenic network. This annotation uses a coronal section of an ex-vivo brain from the BigBrain Project (open-source; https://bigbrainproject.org/) [185]. SOZ = seizure onset zone. iEEG = intracranial electroencephalography.

Figure 2 Demonstration of the anatomical locations of the current propagation points/stimulation targets: (a) the anterior nucleus of the thalamus (ANT; red) and (b) centromedian nucleus of the thalamus (CMT; blue). The images were created using *LeadDBS* [186,187] using simulated trajectories within the BigBrain backdrop [185]. The ANT (anteroventral). and CMT regions-of-interest (ROI) and respective MNI coordinates were taken from the *THOMAS* atlas [188,189]. The MNI coordinates are derived according to the centre of the ROIs of the THOMAS atlas: anteroventral (right, 5,-5,12; left, -5,-6,12) and CMT (right, 10,-19,3; left, -10,-20,3). (c) Unconstrained fibers were seeded from each target using the normative fiber-tracking dataset of 32 adult participants from the Human Connectome Project [190,191].

Figure 3 A simplified schematic of the connections of the current and potential propagation points/stimulation targets. This figure demonstrates the common connections between these current and potential stimulation targets, including the *Circuit of Papez*. Current targets: anterior nucleus of the thalamus (ANT; red), centromedian nucleus of the thalamus (CMT; blue). Potential targets: piriform cortex (PC; yellow), septal area (SA; green), pulvinar (PUL; purple) and subthalamic nucleus (STN; orange). Connections with multiple colours show common connections with the respective stimulation targets.

Figure 4 Demonstration of the anatomical locations of some of the potential propagation points/stimulation targets: the piriform cortex (PC; yellow), septal area (SA; green), pulvinar of thalamus (PUL; purple) and subthalamic nucleus (STN; orange). The images were created using *LeadDBS* [186,187] using simulated trajectories within the BigBrain backdrop [185]. The PC was manually segmented according to the Mai et al atlas [192], the SA

was manually segmented, the PUL is a reconstruction from the THOMAS atlas[188,189] within *LeadDBS* and the STN is a reconstruction from the DISTAL atlas[193] within *LeadDBS*.

Figure 5 Future directions of network-guided neuromodulation for epilepsy. (A) Seizures begin in the seizure-onset zone and propagate to a wider seizure network. Neurostimulation at stimulation targets prevent or limit the spread of seizure activity from the seizure-onset zone to the wider network. Panels (B), (C) and (D) ask forward-thinking questions in network-guided neuromodulation epilepsy and draw on recent key studies[26,77,111,154,160–162,169,175,177]. ANT = anterior nucleus of the thalamus. DBS = deep brain stimulation. RNS = responsive neurostimulation.

Term	Definition
Neuromodulation	"The alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body." (The International Neuromodulation Society definition) (International Neuromodulation Society, 2021)
Connectivity	Connectivity refers to the relationship that a region(s) has with another(s). In terms of brain connectivity, there is a common reference to 'structural connectivity' (e.g. white matter connections between regions) and 'functional connectivity' (e.g. similarity in brain activity (EEG or fMRI signal) between brain regions.
Network	A group of interconnected entities. Networks exist in different scales – for example a whole brain network, or epileptic network.
Synchrony	A functional connectivity measure determined as the similarity or correlation between the temporal signal (e.g. electroencephalography or functional magnetic resonance imaging) of two or more regions.
Node	A specific point or region within a network. Connections (or 'edges') may be measured between nodes.
Seizure-onset zone ('SOZ')	A brain region or network (of multiple regions) that are responsible for the development of seizures.

Glossary. Key definitions in 'network-guided neuromodulation'.

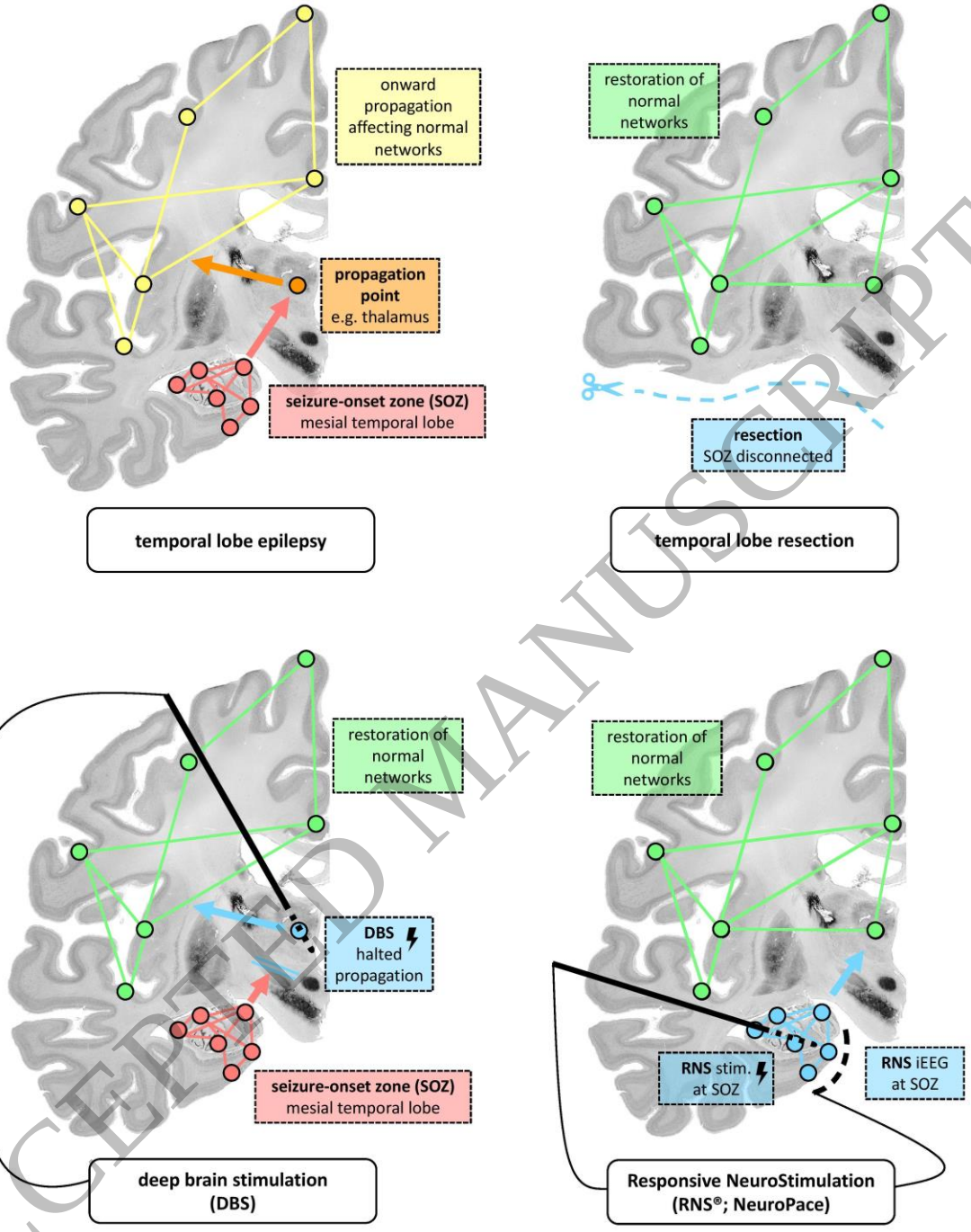

Figure 1
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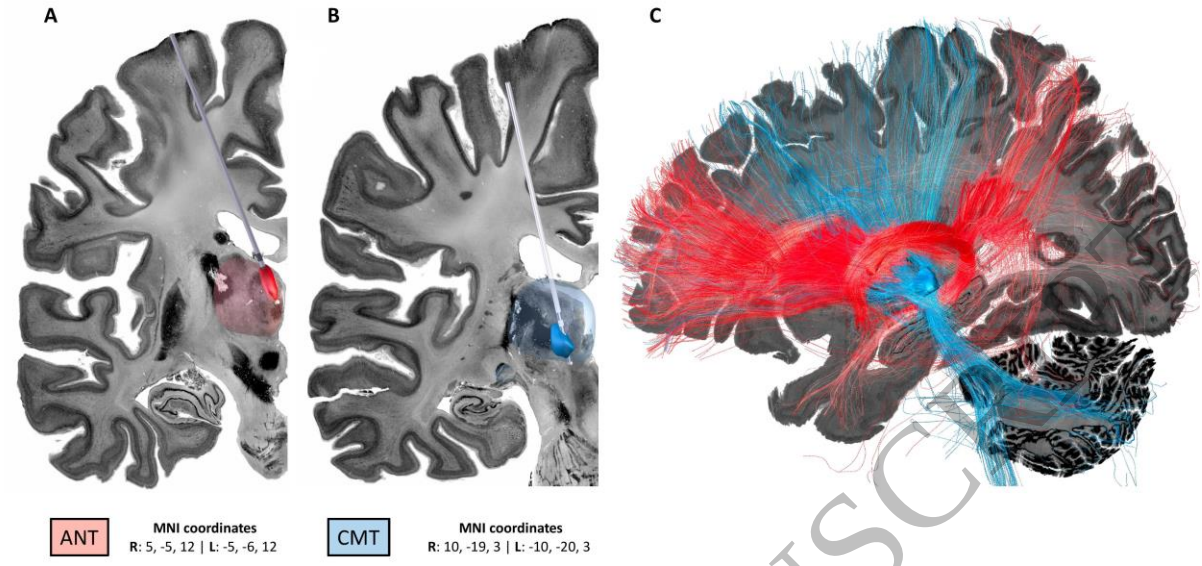

Figure 2
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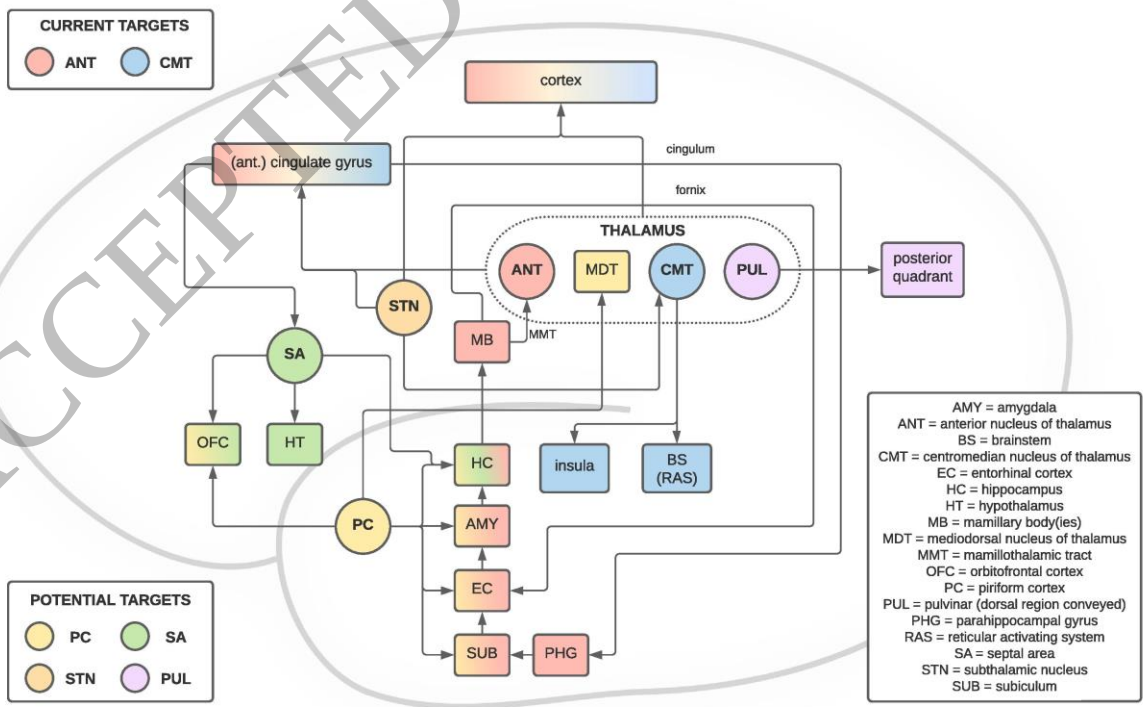

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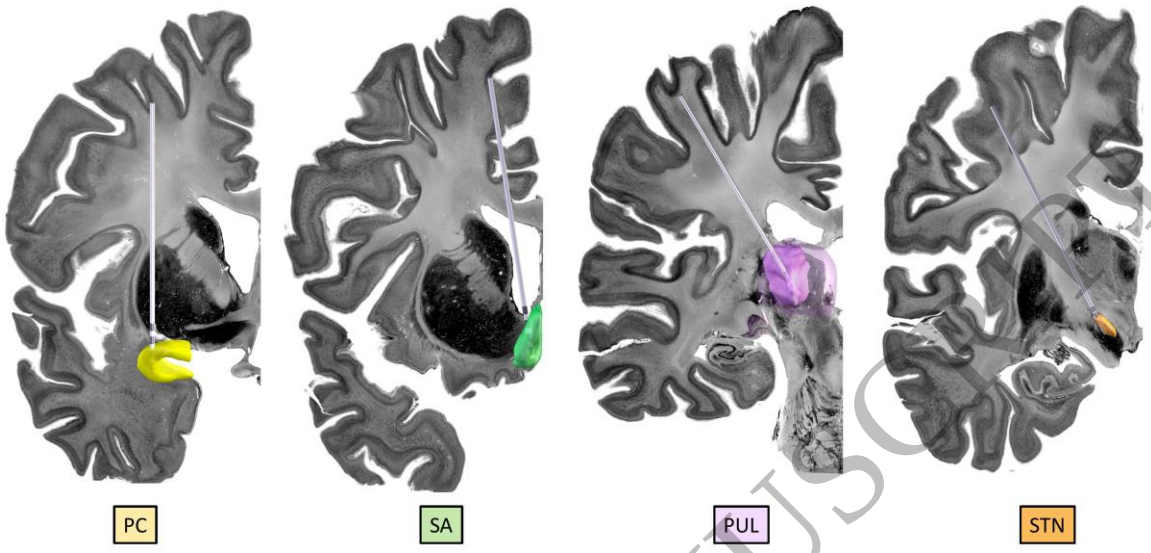

Figure 4
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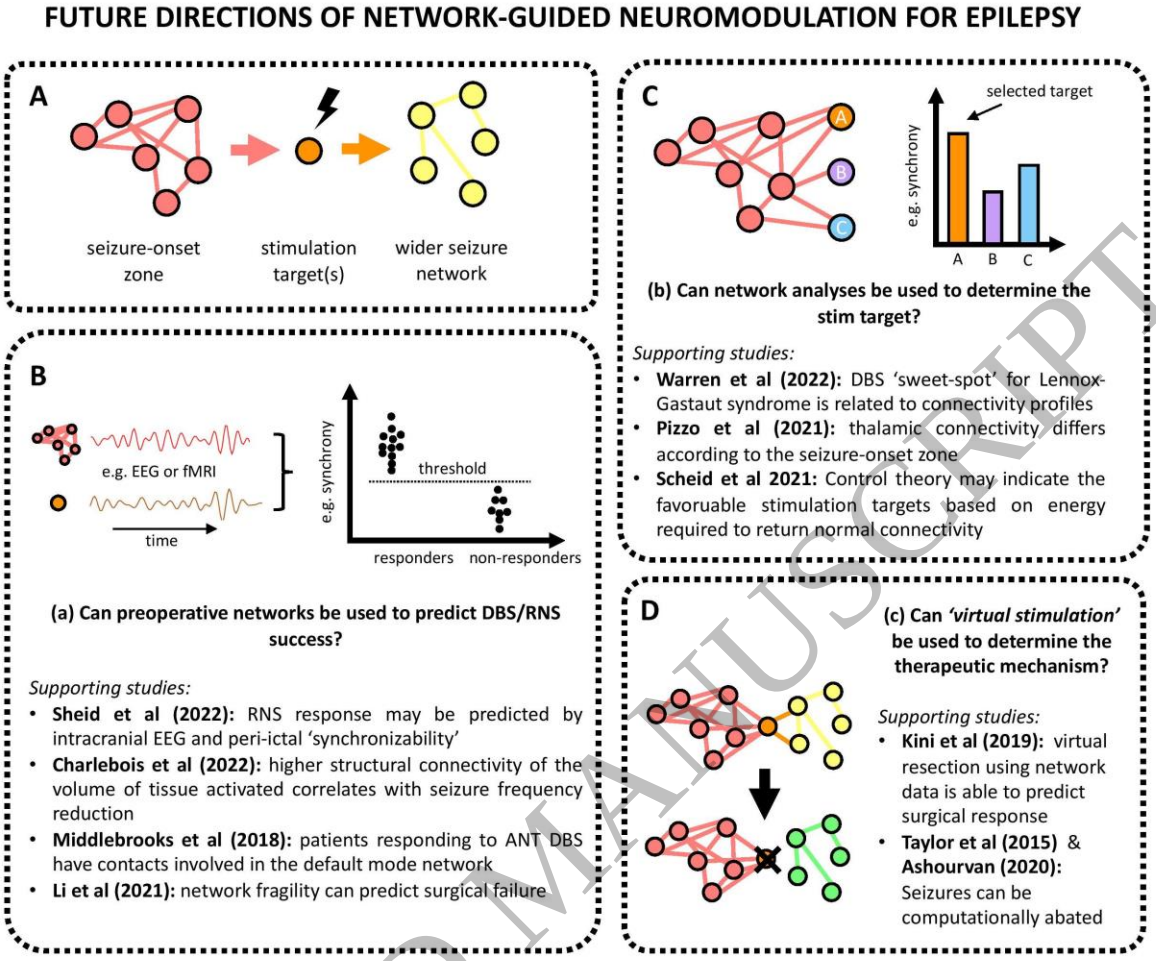

Figure 5
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