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The Temporal Lobe Club: Newer Approaches to Treat Temporal Lobe Epilepsy

Michael R. Sperling, MD[1], Chengyuan Wu, MD[2], Joon Kang, MD[3], Julia Makhalova, MD, PhD[4,5,6], Fabrice Bartolomei, MD, PhD[4,5], and Derek Southwell, MD, PhD[7,8]

[1] Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA
[2] Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, PA, USA
[3] Department of Neurology, Johns Hopkins University, Baltimore, MD, USA
[4] APHM, Timone Hospital, Epileptology and Cerebral Rhythmology, Marseille, France
[5] Aix Marseille Univ, INSERM, INS, Inst Neurosci Syst, Marseille, France
[6] APHM, Timone Hospital, CEMEREM, Marseille, France
[7] Department of Neurosurgery, Duke University, Durham, NC, USA
[8] Department of Neurobiology, Duke University, Durham, NC, USA
*Correspondence: Michael R. Sperling, Department of Neurology, Thomas Jefferson University, 901 Walnut St, Philadelphia, PA 5084, USA.
Email: michael.sperling@jefferson.edu

Abstract
This brief review summarizes presentations at the Temporal Lobe Club Special Interest Group session held in December 2022 at the American Epilepsy Society meeting. The session addressed newer methods to treat temporal epilepsy, including methods currently in clinical use and techniques under investigation. Brief summaries are provided for each of 4 lectures. Dr Chengyuan Wu discussed ablative techniques such as laser interstitial thermal ablation, radiofrequency ablation, focused ultrasound; Dr Joon Kang reviewed neuromodulation techniques including electrical stimulation and focused ultrasound; Dr Julia Makhalova discussed network effects of the aforementioned techniques; and Dr Derek Southwell reviewed inhibitory interneuron transplantation. These summaries are intended to provide a brief overview and references are provided for the reader to learn more about each topic.

Keywords
temporal lobe epilepsy, thermal ablation, neuromodulation, cell transplant, focused ultrasound, inhibitory interneuron

Introduction

Drug-resistant temporal lobe epilepsy (TLE) is often amenable to surgical therapy.[1] Anterior temporal lobectomy and more selective mesial temporal or neocortical resections often offer significant improvement or seizure freedom, yet some patients are either poor candidates for these procedures for several reasons (e.g., high risk of significant memory or language deficit, bitemporal disease) or are unwilling to have a resection. To reduce risk and morbidity, minimally invasive procedures and neurostimulation are now used to treat some patients. Newer techniques such as inhibitory neuron transplant and gene therapy are in human trials. This special interest group focused on several of these techniques, reviewing presumed mechanisms of action and network effects of various interventions. This article will briefly summarize these issues.

Ablative Techniques to Treat Temporal Lobe Epilepsy

Despite excellent long-term outcomes seen with open surgery for drug-resistant TLE, 1 patient perspectives and the stigma of "brain surgery" continue to result in underutilization of

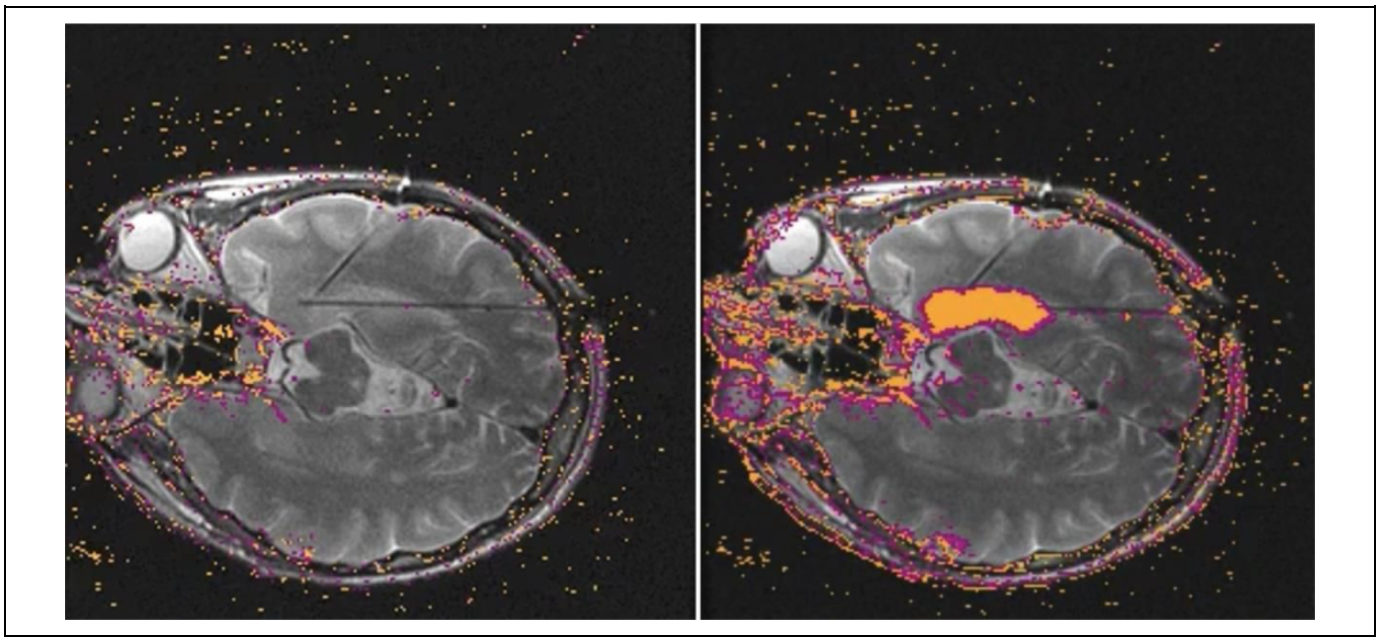

Figure 1. Neuromodulation.

epilepsy surgery.[2,3] Minimally-invasive approaches have therefore grown in popularity, as they represent a more palatable alternative to a traditional craniotomy.

Radiofrequency ablation (RF) has long been used in neurosurgery, with applications in the treatment of movement disorders, chronic pain, brain tumors, psychiatric conditions, and epilepsy. Early series of RF for TLE demonstrated modest results, with an average of 16% patients experiencing seizure freedom and an average of 52% seizure reduction.[4] Of note, these outcomes resulted from ablations focused on the amygdala and hippocampus. In a later series, the adjacent the entorhinal and perirhinal cortices were also ablated and 76% of patients remained seizure free 2 years postoperatively and 15% benefited from significant seizure reduction.[5] Interestingly, overall ablation volume was not associated with seizure outcomes,[6] which highlights that ablation location and anatomical structures involved are more important in determining outcomes from ablations.

Over the past decade, laser interstitial thermal therapy (LITT) has been used to treat TLE (see Figure 1). A major benefit of this technology is its pairing with real-time magnetic resonance thermography,[7] which allows surgeons to visualize the ablation as it is being formed and as such, understand exactly what structures being ablated. As with RF ablations, the location of LITT ablations is of utmost importance for seizure outcome.[8] In addition to ablation of the amygdala, hippocampus, entorhinal, and perirhinal cortices, inclusion of the parahippocampal gyrus and piriform cortex[9,10] have been associated with increased rates of seizure freedom. In terms of the extent of the hippocampal ablation, inclusion of the hippocampal head and body back to a coronal plane in line with the lateral mesencephalic sulcus is typically sufficient. Ablations extending more posteriorly have not be associated with improved outcomes, but have been associated with increased visual field deficits.[11] Given the curve of the amygdalohippocampal complex and the cranial-caudal span between the piriform cortex and entorhinal cortex, use of 2 separate laser trajectories helps to optimize coverage of the aforementioned mesial temporal structures.[12]

While LITT has been reported to provide seizure freedom in 50% to 60% of patients, we must remember that these outcomes represent our early experience with the technology. Now armed with a clearer understanding of structures to be ablated in TLE, we may see improved seizure control with LITT.

More recently, MRI-guided focused ultrasound (MRgFUS) has been investigated as a potential tool for drug-resistant epilepsy. MRgFUS leverages 1024 transducers that ablate intracranial tissue by focusing overlapping ultrasound waves to target structures. This technology is currently used for creating thalamic lesions in patients with refractory tremor, as it is best suited for creating smaller ablations within central structures of the brain. As such, MRgFUS is not particularly well suited for the ablation of mesial temporal lobe structures.[13] Instead, it may find applications in the ablation of other targets within the limbic circuit, such as the anterior nucleus of the thalamus. To further investigate its potential, there are ongoing clinical trials to assess feasibility, safety, and initial effectiveness of MRgFUS in treating focal epilepsy.

Network Effects/Mechanism of Action of Electrical Stimulation

Vagus nerve stimulation (VNS), deep brain stimulation of anterior nucleus of the thalamus (ANT-DBS), and responsive neurostimulation (RNS) all target portions of the limbic network. Vagus nerve stimulation may suppress seizure

generation and propagation by influencing nodes within the thalamo-cortical circuit.[9] The therapeutic effect of ANT-DBS may in part due to the direct stimulation of the anterior thalamus within the Papez circuit.[10] Most RNS targets for TLE include depth lead implanted along the longitudinal axis of the hippocampus.[11]

Acute high-frequency stimulation is thought to interfere with organization, synchronization, and maintenance of seizure activity. Chronic stimulation is thought to be associated long-term network changes, such as increased neurotrophic factor expression and neurogenesis in the mesial temporal structures,[12-15] increased GABAergic neurotransmission in the epileptic hippocampus[16] and changes within the default mode networks.[17] Recent studies utilizing electrocorticography (ECoG), and various connectivity methods support the theory that neuromodulation works by seizure network reorganization rather than by direct seizure interruption.[18-20]

Efficacy for TLE: VNS/ANT-DBS/RNS

There may be an association between location of seizure onset and efficacy for VNS and ANT-DBS. Meta-analysis of 3321 patients[21] demonstrated that patients with generalized epilepsy experienced significantly greater benefit from VNS (57.5% $\pm$ 1.9% decrease in seizures) in the last follow-up than those with partial seizures (42.5% $\pm$ 0.9%). In the SANTE trial,[10] patients with TLE had median 44% reduction in seizure frequency from baseline, whereas no significant seizure reduction was noted in patients with extratemporal epilepsy.

With RNS, seizure reduction rates in TLE did not seem to depend on location of depth lead.[11] Median seizure reduction in 111 subjects with mesial TLE was 70% at 6 years of follow-up with 50% responder rate of 65%. A third of patients and 15% of patients reported seizure freedom lasting $>$6 months and $>$1 year, respectively.

Focused Ultrasound

Focused ultrasound (FUS) is a novel investigational modality that uses one or more ultrasound beams at either low intensity (LIFU) or high intensity (HIFU) to modulate or ablate neural tissue. Compared with other noninvasive techniques, this method, combined with MRI guidance, allows targeting of deep brain structures with high spatial precision. A recent pilot study of 6 patients who completed FUS treatment resulted in a transient decrease in seizure frequency in 2 patients and changes in spectral EEG power with no permanent deficits.[22]

Network Changes With Focal Ablation and Neurostimulation

Temporal lobe epilepsy is a heterogeneous entity with variable functional organization demonstrated based on SEEG recordings. Pathophysiologically, TLE is a network disease characterized by alterations within specific cortico-subcortical networks. The concept of epileptogenic networks[23,24] is the framework for understanding diagnostic and therapeutic challenges in TLE. The epileptogenic zone network (EZN) is conceptualized as a network of hyperexcitable connected brain regions capable of generating seizures that secondarily involve the propagation network (PZN).[25] A lesion that is suspected to cause epilepsy may actually be just a node of the EZN.

At least 4 TLE subtypes can be distinguished based on the hierarchy of the epileptogenicity of different structures established by signal quantification: the mesial, lateral, mesial-lateral, and temporal plus subtypes.[26,27] Patient-specific EZN organization and, when possible, the degree of thalamic involvement[28,29] should be considered when choosing a therapeutic approach that should target the network by destroying or disconnecting some nodes (thermocoagulation, focal ablation) or by modifying nodes connectivity (neuromodulation).

Several connectome-based studies addressed the effects of ablative techniques on epileptic networks in TLE concerning seizure outcome. They demonstrated that temporal lobe surgery had a modest impact on global network efficiency.[30] The likelihood of postsurgical seizure freedom decreases with an increased number of abnormally integrated hubs in the medial and lateral temporal regions.[31] However, a greater reduction of structural connectivity between key EZN and PZN network nodes was associated with seizure freedom.[32]

When the patient is not a surgical candidate, palliative strategies such as thermocoagulation or neurostimulation are available. Thermocoagulation destroys the epileptogenic nodes and can be the method of choice in some etiologies, such as periventricular nodular heterotopia or hypothalamic hamartoma.[33-35] Importantly, it has been demonstrated that there is a reduction of functional connectivity in responders to thermocoagulation.[36] Furthermore, there is by now robust evidence that decrease in functional connectivity correlates with therapeutic response to different modes of neuromodulation (VNS, DBS, transcranial direct current stimulation (tDCS)).[37-39]

Finally, there is a great need for less invasive, personalized interventions targeting the EZN. Recently, in-silico surgery has been proposed to predict the outcome of different surgical scenarios using modeling[40,41] or virtual brain technology.[42,43] It has been shown that virtual resection of the most epileptogenic nodes[42] or of the highly connected nodes, distant from the EZN[43] may be sufficient for effective results. Future development of approaches, such as virtual epileptic patient digital twin[44] will allow simulation of different intervention hypotheses and choosing the surgical option with the highest probability of achieving seizure freedom and minimal resection volume.

Interneuron Transplantation as a Novel Treatment

The pathophysiology of epilepsy involves molecular and cellular processes that promote the hyper-excitability of neural circuits and networks. Numerous preclinical animal studies have demonstrated that the transplantation of cortical

interneurons is a promising approach to altering neural inhibition and correcting seizure phenotypes in the epileptic brain.[45] This section will discuss basic features of cortical interneuron development and function, summarizing early animal data describing the circuit integration and seizure-modifying effects of transplanted interneurons, and reviewing a recently initiated first-in-human trial of interneuron transplantation.

Neocortical and hippocampal interneurons comprise a highly diverse population of cells that provide GABAergic inhibition onto excitatory neurons and other interneurons through dense and primarily local projections.[46] Cortical interneurons are produced mostly during gestation in progenitor regions remote from the developing cortex, including the medial and caudal ganglionic eminences (MGE and CGE, respectively) of the ventral forebrain. From these origins, immature interneurons migrate into the developing neocortex and hippocampus, where they integrate into cortical circuits with locally produced excitatory populations.

Over 20 years ago it was found that, when transplanted from the embryonic ventral forebrain into postnatal mice, rodent MGE interneurons can migrate, survive, and produce GABA in the recipient brain.[47] Subsequent rodent studies have demonstrated that, in both wild type and epileptic recipients, transplanted embryonic MGE- and CGE-derived interneurons also develop distinct histochemical, morphological, and physiological features characteristic of mature interneurons. Transplanted interneurons become physiologically integrated into recipient neural circuits, receiving synaptic inputs and forming inhibitory outputs with host neurons.

Functionally, interneuron transplantation has been found to increase recipient synaptic inhibition, modify network oscillatory patterns, and induce cortical plasticity in the rodent brain.

Given some of these functional impacts, interneuron transplantation has been advanced as a prospective approach to correcting or compensating for some of the circuit and network derangements that underlie epilepsy. Since the initial publication in 2009,[48] a number of preclinical studies have shown that interneuron transplantation can improve seizure phenotypes and correct epilepsy-associated behavioral abnormalities in rodents. The majority of this work has been conducted in models of chronic TLE secondary to chemo-convulsant-induced injury (e.g., pilocarpine or kainate administration), though some studies have also been conducted in genetic models of generalized epilepsy as well as focal, acute chemo-convulsant and electrical kindling models. In anticipation of potential human applications, there has also been significant research efforts dedicated to developing and evaluating donor cell populations that may be best suited for use in human epilepsy patients. This has included studies of primary interneuron cell types harvested from porcine embryos,[49] as well as MGE-like populations derived from human pluripotent stem cell (hPSC) lines and human-induced pluripotent stem cells (hiPSCs).[50]

The United States Food and Drug Administration recently approved a first-in-human Phase 1/2 clinical trial of interneuron transplantation for epilepsy (ClinicalTrials.gov Identifier: NCT05135091). The multisite trial will investigate the safety and efficacy of NRTX-1001, a human allogenic hPSC-derived interneuron cell product developed by Neurona Therapeutics. The trial, which as of the time of this publication has enrolled 5 patients, is studying hippocampal transplantation of NRTX-1001 in adults with unilateral focal onset epilepsy originating from the mesial temporal lobe. Study investigators are collecting patient safety and efficacy data through physical examinations, blood draws, structural imaging, magnetic resonance spectroscopy, EEG, neuropsychometric testing, seizure diaries, and quality-of-life surveys. Data safety monitoring board review has, to date, supported ongoing investigation of NRTX-1001 following transplantation in 2 sentinel subjects.

In reviewing laboratory and human clinical investigations of interneuron transplantation, it is possible that future research may examine how transplantation could be utilized outside of well-localized forms of epilepsy such as mesial TLE. Future clinical applications may benefit from further elucidation of ideal cell donor sources and interneuron cell types, as well as investigation of how patient-specific factors, such as disease chronicity, seizure burden, seizure cycles, drug regimens, and prior surgical history, may influence the functional engraftment and seizure modifying effects of transplants.

Conclusion

Many of the greatest advances in medicine have been accomplished through the introduction of new technology. The techniques described above differ conceptually from traditional methods to treat epilepsy. Some are evolutionary in nature, such as thermal ablation. Others, such as inhibitory interneuron transplantation represent radically different approaches to therapy. These newer techniques have already afforded benefit to many patients and it is hoped that further advances currently in testing or being designed will enable the field to move beyond more invasive treatments and better tailor therapy to the individual.

Declaration of Conflicting Interests

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