Innovations in epilepsy surgery

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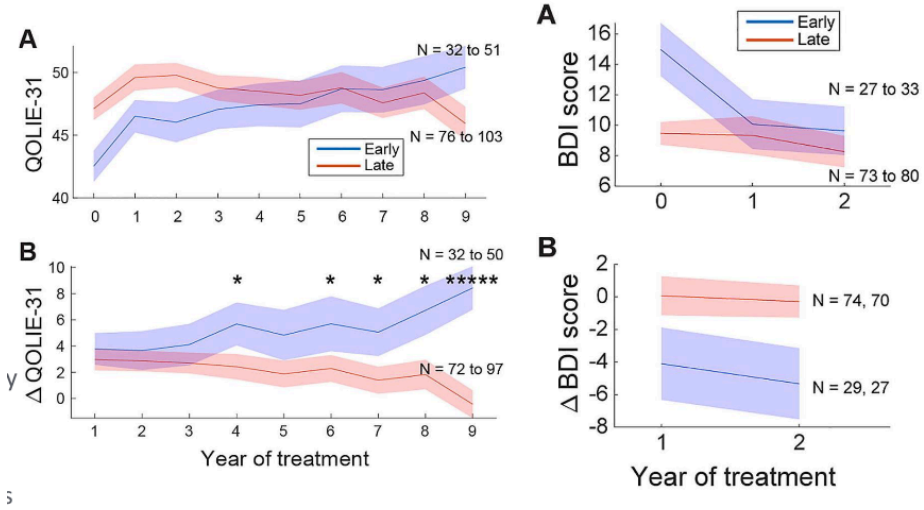
Disclosures

- I have served as a consultant for Medtronic within the past year
- Will discuss investigational/off-label use of devices

Epilepsy patients remain surgically underserved

- Candidacy for surgery
  - Persistent focal* seizures despite 2 or more appropriate AEDs at therapeutic dosages
- More than 1 million patients in the US meet this definition
- Only about 1% of these receive surgery within 2 years of diagnosis of DRE
  - 1.7% absolute mortality increase annually
  - 6 years in pediatric patients
  - 20 years in adult patients
- Quality of life scores improve when patients are treated earlier in their disease course (<10 years)



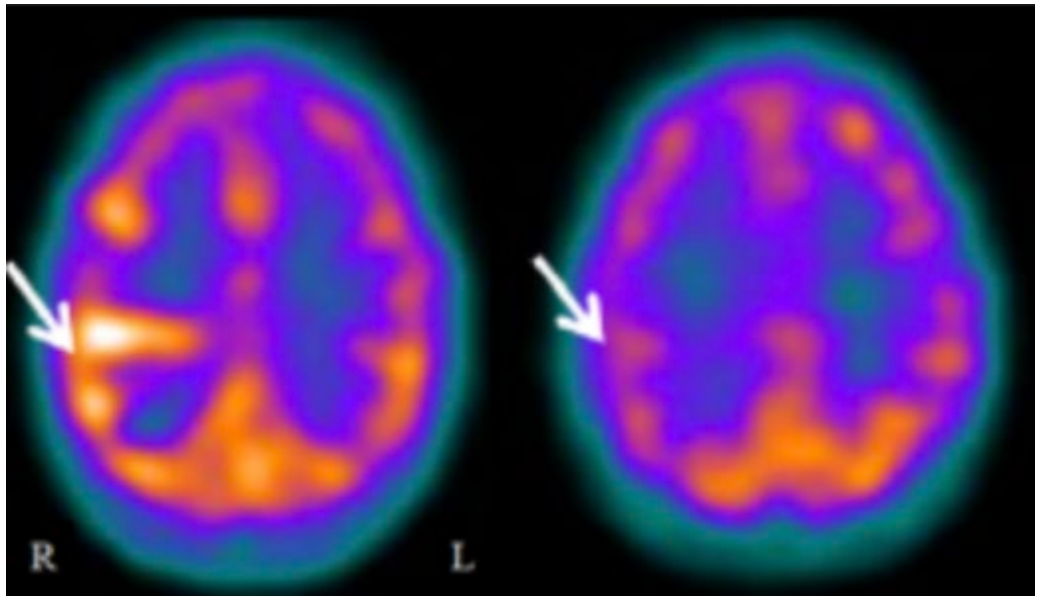
Loring 2021, Wissel 2024

Surgical considerations and planning

- Lesional or non-lesional?
- If lesional, does EEG and semiology correlate?
- If non-lesional (or lesional without definitive concordance), must perform localization surgery
- Once seizure-onset zone is identified, we can:
  - Surgically excise (craniotomy)
  - LASER ablate
  - Offer neuromodulation
- If no seizure-onset zone can be identified, neuromodulation may be considered

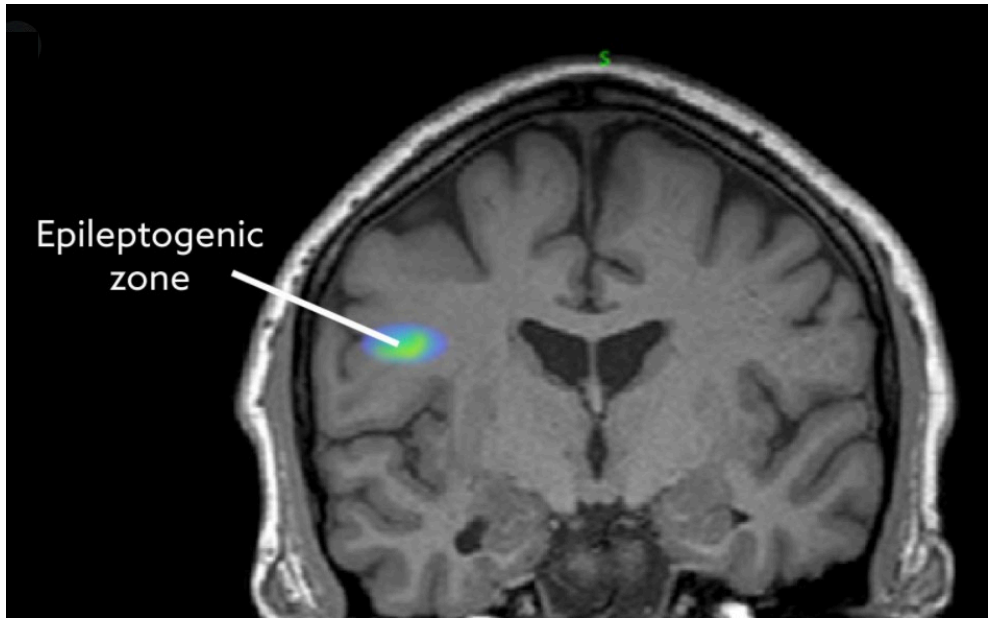
Preoperative workup

- Phase I scalp EEG/EMU
- MRI brain, epilepsy protocol
- Neuropsychological evaluation
- Single-photo emission computerized tomography (SPECT)/positron emission tomography (PET)
- Magnetoencephalography (MEG)
- Functional MRI
- Wada testing**



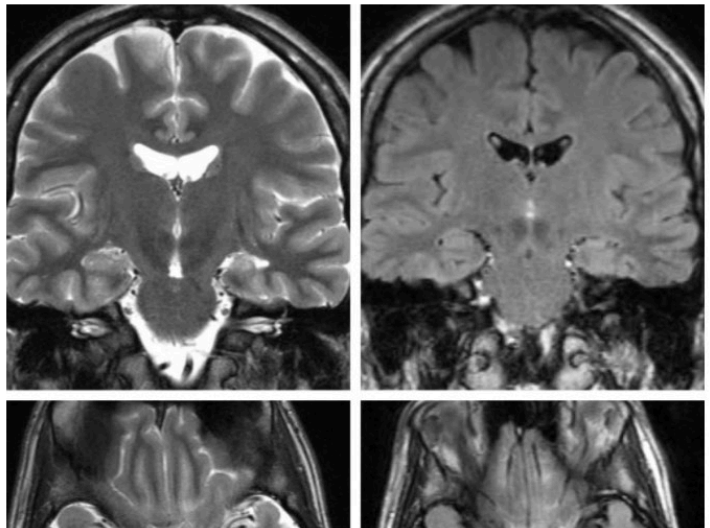
Localization

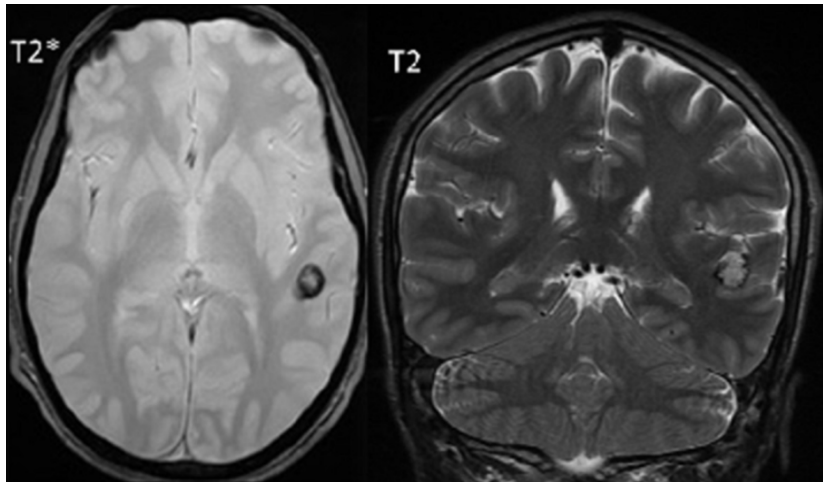
- Epileptogenic zone
- *The goal of any seizure surgery is to destroy only the epileptogenic zone and no additional tissue*
- Tissue may be destroyed through ablation or resection, or reversibly disrupted via neuromodulation

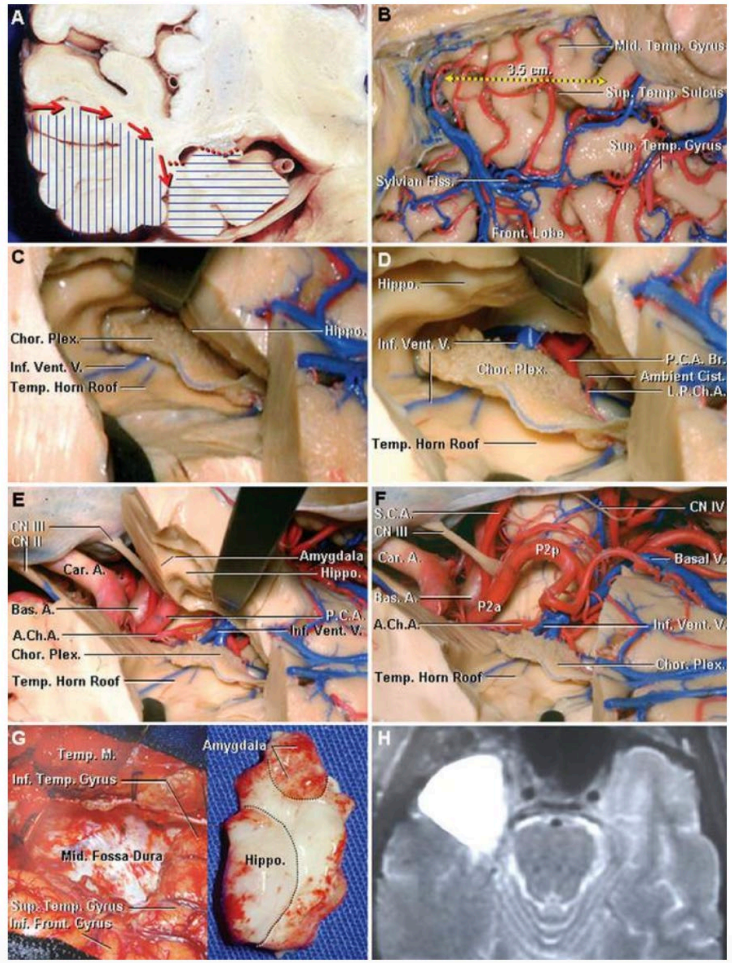


Traditional epilepsy surgery

- Historically reliant on being able to localize a lesion
  - Unilateral mesial temporal sclerosis
  - Other lesion, such as cavernoma
- Resect lesion or perform multiple subpial transections if lesion in eloquent cortex



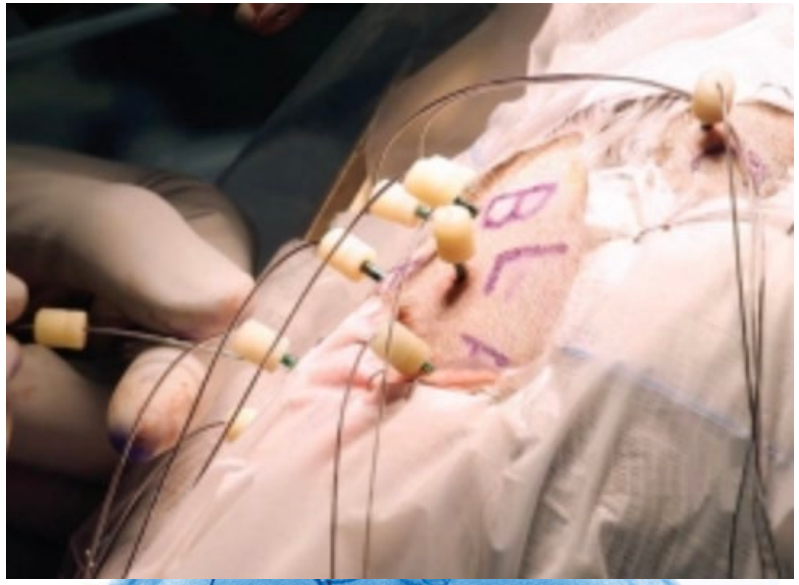


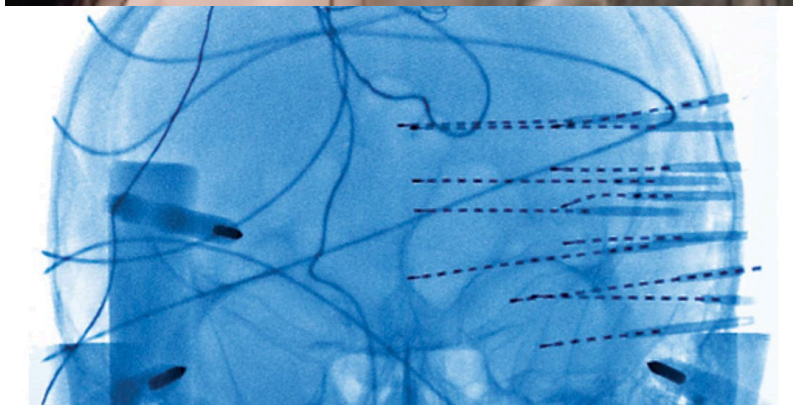


Rhoton

Localization surgery: sEEG

- Multiple depth electrodes used to create 3D map of seizure-onset zone in brain
- In lieu of traditional subdural grids
- Fewer complications than grids
- More difficult to interpret
- Better spatial resolution
- Each bolt is 2.1 mm diameter

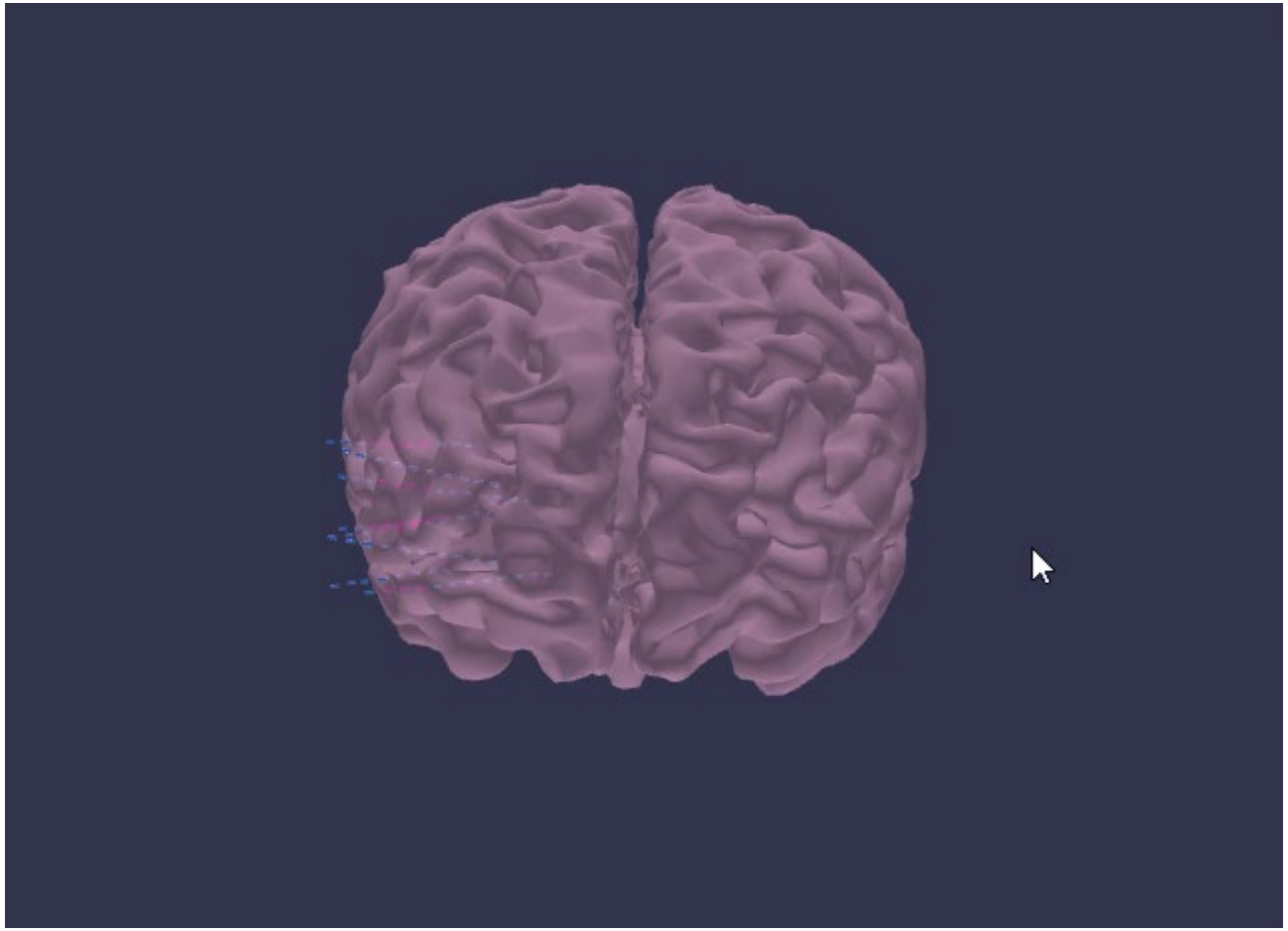




Stereotactic robot

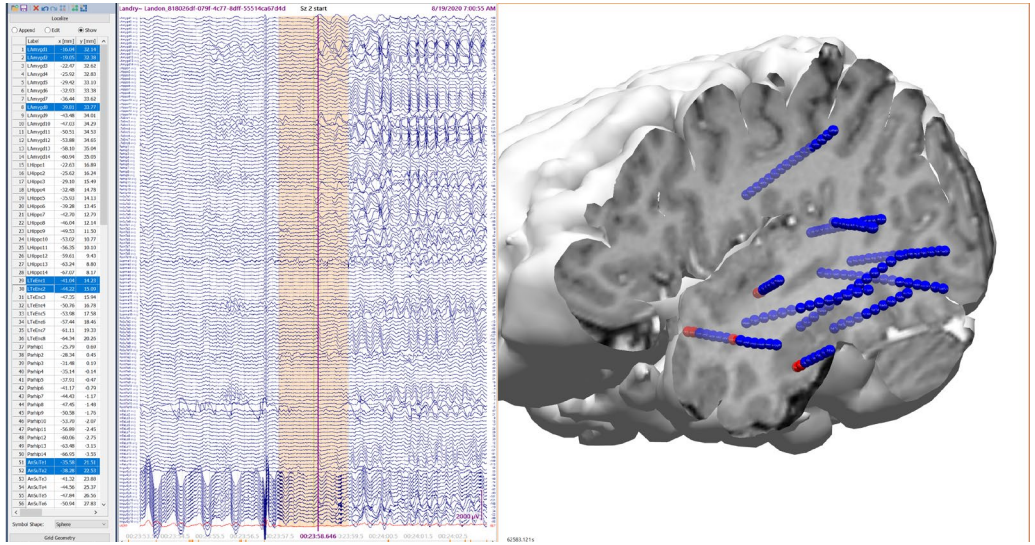
- The robot acts as a trajectory guide to help minimize operative time
- Stereotactically precise way to insert the electrodes and reach target
- Does *not* function in lieu of surgeon

sEEG leads



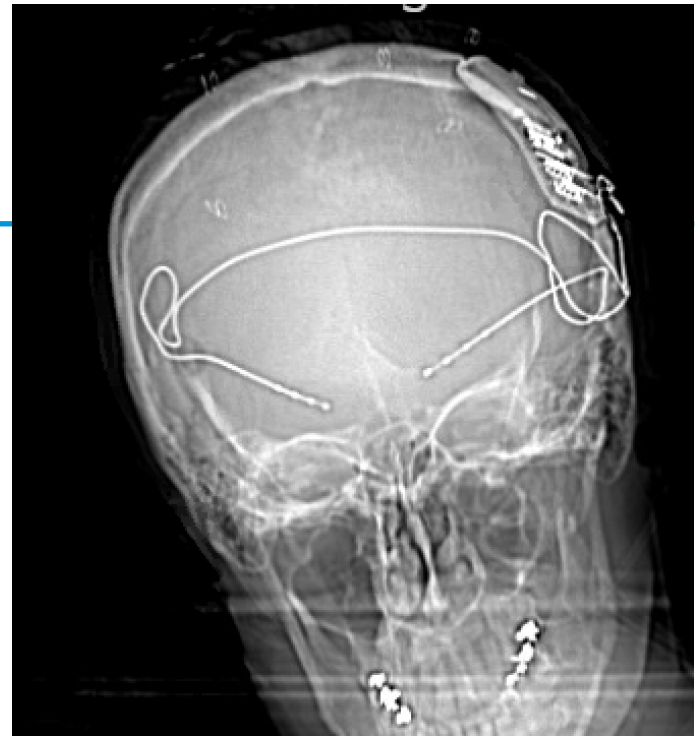
Localization hospitalization

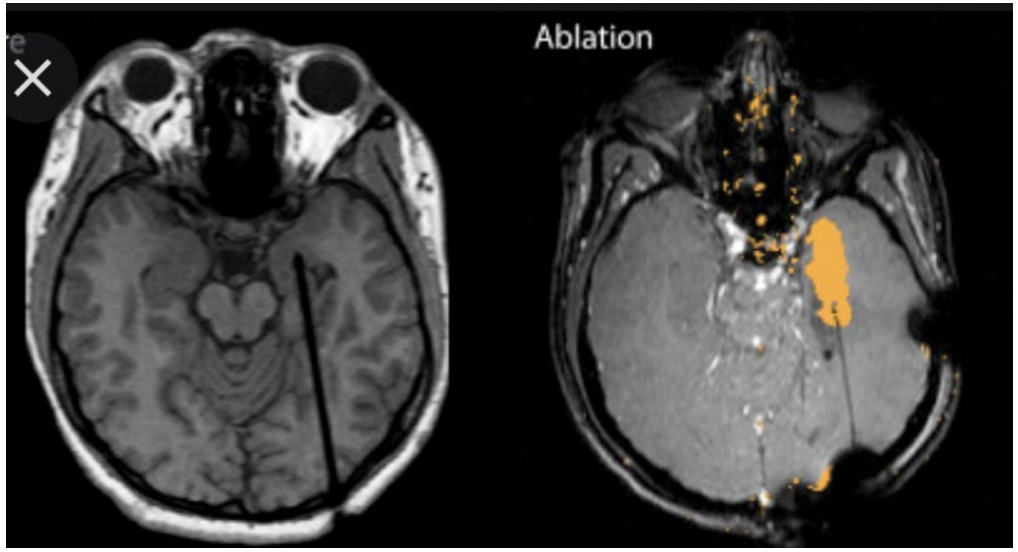
- Patient is monitored in neuro ICU for 1-2 weeks with sEEG electrodes in place
- Returned to OR for removal once sufficient electrographic data accrued
- Patient brought back for sEEG data review with epileptologist and neurosurgeon approximately 2 weeks postop
- Definitive surgical options discussed



Definitive surgical therapy

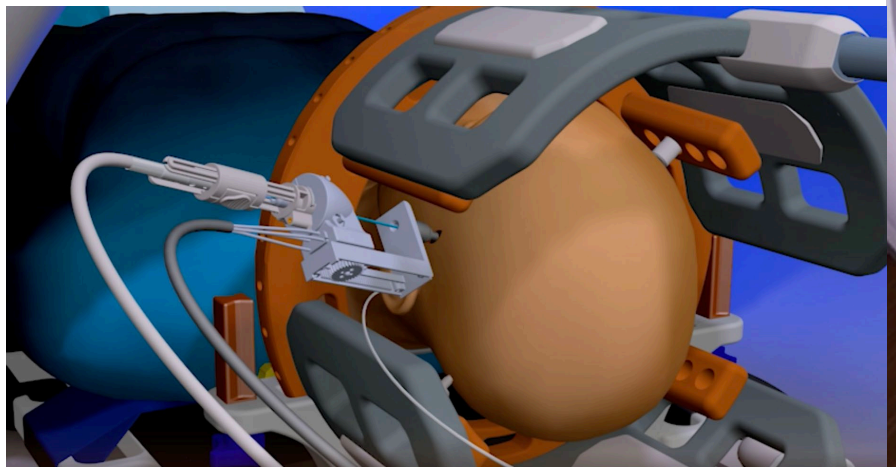
- Once seizure onset is localized, the region may be:
  - Cut out (traditional method)
  - Burned (ablated) with a LASER
  - Temporarily interrupted with electrical stimulation (neuromodulation**)





LASER ablation

- LASER catheter is inserted stereotactically in the brain, then used to ablate a region under direct MRI visualization
- May also be used for lesionectomy, tumor, etc.



LASER amygdalohippocampotomy

Received: 21 February 2019 | Revised: 23 April 2019 | Accepted: 23 April 2019

DOI: 10.1111/epi.15565

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Effects of surgical targeting in laser interstitial thermal therapy for mesial temporal lobe epilepsy: A multicenter study of 234 patients

Chengyuan Wu[1] | Walter J. Jermakowicz[2] | Srijata Chakravorti[3] | Iahn Cajigas[2] | Ashwini D. Sharan[1] | Jonathan R. Jagid[2] | Caio M. Matias[1] | Michael R. Sperling[4] | Robert Buckley[5] | Andrew Ko[5] | Jeffrey G. Ojemann[5] | John W. Miller[6] | Brett Youngerman[7] | Sameer A. Sheth[8] | Guy M. McKhann[7] | Adrian W. Laxton[9] | Daniel E. Couture[9] | Gautam S. Popli[10] | Alexander Smith[11] | Ashesh D. Mehta[11] | Allen L. Ho[12] | Casey H. Halpern[12] | Dario J. Englot[13] | Joseph S. Neimat[14] | Peter E. Konrad[13] | Elliot Neal[15] | Fernando L. Vale[15] | Kathryn L. Holloway[16] | Ellen L. Air[17] | Jason Schwalb[17] | Benoit M. Dawant[3,13] | Pierre-Francois D'Haese[3,13]

LASER amygdalohippocampotomy

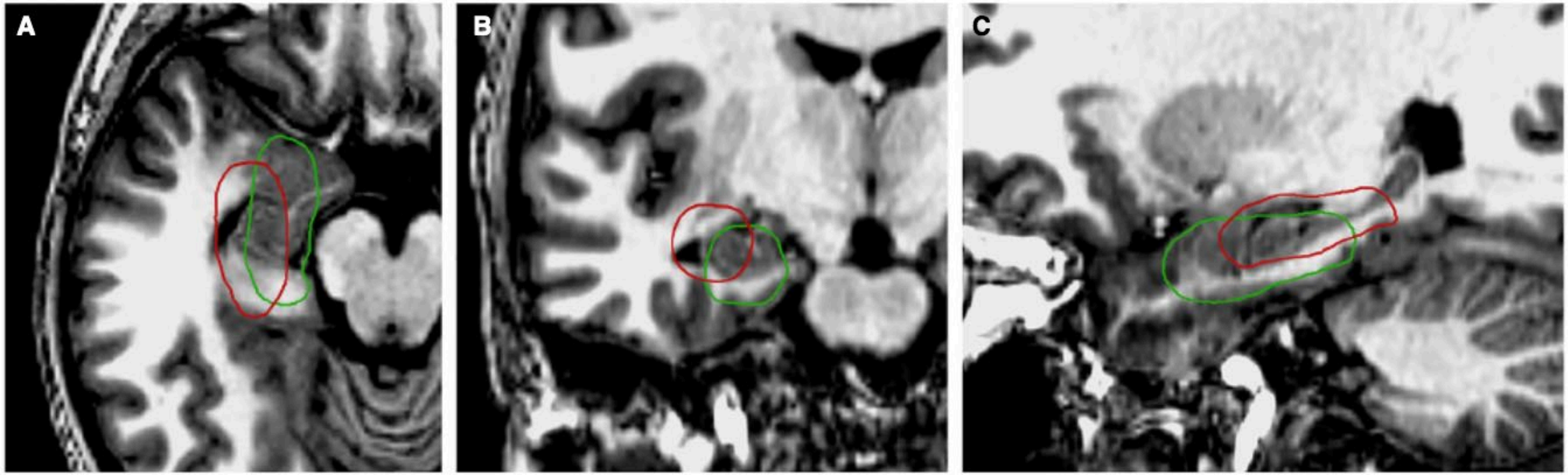


FIGURE 6 Theoretical favorable (green) and unfavorable (red) ablation locations based on the PPV and NPV maps. Both ablations are of roughly the same volume, but are located and oriented differently within the mesial temporal structures. The theoretical favorable ablation is located more anteriorly, medially, and inferiorly to cover the high probability voxels for both the PPV and NPV maps. This ablation covers the amygdala, hippocampus, parahippocampal gyrus, and rhinal cortices. The theoretical suboptimal ablation is located more posteriorly, laterally, and superiorly to exclude the high probability voxels for both the PPV and NPV maps. This ablation covers the posterolateral amygdala and hippocampus, but misses a large part of the amygdala, the mesial hippocampal head, parahippocampal gyrus, and rhinal cortices

LASER amygdalohippocampotomy

- Seizure-freedom rates are about 3-10% points lower than traditional anterior temporal lobectomy
- Improving now that we understand which structures must be included for optimal outcomes (piriform cortex)
- Ongoing studies:
  - Neuropsychological outcomes (82% naming deficit with ATL versus none in laser)
  - Visual fields
  - Complication rates

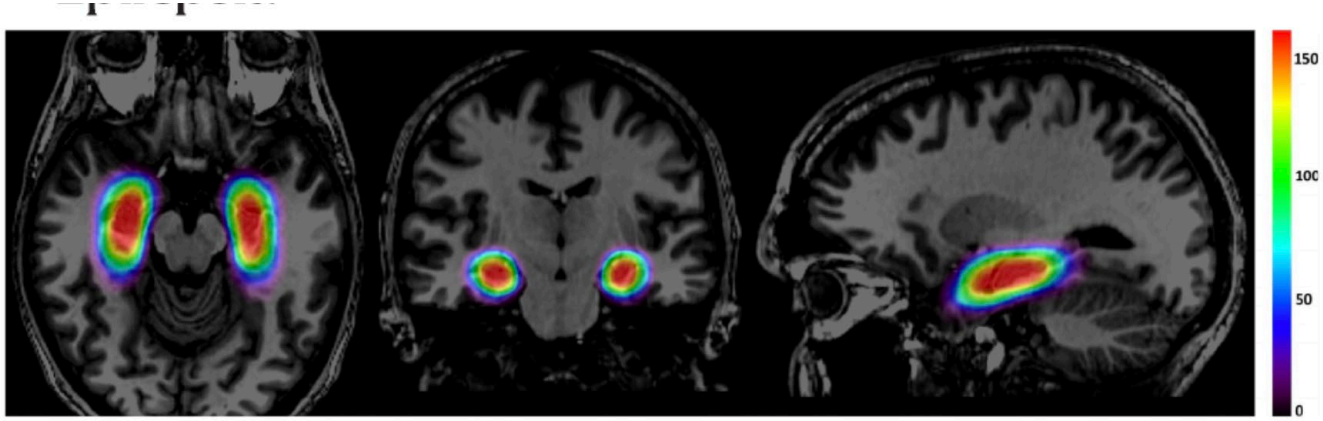


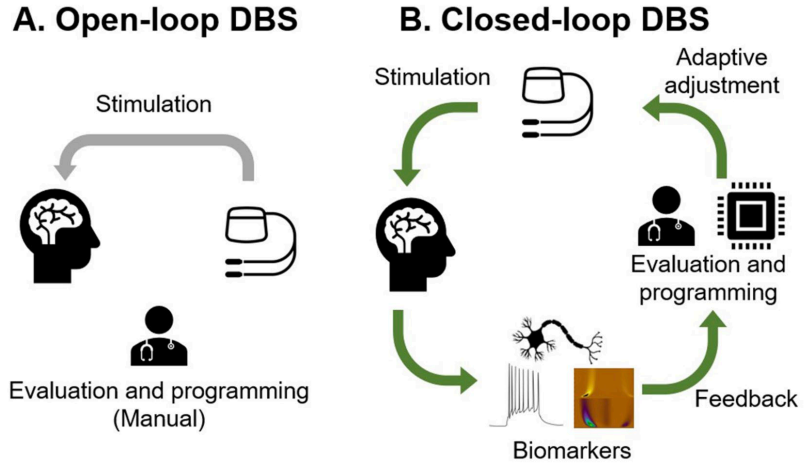
FIGURE 4 Heat map of the distribution of ablations in 175 patients treated across 11 comprehensive epilepsy centers. Effectively all ablations (red) were centered around the long axis of the AHC and extended posteriorly to the level of the lateral mesencephalic sulcus. Variation in ablation location is represented by the less frequently ablated regions (green and blue) extending from this central core

What is neurostimulation?

- Application of electrical current to neural circuit

"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"

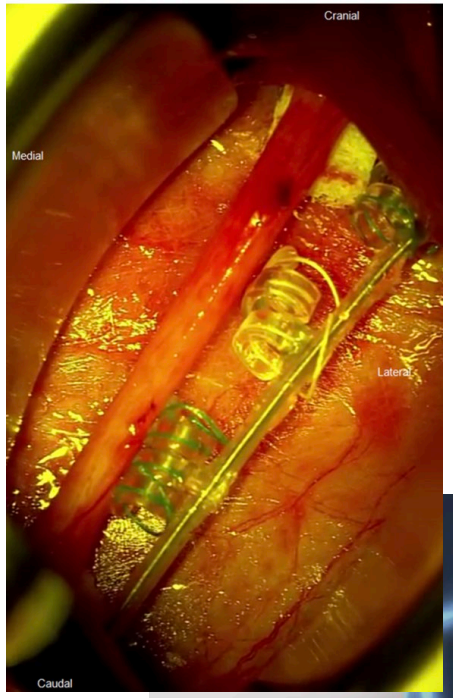
- Open loop
  - Tonic stimulation set regardless of whether patient is seizing
- Closed loop (dynamic)
  - Stimulation is offered in response to a biomarker rather than at a set interval
- Neuromodulation in epilepsy may be applied:
  - Cranial nerve
    - Vagal Nerve Stimulation (VNS)
  - Brain
    - Responsive Neurostimulation (RNS)
    - Deep Brain Stimulation (DBS)

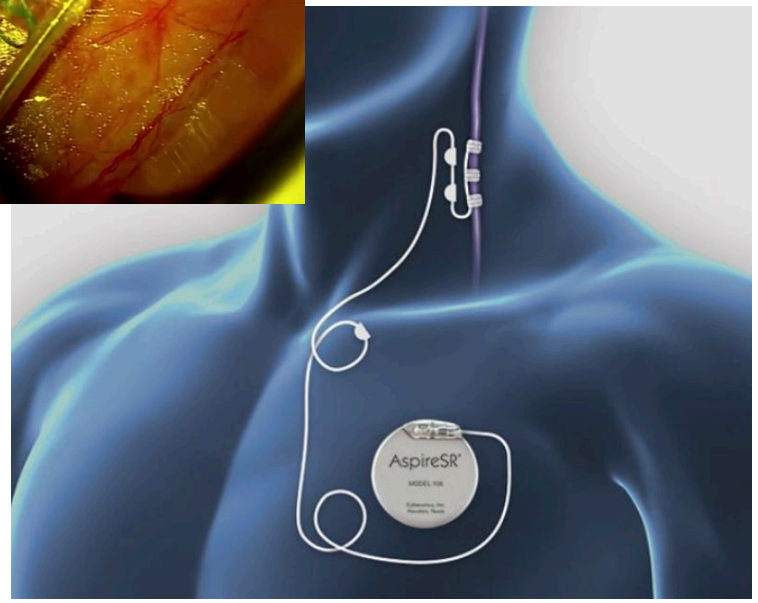


Price 2020

Vagal nerve stimulator

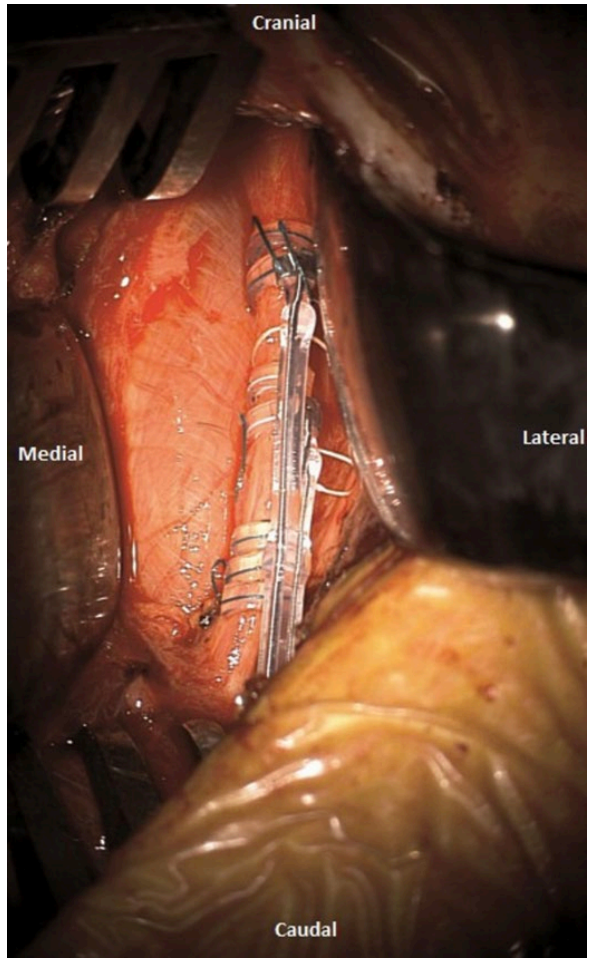
- Lead that wraps around the vagus nerve and connects directly to a generator placed in the chest
- ~50% of patients experience a 50% improvement in seizure frequency and severity at 2 years
- Better outcomes with more years of stimulation
- FDA-approved for partial epilepsy (non-unilesional) since 1997
- Left side preferred so as not to cause effect on the sinoatrial node





VNS

- Improvement in SUDEP
- Improvement in mood
- Improved cognition, memory, and quality of life
- Reduced daytime sleepiness
- Improved verbal communication and school performance
- Thought to be due to locus coeruleus and noradrenergic effects via the nucleus tractus solitarius (norepinephrine, likely serotonin)
- Also FDA-approved for depression (but not CMS: RECOVER coverage with evidence study)



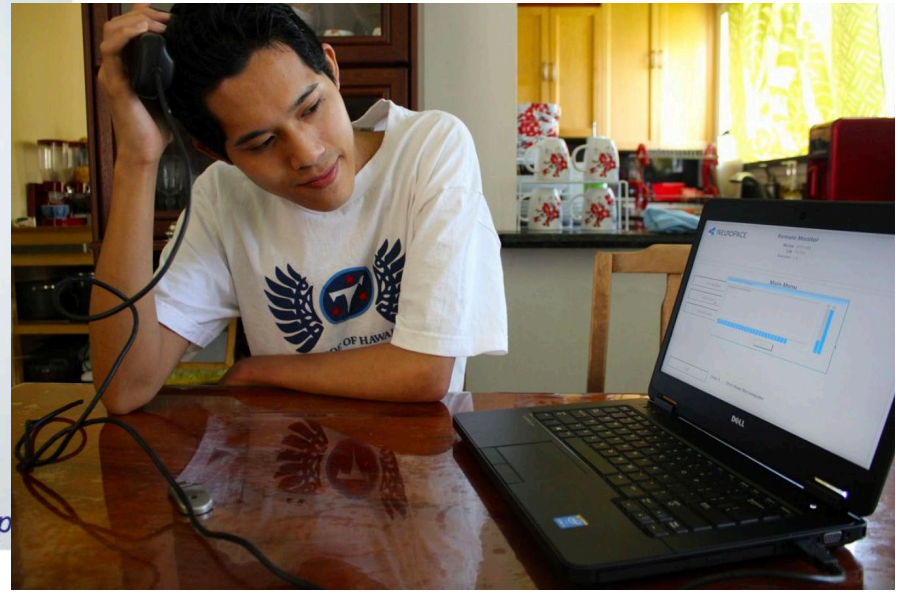
Giordano 2017

Responsive neurostimulation

- Recording and directed stimulation at or between two electrodes (strips or depths with 4 contacts each)
- FDA-approved in 2014 for patients >18 with partial-onset seizures with no more than two epileptogenic foci
- Frequent and disabling seizures despite 2+ AEDs
- Skull-mounted IPG lasts ~10 years

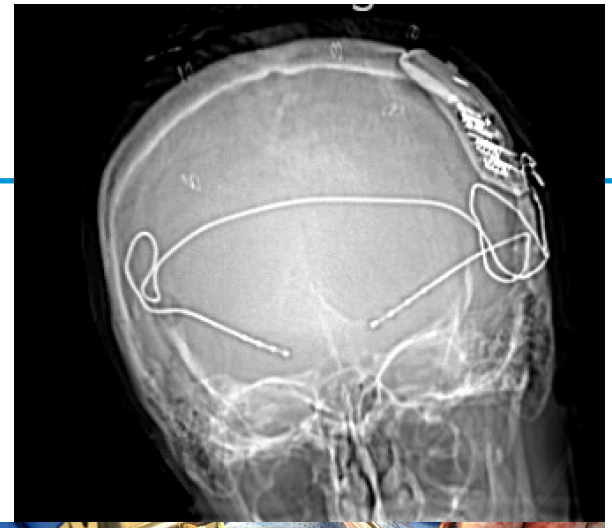
RNS

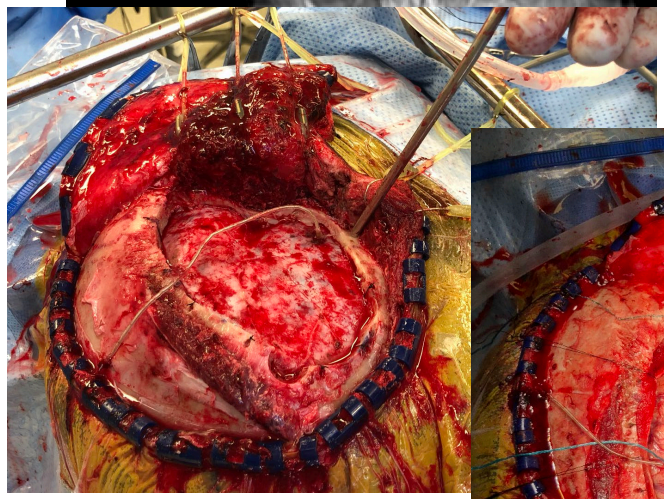
- "Closed loop" system
- Frequent patient download of data to patient remote monitor

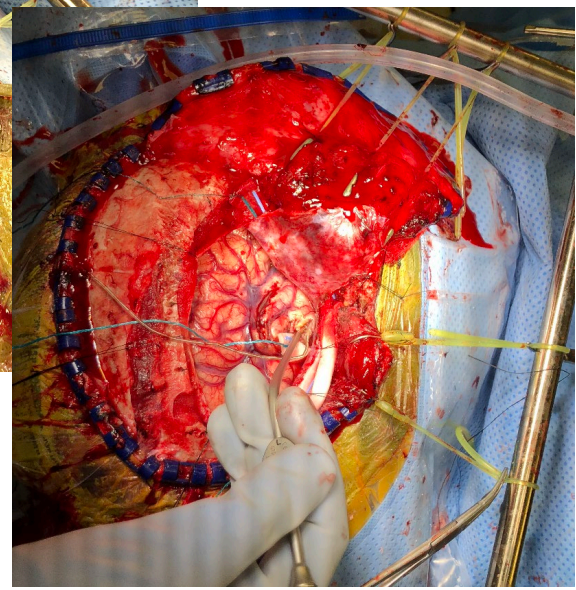


RNS

- Can be used for long-term monitoring and modulation
  - Bilateral mesial temporal sclerosis
  - Sometimes leads to resection/ablation of one side
- Eloquent cortex
- Adjuvant to resection or ablation
  - Multifocal epilepsy
- About 60% improvement in recent UCSF study (57 patients)

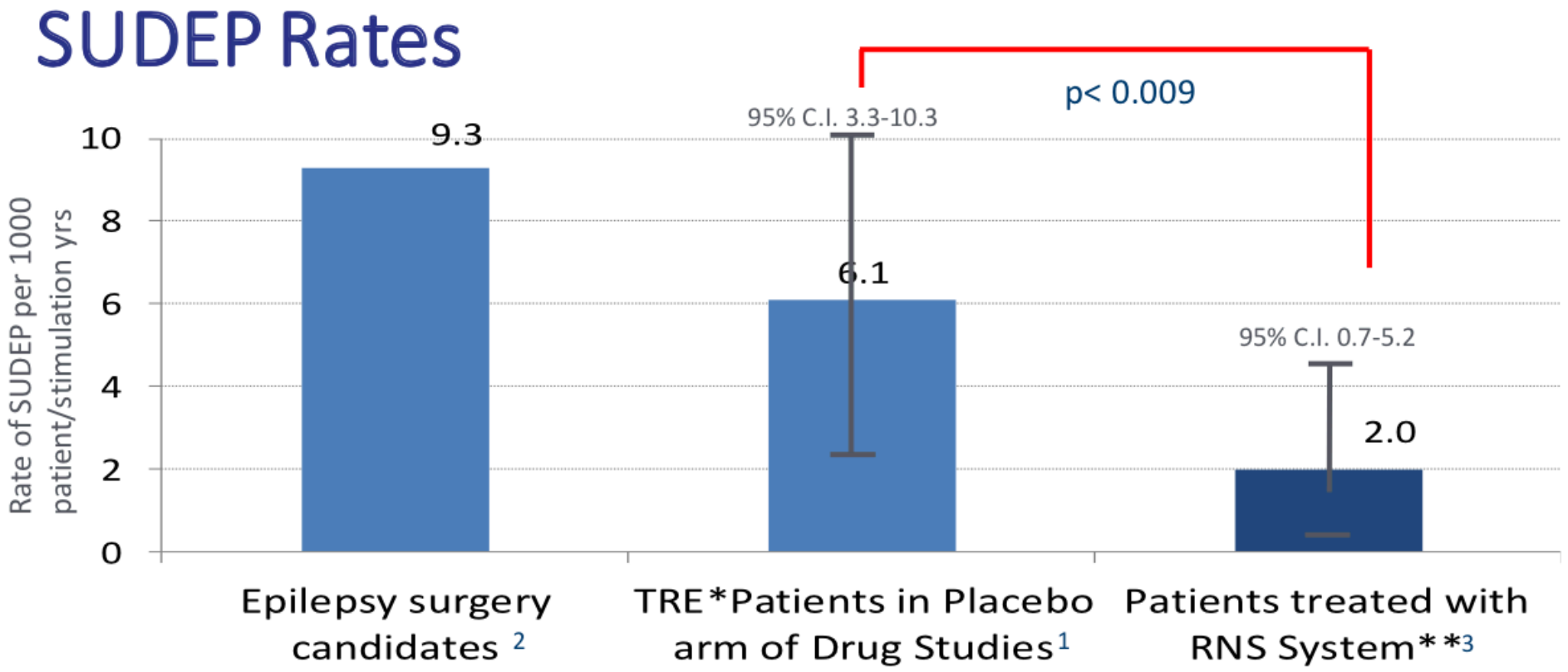






Krucoff 2020

SUDEP rates reduced in RNS



*TRE = Treatment Resistant Epilepsy

**RNS System data represents SUDEP rate per 1000 stimulation years.

[1] Ryvlin P, Cucherat M, Rheims S; Lancet Neurol. 2011; 10:961–8.

[2] Dasheiff, R.M., 1991. J Clin Neurophysiol 8, 216–222.

[3] Devinsky O, Friedman D, et al. Epilepsia. 2018; 1-7.

Long-term outcomes

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy

Dileep R. Nair, MD, Kenneth D. Laxer, MD, Peter B. Weber, MD, Anthony M. Murro, MD, Yong D. Park, MD, Gregory L. Barkley, MD, Brien J. Smith, MD, Ryder P. Gwinn, MD, Michael J. Doherty, MD, Katherine H. Noe, MD, PhD, Richard S. Zimmerman, MD, Gregory K. Bergey, MD, William S. Anderson, MD, PhD, Christianne Heck, MD, Charles Y. Liu, MD, PhD, Ricky W. Lee, MD, Toni Sadler, PA-C, Robert B. Duckrow, MD, Lawrence J. Hirsch, MD, Robert E. Wharen, Jr., MD, William Tatum, DO, Shraddha Srinivasan, MD,

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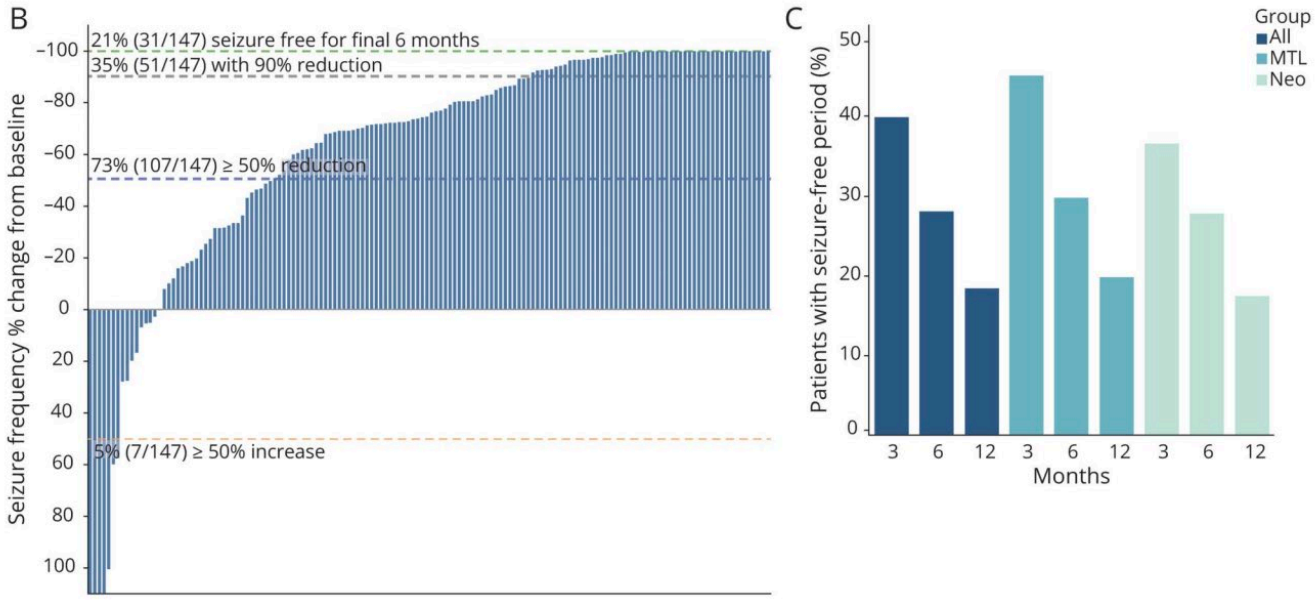

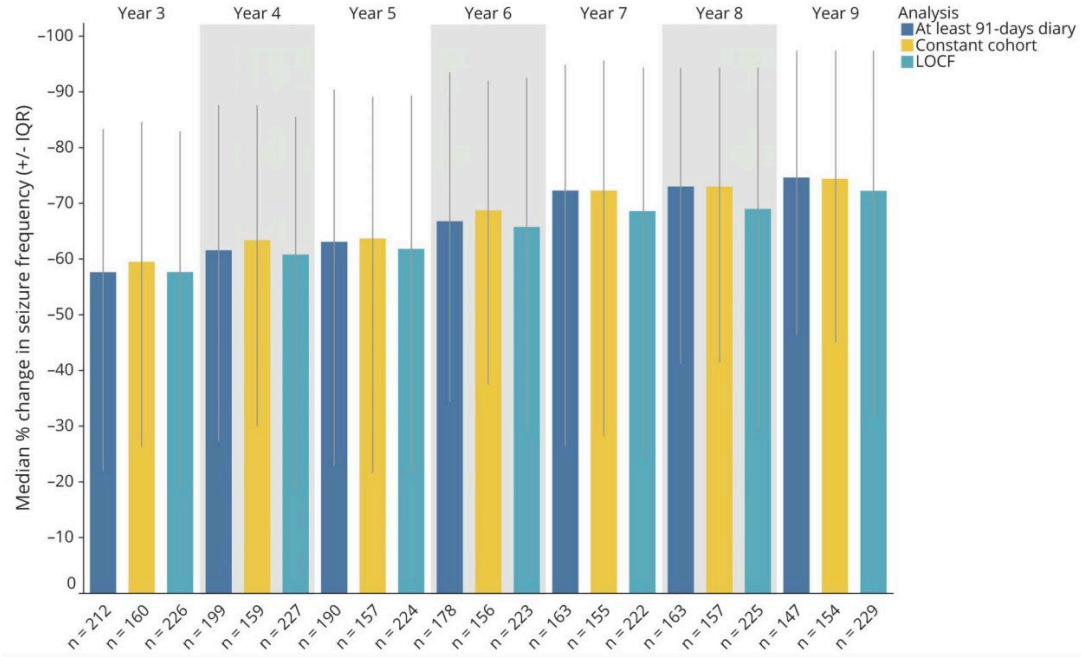

Ongoing applications of closed loop neurostimulation

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-021-01480-w
nature medicine

Check for updates

Closed-loop neuromodulation in an individual with treatment-resistant depression

Katherine W. Scangos[1,2]✉, Ankit N. Khambhati[1,3], Patrick M. Daly[1,2], Ghassan S. Makhoul[1,2], Leo P. Sugrue[1,4], Hashem Zamanian[1,2], Tony X. Liu[1,2], Vikram R. Rao[1,5], Kristin K. Sellers[1,3], Heather E. Dawes[1,3], Philip A. Starr[1,3], Andrew D. Krystal[1,2,6] and Edward F. Chang[1,3,6]

RESEARCH—HUMAN—STUDY PROTOCOLS

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Dan E. Azagury, MD[¶]
Cara Bohon, PhD[§]
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Mahendra T. Bhati, MD[*§]
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Laura B. Dunn, MD[§]
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Brian D. Knutson, PhD[‖]
Maya Yutsis, PhD[#]
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Kara Richardson, BA[*]
Tara L. Skarpaas, PhD[**]
Thomas K. Tcheng, PhD[**]
Martha J. Morrell, MD[**]
Laura Weiss Roberts, MD, MA[§]
Robert C. Malenka, MD, PhD[‡§]
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Casey H. Halpern, MD[*‡#]

*Department of Neurosurgery, Stanford University School of Medicine,

Brain-Responsive Neurostimulation for Loss of Control Eating: Early Feasibility Study

BACKGROUND: Loss of control (LOC) is a pervasive feature of binge eating, which contributes significantly to the growing epidemic of obesity; approximately 80 million US adults are obese. Brain-responsive neurostimulation guided by the delta band was previously found to block binge-eating behavior in mice. Following novel preclinical work and a human case study demonstrating an association between the delta band and reward anticipation, the US Food and Drug Administration approved an Investigational Device Exemption for a first-in-human study.
OBJECTIVE: To assess feasibility, safety, and nonfutility of brain-responsive neurostimulation for LOC eating in treatment-refractory obesity.
METHODS: This is a single-site, early feasibility study with a randomized, single-blinded, staggered-onset design. Six subjects will undergo bilateral brain-responsive neurostimulation of the nucleus accumbens for LOC eating using the RNS® System (NeuroPace Inc). Eligible participants must have treatment-refractory obesity with body

Epilepsy

OPEN ACCESS

Original research

Responsive neurostimulation of the thalamus improves seizure control in idiopathic generalised epilepsy: initial case series

Nathaniel D Sisterson,[1] Vasileios Kokkinos ,[1] Alexandra Urban,[2] Ningfei Li,[3] R Mark Richardson [1,4]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-327512).

[1]Department of Neurosurgery, Massachusetts General Hospital,

ABSTRACT
Objectives Up to 40% of patients with idiopathic generalised epilepsy (IGE) are drug resistant and potentially could benefit from intracranial neuromodulation of the seizure circuit. We present outcomes following 2 years of thalamic-responsive neurostimulation for IGE.

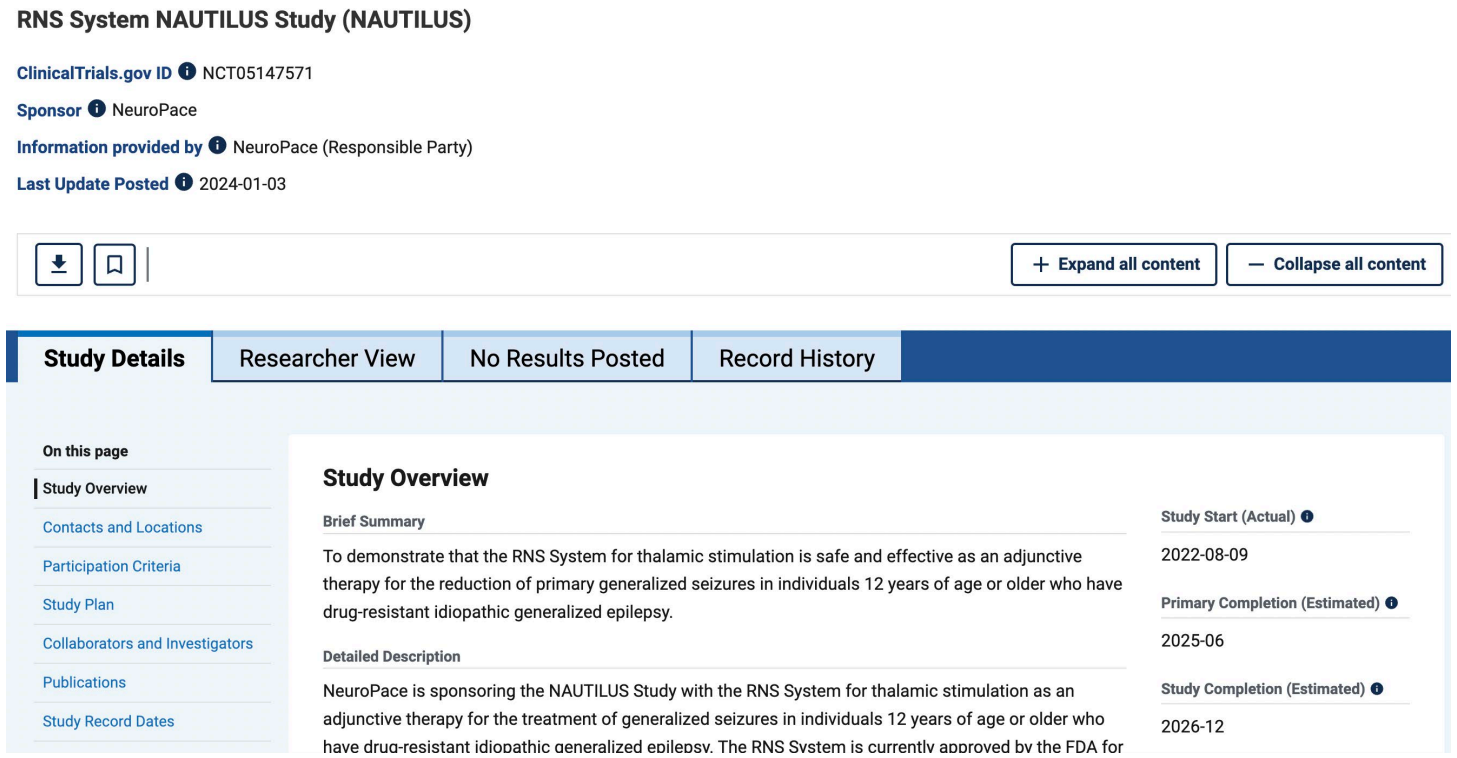
Key messages

What is already known on this topic

► Responsive neurostimulation is an effective treatment for drug-resistant focal epilepsy and may be equally or more effective for drug-resistant idiopathic generalised epilepsy (IGE).

RNS for generalized epilepsy

- About a fifth of epilepsy patients have generalized, rather than focal-onset, epilepsy
- Bilateral centromedian nucleus of thalamus stimulation
- Results are pending, but the study completed enrollment and implantation early



RNS System NAUTILUS Study (NAUTILUS)

ClinicalTrials.gov ID NCT05147571

Sponsor NeuroPace

Information provided by NeuroPace (Responsible Party)

Last Update Posted 2024-01-03

+ Expand all content | — Collapse all content

Study Details | Researcher View | No Results Posted | Record History

On this page

- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Publications
- Study Record Dates

Study Overview

Brief Summary

To demonstrate that the RNS System for thalamic stimulation is safe and effective as an adjunctive therapy for the reduction of primary generalized seizures in individuals 12 years of age or older who have drug-resistant idiopathic generalized epilepsy.

Detailed Description

NeuroPace is sponsoring the NAUTILUS Study with the RNS System for thalamic stimulation as an adjunctive therapy for the treatment of generalized seizures in individuals 12 years of age or older who have drug-resistant idiopathic generalized epilepsy. The RNS System is currently approved by the FDA for

Study Start (Actual) 2022-08-09

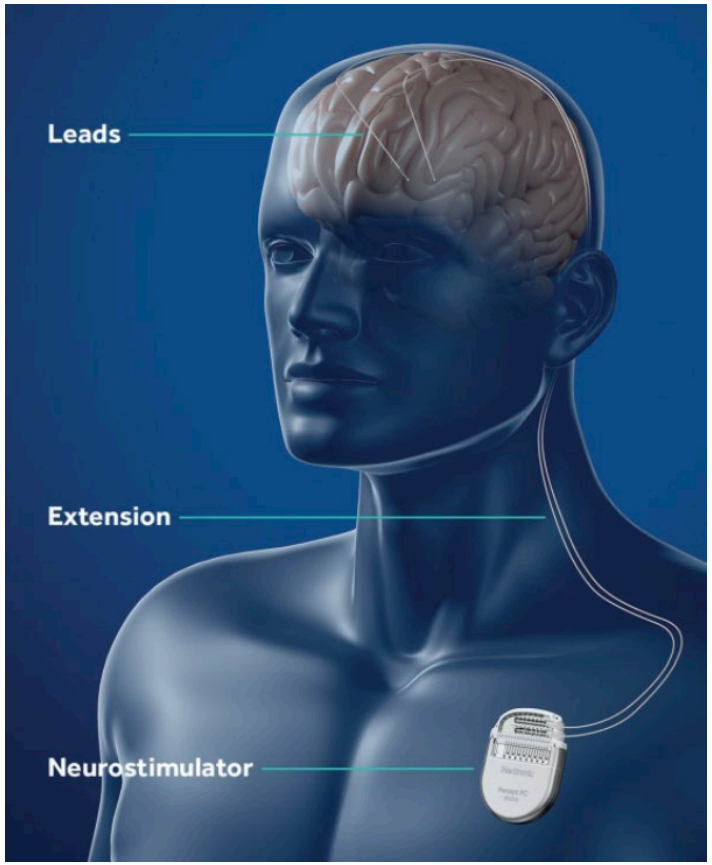
Primary Completion (Estimated) 2025-06

Study Completion (Estimated) 2026-12

Richardson 2022

Deep brain stimulation for epilepsy

- Electrodes implanted bilaterally in the anterior nucleus of the thalamus
- Cranial leads are connected to pulse generator in the chest via extension cables
- Gold-standard practice since 1993 and FDA-approved in 1997 for movement disorders
- FDA-approved for epilepsy in 2018
- IPG 4-7 years



SANTE trial

Epilepsia, 51(5):899–908, 2010
doi: 10.1111/j.1528-1167.2010.02536.x

FULL-LENGTH ORIGINAL RESEARCH

Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy

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Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy

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ABSTRACT

Objective: To report long-term efficacy and safety results of the SANTE trial investigating deep brain stimulation of the anterior nucleus of the thalamus (ANT) for treatment of localization-related epilepsy.

Methods: This long-term follow-up is a continuation of a previously reported trial of 5- vs 0-V ANT stimulation. Long-term follow-up began 13 months after device implantation with stimulation parameters adjusted at the investigators' discretion. Seizure frequency was determined using daily seizure diaries.

Results: The median percent seizure reduction from baseline at 1 year was 41%, and 69% at 5 years. The responder rate (≥ 50% reduction in seizure frequency) at 1 year was 43%, and 68% at 5 years. In the 5 years of follow-up, 16% of subjects were seizure-free for at least 6 months. There were no reported unanticipated adverse device effects or symptomatic intracranial hemorrhages. The Liverpool Seizure Severity Scale and 31-item Quality of Life in Epilepsy measure showed statistically significant improvement over baseline by 1 year and at 5 years ($p < 0.001$).

Conclusion: Long-term follow-up of ANT deep brain stimulation showed sustained efficacy and safety in a treatment-resistant population.

Classification of evidence: This long-term follow-up provides Class IV evidence that for patients with drug-resistant partial epilepsy, anterior thalamic stimulation is associated with a 69% reduction in seizure frequency and a 34% serious device-related adverse event rate at 5 years.
Neurology® 2015;84:1017–1025

GLOSSARY

ANT = anterior nucleus of the thalamus; **CI** = confidence interval; **DBS** = deep brain stimulation; **LSSS** = Liverpool Seizure Severity Scale; **QOLIE-31** = 31-item Quality of Life in Epilepsy; **SAE** = serious adverse event; **SANTE** = Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy; **SUDEP** = sudden unexpected death in epilepsy; **VNS** = vagus nerve stimulation.

Approximately 3 million people in the United States have epilepsy and approximately 30% remain resistant to medical treatment. Some of these patients are candidates for resective surgery.[1,2] For those who are not surgical candidates, or who continue to have seizures after surgery, neuromodulation may offer a viable therapeutic option. Several pilot studies,[3–6] and recent trials including the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial[7] and a trial of responsive cortical stimulation,[8] have demonstrated reduction in seizures. The SANTE trial in 110 subjects with localization-related epilepsy found that seizures were significantly reduced by stimulation.[7] We now report the 5-year efficacy and safety outcomes of this trial.

SANTE

- Failed three AEDs
- 18-65 years old
- Three-month double-blinded phase (after which all participants received neurostimulation)
- 40.4% reduction in stimulated versus 14.5% reduction in non-stimulated group (p=0.0017)
- Efficacy is held/improves over the course of 5 years of follow-up
- Improvement in executive function and attention at 7 years
- Thought to be most effective in patients with temporal-onset seizures

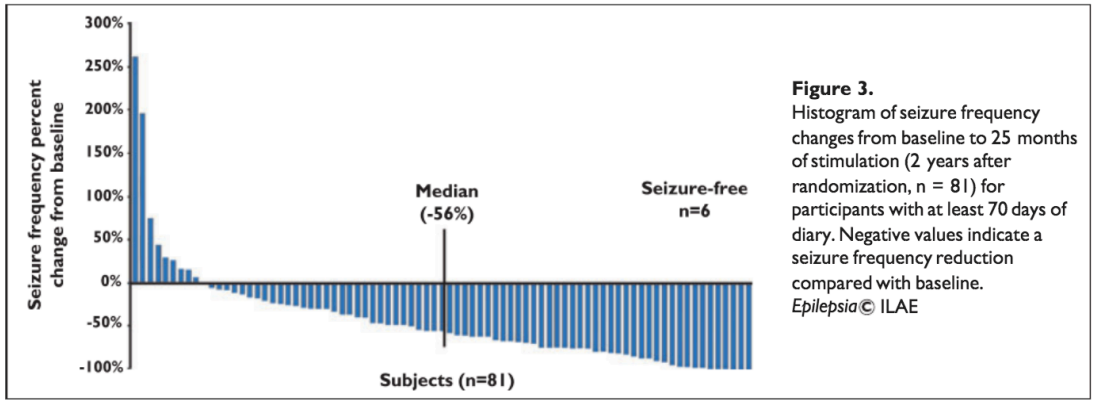
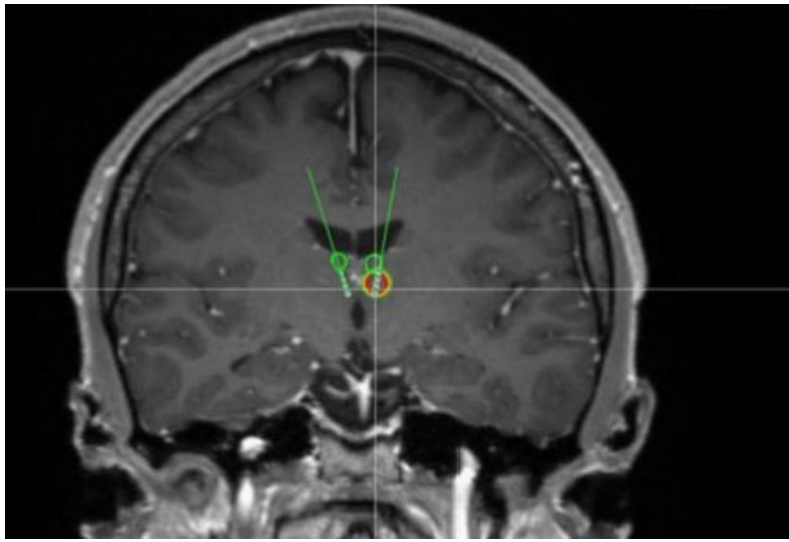
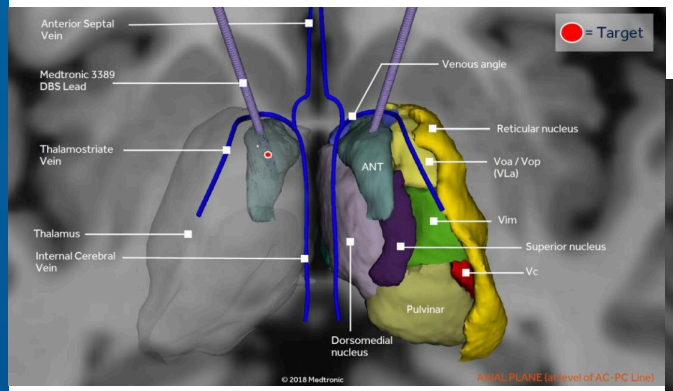


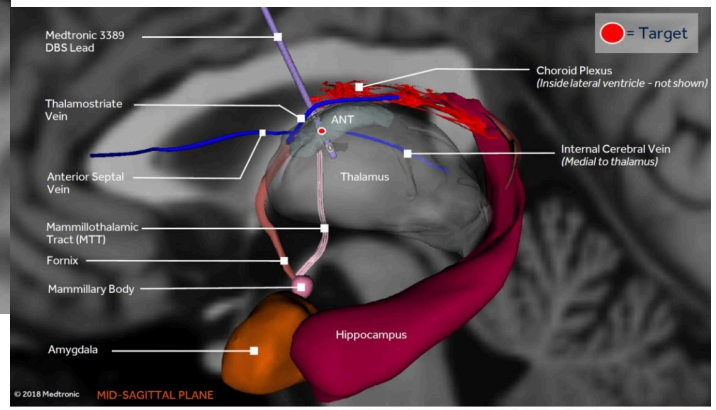
Figure 3.
Histogram of seizure frequency changes from baseline to 25 months of stimulation (2 years after randomization, n = 81) for participants with at least 70 days of diary. Negative values indicate a seizure frequency reduction compared with baseline.
Epilepsia© ILAE

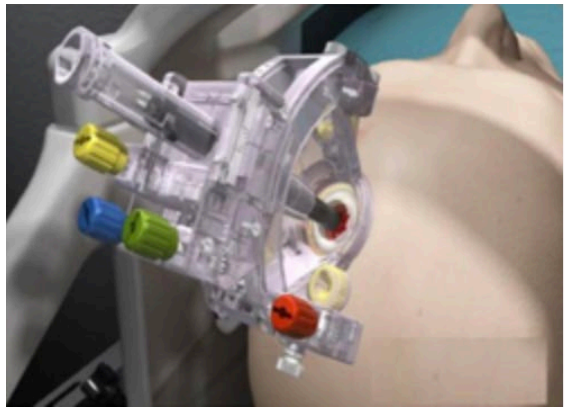
Recommend surgical protocol

- Asleep placement (robot-assisted or direct targeting in MRI)
- 15% lead repositioning rate if cannula not brought fully to target
- Full-body MRI-conditional compatible









Defining success in epilepsy surgery

- Traditionally, “success” has been measured according to Engel outcomes
- As neuromodulation improves, “success” is being defined in terms of:
  - Improving quality of life
  - Reducing seizure frequency/severity (and changing natural history of disease)
  - Reducing rate of SUDEP
- Important to understand each patient’s goals and set expectations realistically and accordingly
  - Potentially curative
  - Disease modifying

Engel Outcomes	
I	Free of all seizures, nondisabling simple partial seizures after surgery but seizure-free x2 years, convulsions only off meds
II	Initially seizure-free, rare disabling seizures since surgery, more than rare seizures initially post-op but now seizure-free x2 years, or only nocturnal
III	Worthwhile seizure reduction or >50% seizure-free over follow-up period (<2 years)
IV	No worthwhile improvement

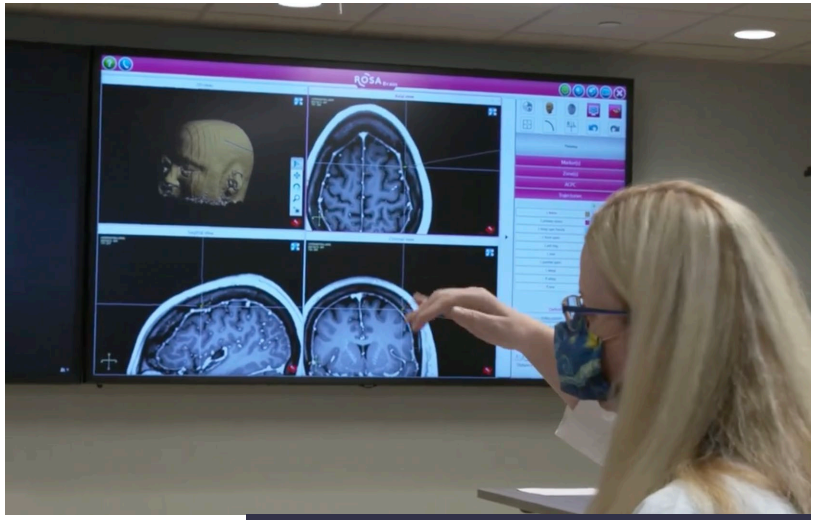
Englot 2024

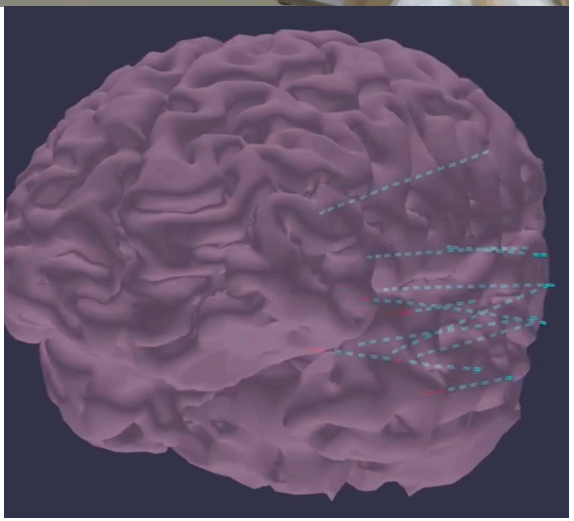
Barriers to access

- Referring physicians (PCP, community neurologists)
- Patients' and families' fear of surgical intervention
- Cost (though actually less than that of continued lifetime seizures)
- Family support in perioperative period

Recommendation:

- *All patients with drug-resistant epilepsy should be referred to an interdisciplinary epilepsy treatment center*
- The center should carefully consider each patient for surgical candidacy, and, as an informed source, talk with each patient individually about risks, benefits, and outcomes





Conclusions

- Epilepsy remains a significant public health burden that is surgically underserved
- Neuromodulation offers an exciting alternative or adjunct to resective/ablative seizure surgery and may be able to serve IGE patients
- Need head-to-head comparison data of one system versus another *
- Multiple systems may have synergistic effect (Khankhanian 2021)
- Closed-loop and/or less predictable programming may result in better efficacy

Thank you

Meet the Team

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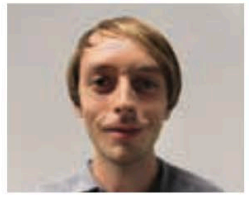
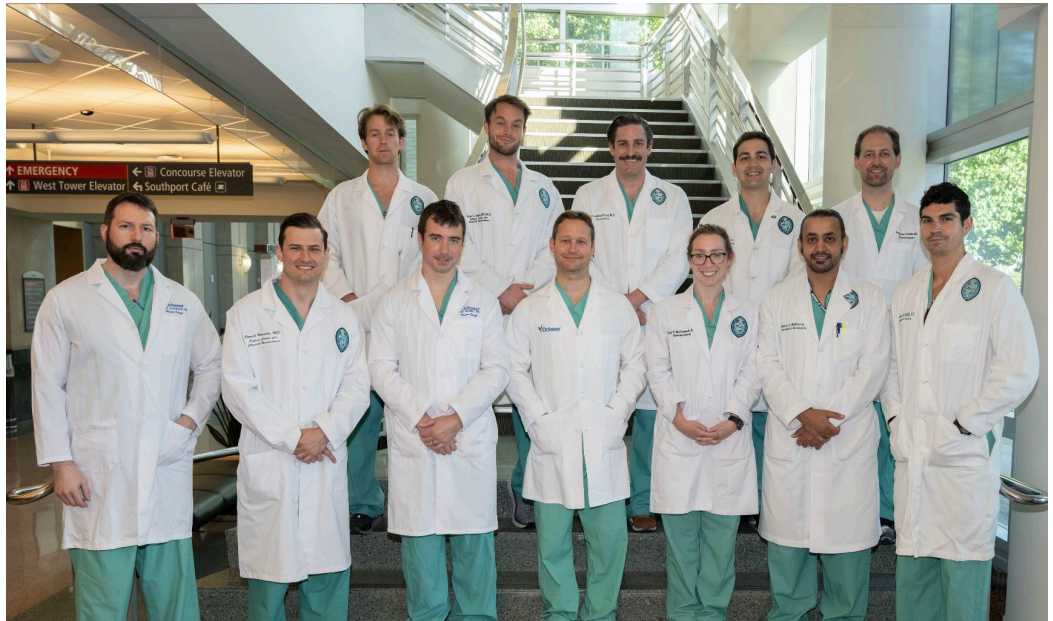

Colin Curtis

Thank you



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