Neuromodulation in epilepsy

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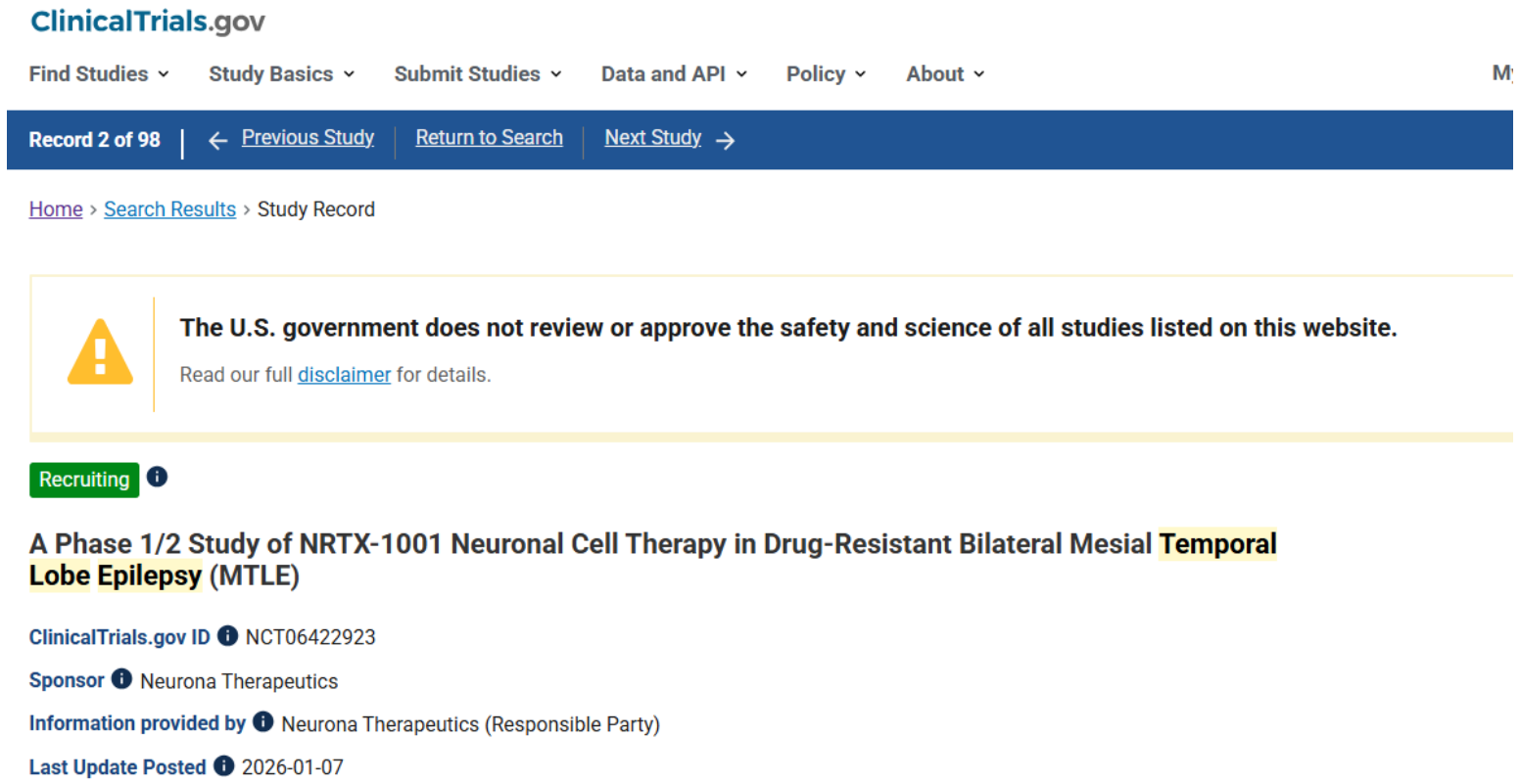
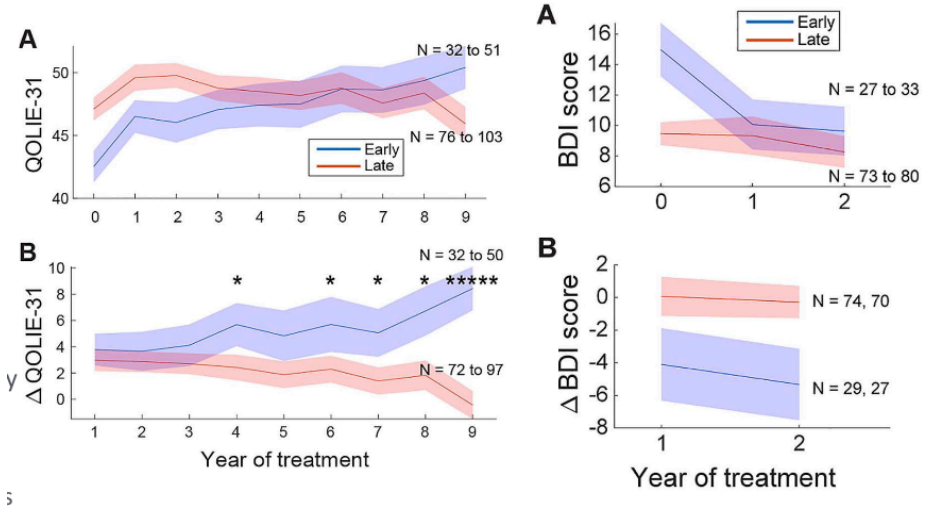
Disclosures

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



Epilepsy patients remain surgically underserved

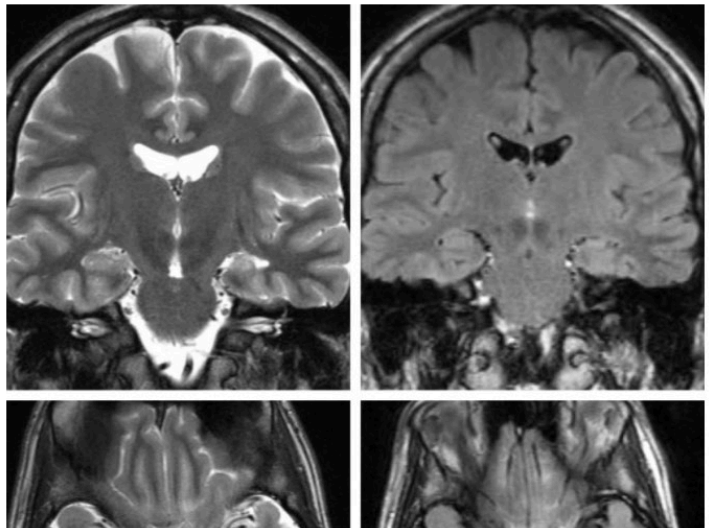
- Candidacy for surgery
  - Persistent focal* seizures despite 2 or more appropriate AEDs at therapeutic dosages
- More than 1 million patients in the US meet this definition
- Only about 1% of these receive surgery within 2 years of diagnosis of DRE
  - 1.7% absolute mortality increase annually
  - 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)

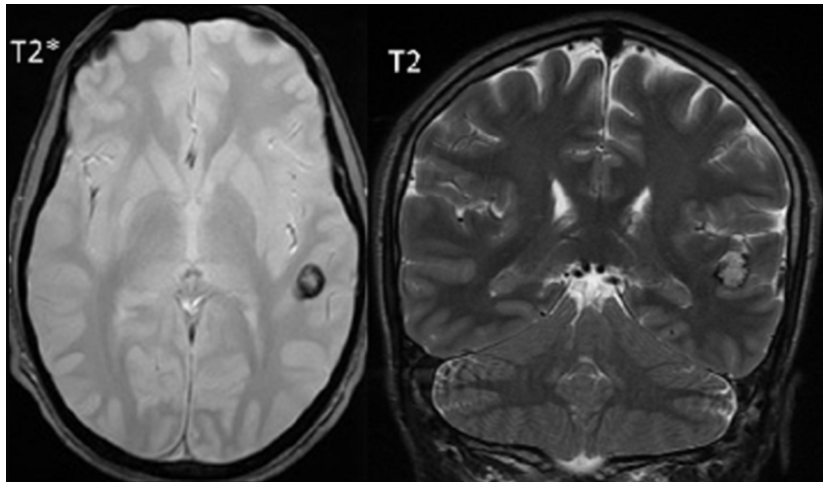


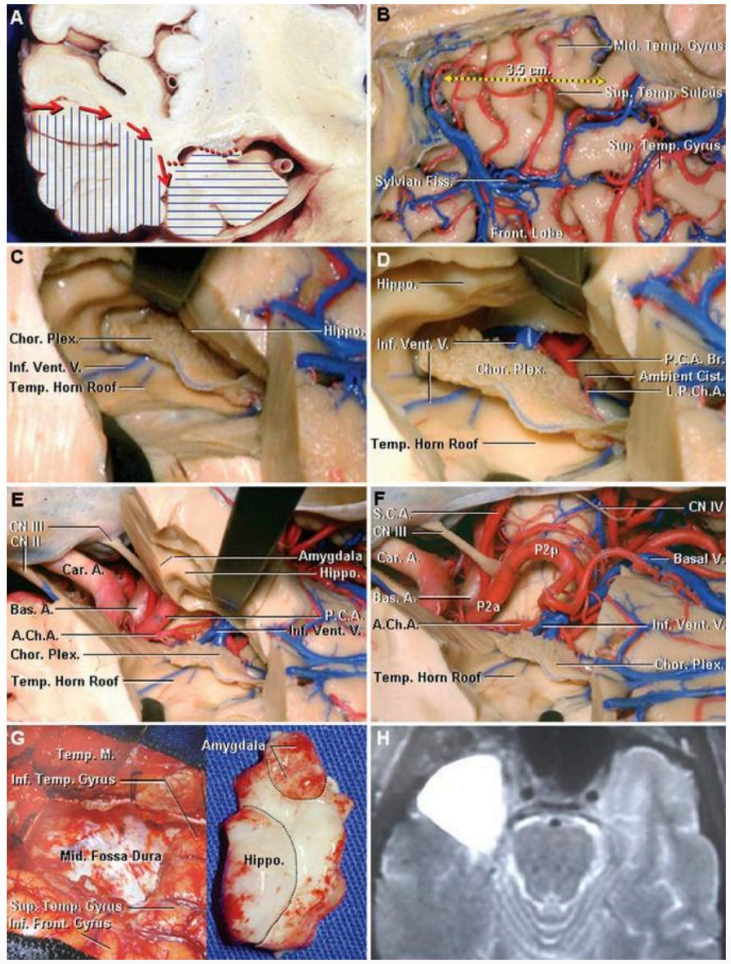
Loring 2021, Wissel 2024

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







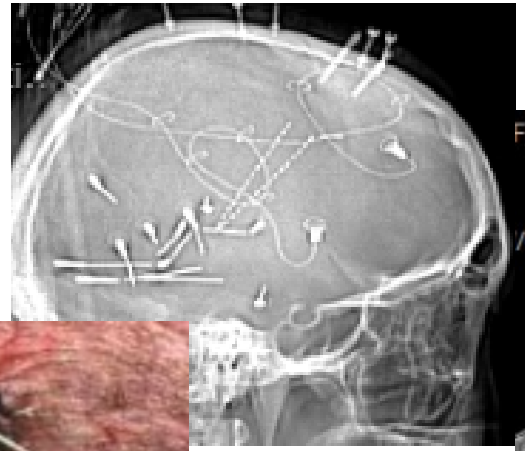
Rhoton

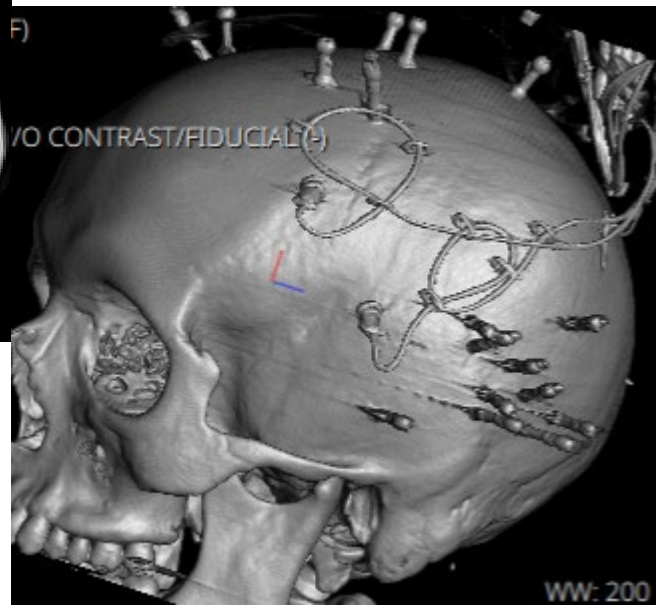
Surgical considerations and planning

- 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

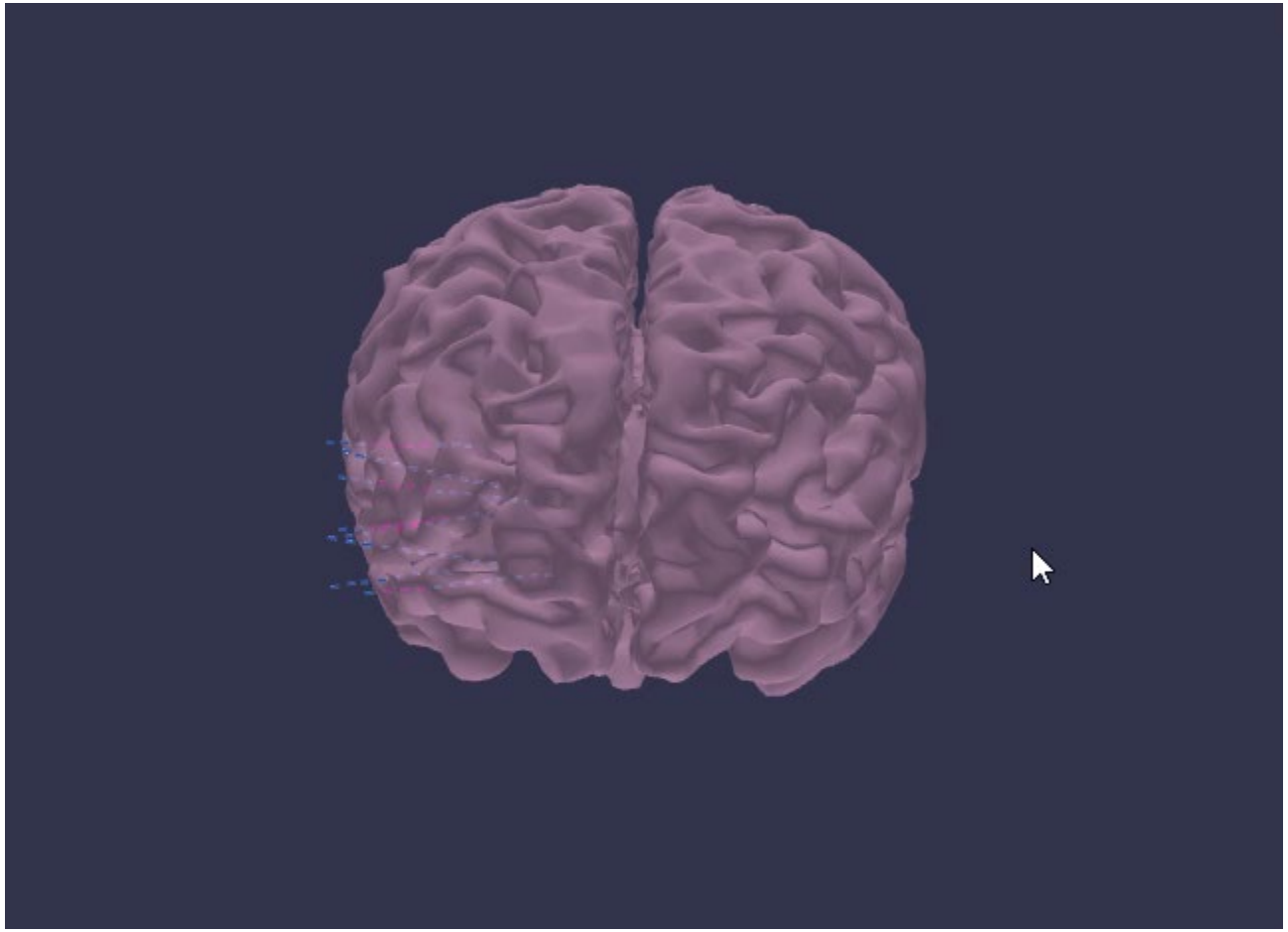
Robotic localization surgery: sEEG

- Multiple depth electrodes used to create 3D map of seizure-onset zone in brain
- Each bolt is 2.1 mm diameter
- 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



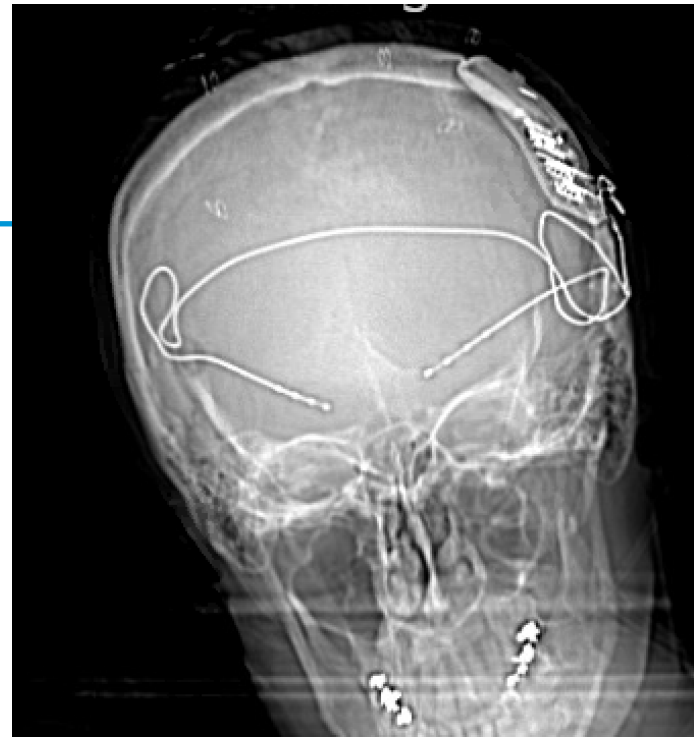


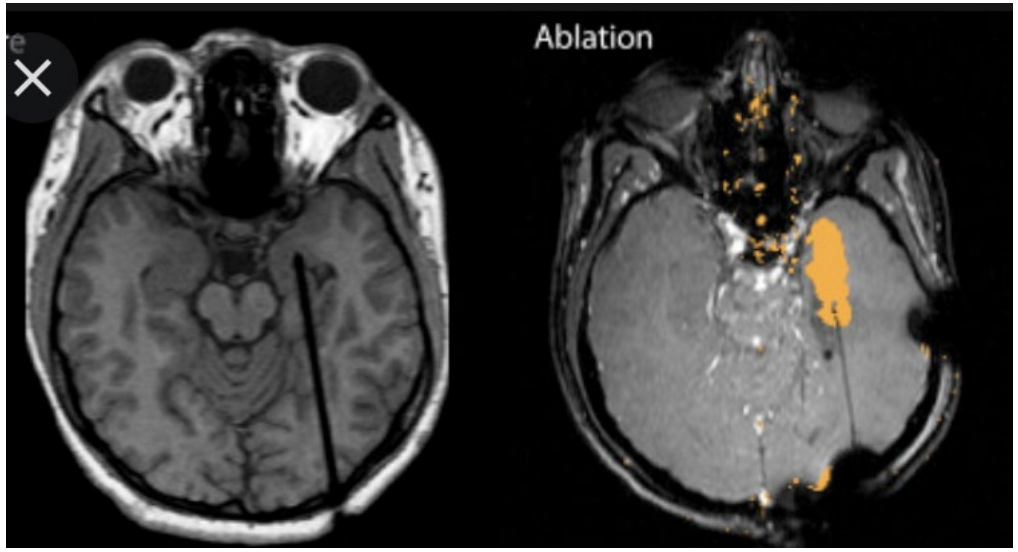
sEEG leads



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**)



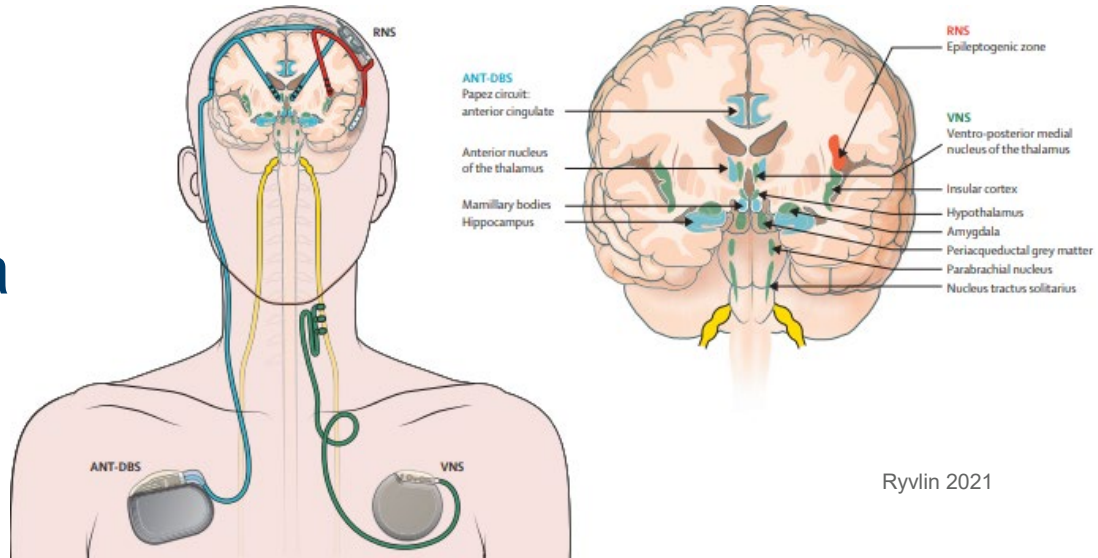


What is neuromodulation?

- Application of electrical current (or pharmaceutical agents) 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"

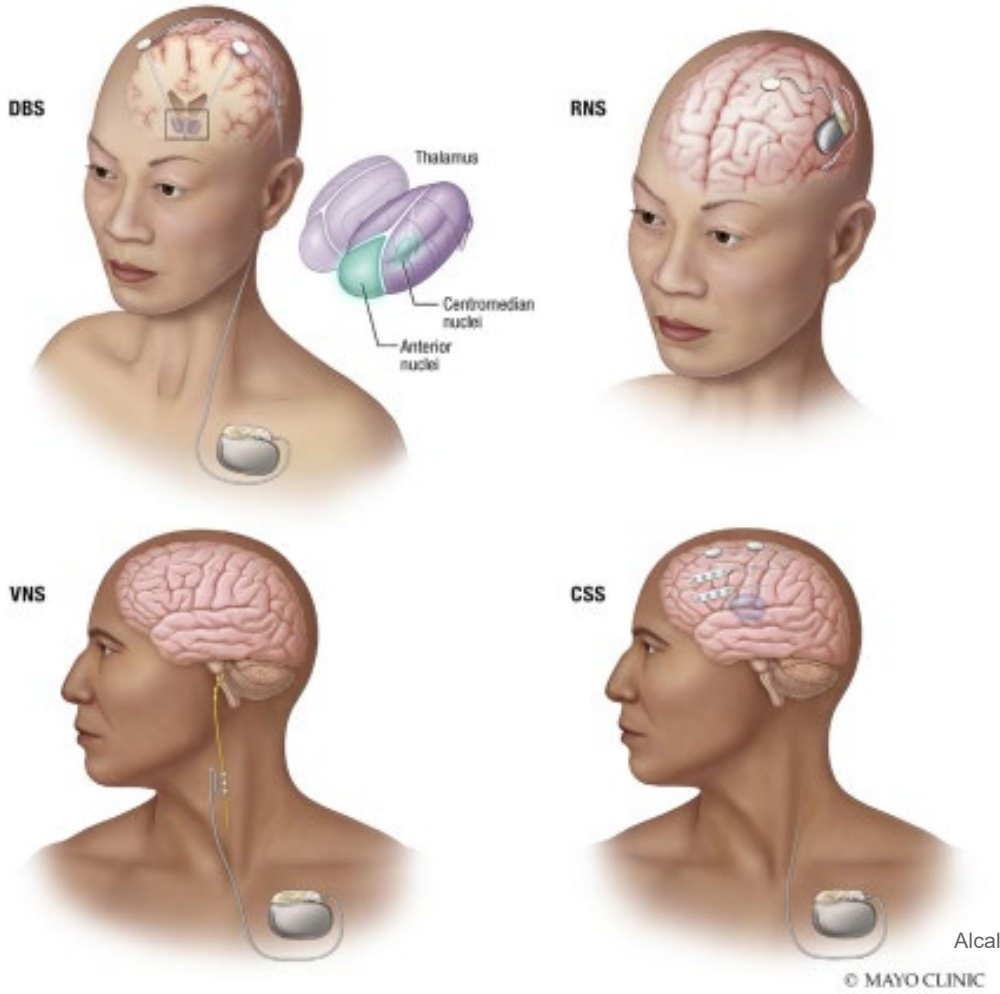
- Penfield 1950s direct cortical stimulation
- Open loop
  - Tonic stimulation set regardless of whether patient is seizing
- Closed loop (dynamic)
  - Stimulation is offered in response to a biomarker rather than at a set interval



Ryvlin 2021

Neuromodulation in epilepsy

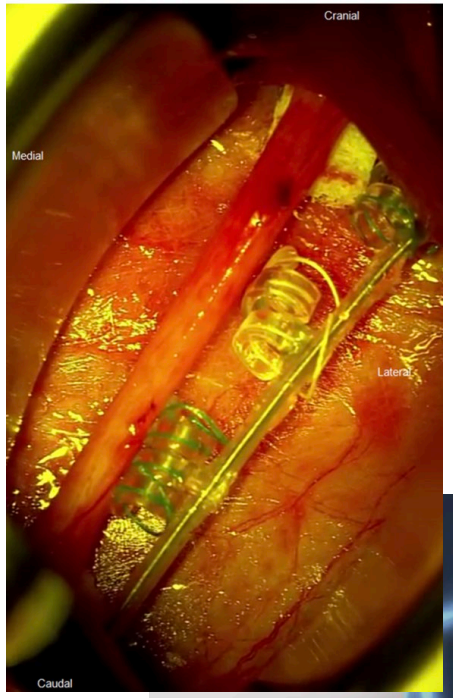
- May be applied:
  - Cranial nerve
    - Vagal Nerve Stmulation (VNS)
  - Brain
    - Responsive Neurostimulation (RNS)
    - Deep Brain Stimulation (DBS)
    - Inhibitory interneurons (in trial)

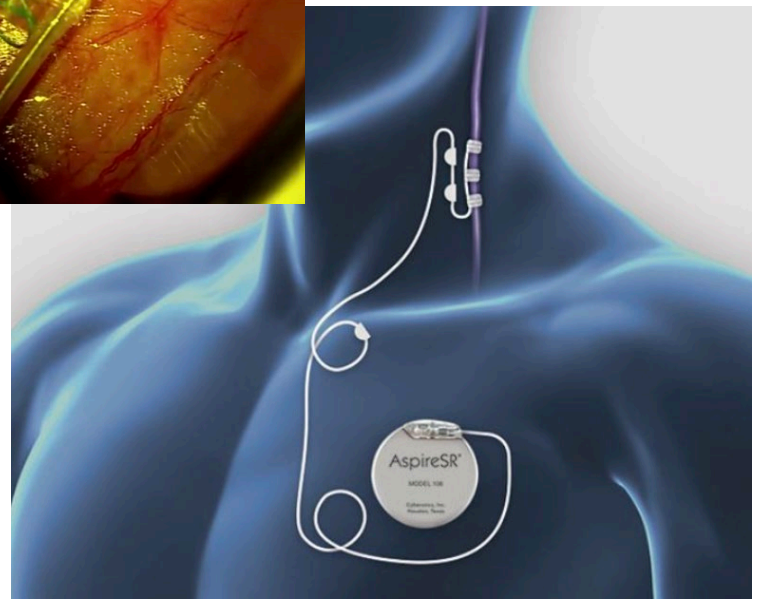


Alcala-Zermeno 2022

Vagal nerve stimulator

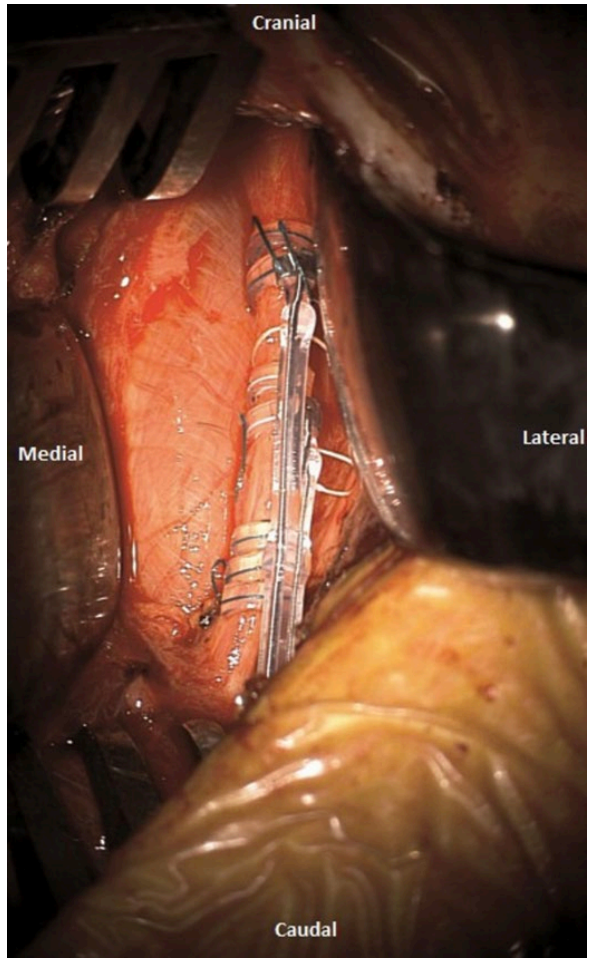
- Lead that wraps around the vagus nerve and connects directly to a generator placed in the chest
- ~50% of patients experience a 50% improvement in seizure frequency and severity at 2 years
- Better outcomes with more years of stimulation
- FDA-approved for partial epilepsy (non-unilesional) since 1997
- 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



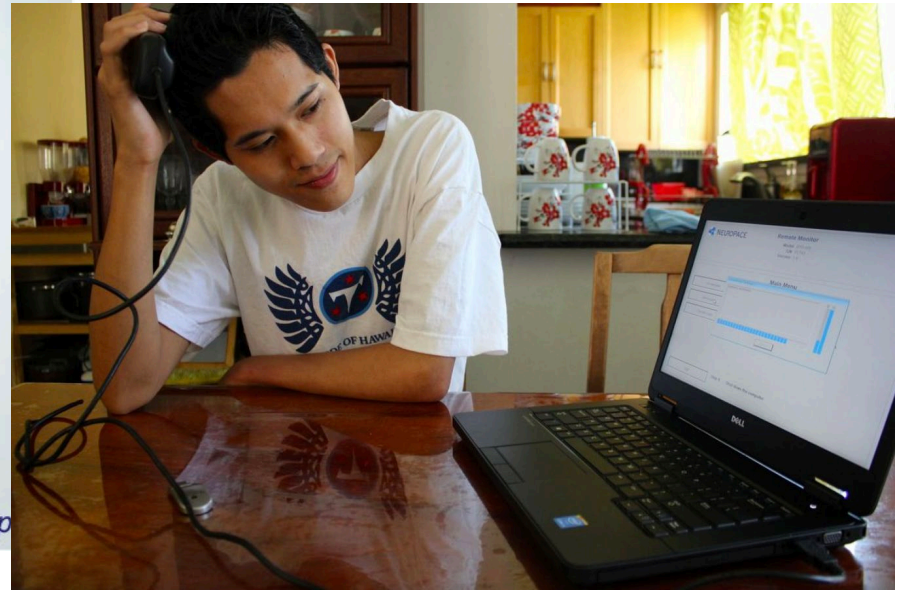
Giordano 2017

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

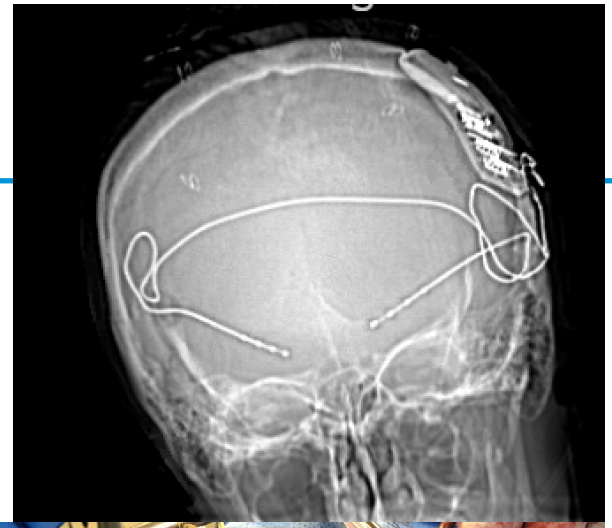
RNS

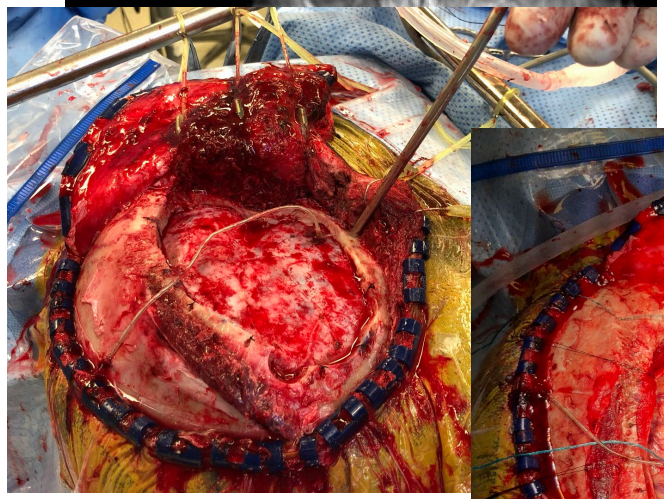
- "Closed loop" system
- Frequent patient download of data to patient remote monitor

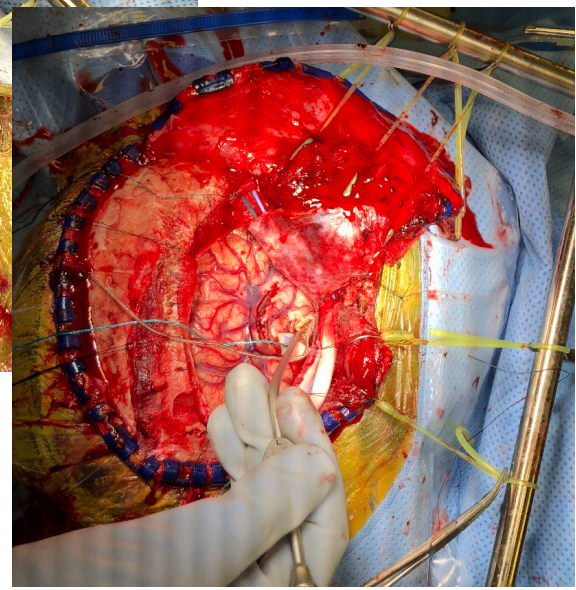


RNS

- 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)

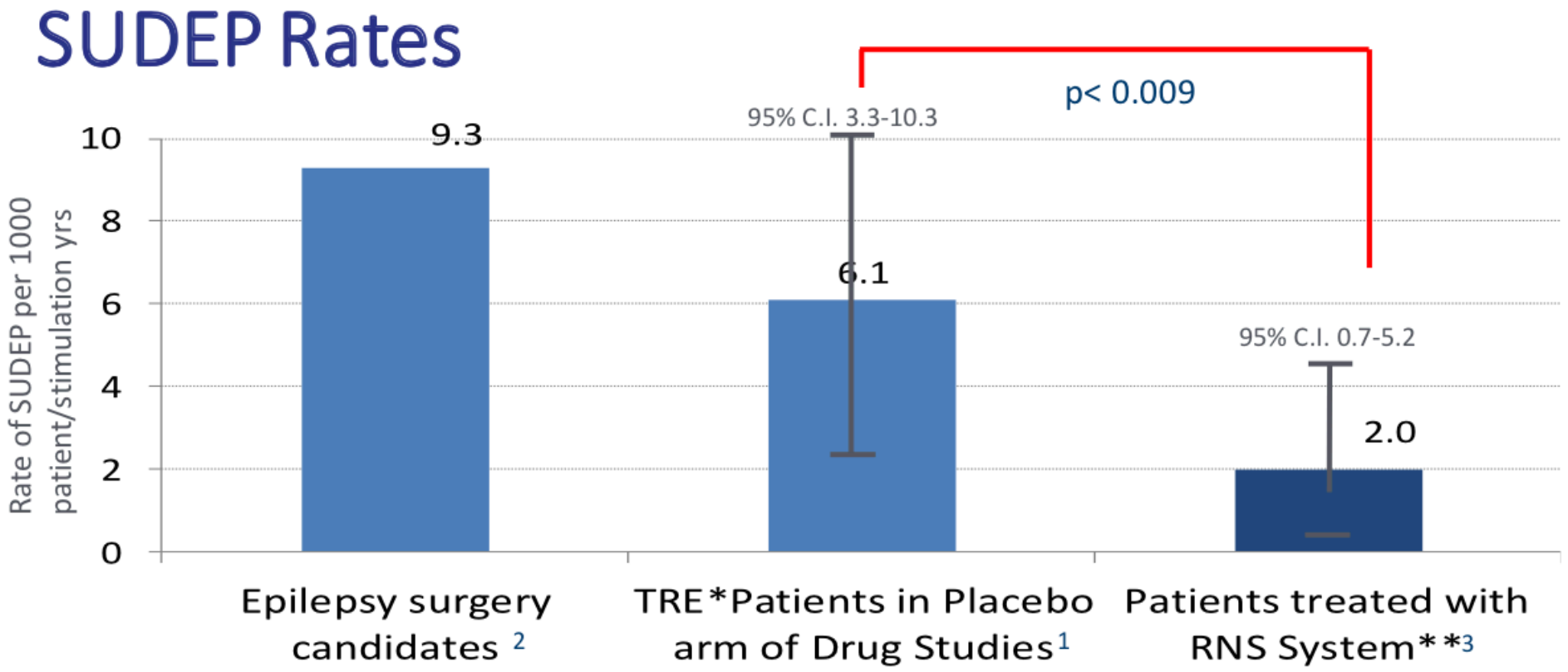






Krucoff 2020

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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Dr. Morrell
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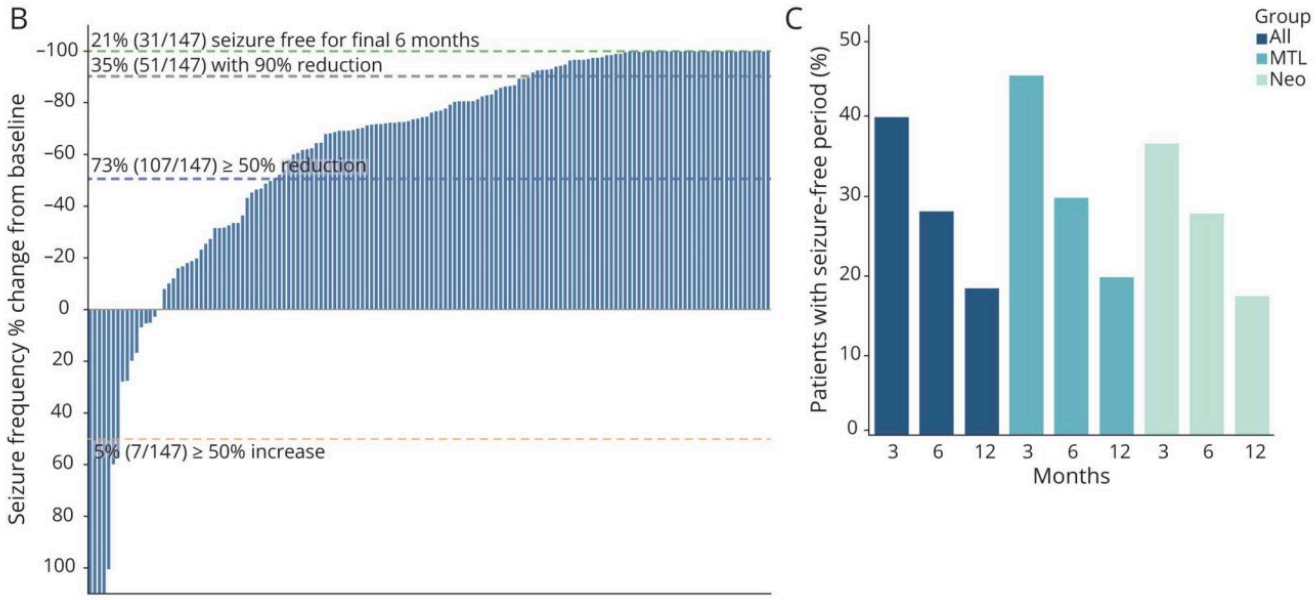
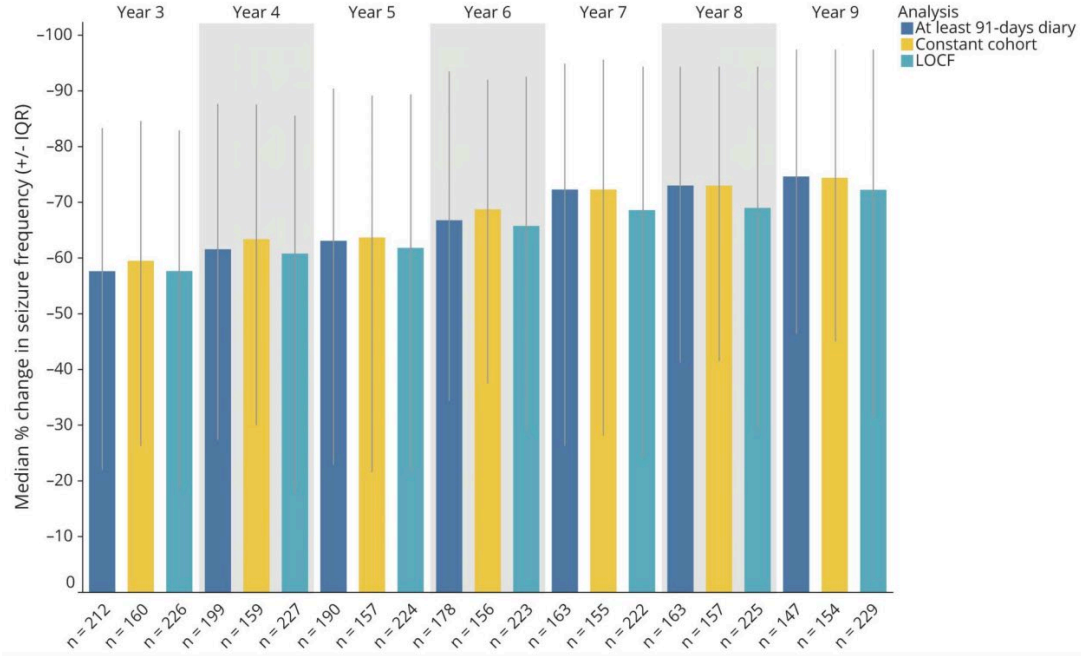
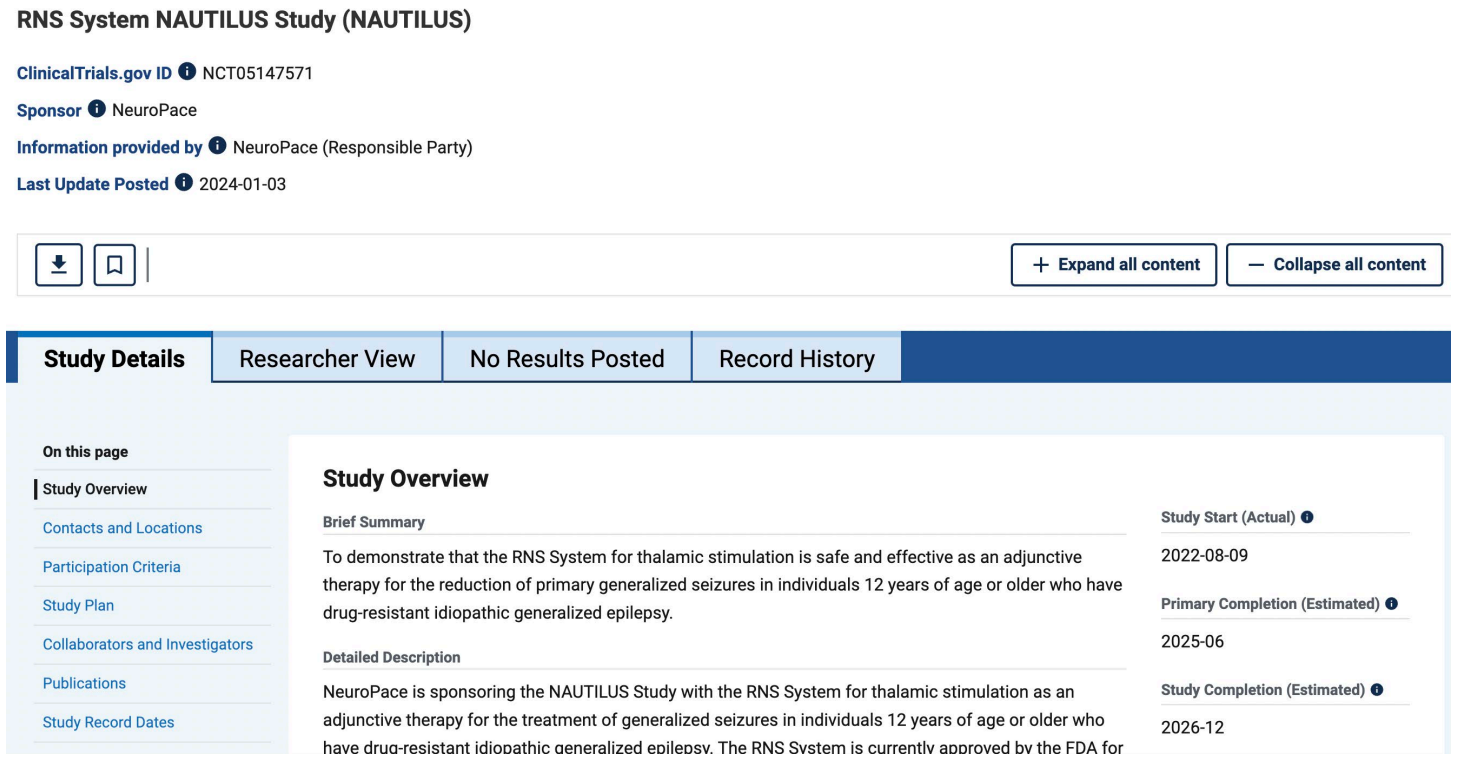




RNS for generalized epilepsy

- About a fifth of epilepsy patients have generalized, rather than focal-onset, epilepsy
- Bilateral centromedian nucleus of thalamus stimulation
- Results are expected this summer



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

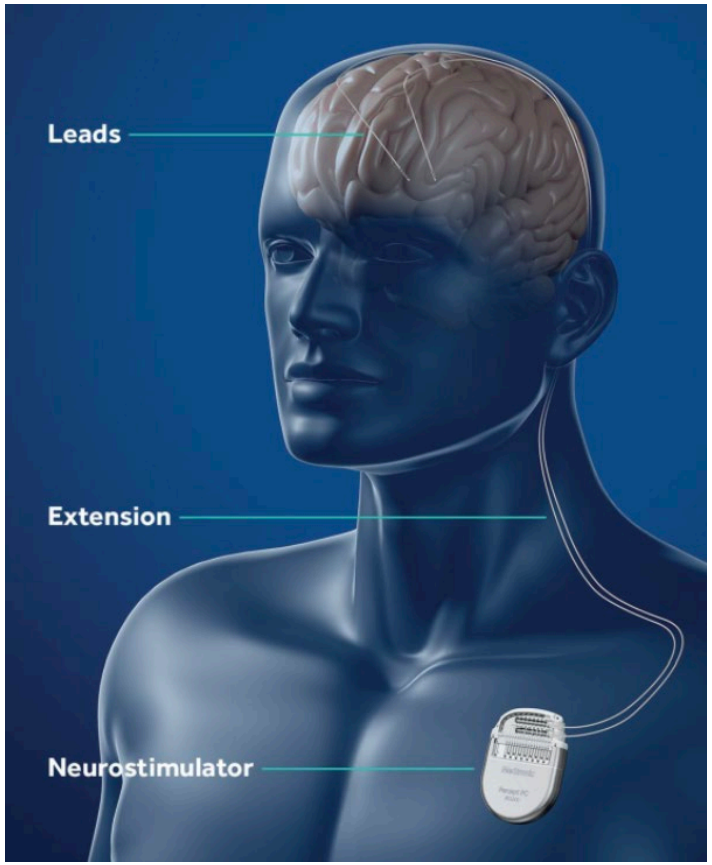
Primary Completion (Estimated) 2025-06

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

***Robert Fisher, †Vicenta Salanova, †Thomas Witt, †Robert Worth, ‡Thomas Henry, ‡Robert Gross, §Kalarickal Oommen, ¶Ivan Osorio, ¶Jules Nazzaro, #Douglas Labar, #Michael Kaplitt, **Michael Sperling, ††Evan Sandok, ††John Neal, ‡‡Adrian Handforth, §§John Stern, ‡‡Antonio DeSalles, ¶¶Steve Chung, ¶¶Andrew Shetter, ##Donna Bergen, ##Roy Bakay, *Jaimie Henderson, ***Jacqueline French, ***Gordon Baltuch, †††William Rosenfeld, †††Andrew Youkilis, ‡‡‡William Marks, ‡‡‡Paul Garcia, ‡‡‡Nicolas Barbaro, §§§Nathan Fountain, ¶¶¶Carl Bazil, ¶¶¶Robert Goodman, ¶¶¶Guy McKhann, ###K. Babu Krishnamurthy, ###Steven Papavassiliou, ‡Charles Epstein, ***John Pollard, ****Lisa Tonder, ****Joan Grebin, ****Robert Coffey, ****Nina Graves, and the SANTE Study Group[!]**

***Stanford University, Stanford, California, U.S.A.; †Indiana University, Indianapolis, Indiana, U.S.A.; ‡Emory University, Atlanta, Georgia, U.S.A.; §University of Oklahoma, Oklahoma City, Oklahoma, U.S.A.; ¶University of Kansas, Kansas City, Kansas, U.S.A.; #Weill-Cornell, New York, New York, U.S.A.; **Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.; ††Marshfield Clinic, Marshfield, Wisconsin, U.S.A.; ‡‡Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California, U.S.A.; §§Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.; ¶¶Barrow Neurological Institute, Phoenix, Arizona, U.S.A.; ##Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois, U.S.A.; ***University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; †††St. Luke's N. Medical Building, St. Louis, Missouri, U.S.A.; ‡‡‡University of California San Francisco, California, U.S.A.; §§§University of Virginia School of Medicine, Charlottesville, Virginia, U.S.A.; ¶¶¶Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.; ###Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, U.S.A.; and ****Medtronic, Minneapolis, Minnesota, U.S.A.**

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

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Thomas Witt, MD
Robert Worth, MD
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Robert E. Gross, MD, PhD
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Nathan B. Fountain, MD
W. Jeffrey Elias, MD
Robert R. Goodman, MD, PhD
John R. Pollard, MD
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Kristin Lambrecht, PA-C
Nina Graves, PharmD
Robert Fisher, MD, PhD
For the SANTE Study Group

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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

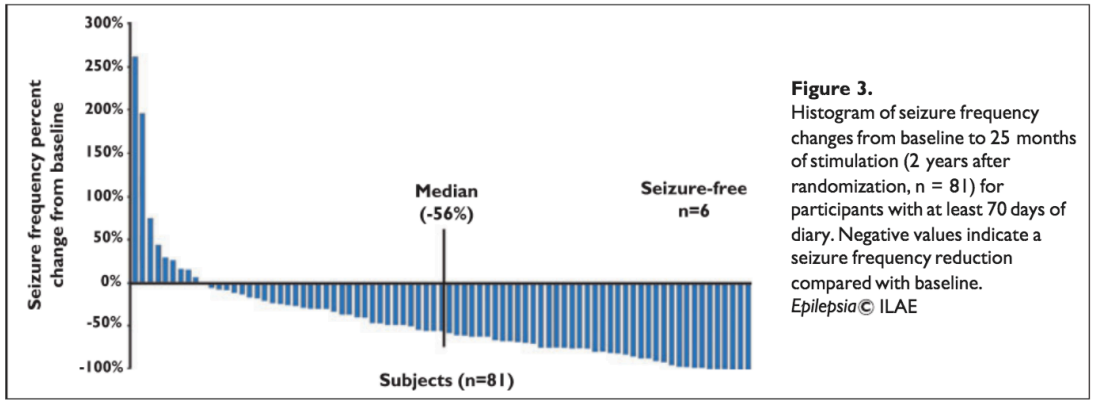


Figure 3.
Histogram of seizure frequency changes from baseline to 25 months of stimulation (2 years after randomization, n = 81) for participants with at least 70 days of diary. Negative values indicate a seizure frequency reduction compared with baseline.
Epilepsia© ILAE

Nonclinical Efficacy: NRTX-1001 is Disease-modifying in a Model of Chronic Mesial Temporal Lobe Epilepsy (MTLE)

Model of Drug-Resistant MTLE

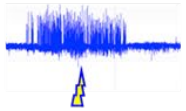
Replicates electrophysiology, histopathology and pharmacology of human MTLE

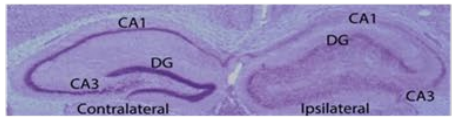
Intra-Hippocampal Kainate for Status Epilepticus

Immunocompromised NOG Mice

1 month

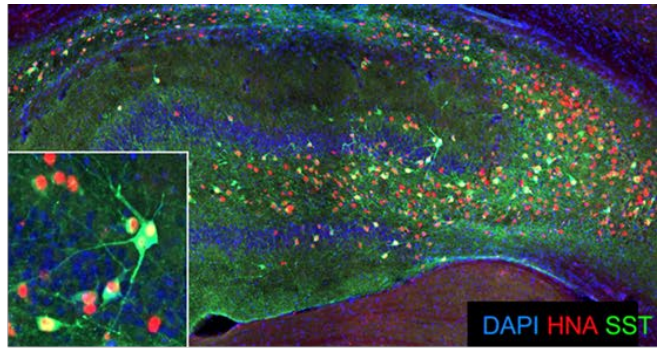
Intra-Hippocampal Electrode at CA1 and iEEG Detect Focal Seizures (20-30 seizures/hr)





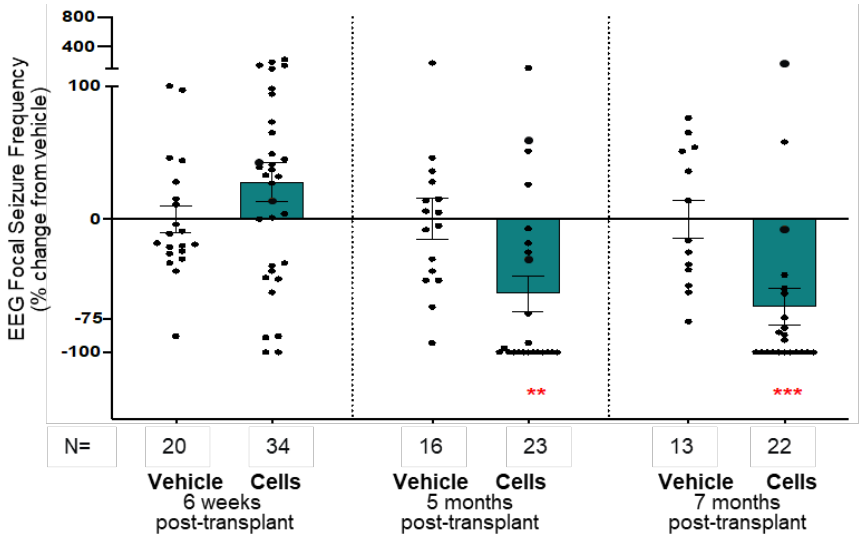
Mesial Temporal Sclerosis (MTS)

Intra-Hippocampal Cell Delivery

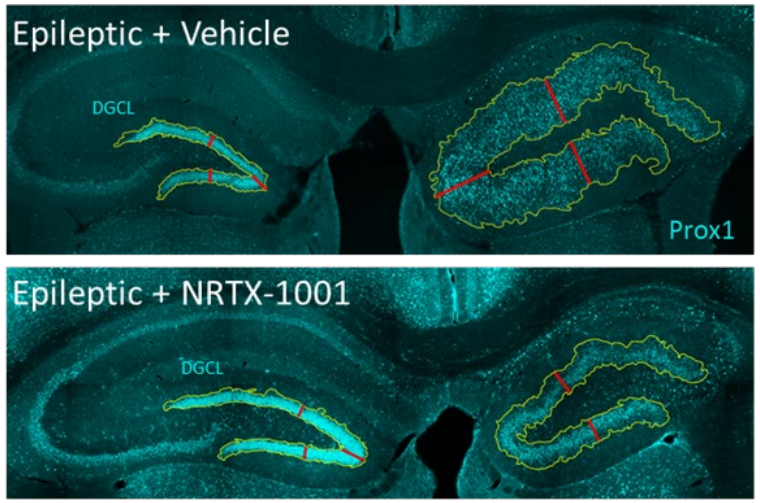


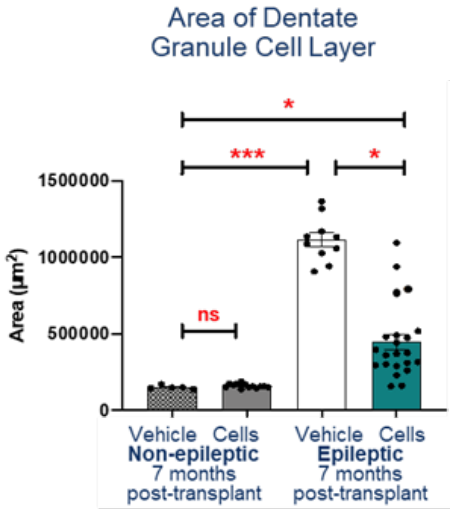
7 Months Post-transplantation

NRTX-1001 suppresses seizures by 5 MPT



NRTX-1001 reduces dentate granule cell dispersion and hippocampal damage





Across 8 independent manufacturing lots of NRTX-1001:

77% (87/113) of epileptic mice with NRTX-1001 have > 75% seizure reduction

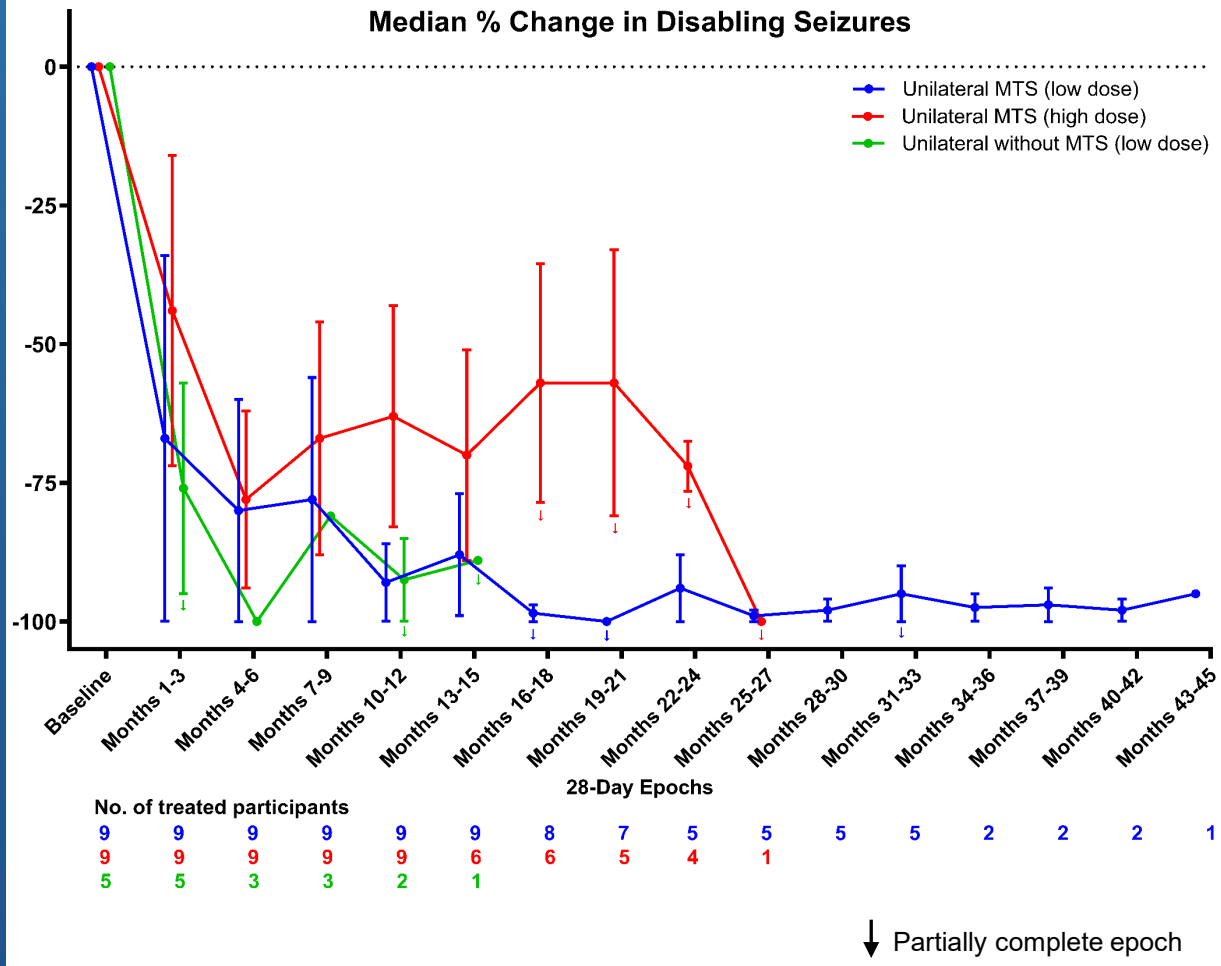
66% (75/113) of epileptic mice with NRTX-1001 become seizure free

At 7 months post-transplant of NRTX-1001 in epileptic mice:

Area and width of dentate granule cell layer are reduced

Hippocampal sclerosis is reduced

NTE001 Unilateral MTLE – Disabling Seizure Reduction and Durability



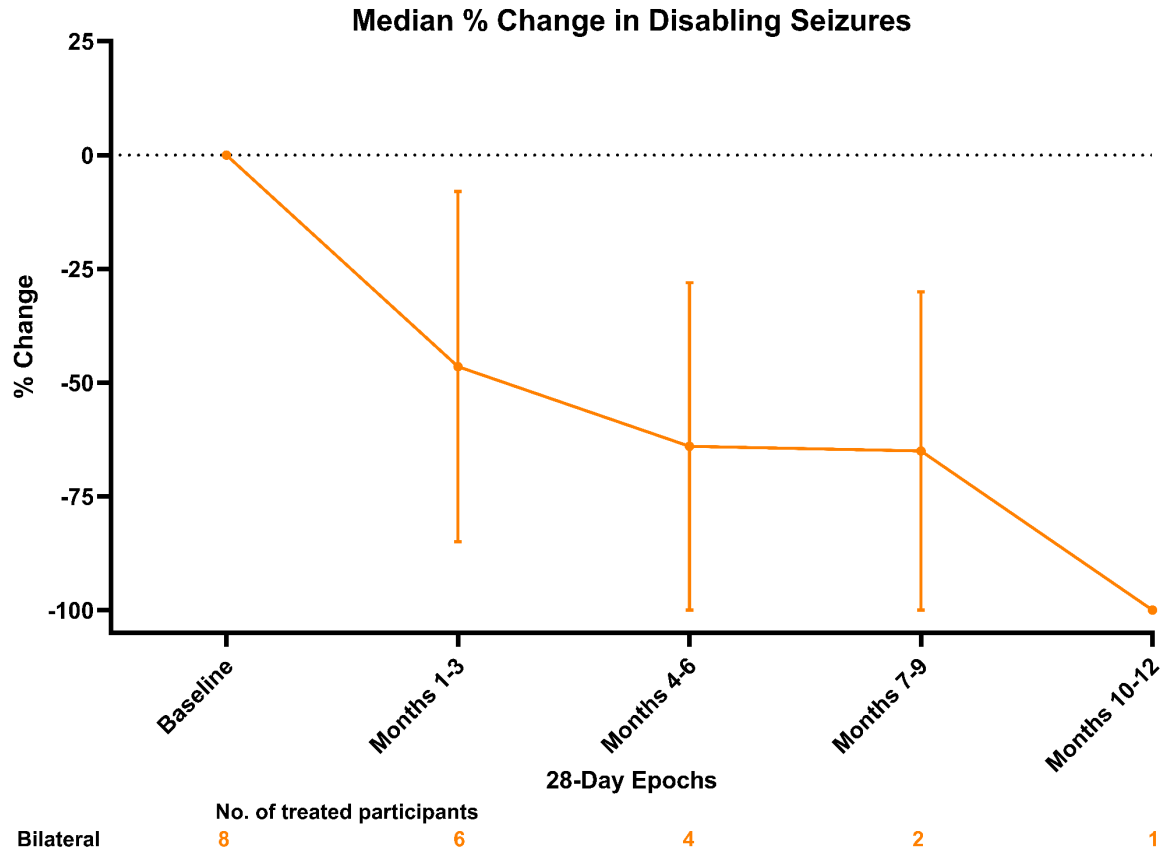
Unilateral MTS (low dose)			
	4-6 mo (n=9)	7-12 mo (n=9)	13+ mo (n=9)
Median disabling seizure reduction	**80%**	**89%**	**89%**
50% RR	67%	78%	89%
75% RR	56%	67%	78%

Unilateral MTS (high dose)			
	4-6 mo (n=9)	7-12 mo (n=9)	13+ mo (n=6)
Median disabling seizure reduction	**78%**	**58%**	**57%**
50% RR	89%	78%	67%
75% RR	56%	33%	33%

Unilateral without MTS (low dose)			
	4-6 mo (n=3)	7-12 mo (n=1)	13+ mo (n=1)
Median disabling seizure reduction	**100%**	**83%**	**67%**
50% RR	67%	100%	100%
75% RR	67%	100%	0%

9MAR2026 data cutoff

NTE002 Bilateral with and without MTS (low dose): Disabling Seizure Reduction



Bilateral with and without MTS (low dose)			
	4-6 months (n=4)	7-9 months (n=2)	10-12 months (n=1)
Median disabling seizure reduction	**64%**	**65%**	**100%**
50% RR	50%	50%	100%
75% RR	50%	50%	100%

9MAR2026 data cutoff

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

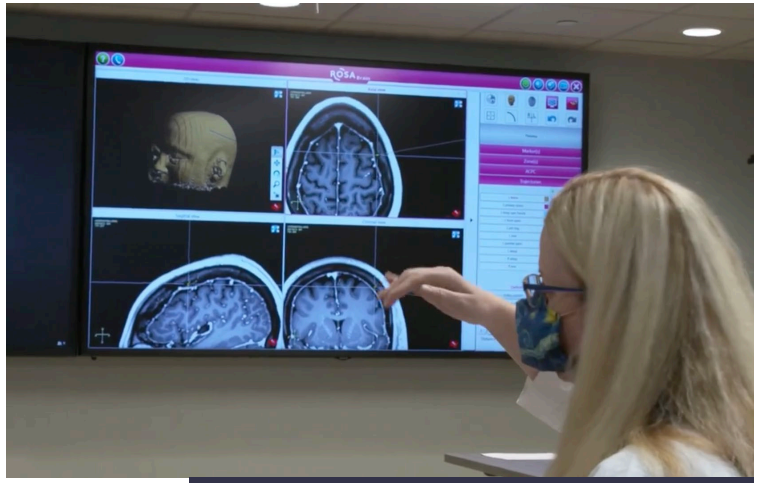
Englot 2024

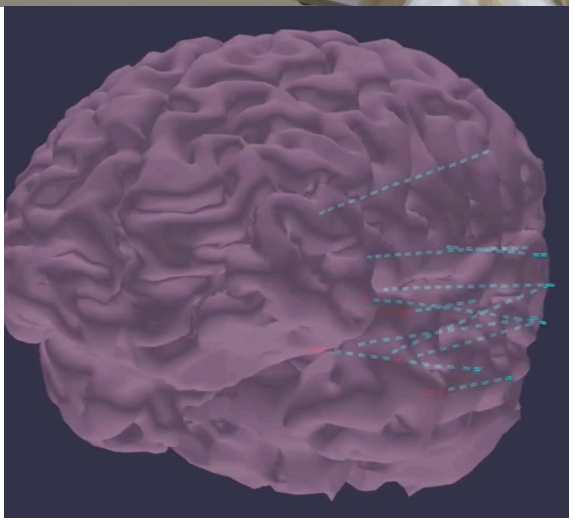
Barriers to access

- 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





Ongoing applications of neuromodulation

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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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).

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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).

frontiers in Neuroscience
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Check for updates

Neurostimulation for Stroke Rehabilitation

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Improved understanding of stimulation efficacy

https://doi.org/10.1093/brain/awad343 BRAIN 2024: 147; 521–531 | 521

BRAIN
ORIGINAL ARTICLE

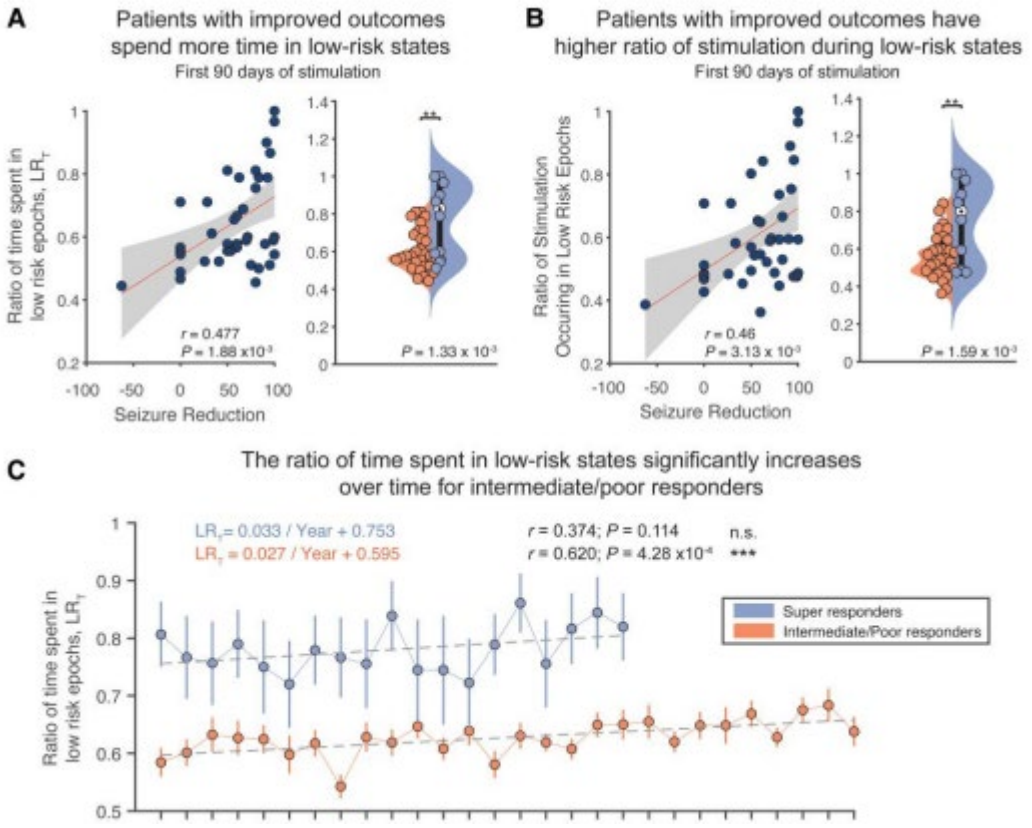
Closed-loop stimulation in periods with less epileptiform activity drives improved epilepsy outcomes

Daria Nesterovich Anderson,[1,2,3] Chantel M. Charlebois,[4,5] Elliot H. Smith,[1] Tyler S. Davis,[1] Angela Y. Peters,[6] Blake J. Newman,[6] Amir M. Arain,[6] Karen S. Wilcox,[2] Christopher R. Butson[7,8,9,10] and John D. Rolston[4,11]

In patients with drug-resistant epilepsy, electrical stimulation of the brain in response to epileptiform activity can make seizures less frequent and debilitating. This therapy, known as closed-loop responsive neurostimulation (RNS), aims to directly halt seizure activity via targeted stimulation of a burgeoning seizure. Rather than immediately stopping seizures as they start, many RNS implants produce slower, long-lasting changes in brain dynamics that better predict clinical outcomes. Here we hypothesize that stimulation during brain states with less epileptiform activity drives long-term changes that restore healthy brain networks. To test this, we quantified stimulation episodes during low- and high-risk brain states—that is, stimulation during periods with a lower or higher risk of generating epileptiform activity—in a cohort of 40 patients treated with RNS.

More frequent stimulation in tonic low-risk states and out of rhythmic high-risk states predicted seizure reduction. Additionally, stimulation events were more likely to be phase-locked to prolonged episodes of abnormal activity for intermediate and poor responders when compared to super-responders, consistent with the hypothesis that improved outcomes are driven by stimulation during low-risk states.

These results support the hypothesis that stimulation during low-risk periods might underlie the mechanisms of RNS, suggesting a relationship between temporal patterns of neuromodulation and plasticity that facilitates long-term seizure reduction.



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 special populations of patients, including IGE and bilateral MTS
- Multiple systems may have synergistic effect (Khankhanian 2022)
- The longer the systems are in effect, the more effective they tend to be

FIGURE 1
AI-rendered neurostimulation future. A Dall-E rendering of what a future clinic visit could look like when prompted, "Draw me a picture of a doctor's office in 100 years, where a neurologist will be sitting with AR Goggles and a tablet, and a patient will be sitting on the chair. There will be a screen in the background that has a 3D picture of the patient's brain and their brainwaves."

Hadar 2024

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Thank you


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