Pipeline of Progress: Device Therapy for Epilepsy

August 20, 2026

CURE EPILEPSY

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CURE Epilepsy

Our mission is to fund breakthrough research that will transform the lives of people with epilepsy as we lead the search for a cure.

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CURE Epilepsy is the leading nongovernmental funder of epilepsy research

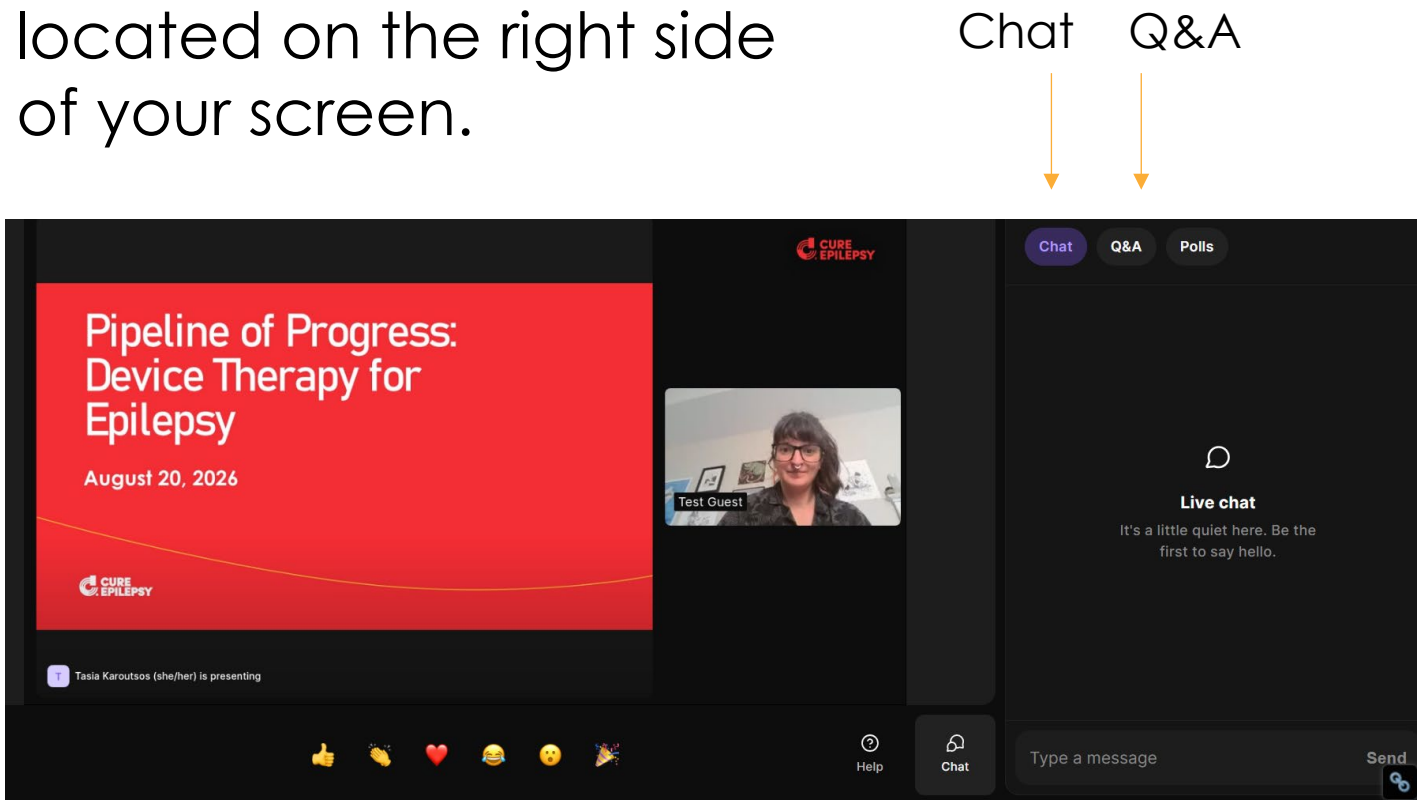
- Raised more than $100M and **funded over 300 epilepsy research projects** since 1998
- Fill critical funding gaps in foundational science to **expand our understanding of underlying biological processes that cause epilepsy**
- Broad and deep portfolio of funded research grants with a **bias towards high risk, high reward**
- **Strong track record of academic and industry grantees** who develop preliminary data with CURE Epilepsy funding, and ultimately secure exponentially larger government grants to advance their findings to new treatments and potentially cures

Today's Agenda

- Background on Neuromodulation and Device Approval
- Survey of the Latest Advances
- Q&A

Accessing Chat and Q&A

Chat and Q&A are located on the right side of your screen.



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Disclosures

Advisory Board

- NeuroPace, Inc.
- Xenon Therapeutics
- Mosaica Therapeutics
- Rapport Therapeutics

Consulting

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Background on Neuromodulation and Device Approval

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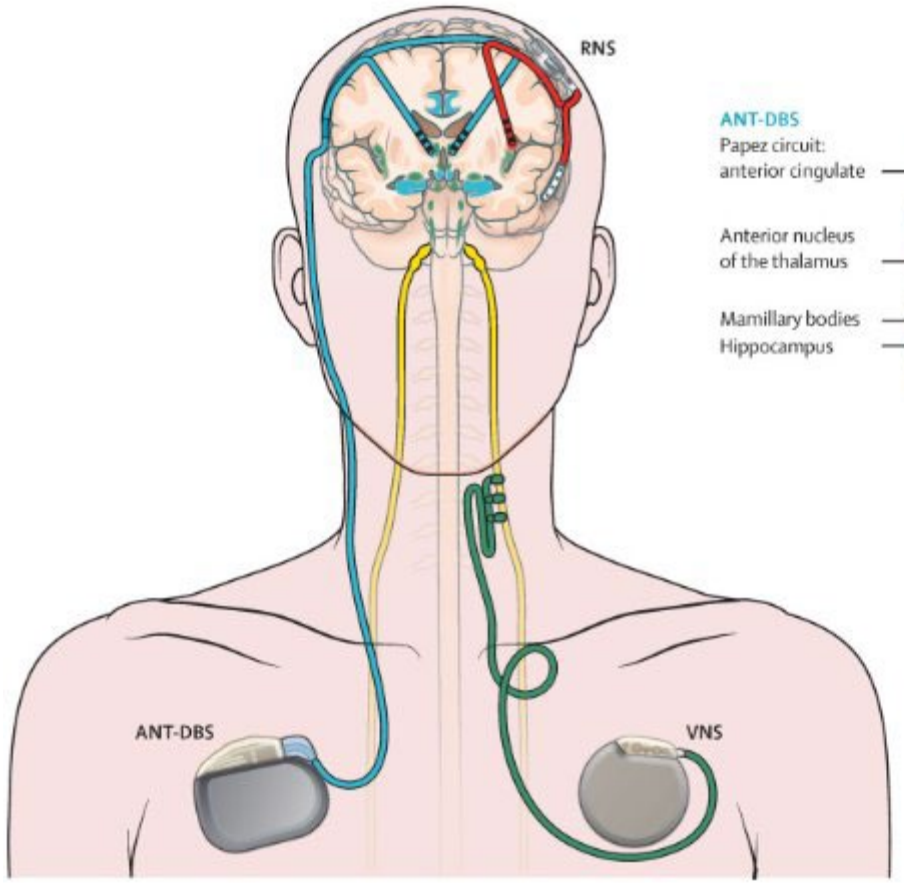
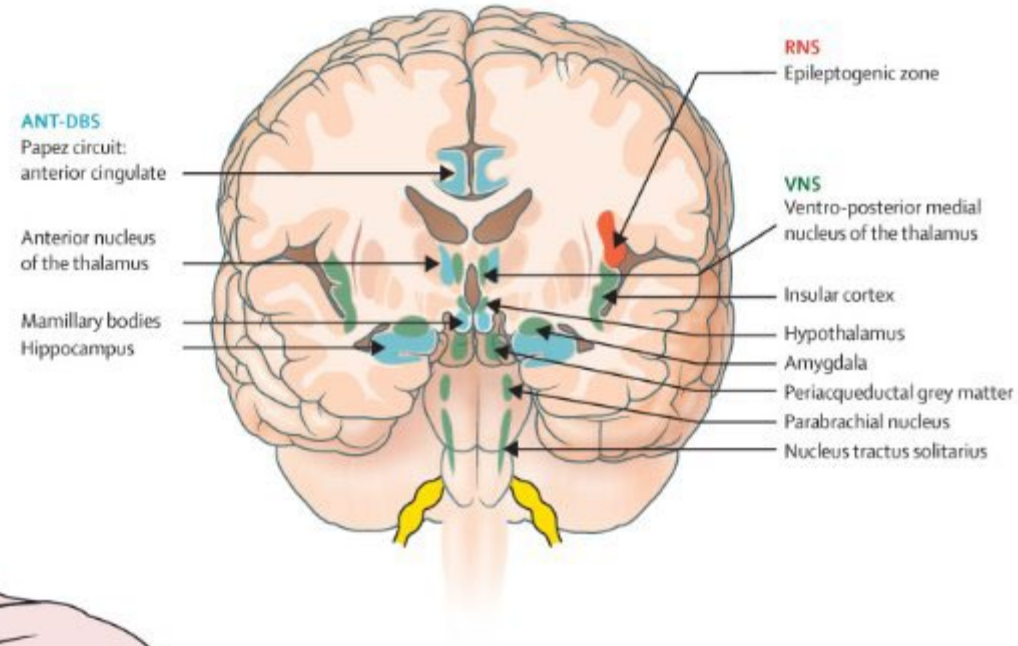
Neuromodulation Basics & Landscape





Path Towards FDA Device Approval –> First Determine Device Classification

Class 1

Low Risk

- May be exempt for the premarket submission process

Class II

Moderate Risk

- 510(k) submission
  - Can prove device is "substantially equivalent" to a legally marketed predicate device
- De novo classification (no predicate device)

Class III

High Risk

- Premarket Approval typically required
  - Clinical trial data to prove safety and effectiveness

RNS® System (NeuroPace): FDA Premarket Approval Timeline

From Investigational Device Exemption to Post-Approval Surveillance — responsive neurostimulation for drug-resistant partial-onset epilepsy

c. 2004

IDE Approved & Feasibility Study

FDA grants an Investigational Device Exemption; NeuroPace launches the RNS feasibility study, establishing safety data and the design for the pivotal trial.

1

2

2004–2009

Pivotal Clinical Trial

Prospective, randomized, double-blind, sham-stimulation-controlled trial; 191 patients with medically refractory partial-onset seizures enrolled at U.S. epilepsy centers.

Jul–Nov 2010

PMA Application Submitted

NeuroPace files its Premarket Approval application; after an initial data request, FDA formally accepts the PMA (Nov 9, 2010) based on pivotal-trial results.

3

4

Feb 22, 2013

Neurological Devices Panel Review

FDA's Neurological Devices Advisory Panel votes 11-0 (2 abstentions) that clinical benefits outweigh risks; recommends approval with post-approval study conditions.

Nov 14, 2013

FDA Grants PMA Approval

RNS System approved for adults with partial-onset seizures uncontrolled by ≥ 2 antiepileptic drugs — the first closed-loop responsive brain stimulator cleared in the U.S.

5

6

2013 → ongoing

Post-Approval Studies

Long-Term Treatment (LTT) study collects up to 7 additional years of safety/efficacy data beyond the pivotal trial; real-world registries continue long-term monitoring.

Sources: FDA/Federal Register (PMA P100026); NeuroPace, Inc. and Epilepsy Foundation press releases, 2010–2013.

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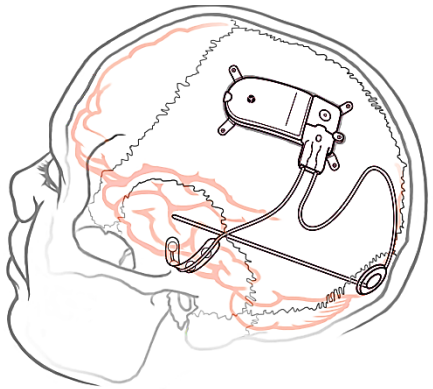
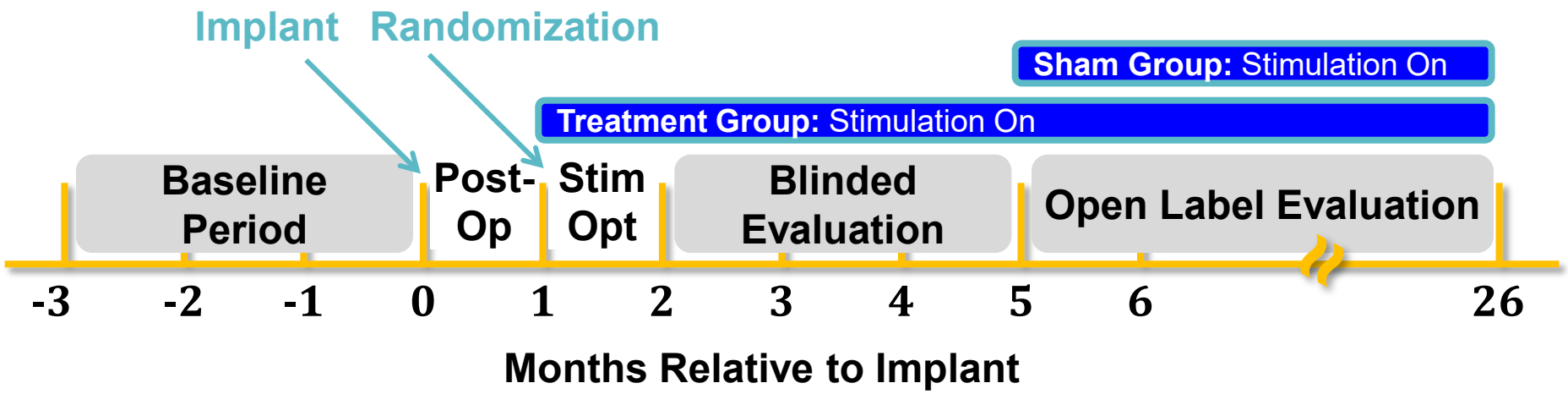
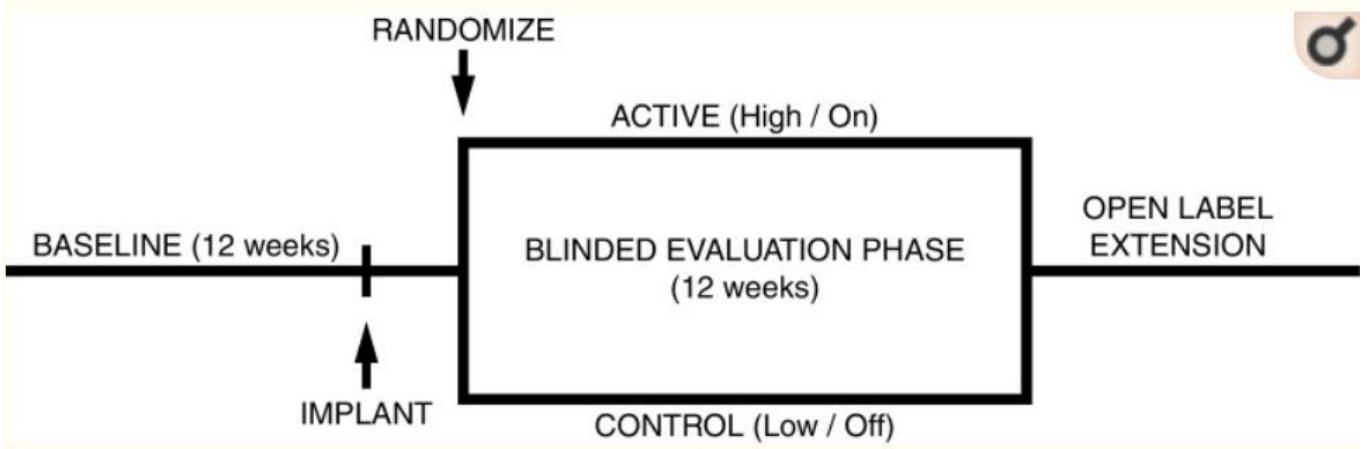
Pivotal Study Designs

RNS

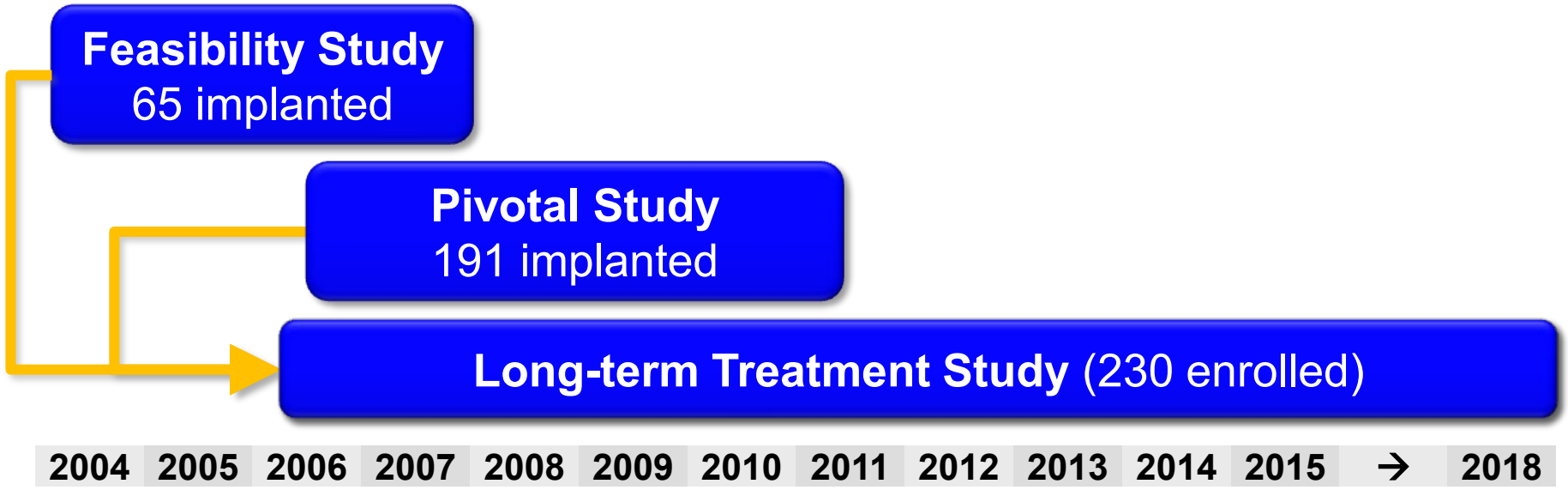




DBS



RNS System Clinical Studies



Ongoing post-approval study – 343 patients enrolled

History of Neuromodulation Devices

VNS

Vagal Nerve Stimulation

- First implant 1988
- FDA approval 1997
- Multiple versions of pulse generators
- Heart rate detection with responsive stim available 2015

RNS

Responsive Neurostimulation System

- FDA approval 11/2013

DBS

Deep Brain Stimulation

- Pilot unblinded studies early 2000s
- SANTE trial began 2003
- FDA approval 2018

Next Generation

Investigational Therapies

- RNS in other indications (LGS, IGE)
- Non-ANT DBS targets
- Transcranial electrical stimulation
- Temporal interference Stimulation
- Transcranial magnetic stimulation
- Focused Ultrasound
  - High intensity
  - Low intensity
  - Targeted drug delivery

Surgical Treatment Options for Drug-Resistant Epilepsy

Destructive Surgery

- Resective surgery
- Laser ablation
- *Radiofrequency* ablation
- *Focused ultrasound*

Extracranial Neuromodulation

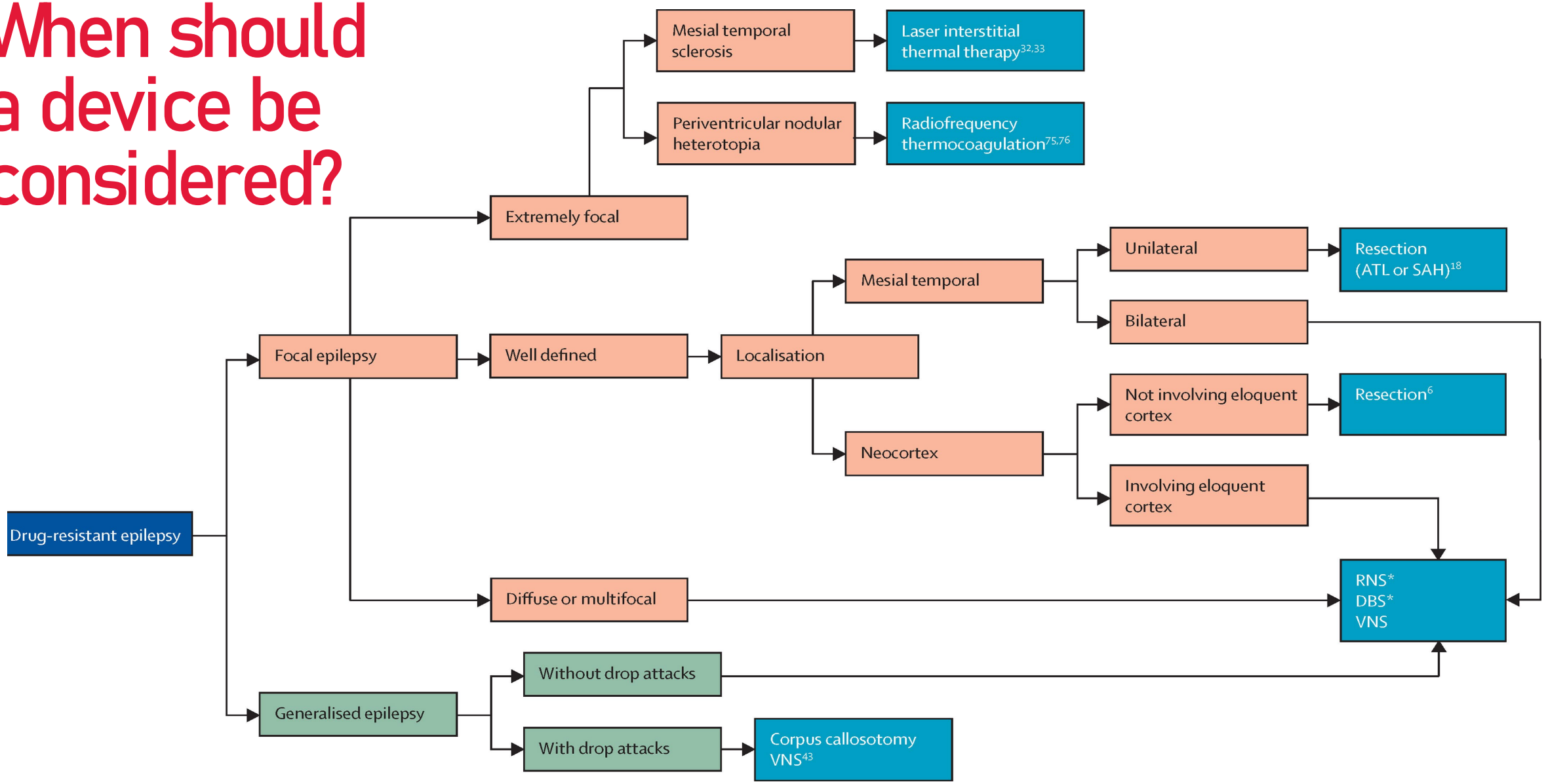
- Vagal nerve stimulation

Intracranial Neuromodulation

- Responsive neurostimulation system

- Deep brain stimulation

When should a device be considered?



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Yardi, et al., Lancet Neurology, 2026

Survey of the Latest Advances

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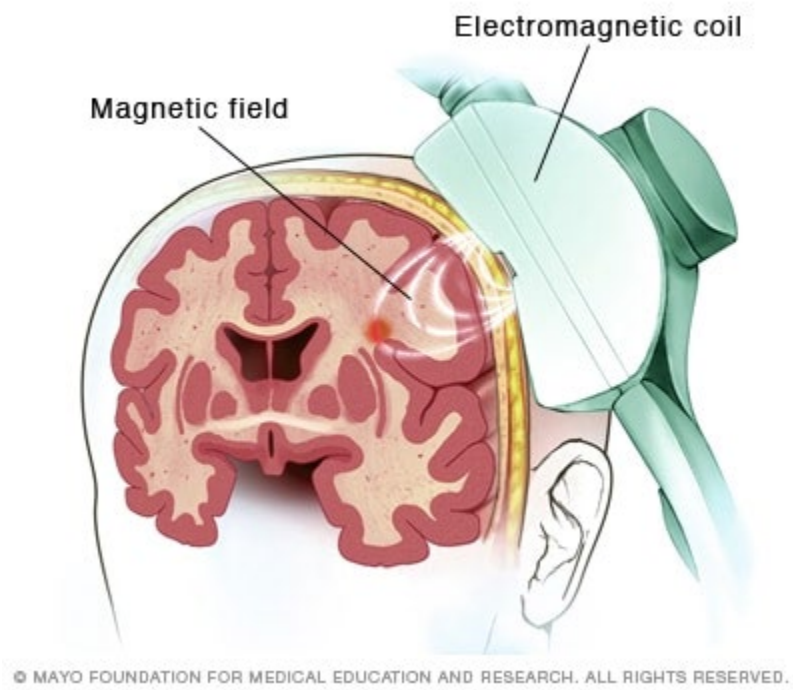
Transcranial electrical stimulation (tDCS, tACS)

Temporal interface stimulation (TI)

Transcranial magnetic stimulation (TMS)

Focused ultrasound (FUS)



Transcranial Electrical Stimulation (tDCS, tACS)

- tDCS applies a weak, constant electrical current (typically 1–2 mA) through scalp electrodes to modulate cortical excitability
- tACS instead applies an oscillating current to entrain or disrupt specific brain rhythms.
- Both are non-invasive, cheap, and portable compared to VNS/RNS/DBS, which all require surgical implantation.

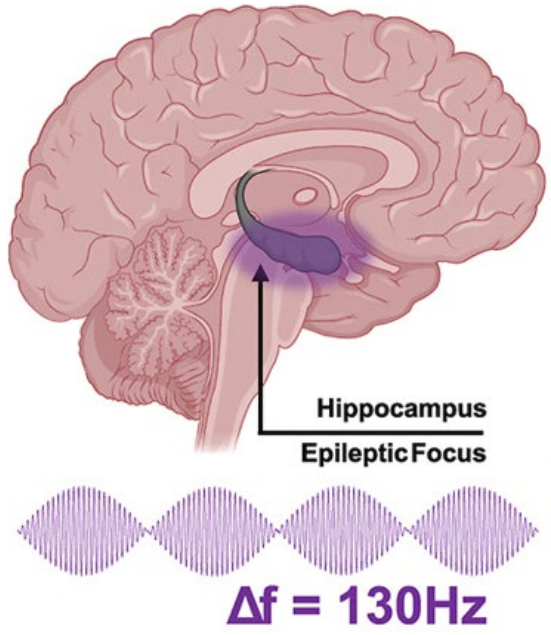
Transcranial Electrical Stimulation (tDCS, tACS)

- Main company developing - **Neuroelectrics** (STARSTIM device)
- **Pilot/feasibility study (NCT02866240)** — completed at Boston Children's Hospital (with adult patients referred from Beth Israel Deaconess) and a parallel site in Mexico City
  - 20 adult/pediatric patients with medically refractory focal epilepsy
  - Results: a 44% median reduction in seizure frequency at 8-week follow-up, with 4 patients seeing ≥75% reduction, and no device-related adverse events.
- **FDA Breakthrough Device Designation** —> granted in 2021 based on those pilot results, giving Neuroelectrics an expedited/more collaborative review track with the FDA.
- 2024 meta-analysis pooled 9 parallel RCTs with total of 267 patients with refractory focal epilepsy with significant seizure reduction at 4 and 8 weeks
- Cons
  - Trials still small, short duration and heterogeneous protocols
  - Durability beyond a few weeks not well established
- Neuroelectrics STARSTIM device completed a pivotal trial in 1/2026 (NCT04770337)
  - Trial meant to support a PMA submission
  - Results forthcoming

Hawas, et al., Neurological Sciences, 2024

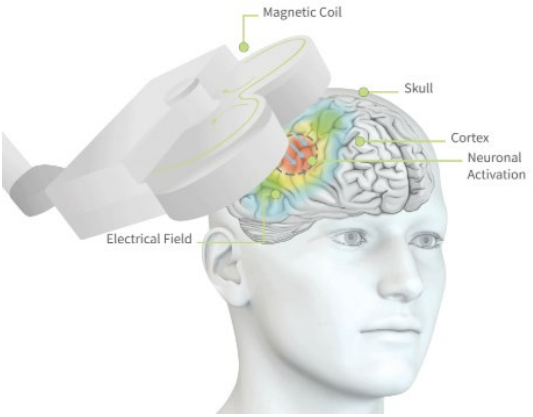
Temporal Interference (TI) Stimulation

- An emerging non-invasive brain therapy that targets deep brain structures like the hippocampus without surgery.
- Two or more high-frequency electrical currents are applied via scalp electrodes to provide neuron modulation where the overlapping frequencies cross
- Ongoing overnight TLE trials at Duke and UC Davis
- Pros
  - Deep brain access without affecting overlying cortex and scalp nerves
  - Demonstrated in pivotal trials to decrease pathological brain spikes and improve sleep rhythms in drug-resistant patients
  - Carry-over effect: suppresses abnormal neural activity even after the stimulation stops



Missey, et al., Brain Stimulation, 2026

Transcranial Magnetic Stimulation (TMS)



- TMS as a *technology* is well-established and FDA-approved — but only for other indications: depression (first approved 2008, Neuronetics NeuroStar), OCD, migraine, and smoking cessation.

- TMS uses a rapidly changing magnetic field from a scalp coil to induce small electrical currents in the brain non-invasively — no direct electrical contact with the skin. **Low-frequency repetitive TMS (rTMS)**, typically ~0.5 Hz, intended to induce long-term depression of excitability at the seizure focus

Transcranial Magnetic Stimulation (TMS)

- There are multiple established FDA cleared devices from companies
- rTMS trials in epilepsy have been run through academic medical centers using off the shelf TMS hardware
- 2020 Cochrane systematic review concluded the certainty of evidence for seizure reduction was low to very low, and that variability in technique and outcome reporting prevented even doing a formal meta-analysis
- Separate 2020 meta-analysis of 7 trials found rTMS did significantly reduce seizure frequency and epileptiform discharges overall, but suggested the effect was short-lived
- Pediatric data looks more promising — one sham-controlled trial in 49 children with focal drug-resistant epilepsy found 76% of patients on active rTMS achieved ≥50% seizure reduction vs. 12.5% on sham

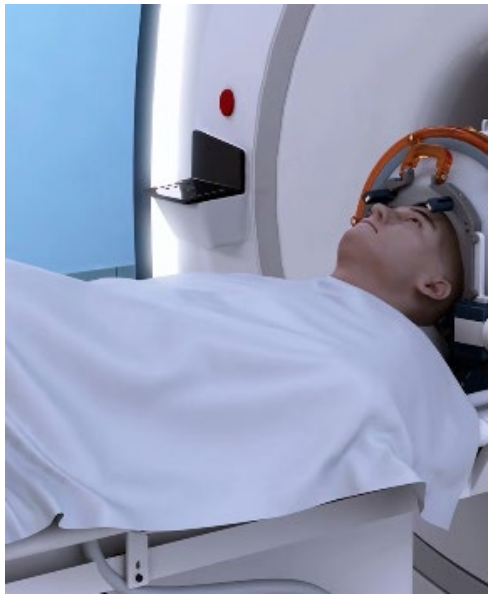
Chen et al., Cochrane, 2020; Mishra et al., J. Clin Neurology, 2020; Sinha et al., Seizure, 2025

Focused Ultrasound

- Focused ultrasound (FUS) delivers acoustic energy transcranially and non-invasively, capable of targeting deep brain structures at millimeter resolution
- **HIFU** – High-intensity Focused Ultrasound (ablation)
  - Uses thermal energy to permanently destroy targeted tissue — essentially a scalpel-free surgical alternative. It works by focusing many ultrasound beams through the intact skull to a single point, heating that spot to ablative temperatures (60–95°C) while sparing surrounding tissue
- **LIFU** – Low-intensity Focused Ultrasound (neuromodulation)
  - Uses much lower energy to transiently modulate neural excitability — closer in concept to RNS or DBS, but fully non-invasive and reversible, without any implanted hardware
- Ultrasound-mediated drug delivery (BBB opening)
  - **BBB disruption with microbubbles:** intravenously injected microbubbles are driven to cavitate by focused ultrasound at the target site, transiently and reversibly opening the BBB right at the seizure focus, letting drugs that normally can't cross get in.
  - **Non-BBB-opening delivery:** LIFU can also increase focal drug uptake without breaching the barrier at all, through mechanisms like reducing plasma protein binding or "drug uncaging" (activating an inert prodrug only at the sonication site).

HIFU

- FDA-approved device: InSightec's ExAblate Neuro system
  - Approved for ablating the thalamus for essential tremor (2016) and Parkinson's tremor (2018)
- Few small trials in epilepsy thus far
  - Hypothalamic hamartomas
  - Hippocampus
  - Anterior nucleus of the thalamus (ExAblate—estimated completion 2028)
- Pro
  - non-invasive substitute for existing ablative surgeries (e.g. laser interstitial thermal ablation)



LIFU

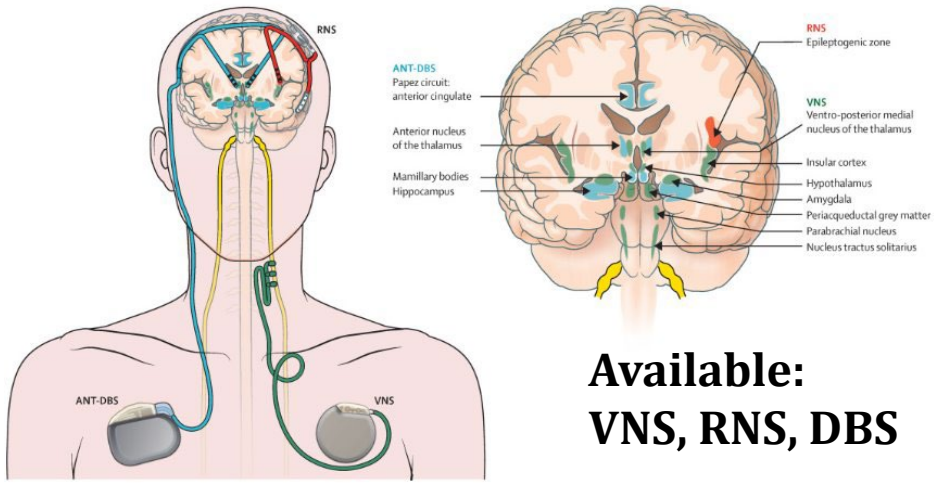
- No current FDA-approved device for epilepsy. Multiple companies with devices in trials (e.g., BrainSonix for TLE completing 2026, NaviFUS for TLE completing 2027, InSightec for focal TBD)
- CURE Funding
  - Dr. Ellen Bubrick: dose testing in TLE patients
  - Dr. Ivan Soltesz: LIFU in animal models of LGS
- Pros
  - Potential non-invasive substitute for existing invasive neuromodulation devices
  - Safety – no tissue damage in patients who underwent LIFU prior to temporal lobectomy
- Cons
  - Unclear duration of therapy
  - Few pilot trials in focal epilepsy thus far
  - Unclear where/how to best target in the brain

Ultrasound mediated drug delivery

- BBB disruption with microbubbles:
  - Technique has been tested in other diseases and in an animal model of epilepsy
  - No in human trials in epilepsy yet

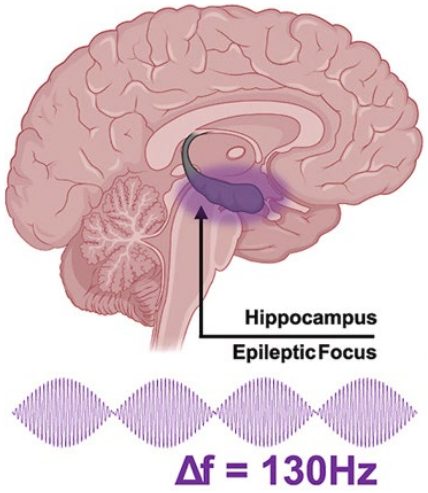
- NaviFUS Corp has developed microbubble-enhanced transcranial LIFU technology specifically for CNS drug delivery

Neuromodulation in the Future

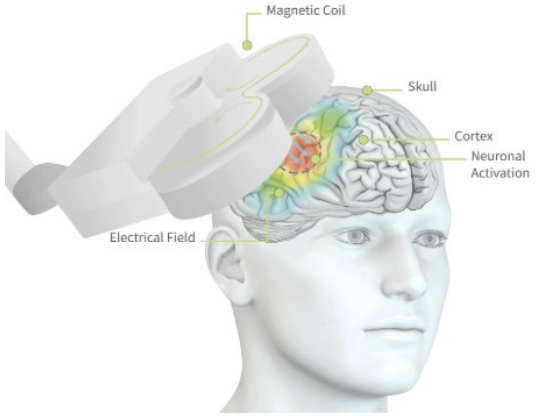


Available:
VNS, RNS, DBS

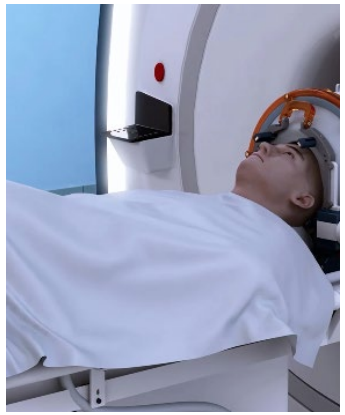
tDCS, tACS



Temporal Interference



TMS



HIFU

LIFU

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THANK YOU!