



AANS Annual Meeting
Community Session 513: Focus on Emerging Treatments of the Nervous System:
Science, Technology and Clinical Application
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Neuromodulation in Neuroscience: From Epilepsy and Parkinson Disease... And Beyond! (in 20 minutes 🍊🍊)

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Disclosures

Company

Medtronic
 Neuropace
 Boston Scientific
 Zimmer Biomet
 NeuroOne
 Nia Therapeutics
 CODA Therapeutics

Financial Interest

Consultant, clinical research grant, fellowship
 Consultant, clinical research grant
 Clinical research grant, fellowship
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 Consultant
 Stock
 Consultant

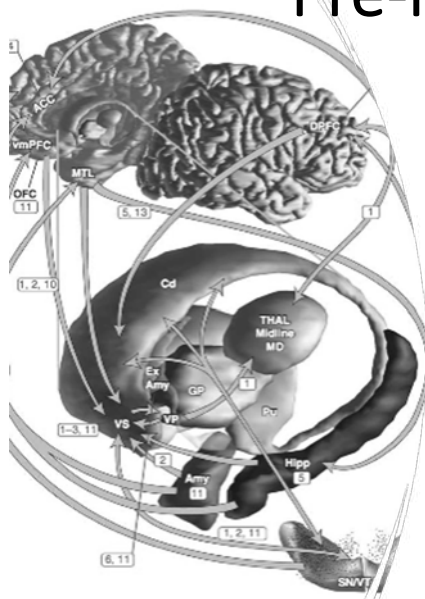
Dr. Gross serves as a consultant to Medtronic, Inc. and receives compensation for these services. Medtronic and Neuropace develop products related to the research described in this presentation. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

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Pre-requisite concepts



Susan Haber et al.

- **Neural NETWORKS** underlie ALL neurological **function**
- → **Neural NETWORKS** underlie ALL neurological **DYS-function** (not a motor cortex stroke that is the problem...but connection to MNs and muscle...)
- → Must **Modulate** the **Neural Network** to ameliorate neurological dysfunction
- = **Neuromodulation**
- **Tools:**
 - Pharmacological (e.g., ASMs, L-dopa, NSAID, baclofen, etc.)
 - Electrical (e.g., DBS, VNS, SCS, RNS, TDCS, etc.)
 - Magnetic (TMS)
 - Ultrasound (FUS)
 - Gene-based (opto-genetics)

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Electrical neuromodulation in neurosurgery: 2026

Approved Indications/Targets

- SCS* (510k, 1989; PMAs 1990s)
- VNS for focal epilepsy
- DBS (Vim thalamus) for ET
- DBS (STN, globus pallidus) for PD
- DBS (GP) for primary dystonia* (HDE,)
- RNS for focal epilepsy (2014)
- DBS (ANT) for focal epilepsy (2018)
- DBS (ALIC) for OCD* (HDE,)
- Occipital nerve stimulation for pain
- VNS for stroke rehabilitation (

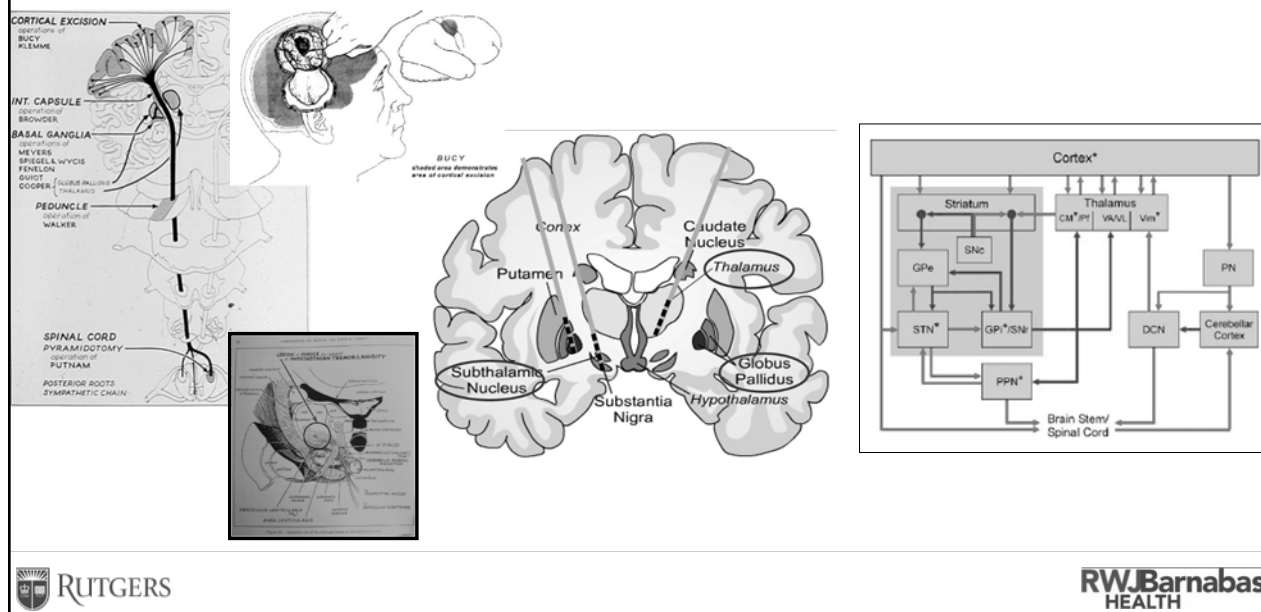


Investigational Indications/Targets

- Movement disorders
 - DBS for Tourettes
 - DBS for HD, secondary dystonia
 - DBS for freezing of gait
- Epilepsy
 - DBS other targets for focal epilepsy
 - DBS/RNS for generalized epilepsy
- Pain
 - DBS
 - Trigeminal stimulation
- Psychiatric disorders other than OCD
- DBS for Alzheimers disease
- Neuro-inflammation
 - VNS

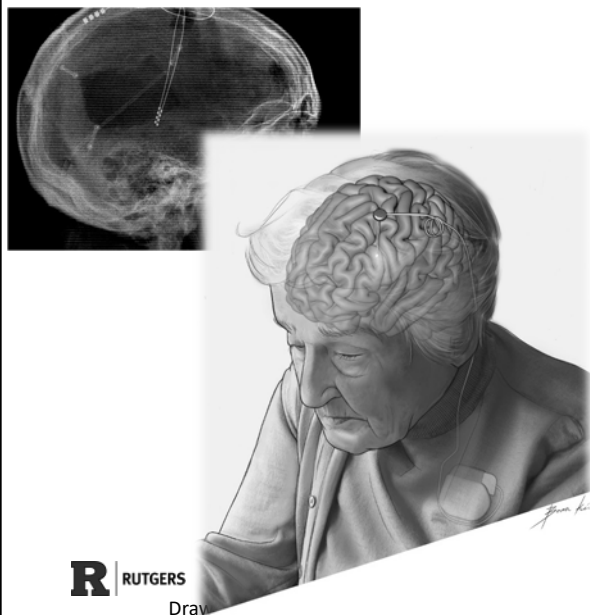
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Movement disorders: Evolution from cortical to subcortical destructive targets... to circuit neuromodulation...and back!



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DBS – pacemaker for the brain



- Implanted pulse generator sends continuous, brief electrical pulses into brain areas responsible for various functions
- Mechanism(s)?
 - Inhibits? (functional lesion)
 - Activates?
 - Inhibits by activating?

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Basic DBS equipment

Brain electrode



IPG/Battery



+ extension cable

Patient programmer



Clinician programmer



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STN DBS is effective treatment for advanced PD

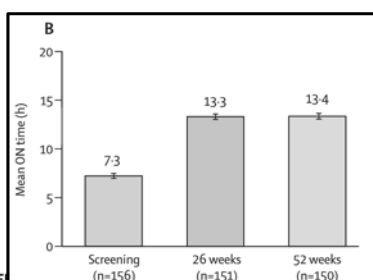
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

2003

Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease

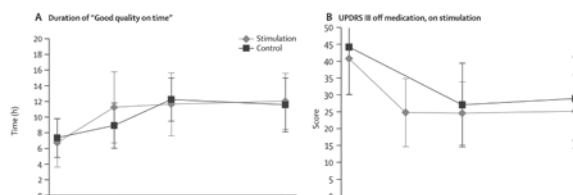
Paul Krack, M.D., Ph.D., Alina Batir, M.D., Nadège Van Blercom, M.D., Stephan Chabardes, M.D., Valérie Fraix, M.D., Claire Ardouin, M.A., Adnan Koudsie, M.D., Patricia Dowsey Limousin, M.D., Ph.D., Abdelhamid Benazzouz, Ph.D., Jean François LeBas, M.D., Ph.D., Alim-Louis Benabid, M.D., Ph.D., and Pierre Pollak, M.D.



Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial

Lancet Neurol 2012

Michael S Okun, Bruno V Gallo, George Mandybur, Jonathan Jagid, Kelly D Foote, Freddy J Revilla, Ron Alterman, Joseph Jankovic, Richard Simpson, Fred Junn, Leo Verhagen, Jeff E Arle, Blair Ford, Robert R Goodman, R Malcolm Stewart, Stacy Horn, Gordon H Baltuch, Brian H Kopell, Frederick Marshall, Delia Peichel, Rajesh Pahwa, Kelly E Lyons, Alexander I Tröster, Jerrold L Vitek, Michele Tagliati, for the SJM DBS Study Group*



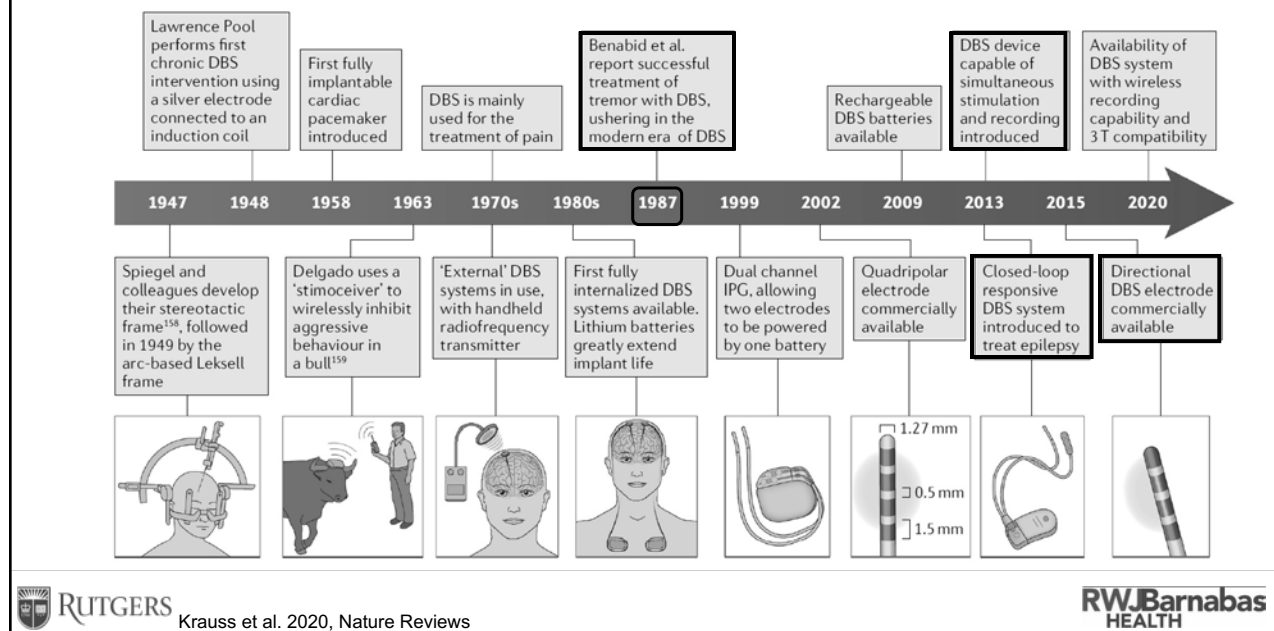
Subthalamic nucleus deep brain stimulation with a multiple independent constant current-controlled device in Parkinson's disease (INTREPID): a multicentre, double-blind, randomised, sham-controlled study

Lancet Neurol 2020

Jerrold L Vitek, Rashini Jain, Lily Chen, Alexander I Tröster, Lauren E Schrock, Paul A House, Monique L Giroux, Adam O Hebb, Sierra M Farris, Donald M Whiting, Timothy A Leichter, Jill L Ostrem, Marta San Luciano, Nicholas Galifianakis, Leo Verhagen Metzman, Sepehr Sani, Jessica A Karl, Mustafa S Siddiqui, Stephen B Tatter, Itzhakul Haq, Andre G Machado, Michal Gostkowski, Michele Tagliati, Adam N Mamelak, Michael S Okun, Kelly D Foote, Guillermo Moguel-Cobos, Francisco A Ponce, Rajesh Pahwa, Jules M Nazzari, Cathrin M Buretefisch, Robert E Gross, Cornelia C Luca, Jonathan R Jagid, Gonzalo J Revuelta, Istvan Takacs, Michael H Pourfar, Alan Y Magilner, Andrew P Duker, George T Mandybur, Joshua M Rosenow, Scott E Cooper, Michael C Park, Suketu M Khandhar, Mark Sedrak, Fenna T Phibbs, Julie G Pilitsis, Ryan J Ulitt, Philip A Starr

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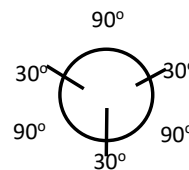
DBS history



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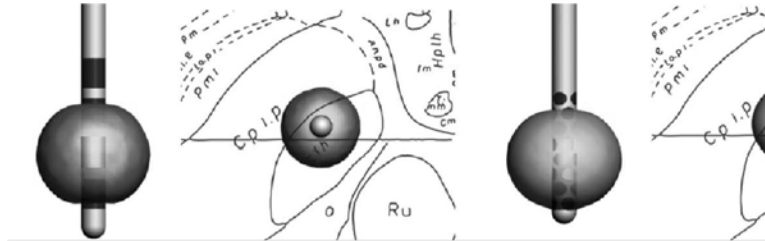
FDA approved segmented leads

- All 3 U.S. manufacturers
- 8 contacts in 1-3-3-1 configuration
- 3 segments can be simultaneously activated to simulate ring contact

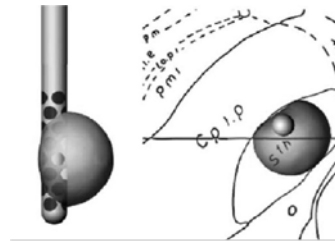


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Directional (segmented) leads



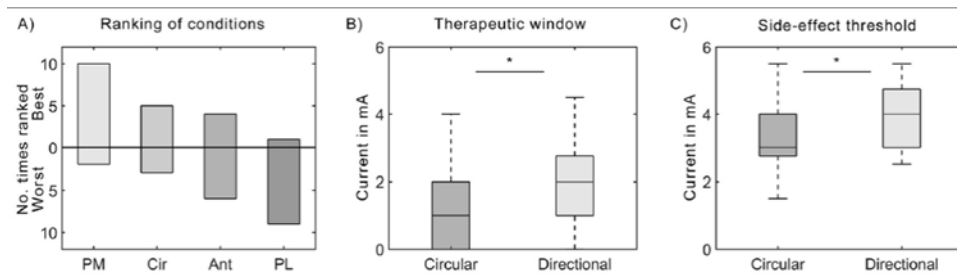
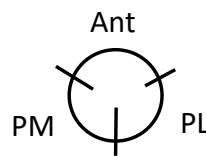
- Programming can be limited by ring contacts with symmetric distribution of electrical field



Contarino et al, Neurology 2014

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Directional DBS study: *Increased therapeutic window*

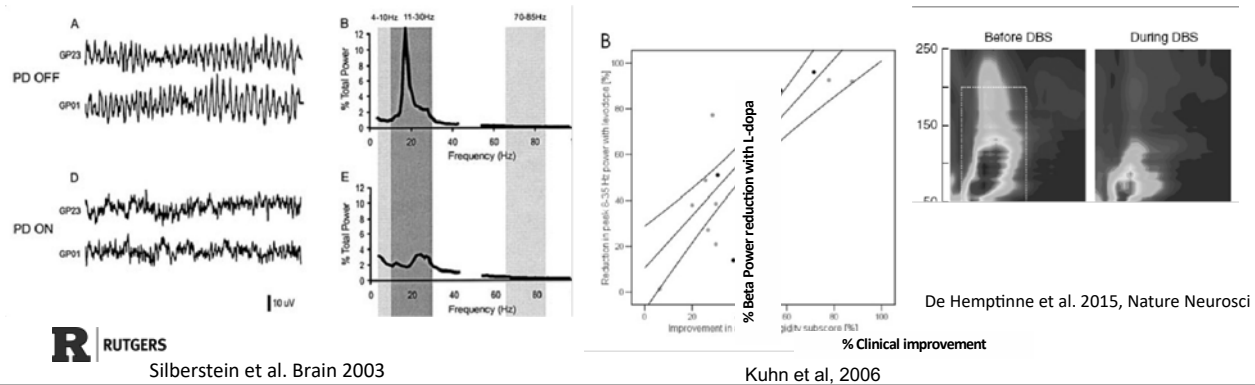


Dembek et al 2017, Movement Disorders

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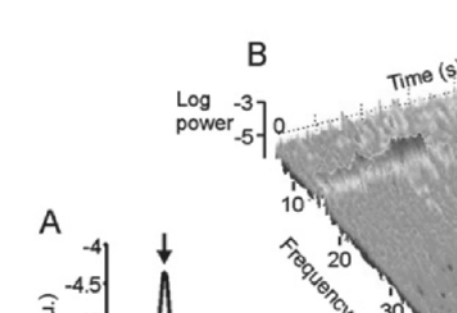
Network mechanisms: *Recording* LFP beta power elevated in PD in basal ganglia and motor ctx

- Exaggerated beta band (13-30Hz) power in basal ganglia nuclei in PD (Silberstein et al 2003; Brown et al 2005)
- Proportional to akinesia/rigidity severity (Kuhn et al 2006)
- Reduced by levodopa and DBS (Kuhn et al 2006, 2008; Giannicola 2010)



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DBS reduces elevated beta power

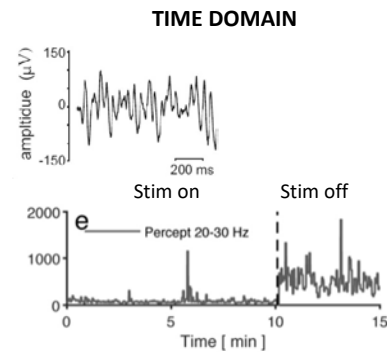
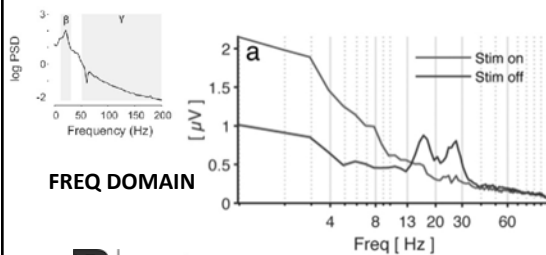


Eusebio et al. J NNP 2011

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Chronic brain recordings

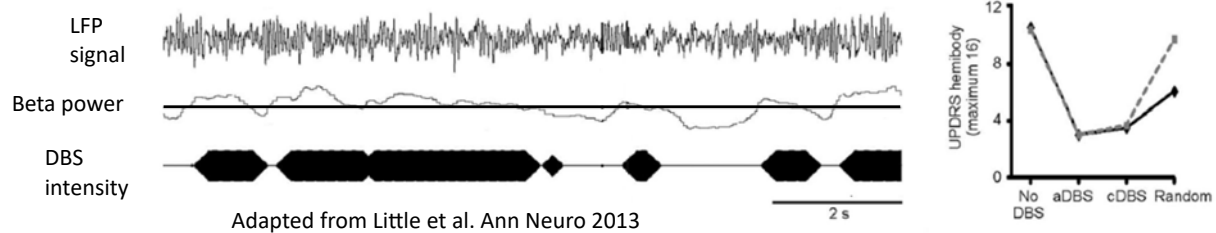
- Medtronic Percept
- Inactive DBS contacts can be used to record local field potentials (LFP) chronically ('sensing' mode)
- Pathway to adaptive (true closed-loop) DBS



Koeglsperger et al 2021, Acta Neurochirurgica

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LFP beta power – Adaptive DBS pilot study



- Many pilot trials
- Early Adapter 1 study (Japan)
- ADAPT-PD study (N. America & Europe)

- Challenges:
 - control signal (LFP, ECoG...)
 - control algorithm
 - clinical adoption
 - implementation



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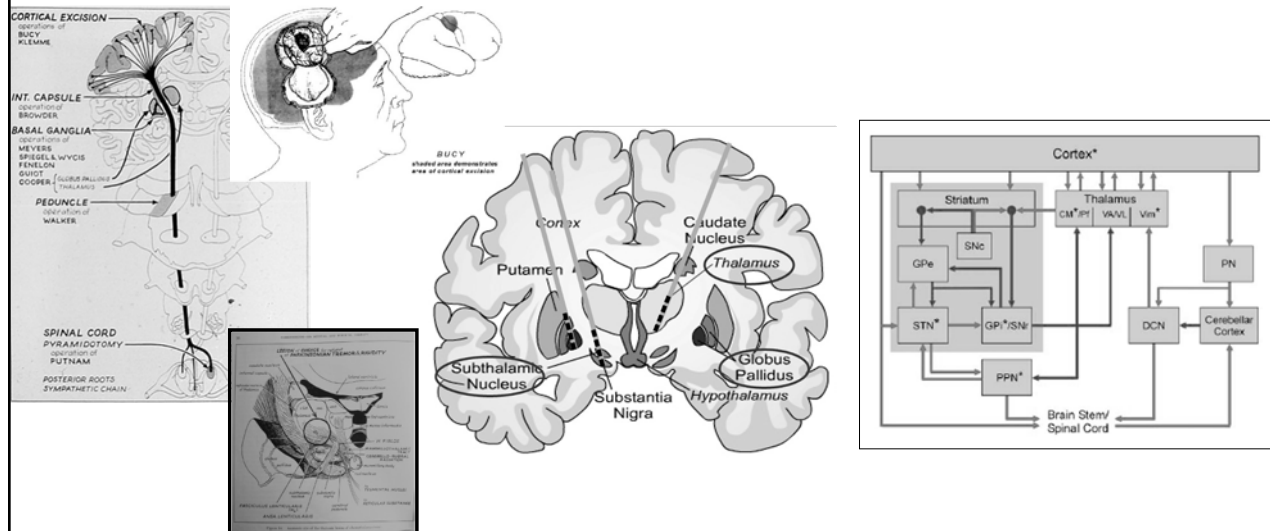
DBS for PD: Limitations

- It is not a cure
- Hardware; requires battery change or recharging
- It does not replace dopaminergic medications
- **Will not treat non-motor symptoms (cognition, depression, lightheadedness, constipation, sleep)**
- **May not improve balance, freezing when walking, speech and swallowing**



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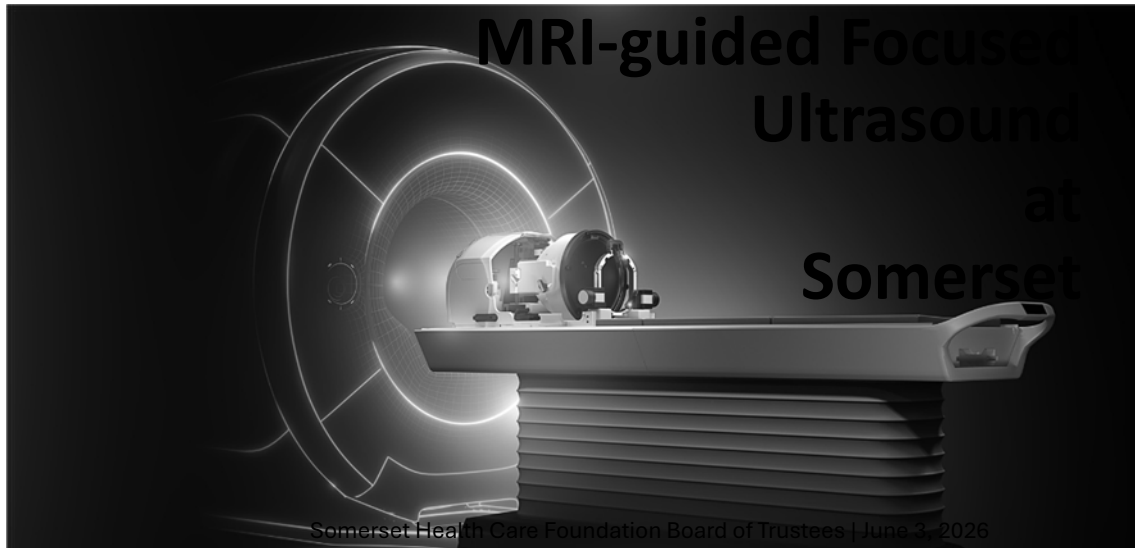
Movement disorders: Evolution from cortical to subcortical destructive targets... to circuit neuromodulation...and back!



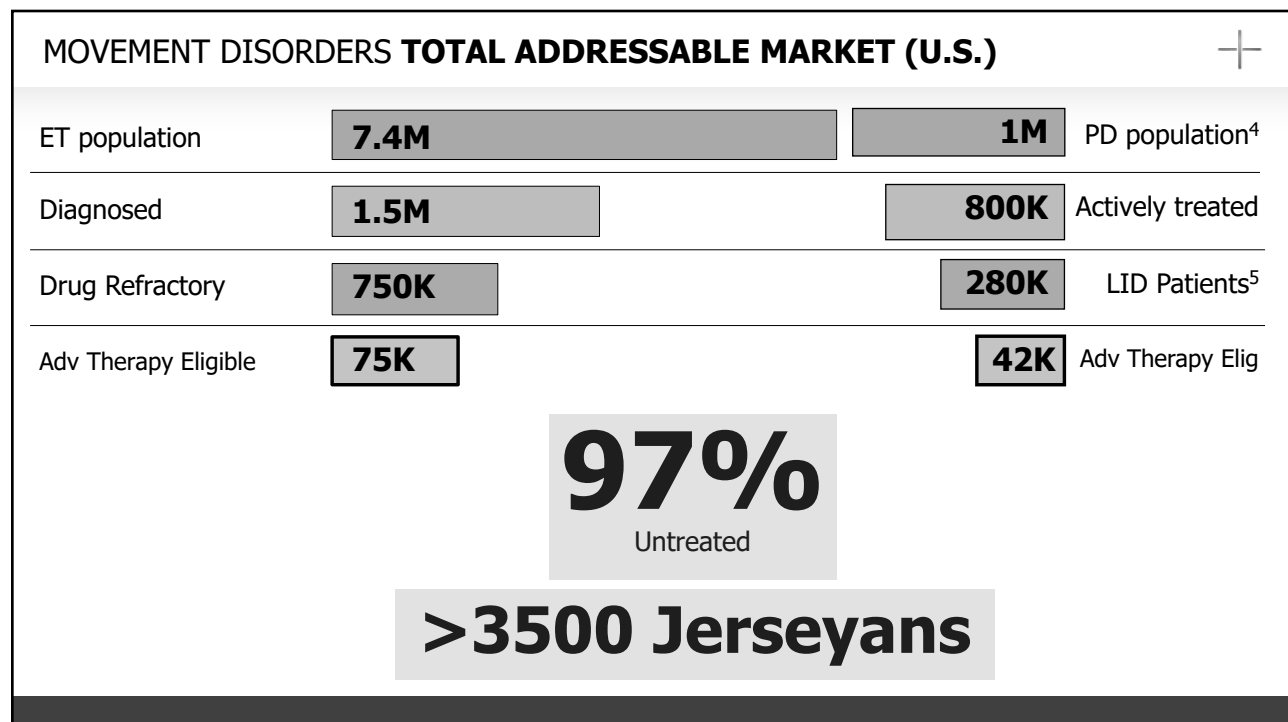
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What's the FUS?



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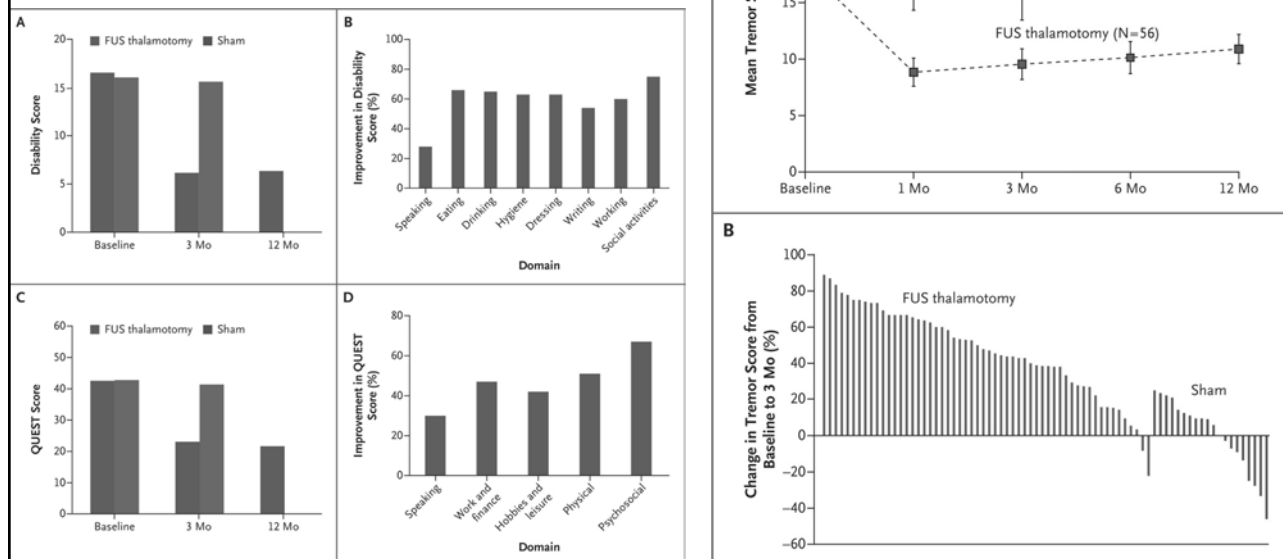
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FOCUSED ULTRASOUND PROCEDURE



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RCT (Elias et al. 2016)



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THREE-YEAR CLINICAL RESULTS

76.5%

tremor improvement
at three-year follow-up⁶

What are patients telling us?

- Tremor relief
- Psychosocial benefit
- Physical perception
- Return to work and financial position
- Enjoyment from hobbies + leisure

6. [Pre-Market Approval \(PMA\) P150038](#)

After treatment, the most common adverse events

(AEs) included:

- imbalance/gait disturbance (26% of study subjects)
- numbness/tingling (33% of study subjects)
- headache/head pain (51% of study subjects)

Of all AEs, 48% resolved within 30 days. Additional infrequent events include dizziness, taste disturbance, slurred speech, fatigue and vomiting

At three-years, persistent AEs included⁶:

- imbalance (4% of study subjects)
- unsteadiness (4% of study subjects)
- gait disturbance (2% of study subjects)
- musculoskeletal weakness (2% of study subjects)
- numbness/tingling (9% of study subjects)

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THREE-YEAR CLINICAL RESULTS

73.1%

tremor improvement
at **five-year** follow-up⁶

What are patients telling us?

- Tremor relief
- Psychosocial benefit
- Physical perception
- Return to work and financial position
- Enjoyment from hobbies + leisure

6. [Pre-Market Approval \(PMA\) P150038](#)

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Data is from Insightec-sponsored clinical subjects of 40 subjects at 5-year time point.

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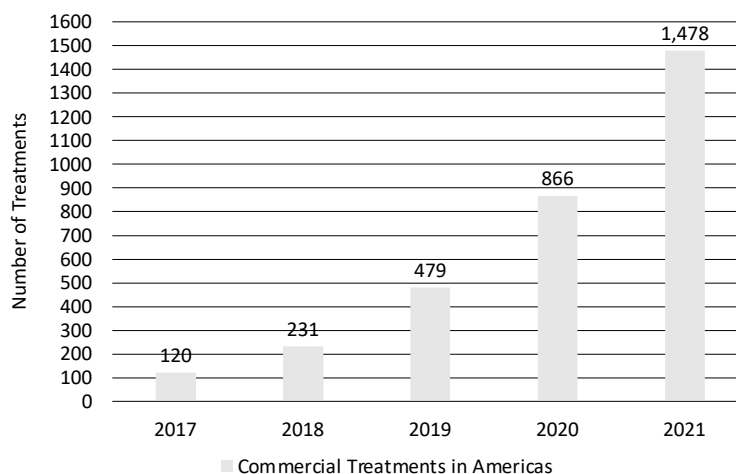
BECOMING STANDARD CARE FOR TREATMENT OF ESSENTIAL TREMOR

1,132%

growth in commercial focused ultrasound treatments for essential tremor from 2017 to 2021 in the Americas⁵

- Average treatment time of 2.5 hours
- 39 commercial Exablate Neuro systems treating essential tremor patients in 2021⁵
- Over 5,900 commercial treatments performed globally from 2017 to 2021⁵

4. Data provided by Insightec as of December 31, 2021



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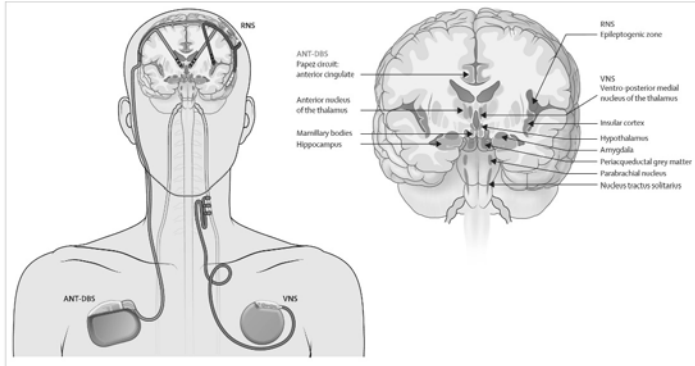
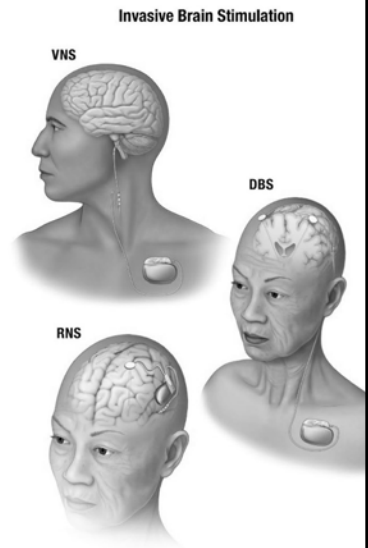
Neuromodulation for movement disorders: *Other coming advances*

- Novel and modifiable stimulation patterns
 - Opto-DBS: DBS informed by gene-based optogenetic neuromodulation
 - Coordinated reset
- Gene-based neuromodulation
 - Opto-genetics
 - Magneto-genetics
 - Chemo-genetics
- Cell based neuromodulation
 - Ongoing trials with hES and iPS-derived DA neurons
- MR-guided Focused Ultrasound
 - Back to the future

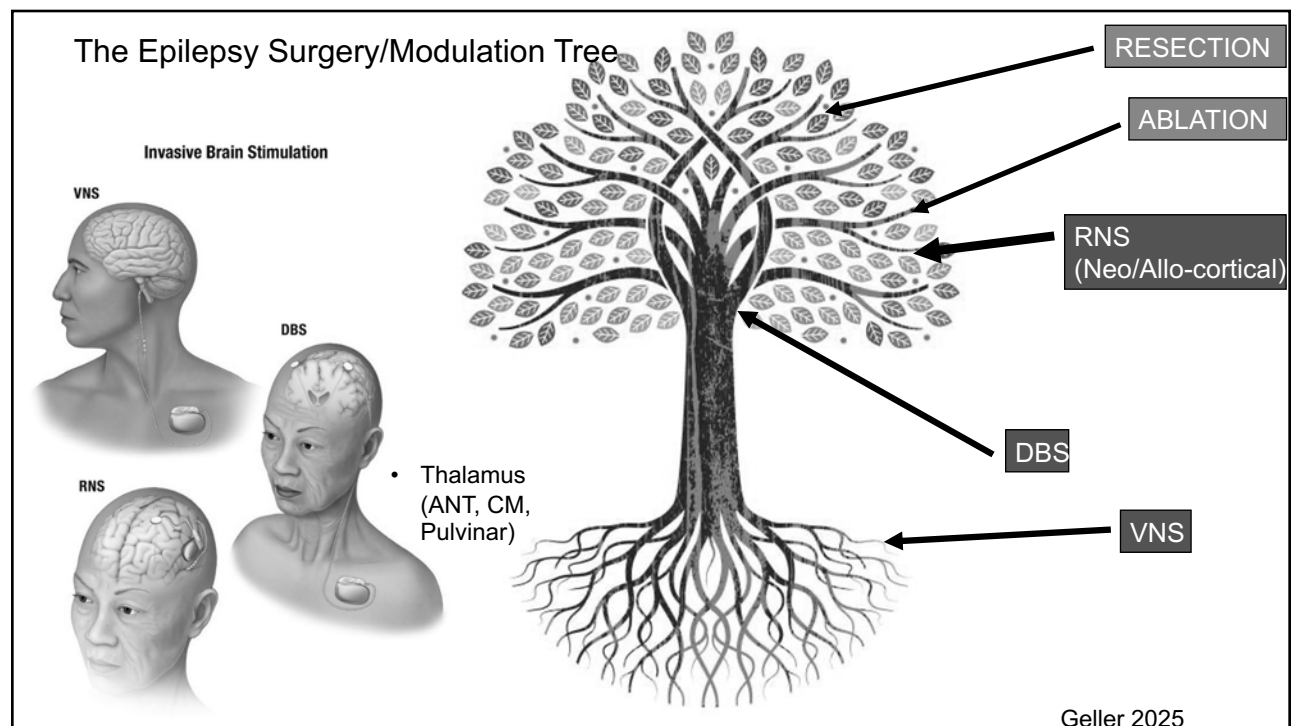
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TABLE 1 Device regulatory approvals in the United States and European Union

	Manufacturer(s)	Approved ages	FDA approval	Year approved	CE mark	Year approved
VNS	Cyberonics/ LivaNova	≥4 years	Focal ^a epilepsy	2017 (latest), 1997 (original)	Focal and generalized epilepsy	2018 (latest), 1994 (original)
DBS-ANT	Medtronic	≥18	Focal ^a epilepsy, ≥6 seizures/ month	2018	Focal epilepsy	2010
RNS	Neuropace	≥18	Focal ^a epilepsy with one or two foci ^a , ≥3 seizures/ month	2013	N/A	N/A

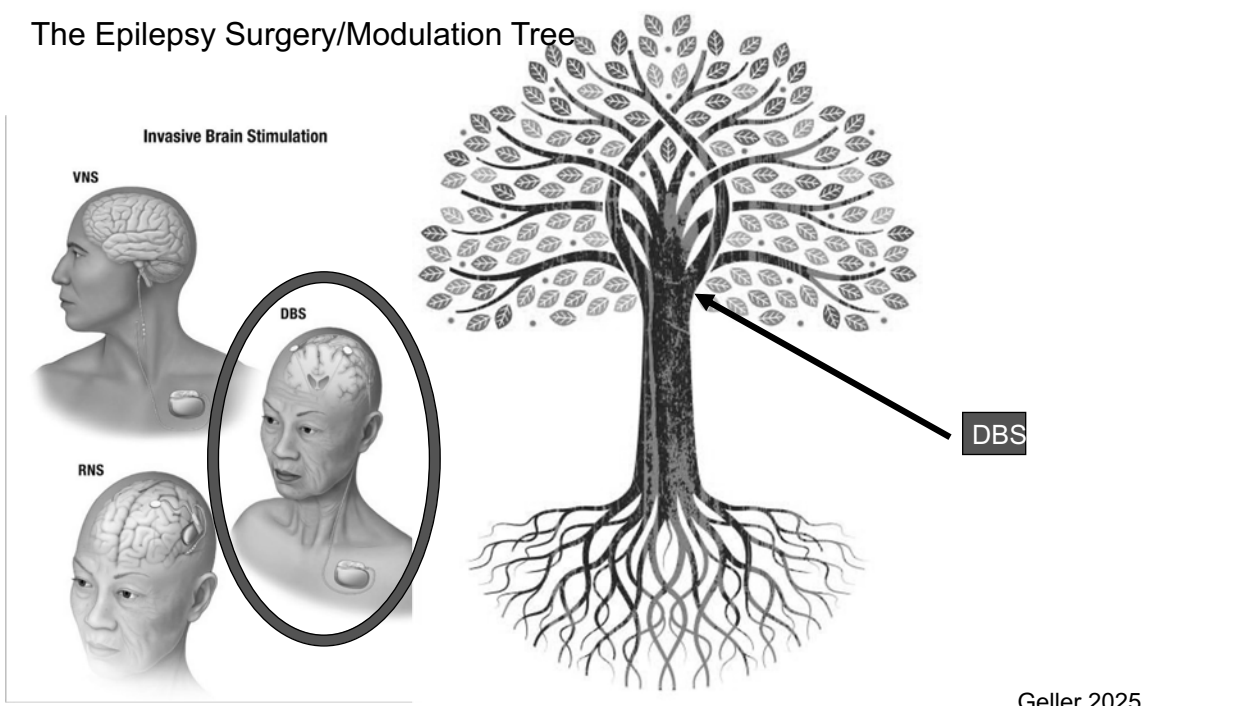
Simpson *et al.*, *Epilepsia*, 2022Ryvlin P, *et al.*, *Lancet Neurol.* 2021

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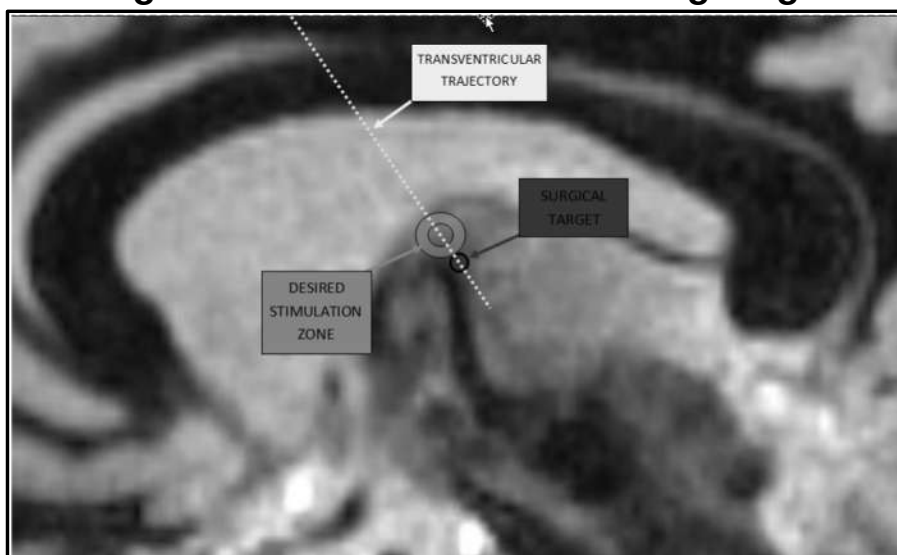
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The Epilepsy Surgery/Modulation Tree



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Surgical Considerations: Direct targeting vs ACPC



Broad range of ACPC coordinates¹

X = 5-6 mm lateral
Y = 0-2 mm anterior
Z = 10-12 mm superior

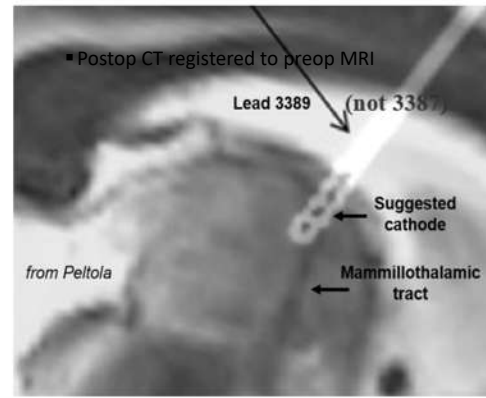
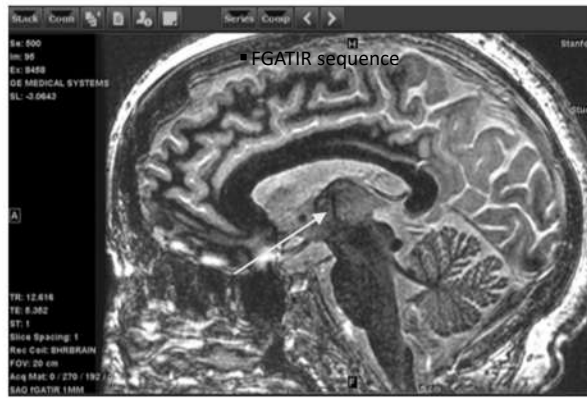
¹Medtronic SANTE Study

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Medtronic Engineering the extraordinary

ACCURATE TARGETING VERIFICATION IS CRITICAL

Fiducials = Trust --- "Trust, But Verify" ^{RR}



From Lehtimäki and also Jiltsova et al. Imaging of anterior nucleus of thalamus using 1.5T MRI for deep brain stimulation targeting in refractory epilepsy. *Neuromodulation: Tech at Interface*. 2016;19: 812-817.

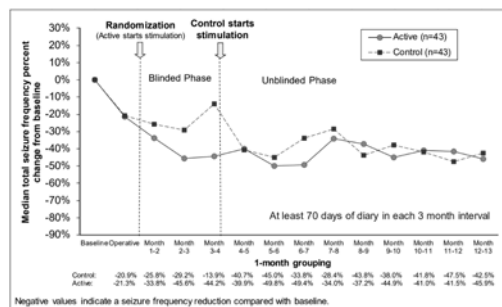
UC202210812EN DBS AES Fisher FY22

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ANT-DBS is GOOD (not great)

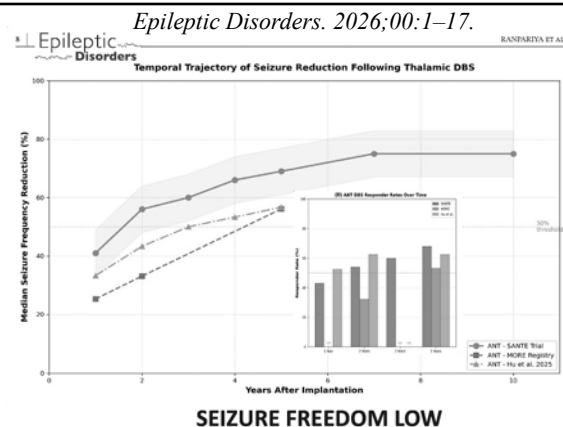
Neither is GREAT

- ~70% of 50% reduction
- 10-20% seizure freedom

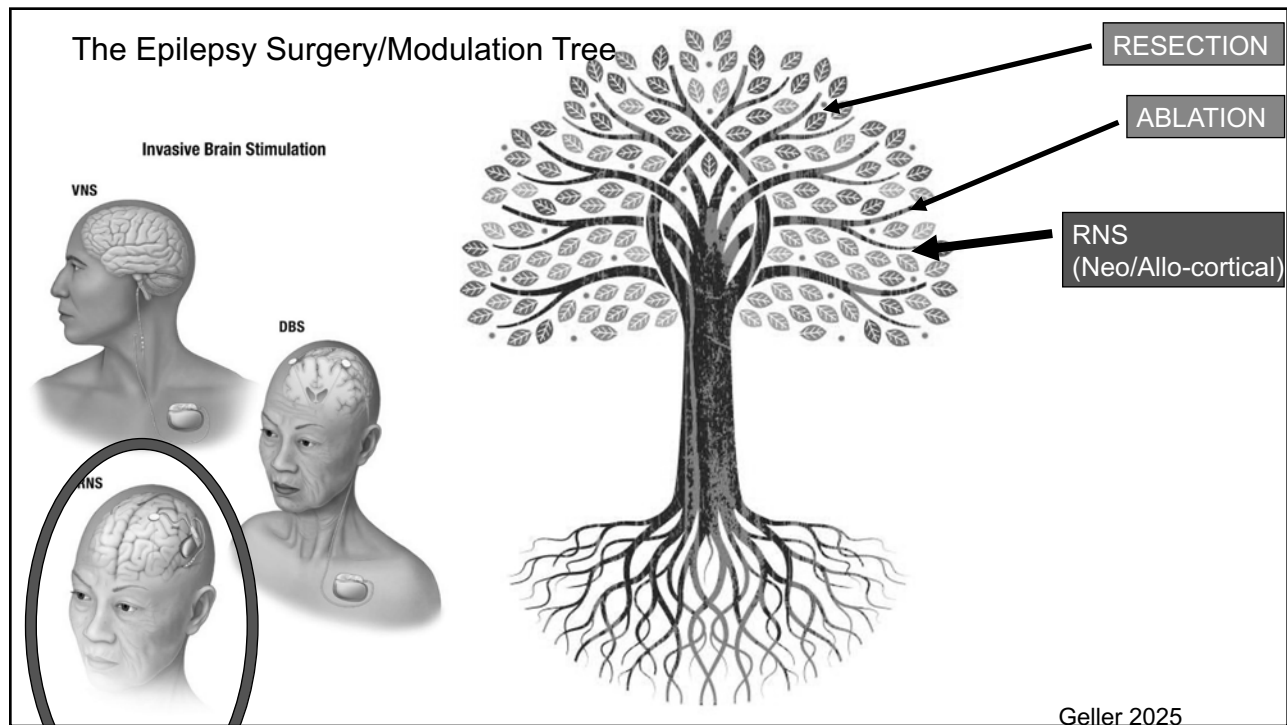


Fisher et al., *Epilepsia*, 2010

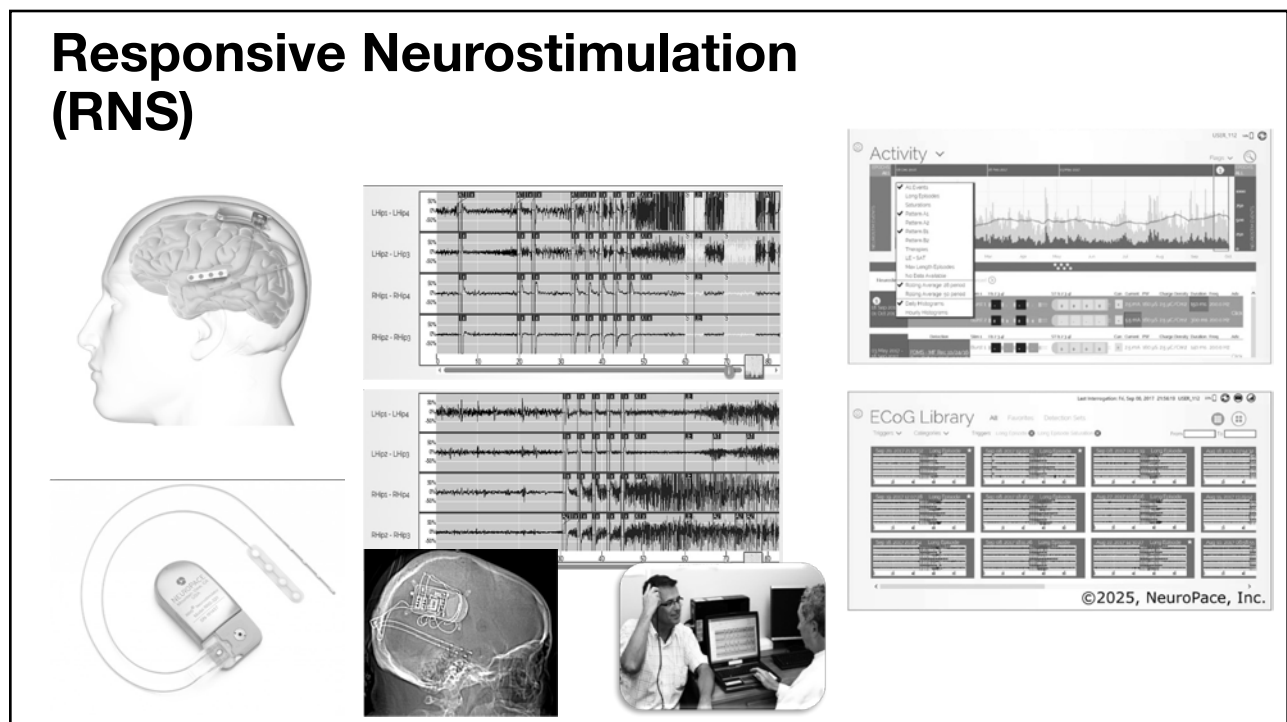
Salanova et al., *Epilepsia*, 2021
10 years open-label results



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Centromedian region thalamic responsive neurostimulation mitigates idiopathic generalized and multifocal epilepsy with focal to bilateral tonic-clonic seizures

Pranav Nanda^{1,2} | Nathaniel Sisterson^{1,2} | Ashley Walton^{1,3} | Catherine J. Chu⁴ | Sydney S. Cash⁴ | Lidia M. V. R. Moura⁴ | Joel M. Oster⁵ | Alexandra Urban⁶ | Robert Mark Richardson^{1,2,3}

Nanda, *Epilepsia*, 2024

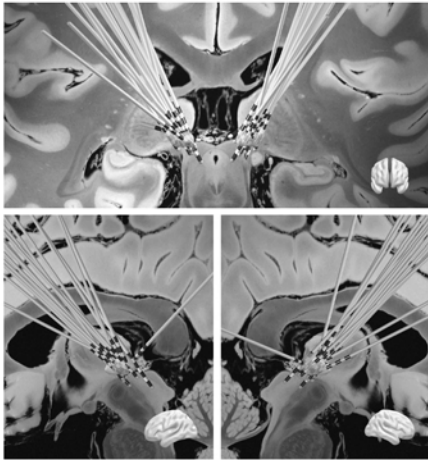


TABLE 1 Patient characteristics before and after RNS implantation.

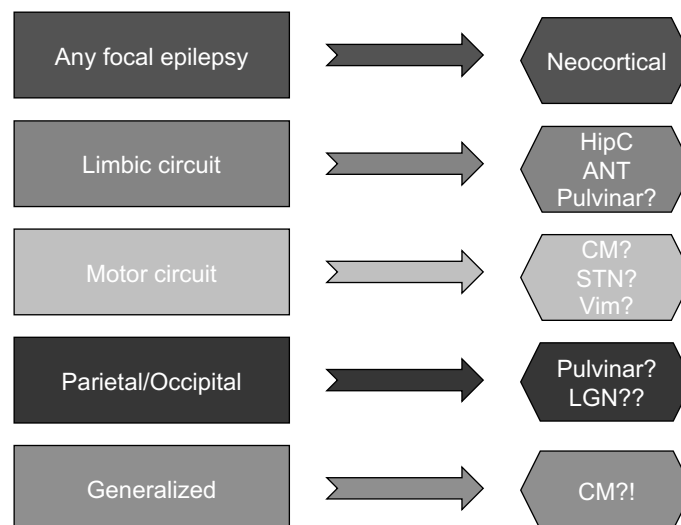
Patient	Age	Sex	Seizure type	Genetic	Seizure frequency (pre)	Seizure frequency (post)	Seizure reduction (%)	ILAE class
1	18	M	FBTC	Multifocal	MCD	23.5	66.7%	3a
2	20	F	FBTC	Multifocal	Postencephalitic	25.6	95.8%	2b
3	11	F	IGT	Presumed genetic				4
4	12	F	IGT	Presumed genetic				4
5	13	F	IGT	Presumed genetic				4
6	14	F	IGT	Presumed genetic				4
7	15	F	IGT	Presumed genetic				4
8	16	F	IGT	Presumed genetic				4
9	17	F	IGT	Presumed genetic				4
10	18	F	IGT	Presumed genetic				4
11	19	F	IGT	Presumed genetic				4
12	20	F	IGT	Presumed genetic				4
13	21	F	IGT	Presumed genetic				4
14	22	F	IGT	Presumed genetic				4
15	23	F	IGT	Presumed genetic				4
16	24	F	IGT	Presumed genetic				4
17	25	F	IGT	Presumed genetic				4
18	26	F	IGT	Presumed genetic				4
19	27	F	IGT	Presumed genetic				4
20	28	F	IGT	Presumed genetic				4
21	29	F	IGT	Presumed genetic				4

Note: Initial outcomes from Patients 1–4 have been reported previously²¹; this report extends these outcomes to a mean follow-up duration of 1157 days after RNS implantation. Abbreviations: FBTC, focal to bilateral tonic-clonic; GTC, generalized tonic-clonic; IGE, idiopathic generalized epilepsy; ILAE, International League Against Epilepsy; MRJFU, most recent follow-up; RNS, responsive neurostimulation.

- Effective for IGE and multifocal onset FBTC seizures
- Mean seizure frequency reduction of 82.6% (SD = 19.0%, median = 91.7%)
- Seizure types respond variably

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Where? ... Approved and investigational (?) targets in epilepsy



See Drs. Fisher and Lundstrom's talks

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How to Choose b/w VNS, DBS, RNS

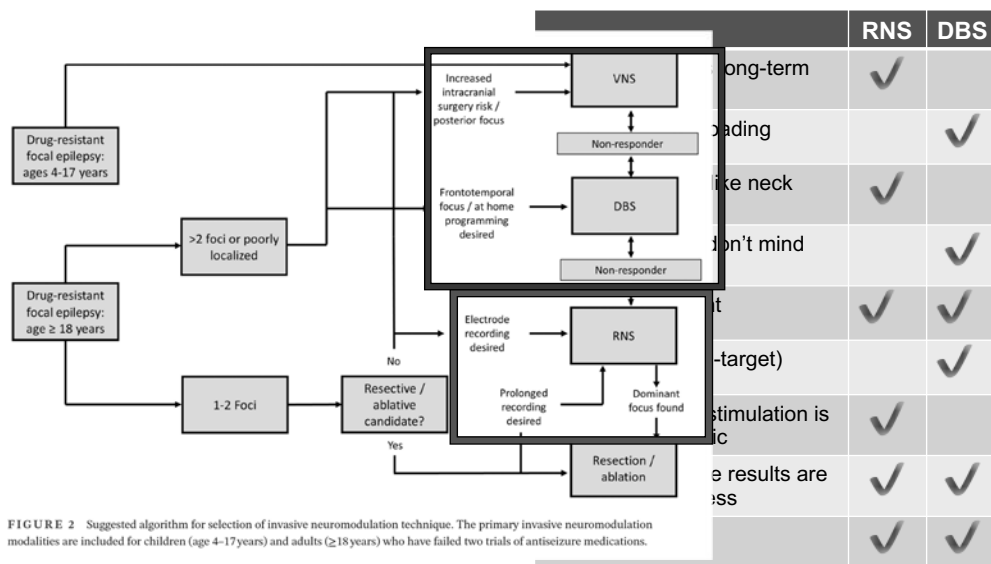


FIGURE 2 Suggested algorithm for selection of invasive neuromodulation technique. The primary invasive neuromodulation modalities are included for children (age 4-17 years) and adults (≥18 years) who have failed two trials of antiseizure medications.

Simpson *et al.*, Practical considerations in epilepsy neurostimulation, *Epilepsia*. 2022;63:2445-2460

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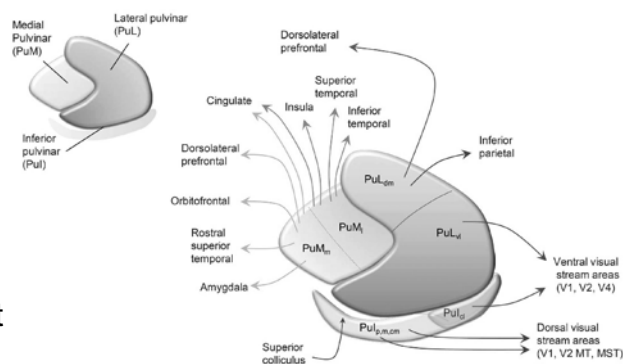
PULVINAR

- The “prototypic association nucleus”, corticothalamocortical connections
- The largest thalamic nucleus (30% by volume)
- “Cushion”

4 Subnuclei

1. Anterior (PuA)
2. Medial (PuM)
3. Lateral (PuL) - vl, dm
4. Inferior (PuI)

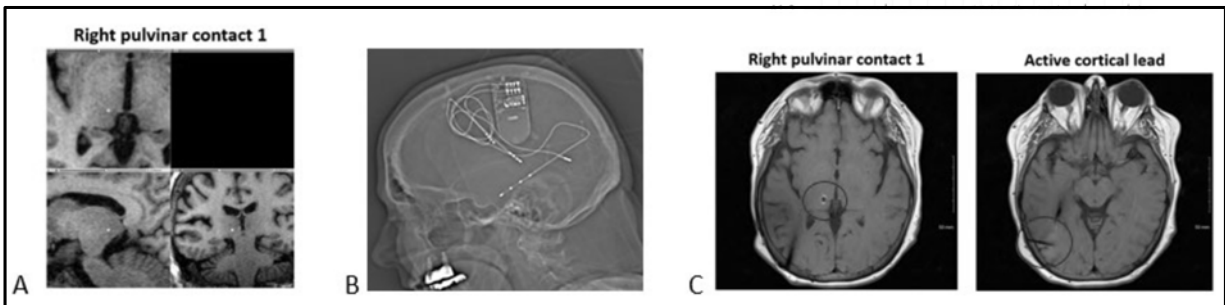
- Increased synchrony between PuM, lat temp neocortex, Ectx, Hc during MTL seizures (Rosenberg 2006 & 2009)
- 80% of TL seizures recorded in PuM (imbalance in reciprocal PULV-Hc)



Benarroch. Pulvinar: Associative role in cortical function and clinical correlations. *Neurology* 2015.

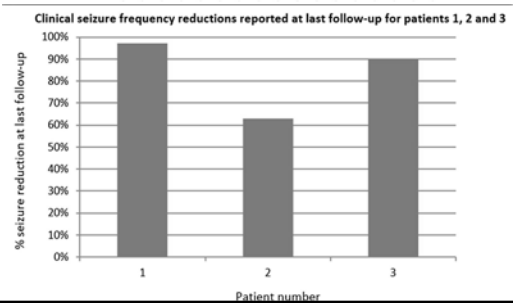
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PULVINAR



2019: Burdette et al. (RNS)

- N=3 patients with PQE-DRE
- 1-2 RNS systems (all with PULV stim, one with neo+PULV)
- 10-15 mo follow-up, no clear adverse effects
- ↓90% in 2 patients, 62% in 3rd; 100% responder rate



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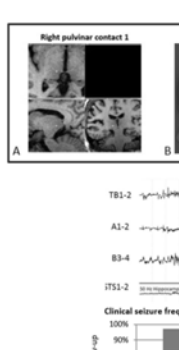
PULVINAR

2019: Filipescu et al. (Bartolomei)

- N=8 patients
- Acute pulvinar stimulation during hippocampal stimulation-induced seizures
- 'Less severe', shorter tonic phase

2021: Deutschova et al. (Bartolomei)

- N=9 patients
- Acute pulvinar stimulation
- Improved awareness associated with decrease in global synchrony due to pulvinar stim



Epileptic Disorders. 2026;00:1–17.

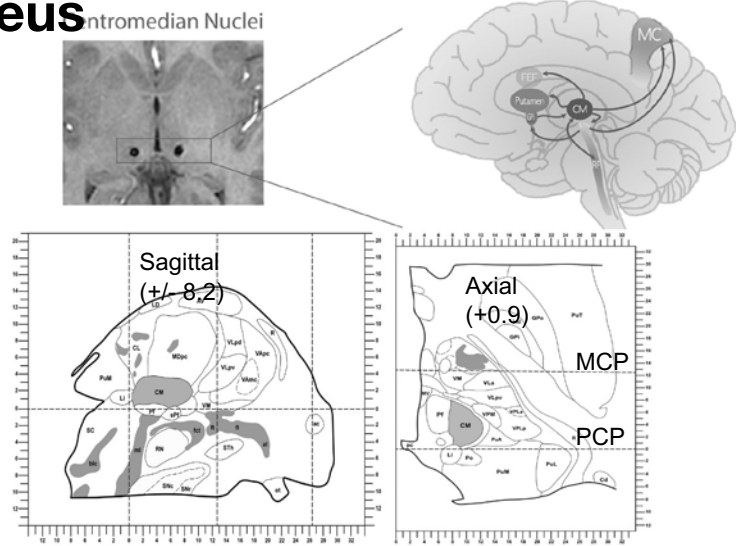
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Centromedian nucleus

- Broad connectivity:

- Basal ganglia (dorsal striatum, caudal sensorimotor putamen, also STN, SN, GP to lesser extent)
- Ventral thalamus
- Cortex (premotor, motor, somatosensory, ACC*)
- Brainstem (reticular formation, vestibular, solitary nuclei, nucleus ambiguus)

- **Functional:** Sensorimotor coordination, cognition, pain



Ilyas et al. The centromedian nucleus: Anatomy, physiology, and clinical implications. *J Clin Neurosci* 2019; 63.

Warsi et al. The anterior and centromedian thalamus: Anatomy, function, and dysfunction in epilepsy. *Epilepsy Research* 2022: 182.

45

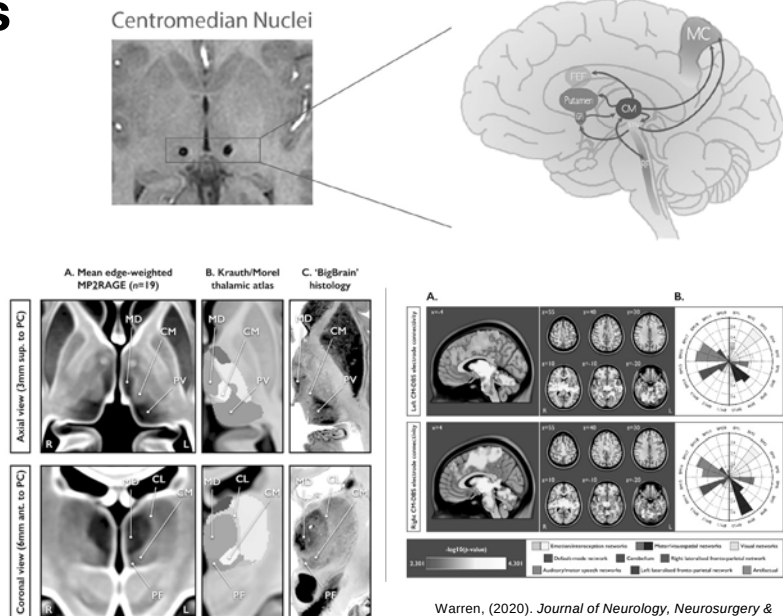
Centromedian nucleus

- Broad connectivity:

- Basal ganglia (dorsal striatum, caudal sensorimotor putamen, also STN, SN, GP to lesser extent)
- Ventral thalamus
- Cortex (premotor, motor, somatosensory, ACC*)
- Brainstem (reticular formation, vestibular, solitary nuclei, nucleus ambiguus)

- **Functional:** Sensorimotor coordination, cognition, pain

Warsi et al. The anterior and centromedian thalamus: Anatomy, function, and dysfunction in epilepsy. *Epilepsy Research* 2022: 182.



Warren, (2020). *Journal of Neurology, Neurosurgery & Psychiatry*.

Warren et al., *Journal of Neurology, Neurosurgery & Psychiatry*, 2019

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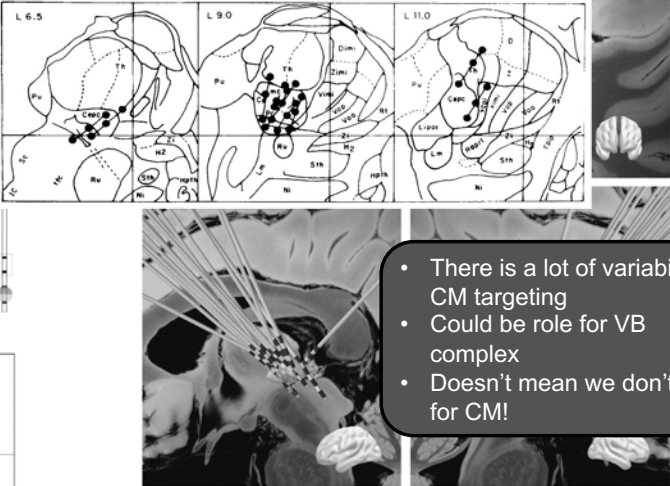
Original research

Responsive neurostimulation of the thalam improves seizure control in idiopathic generalized epilepsy: initial case series

Nathaniel D Sisterson,¹ Vasileios Kokkinos ,¹ Alexandra Urban,² ↑
R Mark Richardson ,^{1,4}

J Neurol Neurosurg Psychiatry 2022

Electrical Stimulation of the Centromedian Thalamic Nucleus in the Treatment of Convulsive Seizures: A Preliminary Report



There is a lot of variability in CM targeting
Could be role for VB complex
Doesn't mean we don't aim for CM!

Nanda, *Epilepsia*, 2024

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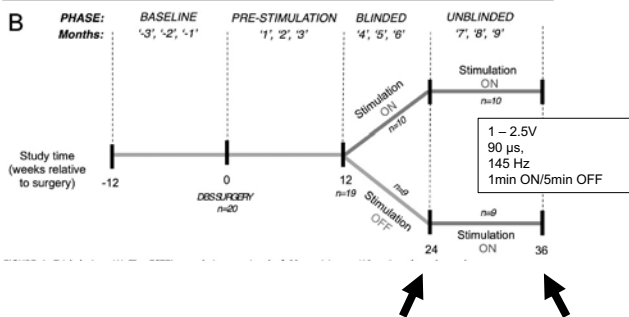
CM DBS

2017-2022: ESTEL trial

19 patients with LGS (≥ 3 failed AEDs)
Prospective, randomized, double-blinded design

ANN NEUROL 2022;91:253-267

Median SR Responder Rate: % with $\geq 50\%$ SR

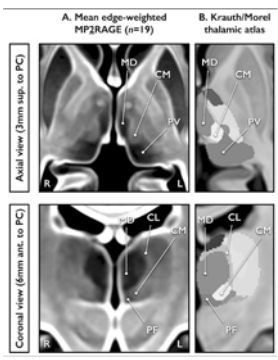


Study time (weeks relative to surgery): -12, 0 (DEB SURGERY), 12, 24, 36

PHASE: Months: -3', -2', -1' (BASELINE); 1', 2', 3' (PRE-STIMULATION); 4', 5', 6' (BLINDED); 7', 8', 9' (UNBLINDED)

Stimulation ON (n=10) at week 12, Stimulation OFF (n=9) at week 24, Stimulation ON (n=10) at week 36

1 - 2.5V, 90 μ s, 145 Hz, 1min ON/5min OFF



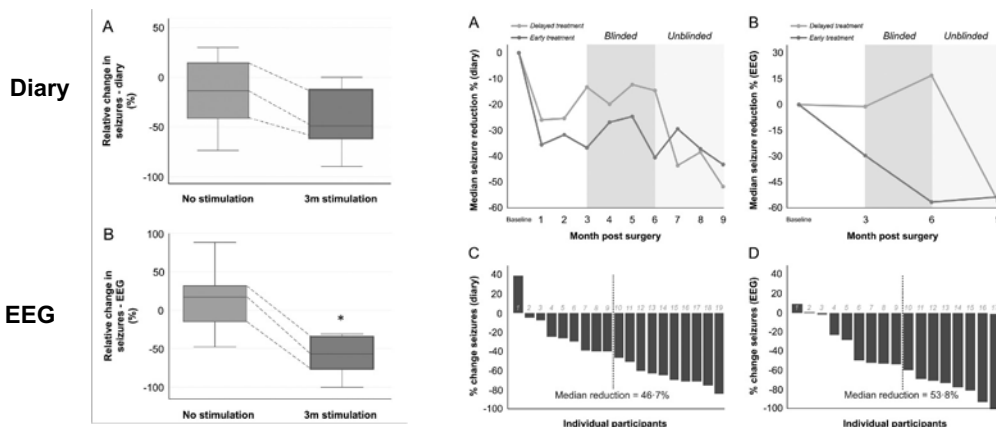
A. Mean edge-weighted MP2RAGE (n=19)
B. Krauth/Morel thalamic atlas

Axial view (3mm sup. to PC)
Coronal view (6mm ant. to PC)

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CM DBS – ESTEL TRIAL

Median SR
Responder Rate:
% with $\geq 50\%$ SR



Caregivers: 74% "better",
16% "same", 5% "worse"
Increased alertness in 95%

****ONLY 6 MONTHS REPORTED****

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NAUTILUS trial: IGE/PGE

RNS System Pivotal Study of Responsive Bilateral Thalamic Stimulation for Idiopathic Generalized Seizures (NAUTILUS) Study

- The study is a prospective, multicenter, single-blind, randomized, sham stimulation controlled pivotal study and participants will be followed for two years after placement of the RNS System.
- The study will enroll a maximum of 100 participants within the United States to ensure that at least 80 participants are implanted with the RNS System

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Can patients have multiple devices?



Yes, but it can present challenges:

- Skin incisions
- Proprietary imaging protocols
 - Indications for transmit receive coils differ
- Programming strategies
 - One one → the other?
 - Which one first?
 - Turn both on at same time?

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b/I Hc RNS + b/I ANT DBS: Emory Experience

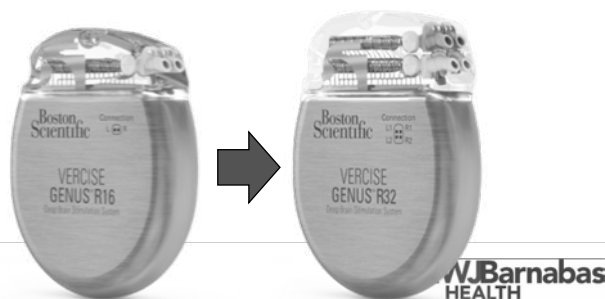
Emory experience:

1. LR: L Hc RNS (5 yr) → b/I ANT DBS (2 yr);
 - **75%, 0% reduction FIA, GTCs**
2. AB: ANT DBS (5 yr) → b/I Hc RNS (3 yr)
 - **No reduction in seizures**
3. JW: b/I Hc RNS (3.5) → b/I ANT DBS (2 yr); Both being stimulated.
 - **100% reduction in GTCs (99% long episodes R Hc)**
4. LJ: b/I ANT + L Hc RNS (5 yr each); Being stimulated through L ANT & L Hc (s/p R ATL):
 - **99% reduction in seizures**

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Rationale for 4 electrodes/4 channel IPG: Generalized epilepsy

- When its straightforward symptomatic generalized epilepsy (LGS, LGS-like with drop attacks → **CM DBS**
 - What about prominent GTCs? → **ANT?**
 - → **DO BOTH: CM + ANT**
 - What about prominent myoclonic features? → **STN?**
 - → **DO BOTH: CM + STN**



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Multitarget deep brain stimulation for epilepsy

Andrew I. Yang, MD, MS,¹ Faical Isbaine, PhD,¹ Abdulrahman Alwaki, MD,² and Robert E. Gross, MD, PhD^{1,2}

Departments of ¹Neurosurgery and ²Neurology, Emory University School of Medicine, Atlanta, Georgia

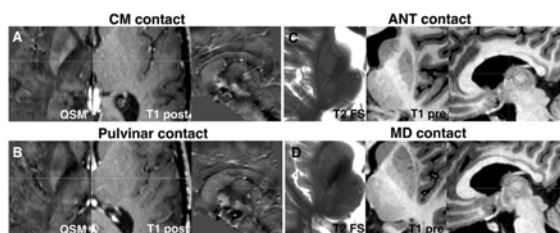


TABLE 3. Indications for thalamic nuclei

Case No.	ANT	CM	Pulvinar	MD	STN
1	Focal onset	Multifocal nonlimbic			
2	Some Szs of focal onset	LGS-like		Atonic Szs, SCCEP	
3	Focal onset	Multifocal nonlimbic	PQE		
4	Focal onset			Head drop/tilt, SCCEP	
5	Focal onset		PQE		
6		Generalized onset			Myoclonic Szs
7		Generalized onset			Myoclonic Szs
8	Focal onset				SMA-onset Szs

J Neurosurg July 14, 2023

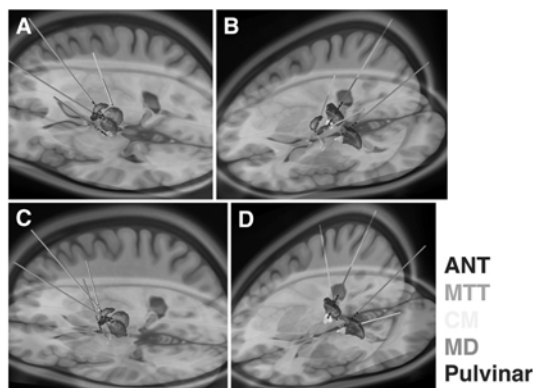


TABLE 5. Programming settings and seizure outcomes at last follow-up*

Case No.	FU Duration (mos)	All Target Nuclei	Stimulated Target Nuclei at Last FU	Configuration	Parameters, mA†	Sz Reduction (%)	Convulsive Sz Reduction (%)	Pre-DBS Convulsive Sz Freq (per yr)
1	21	ANT, CM	ANT	D-monopolar	6	62.5	100	5
2	14	ANT-MD, CM	ANT + CM	Monopolar	4 (ANT), 2.5 (CM)	45.5	100	1.5
3	12	ANT, CM-pulvinar	Pulvinar	D-monopolar	5.5	60	86	30
4	12	ANT, MD	ANT + MD	Monopolar (lt), D-monopolar (rt)	2 (ANT), 5/7 (MD)	37.5	100	2
5	7	ANT, pulvinar	Pulvinar	D-monopolar (lt), bipolar (rt)	10	60.8	NA	NA

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Anterior Nucleus of the Thalamus Deep Brain Stimulation with Concomitant Vagus Nerve Stimulation for Drug-Resistant Epilepsy

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Brian Nils Lundstrom, MD, PhD[†]

Panagiotis Kerezoudis, MD[‡]

Juan Luis Alcalá Zermeno, MD[§]

Gregory A. Worrell, MD, PhD[¶]

Jamie J. Van Gompel, MD^{||}

*Department of Neurosurgery and Gamma Knife Radiosurgery, IRCCS San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy; †Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA; ‡Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota, USA; §Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota, USA

Neurosurgery 89:686–694, 2021

Seizure reduction percentage was not significantly different among groups

- ~50% of subjects who didn't benefit from VNS:
- ~75% of those who did benefit from VNS:

→ Achieved a seizure reduction ≥50% after ANT-DBS surgery.

TABLE 1. ANT-DBS Treatment Groups, Surgical Report

Group	Treatment	No.	%
1	ANT-DBS	9	28
2	ANT-DBS + VNS active	12	36
3	ANT-DBS + VNS inactive	3	9
	ANT-DBS + VNS removed	4	12
	ANT/hippo DBS + VNS removed	5	15
1 + 2 + 3	Total	33	100

CASE REPORT

Combined VNS-RNS Neuromodulation for Epilepsy

Pouya Khankhanian,^{*} Angelica M. Lee,[†] Cornelia N. Drees,[‡] Barbara M. Decker,[§] and Danielle A. Becker[§]

^{*}Department of Neurology, Center for Neuro-engineering and Therapeutics, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; [†]Department of Neurology, Division of Epilepsy, Uniformed Services University of the Health Sciences, Bethesda, Maryland, U.S.A.; [‡]Department of Neurology, Division of Epilepsy, Children's Hospital Colorado, University of Colorado, Denver, Aurora, Colorado, U.S.A.; and [§]Department of Neurology, Division of Epilepsy, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

J Clin Neurophysiol 2021;00: 1–5

Suggests that VNS and RNS are synergistic

Electrocorticography Analysis in Patients With Dual Neurostimulators Supports Desynchronization as a Mechanism of Action for Acute Vagal Nerve Stimulator Stimulation

Lisa D. Ernst,^{*} Paul J. Steffen,[†] Priya Srikant,[‡] Jack Wiedrick,[§] David C. Spencer,^{*} Proleta Dutta,[§] Navya M. Joseph,[§] Magda Wernowsky,^{||} and Danielle A. Becker^{||}

^{*}Department of Neurology, Oregon Health & Science University (OHSU), Portland, Oregon, U.S.A.; [†]Institute of Neuroscience, University of Oregon, Eugene, Oregon, U.S.A.; [‡]Department of Biostatistics, Oregon Health & Science University (OHSU), Portland, Oregon, U.S.A.; [§]Department of Neurology, University of Nebraska Medical Center, Omaha, Nebraska, U.S.A.; and ^{||}Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

Journal of Clinical Neurophysiology Volume 40, Number 1, January 2023

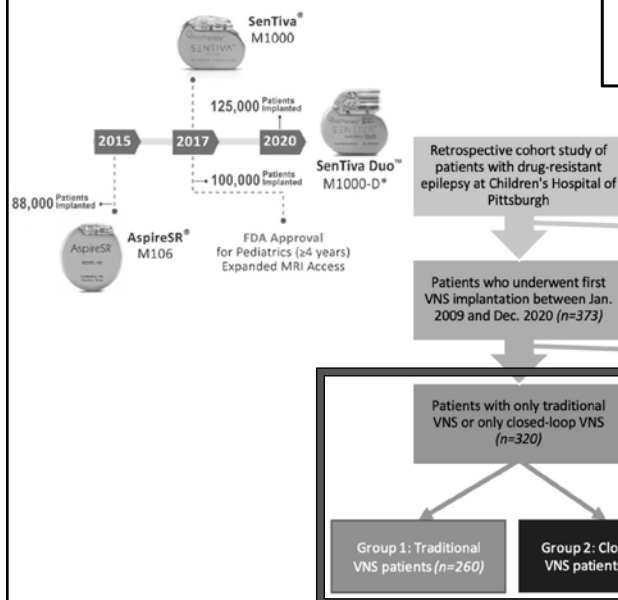
Conclusions:

- ECOGs recorded by the RNS device in patients with dual (VNS and RNS) neurostimulators
- VNS stimulation results in desynchronization of specific frequency bands (salient decrease in theta and beta bands, smaller decrease in alpha band)
- Support for desynchronization as a theorized mechanism of action of VNS.

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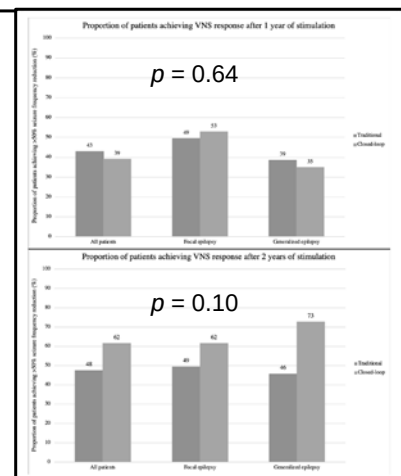
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“Closed-loop” VNS



Comparison of traditional and closed loop vagus nerve stimulation for treatment of pediatric drug-resistant epilepsy: A propensity-matched retrospective cohort study

Nallammai Muthiah[✉], Emefa Akwayena^{||}, Lena Vodovotz^{||}, Nikhil Sharma^{||}, Jong-Hyeon Jeong^{||}, Gretchen E. White^{||}, Taylor J. Abel^{||}



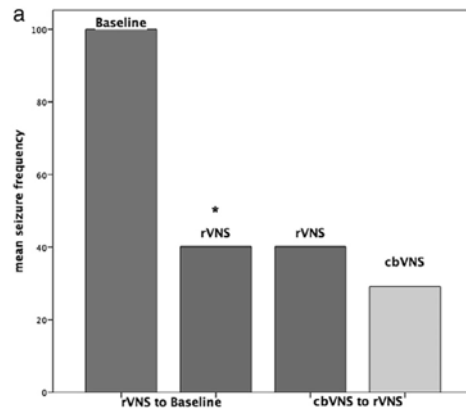
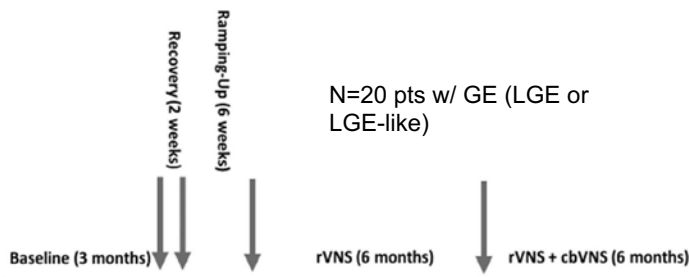
Muthiah et al. (T. Abel), Seizure: European Journal of Epilepsy 94 (2022) 74–81

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Impact of Cardiac-Based Vagus Nerve Stimulation Closed-Loop Stimulation on the Seizure Outcome of Patients With Generalized Epilepsy: A Prospective, Individual-Control Study

Arthur Cukiert, MD, PhD ; Cristine Mella Cukiert, MD, MsC;
Pedro Paulo Mariani, MD; Jose Augusto Burattini, MD

Neuromodulation 2021; 24: 1018–1023



Activation of the cbVNS feature did not add to rVNS efficacy.

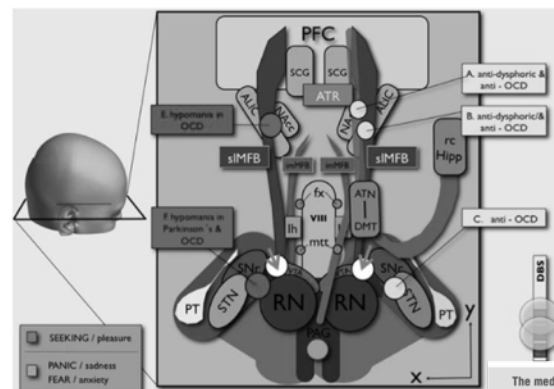
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DBS for OCD



- Targets: *Limbic network*
 - Cingulate cortex
 - Anterior ventral internal capsule
 - Ventral striatum/N. accumbens
 - Subthalamic nucleus/MFG

Intersecting Circuits of Lesion and Stimulation Sites



The medial forebrain bundle as a target for deep brain stimulation for obsessive-compulsive disorder

Volker A. Gonen, ¹ Thomas E. Schlaepfer, ² Peter Gail, ³ Peter C. Reuber, ⁴ Elisabeth Voderholzer, ⁵ Ludger Tobiass von Elm, ⁶ Marc Erhard, ⁷ and Tobias Frey, ⁸

Greenberg, Rauch and Haber; Neuropsychopharmacology Rev. (2010) 35, 317–336

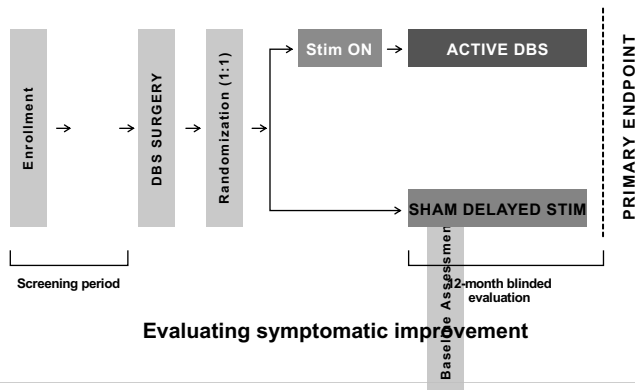
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DBS for Depression: The TRANSCEND Pivotal Study |

TRANSCEND Study Overview

- Prospective, multicenter, double-blind, randomized, & sham-controlled
- 100 implanted patients, up to 25 sites in the US



Leveraging knowledge of delayed response

12-month primary endpoint based on potential delayed effect of DBS for TRD

Highly constrained programming and medication algorithm post-randomization



19-Jul-26

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