



EST 30th ANNIVERSARY
ANNUAL MEETING

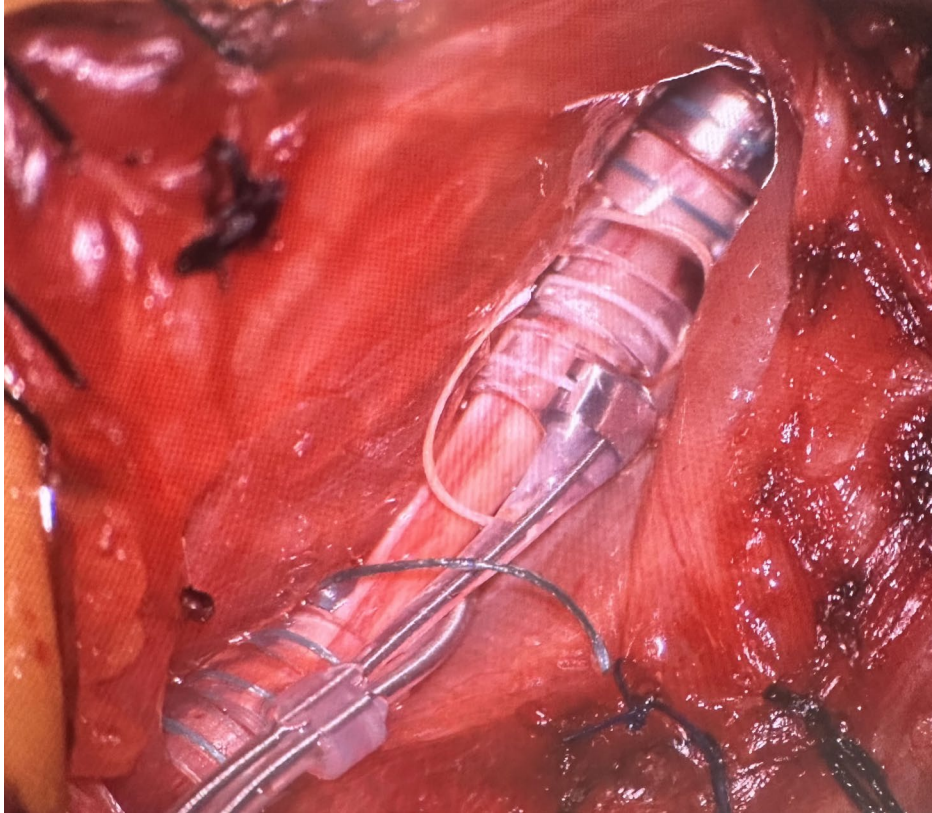
Neurostimulation therapies: VNS, DBS, and RNS

Current evidence and practical use in Thailand

Assoc. Prof. Atthaporn Boongird
Head of neurosurgical unit
Department of surgery, Ramathibodi Hospital



Vagal nerve stimulation



Operative time 2 hours
2 nights admission





A NEW STUDY

CORE-VNS represents the most comprehensive real-world evaluation of VNS Therapy™ in people with drug-resistant epilepsy¹



827 subjects consented



61 sites



16 countries



36 months of follow-up

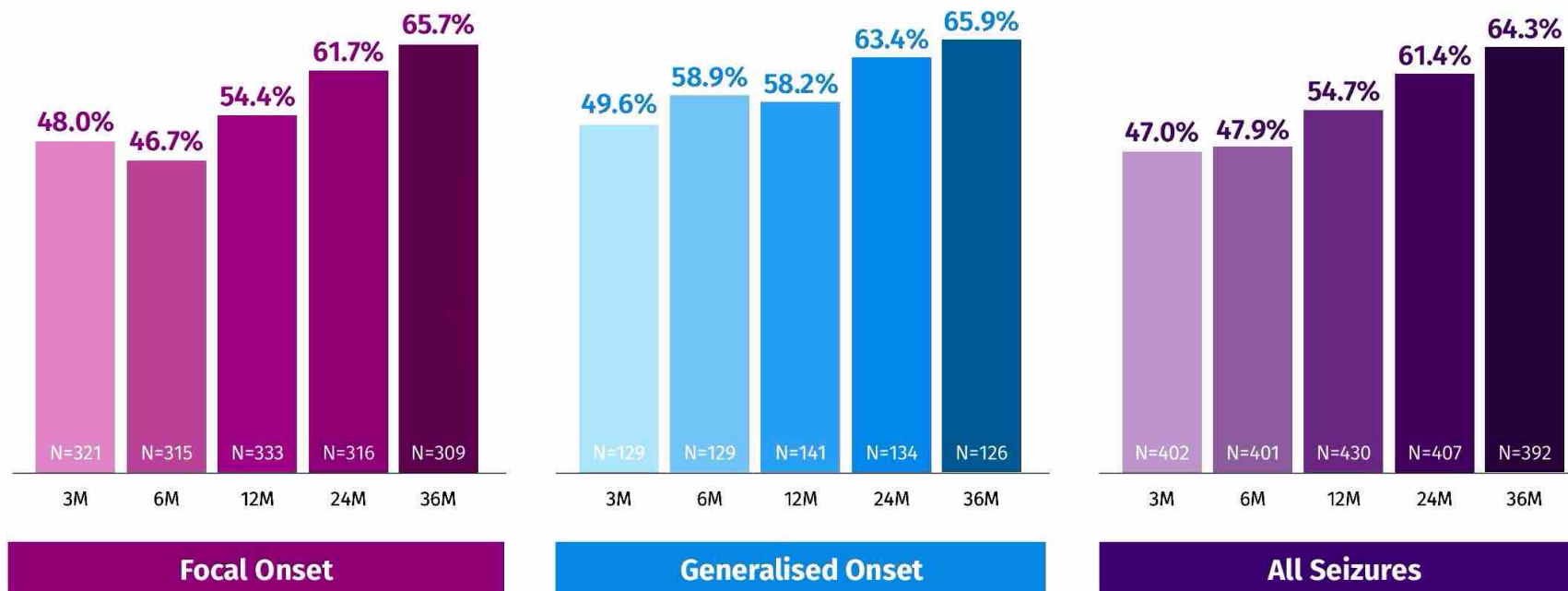
The large sample size and broad inclusion criteria allows for broad applicability. This inclusivity also facilitates in-depth subpopulation analyses, including the evaluation of performance in groups that are typically more challenging to recruit for focused research studies.



In CORE-VNS, the patient responder rate improved across seizure types¹

Participants achieving $\geq 50\%$ reduction from baseline by seizure type

Seizure frequency was measured over the 3 months preceding the follow-up visit; the percentage reduction is based on the individual seizure type(s) reported at baseline.



Generalised myoclonic (collected in days) and generalised non-motor (absences, collected categorically) seizures are excluded from the aggregate analyses by type and overall. These data result from a post hoc analysis that is exploratory and was not pre-specified in the statistical analysis plan. Only includes participants who reported specified seizure type at baseline.

First implanted participants – full analysis set – ad hoc analysis.

In CORE-VNS, nearly half of patients were super responders¹

AT 36 MONTHS

Focal Onset

51%

of patients experiencing focal seizures were super responders (≥80% reduction in seizure frequency)

Generalised Onset

49%

of patients experiencing generalised seizures were super responders (≥80% reduction in seizure frequency)

All Seizures

48%

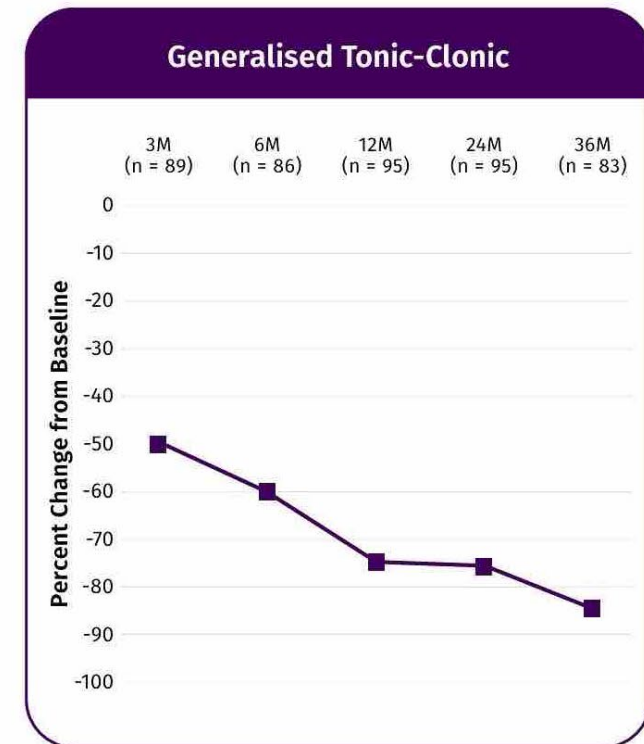
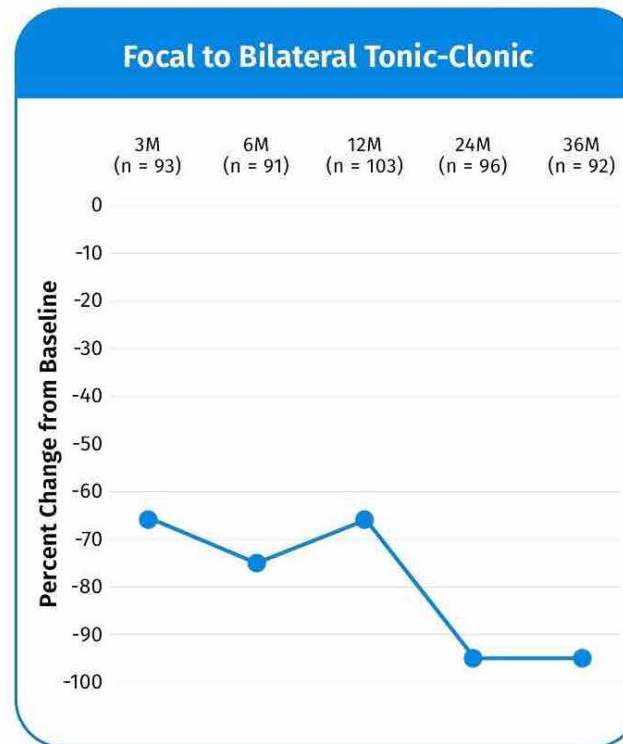
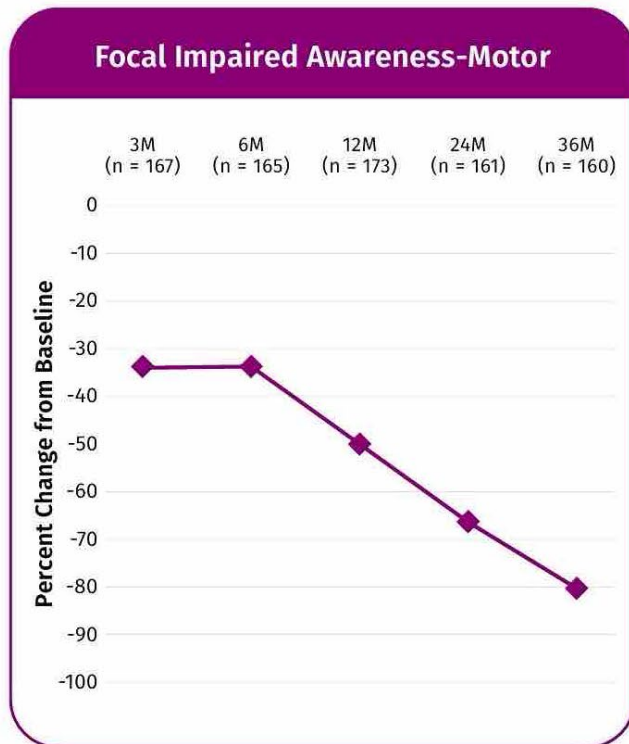
of patients experiencing any seizure type were super responders (≥80% reduction in seizure frequency)

Seizure frequency was measured over the 3 months preceding the follow-up visit; percentage reduction is based on the individual seizure type(s) reported at baseline.



In CORE-VNS, patients with VNS Therapy™ saw reductions in the most severe seizure types¹

Percent change in seizure frequency by seizure type (median with 95% CI)





Reductions in tonic-clonic seizures with VNS Therapy™ have been shown again and again

AT 36 MONTHS

CORE-VNS¹



95%
REDUCTION



49%
FREE
FROM



**Focal to bilateral
tonic-clonic
seizures (FBTC)**

N = 92



84%
REDUCTION



43%
FREE
FROM



**Generalised
tonic-clonic
seizures (GTC)**

N = 83

Japan post-marketing surveillance study²



97%
REDUCTION



49%
FREE
FROM



**Tonic-clonic
seizures (TCS)***

N = 156

For CORE-VNS, seizure free data is from combined adult and paediatric data set. Seizure free is defined as a 100% reduction in seizure frequency compared to baseline over the 3 months preceding the 36 month follow-up visit.

In the Japanese post-marketing survey, seizure freedom was defined as a subject completing a follow-up visit and recording no seizures for 12 months preceding the 36 month follow-up visit.

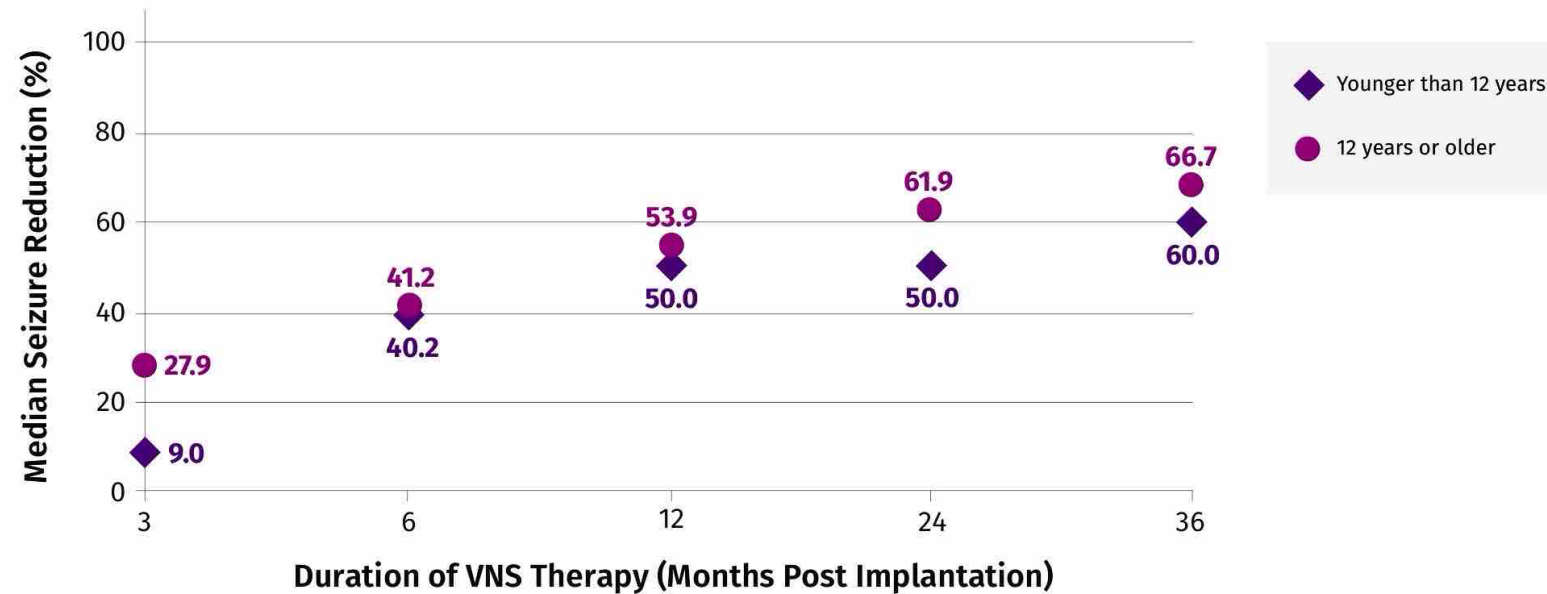
*TCS=GTC+FBTC.



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VNS Therapy™ reduced seizure frequency in children within 6 months—and continued to improve seizure control after implantation

This Japanese post-marketing study included all patients implanted with VNS Therapy in the first three years after approval (N=362). Patients were followed for 36 months with a greater than 90% follow-up rate.¹

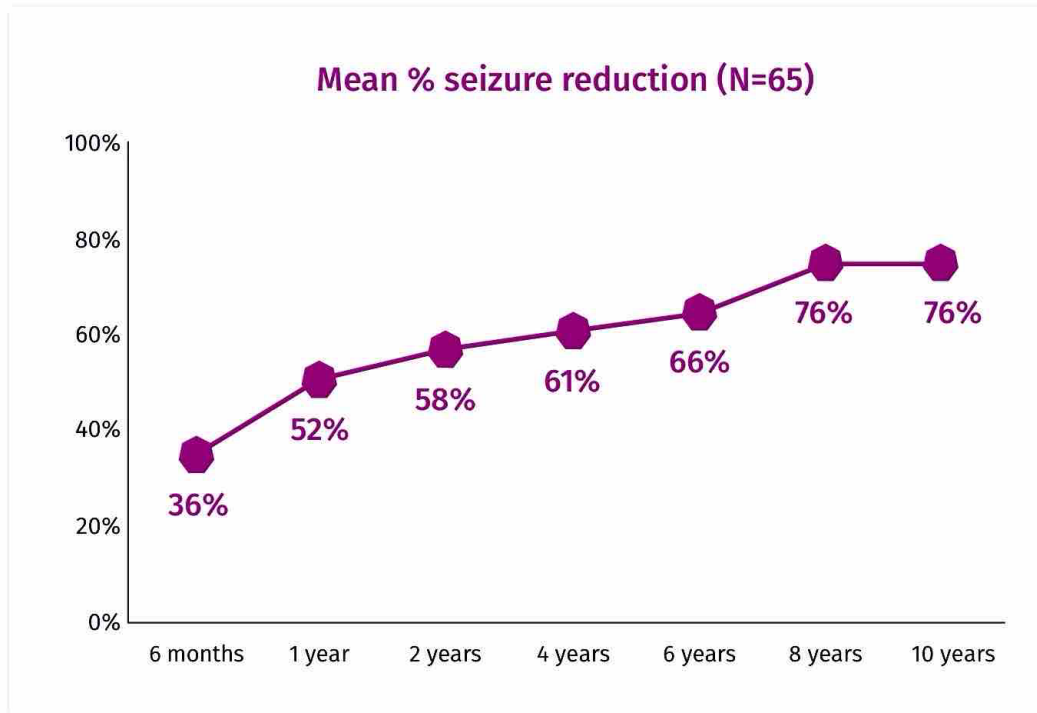




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Patients with VNS Therapy™ experienced early reductions in seizure frequency that continued to improve over time

Improvements in seizure frequency were seen in a highly intractable patient population¹



2.8
ASMs

2.8 ASMs at
baseline (median)

6
ASMs

6 ASMs failed (mean)

20
YEARS

20 years mean
duration of epilepsy

31%

31% prior brain or
epilepsy surgery

The major limitation of this study is the retrospective nature of the data collection. Follow-up data concerning seizure frequency and ASM use were not available for every patient at every time point.

Reference: 1. Elliot RE, et al. *Epilepsy Behav.* 2011;20(3):478-483.



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VNS Therapy™ can help reduce hospitalisations and health-related events

In one study, reductions were seen in¹:



Head Trauma



Fractures



Emergency Room Visits

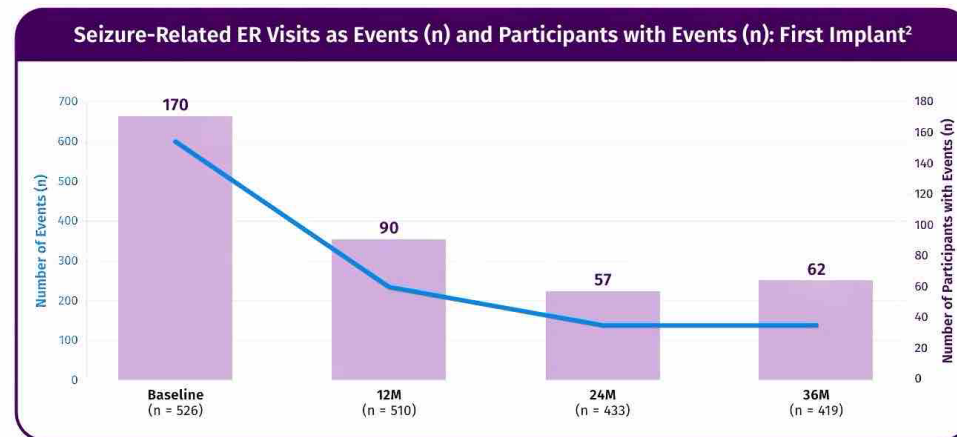


Hospitalisations



Number of Hospital Days

The study population (N=1655) consisted of patients enrolled in Medicaid, a government health insurance programme in the US. Medicaid data were obtained for 5 states: Florida, Iowa, Kansas, Missouri, and New Jersey. Average follow-up was 30.4 months.¹



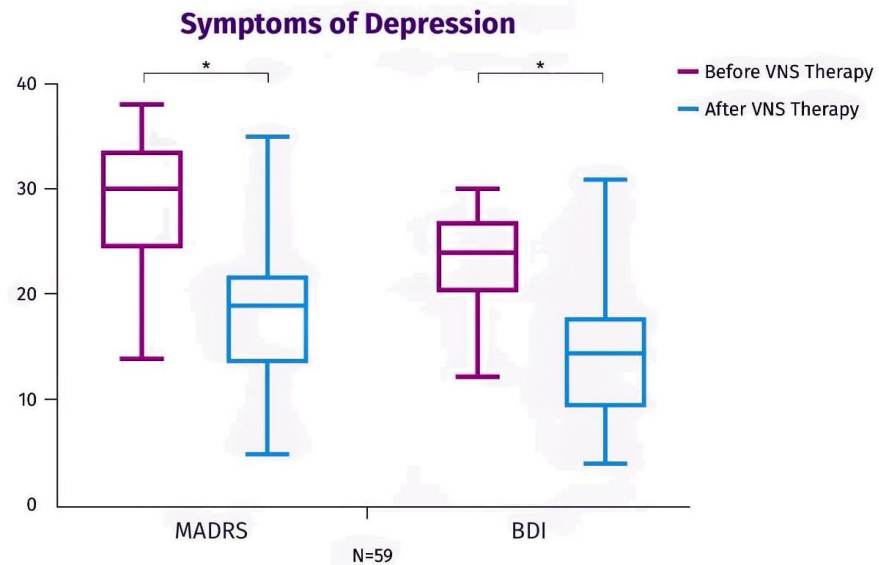
The results for 3M, 6M, and 12M follow-up visits have been combined to provide a consolidated view of the results for the last 12 months, consistently with the approach for all other visits.

ER, emergency room.



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VNS Therapy™ may be associated with mood improvements in patients with drug-resistant epilepsy (DRE)



Overall improvement in symptoms of depression after 1 year treatment with VNS Therapy:

*MADRS 29 to 18 ($P<0.001$) and BDI 24 to 14 ($P<0.001$).¹

MADRS, Montgomery-Asberg Depression Rating Scale; BDI, Beck Depression Inventory.



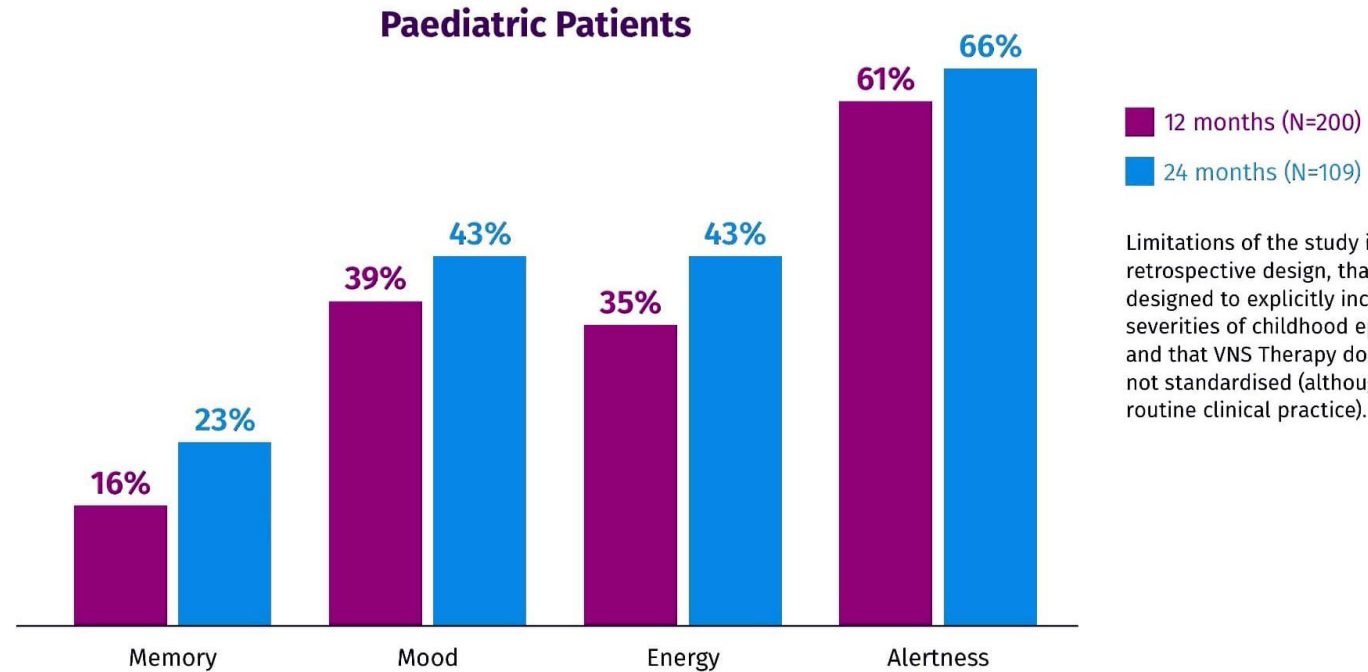
The effect of VNS Therapy on depressive symptoms in patients with DRE has not been evaluated in large-scale randomised double-blinded trials. A systematic review found VNS Therapy to be associated with a reduction of symptoms of depression in patients with DRE in 6 out of 9 studies. Studies using self-rating scales of depressive symptoms only did not find a significant reduction of depressive symptoms, whereas those studies including physician-rated scales did. The authors encourage more rigorous studies addressing this issue.²

References: 1. Spindler P, et al. *Eur J Epil.* 2019;69:77-79. 2. Assenza G, et al. *Neurol Sci.* 2020;41(11):3075-3084.



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Paediatric patients also reported improvements in quality of life



Limitations of the study included its retrospective design, that it was not designed to explicitly include different severities of childhood epilepsies, and that VNS Therapy dosing was not standardised (although it reflected routine clinical practice).



Bella
VNS Therapy™ patient

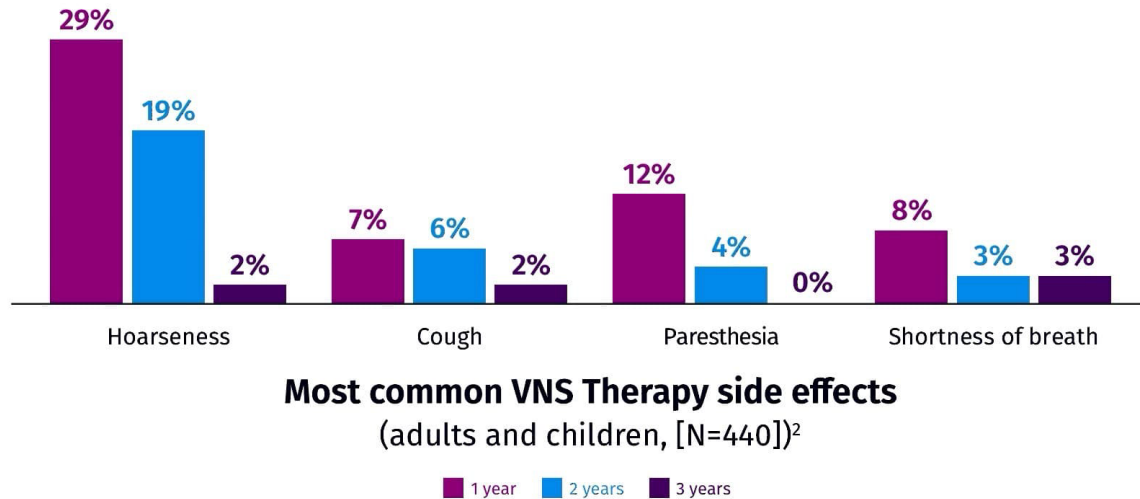
Improvement was defined as patient being “better” or “much better” at 12 (N=200) and 24 months (N=109)¹



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VNS Therapy™ safety profile

VNS Therapy™ has no systemic or CNS side effects that are commonly associated with anti-seizure medications¹



Most side effects may be diminished or eliminated by the adjustment of parameter settings³

The most common adverse events following stimulation (>5%) were voice alterations, increased coughing, pharyngitis, paresthesia, dyspnea, dyspepsia, and nausea. These side effects typically occur only during stimulation and generally become less noticeable over time for most patients.^{1,3}

Infection is the most common complication of the surgical procedure. Children (<12 years of age) may have a greater risk for infection when compared to adolescent and adult patients (≥12 years).³

Clinical Outcomes of Corpus Callosotomy and Vagus Nerve Stimulation in Drug-Resistant Epilepsy:

A Single-Center Experience



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CORPUS CALLOSOTOMY



VAGUS NERVE STIMULATION





Study Overview

- **Study Center:** Ramathibodi Hospital
- **Study Period:** 2011–2025
- **Total Patients:** 42
- **Excluded:** 8 patients who underwent both corpus callosotomy and VNS

Final Study Cohort (n = 34)

Corpus Callosotomy

n = 19

VNS

n = 15



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Baseline Characteristics

Characteristic	Corpus Callosotomy (n = 19)	VNS (n = 15)
Patients, n	19	15
Female : Male	9 : 10	8 : 7
Procedure	Anterior 2/3 CC: 16 (84.2%) Total CC: 3 (15.8%)	VNS implantation
Mean age at surgery, years (range)	8.8 (2–21)	9.5 (4–17)
Mean follow-up time, months (range)	86 (8–160)	66 (11–142)

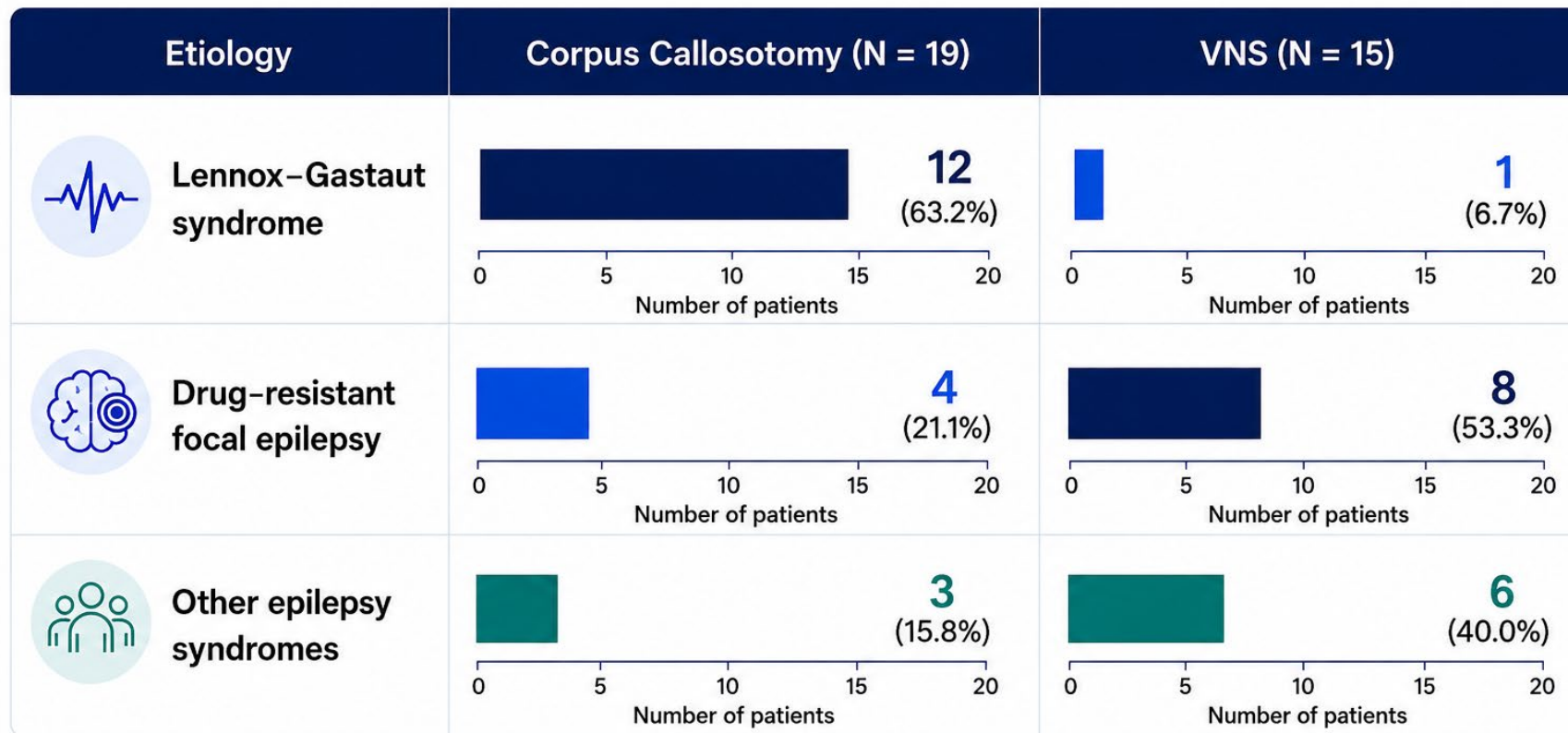


The baseline characteristics were comparable between the corpus callosotomy group and the VNS group.



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Etiology of Epilepsy

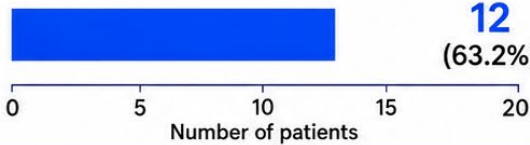
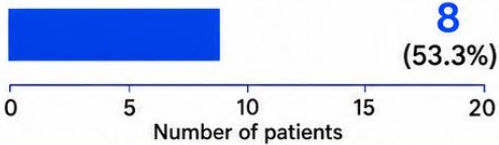
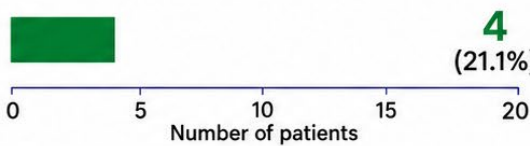
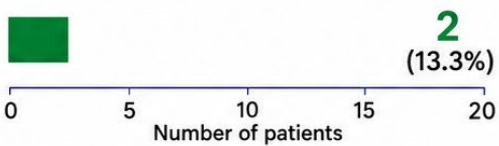
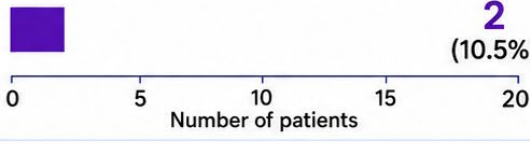
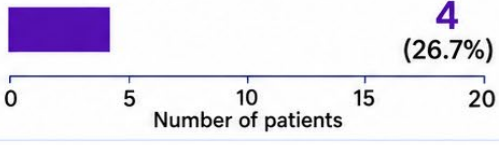
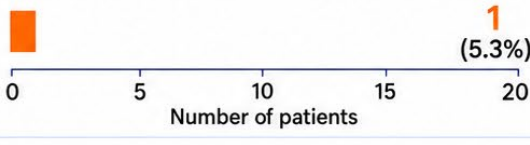
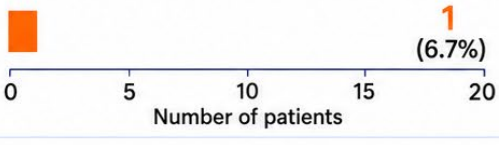


Lennox–Gastaut syndrome was the predominant indication for **corpus callosotomy**, whereas **drug-resistant focal epilepsy** was the most common indication for **VNS**.



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Seizure Semiology

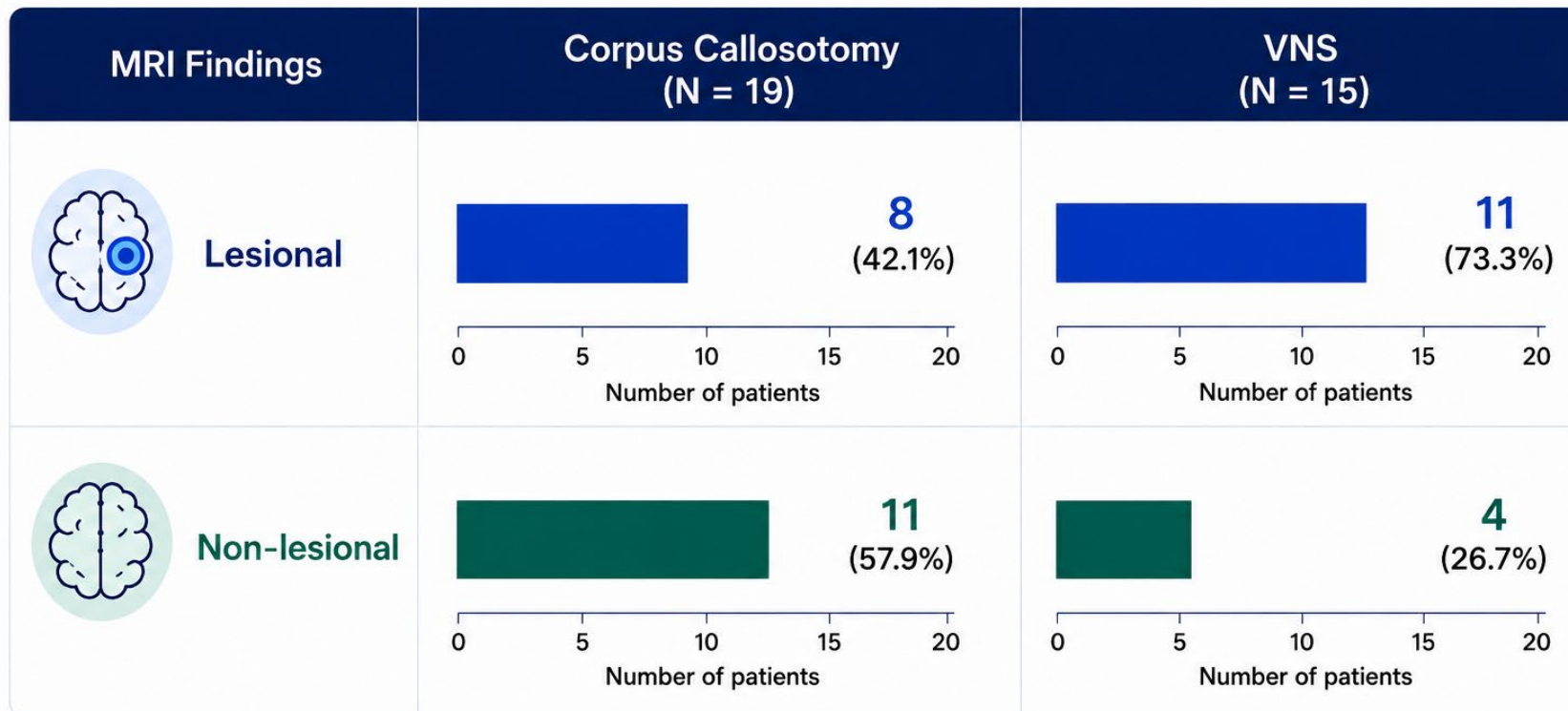
Seizure Semiology	Corpus Callosotomy (N = 19)	VNS (N = 15)
 Multiple seizure types	 12 (63.2%)	 8 (53.3%)
 Generalized tonic-clonic	 4 (21.1%)	 2 (13.3%)
 Generalized tonic	 2 (10.5%)	 4 (26.7%)
 Atonic	 1 (5.3%)	 1 (6.7%)



Multiple seizure types were the predominant seizure semiology in both groups (63.2% of corpus callosotomy vs. 53.3% of VNS).



MRI Findings

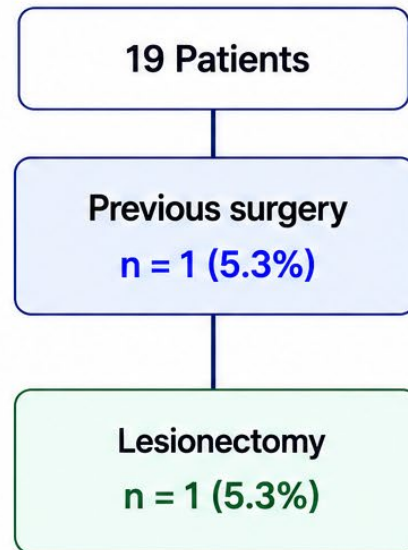


Non-lesional MRI findings were more common in the corpus callosotomy group, whereas **lesional MRI findings** were more common in the VNS group.

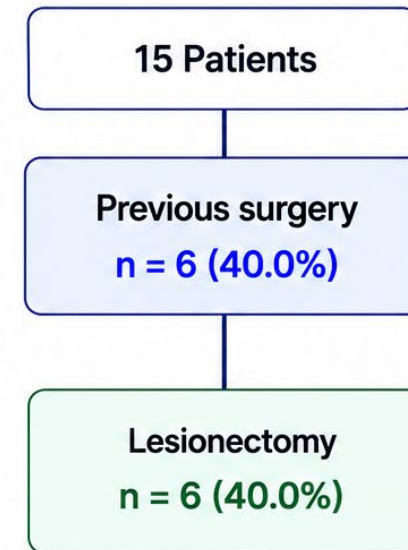


Previous Surgery

Corpus Callosotomy (N = 19)



VNS (N = 15)



Previous surgery was performed in **5.3%** of corpus callosotomy patients and **40.0%** of VNS patients. In the corpus callosotomy group, **1 patient (5.3%)** and in the VNS group, **6 patients (40.0%)** underwent lesionectomy.



Surgical outcome

Postoperative Antiseizure Medication Status

Corpus Callosotomy (N = 19)	VNS (N = 15)
 Decreased 8 (42.1%)	 Decreased 3 (20.0%)
 Unchanged 5 (26.3%)	 Unchanged 9 (60.0%)
 Increased 7 (36.8%)	 Increased 3 (20.0%)



Reduction in the number of antiseizure medications was more common after **corpus callosotomy (42.1%)**, whereas most patients in the VNS group had **no change** in medication number (**60.0%**).



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Responder Rate at Last Follow-up ($\geq 50\%$ Seizure Reduction)

Corpus Callosotomy (N = 19)



18 / 19
(94.7%)

VNS (N = 15)



12 / 15
(80.0%)

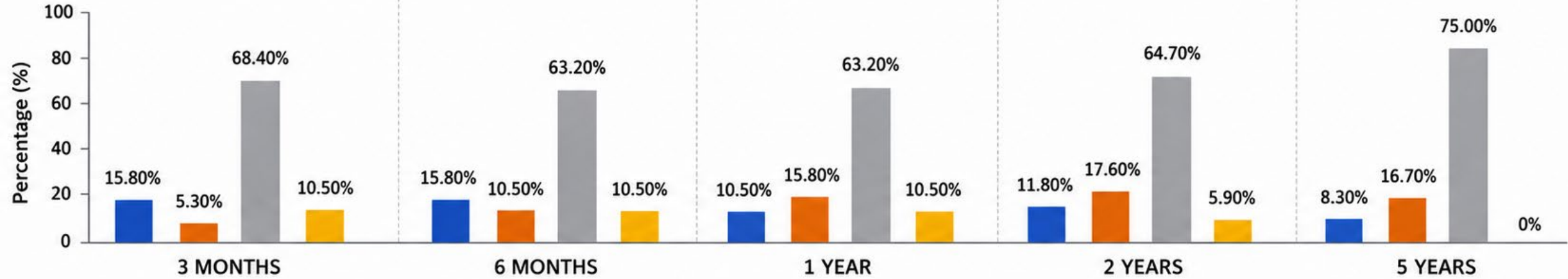


Responder rate at the last follow-up was
higher after corpus callosotomy than after VNS (94.7% vs. 80.0%).

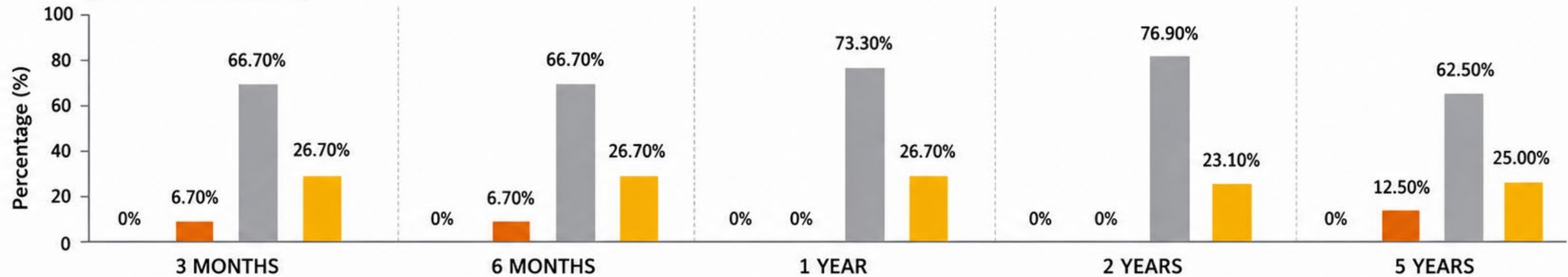
SURGICAL OUTCOME

■ Engel I ■ Engel II ■ Engel III ■ Engel IV

Corpus Callosotomy (N = 19)



VNS (N = 15)

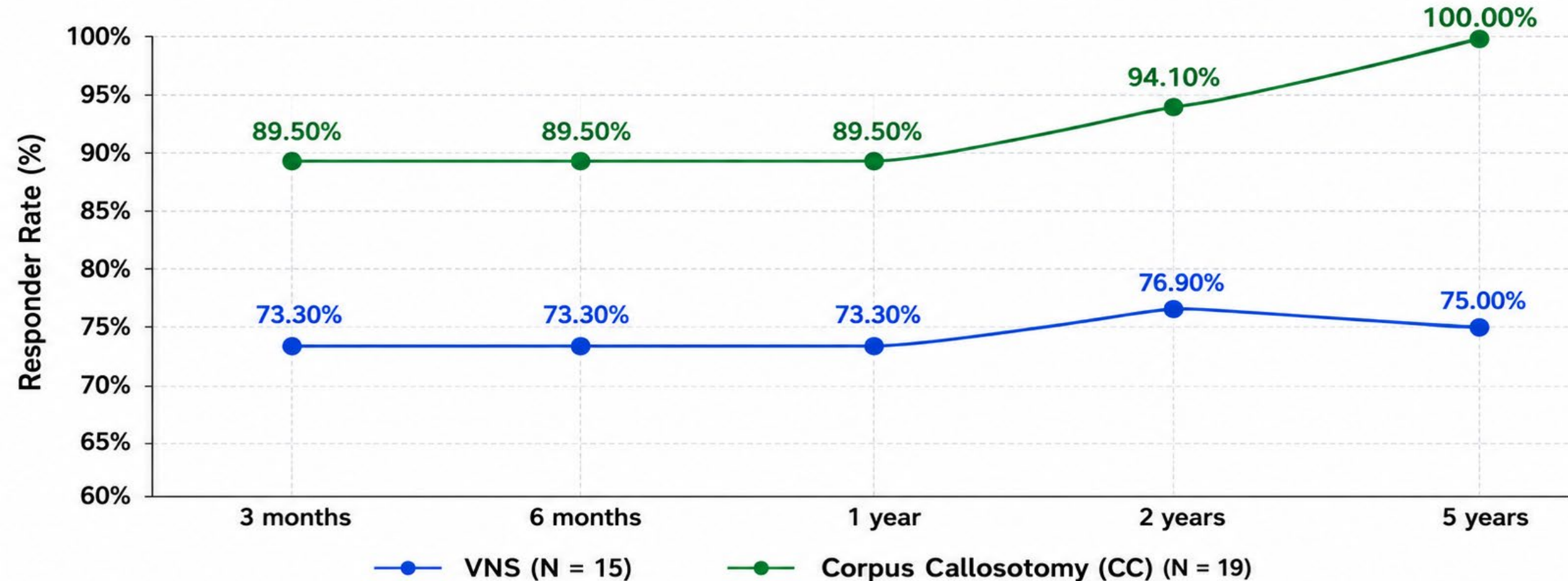


Note: Percentages may not total 100% due to rounding.

N at each time point: Corpus Callosotomy – 3M(19), 6M(19), 1Y(19), 2Y(17), 5Y(12); VNS – 3M(15), 6M(15), 1Y(15), 2Y(13), 5Y(8)

RESPONDER RATE

VNS vs. Corpus Callosotomy



Corpus callosotomy showed higher responder rates than **VNS** at all time points, with an increasing trend over time.

Note: N at each time point — CC: 3M(19), 6M(19), 1Y(19), 2Y(17), 5Y(12); VNS: 3M(15), 6M(15), 1Y(15), 2Y(13), 5Y(8)



Complications

Corpus Callosotomy (N = 19)

No disconnection syndrome:
0 (0%)

Transient minor hemiparesis:
1 (5.3%)
→ Complete functional recovery

VNS (N = 15)

Lead infection:
1 (6.7%)
→ Lead removal

Transient arrhythmia:
2 (13.3%)
→ Resolved spontaneously on POD 0

VNS was associated with minor infection and transient arrhythmia,
whereas corpus callosotomy had no disconnection syndrome
and only one case of transient minor hemiparesis with complete functional recovery.



COMBINED GROUP

*Patients Undergoing Both
Corpus Callosotomy and VNS*





BASELINE CHARACTERISTICS OF COMBINED GROUP

Patients Who Underwent Both Corpus Callosotomy and VNS



 Combined Group (N = 8)	
 Patients, n	8
 Female : Male	4 : 4
 Procedure	Corpus Callosotomy + VNS
 Mean follow-up	81 months (16–146)



KEY MESSAGE

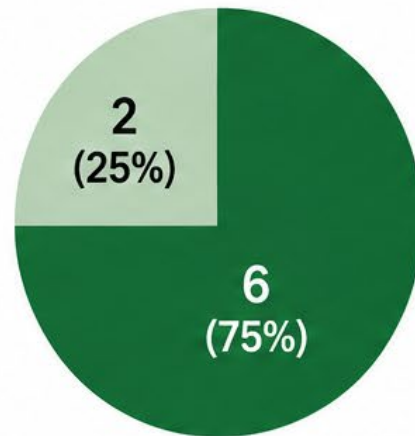
Eight patients underwent both corpus callosotomy and VNS,
with balanced sex distribution and a mean follow-up of 81 months.
All corpus callosotomy procedures were anterior two-thirds callosotomy.

Clinical Characteristics of Combined Group



Etiology

(n = 8)



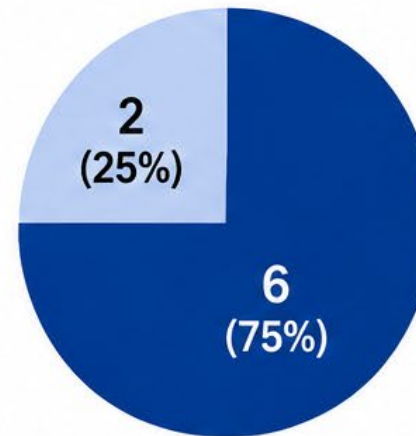
LGS	6 (75%)
Localized related	2 (25%)

- LGS was the most common etiology (75%).



Semiology

(n = 8)



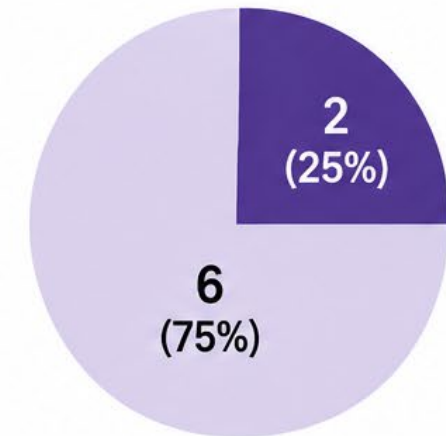
Multiple seizure types	6 (75%)
GTC	2 (25%)

- Multiple seizure types were more frequent (75%).



MRI Findings

(n = 8)



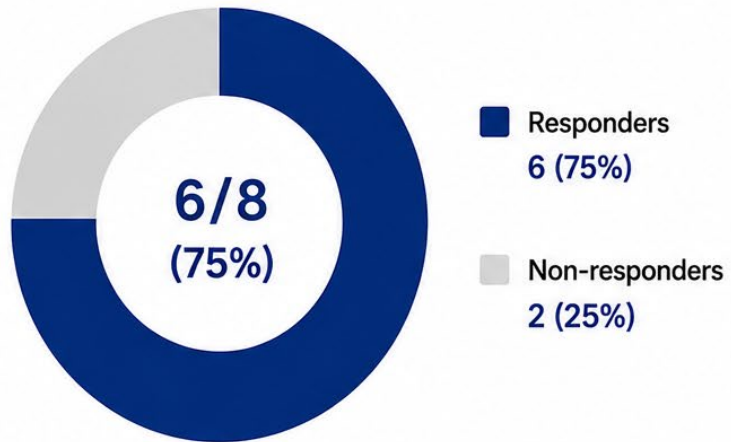
Lesional	2 (25%)
Non-lesional	6 (75%)

- Most patients had non-lesional MRI (75%).



Outcomes of Combined Group

Responder Rate at Last Follow-up



Seizure Outcome (Engel Classification)



All patients were Engel Class III
at last follow-up.

Responder: $\geq 50\%$ reduction in seizure frequency compared with preoperative baseline.



Complication of Combined Group

Complication		No. of Patients (n = 8)	
	Post VNS		
	• Transient arrhythmia	1	(12.5%)
	• Wound dehiscence (required wound revision)	1	(12.5%)
	• VNS turned off due to high impedance	1	(12.5%)
	Post Corpus Callosotomy (CC)		
	• Disconnection syndrome	0	(0%)

Procedure Cost and Hospital Stay



This is a sample of **one patient** who underwent both corpus callosotomy (CC) and VNS.

(Costs may vary depending on individual cases and hospital settings.)

Corpus Callosotomy (CC) (N = 19)



Total Procedural Cost

177,410 THB

Length of Stay



10 days

—
(No device)

VNS (N = 15)



Total Procedural Cost

915,731 THB

Length of Stay



3 days

Implant / Device Cost

869,085 THB
(≈ 94.9% of total VNS cost)



Key Takeaway



VNS cost was approximately **5 times higher** than corpus callosotomy, primarily due to the cost of the implanted device (869,085 THB).



Corpus callosotomy required a **longer hospital stay** postoperative (**10 vs. 3 days**).



VNS is associated with a **higher cost** due to the device, whereas corpus callosotomy involves a **longer hospital stay**.



177,410 THB
(Corpus Callosotomy)

vs.



915,731 THB
(VNS)



Conclusion



Both corpus callosotomy and VNS provided **meaningful seizure reduction** in drug-resistant epilepsy.



Corpus callosotomy achieved **higher responder rates** and **greater reduction in antiseizure medication use** than VNS. Combined corpus callosotomy and VNS **provided additional seizure control** in selected patients.



Both procedures were **safe**, with low complication rates and no permanent neurological deficits.



Corpus callosotomy was **more cost-effective** with lower overall cost, while **VNS device accounted** for most of the total treatment cost.

ANTERIOR THALAMIC DBS

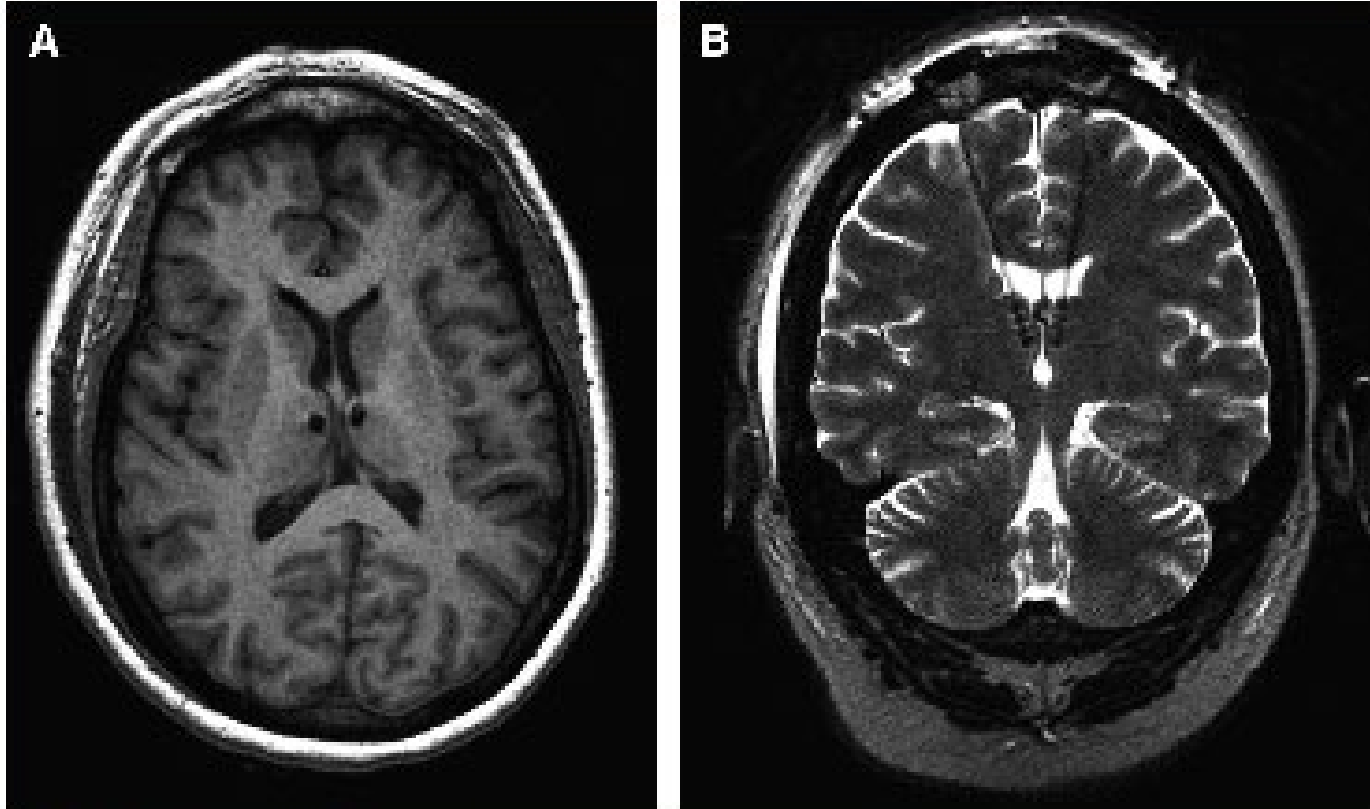


FIGURE 2. A, axial T1 and B, coronal T2-weighted magnetic resonance images depicting bilateral AN-DBS electrodes. AN, anterior thalamic nuclei; DBS, deep-brain stimulation.

Deep brain stimulation of anterior thalamic nuclei for intractable epilepsy in Thailand: case report

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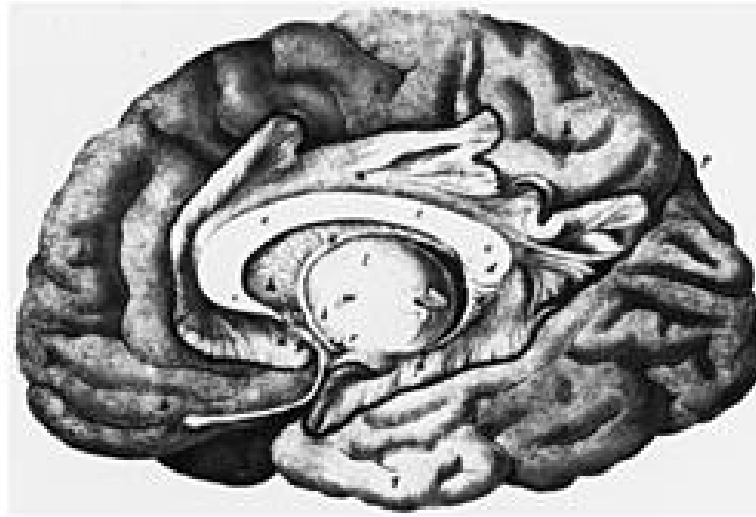
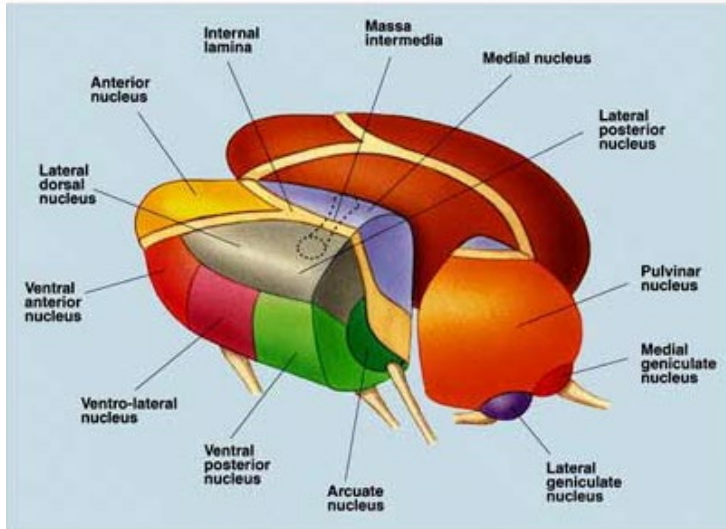
Neurostimulation can be an alternative treatment for medically intractable epilepsy, especially when the resective surgery could not be performed. The author reported a case of 19-year-old, right-handed male patient who had a history of intractable epilepsy for 11 years after post viral encephalitis associated with status epilepticus. Following the failure of antiepileptic medications and then resective surgery, anterior thalamic deep brain stimulation (DBS) was performed. Indirect targeting of anterior thalamic nuclei could not be used because of asymmetric brain shift from prior multilobar resections. Direct targeting of anterior thalamic nuclei from MRI T1 sequence, Short Tau Inversion Recovery (STIR) sequence combined neurophysiological mapping by microelectrode recording were used as a technique for implantation of DBS electrodes. The stimulation was turned on with 145 Hz, pulse width 90 microseconds, 5 volts with cycling mode 1 minute "on" and 5 minutes "Off". The antiepileptic medications continued the same as pre-operative state. Sixty percent seizure reduction was achieved in 24 months after surgery. There were no side effects of DBS during the follow-up period.

Anterior thalamic DBS can be performed safely with satisfactory seizure outcomes. Direct targeting of anterior thalamic nuclei combination with microelectrode recording can be very helpful, especially when asymmetric basal ganglion structures were detected.

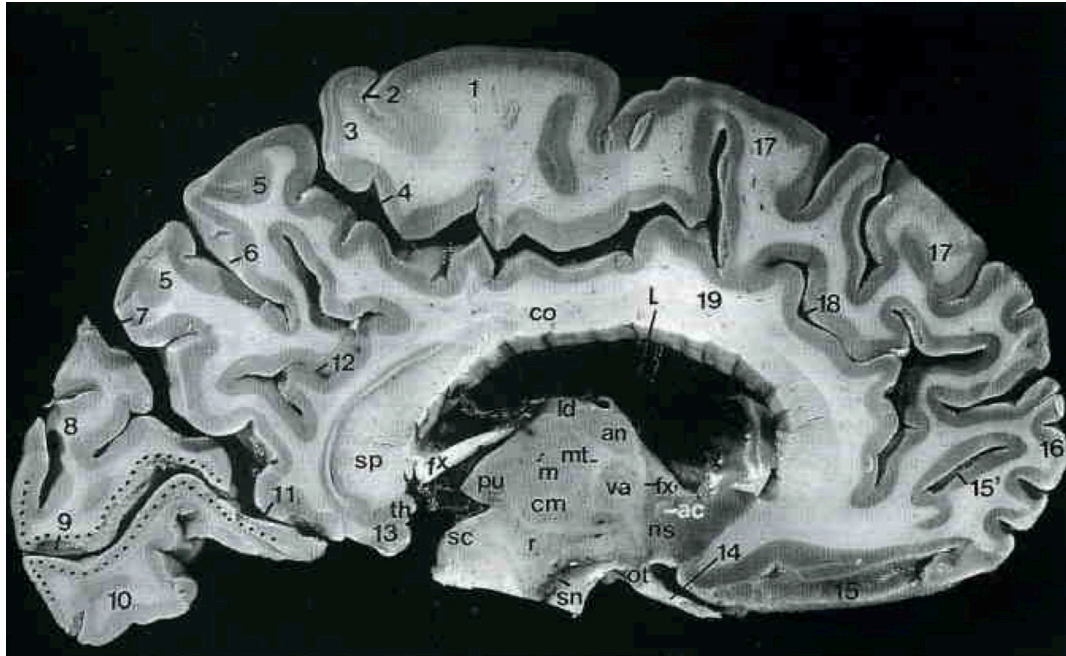
Keywords: Anterior thalamic DBS, medically intractable epilepsy, neurostimulation

J Med Assoc Thai 2016; 99 (Suppl.):

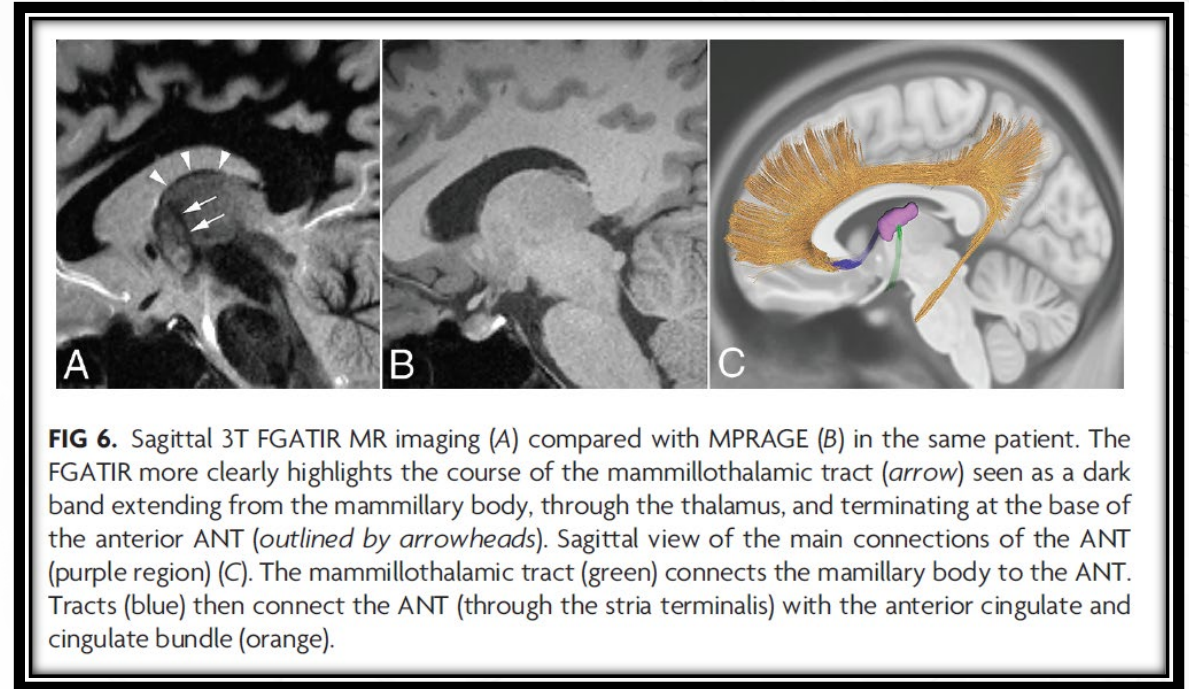
Full text. e-Journal: <http://www.jmatonline.com>

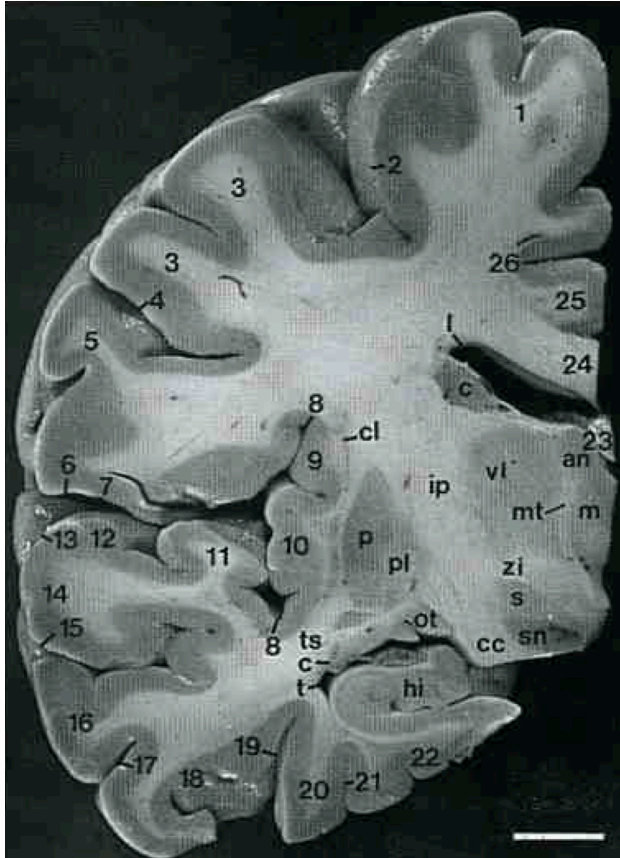


- The anterior nucleus of thalamus is part of the circuit of Papez. Its complex anatomy of this nucleus is divided into 4 parts, Apr (main), AM (medial), AD (dorsal) and DSF (superficial).
- The Apr part are the main principle nucleus, which is about 4*5*10mm³ in dimension.
- The input of ANT mainly arises from hippocampus, fornix and mammillothalamic tract respectively.
- The output of ANT goes to cingulum and paralimbic structures to complete the circuit of Papez.



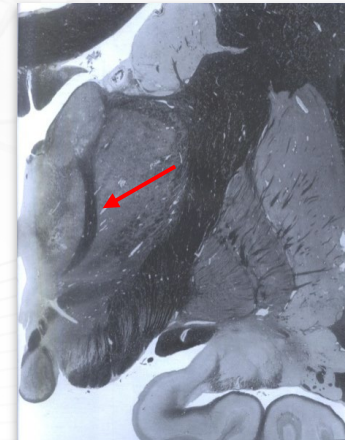
an : anterior thalamic nu.
m : mediodorsal thalamic nu.
mt : mamillothalamic tract
va : ventral anterior thalamic nu.





an : anterior thalamic nu.
m : mediodorsal thalamic nu.
mt : mammillothalamic tract
vl : ventral lateral thalamic nu.

- The boundary of ANT is also important for direct targeting this small nucleus. The ventricular system serves as the broader anteriorly and superiorly.
- The mammillothalamic tract ran into this nucleus inferiorly in the coronal and sagittal planes.
- The lateral boundary separates from other thalamic nuclei by internal laminae.

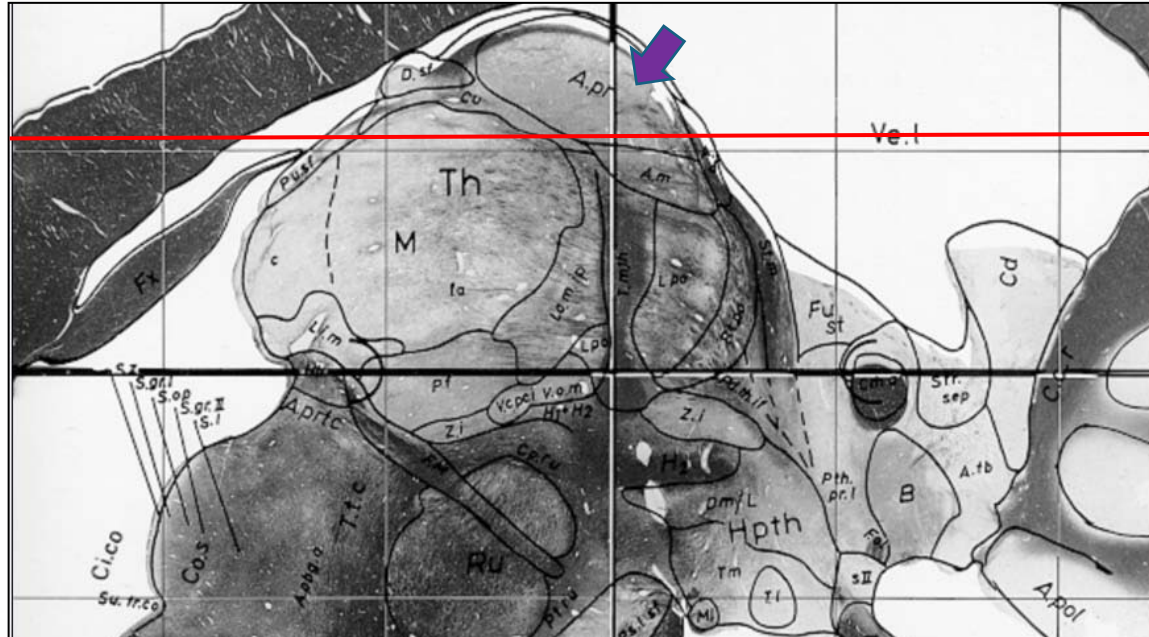




Deep Brain Stimulation

- Advantages:
 - Moderately better outcomes than VNS.
 - More targeted control at seizure spread
 - Known surgical technique
 - No vocal hoarseness
- Disadvantages:
 - Complications rare but potentially more severe than VNS
 - Open Loop design

- Outcomes: SANTE Trial
 - 110 patients randomized, double-blind design.
 - 60% of treated patients had >50% seizure reduction in first 3 months.
 - By 3 years patients had 68% average seizure reduction.
 - At 1 year 9% were seizure free
 - 44.5% had prior VNS, 24.5% had prior surgery



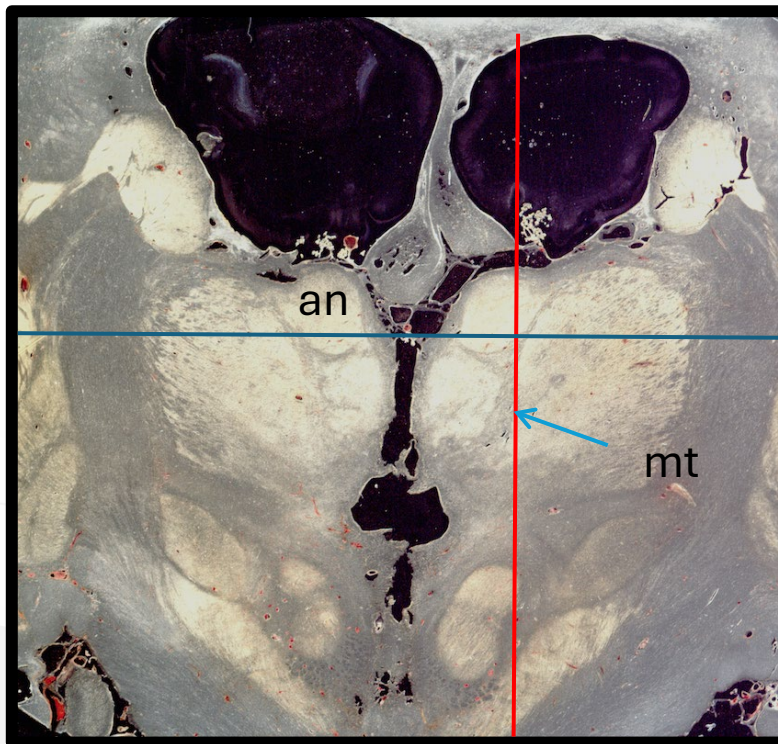
5-6 mm lateral
12mm superior
2 mm anterior to MCP



MCP



- The most important anatomical landmark for defining ANT is the identification of **mammillothalamic tract**, which can be followed as a dark signal from mammillary body to ANT. The **mammillothalamic tract** can be easily seen in coronal and sagittal view during the planning.

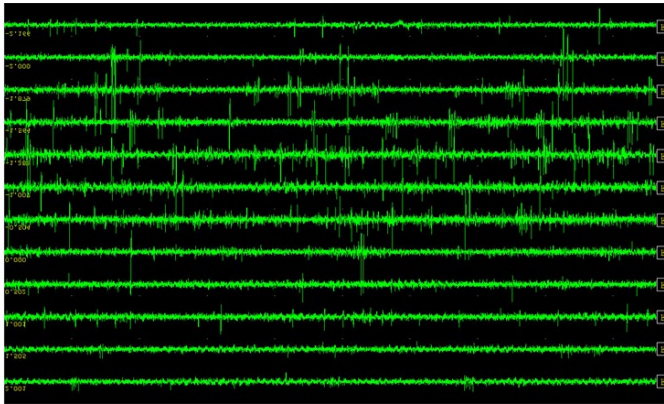


Indirect target

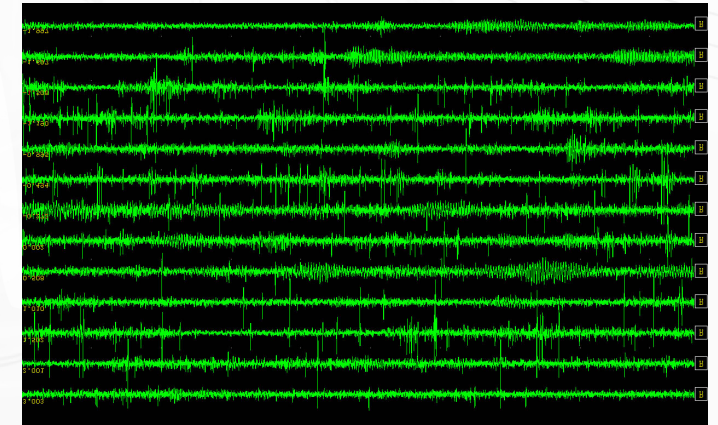
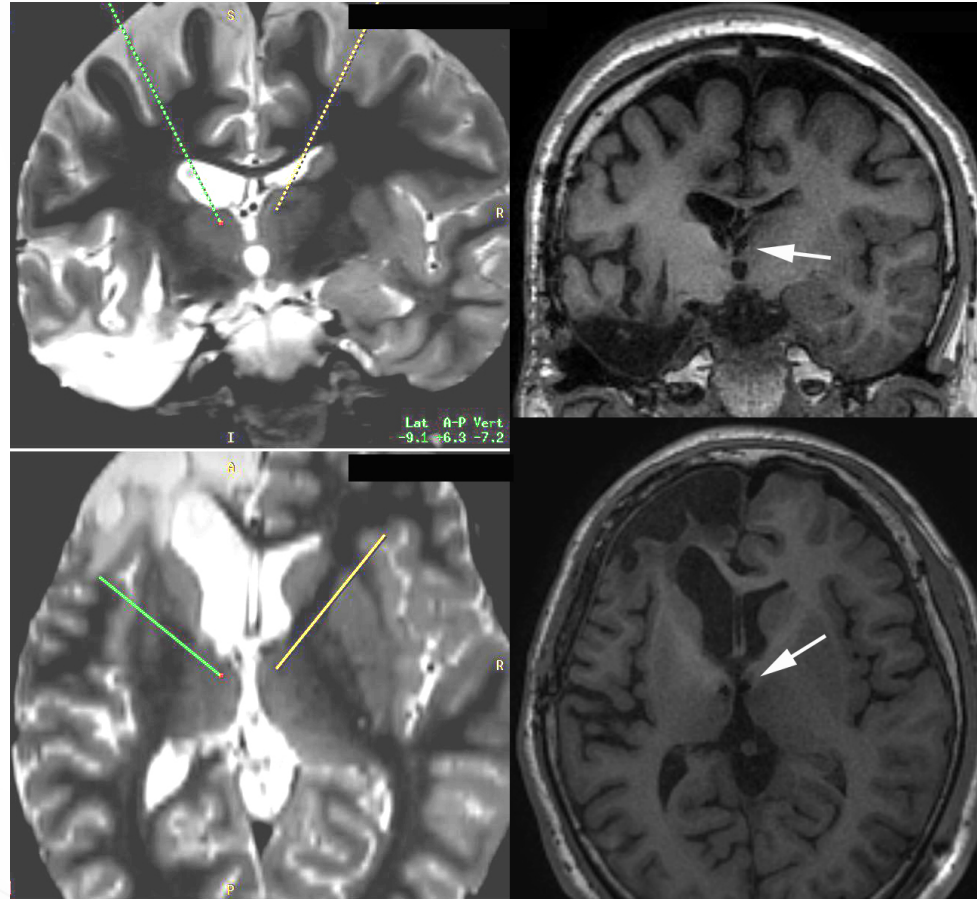
5-6 mm lateral

12mm superior

2 mm anterior to MCP



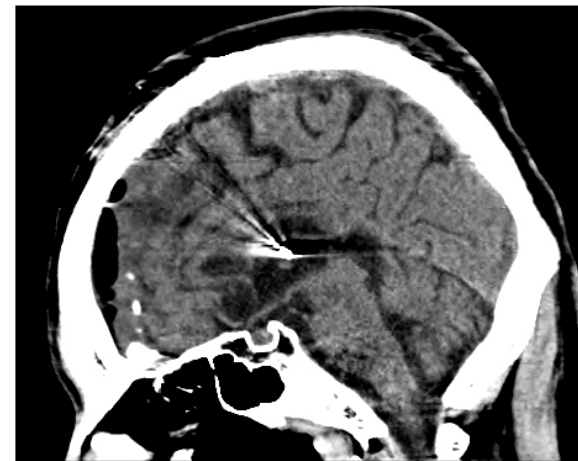
Left ANT MER



Right ANT MER



- The stimulation was turned on with 145 Hz, pulse width 90 microseconds, 3.5 volts with cycling mode 1 minute “on” and 5 minutes “off”. The antiepileptic medications continued at the same rate as the preoperative state. Fifty percent seizure reduction was achieved in 4 months after surgery. Last follow-up May 2026, a few brief seizures per 6 months. (>80% SR) No side effects were observed over 10 years (except for a single breakthrough seizure when the battery spontaneously turned off). The second battery was replaced two years ago.



RESEARCH

Open Access



Long-term efficacy of anterior nucleus of the thalamus deep brain stimulation in drug-resistant epilepsy: a 5-year multicenter study

Tianqi Hu^{1†}, Hutao Xie^{1†}, Ming Shan^{2†}, Lin Sang³, Bowen Yang⁴, Quan Zhang¹, Dongmei Gao¹, Yuanyuan Jiao¹, Qinglong Guo², Sizhe Li⁵, Yuxin Wang⁵, Xinnan Du¹, Anchao Yang^{1,6}, Fangang Meng^{1,6,7}, Jianguo Zhang^{1,6,7*}, Kai Zhang^{1,6*} and Hua Zhang^{1*}

Abstract

Background Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT-DBS) has demonstrated potential in reducing seizure frequency (SF) in patients with drug-resistant epilepsy (DRE). This multicenter retrospective study aimed to comprehensively evaluate the long-term effects of ANT-DBS on seizure reduction and neuropsychological outcomes, as well as to identify prognostic factors associated with postoperative efficacy.

Methods We retrospectively analyzed data from DRE patients who underwent ANT-DBS across three epilepsy centers between July 2019 and December 2022. SF, responder rate, neuropsychological outcomes, and quality of life (QoL) were assessed using seizure diaries and standardized rating scales at baseline and annual follow-up. Univariate and multivariate regression analyses were performed to identify predictors of postoperative SF reduction.

Results A total of 40 patients were included, with a mean age at surgery of 28.6 ± 11.1 years. The average monthly SF decreased from 15 at baseline to 6.5 at the 5-year follow-up (a 56.7% reduction, $p < 0.001$), with a responder rate of 62.5%. Therapeutic effect was most pronounced within the first 24 months after implantation. The Liverpool Seizure Severity Scale (LSSS) scores improved from 26.7 ± 5.2 to 17.9 ± 8.6 ($p < 0.001$). Mood conditions (measured by the Hamilton Depression and Anxiety Rating Scales) improved from baseline to the final follow-up, while cognitive status remained stable. QoL also improved significantly, particularly in Overall QoL, Emotional Well-being, Energy/Fatigue and Social Functioning. Multivariate logistic regression identified temporal lobe seizures (OR 8.3, $p = 0.022$) and stimulation amplitude (OR 4.2, $p = 0.034$) as independent predictors of responder status following DBS implantation. Multivariate linear regression identified baseline LSSS scores (standardized β : 3.5, $p = 0.016$) and temporal lobe seizures (standardized β 35.4, $p = 0.024$) as independent predictors of SF reduction.

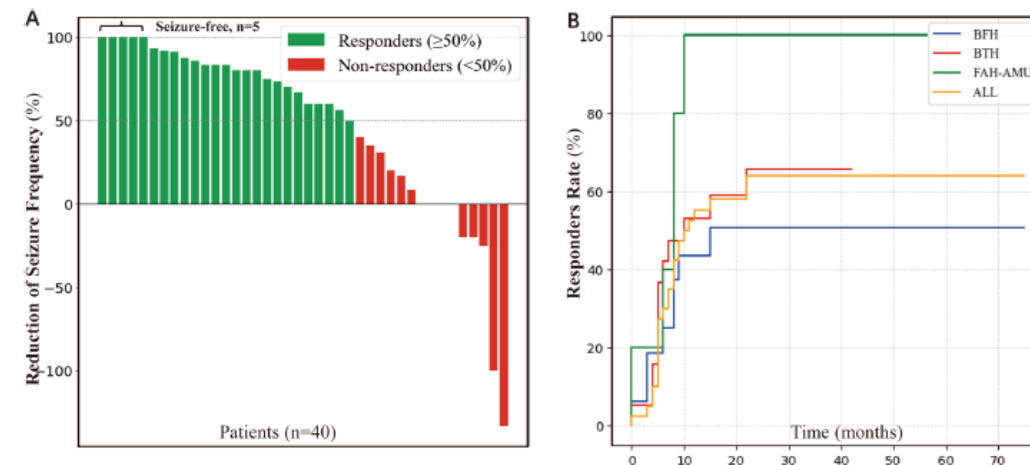
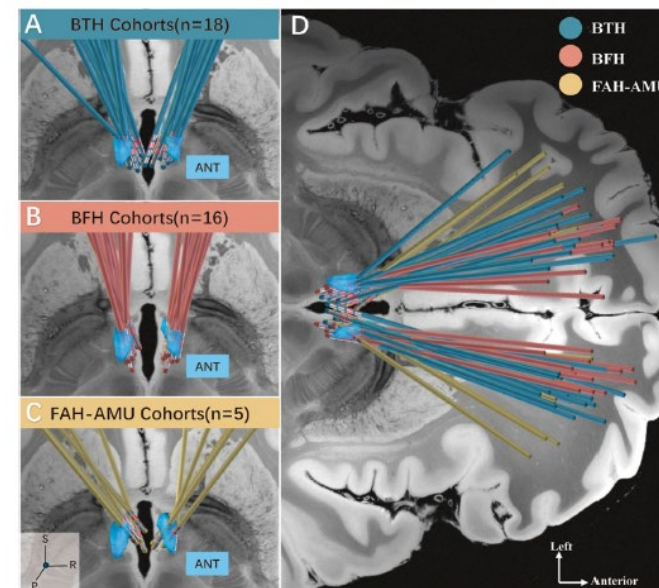


Fig. 4 Distribution and time points of responders. **A** Percent change in total SF from baseline to the last follow-up. Patients with $\geq 50\%$ reduction in SF (green) were defined as responders, while those with $< 50\%$ reduction (red) were considered non-responders. Five patients achieved seizure freedom. **B** Kaplan-Meier analysis of responder rate (RR) across BTH, BFH, and FAH-AMU. All responders achieved their status within the first 24 months





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



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 ($\geq 50\%$ 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

Figure 2 Percentage seizure reduction over time

Median and 25th and 75th percentiles around the median

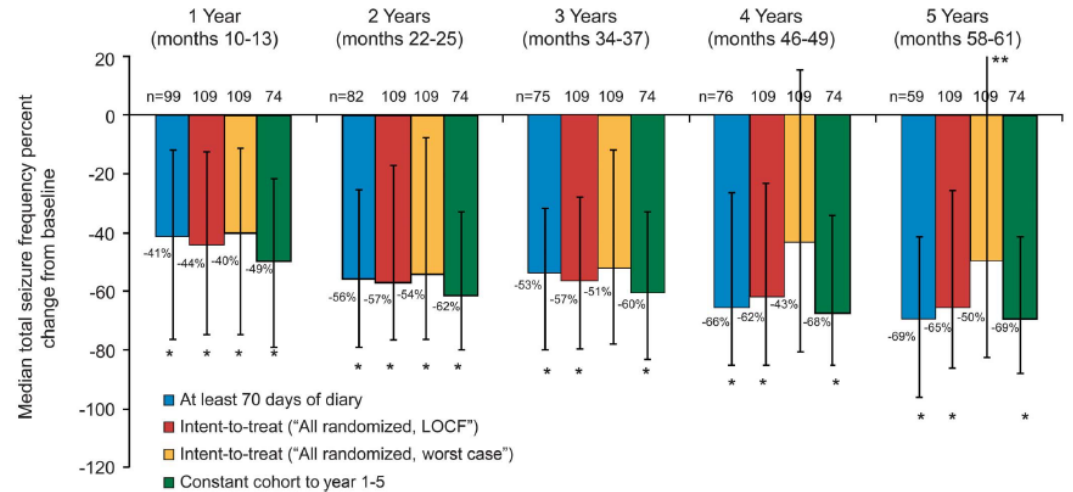
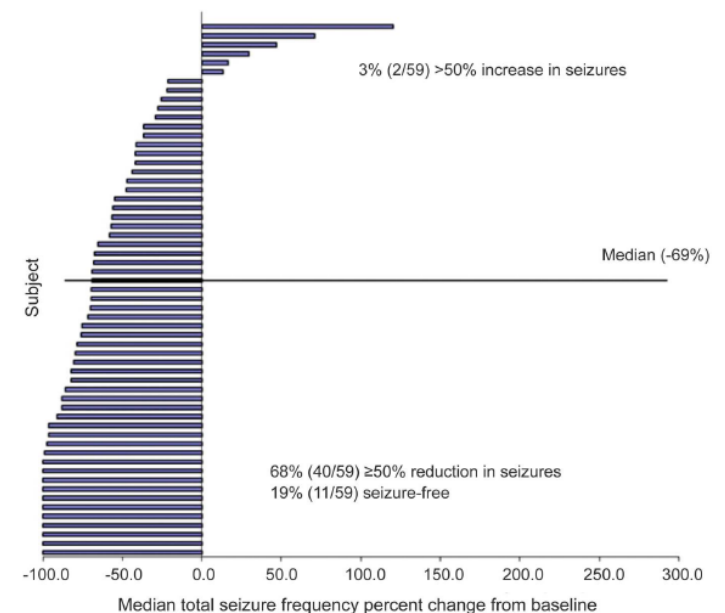


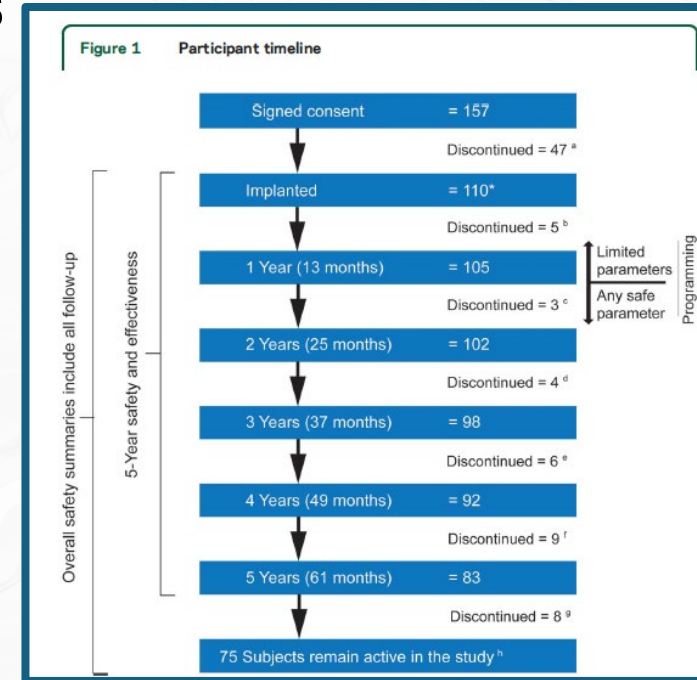
Figure 3 Distribution of individual subject response to treatment



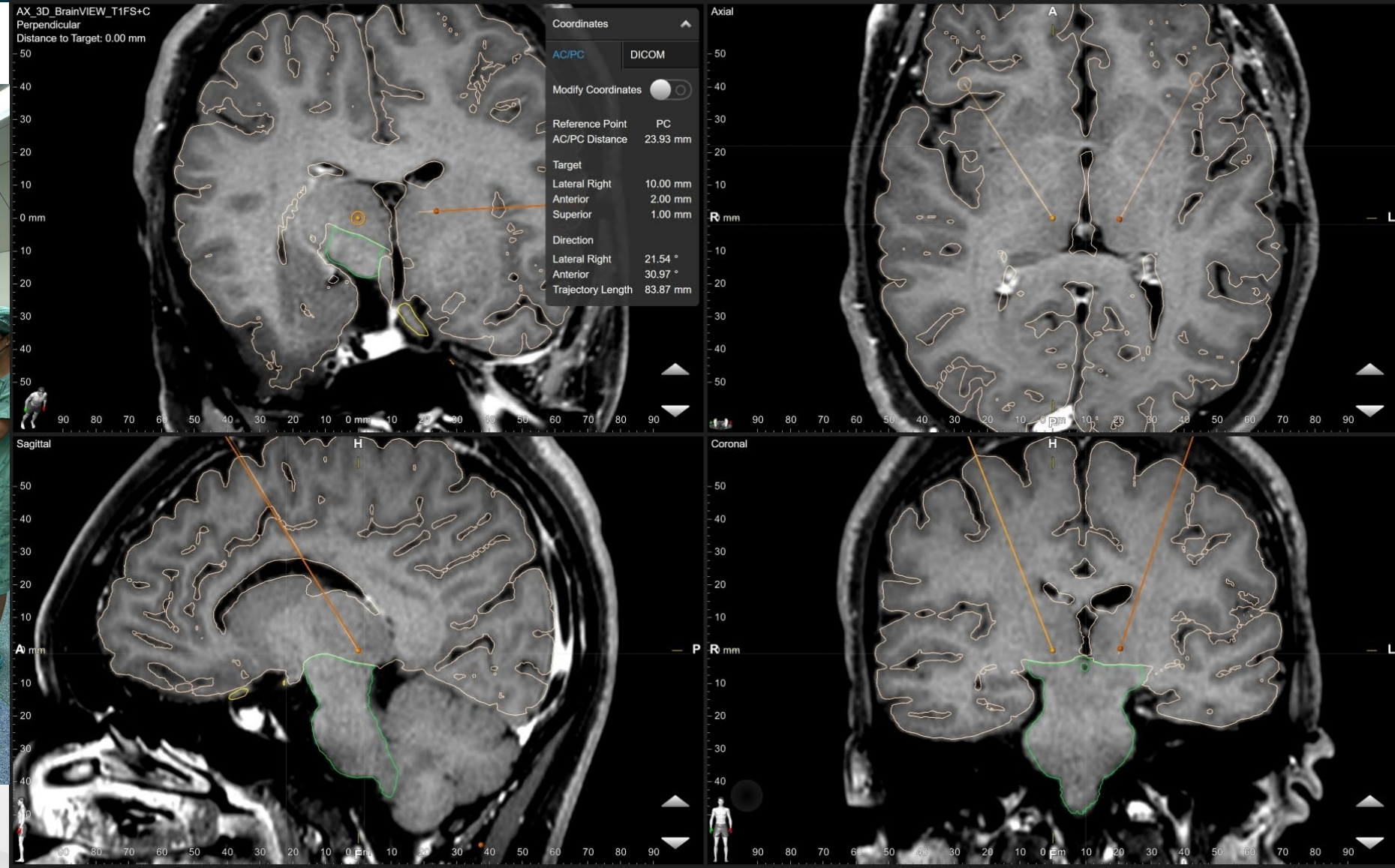
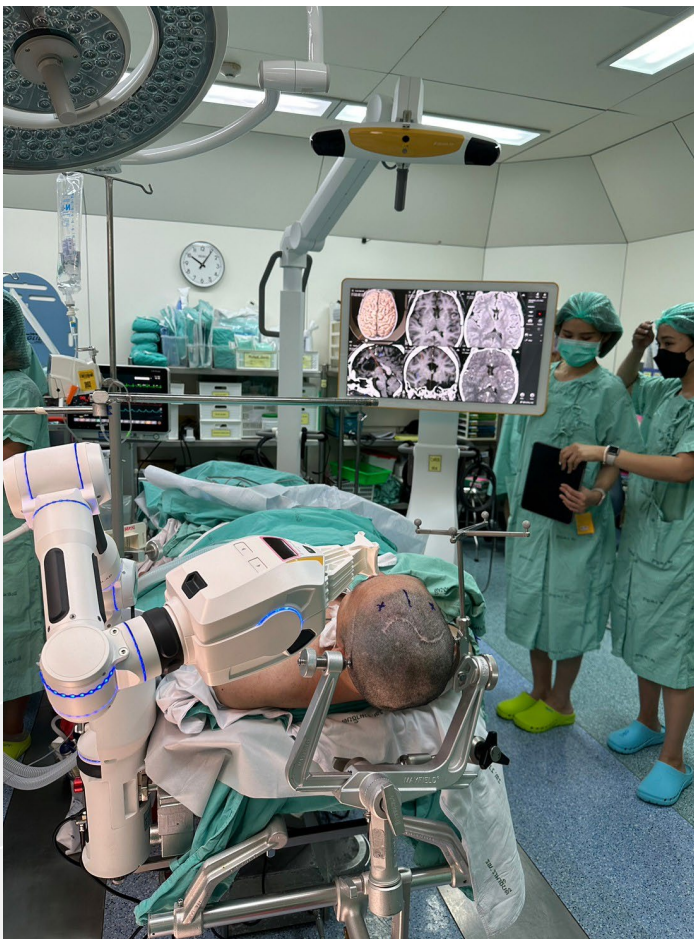


- Discomfort at neurostimulator site: 22.7% in 5 yrs
- Implanted site infection: 12.7%
- Therapeutic product ineffective: 10%
- Leads are not within the targeted: 8.2%
- Memory impairment: 25% in 5 yrs
- Dizziness: 6.4%
- Lead extension fracture: 5.5%
- Neurostimulation migration: 5.5%

Others : Depression: 32.7%, Suicidal ideation: 8%, SUDEP (7 cases)



Robotic-assisted for DBS-CM thalamus

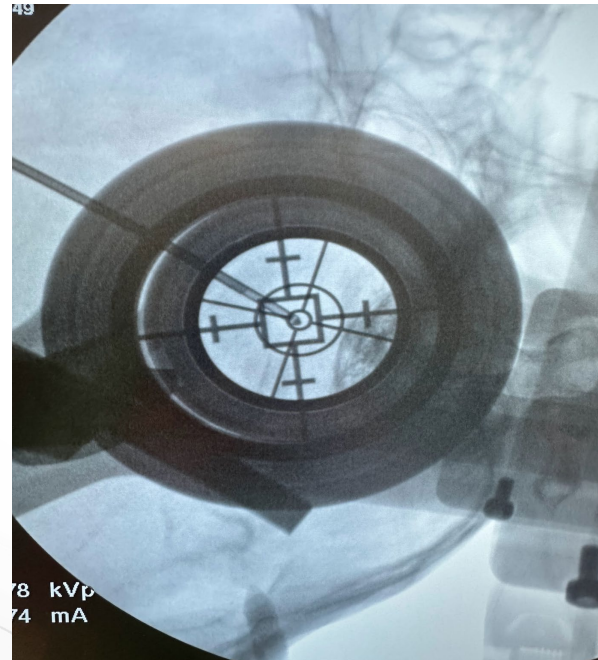




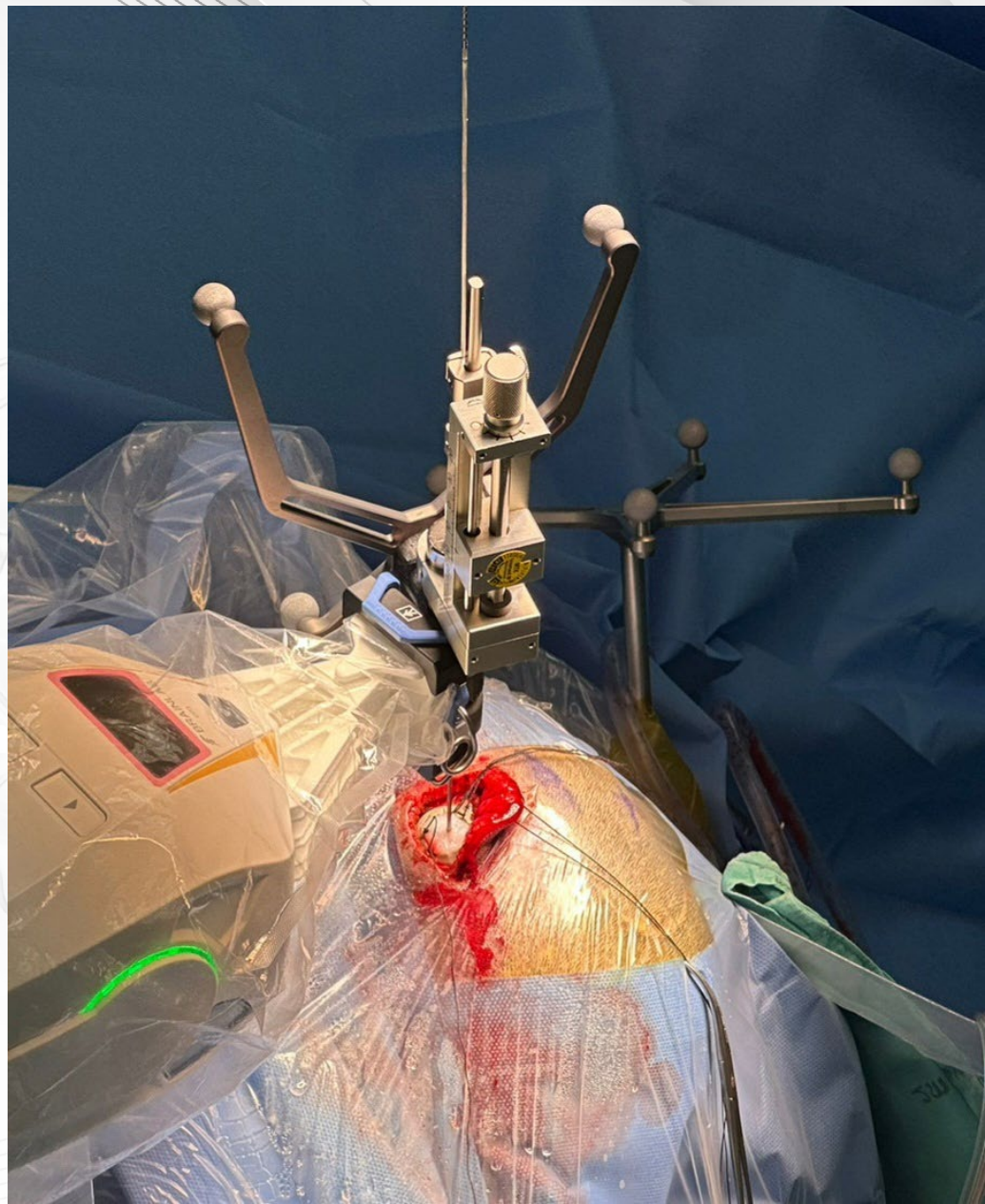
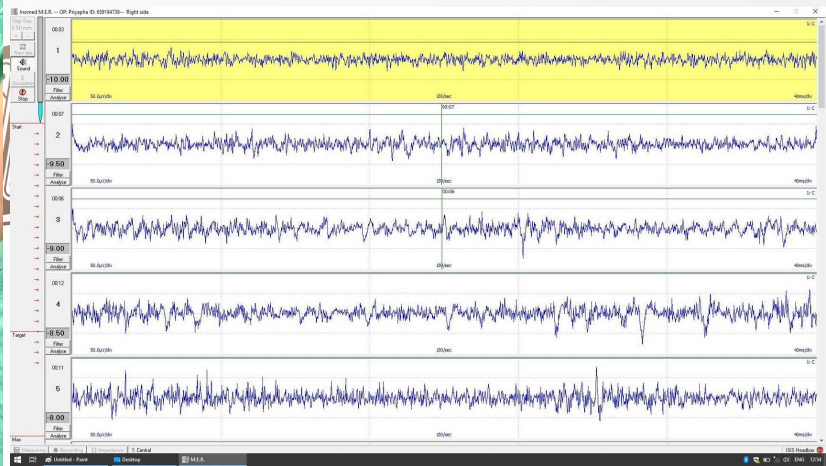
EST 30th ANNIVERSARY ANNUAL MEETING

Stereotactic targeting: evolution of surgery

Frame-based with X-ray for target confirmation

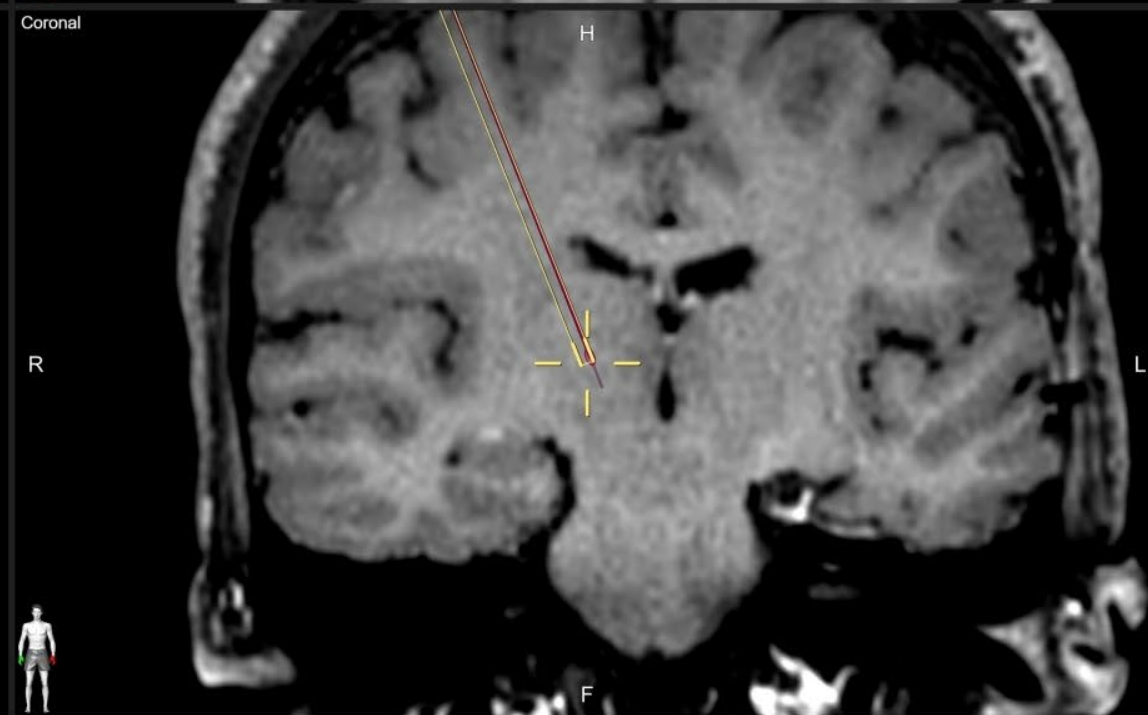
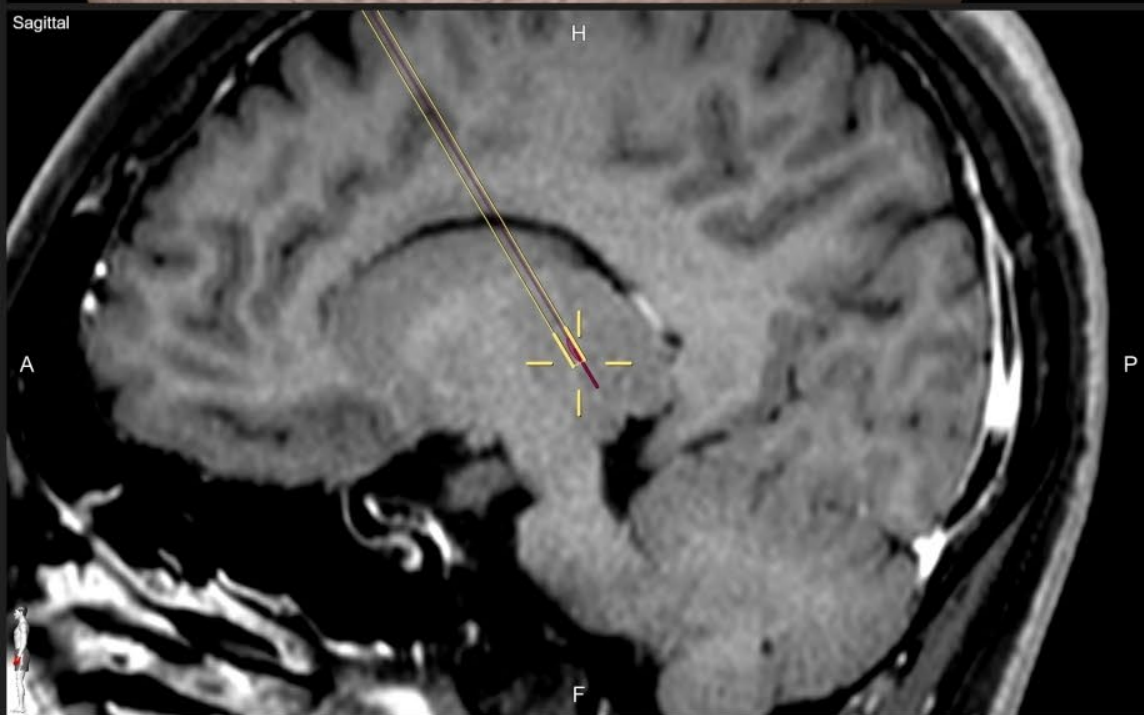
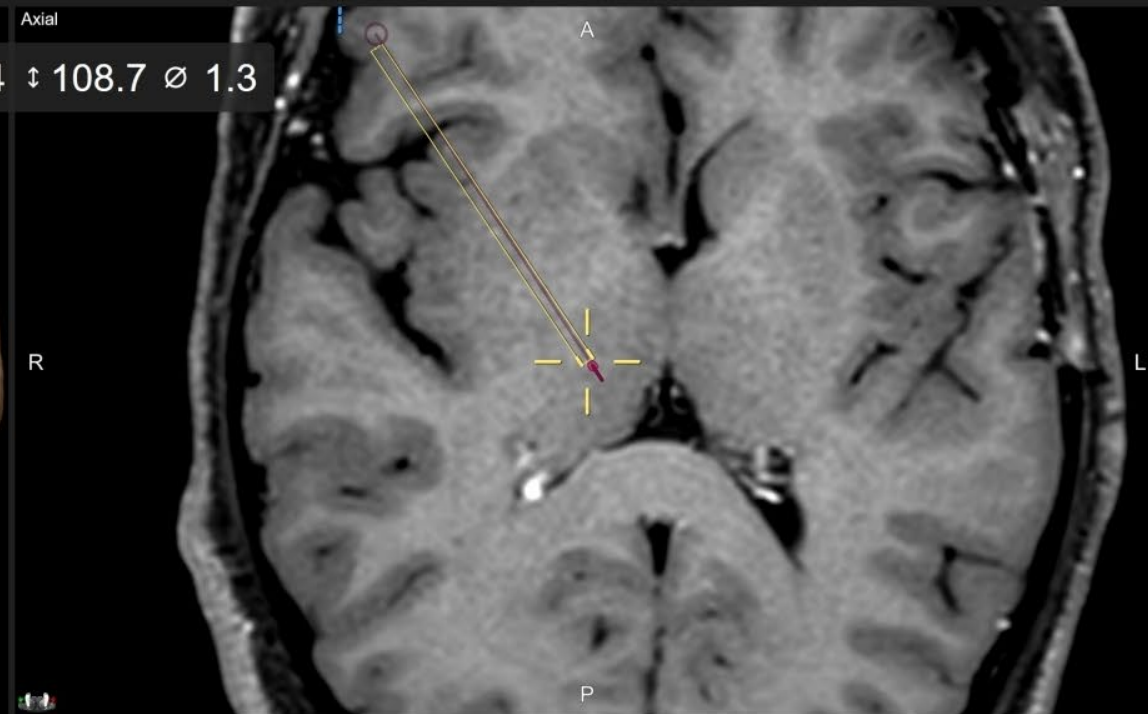


O-ARM fluoroscopy or CT/MRI intraoperative is an alternative for the verification of the electrode positions.





Trajectory 04 $\downarrow 108.7$ $\emptyset 1.3$



PRIYAPHA, LA-O-ONG
4111131

Cirq Robotic Alignment

Camera
Screenshot
Instruments

< Trajectory 04 >

Deviation Monitoring ☒

Threshold: 0.5 mm

Zoom: 220 %

Back Done

BRAINLAB

Trajectory 04 $\downarrow$ 108.7 $\varnothing$ 1.3

7.0 mm

7.0 mm



Camera



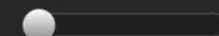
Screenshot



Instruments

< Trajectory 04 >

Deviation
Monitoring



Threshold:
0.5 mm



Zoom: 220 %



Back



Done

BRAINLAB

Trajectory 04 $\downarrow$ 108.7 $\varnothing$ 1.3

0.0 mm

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Camera



Screenshot



Instruments

< Trajectory 04 >

Deviation
Monitoring



Threshold:
0.5 mm



Zoom: 220 %



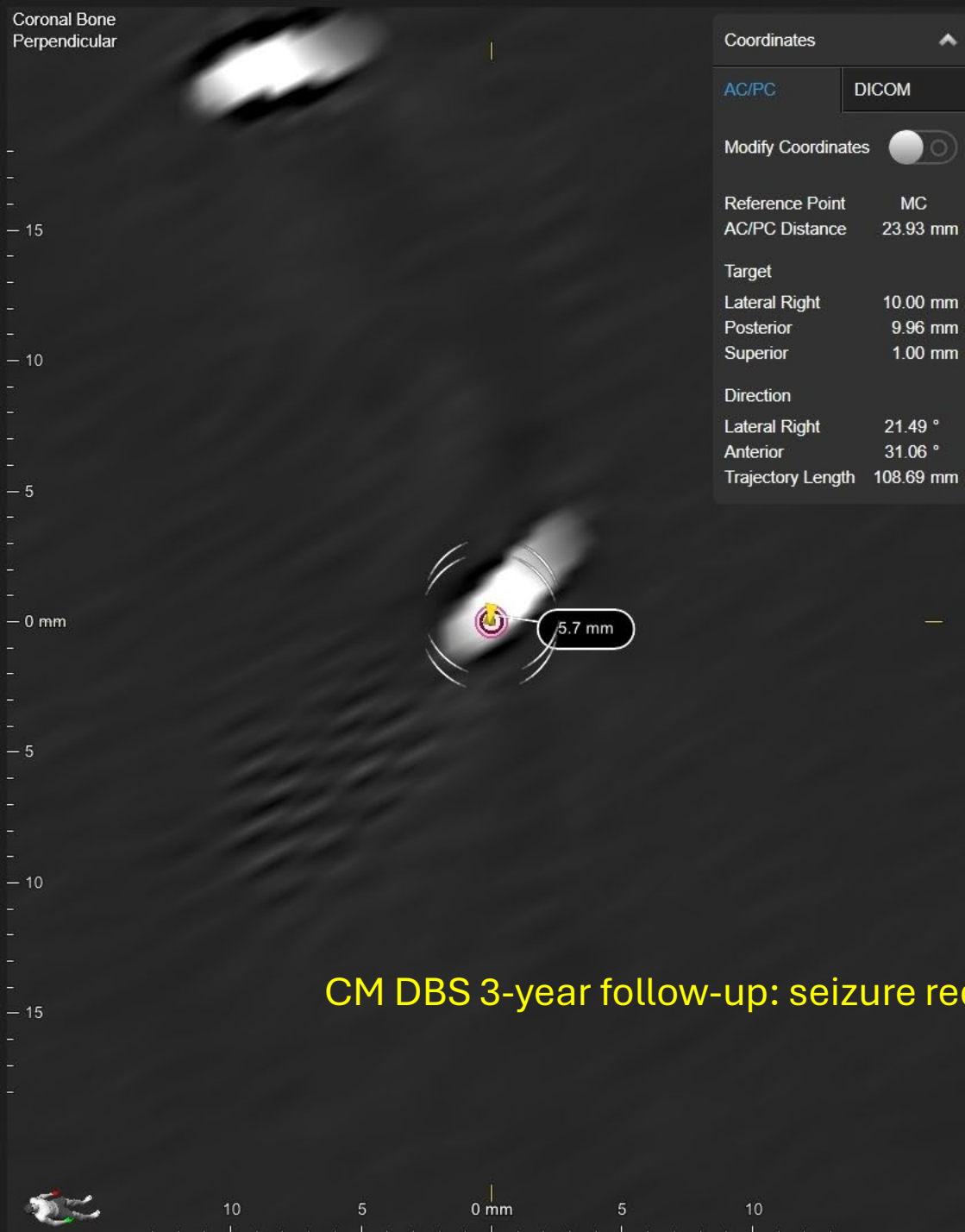
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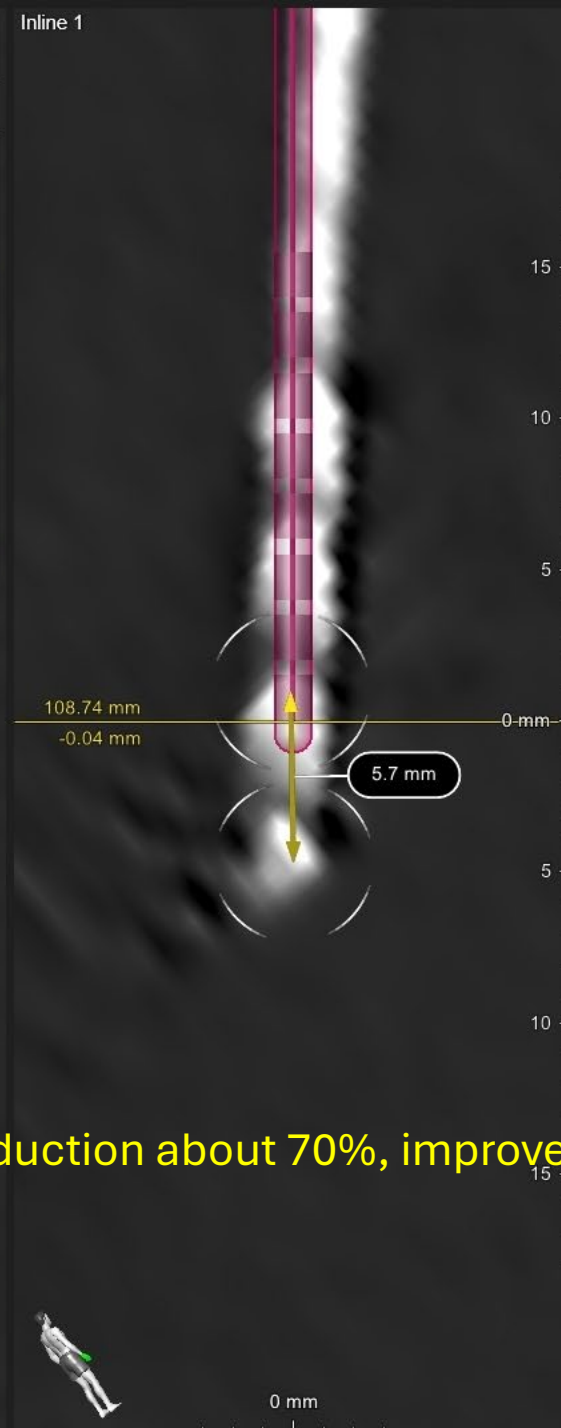
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BRAINLAB

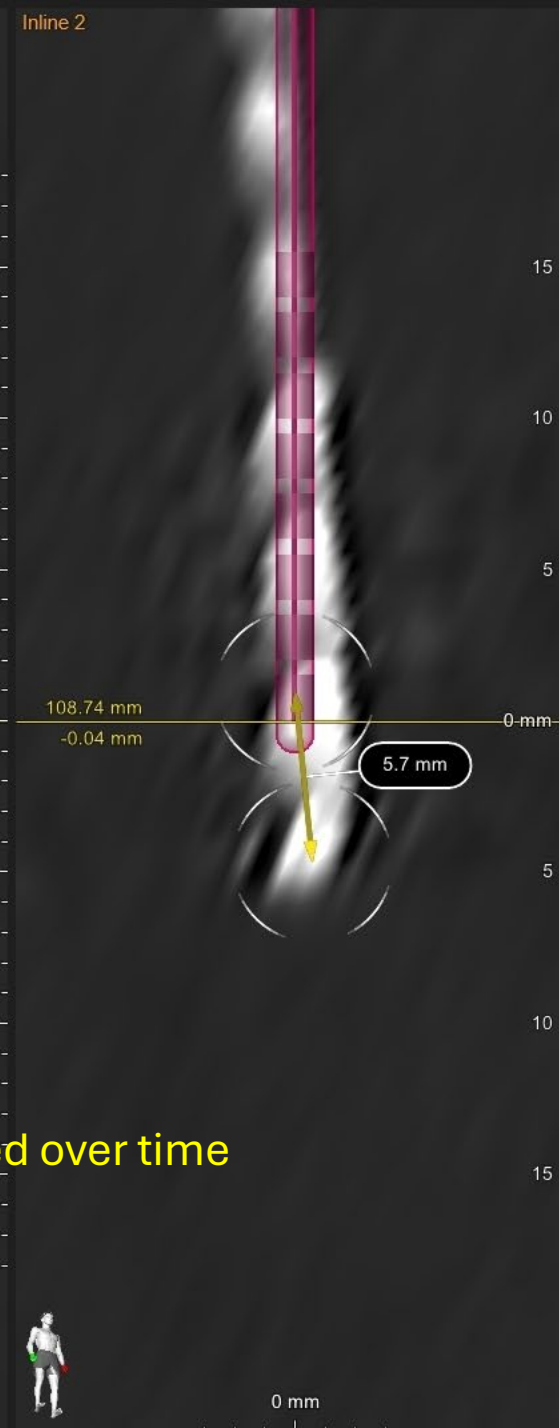
Coronal Bone
Perpendicular



Inline 1



Inline 2



CM DBS 3-year follow-up: seizure reduction about 70%, improved over time

Alerts Data Home

Stereotaxy

Scroll Zoom

Pan Rotate

Center Windowing

Trajectory 04

Trajectory Planning

Measure

Distance Margin

2.0 mm

Frame Planning

Back Done

BRAINLAB



The responsive neurostimulator system (RNS System, NeuroPace) was approved by the FDA in 2013 as an adjunctive therapy for adults with drug-resistant partial-onset seizures localized to no more than two epileptogenic foci.



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, Guy M. McKhann, MD, Mark A. Agostini, MD, Andreas V. Alexopoulos, MD, MPH, Barbara C. Jobst, MD, David W. Roberts, MD, Vicenta Salanova, MD, Thomas C. Witt, MD, Sydney S. Cash, MD, PhD, Andrew J. Cole, MD, Gregory A. Worrell, MD, PhD, Brian N. Lundstrom, MD, PhD, Jonathan C. Edwards, MD, Jonathan J. Halford, MD, David C. Spencer, MD, Lia Ernst, MD, Christopher T. Skidmore, MD, Michael R. Sperling, MD, Ian Miller, MD, Eric B. Geller, MD, Michel J. Berg, MD, A. James Fessler, MD, Paul Rutecki, MD, Alica M. Goldman, MD, PhD, Eli M. Mizrahi, MD, Robert E. Gross, MD, PhD, Donald C. Shields, MD, Theodore H. Schwartz, MD, Douglas R. Labar, MD, PhD, Nathan B. Fountain, MD, W. Jeff Elias, MD, Piotr W. Olejniczak, MD, PhD, Nicole R. Villemarette-Pittman, PhD, Stephan Eisenschenk, MD, Steven N. Roper, MD, Jane G. Boggs, MD, Tracy A. Courtney, BS, Felice T. Sun, PhD, Cairn G. Seale, MS, Kathy L. Miller, BS, Tara L. Skarpaas, PhD, and Martha J. Morrell, MD, on behalf of the RNS System LTT Study

Correspondence
Dr. Morrell
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Neurology® 2020;95:e1244-e1256. doi:10.1212/WNL.00000000000010154



Abstract

Objective

Neurology | Volume 95, Number 9 | September 1, 2020

To prospectively evaluate safety and efficacy of brain-responsive neurostimulation in adults with medically intractable focal onset seizures (FOS) over 9 years.

Methods

Adults treated with brain-responsive neurostimulation in 2-year feasibility or randomized controlled trials were enrolled in a long-term prospective open label trial (LTT) to assess safety, efficacy, and quality of life (QOL) over an additional 7 years. Safety was assessed as adverse events (AEs), efficacy as median percent change in seizure frequency and responder rate, and QOL with the Quality of Life in Epilepsy (QOLIE-89) inventory.

Results

Of 256 patients treated in the initial trials, 230 participated in the LTT. At 9 years, the median percent reduction in seizure frequency was 75% ($p < 0.0001$, Wilcoxon signed rank), responder rate was 73%, and 35% had a $\geq 90\%$ reduction in seizure frequency. We found that 18.4% (47 of 256) experienced ≥ 1 year of seizure freedom, with 62% (29 of 47) seizure-free at the last follow-up and an average seizure-free period of 3.2 years (range 1.04–9.6 years). Overall QOL and epilepsy-targeted and cognitive domains of QOLIE-89 remained significantly improved ($p < 0.05$). There were no serious AEs related to stimulation, and the sudden unexplained death in epilepsy (SUDEP) rate was significantly lower than predefined comparators ($p < 0.05$, 1-tailed χ^2).

Class IV evidence for safety for 9 years follow up



Table 3 Seizure frequency reduction and responder rates at 9 years according to region of seizure onset

Region of seizure onset	Median reduction (IQR), %	Responder rate, %
All MTL (n = 66)	73 (58–96)	77
MTL bilateral (n = 48)	71.9 (56–90)	77
MTL unilateral (n = 18)	94 (64–100)	78
All temporal (n = 95) MTL, lateral, MTL + lateral	73 (47–93)	72
All neocortical (n = 70)	81 (34–100)	70
Lateral temporal (n = 19)	81 (33–99)	58
Frontal (n = 21)	93 (31–100)	71
Other (n = 30)	79 (52–93)	77

Abbreviations: IQR = interquartile range; MTL = mesial temporal lobe.
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Long-term outcomes after responsive neurostimulation for treatment of refractory epilepsy: a single-center experience of 100 cases

Jorge A. Roa, MD,¹ Lara Marcuse, MD,² Madeline Fields, MD,² Maite La Vega-Talbot, MD,² Ji Yeoun Yoo, MD,² Steven M. Wolf, MD,³ Patricia McGoldrick, NP,³ Saadi Ghatan, MD,¹ and Fedor Panov, MD¹

Departments of ¹Neurosurgery and ²Neurology, Icahn School of Medicine at Mount Sinai, New York; and ³Department of Neurology, Boston Children's Health Physicians, New York Medical College, New York, New York

OBJECTIVE Despite antiepileptic drugs, more than 30% of people with epilepsy continue to have seizures. Patients with such drug-resistant epilepsy (DRE) may undergo invasive treatment such as resection, laser ablation of the epileptogenic focus, or vagus nerve stimulation, but many are not candidates for epilepsy surgery or fail to respond to such interventions. Responsive neurostimulation (RNS) provides a neuromodulatory option. In this study, the authors present a single-center experience with the use of RNS over the last 5 years to provide long-term control of seizures in patients with DRE with at least 1 year of follow-up.

METHODS The authors performed a retrospective analysis of a prospectively collected single-center database of consecutive DRE patients who underwent RNS system implantation from September 2015 to December 2020. Patients were followed-up postoperatively to evaluate seizure freedom and complications.

RESULTS One hundred patients underwent RNS placement. Seven patients developed infections: 2 responded to intravenous antibiotic therapy, 3 required partial removal and salvaging of the system, and 2 required complete removal of the RNS device. No postoperative tract hemorrhages, strokes, device migrations, or malfunctions were documented in this cohort. The average follow-up period was 26.3 months (range 1–5.2 years). In terms of seizure reduction, 8 patients had 0%–24% improvement, 14 had 25%–49% improvement, 29 experienced 50%–74% improvement, 30 had 75%–99% improvement, and 19 achieved seizure freedom. RNS showed significantly better outcomes over time: patients with more than 3 years of RNS therapy had 1.8 higher odds of achieving 75% or more seizure reduction (95% CI 1.07–3.09, $p = 0.02$). Also, patients who had undergone resective or ablative surgery prior to RNS implantation had 8.25 higher odds of experiencing 50% or more seizure reduction (95% CI 1.05–65.1, $p = 0.04$).

CONCLUSIONS Responsive neurostimulator implantation achieved 50% or more seizure reduction in approximately 80% of patients. Even in patients who did not achieve seizure freedom, significant improvement in seizure duration, severity, or postictal state was reported in more than 68% of cases. Infection (7%) was the most common complication. Patients with prior resective or ablative procedures and those who had been treated with RNS for more than 3 years achieved better outcomes.

<https://thejns.org/doi/abs/10.3171/2023.2.JNS222116>

KEYWORDS responsive neurostimulation; epilepsy; refractory; predictor; outcome; complications

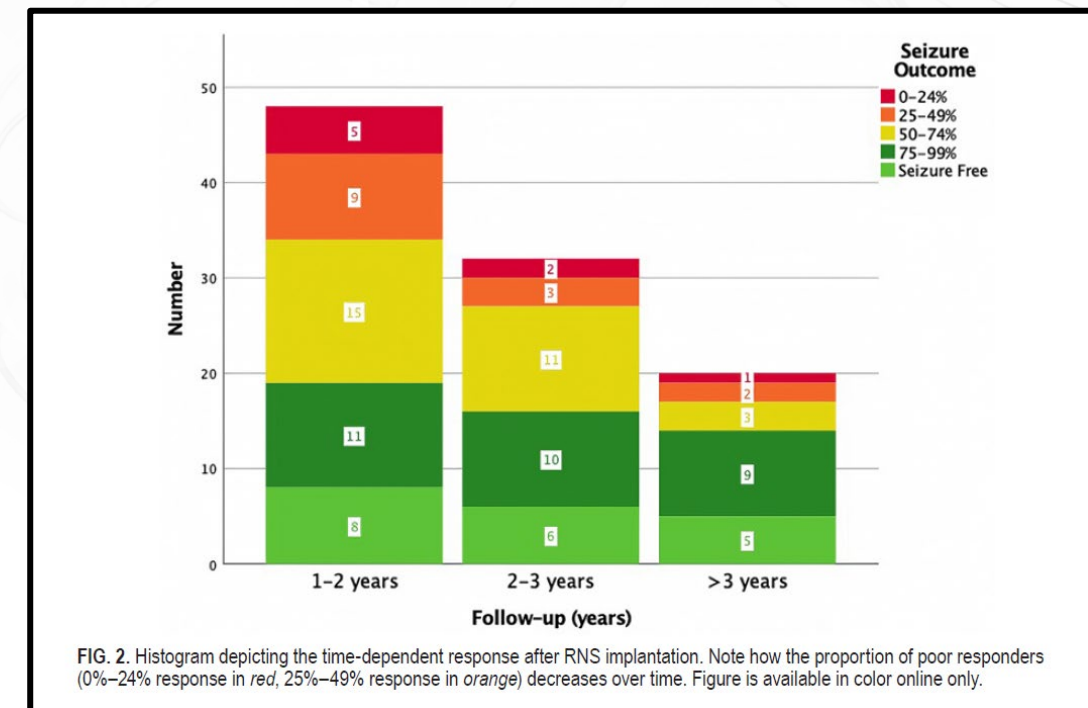
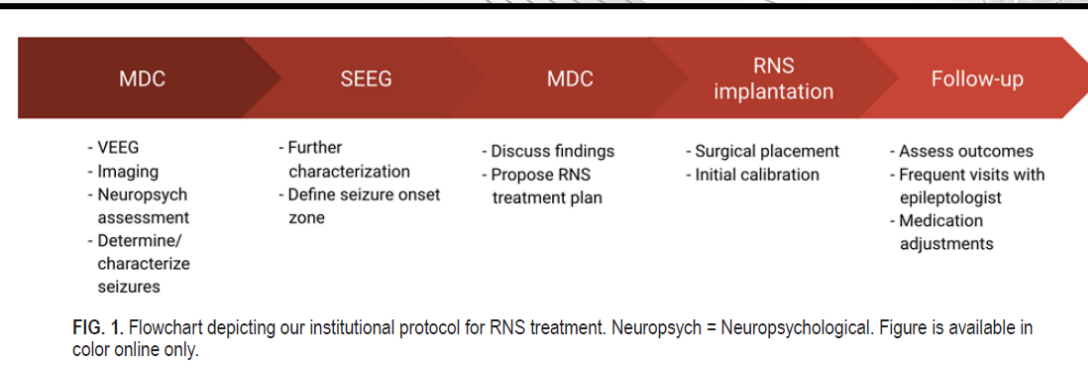




TABLE 3. Outcomes based on the relative reduction in seizure frequency

Relative Reduction in Seizure Frequency	0%–24%, n = 8	25%–49%, n = 14	50%–74%, n = 29	75%–99%, n = 30	Seizure-Free, n = 19
Improvement in seizure duration	2 (25%)	10 (71.4%)	23 (79.3%)	28 (93.3%)	NA
Improvement in seizure severity	1 (12.5%)	6 (42.9%)	21 (72.4%)	29 (96.7%)	NA
Improvement in postictal state	1 (12.5%)	7 (50%)	19 (65.5%)	28 (93.3%)	NA
Reduction in AED regimen	0 (0%)	3 (21.4%)	10 (34.5%)	20 (66.7%)	NA

NA = not applicable.

Percentages are based on column totals.

Conclusion: RNS implantation achieved $\geq 50\%$ seizure control in approximately 80% of patients. Even in those patients who did not achieve seizure freedom, a significant reduction in seizure duration, severity, or postictal state was reported in $\geq 68\%$ of cases. Infection was the most common complication.(7%) Patients with prior resective or ablative procedures and those who had been treated with RNS for ≥ 3 years achieved better outcomes.

NEUROMODULATION THERAPIES FOR EPILEPSY

Different Mechanisms, Different Targets. One Goal: Reduce Seizures.

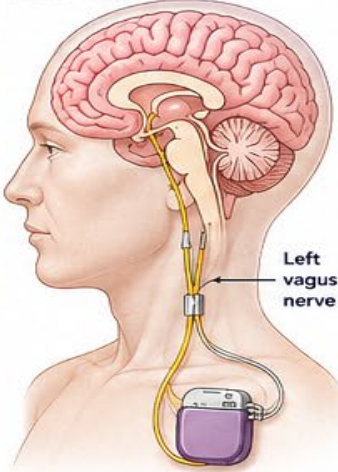
VAGUS NERVE STIMULATION (VNS)

Open-loop • Indirect • Body-to-brain



TARGET

Left vagus nerve in the neck



MECHANISM

1. Activates vagal afferent fibers (80%)
↓
2. Signals travel to the nucleus tractus solitarius (NTS) in the brainstem
↓
3. Activates neuromodulatory nuclei
 - Locus coeruleus (norepinephrine)
 - Dorsal raphe nucleus (serotonin)
 - Parabrachial nucleus
4. Produces widespread projections to multiple brain regions

5. Modulates neurotransmitters and networks to reduce seizure likelihood

HOW IT WORKS (Key Effects)

- ↑ Norepinephrine → enhances inhibition, reduces cortical excitability
- ↑ Serotonin → stabilizes mood, increases inhibitory tone
- ⬇️ GABAergic activity → strengthens inhibitory control
- ⬇️ Glutamate release → reduces excitatory drive
- ⚡ Modulates widespread brain networks → decreases probability of seizure initiation and spread

KEY POINTS

- Open-loop (scheduled stimulation)
- Indirect and diffuse mechanism
- Does not require intracranial surgery
- Broad applicability (focal or generalized epilepsy)
- Effect often improves over months to years

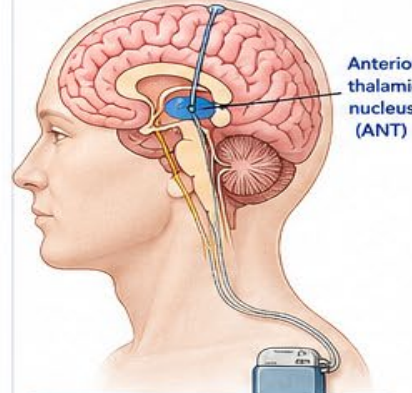
DEEP BRAIN STIMULATION (DBS)

Open-loop • Direct • Continuous or intermittent



TARGET (MOST COMMON)

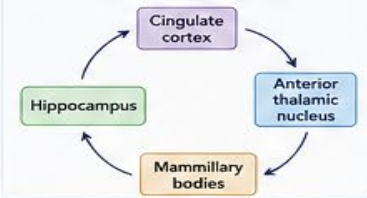
Anterior nucleus of the thalamus (ANT)



MECHANISM

1. Disrupts seizure propagation
High-frequency stimulation interferes with abnormal transmission through thalamocortical and limbic circuits.
 2. Desynchronization
Reduces hypersynchronous neuronal firing across connected networks.
 3. Axonal modulation
Alters both orthodromic and antidromic signaling in axons, reducing coordinated spread.
- Thalamocortical regulation**
Normalizes abnormal connectivity between thalamus and cortex.
- Long-term neuroplasticity**
Induces lasting network remodeling and changes in excitability, which may explain continued improvement over years.

PART OF THE PAPEZ CIRCUIT



HOW IT WORKS (Key Effects)

- ↓ Seizure propagation through networks
- ↓ Abnormal synchronization
- ↓ Cortical excitability
- ↑ Long-term network stability

KEY POINTS

- Open-loop (continuous or cycling)
- Requires intracranial leads
- Best evidence for focal epilepsy, especially temporal)
- Benefits increase over time

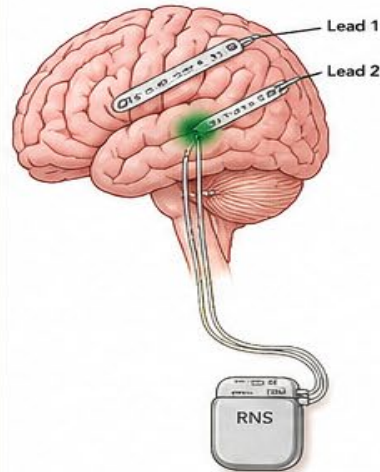
RESPONSIVE NEUROSTIMULATION (RNS)

Closed-loop • Direct • On-demand



TARGET

Seizure onset zone (cortical area)



MECHANISM (CLOSED-LOOP)

1. Detects abnormal activity
Electrodes continuously record brain activity (ECoG).
2. Recognizes seizure patterns
Device identifies abnormal patterns that indicate a seizure may start.
3. Delivers responsive stimulation
Targeted stimulation is delivered to disrupt the activity.
4. Interrupts seizure evolution
Aborts or reduces seizure before it becomes clinical.
5. Promotes long-term network change
Repeated stimulation leads to reduced excitability and improved network stability over time.

HOW IT WORKS (Key Effects)

- ⚡ Detects abnormal activity in real time
- ⚡ Delivers stimulation only when needed
- ⚡ Interrupts seizure at the focus
- ⚡ Reduces seizure frequency over time
- ⚡ Provides chronic intracranial EEG data
- ⚡ Helps guide treatment decisions

KEY POINTS

- Closed-loop (responsive)
- Requires intracranial leads at seizure focus(es)
- Best for 1-2 well-defined foci
- Many patients show ≥50% reduction and some achieve seizure-free periods

AT A GLANCE

ANATOMICAL TARGET

STIMULATION TYPE

MAIN MECHANISM

ACTS BEFORE SEIZURE STARTS?

DETECTS SEIZURES?

BEST SUITED FOR

TYPICAL SEIZURE REDUCTION*



VNS
(Vagus Nerve Stimulation)



Left vagus nerve → brainstem neuromodulatory systems → widespread brain regions



Open-loop
(scheduled)

Modulates neuromodulators (NE, 5-HT, GABA, Glutamate) and widespread networks to reduce overall excitability and seizure probability.

NE NE 5-HT GABA Glu

No
(indirect)

No

Focal, multifocal, generalized, or poorly localized epilepsy; children and adults

~45-65% achieve ≥50% reduction; ~5-8% seizure freedom



DBS
(Deep Brain Stimulation)



Deep brain nucleus (usually ANT)



Open-loop
(continuous or intermittent)

Interrupts seizure propagation through thalamocortical and limbic networks; desynchronizes circuits; induces long-term neuroplastic changes.

Partially
(reduces spread)

No

Focal epilepsy with bilateral, multifocal or poorly localizable onset (esp. temporal, limbic)

~60-75% median reduction at long-term follow-up



RNS
(Responsive Neurostimulation)



Seizure onset zone (cortical area)



Closed-loop
(responsive)

Detects abnormal ECoG activity and delivers targeted stimulation to abort seizures and remodel networks over time.

Yes

Yes
(real-time)

Focal epilepsy with 1-2 well-defined seizure onset zones (eloquent or bilateral)

~60-80% median reduction; ~20-25% seizure-free periods (6-12 months)

* Outcomes vary by study, patient population, and follow-up duration.

NE = Norepinephrine

5-HT = Serotonin

GABA = Gamma-aminobutyric acid

Glu = Glutamate

NEUROMODULATION THERAPIES IN CHILDREN WITH EPILEPSY

Ranking VNS, DBS and RNS for Drug-Resistant Epilepsy in Children (2025–2026)



No single therapy is best for every child.

Choice depends on epilepsy type, age, seizure focus, and previous treatments.



1

BEST
ESTABLISHED

VNS

VAGUS NERVE STIMULATION

How it works

Stimulates the left vagus nerve → activates brainstem pathways → modulates widespread brain networks to reduce seizures.

Why it ranks #1 in children

- Largest body of pediatric evidence
- Broadest range of indications
- Long-term safety record
- Least invasive surgery

Typical Outcomes*

≥50% seizure reduction	50–70%
≥75% seizure reduction	25–40%
Seizure freedom	5–10%

Best for

Lennox–Gastaut syndrome, Dravet syndrome, multifocal epilepsy, generalized epilepsy, poorly localized focal epilepsy, not surgical candidates

2

RAPIDLY
EMERGING

DBS (CM)

CENTROMEDIAN THALAMIC STIMULATION

How it works

Stimulates the centromedian nucleus of the thalamus → modulates thalamocortical networks involved in generalized seizures.

Why it ranks #2

- Growing evidence in children, especially for generalized epilepsies
- Effective for severe seizure types (tonic, atonic, GTC)
- Beneficial for Lennox–Gastaut syndrome

Typical Outcomes*

Median seizure reduction	60–80%
Especially effective for: tonic, atonic (drop) and generalized tonic-clonic seizures	

Best for

Lennox–Gastaut syndrome, generalized epilepsy, tonic/atonic seizures, adolescents when VNS has failed or is not tolerated

3

SELECTIVE
OPTION

RNS

RESPONSIVE NEUROSTIMULATION

How it works

Continuously monitors brain activity → detects abnormal patterns → delivers stimulation to abort seizures before they spread.

Why it ranks #3

- Closed-loop, on-demand stimulation
- Best for 1–2 well-defined seizure foci
- Evidence in children is increasing but still more limited

Typical Outcomes*

Median seizure reduction	60–80%
>90% seizure reduction in a subset of patients	
Progressive improvement over time	

Best for

Older children and adolescents with 1–2 well-defined seizure foci (e.g., bilateral mesial temporal epilepsy, eloquent cortex)

*Outcomes vary by study, age, epilepsy syndrome, baseline seizure frequency, duration of follow-up, and prior treatments.

AT A GLANCE COMPARISON

FEATURE	VNS	DBS (CM)	RNS
Type of stimulation	Open-loop (scheduled)	Open-loop (continuous or cycling)	Closed-loop (responsive)
Surgical approach	Neck (vagus nerve) – least invasive	Intracranial (depth electrode in thalamus)	Intracranial (cortical/depth electrodes)
Main target	Vagus nerve → brainstem pathways → widespread brain networks	Centromedian nucleus of the thalamus (network modulation)	Seizure onset zone (cortical area)
Detects seizures?	No	No	Yes (real-time detection)
Age used in children	As young as ~2–4 years (varies by region)	Generally ≥4–8 years (usually school-age/adolescents)	Generally ≥12–18 years (older children/adolescents)
Battery life (approx.)	5–10 years	3–5 years (non-rechargeable) up to 10–15 years (rechargeable)	8–12 years
MRI considerations	MRI conditional	MRI conditional (target & system specific)	MRI conditional (limited head MRI with specific protocols)

WHY NEUROMODULATION MATTERS



Reduces seizure burden and severity



Supports brain development, learning and cognition



Improves behavior, mood, sleep and quality of life



Relieves caregiver stress and improves family life



Resective or ablative surgery remains the first choice when a seizure focus can be safely removed.



KEY TAKEAWAYS



VNS is the most established and broadly applicable neuromodulation therapy in children.



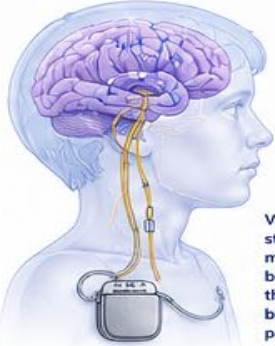
CM-DBS is a rapidly expanding option, especially for generalized epilepsies and LGS.



RNS is a promising, closed-loop therapy for carefully selected older children/adolescents with 1–2 foci.



Treatment must be individualized and managed by a multidisciplinary epilepsy team.



Vagus nerve stimulation modulates brain networks through brainstem pathways.

THE NEXT GENERATION OF VNS® THERAPY

Smarter Stimulation. Broader Impact. Better Lives.

Vagus Nerve Stimulation is evolving from open-loop therapy to intelligent, personalized neuromodulation that adapts to each patient's brain and body.



Today's VNS Benefits

- ✓ Reduces seizure frequency
- ✓ Improves mood and alertness
- ✓ Enhances quality of life
- ✓ Broadly applicable for focal and generalized epilepsies

THE NEXT GENERATION INNOVATIONS

1 SMARTER, ADAPTIVE STIMULATION

From open-loop to closed-loop+



Senses physiological signals and delivers stimulation only when needed.

- Detects biomarkers of impending seizures or state changes
- Adaptive intensity, frequency, pulse width, and timing
- Maximizes efficacy, minimizes side effects, saves battery

2 MULTIMODAL BIOSENSING

More signals. More insight.



Integrated sensors provide a richer picture of the body-brain state.

3 PERSONALIZED THERAPY PLATFORM

AI-guided. Patient-specific.



AI/ML algorithms analyze multi-modal data to:

- Predict events
- Optimize parameters
- Personalize therapy over time
- Learn and adapt continuously

4 NEXT-GEN HARDWARE DESIGN

Smaller. Smarter. Longer lasting.



- Smaller, lighter pulse generator
- Longer battery life (10-15+ years)
- MRI-full body compatibility (aim)
- Rechargeable & non-rechargeable options
- Improved lead design for consistency and durability

5 EXPANDED THERAPEUTIC POSSIBILITIES

Beyond seizures.



Treatment of comorbid conditions:



Depression



Anxiety



Migraine



Sleep disorders



Cognitive dysfunction



Heart failure (investigational)



Inflammatory diseases (investigational)

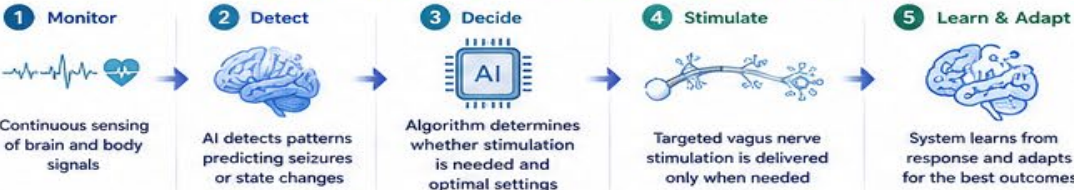
6 DIGITAL HEALTH INTEGRATION

Connected care. Continuous support.



- Remote monitoring
- Data analytics dashboard
- Therapy adherence support
- Alerts & clinical insights
- Telemedicine integration

HOW NEXT-GEN VNS MAY WORK (Closed-Loop+ Concept)



BENEFITS OF NEXT-GEN VNS



Better seizure control



Longer battery life



Fewer side effects



Improved quality of life



Broader therapeutic potential

WHO MAY BENEFIT?



• Children and adults with drug-resistant epilepsy



• Patients with multiple seizure types (focal, generalized or multifocal)



• Patients with comorbid psychiatric or cognitive conditions



• Patients not candidates for resective surgery

THE ROAD AHEAD

TODAY
(2020s)



Open-loop VNS
Scheduled stimulation with fixed parameters

NEAR FUTURE
(1-3 years)



Adaptive algorithms + multimodal sensing
Smarter detection and personalized parameter adjustment

MID TERM
(3-5 years)



Digital integration & remote optimization
Real-time data, remote programming, better patient engagement

LONG TERM
(5-10 years)



Closed-loop+ VNS
Predictive, on-demand stimulation for maximum efficacy and minimal intervention

FUTURE VISION
(10+ years)



Fully personalized neuromodulation
Network-based therapy for epilepsy and beyond, integrated with precision medicine and AI-driven healthcare



Our Vision: Intelligent VNS. Personalized Care. Transforming Lives.

VNS® Therapy is indicated for drug-resistant epilepsy. Outcomes vary. Consult prescribing information.

THE FUTURE OF DBS FOR EPILEPSY CONTROL

Next-Generation Targets. Smarter Stimulation. Better Outcomes.



Deep Brain Stimulation (DBS) is evolving from open-loop, one-size-fits-all therapy to personalized, network-based neuromodulation that adapts in real time to each patient's unique epilepsy network.



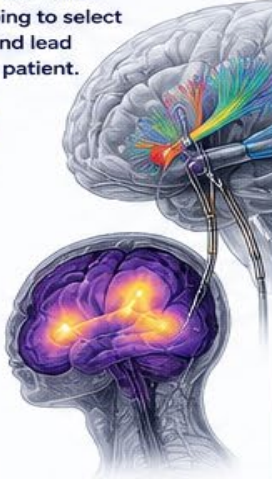
1. ADVANCED TARGETING

Beyond One-Size-Fits-All

Future DBS will use individual brain network mapping to select the optimal target and lead placement for each patient.

- Connectomics-guided targeting (tractography + functional MRI)
- Electrophysiological mapping (sEEG, MEG, scalp EEG)
- AI-assisted target prediction

- Targets may include:
 - Anterior nucleus of thalamus (ANT)
 - Centromedian nucleus (CM)
 - Hippocampus
 - Pulvinar nucleus
 - Subthalamic nucleus (STN)
 - Cerebellum
 - Patient-specific network nodes



2. SMARTER STIMULATION

Adaptive, Closed-Loop DBS

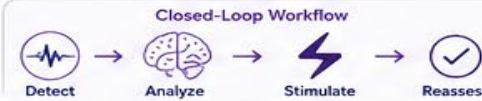
Next-generation systems will sense brain activity and deliver stimulation only when and where it is needed.

Real-time detection of pre-seizure and ictal patterns

Adaptive stimulation that adjusts amplitude, frequency, pulse width, and location

On-demand or predictive stimulation to prevent seizure spread

Bidirectional communication between device and clinician



3. NEXT-GEN TECHNOLOGY

Smaller, Longer, Smarter

Rechargeable, long-life batteries (>10–15 years)

Directional current steering for precise activation

Multiple independent channels to stimulate multiple targets or regions

Miniaturized, MRI-friendly hardware

Sensing beyond LFPs (multimodal: field potentials, spikes, hemodynamics)

Wireless programming and cloud-based data for optimization



4. PERSONALIZED & PRECISION THERAPY

Right Patient, Right Target, Right Stimulation

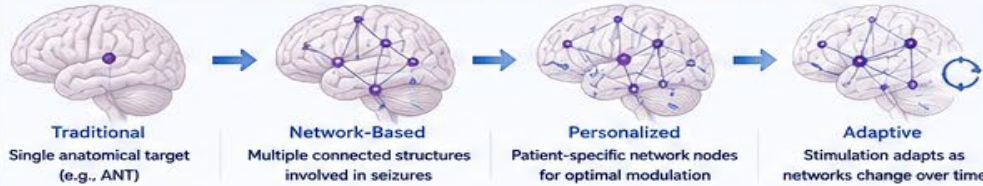
- Biomarker-driven patient selection
- AI/ML algorithms to predict response and optimize settings
- Continuous learning from each patient's brain data
- Integrated platform for DBS + medication + RNS/VNS data
- Pediatric-optimized systems for growth and development



GOAL

Maximize seizure freedom, minimize side effects, and improve quality of life.

EVOLVING TARGETS: FROM FIXED NUCLEI TO NETWORK NODES



POTENTIAL BENEFITS OF FUTURE DBS

Greater seizure reduction and seizure freedom

Fewer side effects with precise stimulation

Longer battery life and fewer surgeries

Neuroplastic changes and network normalization

Better cognition, mood, and quality of life

CURRENT LIMITATIONS ADDRESSED

- Individual variability in anatomy and networks
- Open-loop stimulation (not responsive)
- Suboptimal targeting
- Shorter battery life
- Limited integration of multimodal data

THE ROAD AHEAD: TOWARD INTELLIGENT, NETWORK-BASED DBS



Today
(Open-Loop DBS)

Continuous or intermittent stimulation with fixed parameters.

Near Term (1–3 years)

- Directional leads
- Better imaging & targeting
- Longer battery life
- More sensing capabilities

Mid Term (3–7 years)

- Adaptive (closed-loop) DBS
- Multi-channel stimulation
- AI-assisted programming
- Cloud-based data platforms



Long Term (7+ years)

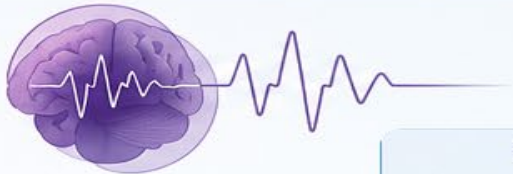
- Fully adaptive, predictive DBS
- Personalized network therapy
- Integration with other neuromodulation (RNS, VNS, tDCS, BCI)
- Precision therapy for every patient



A FUTURE WHERE DBS ADAPTS TO THE BRAIN—NOT THE OTHER WAY AROUND.

Our vision: A world where intelligent DBS prevents seizures before they start and restores the brain's natural balance.

Research • Innovation • Personalization • Better Lives



THE NEXT GENERATION OF RNS® SYSTEM

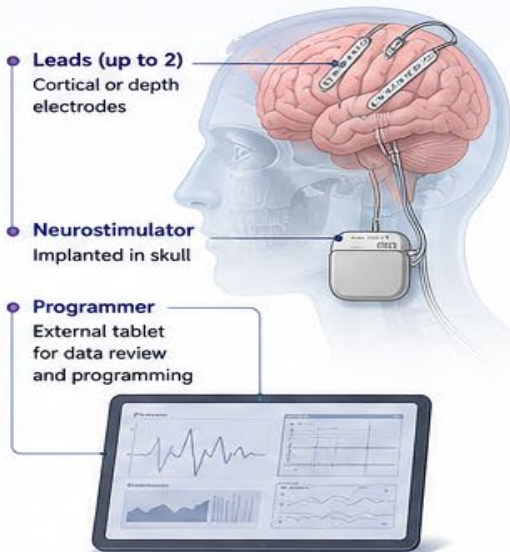
Smarter Detection. Personalized Therapy. Better Outcomes.

RNS®
Responsive
Neurostimulation

RNS® is the only approved, closed-loop neurostimulation system that detects abnormal brain activity and delivers targeted stimulation to stop seizures before they spread.

CURRENT RNS® SYSTEM (GENERATION 1)

Proven. Personalized. Transformative.



- **Leads (up to 2)**
Cortical or depth electrodes
- **Neurostimulator**
Implanted in skull
- **Programmer**
External tablet for data review and programming

KEY FEATURES

- ✓ Continuous EEG monitoring (chronic ECoG)
- ✓ Detects abnormal activity
- ✓ Delivers responsive stimulation
- ✓ Stores brain data to guide therapy

NEXT GENERATION RNS® SYSTEM (GENERATION 2 AND BEYOND)

More Intelligence. More Insight. More Impact.



1. ADVANCED AI-POWERED DETECTION

Deep learning algorithms trained on large datasets for earlier and more accurate detection of seizure patterns.

- Improved sensitivity
- Fewer false detections
- Personalized to each patient



3. MULTIPLE STIMULATION MODES

More options to match physiology and seizure networks.

- High-frequency
- Burst stimulation
- Patterned stimulation
- Future: phase-locked stimulation



5. HIGH-DENSITY & STEREOTACTIC LEADS

Next-generation leads for more precise recordings and stimulation.

- Smaller, thinner, more flexible
- Directional stimulation
- More contacts for complex networks



2. ADAPTIVE (CLOSED-LOOP+) STIMULATION

Adjusts stimulation parameters in real time based on brain state and treatment response.

- Dynamic intensity, frequency and pulse width
- Stimulates only when needed
- Maximizes efficacy, preserves battery



4. LONGER BATTERY LIFE & SMART POWER MANAGEMENT

New hardware and algorithms extend battery life.

- Target: 12–15+ years
- Adaptive duty cycling
- Remote performance monitoring



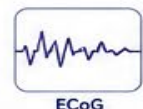
6. ENHANCED DATA & CONNECTIVITY

Secure wireless connectivity and advanced analytics.

- Remote programming & data review
- Cloud-based insights
- Integration with digital health platforms

7. PERSONALIZED THERAPY PLATFORM

Combines multi-modal data and analytics to guide precision treatment.



ECoG



Clinical data



Wearables



Imaging



Personalized therapy
for every patient

EXPECTED BENEFITS



EARLIER SEIZURE INTERVENTION

Detects and treats seizures earlier to prevent clinical events.



GREATER SEIZURE REDUCTION

More precise detection and adaptive stimulation for better outcomes.



IMPROVED QUALITY OF LIFE

Fewer seizures, less severity, and better daily functioning.



LONGER DEVICE LIFE

Fewer surgeries and lower long-term device burden.



DEEPER INSIGHTS

Rich longitudinal brain data to optimize treatment decisions over time.

INNOVATION PIPELINE & ROADMAP



Current
RNS® System
(Generation 1)

Now



Generation 2
(Next-Gen
Hardware)

Near Term
(1–3 years)



AI & Adaptive
Intelligence
Platform

Mid Term
(3–5 years)



Future Vision
Fully Personalized
Brain Therapy

Long Term
(5+ years)

OUR VISION



A future where the RNS® System continuously learns, adapts and partners with patients to achieve the best possible seizure control and brain health.

TRANSFORMING EPILEPSY CARE



Smarter Detection
with AI



Adaptive Therapy
in Real Time



Personalized
for Every Patient



Better Outcomes,
Better Lives

IDEAL CANDIDATES



- Drug-resistant focal epilepsy
- 1–2 well-defined seizure foci (may be bilateral)
- Adults and adolescents (expanding evidence in younger populations)

RNS® System is approved for adults 18 years and older. Use in children is investigational in many regions. The next-generation RNS® System is under development and not yet commercially available.



EST **30**th ANNIVERSARY
ANNUAL MEETING



Thank you for your attention