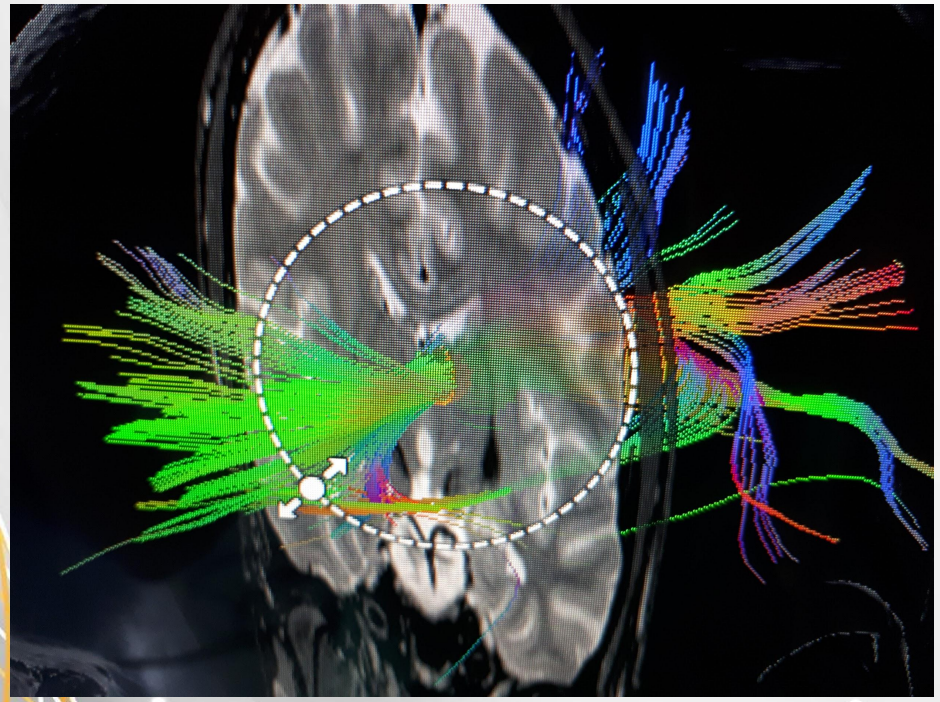
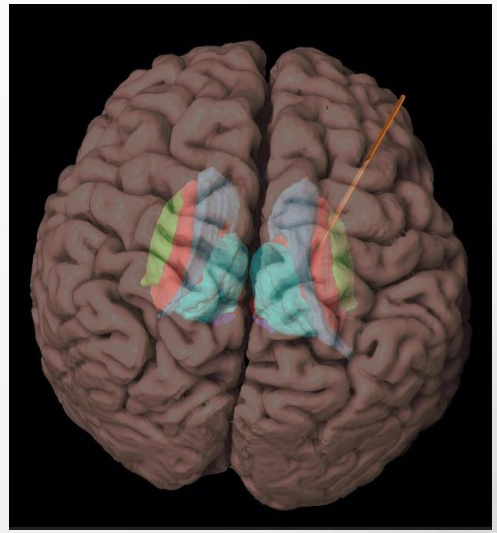
New targets and new indications of neuromodulation



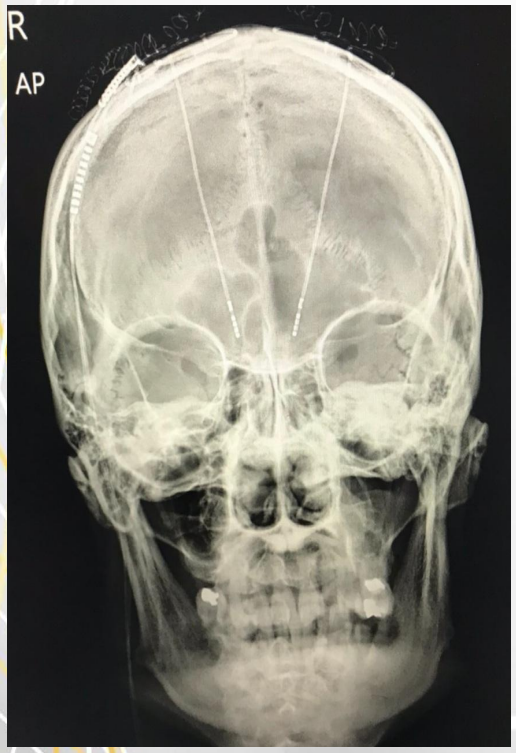


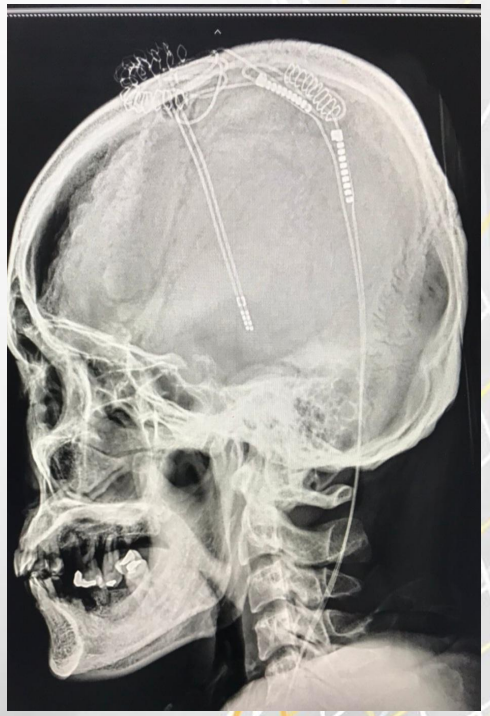
Atthaporn Boongird,MD.
Ramathibodi hospital

Disclosure

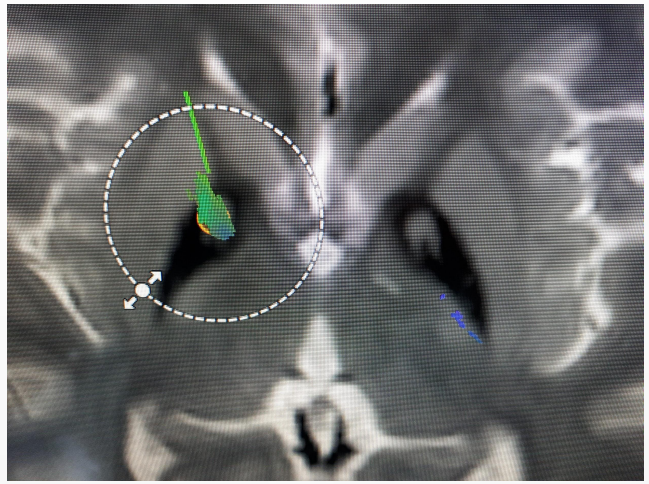
no conflicts of interest of any medical devices company

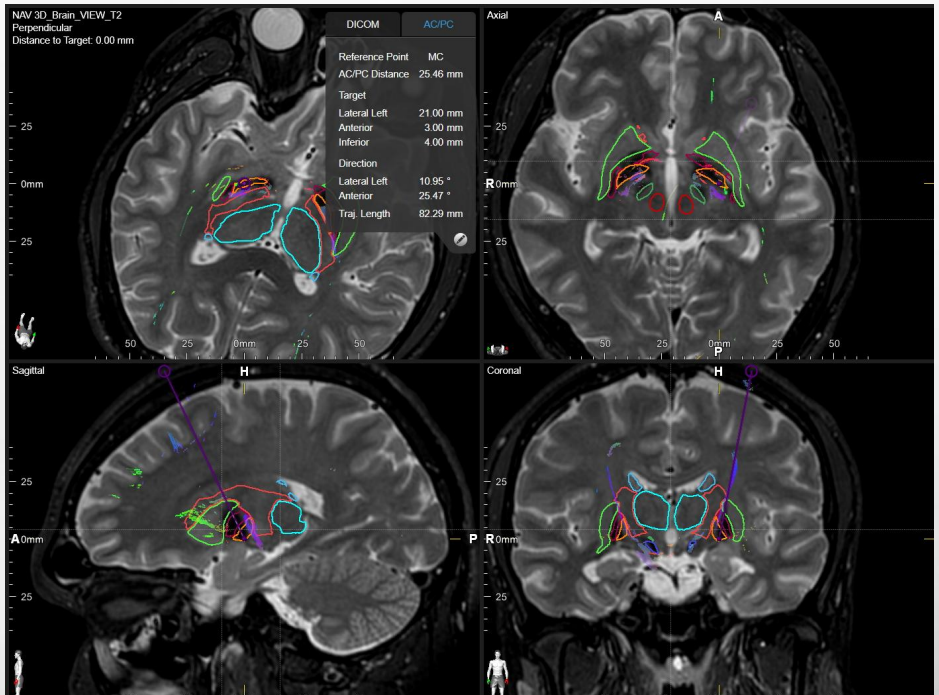
STN and Parkinson’s disease

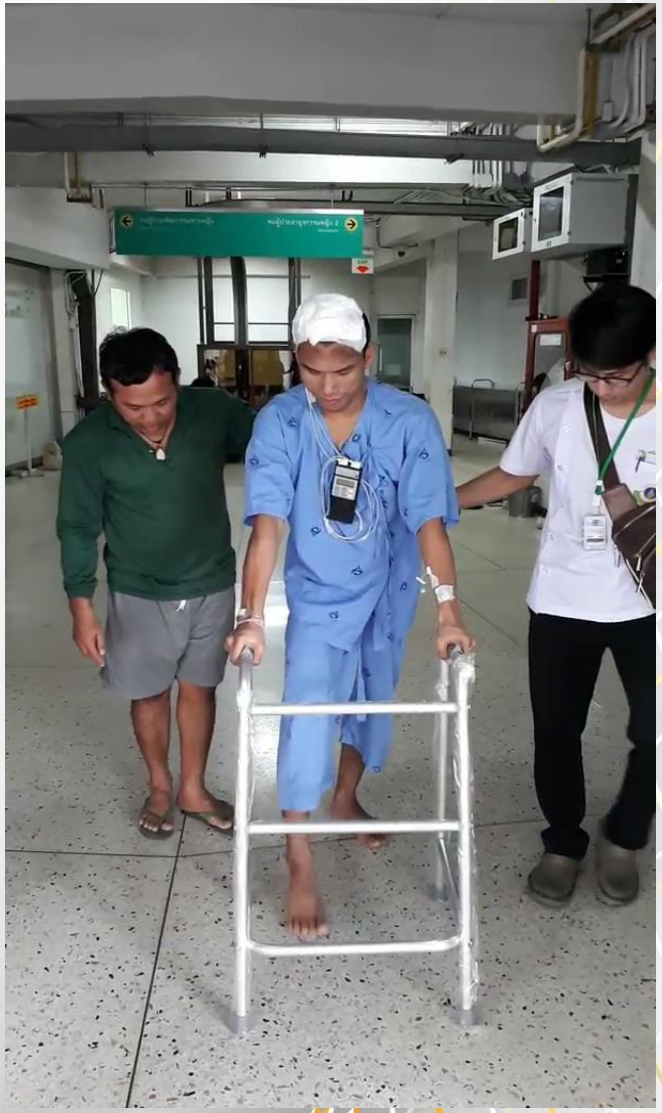




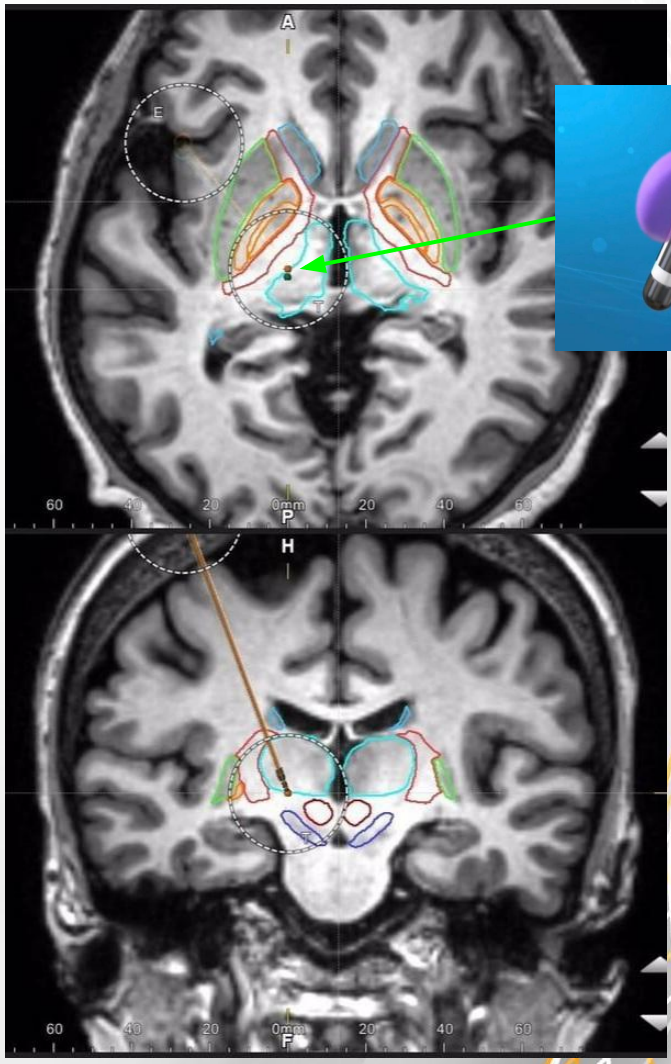
GPi for generalized dystonia



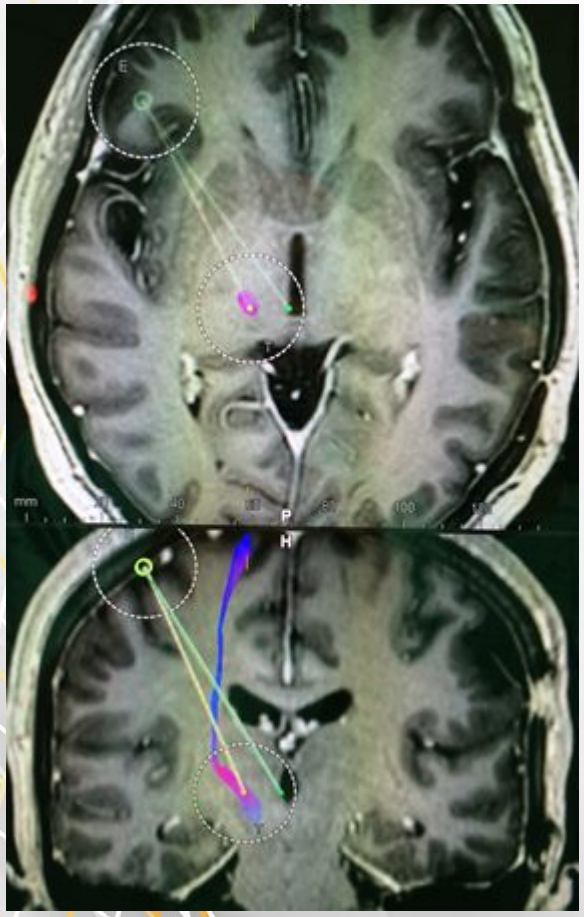


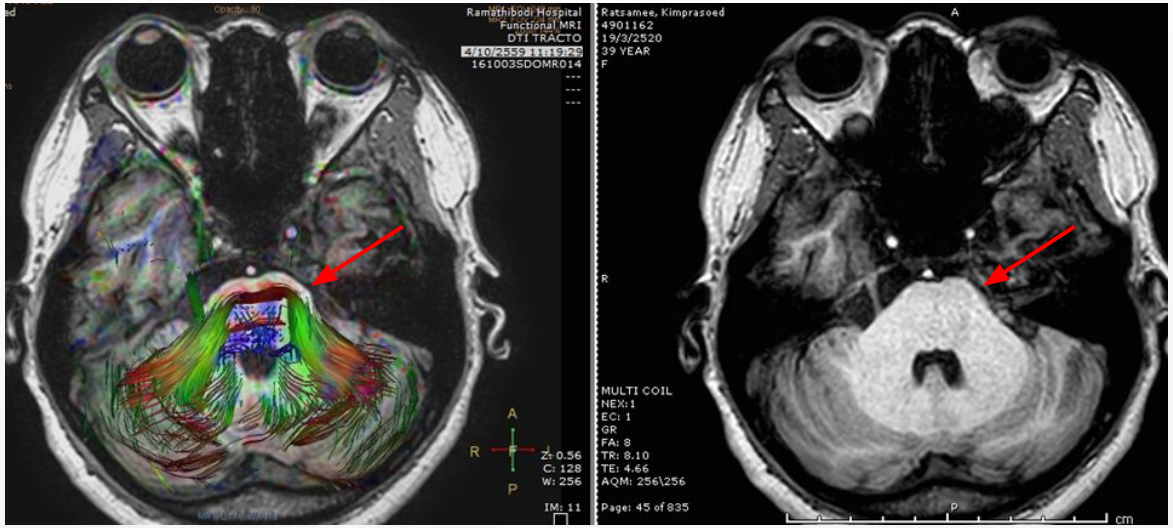


Vim Thalamus for Essential tremor

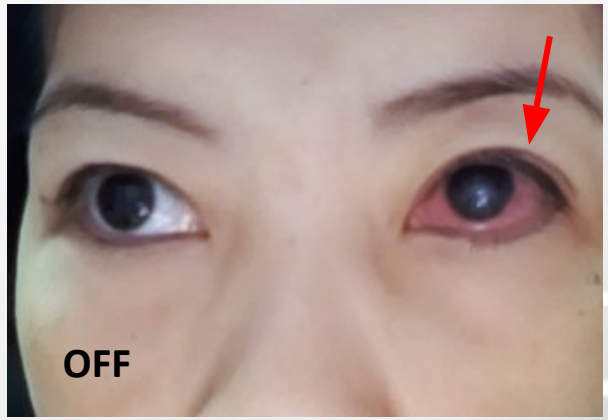


Vc Thalamus and PAG for intractable facial pain





Deafferentation pain post meningioma removal

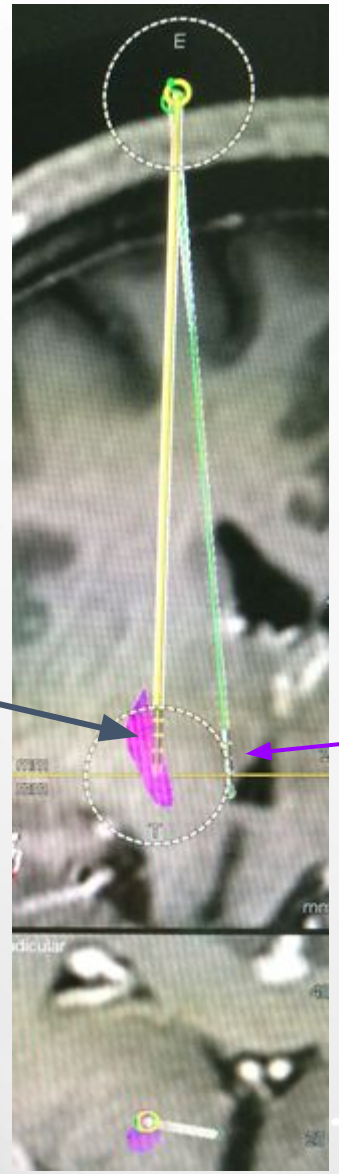


Pre-op base line
all pain medications used

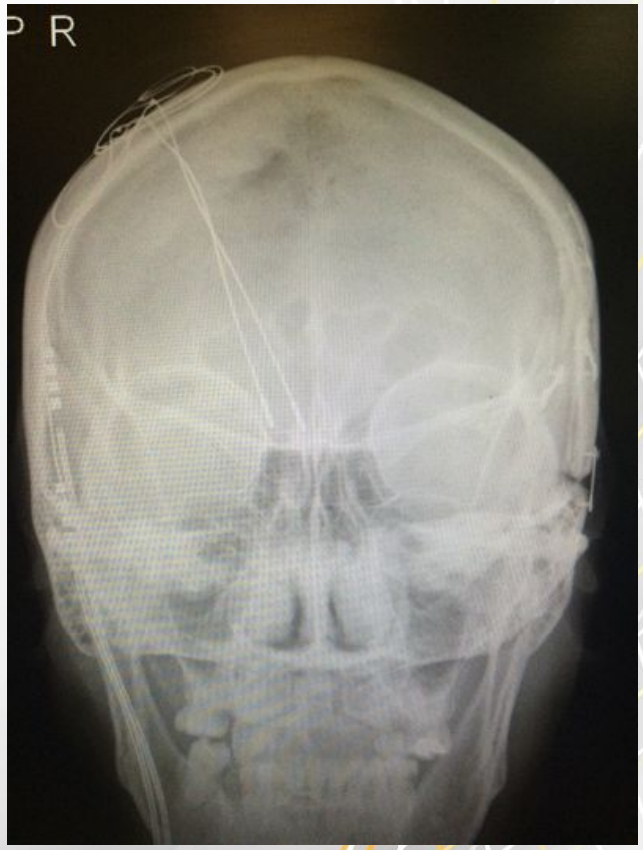
3 yrs FU 50% off medication

Two targets stimulation for different purpose/network

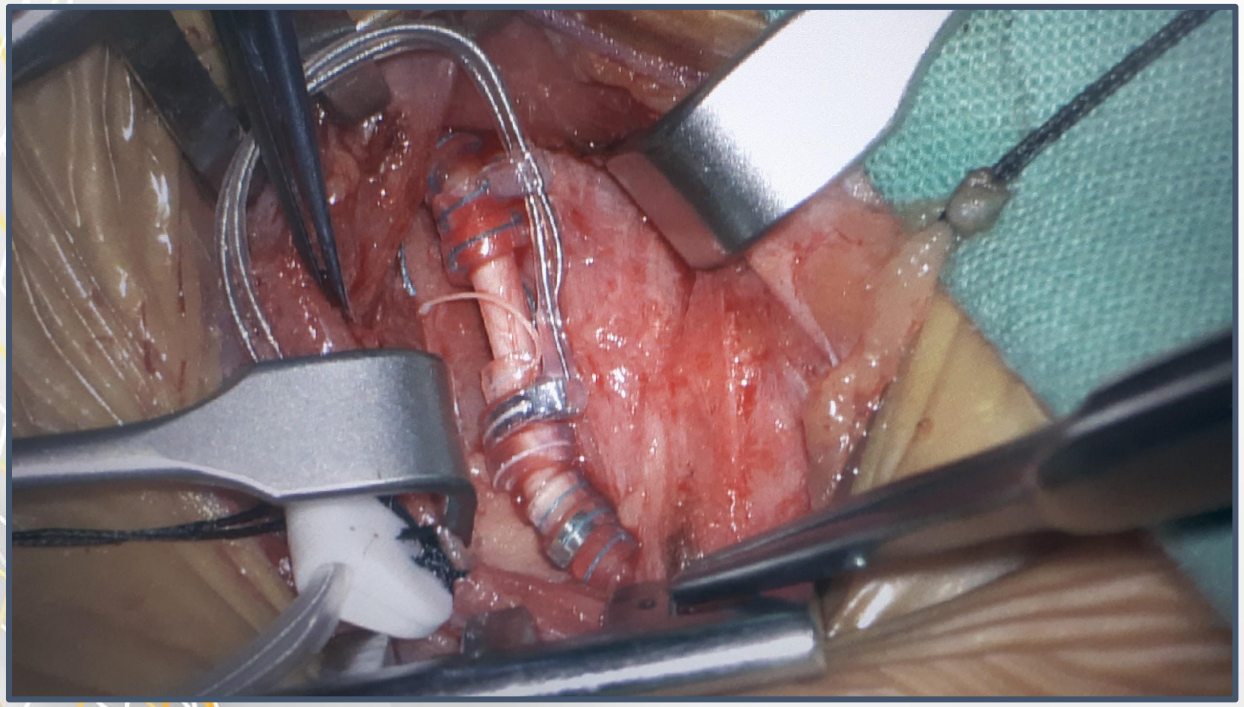
Right VPM
Contact 1+, 2 and 3 –
2 volt, PW 200 microsec
150 Hz
Good facial coverage
Include corneal sensation
Periorbital (max pain)



Right PVG
Contact 0+,1-
1 volt, PW 60 microsec
150 Hz
Feeling relief, warmth



Vagal nerve stimulation : old neuromodulation



Palliative surgical outcome for intractable seizure patients in Ramathibodi Hospital

- Intractable epilepsy patients who underwent Corpus Callosotomy and VNS from 2009 to 2019 in Ramathibodi Hospital
- 32 operations in 28 patients
- 12 VNS implantations and 20 CC
- In CC group : 17 anterior two-third CC and 3 complete CC
- 5 patients underwent combined CC and VNS
- Follow up time at least 12 months
- No permanent neurological deficit in CC group
- One transient arrhythmia in VNS group

Demographic Data

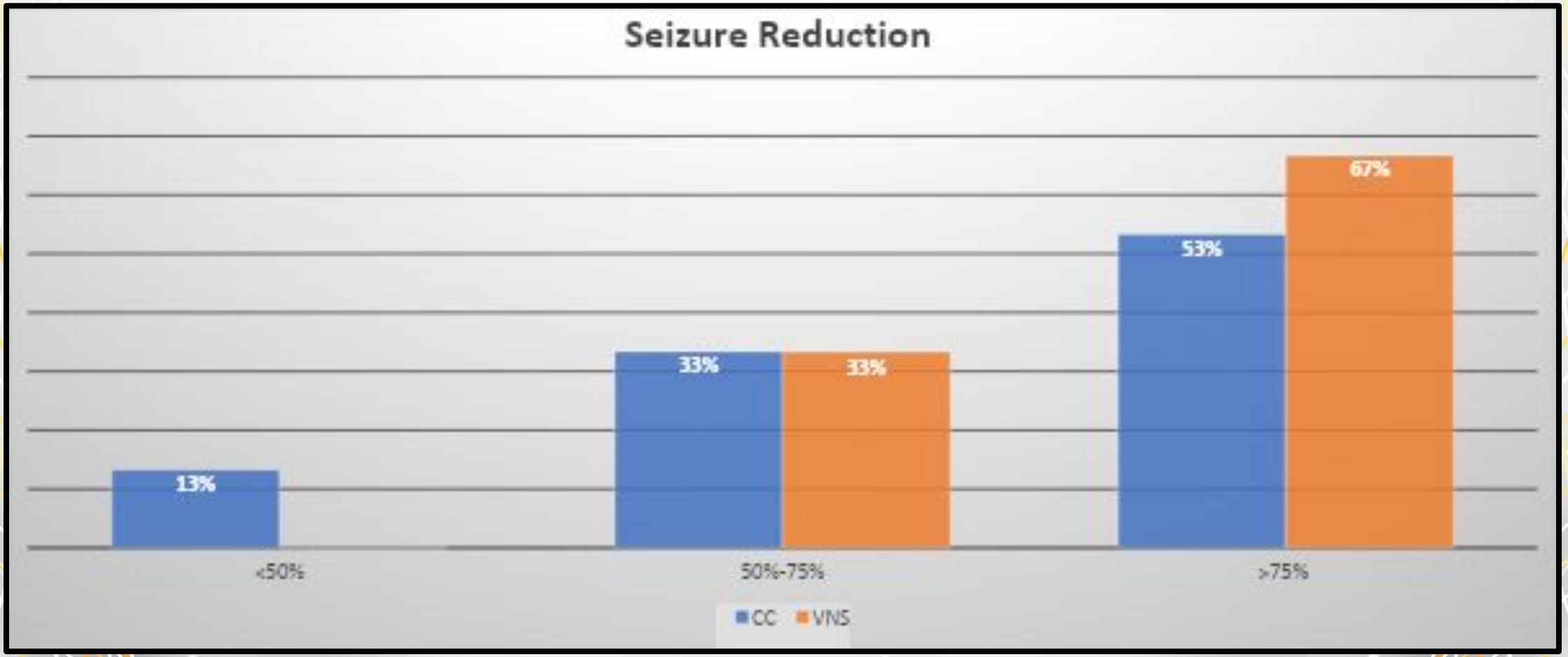
	Total	VNS	CC	P-value
No		12	20	
Sex (M/F)		8/12	5/7	0.926
Age (Y) mean± SD	11.1±5.7	12.6±4.5	10.2±6.2	0.249
Onset (m) median(IQR)	6(4,24)	6(4,26)	6(3,24)	0.906
Duration of seizure (Y) mean ± SD	10.2±5.0	10.9±4.2	9.7±5.5	0.513
Follow up time (m) mean ± SD	60.3±29.3	57.9±27.5	61.8±30.9	0.723

	Total	VNS	CC	P-value
Etiologies				
Lennox-Gastuat Syndrome	16	12(60%)	4(33.33%)	0.144
Non- LGS	16	8(40%)	8(66.67%)	
Major seizure types				
GTC	12	6(30%)	6(50%)	0.575
GT	14	10(50%)	4(33.33%)	
Atonic	6	4(20%)	2(16.67%)	

	Total	VNS	CC	P-value
Number of AEDs, mean ± SD				
Preoperative	3.3±0.7	3.4±0.7	3.3±0.8	0.545
Postoperative	3.4±1.0	3.7±0.8	3.2±1.1	0.235

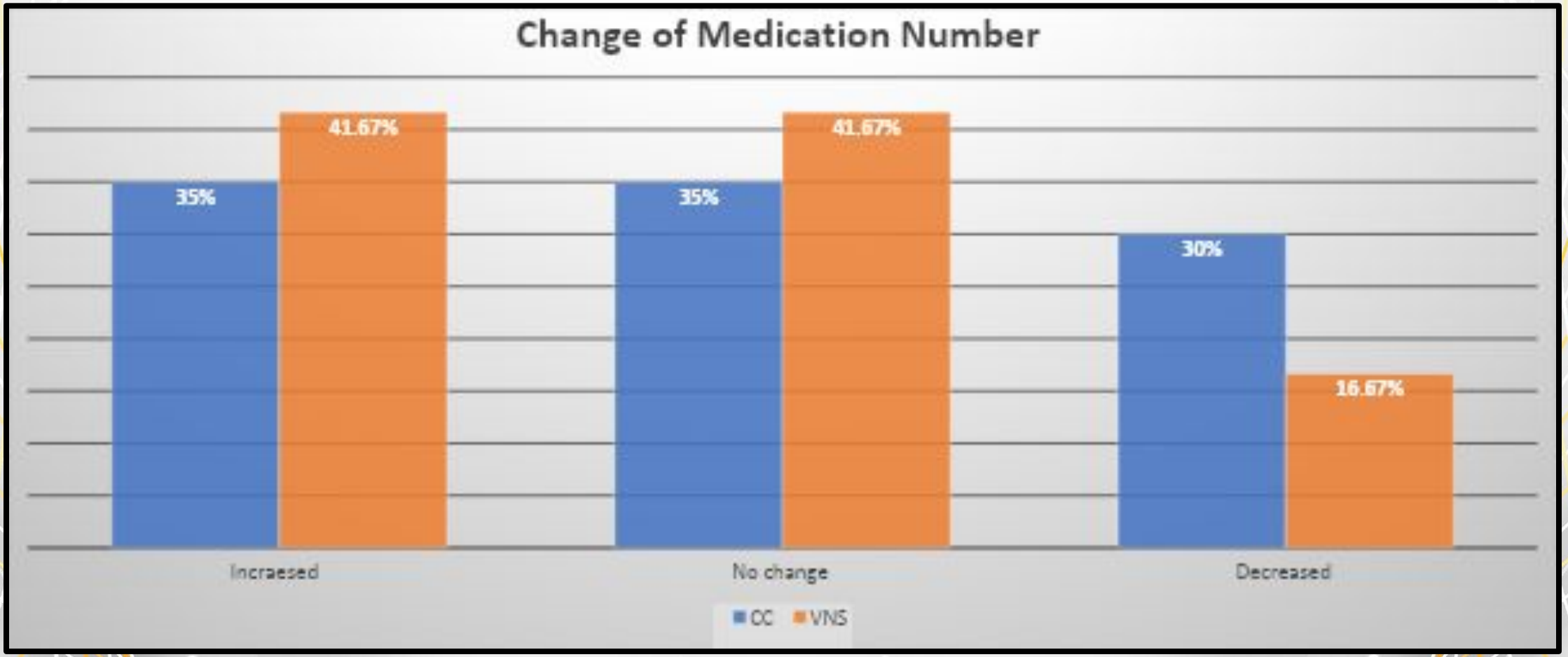
Seizure Frequency

	Total	CC	VNS	P-value
Increased		1/20(5%)	3/12(25%)	0.095
No change		4/20(20%)	0	
Decreased		15/20(75%)	9/12(75%)	
Seizure Reduction				
< 50% reduction	2(8.4)	8(53.3)	0	0.829
50%-75%reduction	8(33.3)	5(33.4)	3(33.3)	
> 75% reduction	14(58.3)	2(13.3)	6(6.67)	


Seizure Reduction
13%
33%
33%
53%
67%
<50%
50%-75%
>75%
CC
VNS

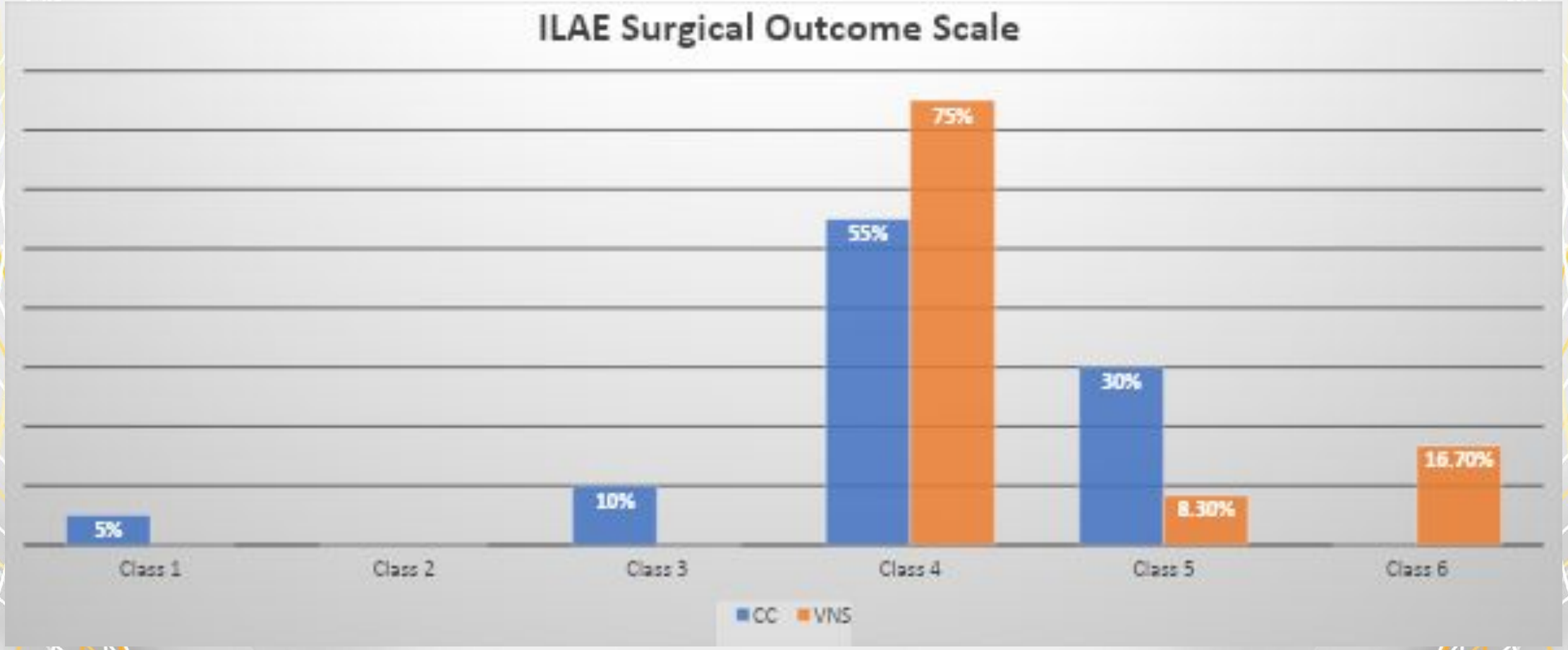
The changes of medication number

	CC	VNS	P-value
Increased	7/20(35%)	5/12(41.67%)	0.806
No change	7/20(35%)	5/12(41.67%)	
Decreased	6/20(30%)	2/12(16.67%)	


Change of Medication Number
41.67%
35%
35%
41.67%
30%
16.67%
Incraesed
No change
Decreased
OC
VNS

	Total (N=32)	CC(N=20)	VNS(N=12)
Operative responders			
Seizure reduction≥50%	11(34.4%)	6(30%)	5(41.7%)
All seizure reduction	13(40.6%)	8(40%)	5(41.7%)

ILAE surgical outcome scale	CC	VNS	P-value
Class 1	1/20(5%)	0	0.119
Class 2	0	0	
Class 3	2/20(10%)	0	
Class 4	11/20(55%)	9/12(75%)	
Class 5	6/20(30%)	1/12(8.3%)	
Class 6	0	2/12(16.7%)	


ILAE Surgical Outcome Scale
5%
10%
55%
75%
30%
8.30%
16.70%
Class 1
Class 2
Class 3
Class 4
Class 5
Class 6
CC
VNS

Engel's classification	CC	VNS	P-value
Class I	2/20(10%)	0	0.516
Class II	0	0	
Class III	0	0	
Class IV	18/20(90%)	12/12(100%)	
IVA	6(33.3%)	4(33.3%)	0.391
IVB	11(61.1%)	5(41.7%)	
IVC	1(5.6%)	3(25%)	

Conclusion

- As a palliative procedure both CC and VNS are effective in reducing seizures frequency and they have propensity to decrease AEDs number especially in good responder.
- There was no significant difference between CC and VNS in term of surgical outcome both frequency of seizures and changes of medications number during 60 months follow up.
- Continued research aimed to attaining cost effectiveness of CC and VNS.

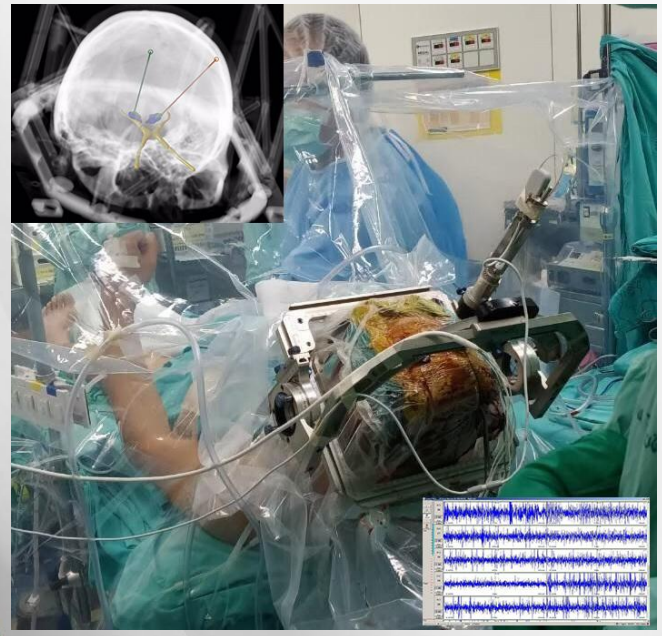
Brain stimulation as a neuromodulation

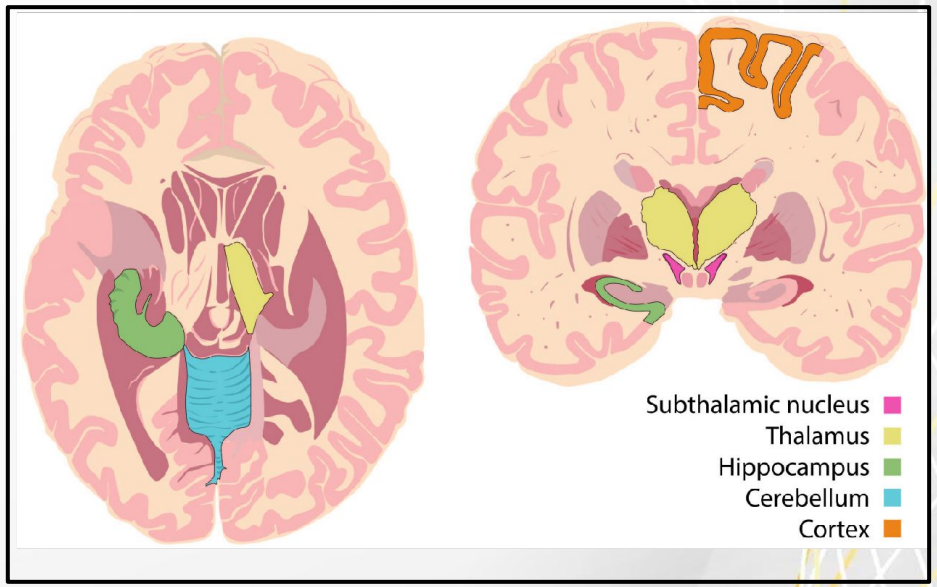
- FDA approved

  DBS for tremor(1997)

  VNS for epilepsy (1997)

  DBS for Parkinson's disease(2002)





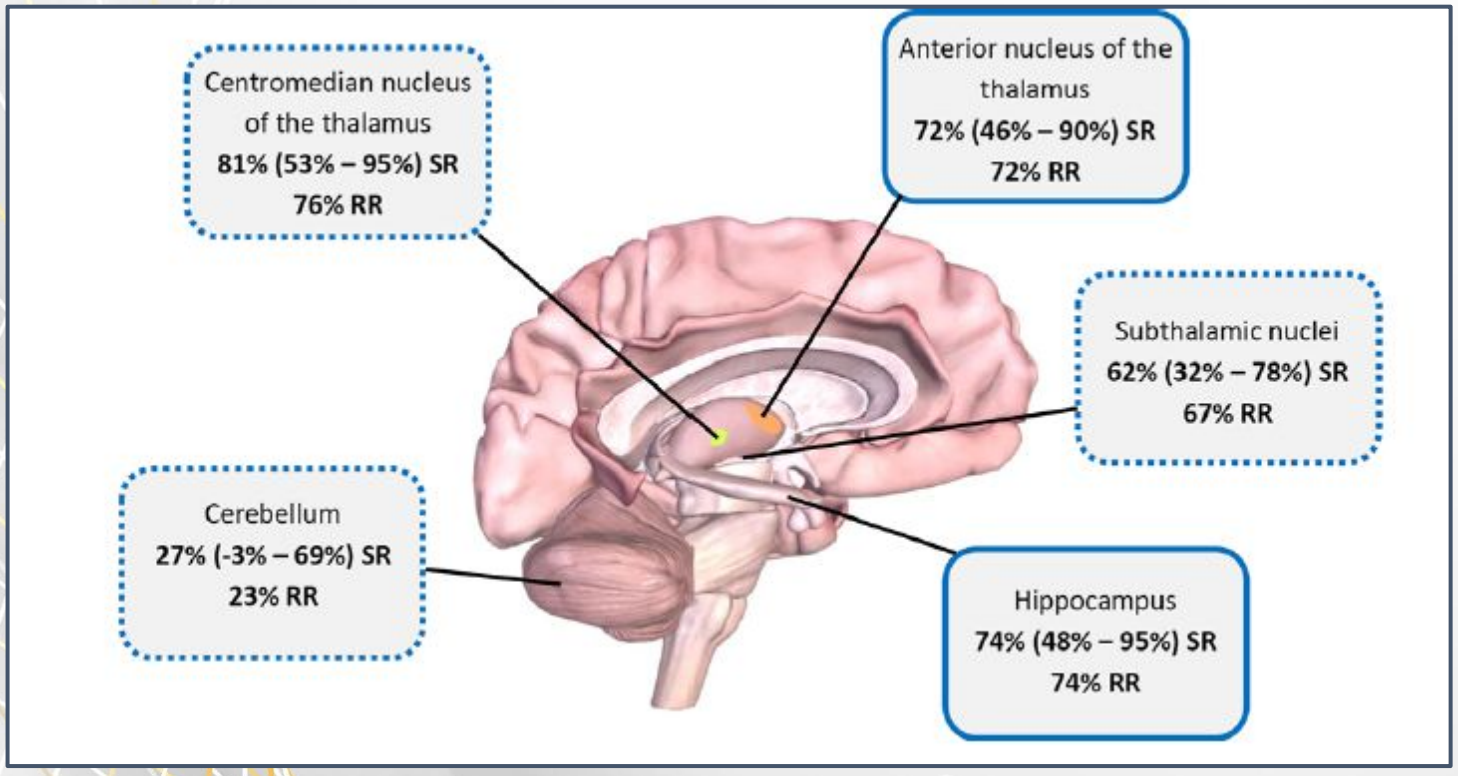
Anterior thalamic DBS (2018)

Responsive neurostimulation (RNS):closed loop(2013,MRI label 2020)

CRITICAL REVIEW AND INVITED COMMENTARY

Deep brain stimulation for drug-resistant epilepsy

Michael C. H. Li | Mark J. Cook



Key Points

- Long-term ANT and HC stimulation decreased seizures by 46%-90% and 48%-95% among half of all patients studied; DBS of other targets remains inconclusive
- More than 70% of patients receiving ANT or HC stimulation among existing studies are responders (experiencing a seizure reduction of at least 50%)
- Side effects and complications of DBS for drug-resistant epilepsy are similar in nature to those observed from DBS therapy for other indications
- Individual responses vary markedly—potential predictors of efficacy include seizure syndrome, absence of structural abnormality, and electrode position
- More robust clinical trials are needed to investigate the determinants of efficacy and to personalize DBS therapy for patients with drug-resistant epilepsy

Epilepsia 2018: 59:273-290

TABLE 6 Possible predictors of the efficacy of DBS for drug-resistant epilepsy

Target	Evidence base	Possible factors associated with efficacy
ANT	1 large RCT 16 open-label studies.	• Anterior electrode location[30,33] • Seizures of deep temporal/temporo-frontal limbic onset.[3,18,29] • Normal MRI without structural abnormality.[29] • Efficacy with trial of closed-loop stimulation.[24]
HC	3 small RCTs of HC-DBS (+1 large RCT including HC-RNS) 9 open-label studies.	• Normal MRI without hippocampal sclerosis.[35–37] • Electrodes close to subiculum,[44] or within hippocampal formation and gyrus.[39] • "Stronger" stimulation for hippocampal sclerosis.[42]
CMT	2 small RCTs. 7 open-label studies.	• Electrode placement confirmed radiologically and electrophysiologically.[12,50] • Patients with Lennox-Gastaut syndrome,[50] or generalized epilepsy.[54]
CB	2 small RCTs. 6 open-label studies.	• None identified.
Others	1 small RCT for NA. Open-label studies for STN (6), PH (2), CN (2), NA (1), CZI (1), & fornix (1).	• None identified.

RCT, randomized controlled trial; ANT, anterior nucleus of the thalamus; HC, hippocampus; CMT, centromedian nucleus of the thalamus; CB, cerebellum; STN, subthalamic nuclei; NA, nucleus accumbens; PH, posterior hypothalamus; CN, caudate nucleus; CZI, caudal zona incerta.

Open-loop deep brain stimulation for the treatment of epilepsy: a systematic review of clinical outcomes over the past decade (2008–present)

James J. Zhou, MD, Tsinsue Chen, MD, S. Harrison Farber, MD, Andrew G. Shetter, MD, and Francisco A. Ponce, MD

Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

OBJECTIVE The field of deep brain stimulation (DBS) for epilepsy has grown tremendously since its inception in the 1970s and 1980s. The goal of this review is to identify and evaluate all studies published on the topic of open-loop DBS for epilepsy over the past decade (2008 to present).

METHODS A PubMed search was conducted to identify all articles reporting clinical outcomes of open-loop DBS for the treatment of epilepsy published since January 1, 2008. The following composite search terms were used: ("epilepsy" [MeSH] OR "seizures" [MeSH] OR "kindling, neurologic" [MeSH] OR epilep* OR seizure* OR convuls*) AND ("deep brain stimulation" [MeSH] OR "deep brain stimulation" OR "DBS") OR ("electric stimulation therapy" [MeSH] OR "electric stimulation therapy" OR "implantable neurostimulators" [MeSH]).

RESULTS The authors identified 41 studies that met the criteria for inclusion. The anterior nucleus of the thalamus, centromedian nucleus of the thalamus, and hippocampus were the most frequently evaluated targets. Among the 41 articles, 19 reported on stimulation of the anterior nucleus of the thalamus, 6 evaluated stimulation of the centromedian nucleus of the thalamus, and 9 evaluated stimulation of the hippocampus. The remaining 7 articles reported on the evaluation of alternative DBS targets, including the posterior hypothalamus, subthalamic nucleus, ventral intermediate nucleus of the thalamus, nucleus accumbens, caudal zone incerta, mammillothalamic tract, and fornix. The authors evaluated each study for overall epilepsy response rates as well as adverse events and other significant, nonepilepsy outcomes.

CONCLUSIONS Level I evidence supports the safety and efficacy of stimulating the anterior nucleus of the thalamus and the hippocampus for the treatment of medically refractory epilepsy. Level III and IV evidence supports stimulation of other targets for epilepsy. Ongoing research into the efficacy, adverse effects, and mechanisms of open-loop DBS continues to expand the knowledge supporting the use of these treatment modalities in patients with refractory epilepsy.

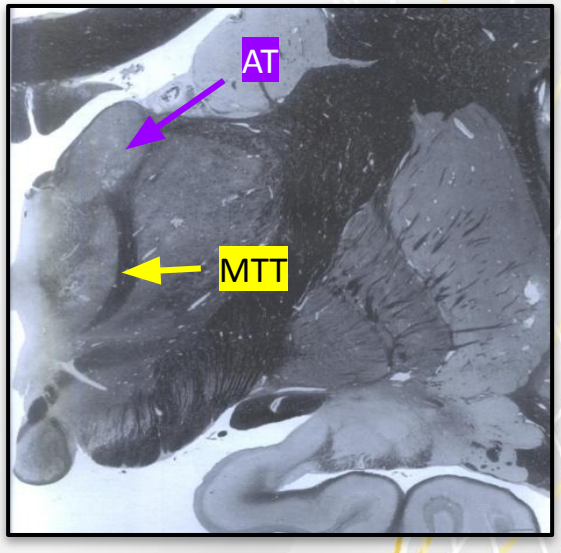
https://thejns.org/doi/abs/10.3171/2018.5.FOCUS18161

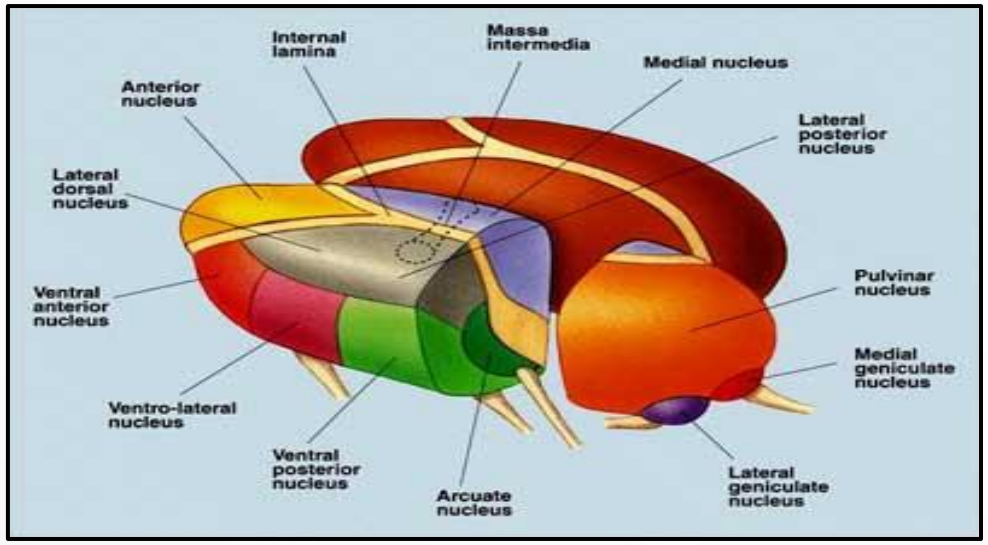
KEYWORDS DBS; deep brain stimulation; epilepsy; seizures; Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE)

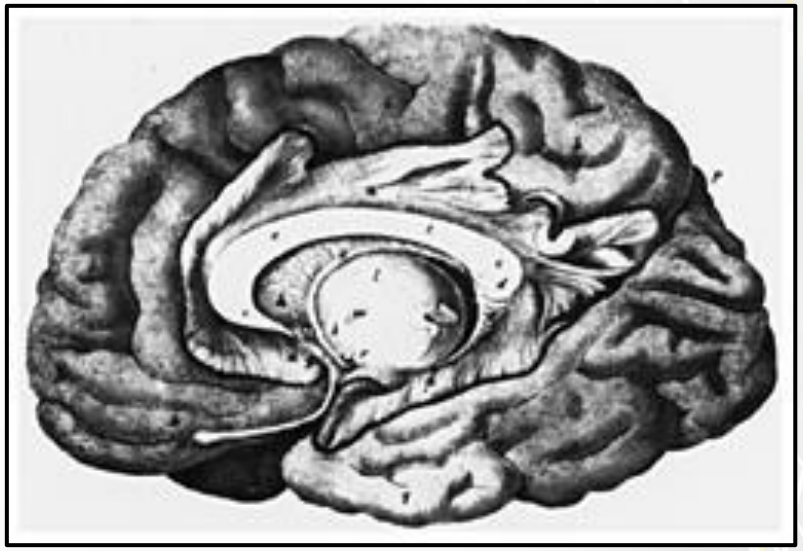
Neurosurg focus 45(2):2018

Anterior thalamic nucleus DBS

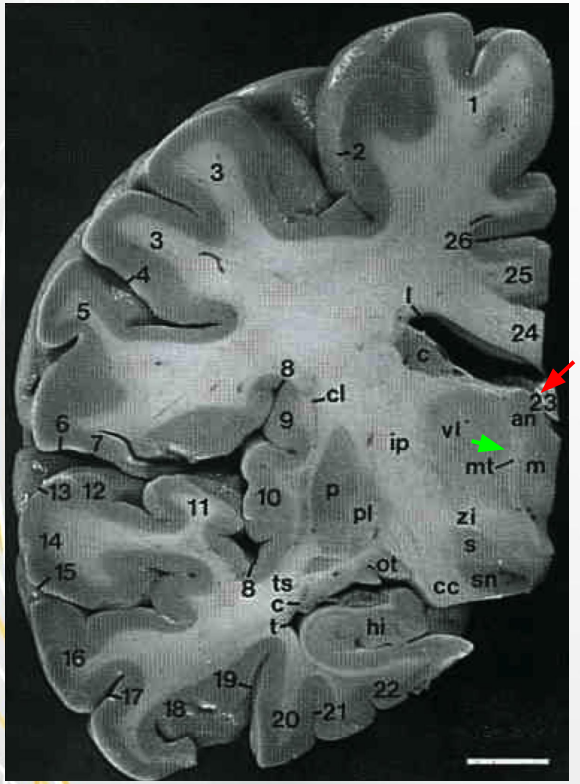
- Anatomy and its connection
- Imaging and targeting methods
- long term outcome
- neuroprotective effect





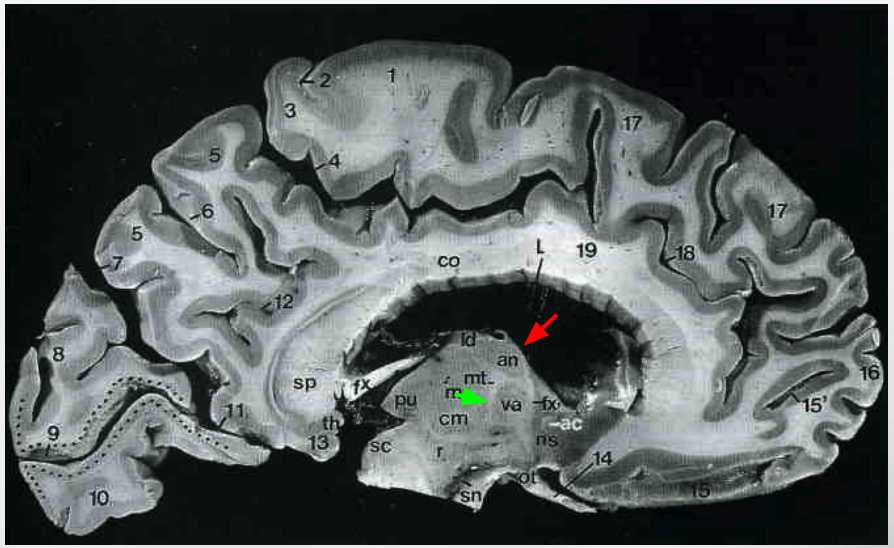


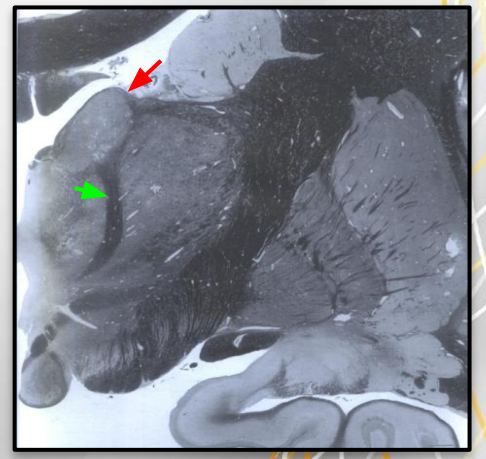
- The anterior nucleus of thalamus is part of the circuit of Papez. Its complex anatomy of this nucleus is divided into 4 parts, Apr (main),AM(medial),AD(dorsal) and DSF(superficial).
- The Apr part are the main principle nucleus, which is about 4*5*10mm3 in dimension.
- The input of ANT mainly arises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



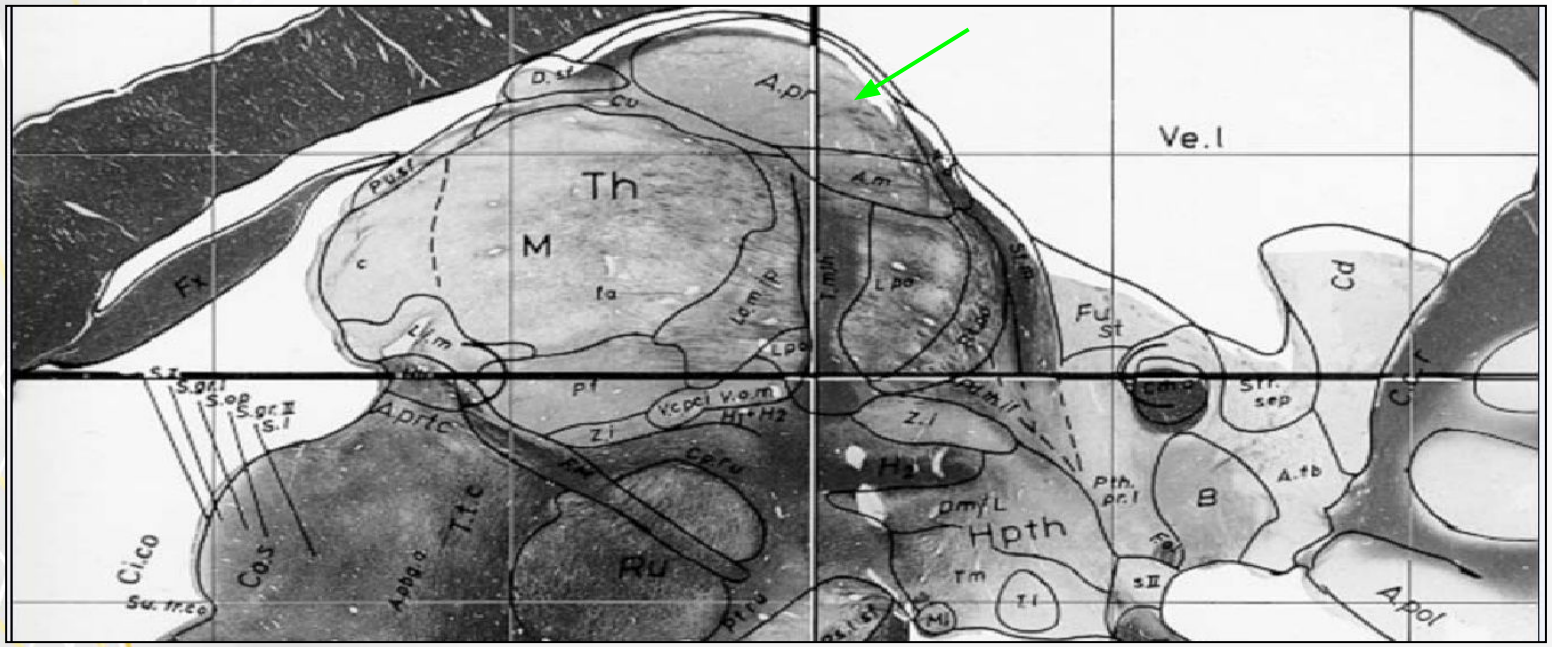
- The boundary of ANT is also important for direct targeting this small nucleus. The ventricular system serves as the broader anteriorly and superiorly.
- The mammillothalamic tract ran into this nucleus inferiorly in coronal and sagittal plane.
- The lateral boundary separated from other thalamic nucleus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

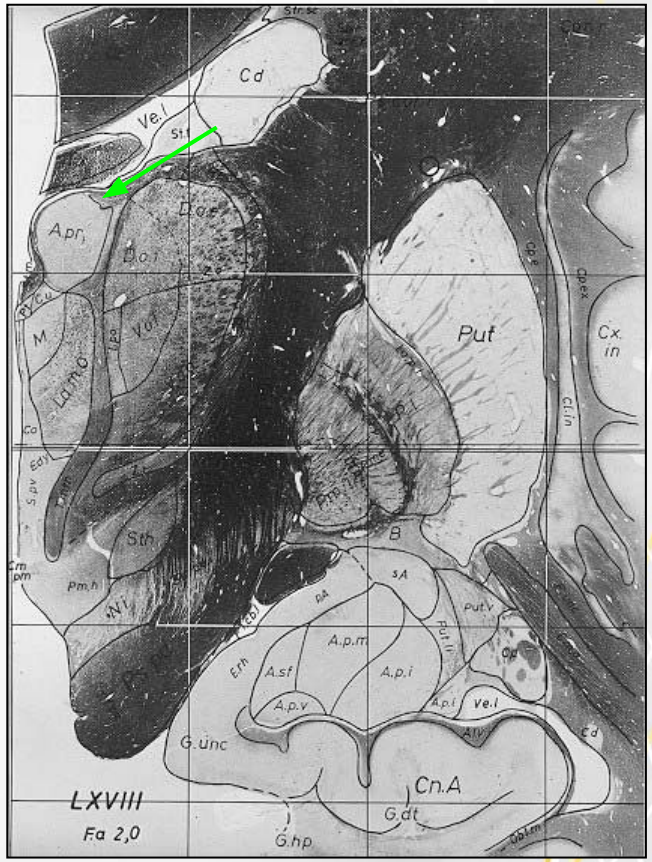
an : anterior thalamic nu.
m : mediodorsal thalamic nu.
mt : mammillothalamic tract
vl : ventral lateral thalamic nu.



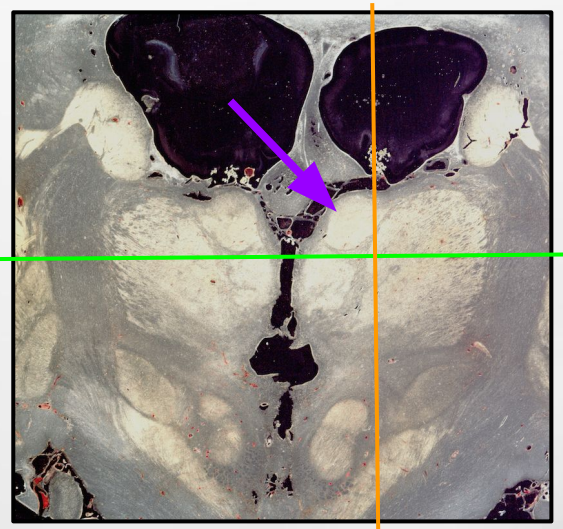


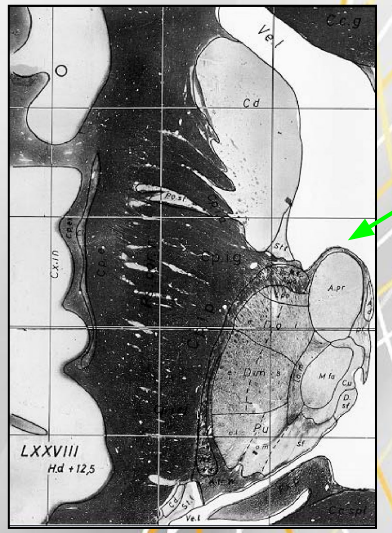
Schaltenbrand atlas



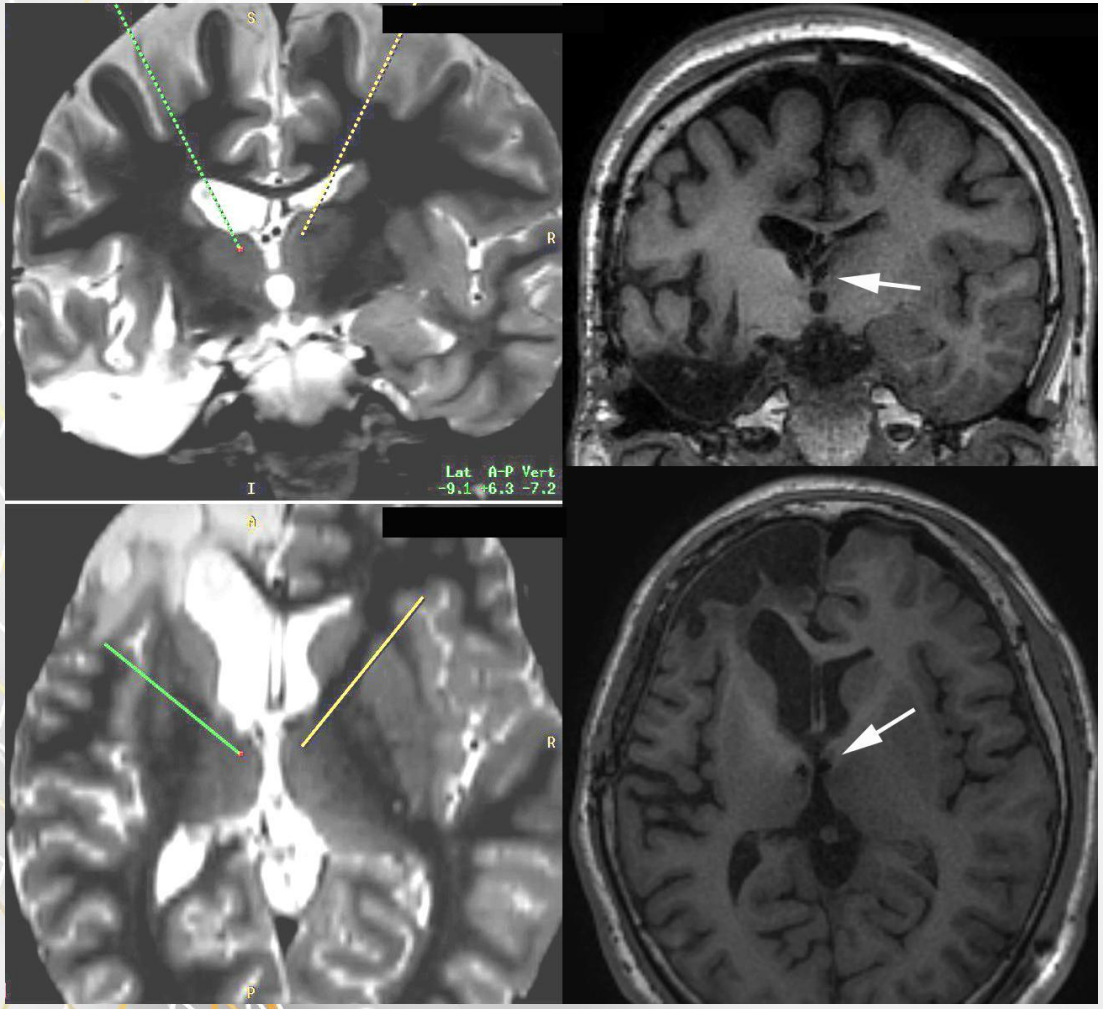


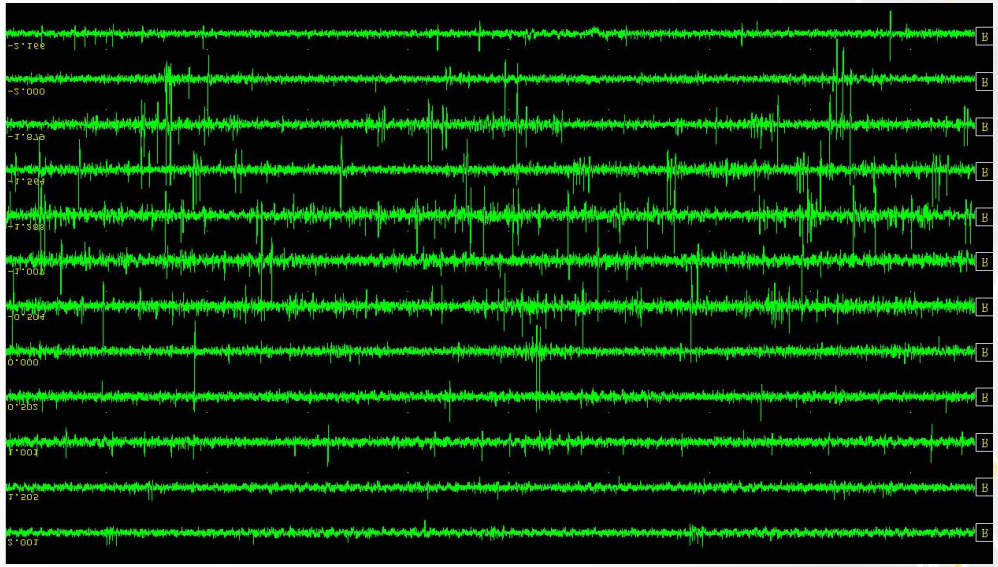
5-6 mm lateral
12mm superior
2 mm anterior to MCP



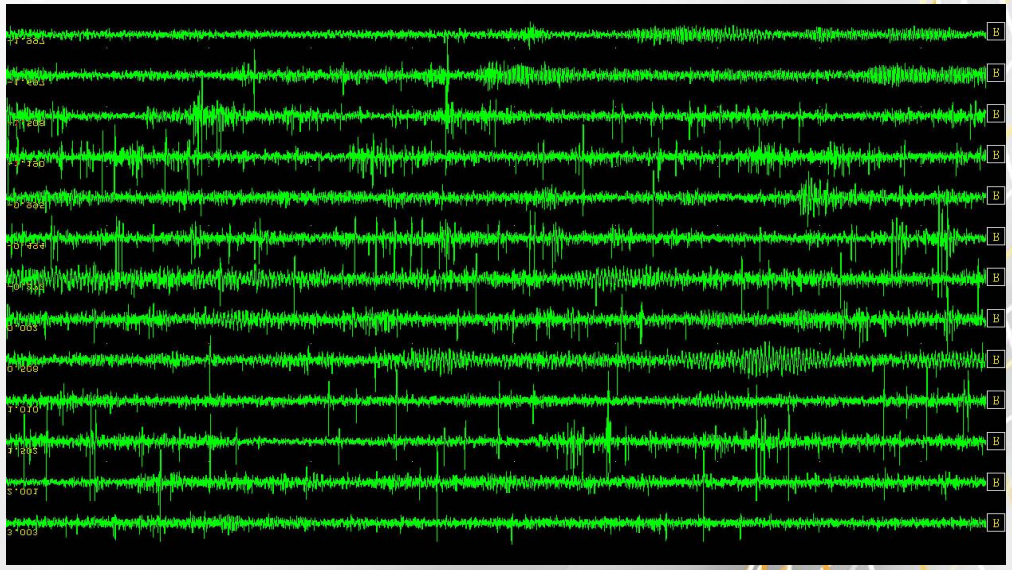


Direct targeting: ANT





Left thalamic MER



Right thalamic MER

With 7 yrs follow up: 1-2 brief seizure per months, 2 AEDS

Case Report

Deep Brain Stimulation of Anterior Thalamic Nuclei for Intractable Epilepsy in Thailand: Case Report

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Lunliya Thampratankul MD***, Anannit Visudtibhan MD***

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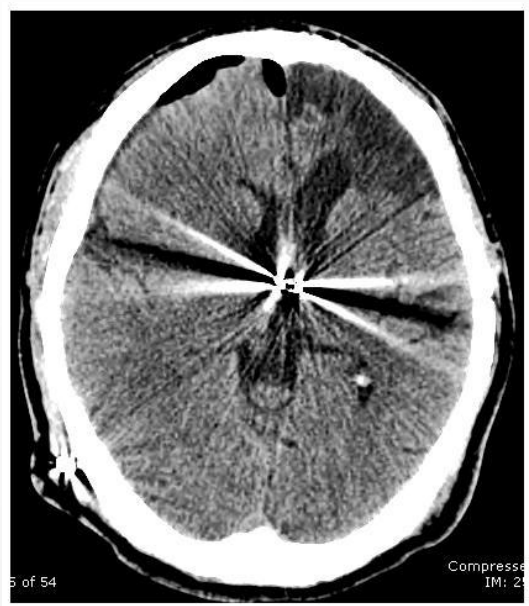
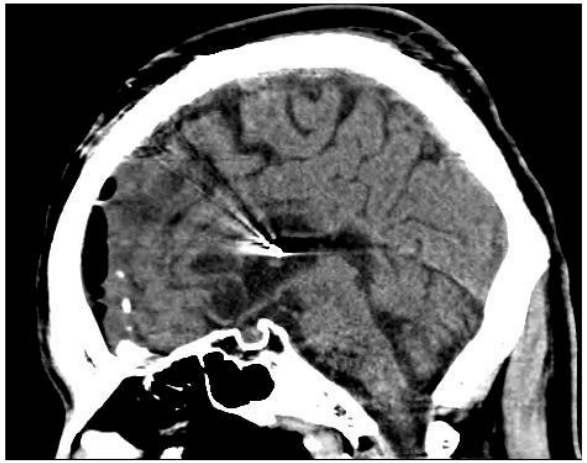
Neurostimulation can be an alternative treatment for medically intractable epilepsy, especially when the resective surgery could not be performed. The author reported a case of 19-year-old, right-handed male patient who had a history of intractable epilepsy for 11 years after post viral encephalitis 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 "0ff". 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.



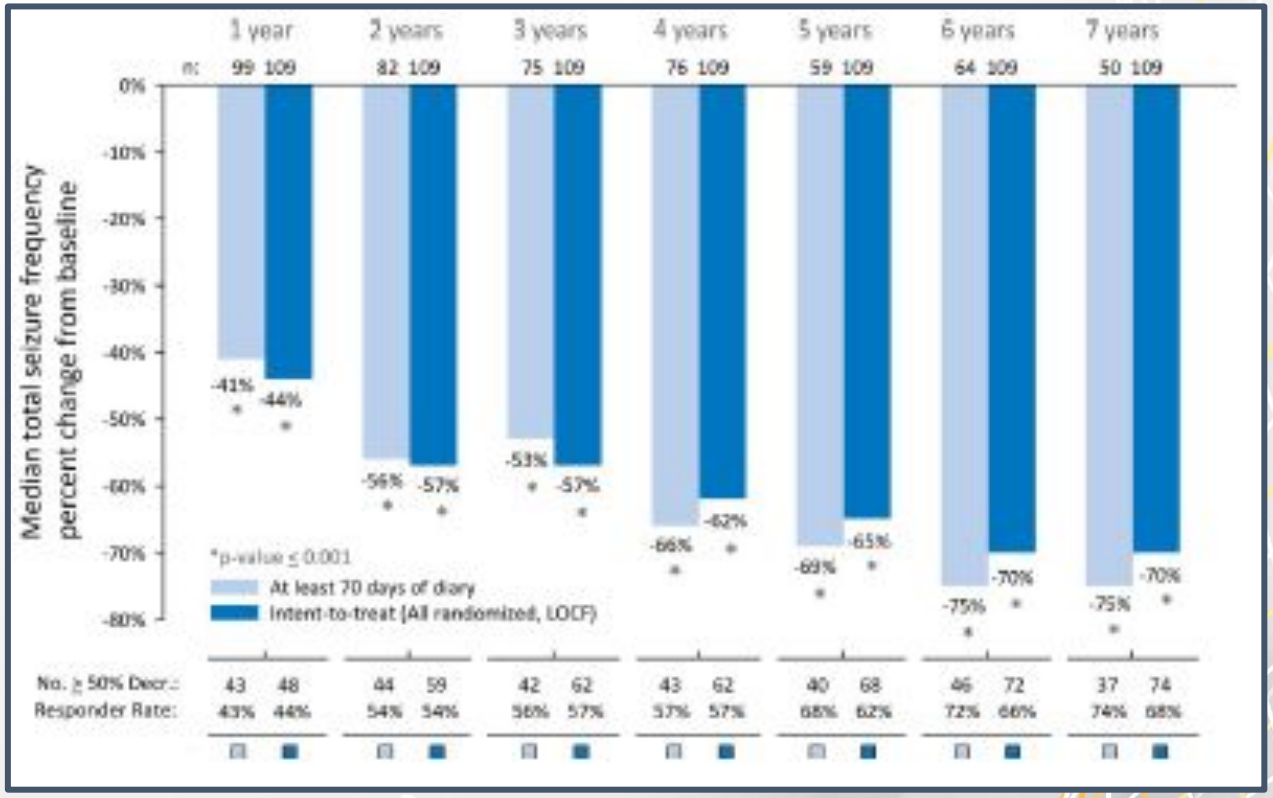


The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy

Vicenta Salanova[1] | Michael R. Sperling[2] | Robert E. Gross[3] | Chris P. Irwin[4] | Jim A. Vollhaber[4] | Jonathon E. Giftakis[4] | Robert S. Fisher[5] | SANTÉ Study Group

Key Points

- Subjects with ANT DBS demonstrated a gradual and sustained improvement in seizure reduction over time, with a median percent reduction in seizures from baseline of 75% at 7 years
- No trends in worsening of adverse events were observed after more than 10 years of follow-up, indicating a stable long-term safety profile
- The overall mortality and SUDEP rates reported in this study (6.9 and 2.0 deaths per 1000 person-years, respectively) are favorable
- Our results suggest SUDEP risk may be reduced with long-term ANT DBS therapy, a finding consistent with other neuromodulation treatments (i.e., VNS, RNS) for drug-resistant focal epilepsy



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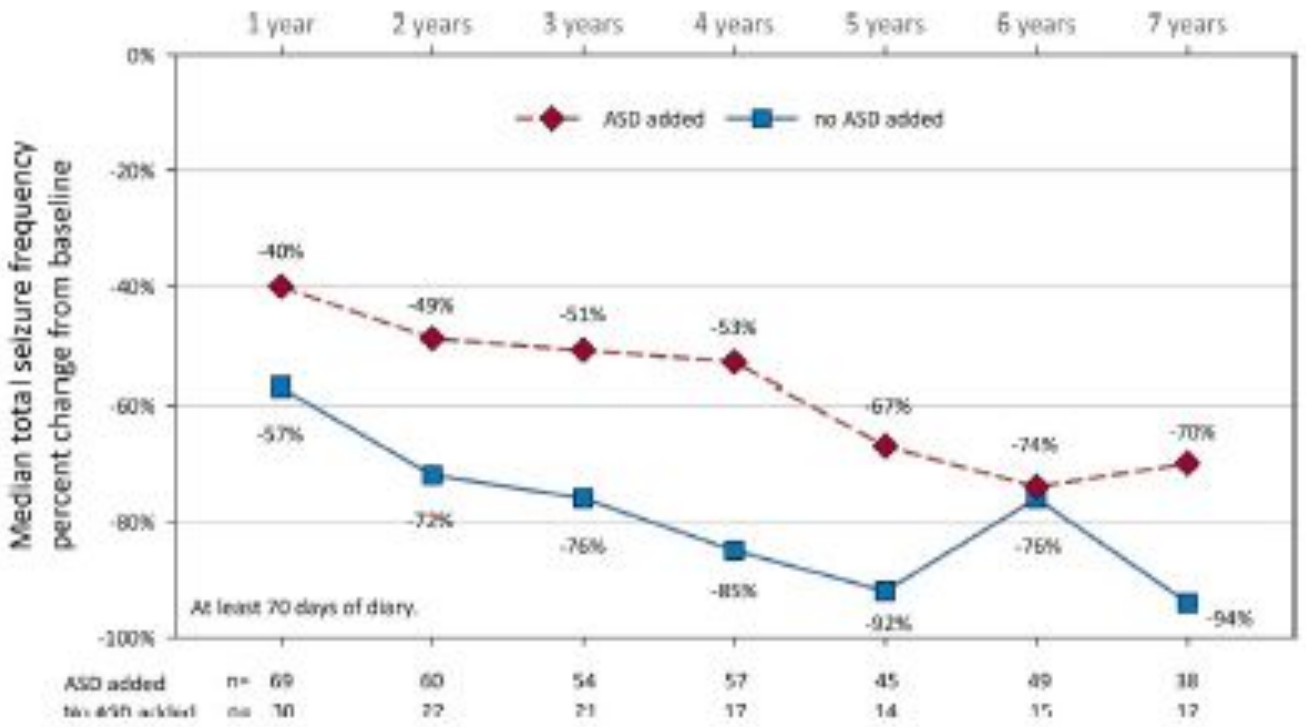

FIGURE 3 Total seizure frequency by medication addition. New antiseizure drug (ASD) use and median total seizure frequency percent change from baseline at Years 1–7 are shown. Subjects in the "ASD added" category had at least one new medication added after implant, whereas those in the "no ASD added" category had no medications added through Year 7

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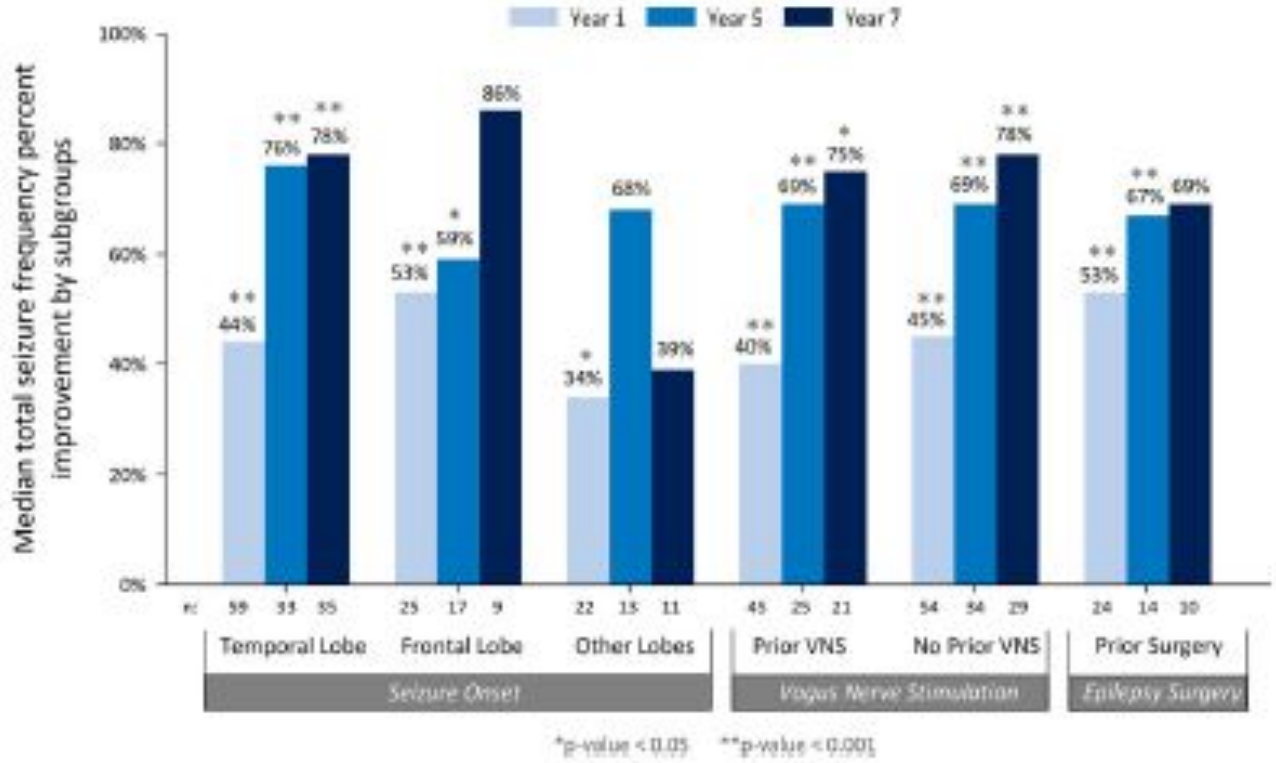
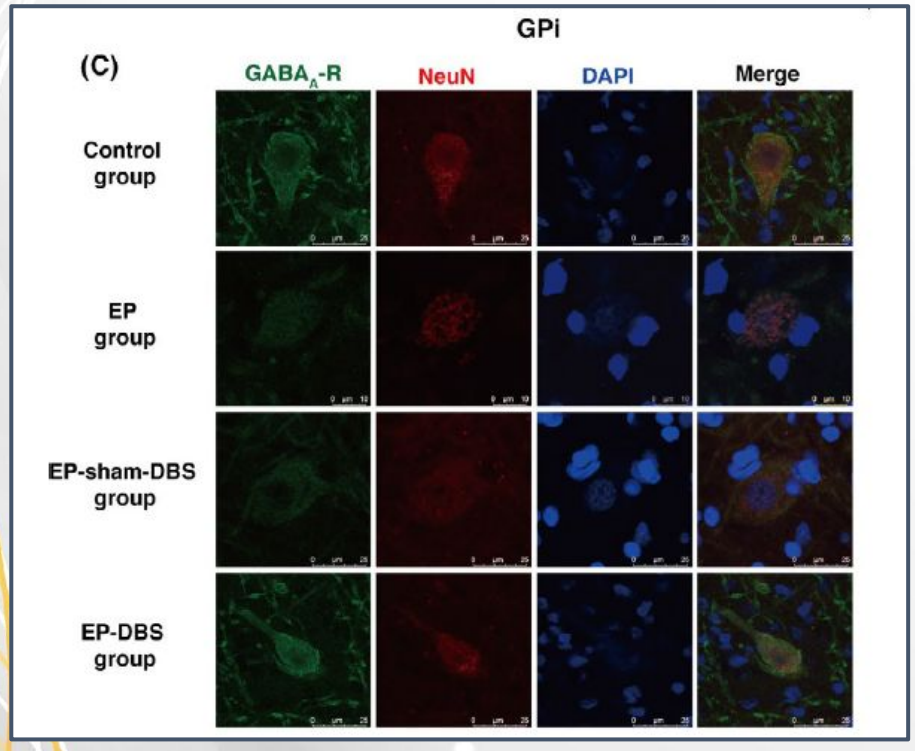


FIGURE 4 Seizure frequency subgroups: seizure onset, prior vagus nerve stimulation (VNS), prior surgery. Median seizure frequency percent improvement is shown by subgroups at Years 1, 5, and 7, as compared to baseline. Analyses were performed by seizure onset location, previous VNS device implant, and previous epilepsy surgery

Deep brain stimulation of the anterior nuclei of the thalamus relieves basal ganglia dysfunction in monkeys with temporal lobe epilepsy

Tingting Du[1] | Yingchuan Chen[2] | Lin Shi[2] | Defeng Liu[2] | Yuye Liu[2] | Tianshuo Yuan[2] | Xin Zhang[1] | Guanyu Zhu[2] | Jianguo Zhang[1,2,3]



Abstract

Aims: Deep brain stimulation of the anterior nuclei of the thalamus (ANT-DBS) is effective in temporal lobe epilepsy (TLE). Previous studies have shown that the basal ganglia are involved in seizure propagation in TLE, but the effects of ANT-DBS on the basal ganglia have not been clarified.

Methods: ANT-DBS was applied to monkeys with kainic acid–induced TLE using a robot-assisted system. Behavior was monitored continuously. Immunofluorescence analysis and Western blotting were used to estimate protein expression levels in the basal ganglia and the effects of ANT stimulation.

Results: The seizure frequency decreased after ANT-DBS. D1 and D2 receptor levels in the putamen and caudate were significantly higher in the ANT-DBS group than in the epilepsy (EP) model. Neuronal loss and apoptosis were less severe in the ANT-DBS group. Glutamate receptor 1 (GluR1) in the nucleus accumbens (NAc) shell and globus pallidus internus (GPi) increased in the EP group but decreased after ANT-DBS. γ-Aminobutyric acid receptor A (GABA$_A$-R) decreased and glutamate decarboxylase 67 (GAD67) increased in the GPi of the EP group, whereas the reverse tendencies were observed after ANT-DBS.

Conclusion: ANT-DBS exerts neuroprotective effects on the caudate and putamen, enhances D1 and D2 receptor expression, and downregulates GPi overactivation, which enhanced the antiepileptic function of the basal ganglia.

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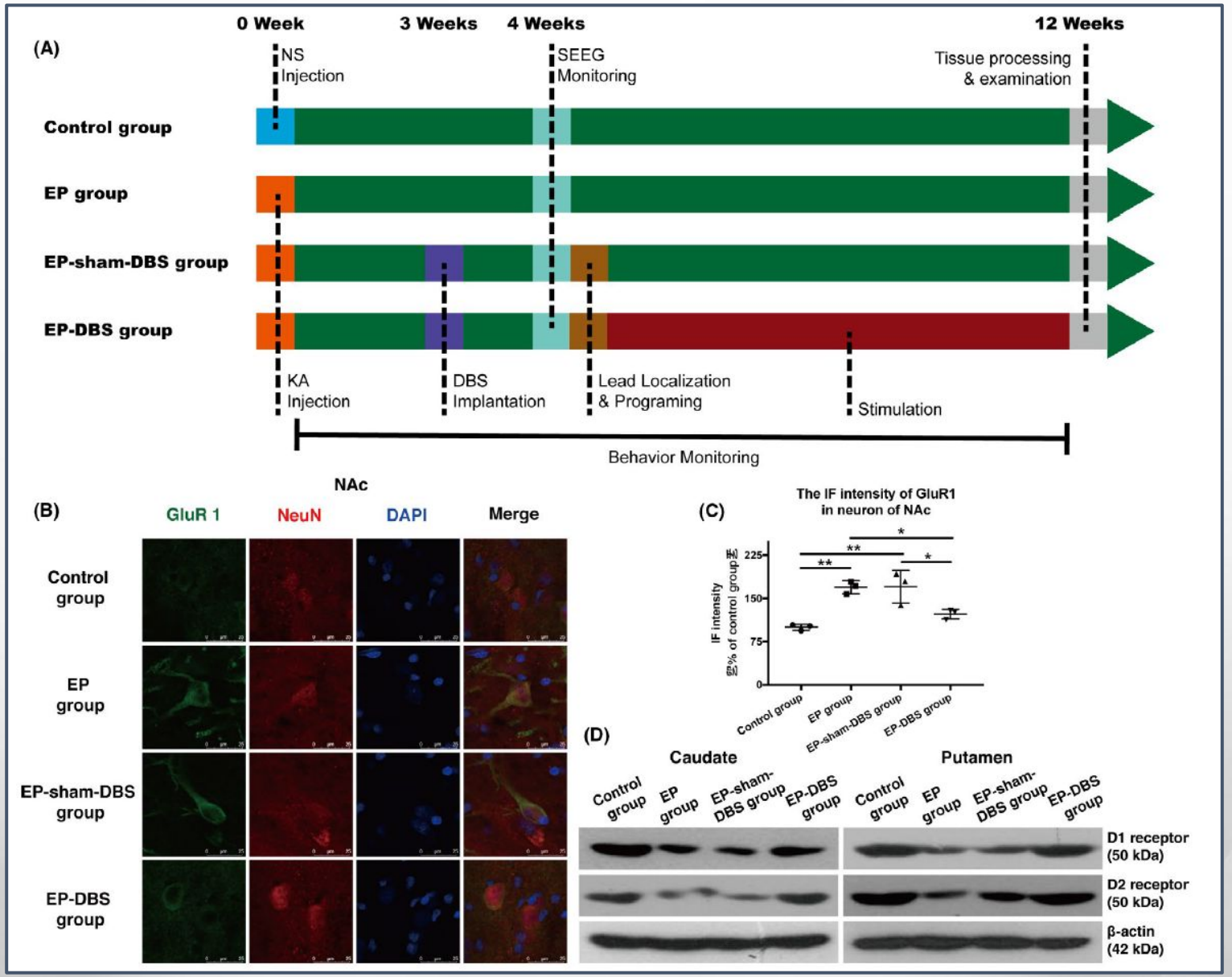
(A)
0 Week
3 Weeks
4 Weeks
12 Weeks
NS Injection
SEEG Monitoring
Tissue processing & examination
Control group
EP group
EP-sham-DBS group
EP-DBS group
KA Injection
DBS Implantation
Lead Localization & Programing
Stimulation
Behavior Monitoring
(B)
NAc
GluR 1
NeuN
DAPI
Merge
Control group
EP group
EP-sham-DBS group
EP-DBS group
(C)
The IF intensity of GluR1 in neuron of NAc
IF intensity (% of control group)
225
150
75
0
Control group
EP group
EP-sham-DBS group
EP-DBS group
(D)
Caudate
Putamen
Control group
EP group
EP-sham-DBS group
EP-DBS group
D1 receptor (50 kDa)
D2 receptor (50 kDa)
β-actin (42 kDa)

Emerging technologies for improved deep brain stimulation

Hayriye Cagnan[1,2,*], **Timothy Denison**[1,2,3], **Cameron McIntyre**[4], **Peter Brown**[1,2]
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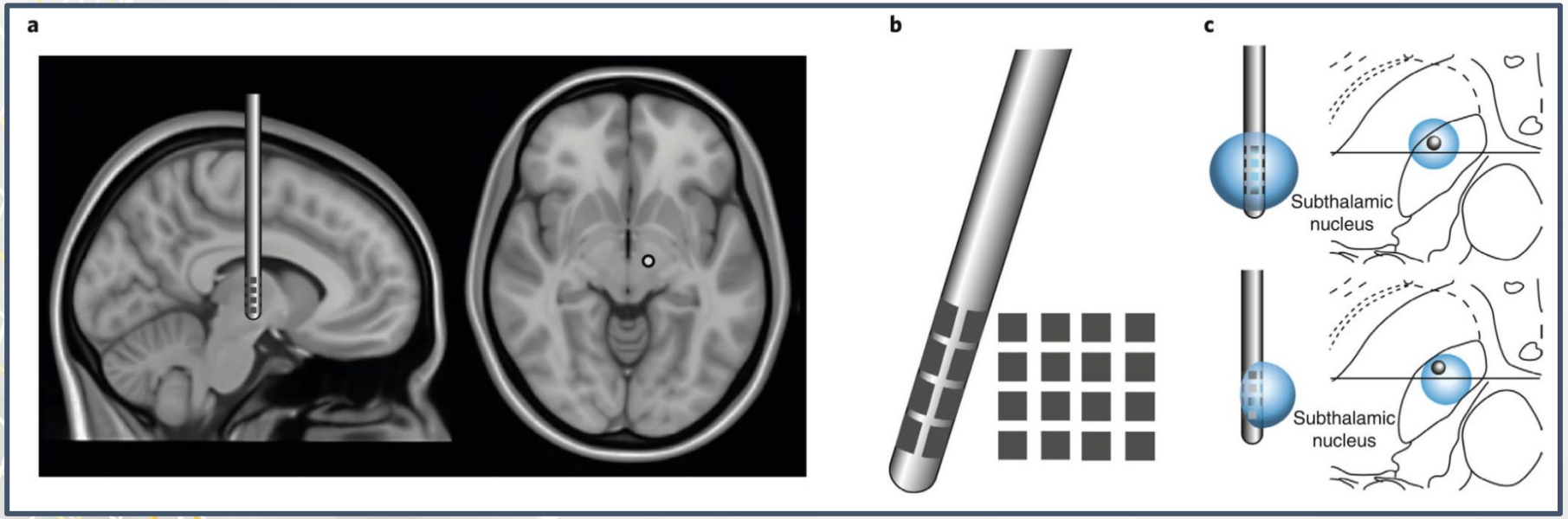
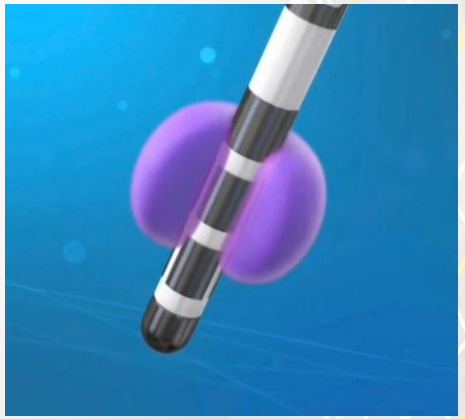
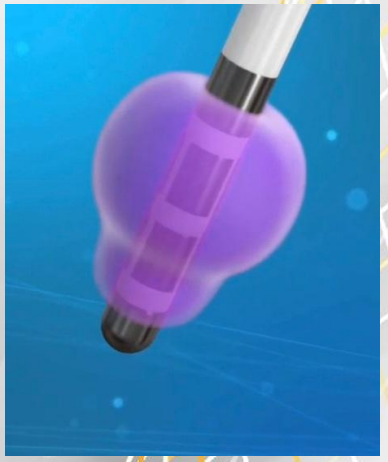
[2]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[3]Department of Engineering Sciences, University of Oxford, Oxford, UK
[4]School of Medicine, Case Western Reserve University, Cleveland, OH, USA







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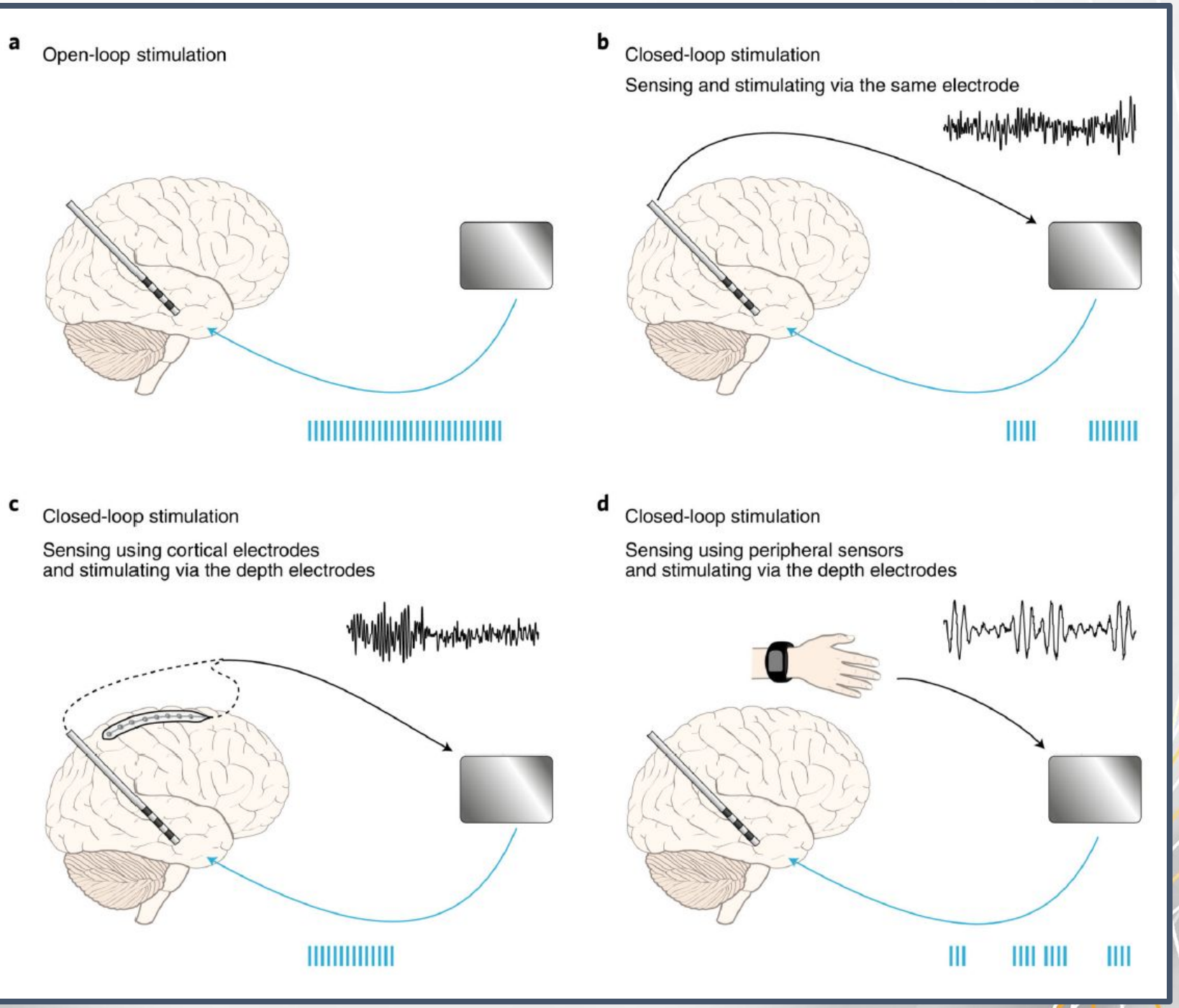
a
Open-loop stimulation
b
Closed-loop stimulation
Sensing and stimulating via the same electrode
c
Closed-loop stimulation
Sensing using cortical electrodes
and stimulating via the depth electrodes
d
Closed-loop stimulation
Sensing using peripheral sensors
and stimulating via the depth electrodes

Closed loop vs open loop

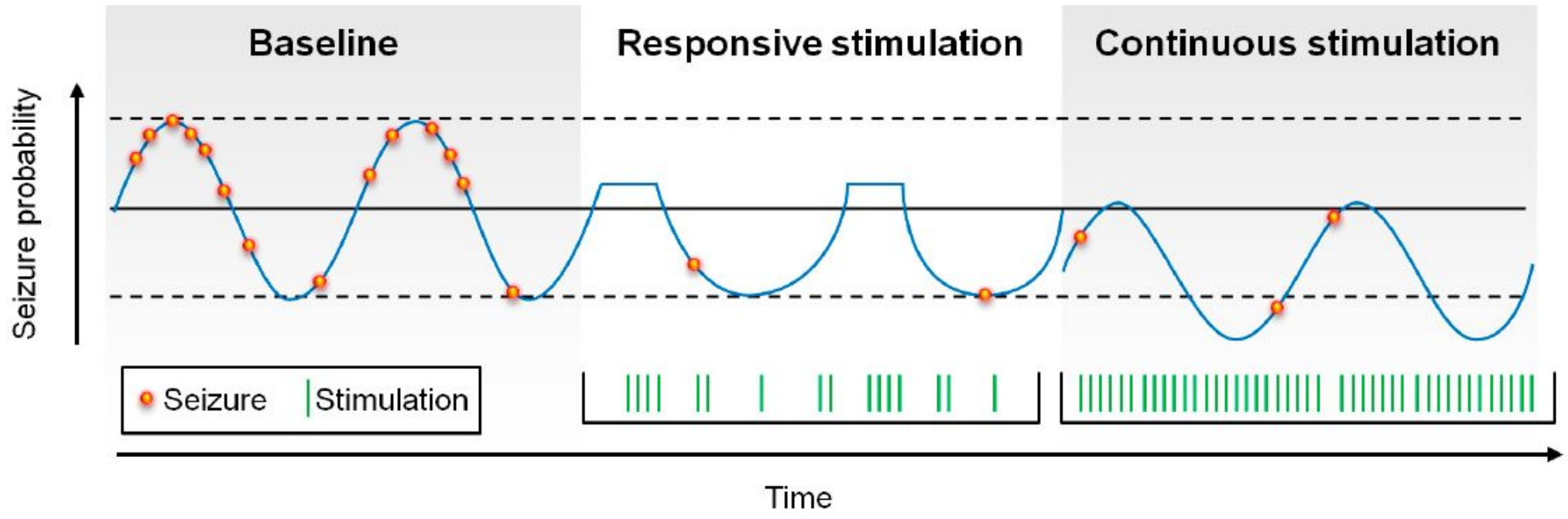

Figure 2. Schematic of the possible affects upon seizure probability by responsive and continuous stimulation. Responsive stimulation may abort seizures in real time, reducing the time in which the patient is at high-risk for seizures, whereas continuous stimulation may "shift" seizure probability down by modulating broader epileptogenic networks.

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Conclusion

- Long term outcome of anterior thalamic DBS proved its efficacy for selected intractable epilepsy case who is not a surgical candidate for resection.
- Evidence of network modulation and neuroprotective effect have been proven in animal model, this result encourage the benefit of neuromodulation not only improved seizure outcome and prevent of neuronal damage.
- Common side effects of ANT-DBS : depression and memory (30%)
- The closed loop DBS is developing as the same principle of responsive neurostimulation. Multiple leads implant is possible for multiple foci epilepsy.
- Limitations : high cost of device, RCT study (? bias)