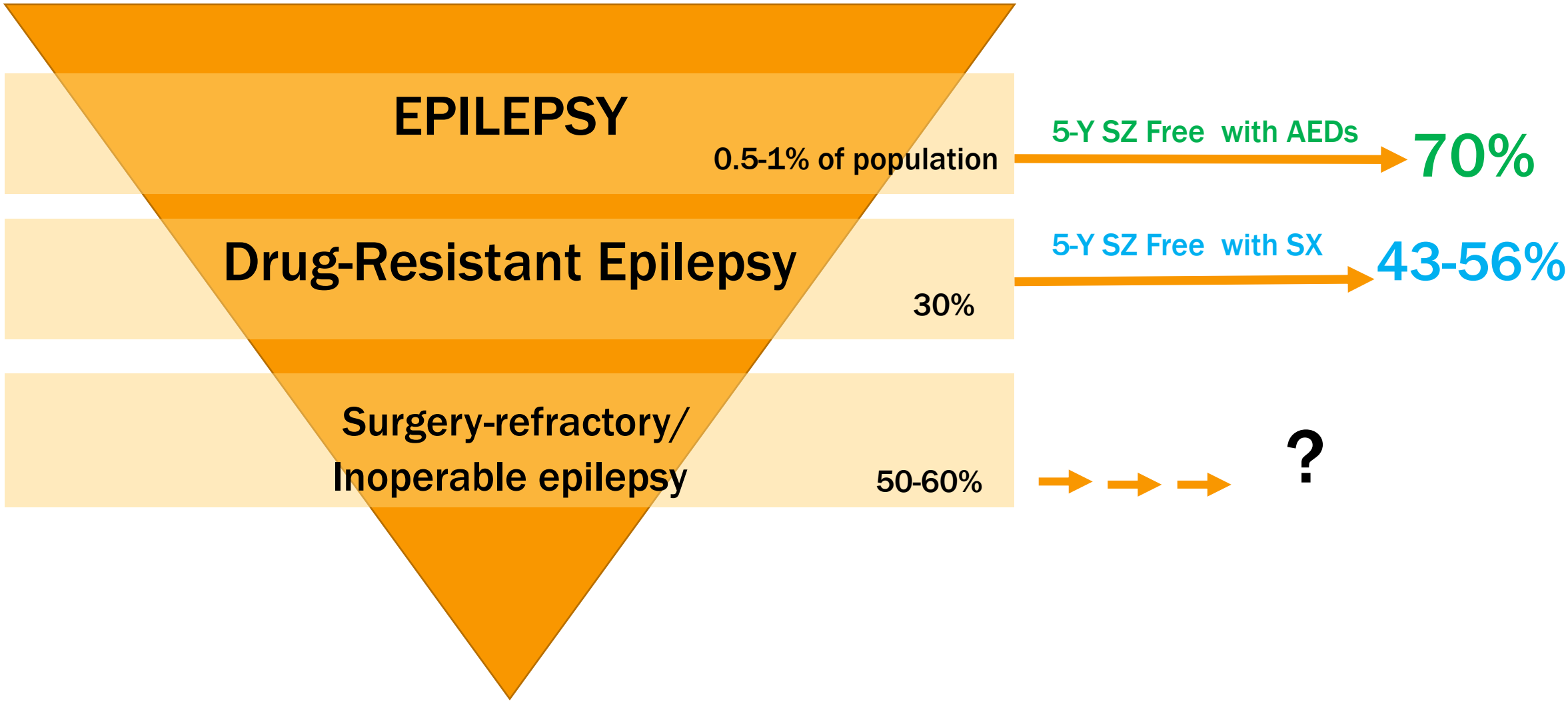
NEUROMODULATION FOR DRUG-RESISTANT EPILEPSY

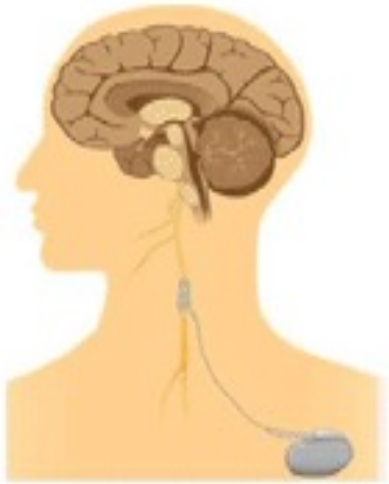
Major General Siraruj Sakoolnamarka, MD., FRCNST


Phayathai Palace, Bangkok

EPILEPSY


EPILEPSY
0.5-1% of population
5-Y SZ Free with AEDs
70%
Drug-Resistant Epilepsy
30%
5-Y SZ Free with SX
43-56%
Surgery-refractory/
Inoperable epilepsy
50-60%
?

DRE:
Drug Resistant Epilepsy



Brain Surgery

- Neuro-modulation
- Resective surgery
  - Hemispherctomy
  - Corpus Callosotomy
  - Multiple subpial Transsection
- MR Laser Ablation

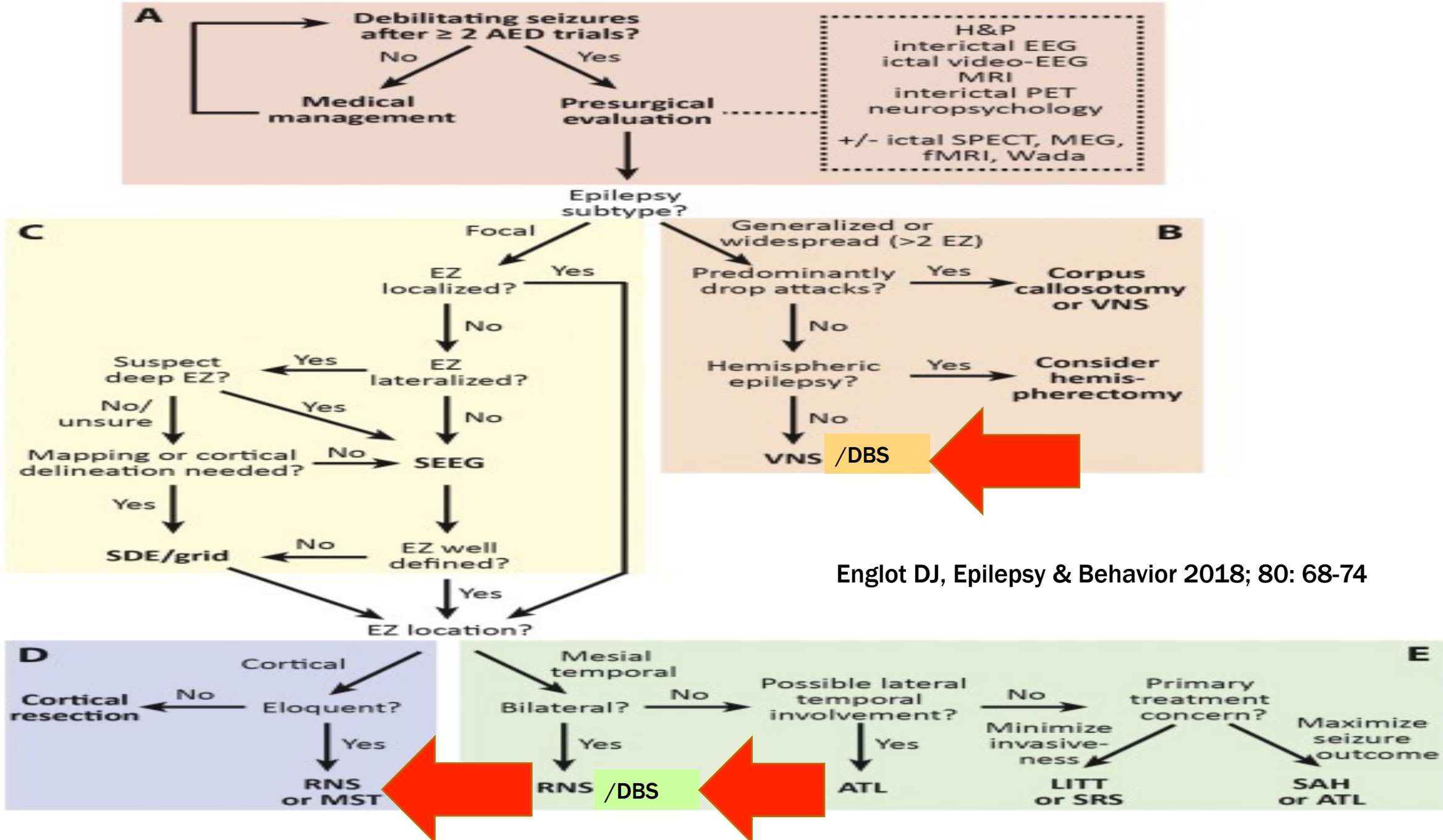
Diet

- Ketogenic
- Modified Atkins
- Low glycemic

Allopathic Treatment

- AEDs
- Various Pharmacological treatment

Epilepsy surgery treatment algorithm



Englot DJ, Epilepsy & Behavior 2018; 80: 68-74

SCOPE

What is Neuromodulation?

Classification and History of Neuromodulation for Epilepsy

Common types of Neuromodulation used in DRE

- Indication,
- Mechanism of actions,
- Evidence related to the outcome,
- Adverse effects

Conclusion

WHAT IS NEUROMODULATION?

Neuromodulation is technology

that acts directly upon neurological system.

It is the alteration of nervous system activities by delivering electrical or pharmaceutical agents directly to a target area.

Krames, Peckham, and Rezai (eds) *Neuromodulation v.1-2,* (2009) , 2nd ed (2018)

HOW NEUROMODULATION WORKS

Neuromodulation works

by either actively stimulating nervous areas to produce a natural biological response /

by applying targeted pharmaceutical agents in tiny doses directly to site of action.

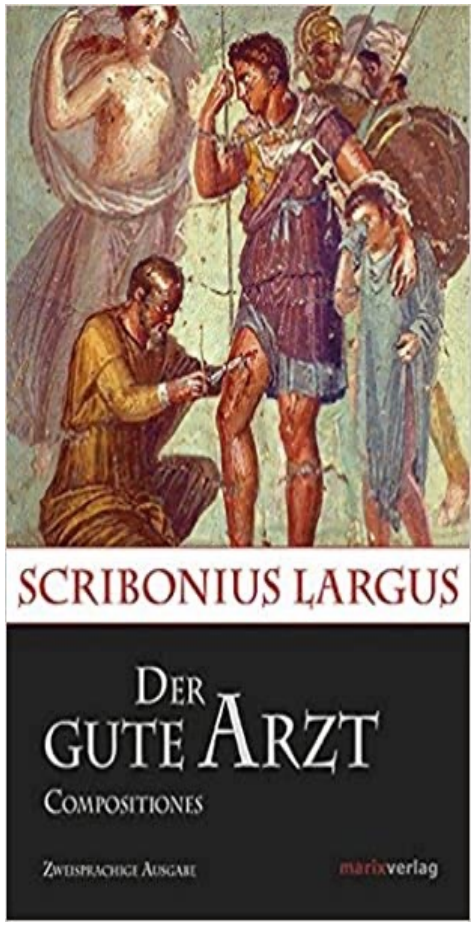
Krames, Peckham, and Rezai (eds) *Neuromodulation v.1-2,* (2009) , 2nd ed (2018)

Use of electrical torpedo fish

Electric ray, Torpedo sp.

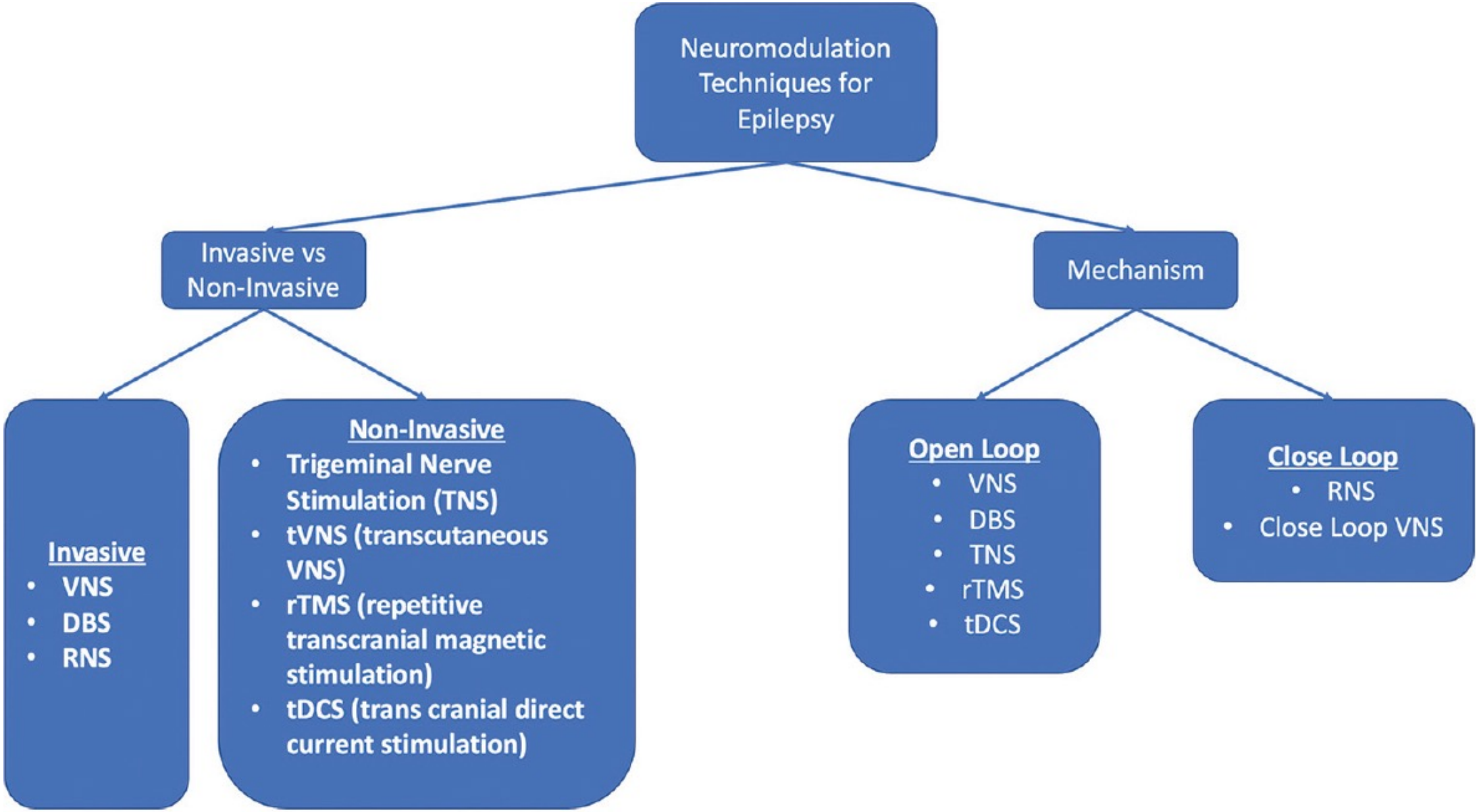
In treatment of gout

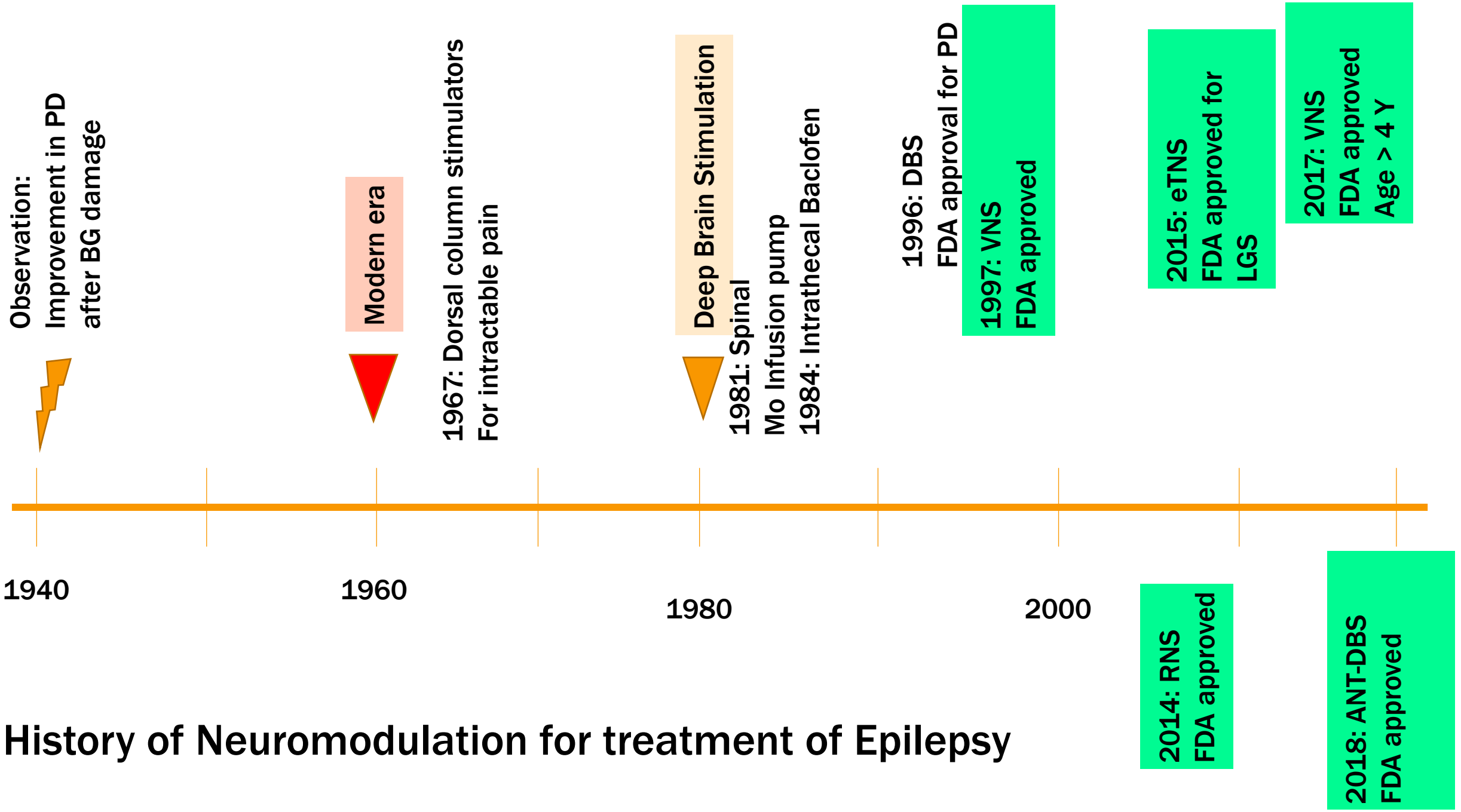
In treatment of headache



Perdikis P, S Afr J Surg 1977;15:81-86

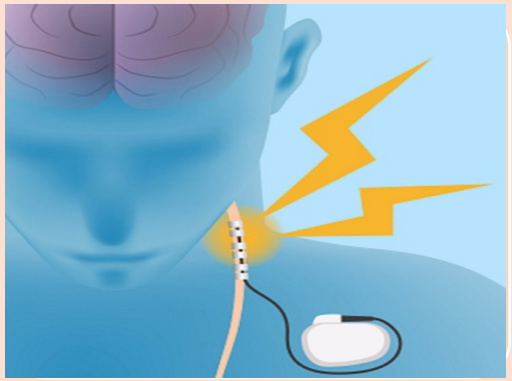
Classification of Neuromodulation device for Epilepsy



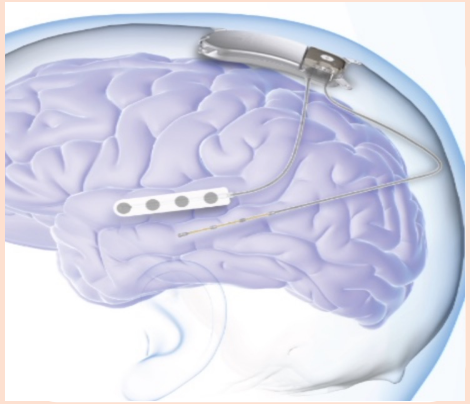


History of Neuromodulation for treatment of Epilepsy

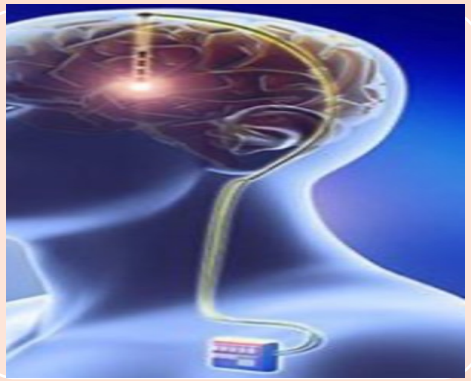
Neuromodulation for DRE



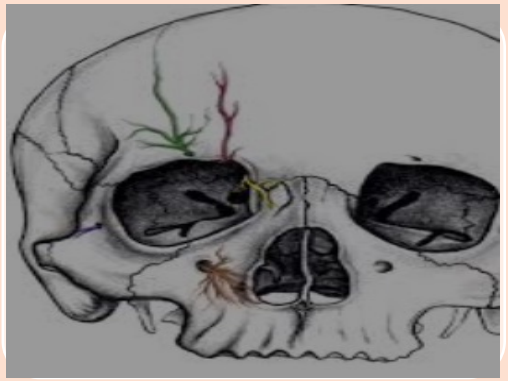
VNS



RNS



DBS



eTNS

VNS

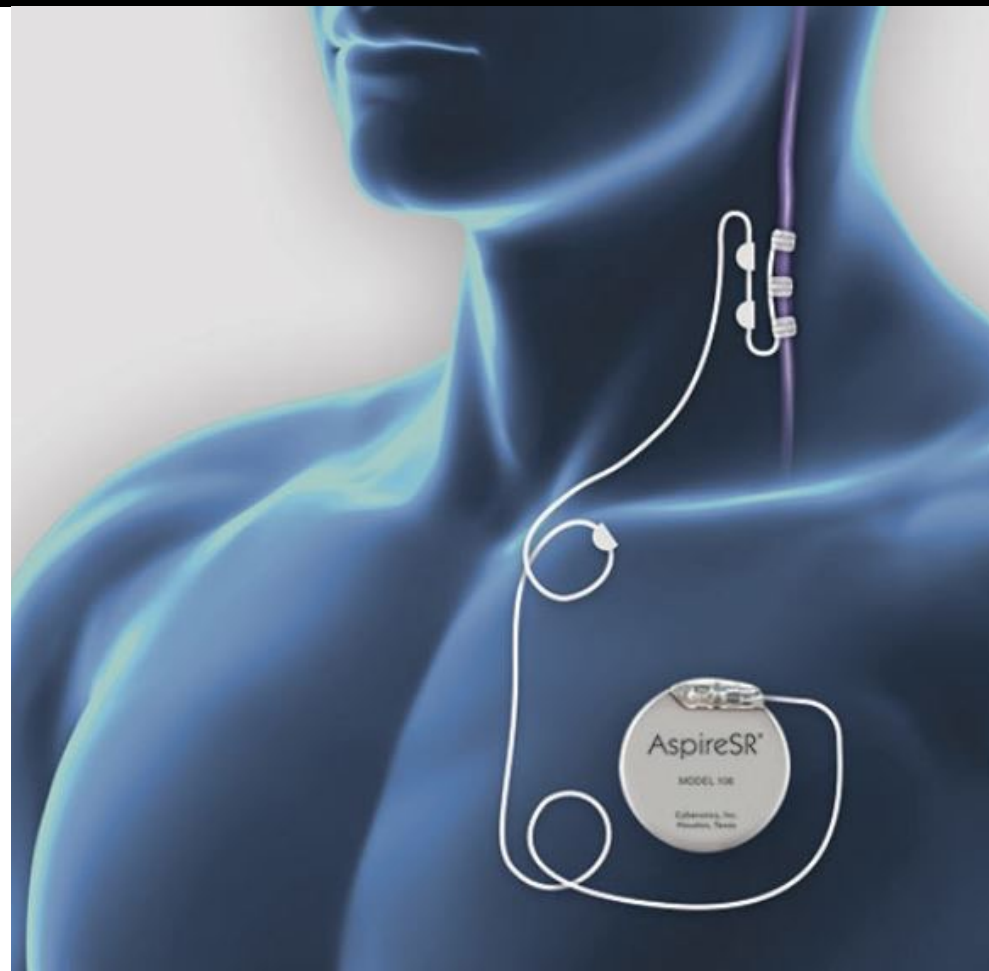
Indications Medically refractory focal onset seizures/ major depression.
Commonly used for generalized seizures as well.

The first neuromodulator device approved for use by USFDA since 1997

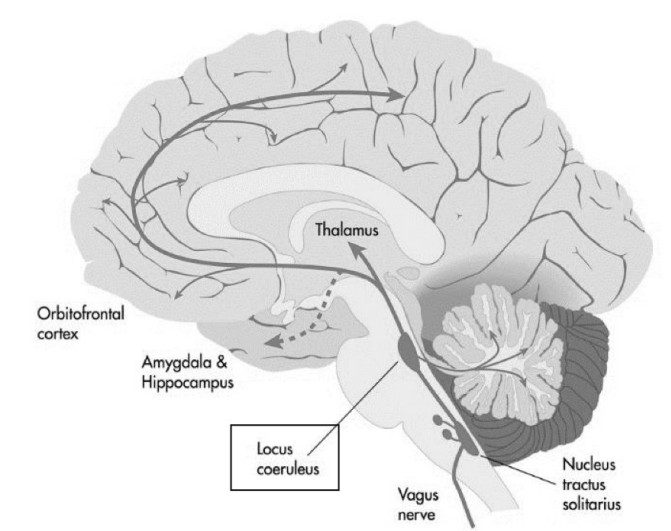
An Invasive, Open-loop/Closed-loop device.

Initially for use in patient with focal onset seizure with DRE > 12 Y

In 2017, approved for use in children > 4 Y



VNS: MECHANISM



Hypothesis:

A decrease in the brain venous hyperemia and, hence seizure abortion.

Fan JJ, et al. CNS Neurosci Ther 2019;25:1222-8

Desynchronization of sz network activity, modulate NT release with increase GABA levels & decreased glutamate levels.

Hammond EJ, et al. Brain Res 1992;583:300-3
Zabara J. Epilepsia 1992;33:1005-12

A Role in Sz modulation

Krahl SE, Clark KB. Surg Neurol Int 2012;3 (Suppl 4):S255-9

VNS: EFFICACY

	Approval	Indication	Clinical Trial Outcomes
Open-loop			
VNS	1997	Adults and adolescents older than 12 y of age with partial-onset seizures that are refractory to antiepileptic medications	E01, E02, E03, E04, E05 454 participants 35% reduction at 1 y 37% responder rate at 1 y 44% reduction at 2 y 43% responder rate at 2 y
	2017	Extended to use in patients 4 y of age and older	E3, E4, E5, E6, postapproval study (Japan) 117 participants 24.7% reduction at 1 y 35% responder rate at 1 y

Morris GL 3rd, et al. Neurology 1999;53:1731-5

VNS: QoL

VNS with best medical therapy had significant improvement in health-related QoL VS medical alone group.

Ryvlin P, et al. Epilepsia 2014;55:893-900
Tsai JD, et al. Epilepsy Behav 2016;56:95-8

(Overall improvement in attention, cognitive ability, memory, creativity and decision-making)

Improvement in quality-adjusted life years of 5.96 years (age 1-11 Y) and 4.82 years (age 12-17 Y)

Helmers SL, et al Eur J Paediatr Neurol 2012;16:449-58

Reduction in total health care cost (by 3000 USD/Pt/Y) and decrease ER visits, but not having a significant reduction in Sz.

Marras CE, et al. Int J Environ Res Public Health 2020;17:6150
Ben-Meachem E, et al. Neurology 2002;59 (6 Suppl4):S44-7

VNS: ADVERSE EFFECTS

VNS implantation is relatively safe operation.

Most common side effects

Hoarseness of voice, coughing & laryngeal paresthesia about 60% but this is often reduced with habituation/adjustment in stimulation parameters.

By 2 years, hoarseness 19.8%

Elliot RE, et al. Epilepsy Behav 2011;20(3):478-83

Infections 3-6%, Vocal cord paralysis 1%,Lead damage 3%, Bradycardia

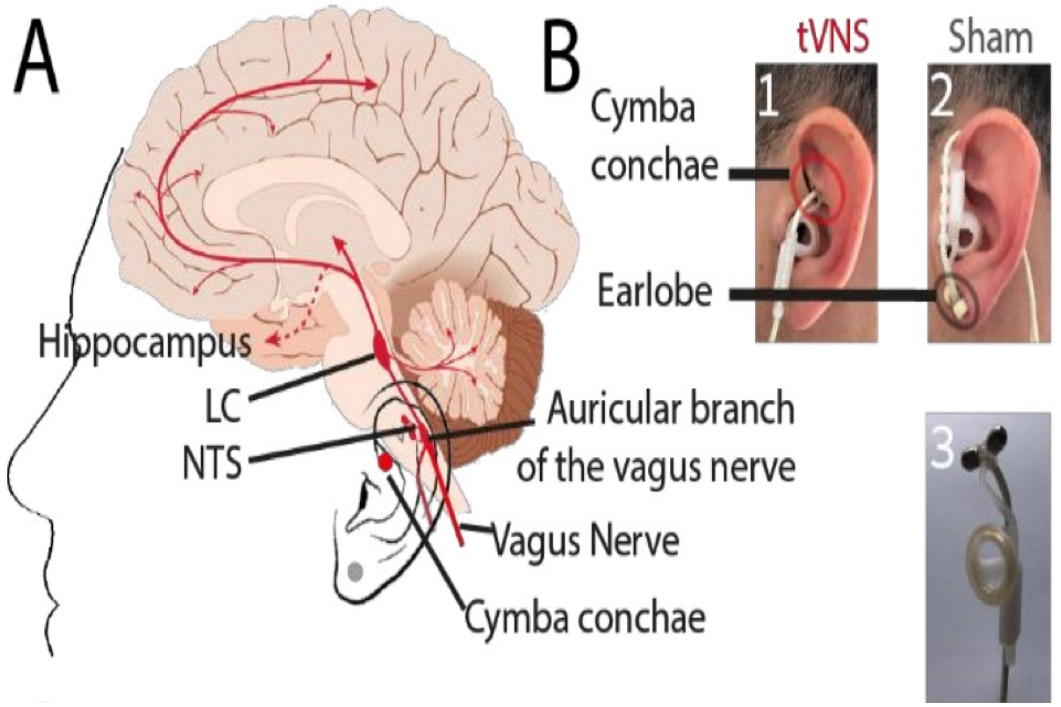
Handforth A, et al. Neurology 1998;51:48-55
Wheless JW, et al. Epilepsy Behav 2018;88S:2-10
Morris GL 3rd Mueller VM. Neurology 1999;53:1731-5
Englot DJ, et al. J Neurosurg 2011; 115:1248-55

VNS: RECENT ADVANCES

Transcutaneous VNS (tVNS) as non-invasive device

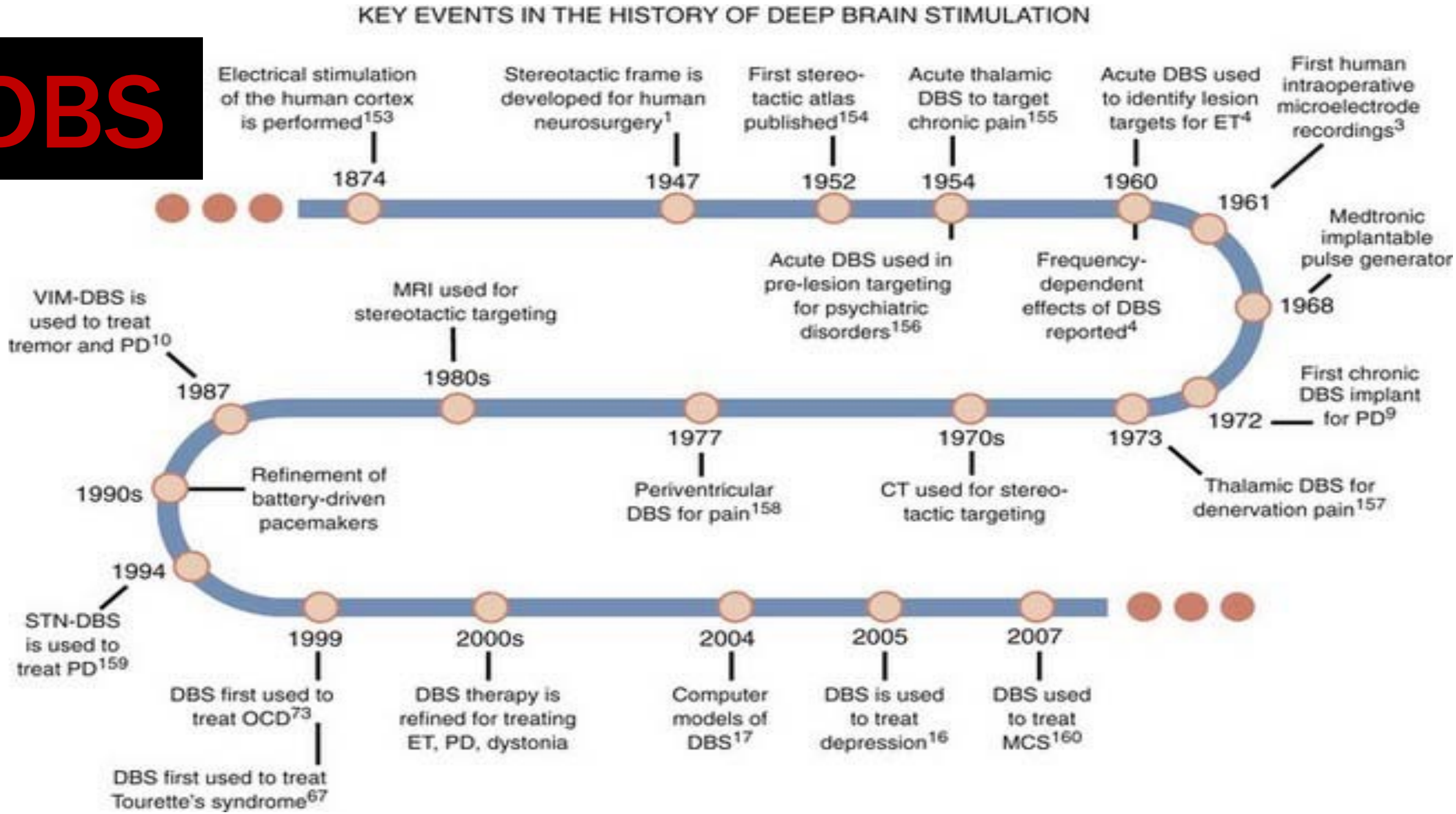
Closed-loop VNS (2015), detects tachycardia due to SZ & automatic stimulus

Biomarkers of VNS



Transcutaneous VNS (tVNS)

DBS


KEY EVENTS IN THE HISTORY OF DEEP BRAIN STIMULATION
Electrical stimulation of the human cortex is performed[153]
1874
Stereotactic frame is developed for human neurosurgery[1]
1947
First stereo-tactic atlas published[154]
1952
Acute thalamic DBS to target chronic pain[155]
1954
Acute DBS used to identify lesion targets for ET[4]
1960
First human intraoperative microelectrode recordings[3]
1961
Medtronic implantable pulse generator
1968
First chronic DBS implant for PD[9]
1972
Thalamic DBS for denervation pain[157]
1973
CT used for stereo-tactic targeting
1970s
Periventricular DBS for pain[158]
1977
MRI used for stereotactic targeting
1980s
VIM-DBS is used to treat tremor and PD[10]
1987
Refinement of battery-driven pacemakers
1990s
STN-DBS is used to treat PD[159]
1994
DBS first used to treat OCD[73]
1999
DBS first used to treat Tourette's syndrome[67]
DBS therapy is refined for treating ET, PD, dystonia
2000s
Computer models of DBS[17]
2004
DBS is used to treat depression[16]
2005
DBS used to treat MCS[160]
2007
Acute DBS used in pre-lesion targeting for psychiatric disorders[156]
Frequency-dependent effects of DBS reported[4]

DBS

Indications Medically refractory focal onset seizures

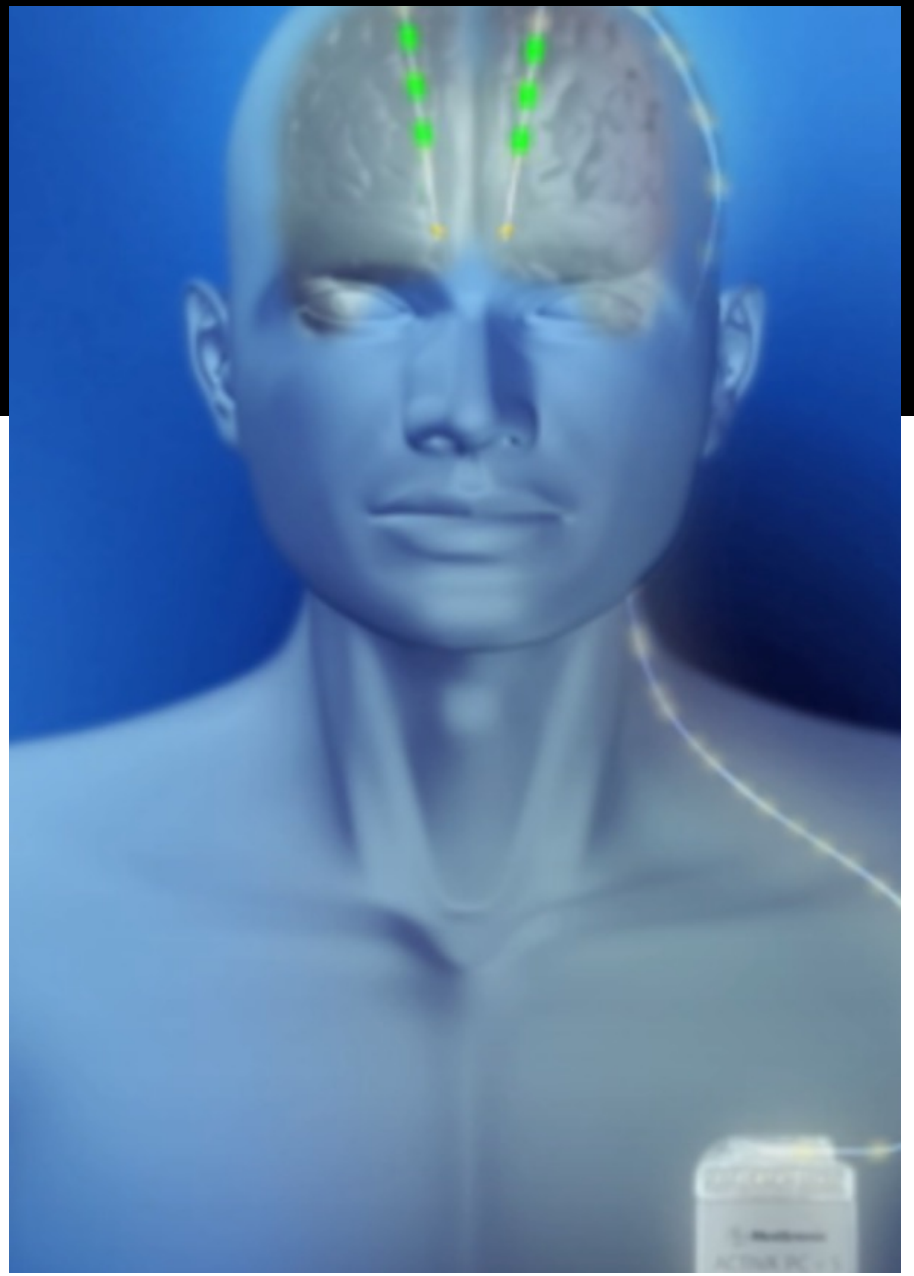
Electrodes are directly implanted into deep brain nucleus

Currently three targets in epilepsy:

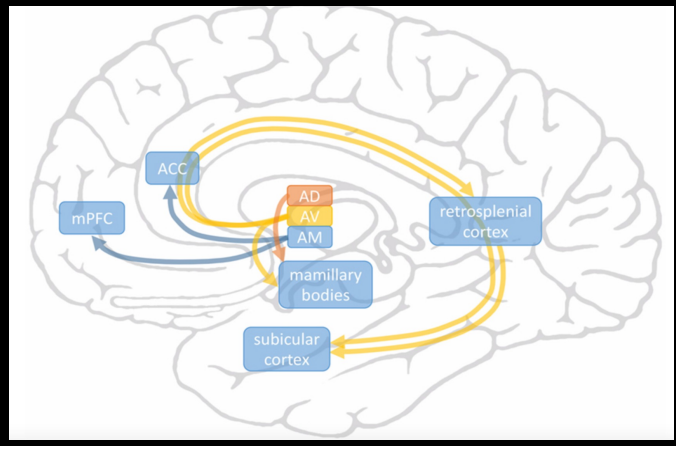
Anterior thalamus (ANT), Centromedian thalamus (CMT) and Hippocampus (HIP)

An Invasive, open-loop device.

Direct targeting of the anteroventral in Anterior Thalamus for DRE (ANT-DBS) approved by EUFDA since 2010, followed by USFDA in 2018



DBS: MECHANISM



Anterior nucleus of Thalamus is well connected to the limbic circuit and sends projections to various cortical structures eg. Orbito-frontal, cingulate & mesial frontal cortices.

High-frequency stimulation prevents seizure activities in rats.

Mirski MA, et al. Epilepsy Res 1997;28:89-100

Chronic stimulation was efficacious in seizure control in human.

Cooper IS, Upton AR. Clin Neurophysiol Suppl 1978:349-54
Upton AR, et al. Int J Neurol 1985;19-20:223-30

Stimulation induced changes in the ion channels, synaptic levels of NT and glial changes leading to overall network modulation.

McIntyre CC, et al. Clin Neurophysiol 2004;115:1239-48
Zumsteg D, et al.Clini Neurophysiol 2006; 117:2272-8
Witcher MR, Ellis TL. Front Comput Neurosci 2012;6:61

DBS: EFFICACY

	Approval	Indication	Clinical Trial Outcomes
Open-loop			
DBS	2017	Adults with partial-onset seizures that are refractory to antiepileptic medications	SANTÉ 157 participants 41% reduction at 1 y 43% responder rate at 1 y 69% reduction at 5 y 68% responder rate at 5 y

Salanova V, et al. Neurology 2015;84:1017-25
Yan H, et al. J Neurosurg Pediatr 2018;23:274-84

DBS: QoL

Significant improvement in QoL at long-term follow-up.

Initially reported about depression 13%, memory decline 13%

Salanova V, et al. Neurology 2015;84:1017-25
Fisher R, et al. Epilepsia 2010;51:899-908

Long-term studies (7Y follow-up),

Improvement in attention & executive function

no significant decline memory and depression.

Thomas GP, Jobst BC. Med Devices (Auckl) 2015;8:405-11

DBS: OTHER TARGETS

CMT: Be considered as a treatment option in **refractory generalized** epilepsy

80% seizure reduction in Lennox Gastaut syndrome with severe generalized epilepsy and >70% sz reduction (10/13 pts) at 18 months

Osorio I, et al. Epilepsia 2015;56(10): e156-60

HIP: Be considered when **bilateral onset mTLE**/ **high risk of neurocognitive deficit** is expected after resection

Small numbers of pts in clinical studies, showing >50% Sz reduction.

Velasco AL, et al.Epilepsia 2007;48:1895-1903
Tellez-Zenteno JF, et al. Neurology 2006; 66:1490-94
Velasco AL, et al.Epilepsia 2000;41:158-69

Cerebellar: Inconsistent outcomes

Fountas KN, et al. Neurosurg Focus 2010;29: E8

DBS: ADVERSE EFFECT

Common AE Implant site pain 23.6%, Paresthesia 22.7%,

Serious AE Implant site infection 10%, Lead mis targeting 8.2%

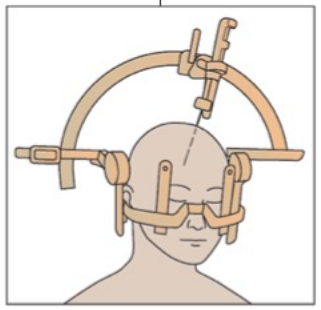
Hemorrhage 2.4%

Salanova V, et al. Neurology 2015;84:1017-25

Voges J, et al. J Neurol Neurosurg Psychiatry 2006;77:868-72

Timeline of technology development for DBS

1947 — Spiegel and colleagues develop their stereotactic frame[158], followed in 1949 by the arc-based Leksell frame



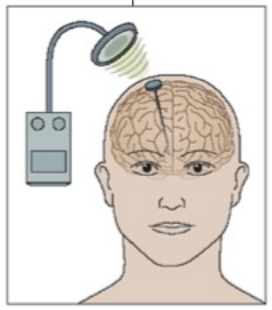
1948 — Lawrence Pool performs first chronic DBS intervention using a silver electrode connected to an induction coil

1958 — First fully implantable cardiac pacemaker introduced

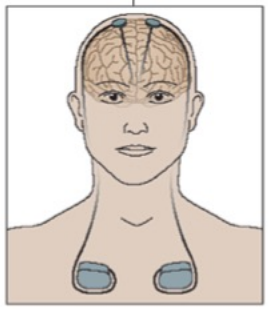
1963 — Delgado uses a 'stimoceiver' to wirelessly inhibit aggressive behaviour in a bull[159]

1970s — DBS is mainly used for the treatment of pain

'External' DBS systems in use, with handheld radiofrequency transmitter

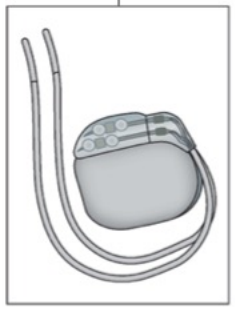


1980s — First fully internalized DBS systems available. Lithium batteries greatly extend implant life



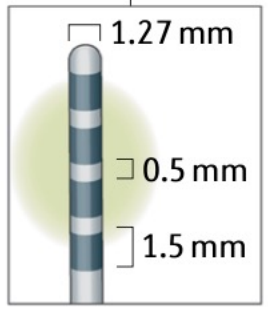
1987 — Benabid et al. report successful treatment of tremor with DBS, ushering in the modern era of DBS

1999 — Dual channel IPG, allowing two electrodes to be powered by one battery



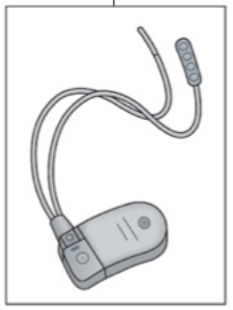
2002 — Rechargeable DBS batteries available

2009 — Quadripolar electrode commercially available



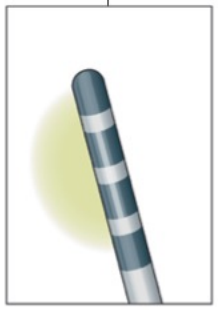
2013 — DBS device capable of simultaneous stimulation and recording introduced

Closed-loop responsive DBS system introduced to treat epilepsy

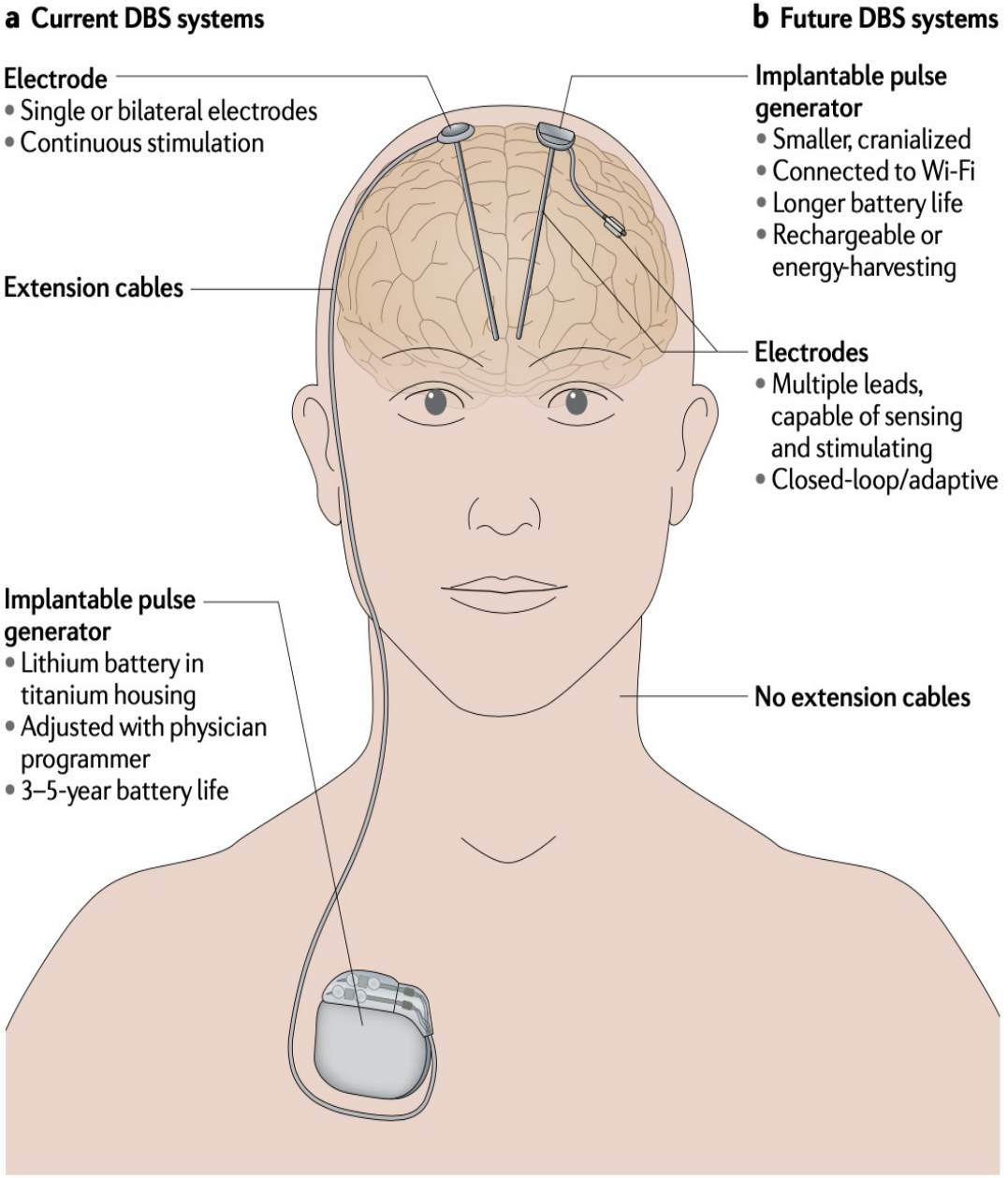


2015 — Availability of DBS system with wireless recording capability and 3 T compatibility

2020 — Directional DBS electrode commercially available



DBS:RECENT ADVANCE



RNS

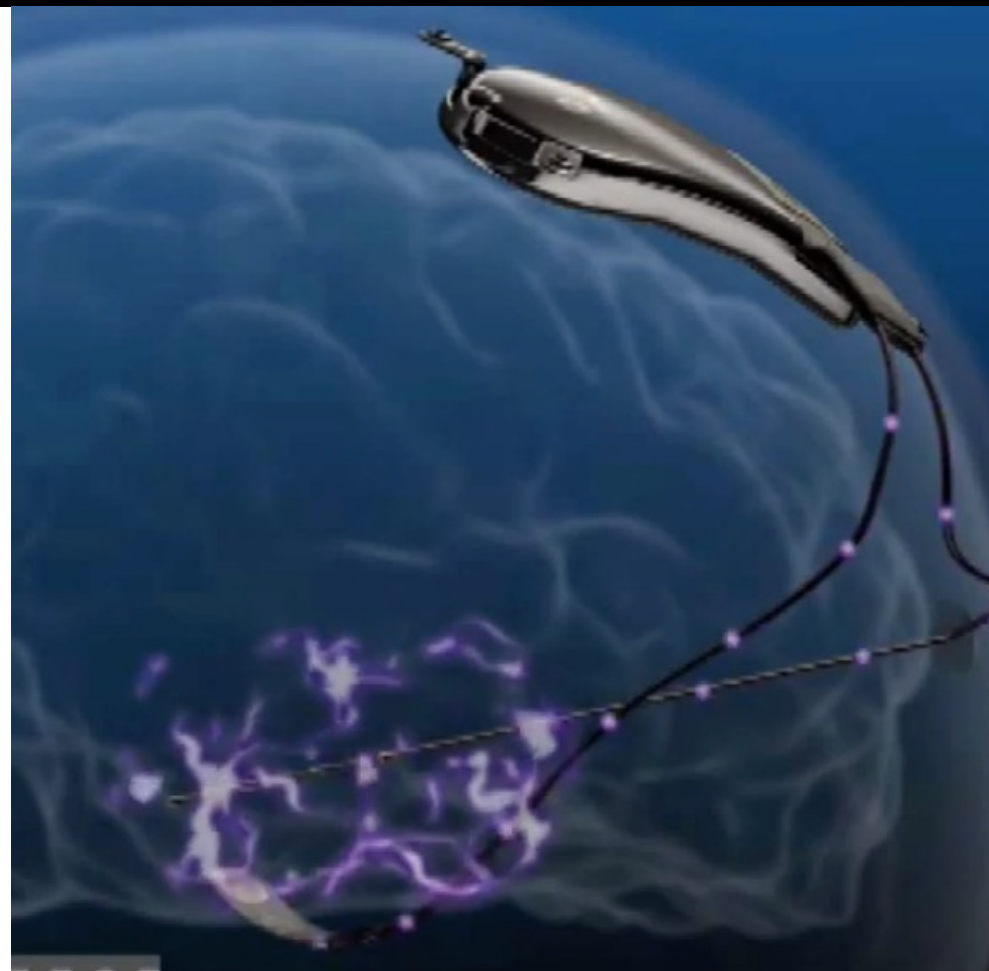
Indications Medically refractory focal unresectable onset seizures or focal onset with up to two identified seizure foci.

An invasive, closed-loop device.

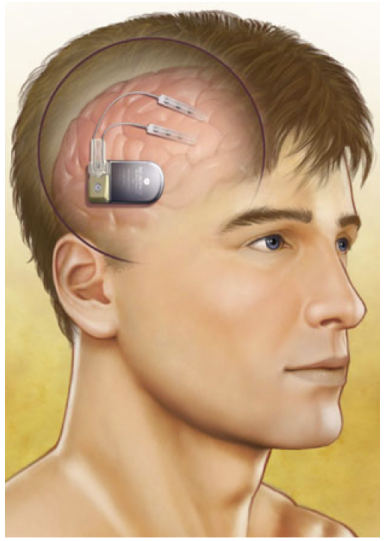
A set of recording ECoGs with electrical stimulus to the Sz focus.

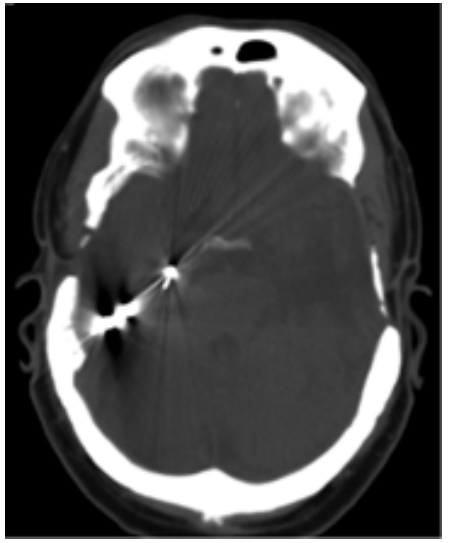
USFDA approved since 2013

Safety & efficacy is supported by Class I evidence



RNS





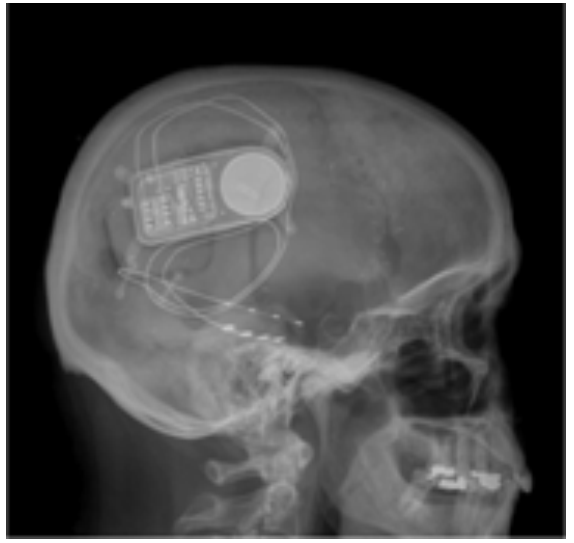
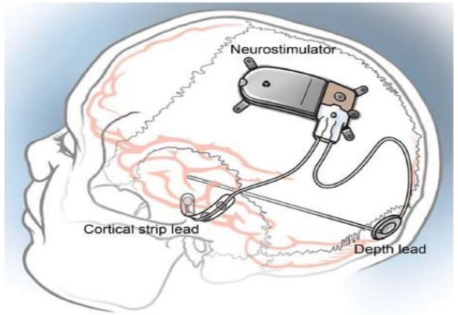
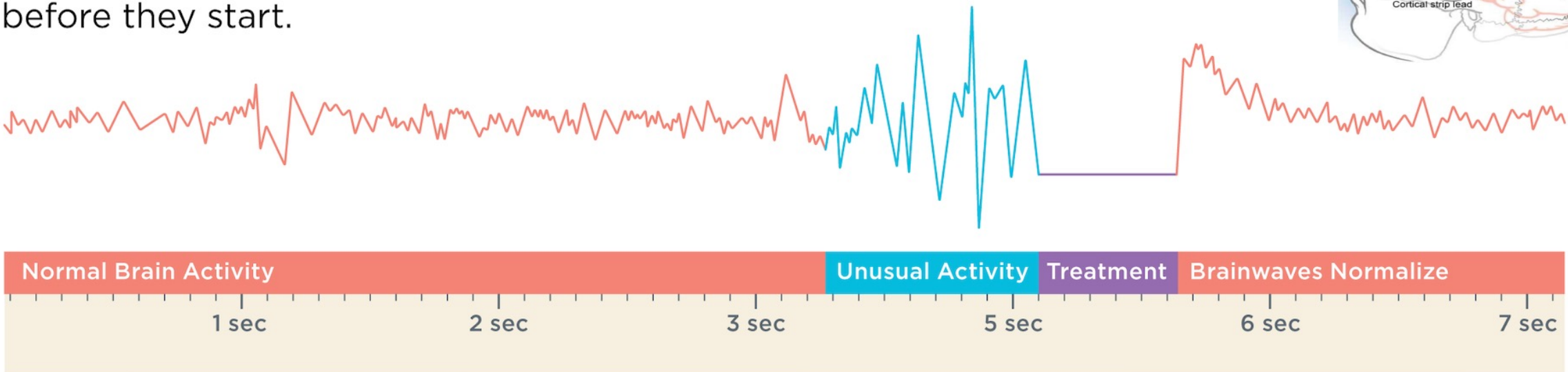


Image Courtesy NeuroPace, Inc.
Caption: Illustration of a closed-loop, responsive neurostimulation system.

The RNS® System is the only medical device designed to monitor and respond to your brain's electrical activity to prevent seizures before they start.





Monitors your brain activity 24 hours a day

Recognizes & Responds to your specific seizure patterns

Records with a small electrical pulse to prevent a seizure from occuring

RNS: MECHANISM

DIRECT EFFECTS

Disrupting ictal evolution & returning Sz network to it baseline interictal state

Transient stimulation-induced activation of local postsynaptic potentials.

Upregulation of local GABA activity

Depletion of NT has detected at synaptic terminals causing depression of electrical foci.

Reduced the excitability of underlying epileptogenic neuronal populations.

Thomas GP, Jobst BC. Med Devices (Auckl) 2015;8:405-11
Lundstrom BN, et al. JAMA Neurol 2016;73(11) :1370
Kokkinos V, et al. JAMA Neurol 2019;76(7): 800-8

INDIRECT EFFECTS

Stimulation acting as a desynchronizer

Isolating excitatory neuronal pools

Failures of modulated epileptogenic network to generate sufficient synchronization

Long-term effects have been postulated to be mediated via induced changes in gene expression with chronic stimulation.

Bragin A, et al. Epilepsia 2000;41(s6):S144-52
Schevon CA, et al. J Clin Neurophysiol 2008; 25(6):321-30

RNS: CLINICAL TRIALS

Pivotal trail, double blind RCT 191 patients implanted RNS

Duration	Sz reduction	
	Treatment group, n=97	Control group, n=94
12-wks	37.9%	17.3%

No significant difference was observed in the adverse effects and favorable outcome was seen in both groups

Morrell MJ, Group RNSSiES. Neurology 2011; 77:1295-304

1 Year	44%
2 Year	53%

Heck CN, et al. Epilepsia 2014;55:432-41

RNS: CLINICAL TRIALS

A 9-year F/U of patients w focal epilepsy (n=230), multicenter open label trials of RNS

75%Sz reduction, 73% responder rate, significantly reduced SUDEP rate Nair DR, et al. Neurology 2020; 95:e1244-56

An average 6-year F/U , in pt with pt with partial Sz (n=112) in eloquent & neocortical areas

70% Sz reduction in pt with frontal & parietal foci

58% Sz reduction in pt with temporal neocortical foci

51% Sz reduction in pt with multi-lobar foci Jobst BC, et al. Epilepsia 2017;58 (6):1005-14

An average 6-year F/U, in pt with MTLE (n=111) 72% bilateral and 28% unilateral

70% Sz reduction (29% had one Sz free period of > 6 mo, 15% Sz free > 1Y)

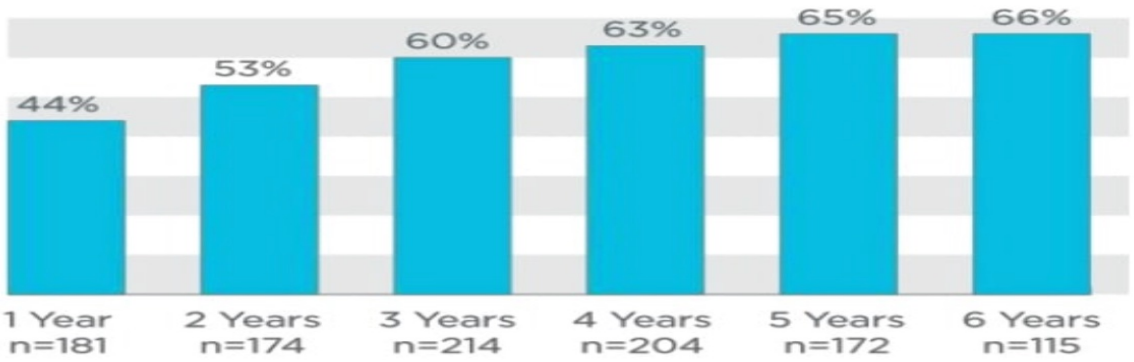
Most frequent serious AE was soft tissue implant-site infection 0.3/implant year

Geller EB, et al. Epilepsia 2017;58(6): 994-1004

RNS: EFFICACY

Established seizure control that improves over time

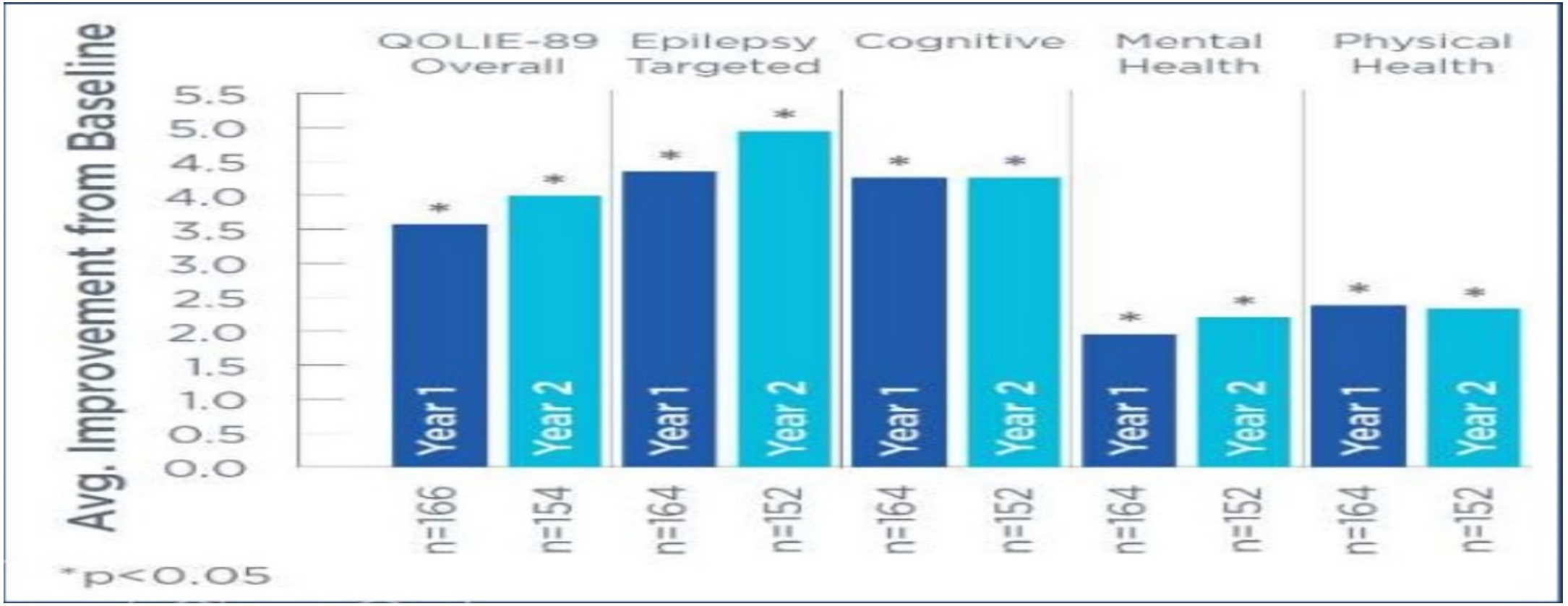
- Median % Seizure Reduction



- Seizure-Free Intervals
  - ≥ 3 months: 37%
  - ≥ 6 months: 23%
  - ≥ 1 year: 13%

Heck CN, et al. *Epilepsia*, 2014.
Bergey GK, et al. *Neurology*, 2015.

RNS: QoL



Morrell MJ, Group RNSSiES. Neurology 2011; 77:1295-304

RNS: ADVERSE EFFECTS

Common AE: Infected related 40% of all complications

Lead breakage 12%

Giles TX, et al. Neuromodulation 2020

Overall risk of infection 4.1%

Rate of hemorrhage 2.7%

Jobst BC, et al. Epilepsia 2017;58 (6):1005-14
Geller EB, et al. Epilepsia 2017;58(6): 994-1004

EXTERNAL TNS

Indications

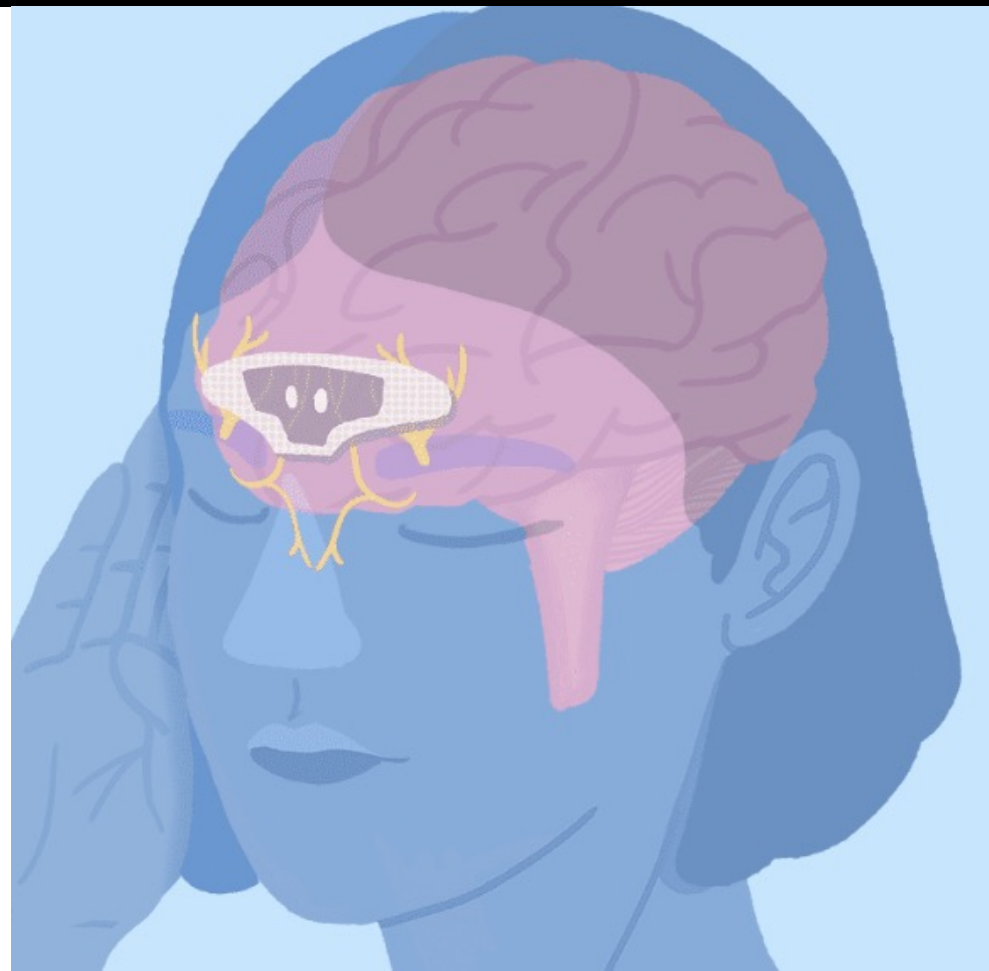
Medically refractory focal onset seizures
and depression.
As with VNS, it may be helpful for generalized seizures.

2012: European approval for use in patient with DRE

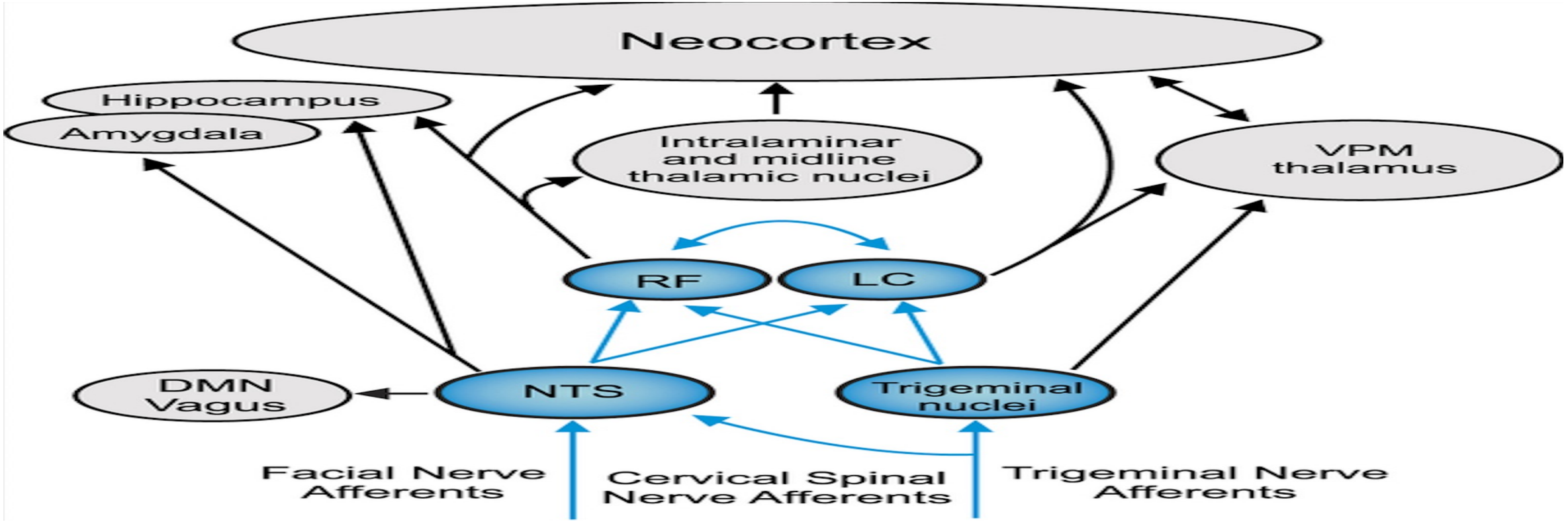
2015: eTNS received Humanitarian Use Device designation from FDA for Lennox-Gastaut Syndrome

2019: USFDA approval for pediatric attention deficit/hyperactivity disorder

Comprised of an external pulse generators with disposable bipolar transcutaneous electrodes



EXTERNAL TNS : MECHANISM



EXTERNAL TNS : EFFICACY

	Approval	Indication	Clinical Trial Outcomes
Open-loop			
TNS	2015[a]	Adults with partial-onset seizures that are refractory to antiepileptic medications	eTNS for DRE 50 participants 16.1% reduction at 18 wk 40.5% responder rate at 18 wk
		Approved for children 9 years and older in Europe	27.4% reduction at 6 months 36.8% of 50% responder rate at 12 months

Soss J, et al. Epilepsy Behav 2015;42:44-7
Slaght Sj, Nashef L. Seizure 2017;52:60-2

EXTERNAL TNS : ADVERSE EFFECTS

Common AE: Skin irritation 14%, headache 4%, and anxiety 4%

Serious AE: None

27.4% reduction at 6 months
36.8% of 50% responder rate at 12 months

Soss J, et al. Epilepsy Behav 2015;42:44-7
Slaght Sj, Nashef L. Seizure 2017;52:60-2

DEFAULT STIMULATION SETTING

	Default Stimulation Settings				
Device	Output	Frequency (Hz)	Pulse Width (μs)	On Time (s)	Off Time (min)
VNS	1.0 mA	30	500	30	5
DBS	5.0 V	145	90	60	5
TNS	<10.0 mA	120	<250	—	—
RNS	1.0 mA	200	160	—	—

Sisterson ND, Kokkinos V. Neurosurg Clin N Am 2020;31:459-70

OTHERS

Transcranial Stimulation:

Transcranial magnetic stimulation (TMS), Transcranial Direct Current stimulation (tDCS), Transcranial alternating Current Stimulation (tACS)

Glossopharyngeal Nerve Stimulation

Focal Delivery of AED therapy

Neuronal Grafting & Tissue Transplant

Gene therapy

Focal Cortical Cooling

Summary of Focal Drug Delivery Studies

Author (Date)	Anticonvulsant Agents	Epilepsy Model
Uemura (1991)[265]	Taurine and valytaurine	Amygdaloid electrically kindled seizure in rats
Smith (1993)[266]	Lidocaine hydrochloride	Prepiriform cortex GABA antagonist bicuculline microinjection in rats
Wada (1993)[267]	Serotonin (5-HT) 1 A agonist	Hippocampal electrical kindling in cats
Eder (1997)[263]	Diazepam	Hippocampal, motor cortex bicuculline kindled seizure in rats
Eder (1997)[264]	Diazepam	Hippocampal cobalt injection/systemic pilocarpine kindling in rats
Attwell (1998)[268]	Group II metabotropic glutamate receptor agonist	Amygdaloid electrically kindled seizure in rats
Croucher (1988)[269]	Excitatory amino acid antagonists	Prepyriform cortex electrical kindling
Kubek (1998)[270]	Polymer-thyrotropin-releasing hormone	Amygdaloid electrically kindled seizure in rats
Boison (1999)[271]	Adenosine	Hippocampal electrical kindling
Tamargo (2002)[272]	Phenytoin	Cobalt-induced seizure
Costantin (2005)[279]	Botulinum neurotoxin	Kainic acid kindling
Wang (2007)[280]	Omega-Conotoxin MVIIA (N-type calcium channel antagonists)	Amygdaloid electrically kindled seizure in rats
Gasior (2007)[281]	Omega-Conotoxin MVIIA	Amygdaloid electrically kindled seizure in rats
Ludvig (2006)[282]	Pentobarbital	Acetylcholine-induced seizure
Ludvig (2009)[283]	Muscimol	Acetylcholine-induced seizure

Al-Otaibi FA, et al. Neurosurgery 2011;69:957-79

CONCLUSION

Neuromodulation is an option for DRE not resectable / not responsive to surgical resection.

It is effective and relatively safe treatment.

However, the complete seizure freedom is rarely achieved.

The choice of device depends on the type of epilepsy, age of patient, device availability and affordability


THANK YOU FOR YOUR ATTENTION