Alternative treatment in Epilepsy

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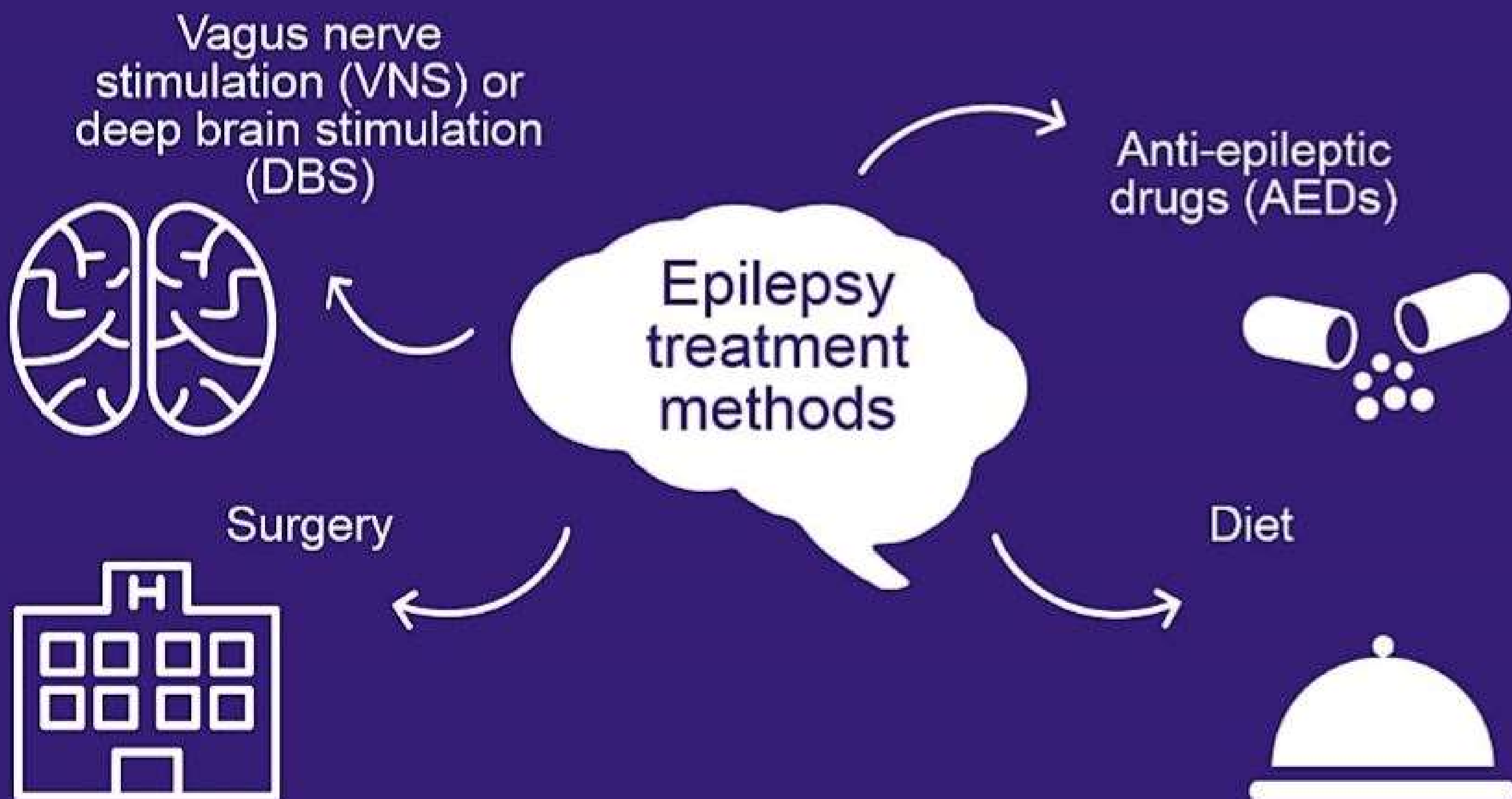
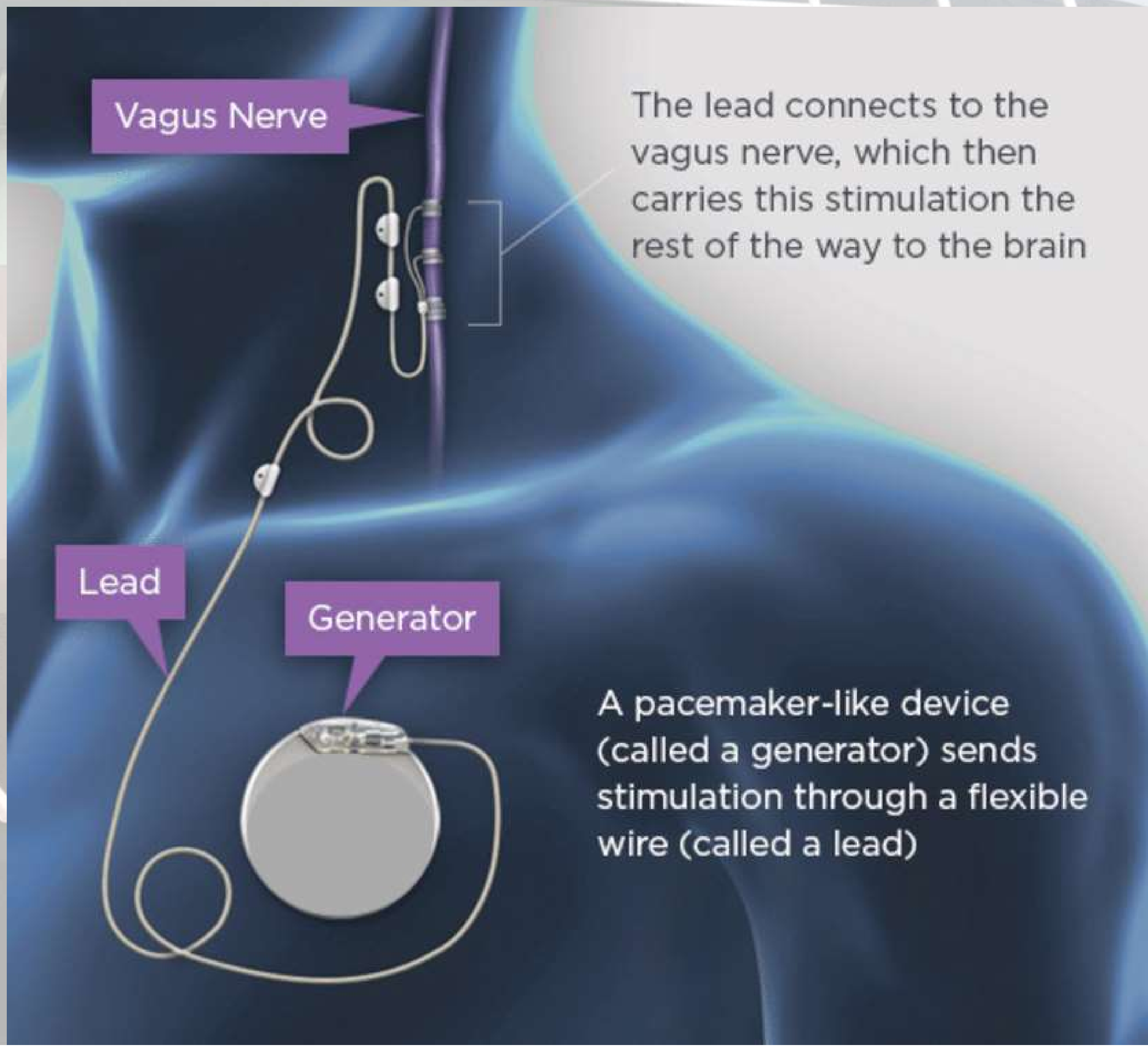
Current treatments



Neurostimulation devices

- Vagus Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)
- Responsive NeuroStimulation (RNS)
- External Trigeminal Stimulation
- Transcranial Magnetic Stimulation (TMS)
- Direct Current Stimulation (DCS)

VNS


Vagus Nerve
The lead connects to the vagus nerve, which then carries this stimulation the rest of the way to the brain
Lead
Generator
A pacemaker-like device (called a generator) sends stimulation through a flexible wire (called a lead)

Efficacy

Pediatric intractable epilepsy: 50% Sz reduction achieve in

9.8% (6th mo)→ 24% (2th yr)→ 46.4% (3rd yr)→ 54% (5th yr)→ 62.4% (> 5th yr)

Serdaroglu A, Arhan E, Kurt G, et al. Long term effect of vagus nerve stimulation in pediatric intractable epilepsy: an extended follow-up. Childs Nerv Syst 2016;32:641–646

VNS therapy Patient Outcome Registry

49% had >50% Sz reduction with 5.1% Sz free(4 mo)
63% had >50% Sz reduction with 8.2% Sz free(24-48 mo)

Englot DJ, Rolston JD, Wright CW, et al. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. Neurosurgery 2016;79:345–353

Efficacy

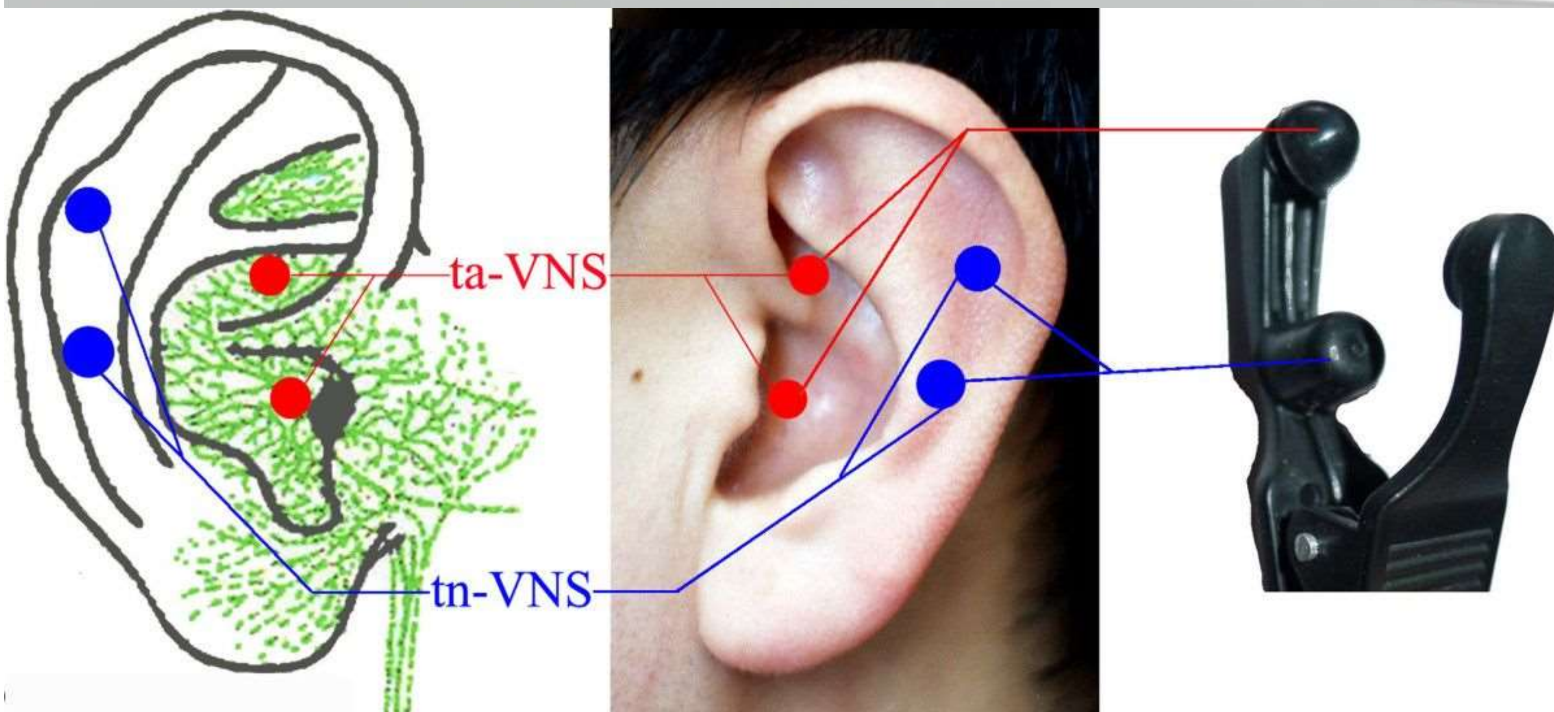
Cochrane 2015 : 40% had >50% Sz reduction
High stimulation Sz reduction better than low stimulation
AEs : hoarseness, cough, dyspnea, paresthesia, headache, pain , N/V→ resolved after 1 yr of continue Tx

Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2015;(4):CD002896

Need 1-2 yr of OPD visit for adjust stimulation paradigms
Battery lasts 2.8-8.2 yr
Cost about 25,000-30,000 USD

Kotagal P. Neurostimulation: vagus nerve stimulation and beyond. Semin Peadiatr Neurol 2011;18:186–194

Transcutaneous VNS



Sham Stimulation

- Stimulate Auricular skin branch of Vagus nerve

Efficacy

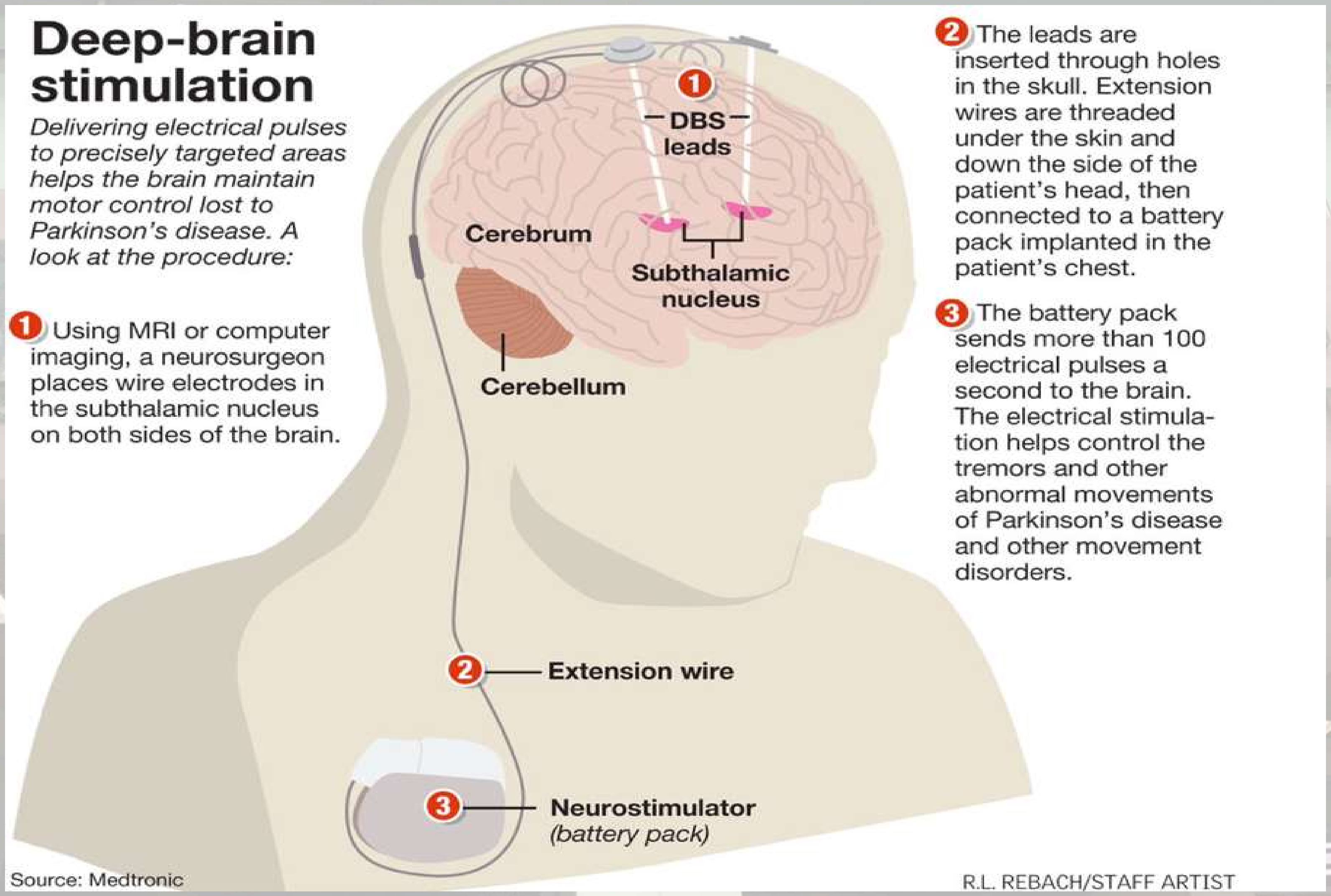
Bilateral stimulation : better toleration
Sz frequency decrease compare to baseline after 12 mo ($p<0.001$)
Sz frequency decrease compare to control group after 12 mo ($p<0.001$)

Unilateral stimulation : not well tolerate
-42.6% Sz reduction after 8 wk
-47.7% Sz reduction after 24 wk
<u>After 8 wk</u> : control gr switched to tVNS→
47.5% Sz reduction after additional 16 wk (total 24 wk)

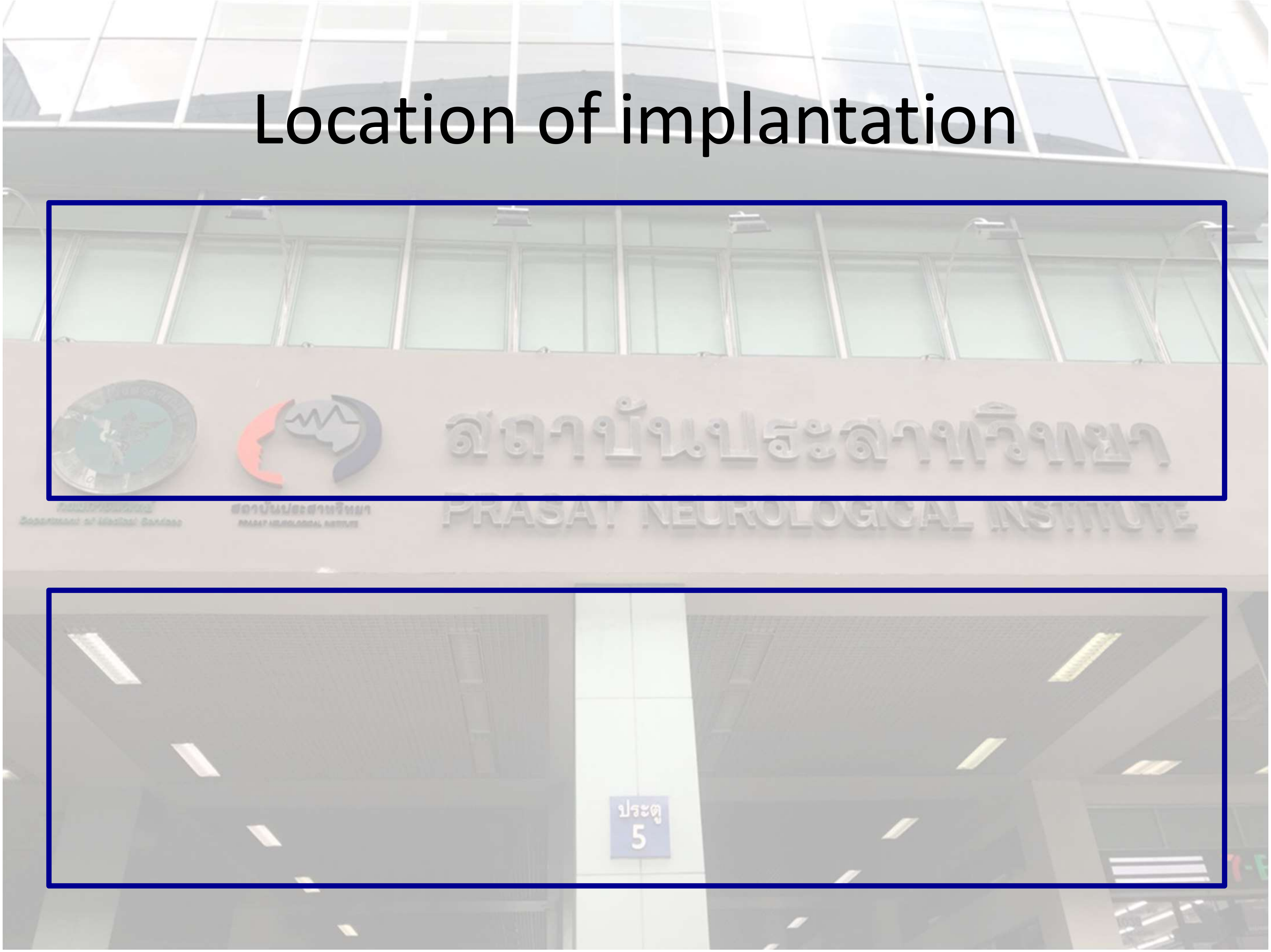
New tVNS was approved in Europe;
Able to detect HR increase and automatically deliver additional stimulus

Aihua L, Lu S, Liping L, et al. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy Behav 2014;39:105–110

Direct Brain Stimulation (DBS)



Location of implantation



Efficacy

ANT :
Most promising target and has been approved in Europe for Tx of focal epilepsy in pt 18-65 yr and waiting for approve in USFDA

Sz reduction : 40.4%
Median Sz reduction decrease from baseline to 56% by the end of 2 yr and 69% by the end of 5 yr
Temporal lobe Sz more benefit than other form of epilepsy

Complication : site pain, parestheisa, depression, memory problem

Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84:1017–1025

Efficacy

Cerebellar : conflicting result in 3 studies
- 2 : No significant Sz recuction
- 1 : Sz reduction up to 57-76%

Common complication : wound infection

Velasco F, Carrillo-Ruiz JD, Brito F, et al. Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 2005;46:1071–1081

Hippocampus : MTLE with Sx is contraindicated

-15-33% Sz reduction and 55% responder rate

-45-93% Sz reduction and 57-100% responder rate

Velasco AL, Velasco F, Velasco M, et al. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia 2007;48:1895–1903

Efficacy

CM : most effective in Generalized epilepsy esp. LGS
-2 Double blind , one single blind : 30-98% Sz reduction
50-100% responder rate for generalized epilepsy
20-70% responder rate for focal onset epilepsy

Parent M, Parent A. Single-axon tracing and three-dimensional reconstruction of centre median-parafascicular thalamic neurons in primates. J Comp Neurol 2005;481:127–144

STN : limit study with approximately 50% median Sz reduction

Handforth A, DeSalles AA, Krahl SE. Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. Epilepsia 2006;47:1239–1241

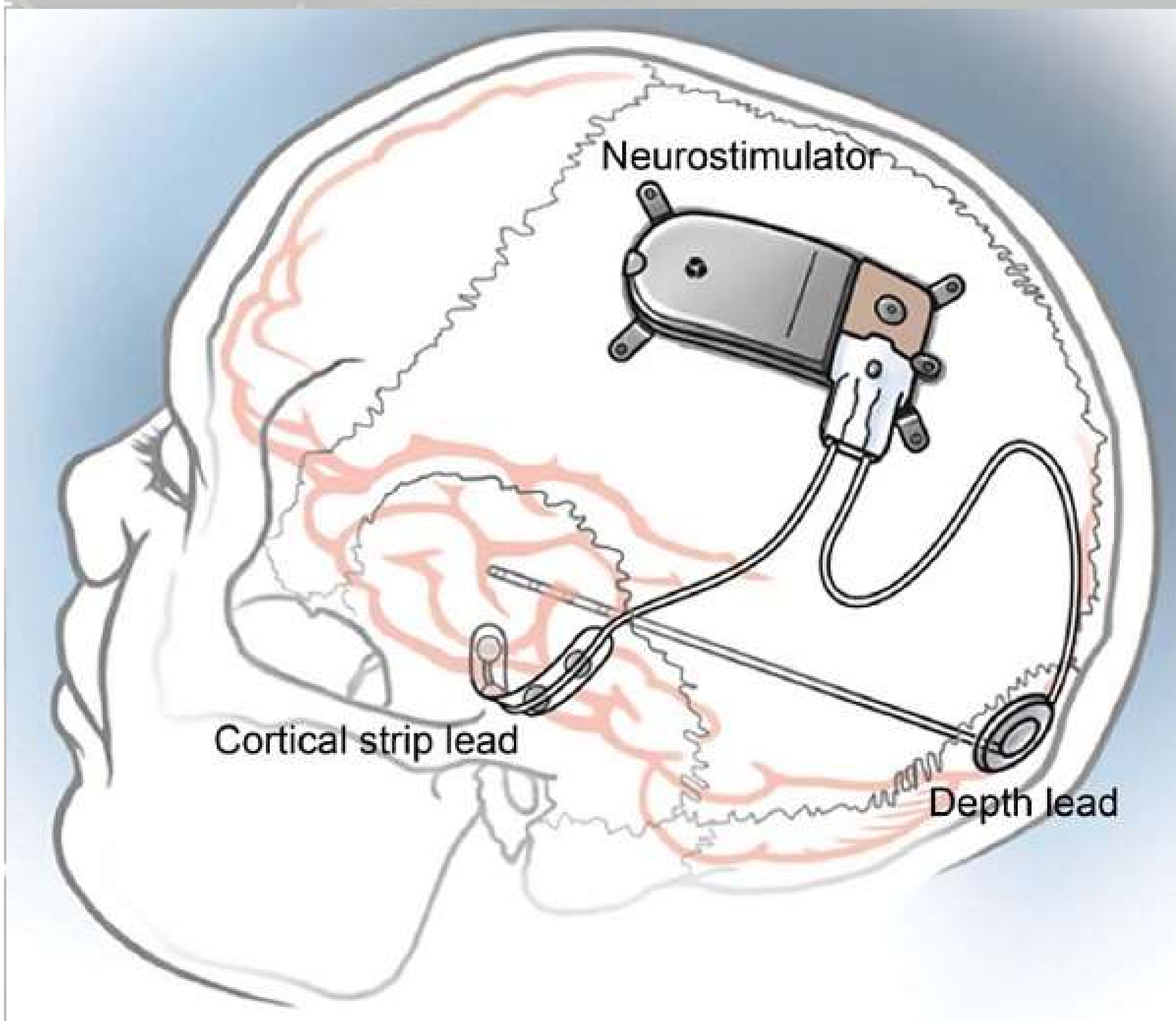
Complication : misplace electrode and electrode migration

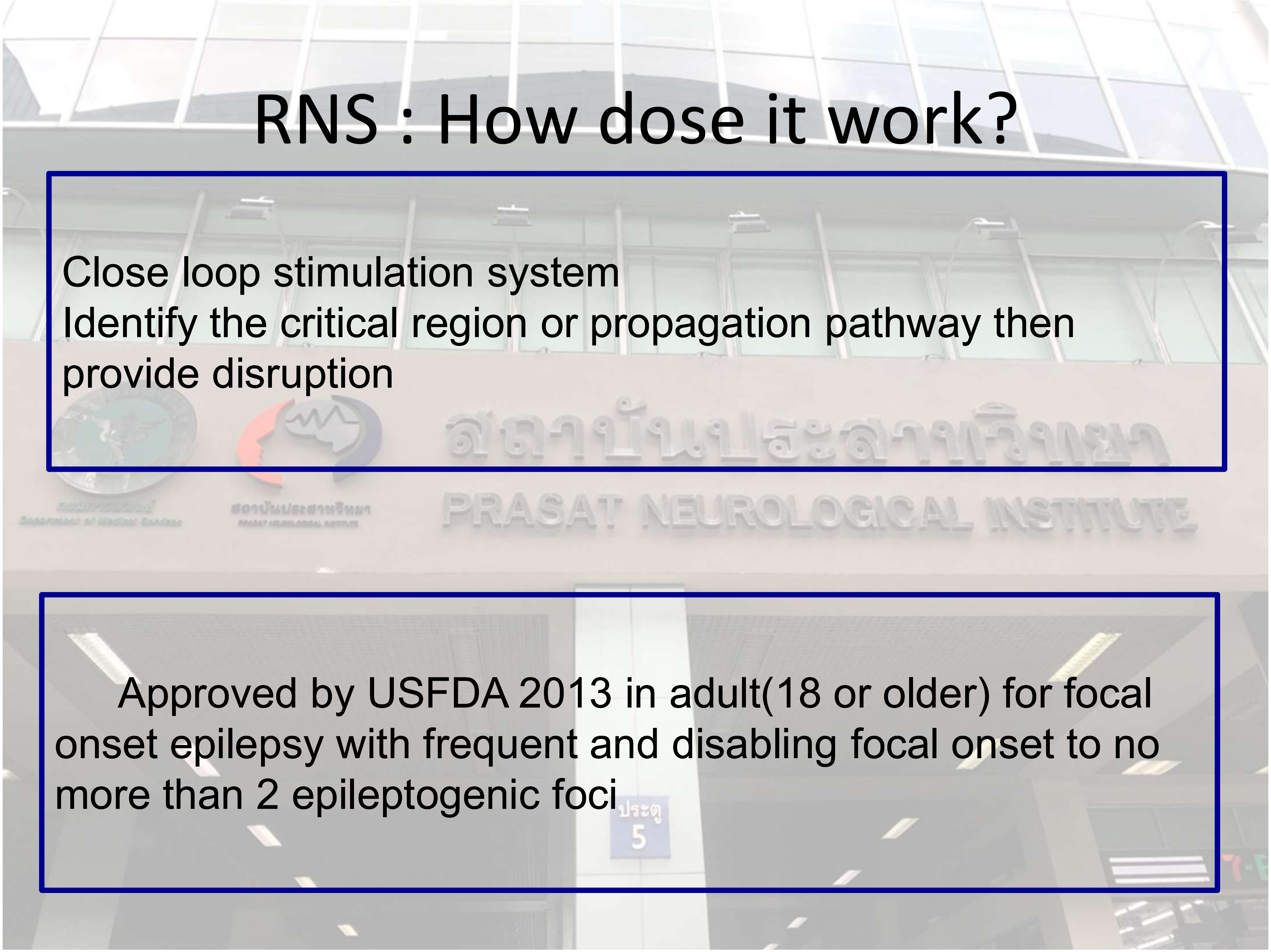
VNS vs DBS

- Efficacy form available data : DBS > VNS
- Application : DBS more complicated than VNS
- Complication : DBS more numerous and serious than VNS
- Cost : DBS > VNS (29,000-34,000 USD)
- Battery life : same (DBS 4-7 yr)
- Both need regular F/U for adjust parameter setting

Pietzsch JB, Garner AM, Marks WJ Jr. Cost-effectiveness of deep brain stimulation for advanced Parkinson's disease in the United States. Neuromodulation 2016;19:689–697

Responsive NeuroStimulation(RNS)





RNS : How dose it work?

Close loop stimulation system
Identify the critical region or propagation pathway then provide disruption

Approved by USFDA 2013 in adult(18 or older) for focal onset epilepsy with frequent and disabling focal onset to no more than 2 epileptogenic foci

Efficacy

Double blind RCT :
Sz frequency reduce in 37.9% (12 wk)
Sz frequency reduction 44% (1yr)→53%(2yr)
44% had >50% SZ reduction (1 yr)
55% had >50% SZ reduction (2 yr)

All improve QOL

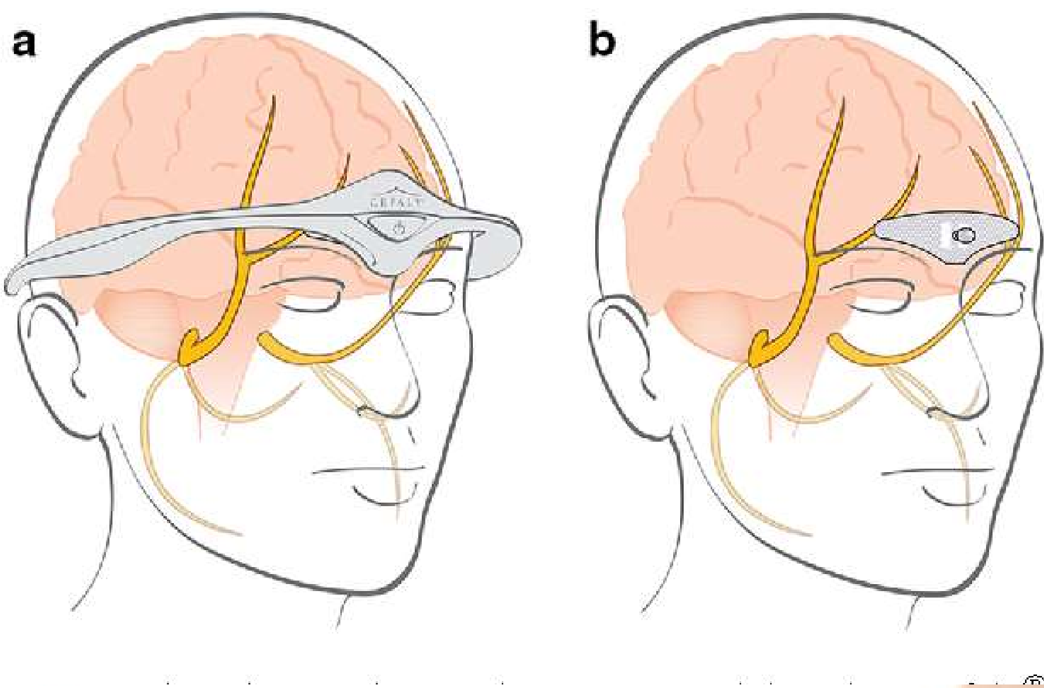
Thomas GP, Jobst BC. Critical review of the responsive neurostimulator system for epilepsy. Med Devices (Auckl) 2015;8:405–411

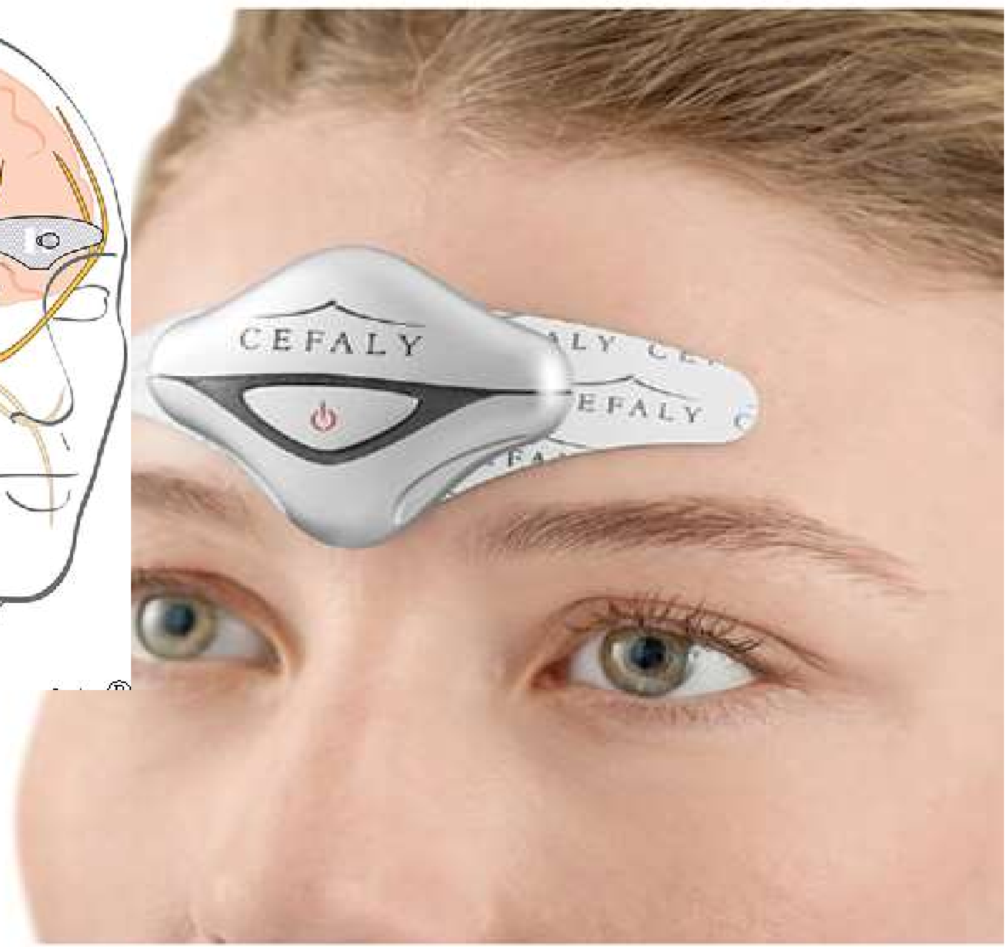
7 yr multicenter study : median Sz reduction from 48% to 66% over 3 to 6 yr

Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology 2015;84:810–817

Complication : Implant site infection

External Trigeminal nerve Stimulation





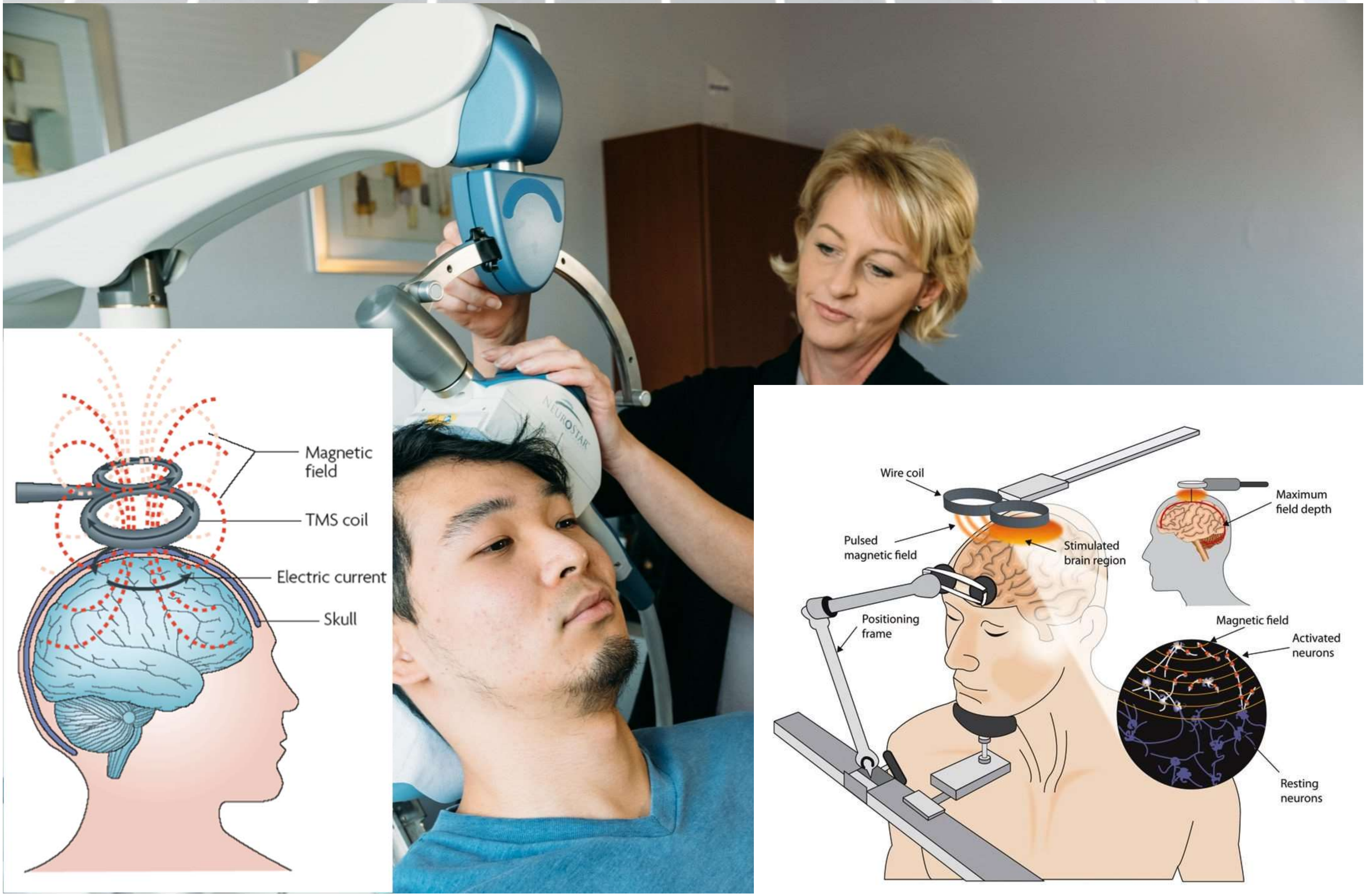
Efficacy

Responder rate in Sz improve 40.5% after 18 wk
After 6 to 12 Mo Sz reduction : 27.4% to 34.8%→ all response rate is 30.6%

DeGiorgio CM, Soss J, Cook IA, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. Neurology 2013;80:786–791

Not as effective as VNS but less invasive and more economically

Transcranial Magnetic Stimulation



Efficacy

8 RCT : positive result
Decrease in Sz frequency 72%
The effect lasted for > 2 mo
Decrease epileptiform discharge 31%(immediate) and 16% at 4 wk

6 RTC : no positive result but 4 of them showed improvement of EEG change

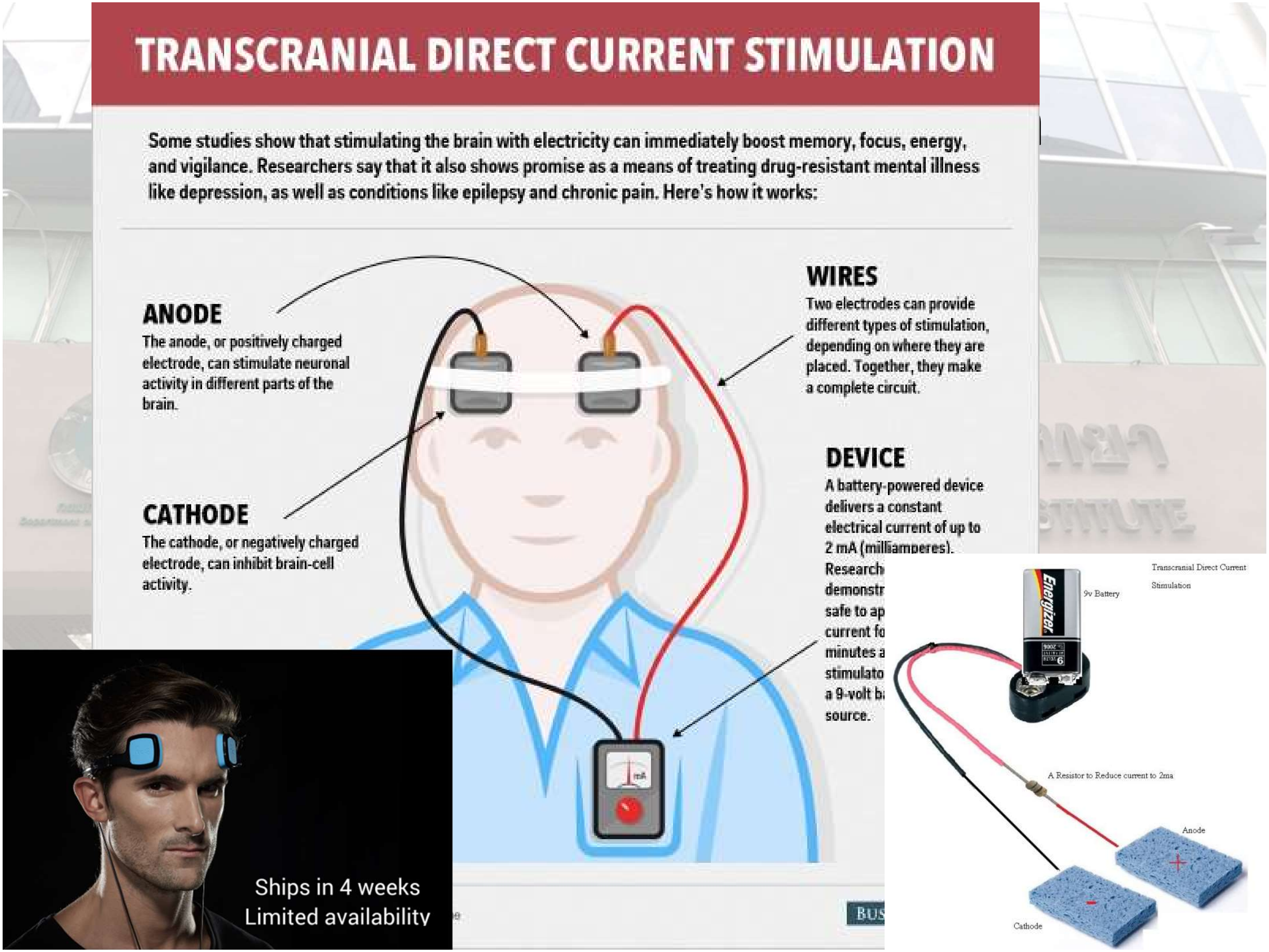
Yicong Lin and Yuping Wang.Neurostimulation as a promising epilepsy therapy. Epilepsia 2017

Suitable cases for TMS

TMS reduce of epileptiform discharge but insufficient of evidence of seizure reduction

Neocortical lesion with visible on MRI in cortical convexity may benefit from TMS
Deeper foci are less likely to response

Unclear this therapeutic effect can last



TRANSCRANIAL DIRECT CURRENT STIMULATION
Some studies show that stimulating the brain with electricity can immediately boost memory, focus, energy, and vigilance. Researchers say that it also shows promise as a means of treating drug-resistant mental illness like depression, as well as conditions like epilepsy and chronic pain. Here's how it works:
ANODE
The anode, or positively charged electrode, can stimulate neuronal activity in different parts of the brain.
CATHODE
The cathode, or negatively charged electrode, can inhibit brain-cell activity.
WIRES
Two electrodes can provide different types of stimulation, depending on where they are placed. Together, they make a complete circuit.
DEVICE
A battery-powered device delivers a constant electrical current of up to 2 mA (milliamperes).
mA
Ships in 4 weeks
Limited availability
Transcranial Direct Current Stimulation
9v Battery
Energizer
A Resistor to Reduce current to 2ma
Anode
Cathode

Efficacy

Adult :
44% reduction in Sz frequency
64.3% reduction in epileptiform discharge

Fregni F, Thome-Souza S, Nitsche MA, et al. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. Epilepsia 2006;47:335–342

Children : LGS
reduction in Sz frequency

45.3% reduction in epileptiform discharge immediate and 57.6% at 48 hr after Tx

Auvichayapat N, Rotenberg A, Gersner R, et al. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul 2013;6:696–700

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