IS THERE A ROLE FOR NEUROMODULATION IN THE EPILEPTIC ENCEPHALOPATHIES?

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ROLE OF NEUROMODULATION

DISCUSSION ITEMS:

WHAT IS NEUROMODULATION?

WHEN IS NEUROSTIMULATION AN OPTION, IF AT ALL?

REVIEW THE CURRENT OPTIONS FOR NEUROSTIMULATION?

WHAT'S NEW IN NEUROSTIMULATION
FUTURE DIRECTIONS FOR NEUROSTIMULATION?

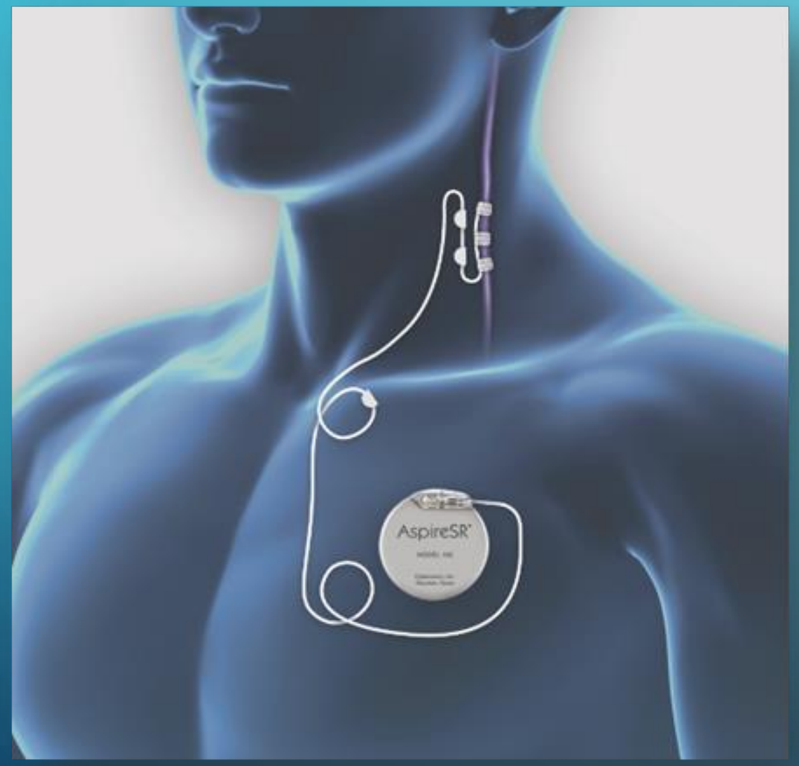
IS THERE A ROLE FOR NEUROMODULATION?

WHAT IS NEUROMODULATION

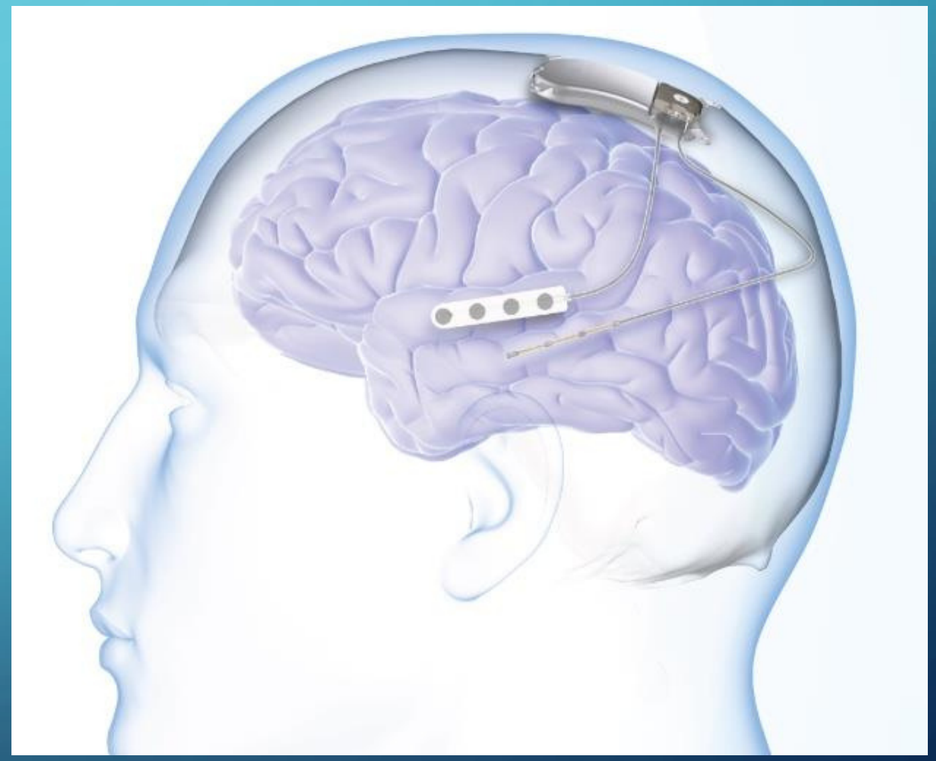
- Therapeutic nervous system stimulation in those who fail medication/dietary therapy and who are not surgical candidates
- Alters neuronal activity via an open (VNS or DBS) or closed-loop system (RNS) to a specific site in the body
- Exact MOA of neuromodulation is not known, but theories include:
  - Alteration of voltage dependent currents
  - Alteration of synaptic efficacy
  - Alteration of neuronal “bursting” activity
  - Reconfiguration of synaptic connectivity via alteration of CNS neurotransmitters

WHAT IS NEUROMODULATION:

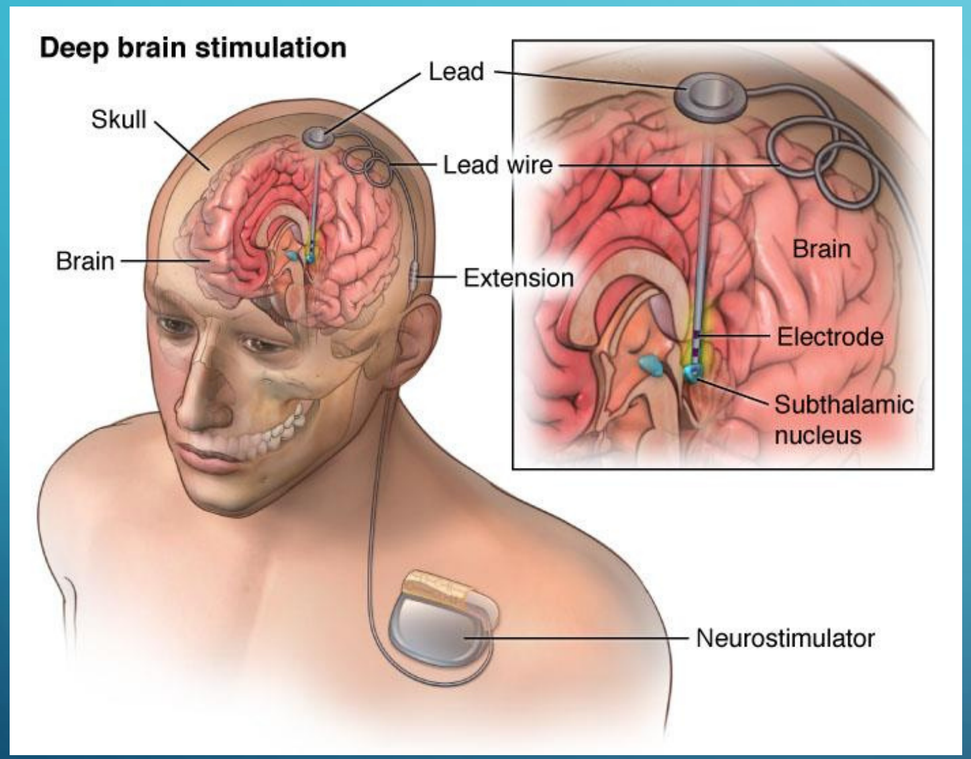
VNS

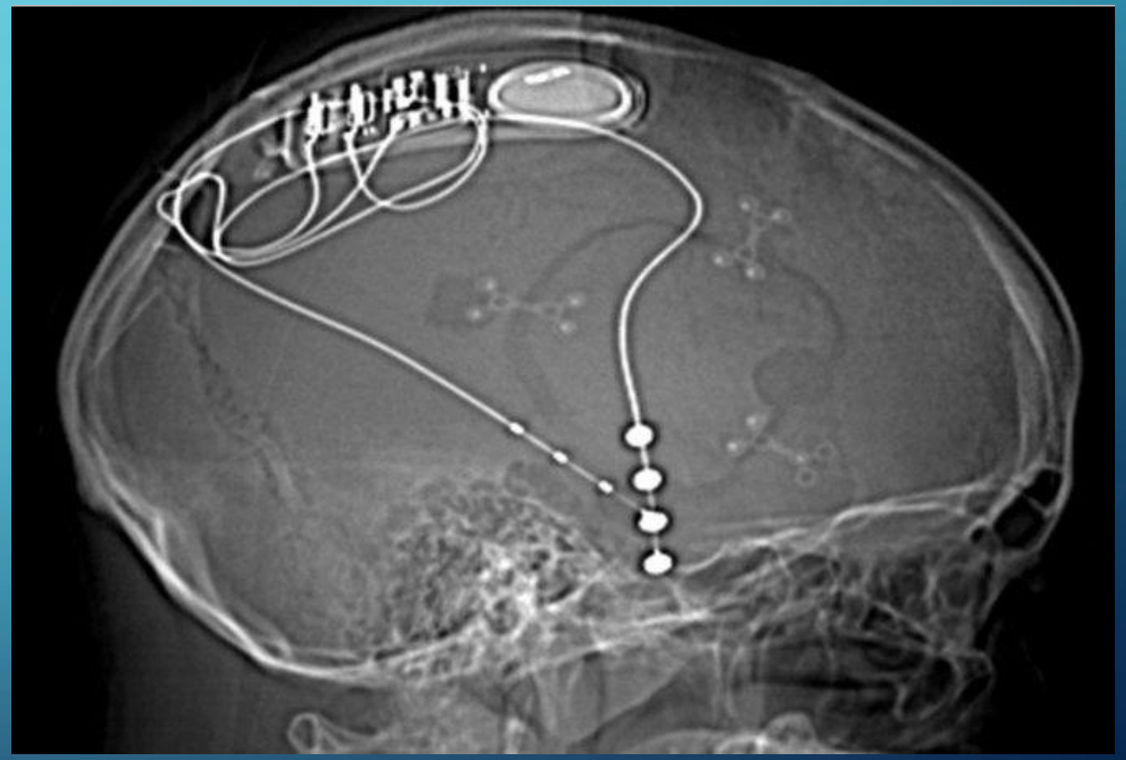


RNS



WHAT IS NEUROMODULATION: DBS





WHEN IS NEUROMODULATION AN OPTION?

- Consider alternative therapy in drug resistant epilepsy after the failure of 2 medications
- That discussion would include an opportunity for surgical intervention initially
- Additionally, you would also consider alternative therapies which would include dietary therapy
  - Ketogenic diet
    - Modified Atkins
    - Glycemic index diet
- Neuromodulation

WHEN IS NEUROMODULATION AN OPTION?

- Important to consider defining success in these epileptic encephalopathies and which alternative therapy will most likely achieve that goal
- Those goals for success need to be realistic and may include:
  - Improvement in sz frequency and/or severity (likely not sz freedom)
  - Improving quality of life (less meds-less side effects and drug interactions)
  - Reducing SUDEP risk
  - Reducing rescue med use
  - Reducing injury or need to visit ER

NEUROMODULATION
VNS

- Indication is for adjunctive therapy age 4 and older for focal epilepsy
- Studies have shown efficacy for generalized epilepsy as well
- Likely exerts its effect via neurotransmitter modulation at locus coeruleus and its connections tohippocampus, thalamus, hypothalamus and orbitofrontal cortex
- Sentiva is the newest model and is a “responsive” neuromodulating device

NEUROMODULATION
VNS

- “Responsive” VNS operates in 3 modes: normal mode, auto-stim and magnet modes
- Normal mode is the baseline setting for sz prevention; autostim is a responsive setting based on a biomarker (tachycardia) and magnet mode an on-demand setting to interrupt a sz
- Magnet mode is activated when a magnet is waved over the device and will run thru its cycle despite how many times the device is swiped
- Autostim mode is activated when the device detects a percentage change from baseline heartrate

NEUROMODULATION
VNS

- Normal mode has 5 primary settings: output current(milliamps), frequency(hertz), pulse width(microseconds), on-time (seconds), off-time(minutes)

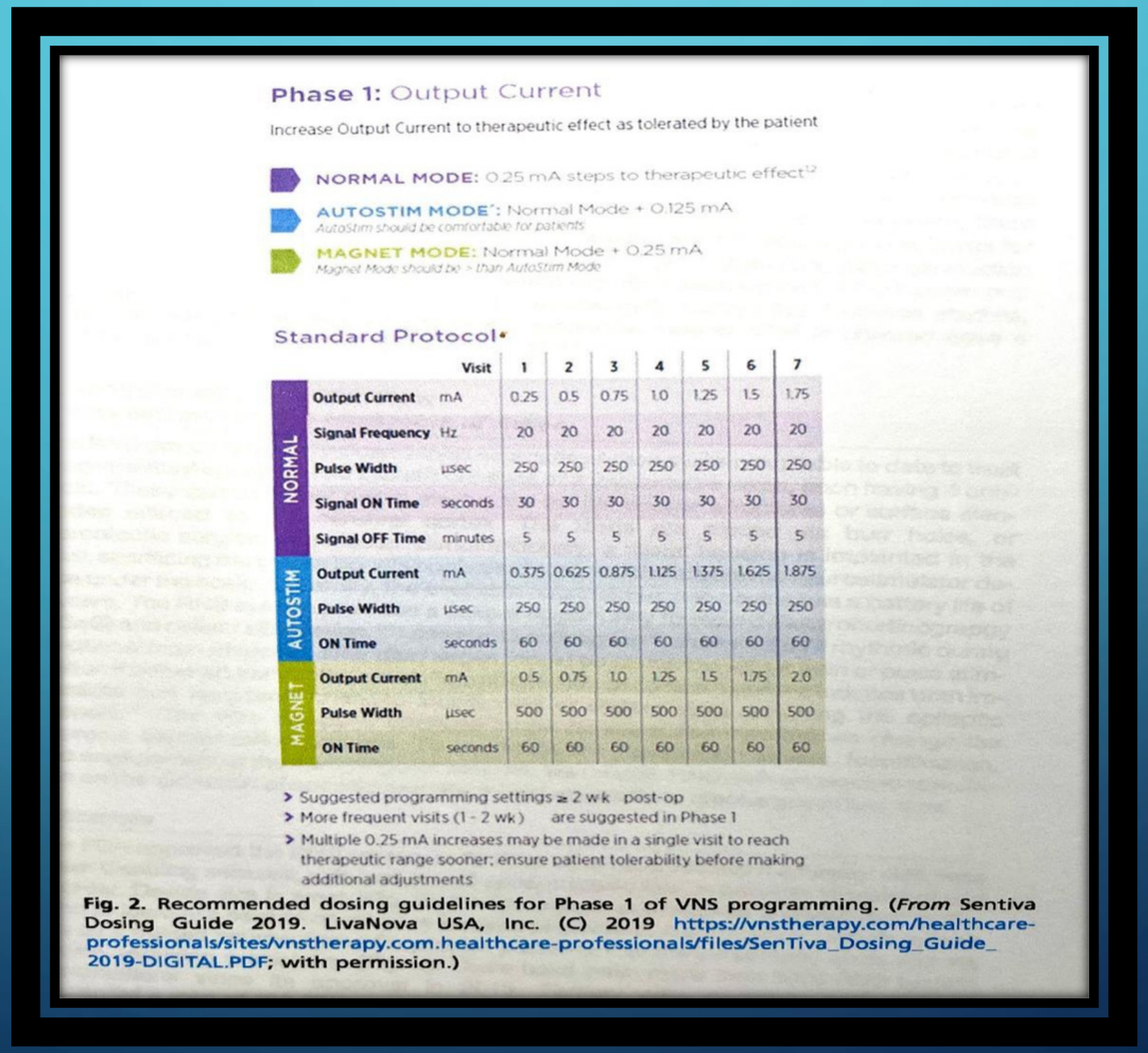
STIMULATION PARAMETER SETTING RANGES

Median Settings

		Pediatric (n = 743)		Adult (n = 1,486)	
Parameter	**Typical Range**	**3 Months**	**12 Months**	**3 Months**	**12 Months**
Output current	1.50–2.5 mA	1.25 mA	1.75 mA	1.25 mA	1.50 mA
Signal frequency	20–30 Hz	30 Hz	30 Hz	30 Hz	30 Hz
Pulse width	250–500 μs	500 μs	500 μs	500 μs	250 μs
Signal on time	7–30 s	30 s	30 s	30 s	30 s
Signal off time	0.3 s–5 min	5 min	3 min	5 min	5 min

No standard settings have been defined on the basis of patient age or seizure type. The median settings shown here are taken from the VNS therapy patient outcome registry (Cyberonics, Inc.; Houston, Texas).

NEUROMODULATION
VNS



Phase 1: Output Current

Increase Output Current to therapeutic effect as tolerated by the patient

- **NORMAL MODE:** 0.25 mA steps to therapeutic effect[12]
- **AUTOSTIM MODE*:** Normal Mode + 0.125 mA
  AutoStim should be comfortable for patients
- **MAGNET MODE:** Normal Mode + 0.25 mA
  Magnet Mode should be < than AutoStim Mode

Standard Protocol•

		Visit	1	2	3	4	5	6	7
NORMAL	Output Current	mA	0.25	0.5	0.75	1.0	1.25	1.5	1.75
	Signal Frequency	Hz	20	20	20	20	20	20	20
	Pulse Width	µsec	250	250	250	250	250	250	250
	Signal ON Time	seconds	30	30	30	30	30	30	30
	Signal OFF Time	minutes	5	5	5	5	5	5	5
AUTOSTIM	Output Current	mA	0.375	0.625	0.875	1.125	1.375	1.625	1.875
	Pulse Width	µsec	250	250	250	250	250	250	250
	ON Time	seconds	60	60	60	60	60	60	60
MAGNET	Output Current	mA	0.5	0.75	1.0	1.25	1.5	1.75	2.0
	Pulse Width	µsec	500	500	500	500	500	500	500
	ON Time	seconds	60	60	60	60	60	60	60

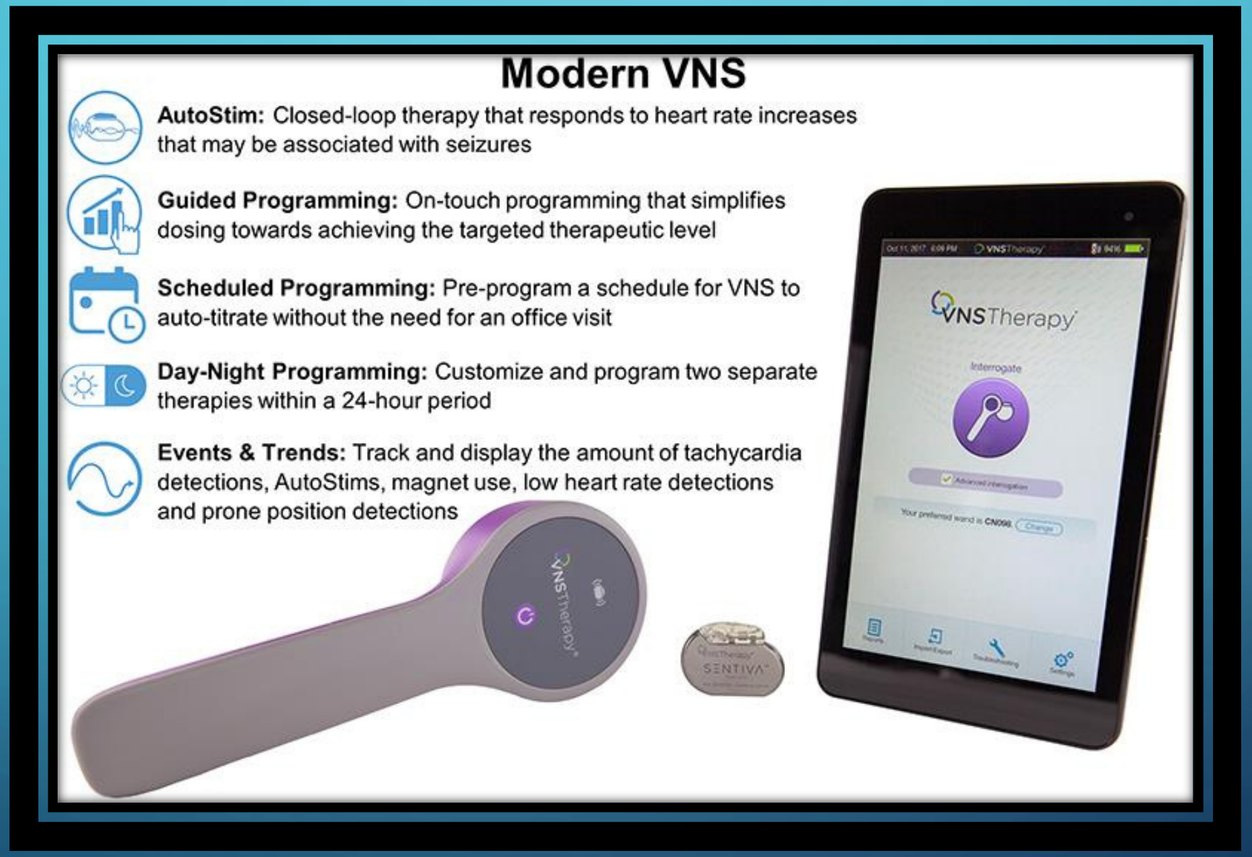
- Suggested programming settings ≥ 2 wk post-op
- More frequent visits (1 - 2 wk) are suggested in Phase 1
- Multiple 0.25 mA increases may be made in a single visit to reach therapeutic range sooner; ensure patient tolerability before making additional adjustments

Fig. 2. Recommended dosing guidelines for Phase 1 of VNS programming. (*From* Sentiva Dosing Guide 2019. LivaNova USA, Inc. (C) 2019 https://vnstherapy.com/healthcare-professionals/sites/vnstherapy.com.healthcare-professionals/files/SenTiva_Dosing_Guide_2019-DIGITAL.PDF; with permission.)

NEUROMODULATION
VNS TITRATION

- After implantation, titration is usually accomplished in 2 week intervals
- Titration is initially focused on Output current (to range 1.5-2Ma or to tolerability)
- Depending on response, duty cycle can then be adjusted next (defined as the % of time the device is stimulating)
- Adjustments in pulse width & frequency alone or together improve tolerability
- Sentiva can also have adjustments in Day/Night settings
- Remember the higher the duty cycle or output current, the greater the affect on battery longevity

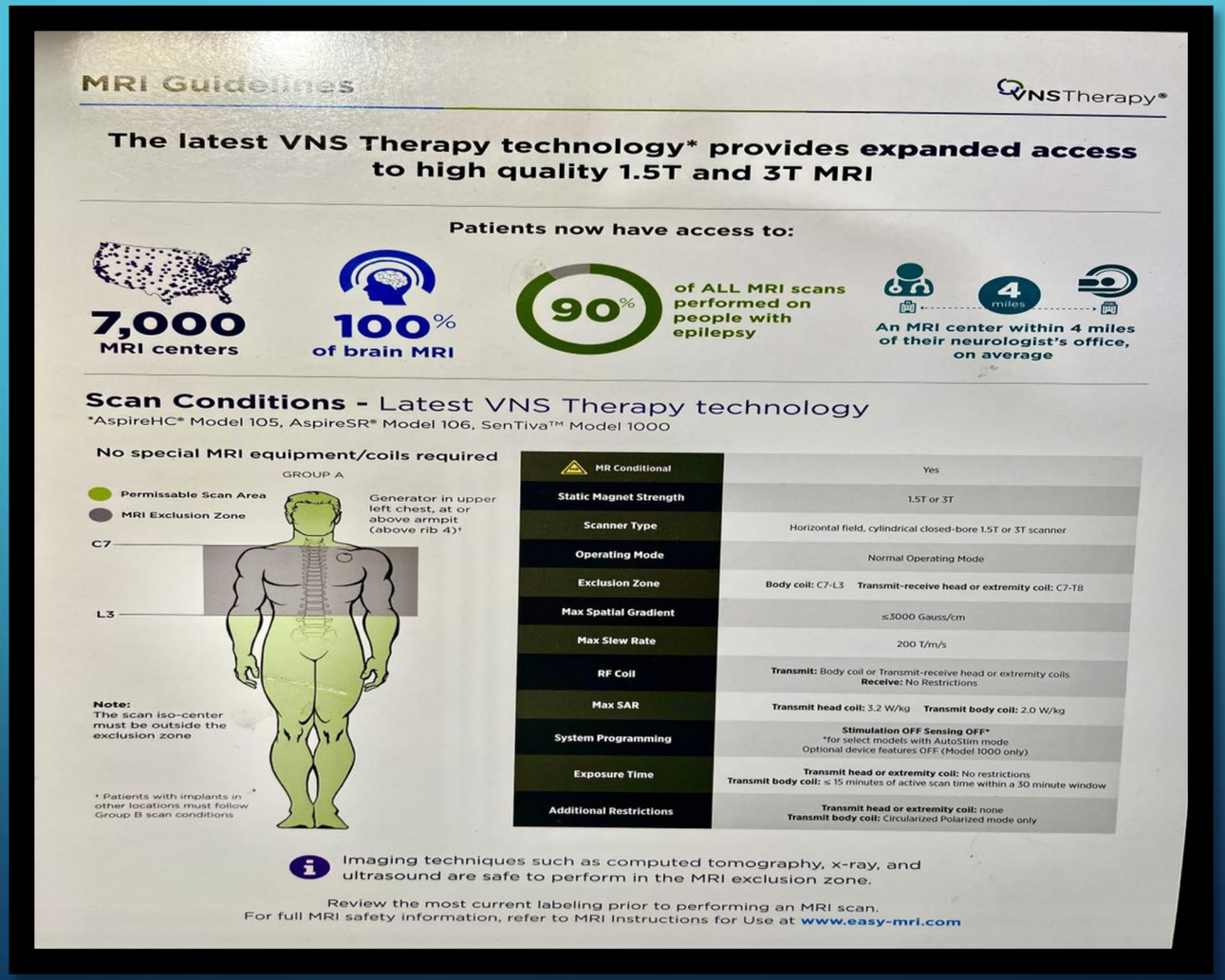
NEUROMODULATION
VNS



NEUROMODULATION
VNS COMPLICATIONS

- Usually well tolerated
- Minimally invasive surgery
- Hoarseness, cough, paresthesia, shortness of breath and potential worsening of obstructive sleep apnea can occur
- Post operative infection (<3%) should be monitored for
- Device may be explanted but lead removal is quite difficult

NEUROMODULATION
VNS AND NEUROIMAGING



MRI Guidelines

VNS Therapy®

The latest VNS Therapy technology* provides expanded access to high quality 1.5T and 3T MRI

Patients now have access to:

7,000 MRI centers

100% of brain MRI

90% of ALL MRI scans performed on people with epilepsy

4 miles

An MRI center within 4 miles of their neurologist's office, on average

Scan Conditions - Latest VNS Therapy technology

*AspireHC® Model 105, AspireSR® Model 106, SenTiva™ Model 1000

No special MRI equipment/coils required

GROUP A

Permissable Scan Area

MRI Exclusion Zone

Generator in upper left chest, at or above armpit (above rib 4)†

C7

L3

Note:
The scan iso-center must be outside the exclusion zone

† Patients with implants in other locations must follow Group B scan conditions

MR Conditional	Yes
Static Magnet Strength	1.5T or 3T
Scanner Type	Horizontal field, cylindrical closed-bore 1.5T or 3T scanner
Operating Mode	Normal Operating Mode
Exclusion Zone	**Body coil:** C7-L3 **Transmit-receive head or extremity coil:** C7-T8
Max Spatial Gradient	≤3000 Gauss/cm
Max Slew Rate	200 T/m/s
RF Coil	**Transmit:** Body coil or Transmit-receive head or extremity coils **Receive:** No Restrictions
Max SAR	**Transmit head coil:** 3.2 W/kg **Transmit body coil:** 2.0 W/kg
System Programming	**Stimulation OFF Sensing OFF*** *for select models with AutoStim mode Optional device features OFF (Model 1000 only)
Exposure Time	**Transmit head or extremity coil:** No restrictions **Transmit body coil:** ≤ 15 minutes of active scan time within a 30 minute window
Additional Restrictions	**Transmit head or extremity coil:** none **Transmit body coil:** Circularized Polarized mode only

Imaging techniques such as computed tomography, x-ray, and ultrasound are safe to perform in the MRI exclusion zone.

Review the most current labeling prior to performing an MRI scan.
For full MRI safety information, refer to MRI Instructions for Use at **www.easy-mri.com**

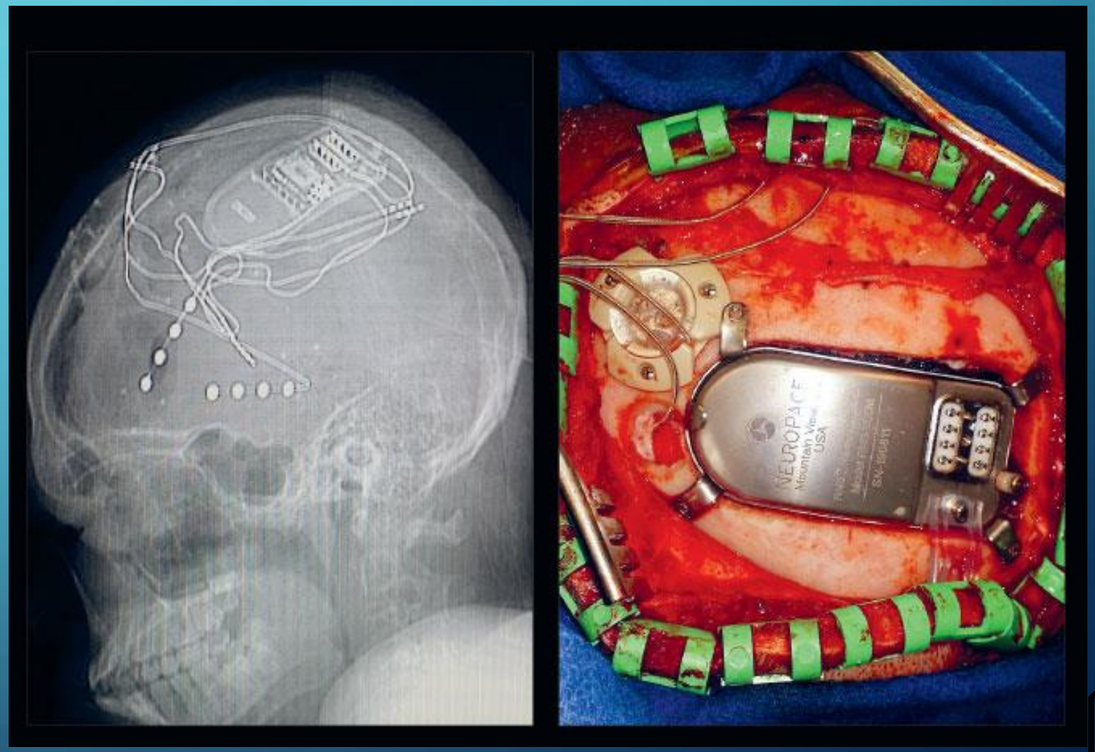
NEUROMODULATION
VNS CLINICAL OUTCOMES

- Several studies have shown a responder rate >50% in 1/2 to 2/3rds of the patients implanted
- Seizure-reduction effect appears to improve over time (1yr time frame)
- There is also clinical data noting reduction in seizure duration and intensity with improved post-ictal recovery time; which also impacts SUDEP risk and risk of status epilepticus in a positive way
- Additionally, improvement in quality of life measures have also been documented in responders

NEUROMODULATION
VNS CLINICAL OUTCOMES

- Data for off-label use in LGS and Dravet and CDKL5 noted efficacy response for generalized epilepsies
- VNS has also been shown to be an alternative prior to corpus callosotomy for control of atonic seizures
- Finally, the cost-effectiveness of VNS has clearly been demonstrated against the direct health care costs of hospitalizations, ER visits, ICU and drug costs

NEUROMODULATION
RNS



NEUROMODULATION
RNS

- Approved in 2014, it is the only closed-loop neurostimulation system available to treat drug-resistant epilepsy
- Consists of 2 implantable leads , each with 4 contacts(depth or surface contacts)
- Approved for use in age 18 and older and with less than 2 epileptogenic foci
- Delivers electric stimulation on the detection of specific predetermined epileptiform discharges in real-time

NEUROMODULATION
RNS APPLICATION

- •. Operates in detection only, detection and treatment and MRI safety modes
- Seizures are detected using line length, area or band pass and time domain analysis via electrocorticography (ECoG) with initial recording after implantation in detection mode
- •. Most common ECoG recording is with electrographic sz detection, magnet swipe and a preset time of day
- •. 12 minutes of ECoG can be record by the device in divided epochs

NEUROMODULATION
RNS APPLICATION

- After recording for a month, the data is reviewed and detection parameters for stimulation are programmed
- Selective individual contacts can be programed for stimulation within each electrode
- Following a “trigger” the RNS delivers 2 bursts of stimulation to the targeted area
- Typically review data and adjust parameters in 3 month intervals

NEUROMODULATION
RNS APPLICATION

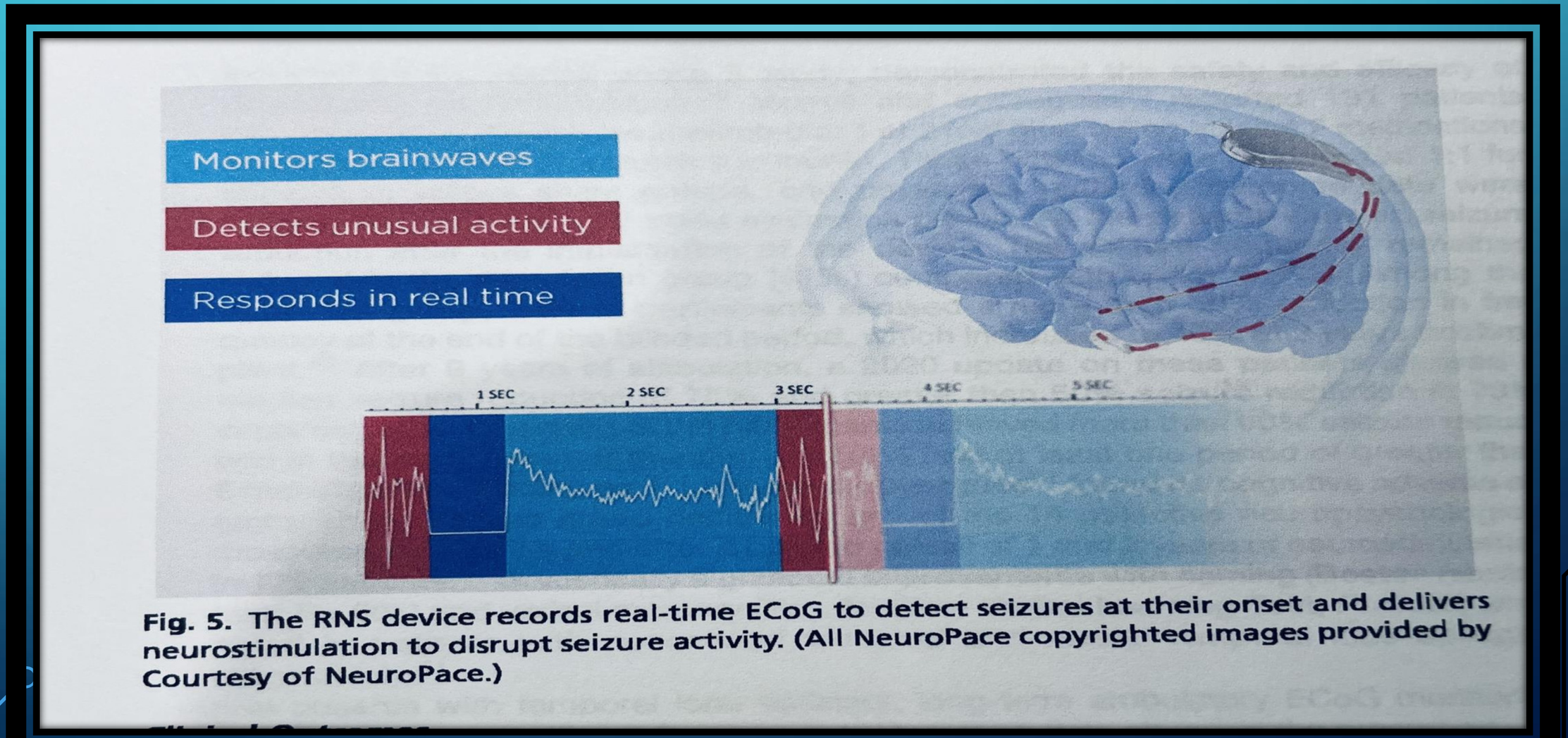


Fig. 5. The RNS device records real-time ECoG to detect seizures at their onset and delivers neurostimulation to disrupt seizure activity. (All NeuroPace copyrighted images provided by Courtesy of NeuroPace.)

NEUROMODULATION
RNS APPLICATION

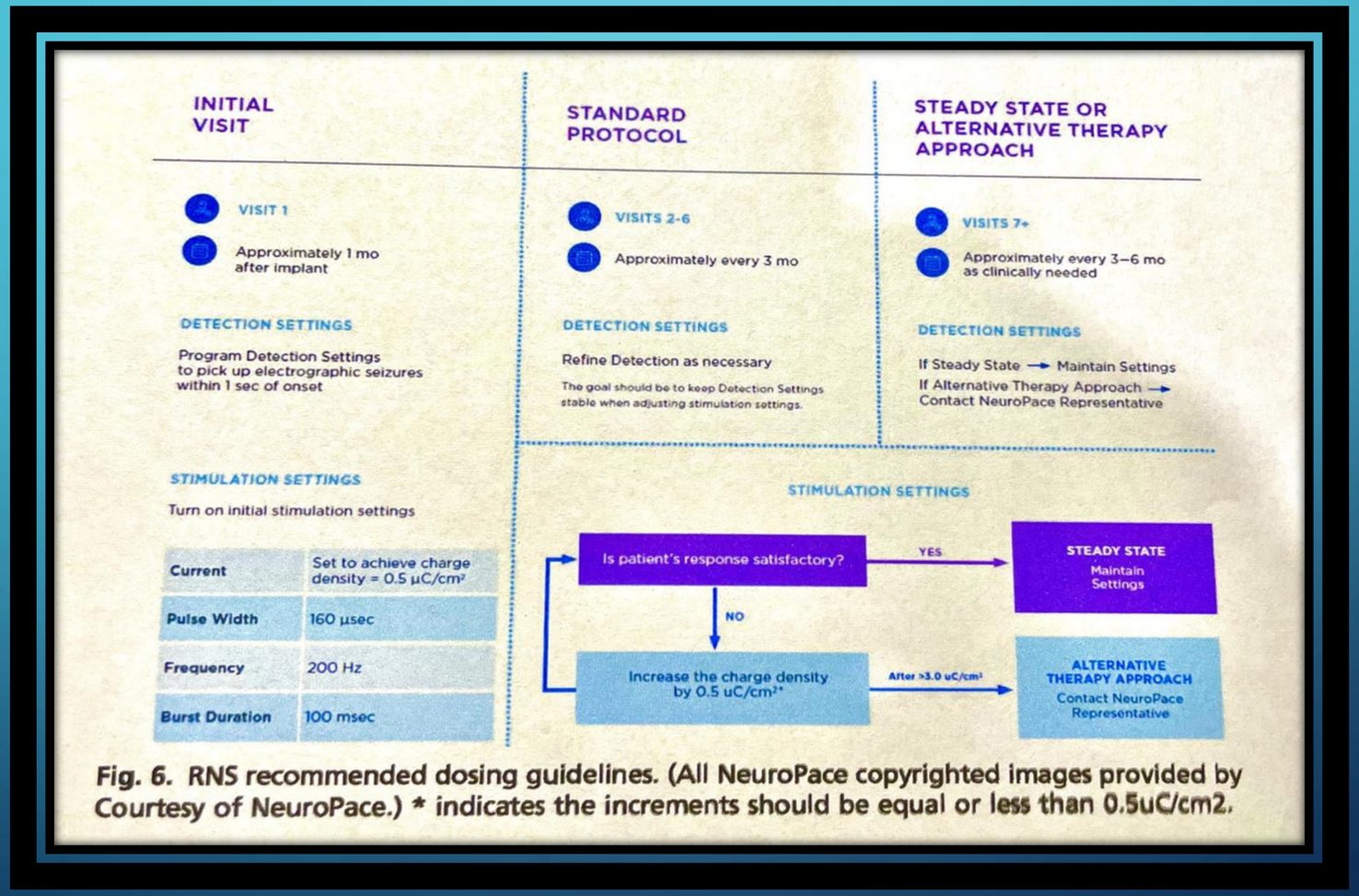


Fig. 6. RNS recommended dosing guidelines. (All NeuroPace copyrighted images provided by Courtesy of NeuroPace.) * indicates the increments should be equal or less than 0.5uC/cm2.

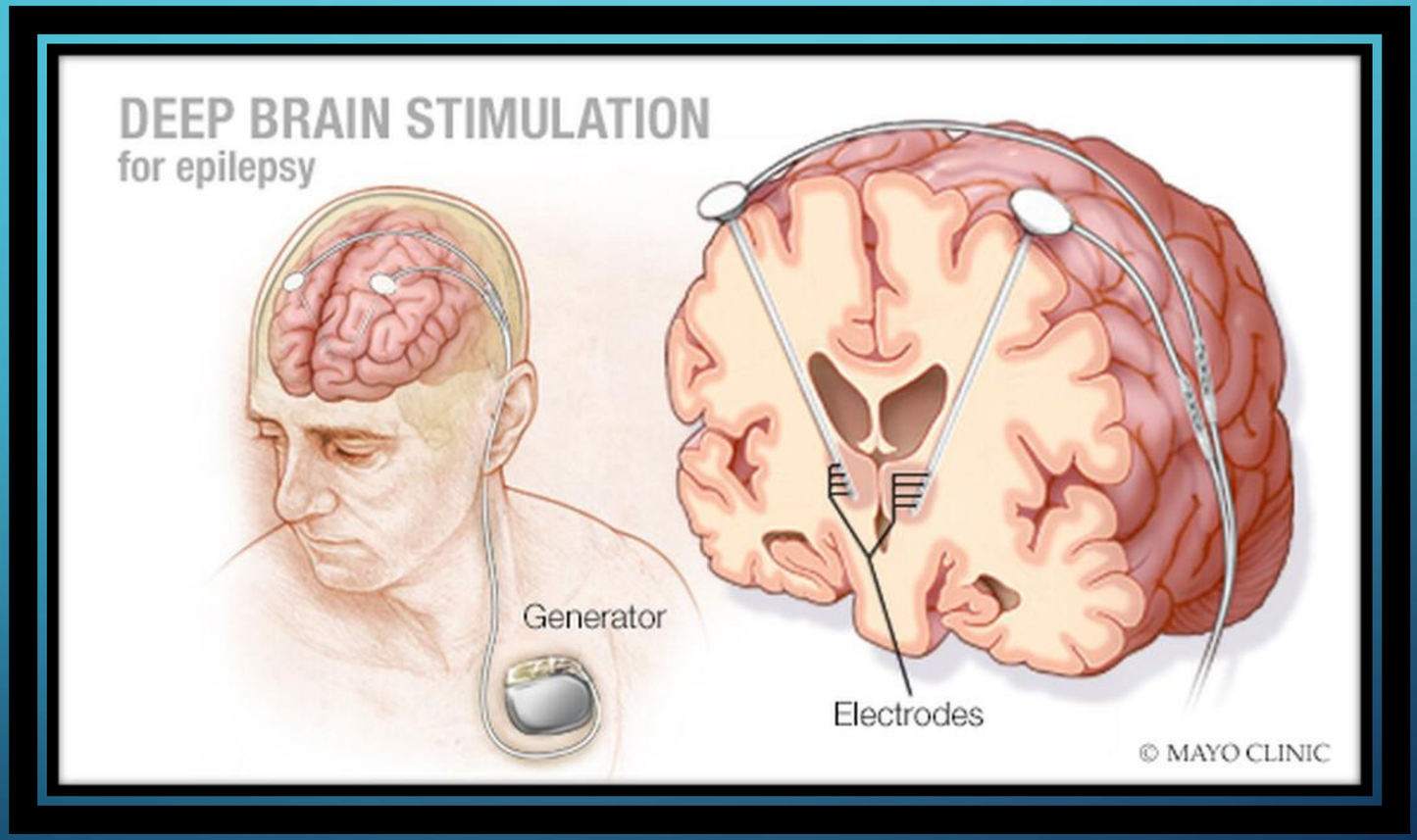
NEUROMODULATION
RNS CLINICAL OUTCOMES

- Several clinical trials have demonstrated efficacy response for focal epilepsy*
- Appears to demonstrate improved efficacy over time (similar to VNS)
- 50% responder rate at 9yr follow-up ranges from 40-72%
- 28% of long term RNS use enjoyed > 6 month sz freedom periods
- No cognitive adverse events and pts have demonstrated improvement in naming and verbal memory scores over time
- Also appear to demonstrate a decrease in SUDEP risk

NEUROMODULATION
RNS COMPLICATIONS/ISSUES

- 2.7% intracranial hemorrhage rate with implantation procedure
- Infection risk is 3.7% but can increase to 12% over years requiring explantation; the erosion risk <1%
- Approved 18yrs older (limited pediatric use)
- Skull size and thickness important in placement and battery life is approximately 5-8 years
- Procedures such as ECT therapy, TMS and diathermy procedures would be contraindicated

NEUROMODULATION
DBS



NEUROMODULATION
DBS

- Approved to treat drug-resistant focal epilepsy in pts 18 and older as adjunctive therapy
- Depth electrode implanted stereotactically in the anterior nucleus of the Thalamus and a pulse generator in the chest or abdomen
- It is thought the mechanism is via increased transmission of both excitatory and inhibitory neurotransmitters within the basal ganglia-thalamocortical circuitry
- This includes inhibition of action potential through Na channel-mediated depolarization inhibition, direct distal axonal synaptic inhibition and depletion of neurotransmitters at distal terminals

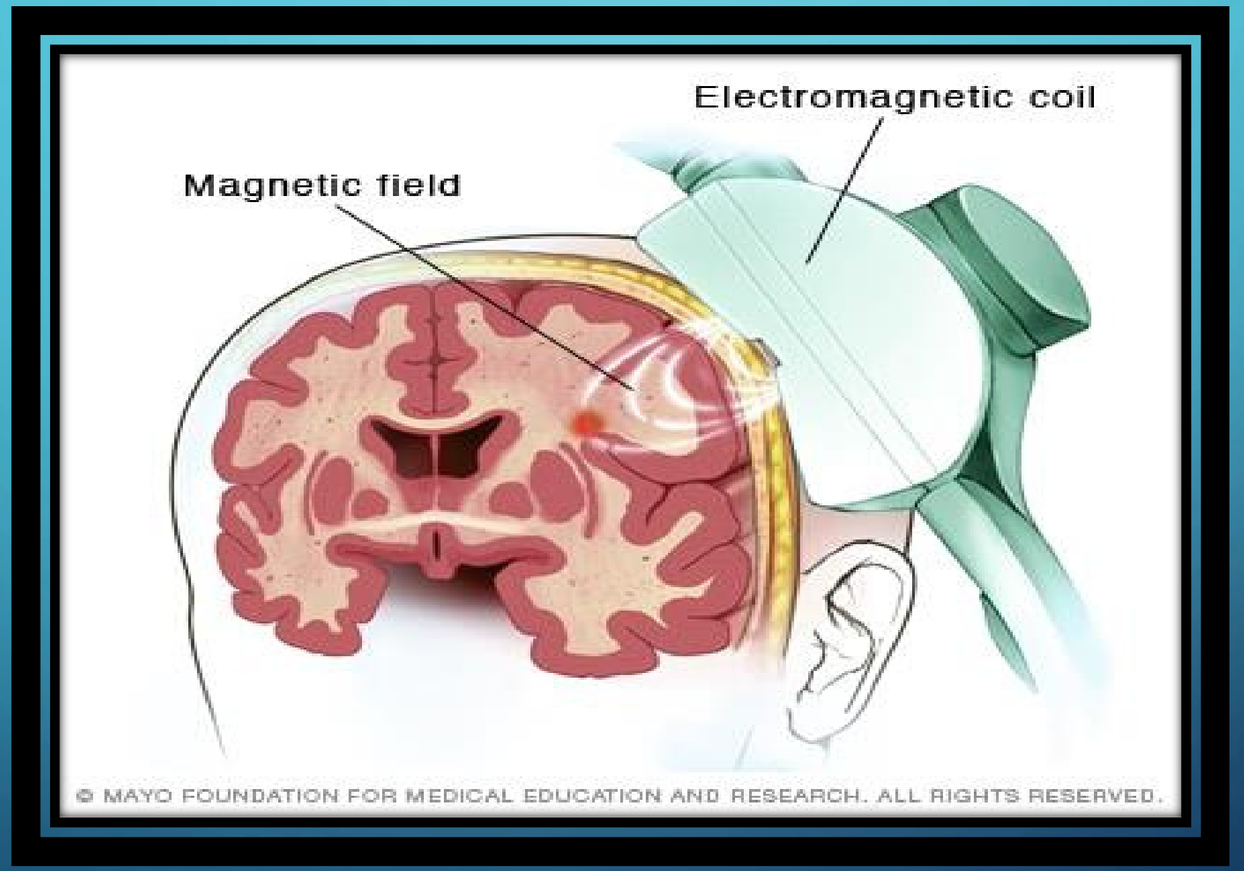
NEUROMODULATION
DBS CLINICAL DATA

- Median reduction seizure rate ranges from 40-54 % in 5yr follow-up data
- Appears to demonstrate a sustained and incremental beneficial effect over time
- Quality of life data also has noted improvement over time
- Prior VNS response does not influence the chances of responses to DBS

NEUROMODULATION
DBS COMPLICATIONS

- Up to 20% may experience implant site infection and pain (temporary for pain)
- Hemorrhage, paralysis, “dizziness” and increase in seizures have been reported
- Minor cognitive and behavioral issues have also been reported
- Hardware complications and loss of function should also be reviewed with potential candidates

NEUROMODULATION FUTURE: TMS



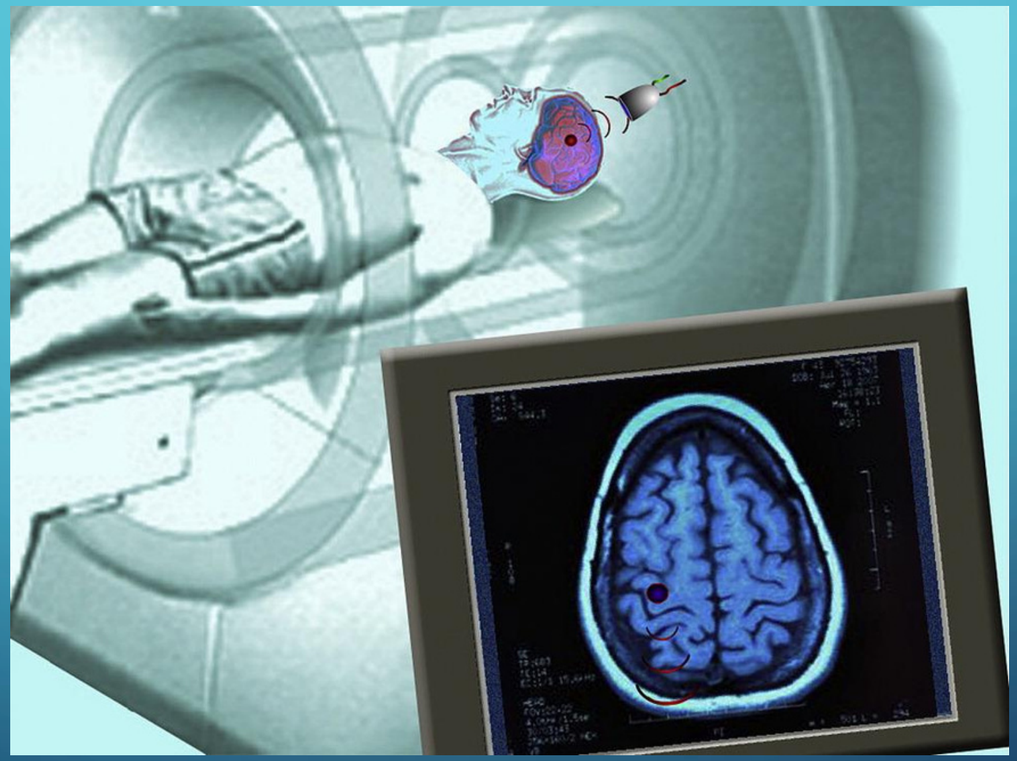
NEUROMODULATION
TMS

- Noninvasive procedure that uses magnetic fields to induce electric field changes which leads to induction of electrical currents that activate neurons in the brain
- Stimulation area is 2-3 cm deep from brain surface using a magnetic coil and MRI stereotactic localization
- With rTMS, targeted areas of cortex is inhibited by repeated magnetic pulses
- Though not currently approved to treat epilepsy, clinical trials have demonstrated efficacy response
- Currently useful for treatment of depression and mapping of motor cortex

NEUROMODULATION
TMS COMPLICATIONS

- Overall is well tolerated
- Headache, lightheadedness, transient paresthesia or spasms of the face
- No increase in seizure has been noted with TMS
- No efficacy in deep-seated epileptic foci (i.e.-hippocampus) which limits its utilization for epilepsy

NEUROMODULATION
FUTURE: FOCUSED ULTRASOUND (FUS)



NEUROMODULATION
FUTURE: FOCUSED ULTRASOUND (FUS)

- Noninvasively targets tissue with a spatial distribution of highly focused acoustic energy in a “beam” type focus
- Generally classified in 2 categories: high and low intensity
- High intensity is used for ablation of tissue
- Low intensity is the modality used for neuromodulation(LIFUS)
- Several clinical trials are on-going for LIFUS and no complications or adverse events have been reported

NEUROMODULATION
FUTURE: FOCUSED ULTRASOUND (FUS)

- Proposed MOA of low intensity focused ultrasound include:
  - Cavitation-eruption of gas bubbles forming inside the neural membrane changing its capacitance or structure
  - Increased potassium channel conductance leads to reduced resting membrane potential
  - Mechanosensitive membrane displacement
  - Subsequently, inhibition via LIFUS would render the epileptogenic focus less able to mount the aberrant discharge while preserving the integrity of the cell

NEUROMODULATION
FUTURE: FOCUSED ULTRASOUND (FUS)

- Issues include confirming target engagement and assessing neural efficacy
- Also, the are no exact parameters yet for amount of stimulation energy or for how long and how often to achieve suppression of epileptogenic foci
- The skull and the target engagement region will also need to be addressed as there is skull thickness variability that could distort beam and influence outcome

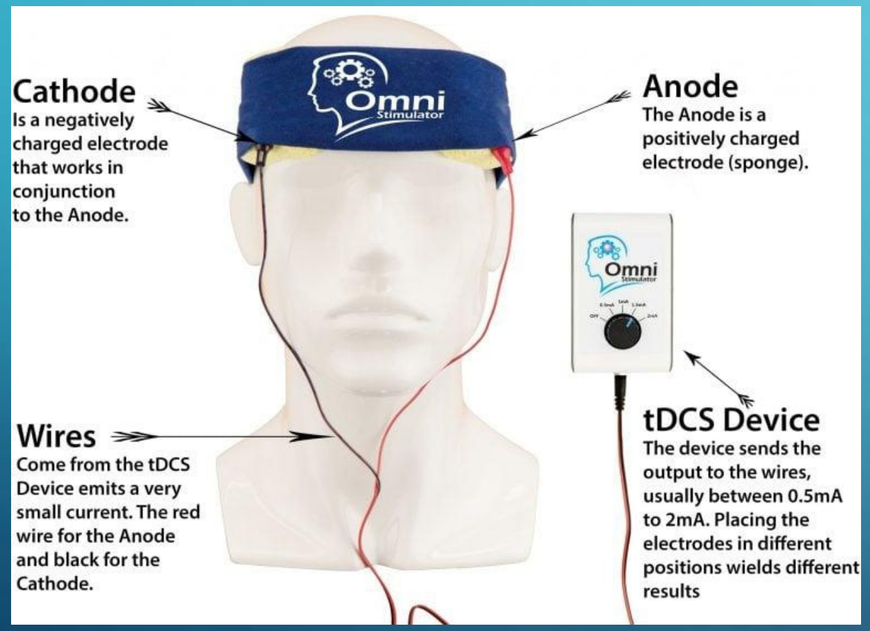
NEUROMODULATION
FUTURE DEVICES

- External trigeminal nerve stimulation

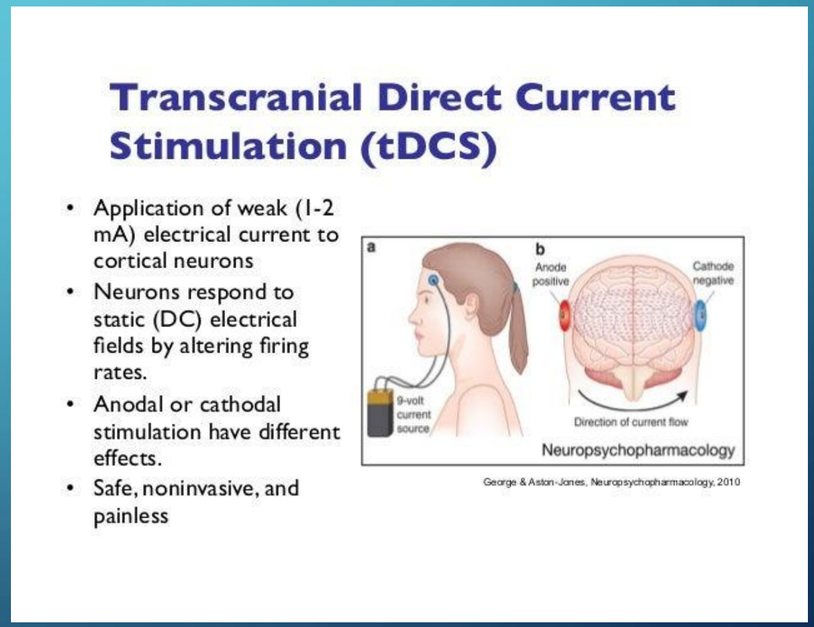
- Transcutaneous VNS

NEUROMODULATION FUTURE DEVICES

- Transcranial alternating current stim



- Transcranial direct current stim



NEUROMODULATION
IS THERE A ROLE FOR IT IN EPILEPTIC ENCEPHALOPATHIES?

- Well documented that VNS has proven efficacious for LGS and other drug resistant epilepsies with further improvement as responsive VNS therapy has evolved
- “New” targets for RNS therapy are now being employed with promising early data (Neuropace trial sponsored by NIH)
- Those newtargetsfocusingon the ventral anterior nucleus of the thalamus and the Centromediannucleus of the thalamus

NEUROMODULATION
IS THERE A ROLE FOR IT IN EPILEPTIC ENCEPHALOPATHIES?

- Targeting the Anterior nucleus is due to the fact that it's a key component in the "Papez" circuit and its connections to the cingulate gyrus and the lateral temporal cortex
- Targeting theCentromediannucleus is due to its connectivity to the anterior cingulate gyrus, striatum and the motor cortex
- Recent (small) trial notedan81%improvementingeneralizedseizureswhen this unique approach was used in a group of LGS pts

NEUROMODULATION
IS THERE A ROLE FOR IT IN EPILEPTIC ENCEPHALOPATHIES?

Yes! There is a role today and perhaps a greater role in the future as neuromodulation evolves

It is safe,well tolerated, cost effective, lowers SUDEP risk and improves quality of life in patients who are not surgical candidates and remain refractory

NEUROMODULATION
TRIBUTE TO EARLY YEARS/PIONEERS