Responsive Neurostimulation (RNS)

Last updated: February 8, 2023

Comparison of Neuromodulations (RNS, DBS, VNS) – see p. E11 >>

RNS = responsive neurostimulation on demand + diagnostic modality.
Advent of RNS decreased tolerance to functional consequences of epilepsy surgery.

BROCHURES

- see >>

Reading

E. Geller. Responsive neurostimulation: Review of clinical trials and insights into focal epilepsy. Epilepsy Behav, 88 (2018), pp. 11-20

O. Devinsky, D. Friedman, R.B. Duckrow, N.B. Fountain, R.P. Gwinn, J.W. Leiphart. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia, 59 (2018), pp. 555-561

INDICATIONS

FDA APPROVED (2013)

- *adjunctive* therapy in **reducing frequency of seizures** in individuals ≥ 18 years**** with **partial onset** seizures who have undergone diagnostic testing that localized **no more than 2* epileptogenic foci**, are **refractory** to ≥ 2 antiepileptic medications, and currently have ***frequent**** ***and disabling***** ***seizures***.

*Neuropace has receptacle only for two leads.

** ≥ 3 disabling seizures per month over three most recent months (with no month with fewer than two seizures); RNS® System has not been evaluated in patients with less frequent seizures.

***motor partial seizures, complex partial seizures and / or secondarily generalized seizures

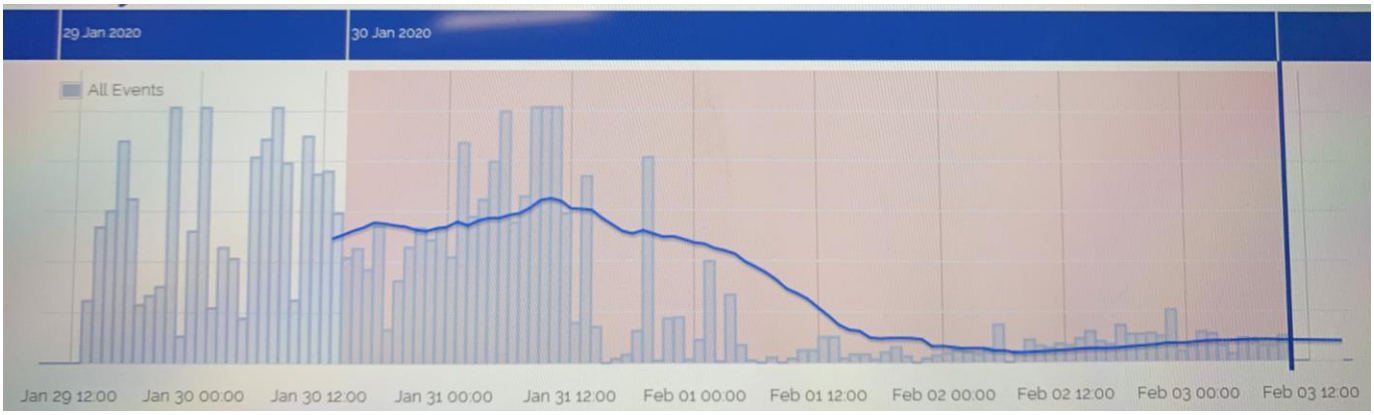
****FDA indication for RNS is age > 18 years, but it likely has efficacy in adolescents and children (limitation in young children is skull thickness before it reaches adult size, so it could certainly be used in adolescents).

Summary

a) ≥ 2 foci
b) eloquent areas
c) mesial temporal lobe (uni- or bilateral)
d) difficult to resect (e.g. insula, large regional onsets, interhemispheric)
e) failed previous surgery or VNS (24% RNS patients have VNS)

VNS, RNS, and DBS are all palliative and comparable in efficacy, both in pivotal trials and over longer-term trials. VNS is sometimes a first choice as it is extracranial. A specific scenario where RNS may have an advantage is ***bilateral mesiotemporal epilepsy*** – RNS allows for long-term ECoG recording, which may in turn (occasionally) allow for an eventual resection (of seizure-dominant hippocampus or prove that "bilateral" disease is de facto unilateral) in a small number of patients.

Case reports of efficacy in ***refractory status epilepticus***:



Source of picture: Dr. Kathryn Holloway (VCU)

Modern approach – implant in thalamus for generalized epilepsies (such as Lennox-Gastaut).

CONTRAINDICATIONS

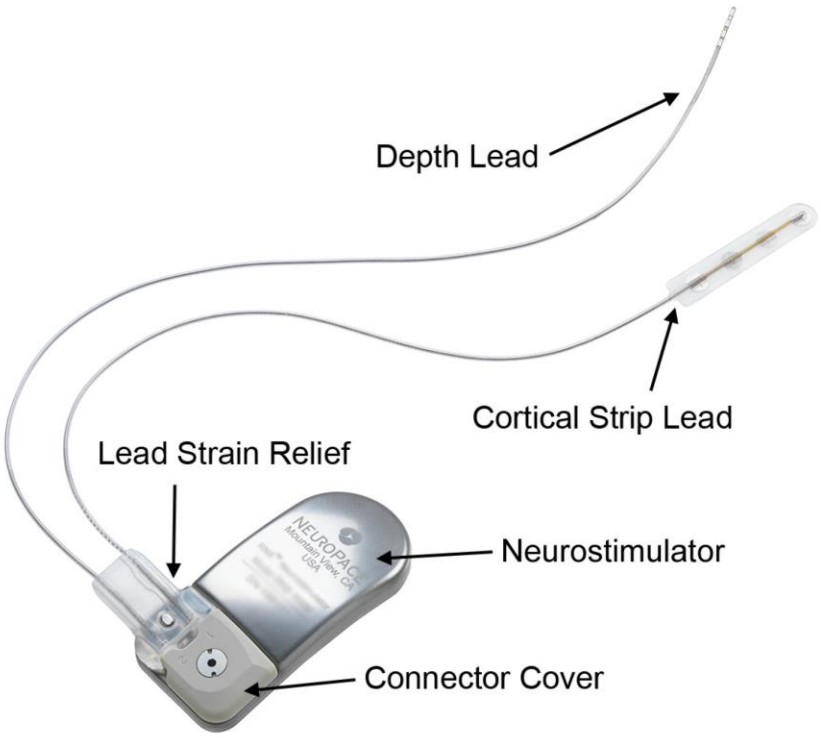
From RNS® System manual:

- high risk for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies) or platelet count < 50,000.
- patients who have medical devices implanted that deliver electrical energy to the brain.
- patients who are unable, or do not have the necessary assistance, to properly operate the NeuroPace® Remote Monitor or magnet.

PATHOPHYSIOLOGY

- Penfield and Jasper noted: inhibitory polarization caused by transmembrane currents of applied current → flattened local electrocorticography pattern.

HARDWARE



- RNS Neurostimulator Kit Model # RNS-300M-K.
- four cortical 5 mm bone screws.

DEVICE

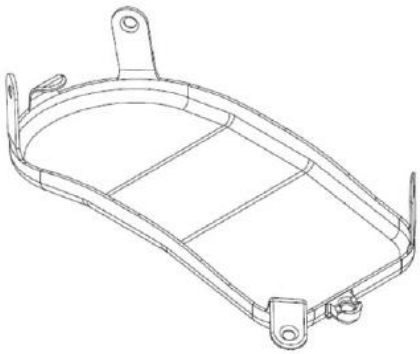
- accepts two electrode arrays; if uncertain – may implant more and leave contact end capped (may switch and reconnect later).

Feature	RNS-320-K	RNS-300M-K
Battery life	8.4 yrs (under "medium" settings)	3.9 yrs
Data capacity	1 MB - stores 8 ECoGs (90 sec duration each)*	0.5 MB
Price	6000 USD more expensive (31,950 USD)	25,950 USD

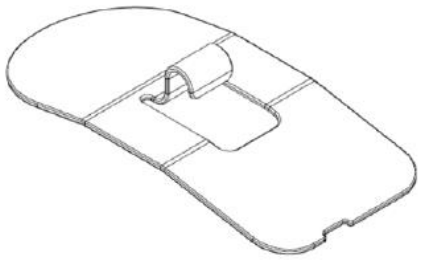
*still no warning to the patient when memory is full and data is overwritten

Q: who should be getting **model 300**? A: nobody.

Kit includes also ferrule (675 USD):



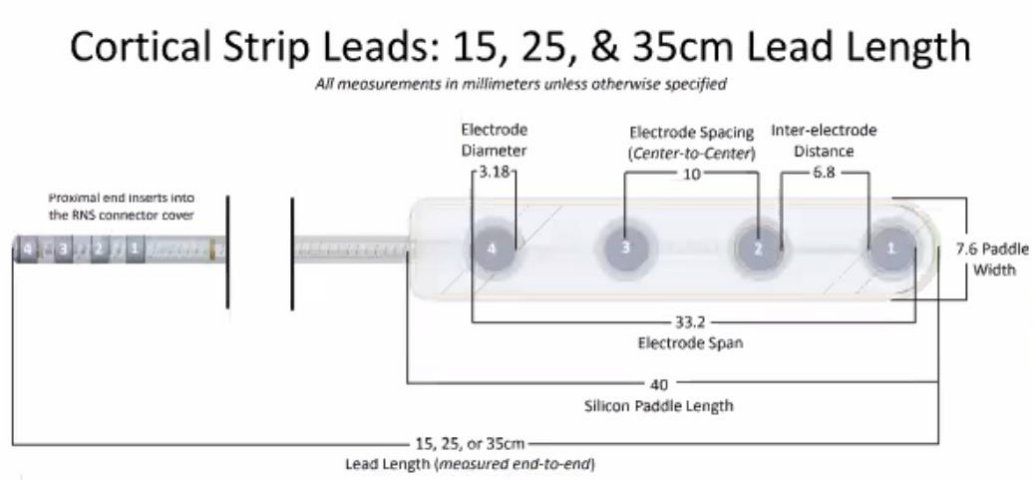
Kit does not include craniectomy template (375 USD):



Practical tip – use nonsterile template (from rep) to plan craniotomy scalp incision; for craniectomy – use ferrule to draw lines on skull.

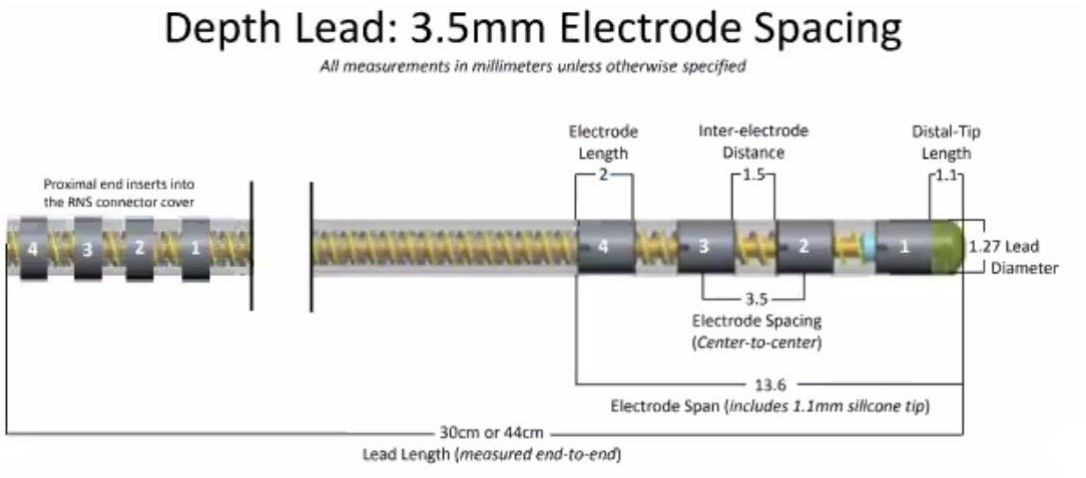
STRIPS

- 4100 USD
- 4 contacts spaced 10 millimeters apart - spans 33 mm
- lead lengths (tip - beware unnecessarily long leads):
  - 15 cm (model CL-315-10)
  - 25 cm (model CL-325-10)
  - 35 cm (model CL-335-10)

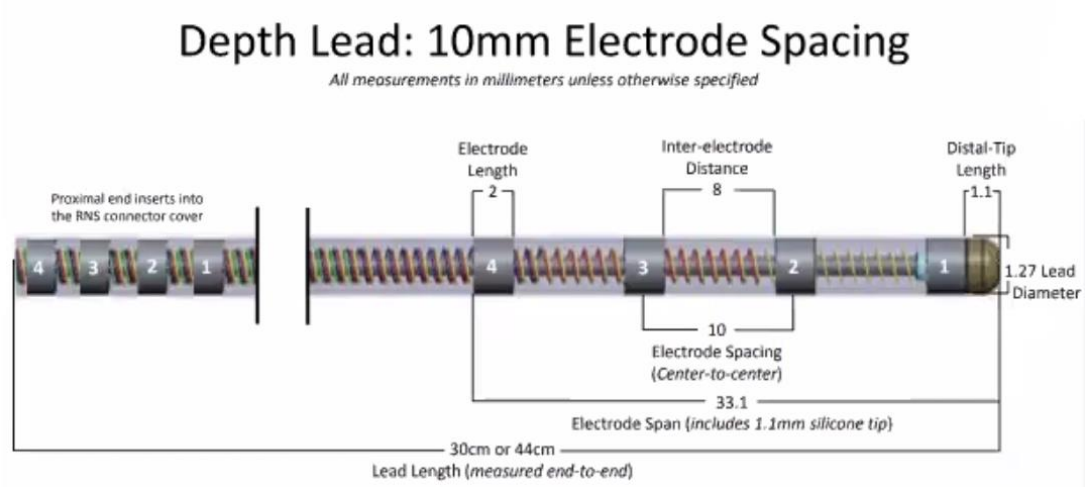


DEPTHS

- 4100 USD
- 4 contacts
- diameter 1.27 mm (same as older DBS electrodes); slotted cannula 2.1 mm.
- two configurations (tip - beware unnecessarily long leads):
  - 3.5 mm contact spacing, 30 cm length (model DL-330-3.5) – electrode span 12.5 mm
  - 3.5 mm electrode spacing, 44 cm length (model DL-344-3.5) – electrode span 12.5 mm
  - 10 mm electrode spacing, 30 cm length (model DL-330-10) – electrode span 32 mm
  - 10 mm electrode spacing, 44 cm length (model DL-344-10) – electrode span 32 mm

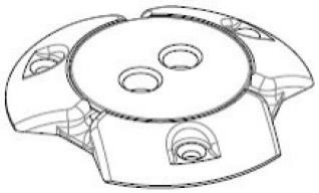


Particularly useful for small targets (such as thalamic implantation)



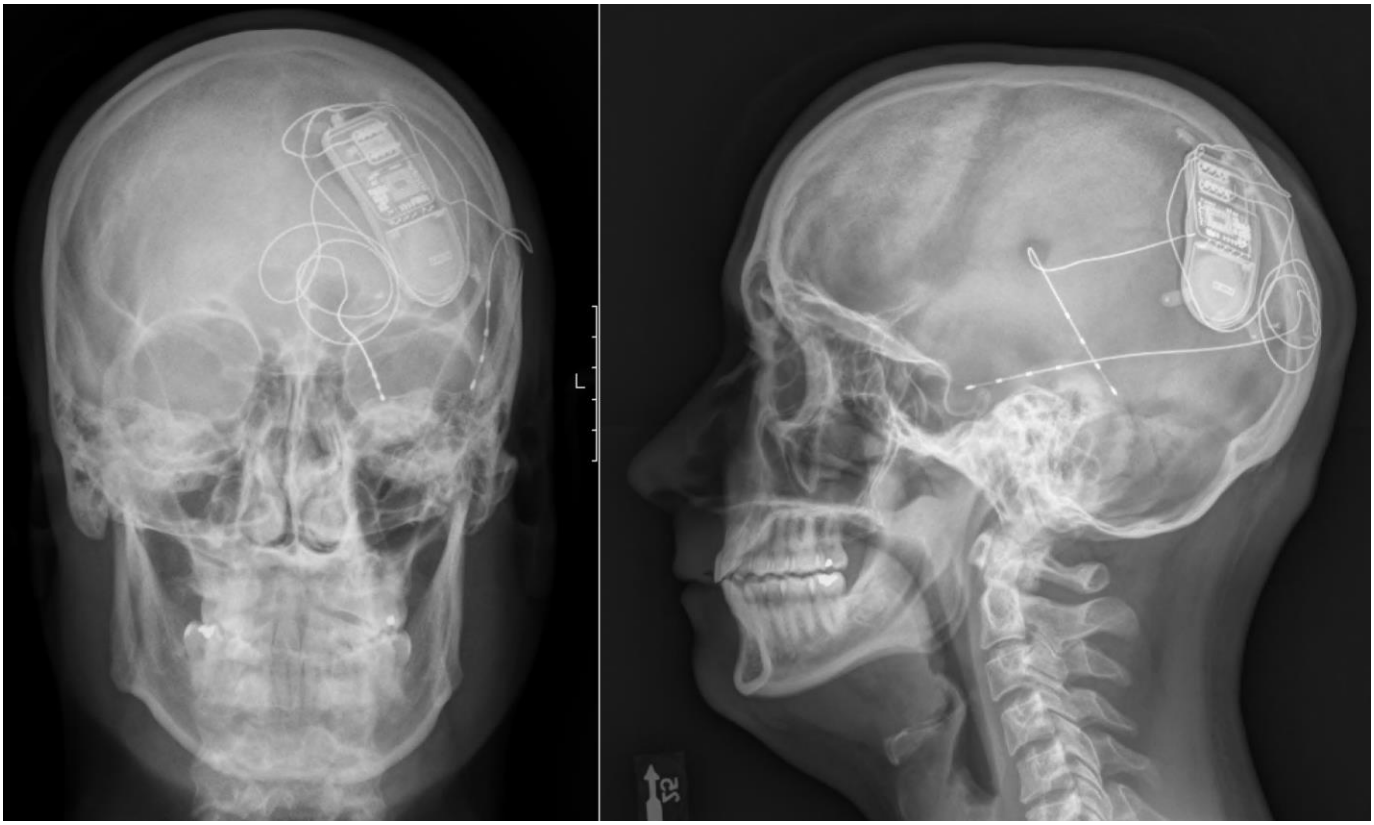
Wider spacing is for hippocampal depths!

BURR HOLE COVER



- 325 USD
- requires three 1.5 – 1.8 mm screws.
- there are other alternatives – see below >>

ON IMAGING



Source of picture: Viktoras Palys, MD >>

PREOP COUNSELLING

I explained the alternative of the VNS, pros and cons of each as well as the risks of surgery to include no change or worsening of seizures, visual fields compromise, memory compromise, or other injury to the brain. I explained that how the computer was placed to replace the skull and the electrodes that pass through the brain to the hippocampus. We talked about shaving some of the head. The patient understands the risk of an infection, which would require removal.

STRATEGIES

ECOG VIA RNS

- may use RNS strip electrodes for live ECoG intraop but only if connected to IPG (it has to be grounded); RNS electrodes do not have adapters to connect to conventional ECoG machine.

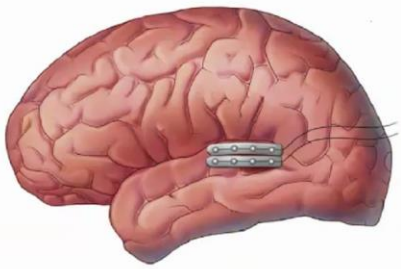
NEOCORTICAL BROAD ONSETS

Neocortical seizure onsets localized to one "regional" (broad) area of cortex are difficult to treat with resective surgery.

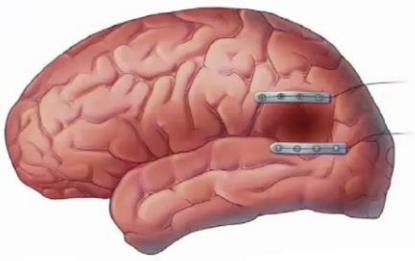
- RNS may encompass 8-11 cm in regional stimulation.
- electrode contacts have to be on EZ else detection may not work well.

- Eloquent Cortex
  - The RNS System therapy is usually well tolerated in eloquent cortical regions (no chronic stimulation side effects)[1]
  - The RNS System electrodes can be implanted at the conclusion of Phase II monitoring.
- Combination RNS + Resection
  - The RNS System can be used in conjunction with resection to augment the margins of the resection or to treat a separate onset location, or both.[2]

Focal Onset[3]



Broad Onset[3]

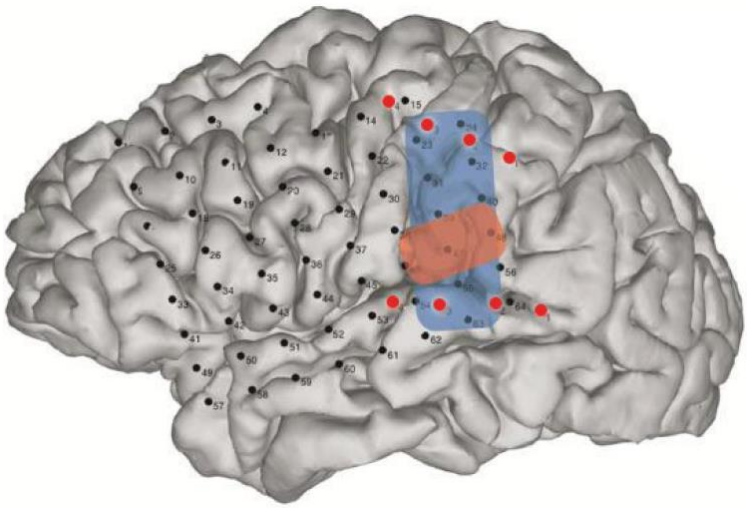


1. Jobst, B et al, *Epilepsia*,2017
2. Perven et al, Poster, AES 2019
3. Ma, BB and Rao, VR, *Epilepsy and Behavior*, 2018

Strategy #1 – **strip** electrodes

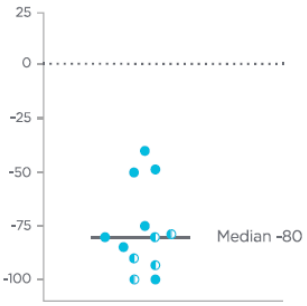
Case series

Brandy Ma, Emily Mirro, Robert Knowlton, Edward Chang, Vikram Rao



Subdural grid electrode
Seizure onset zone
Resection
NeuroPace Cortical Stip Lead electrode

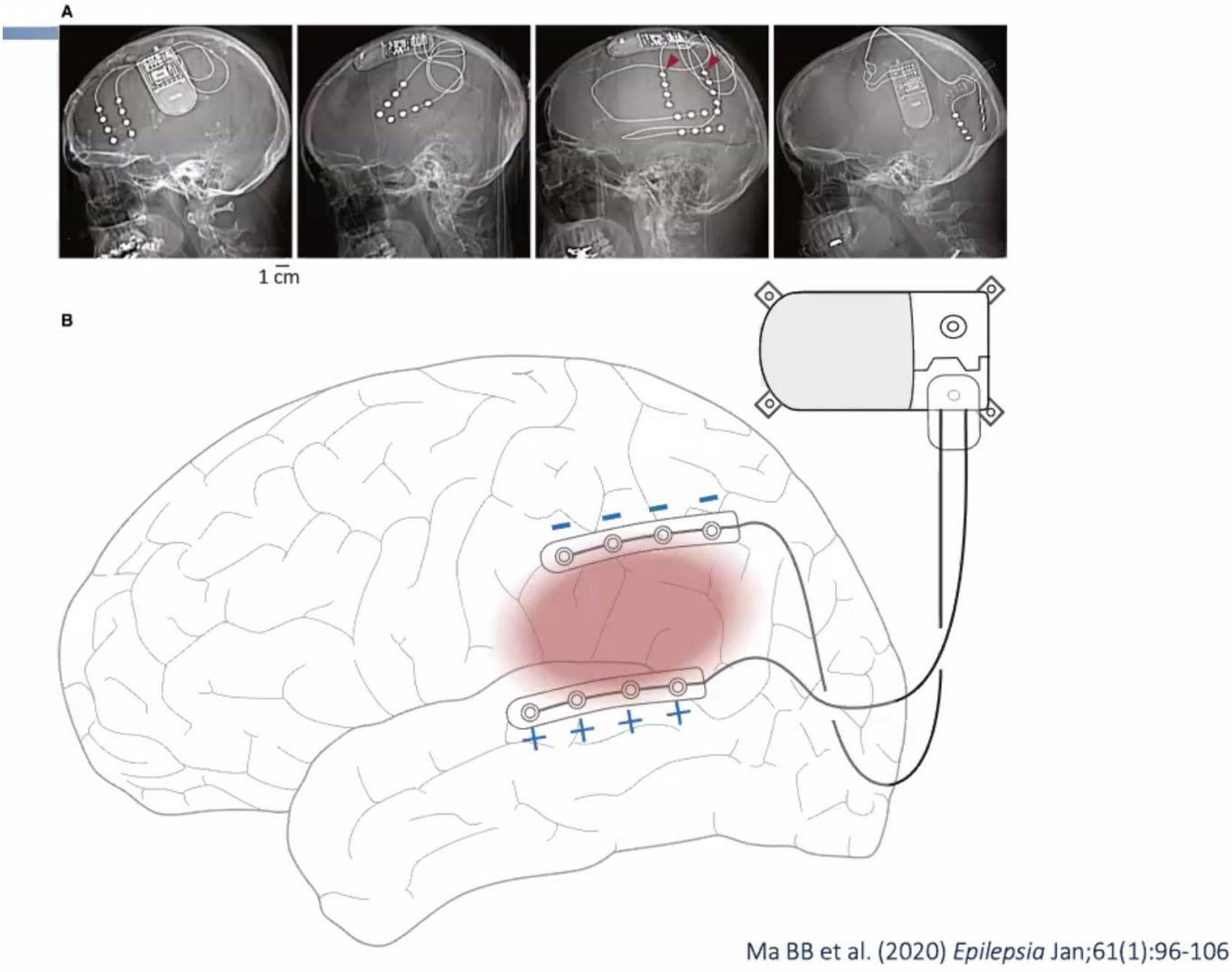
Seizure Reduction for 12 Regional Onset Patients Treated with the RNS System



Patients who had concurrent resection

- 12 patients who had one "regional" seizure onset zone were treated with the RNS System at UCSF.
- two depth and/or cortical strip leads were on average 3.3 cm apart (range: 1.2 cm - 6.0 cm).

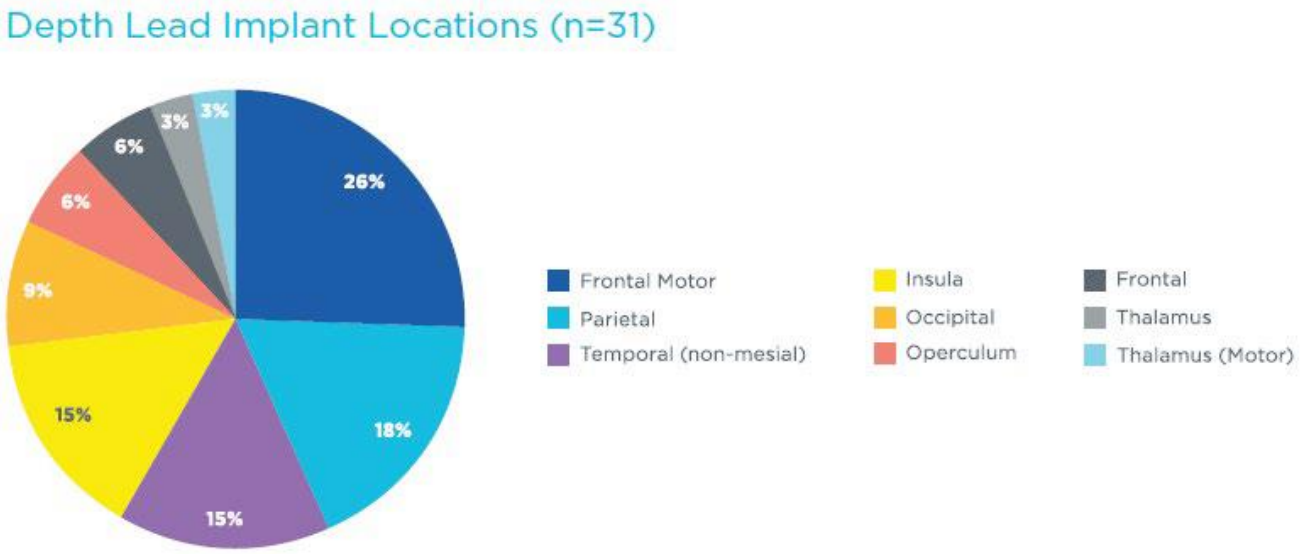
- 80% median seizure reduction and 83% responder rate was achieved.

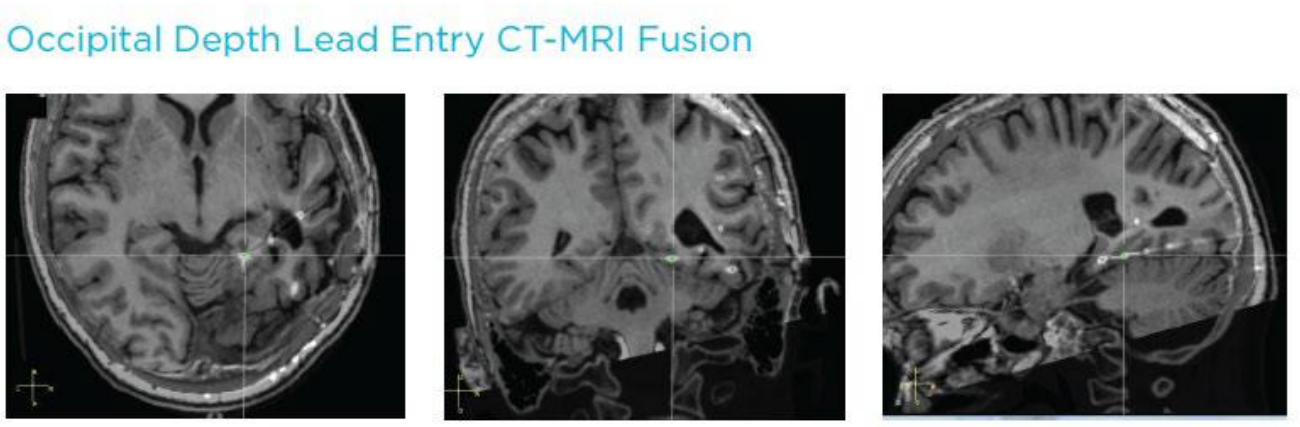


Strategy #2 – **depth** electrodes into neocortex
- can be preferred strategy for neocortical seizure onsets when cortical strip leads are not feasible or the localization was done with SEEG.

Case series

Allen Ho, Jonathon Parker, Emily Mirro, Babak Razavi, Kai Miller, Dora Hermes, Matthew Markert, Gerald Grant, Jaimie Henderson, Casey Halpern. Anatomic early electrographic seizure onset localization and clinical response with responsive neurostimulation of depth leads placed in neocortex.





- 16 patients who had ≥ 6 months follow-up had a median seizure frequency reduction of 65%.

Strategy #3 – **depth** electrode(s) into thalamus (e.g. centromedian nucleus)

- for generalized epilepsies (such as Lennox-Gastaut).

CONCURRENT PARTIAL RESECTION + RNS

RNS can be used concurrently with a resection such that treatment is extended to an unresectable area of the seizure focus.

Case series

Babak Razavi, Emily Mirro, Lawrence Shuer

- 3 patients at Stanford had a concurrent resection with RNS placement.
- all 3 patients had electrographic and clinical seizures after resection.
- 2 patients became seizure free and the 3rd patient reported 62.5% reduction and less severe seizures.

PATIENT	AGE	ETIOLOGY	MRI RESULTS	NEUROPACE LEAD LOCATION	LOCATION OF PARTIAL RESECTION	DURATION OF RNS SYSTEM TREATMENT	% SEIZURE REDUCTION*
1	26	Focal Cortical Dysplasia	Right Parietal Focal Cortical Dysplasia Type IIb	Sensory	Parietal	1.3 (Yrs)	100%
2	20	Focal Cortical Dysplasia	Left Frontal Focal Cortical Dysplasia Type IIb	Motor	Frontal (2 cm)	1.3 (Yrs)	100%
3	20	Focal Cortical Dysplasia	Left Parietal Focal Cortical Dysplasia Type Ia	Motor	Left parietal (up to motor strip)	1.4 (Yrs)	62.50%

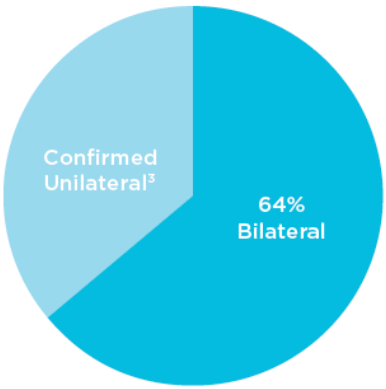
BILATERAL MESIAL TEMPORAL LOBE EPILEPSY

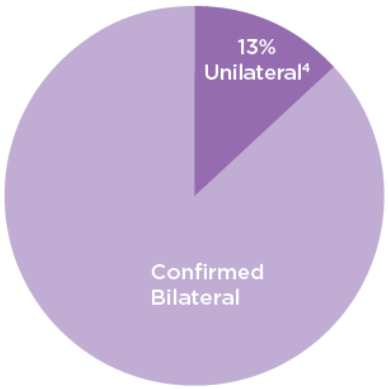
Long-term ambulatory ECoG monitoring of bilateral mesial temporal lobes with the RNS System can potentially lead to an efficacious resective or ablative procedure

<u>Pre-RNS presumed lateralization changes in 20% of patients after chronic ambulatory ECoG</u>:

11 patients presumed unilateral;
7/11 (64%) had bilateral electrographic seizures

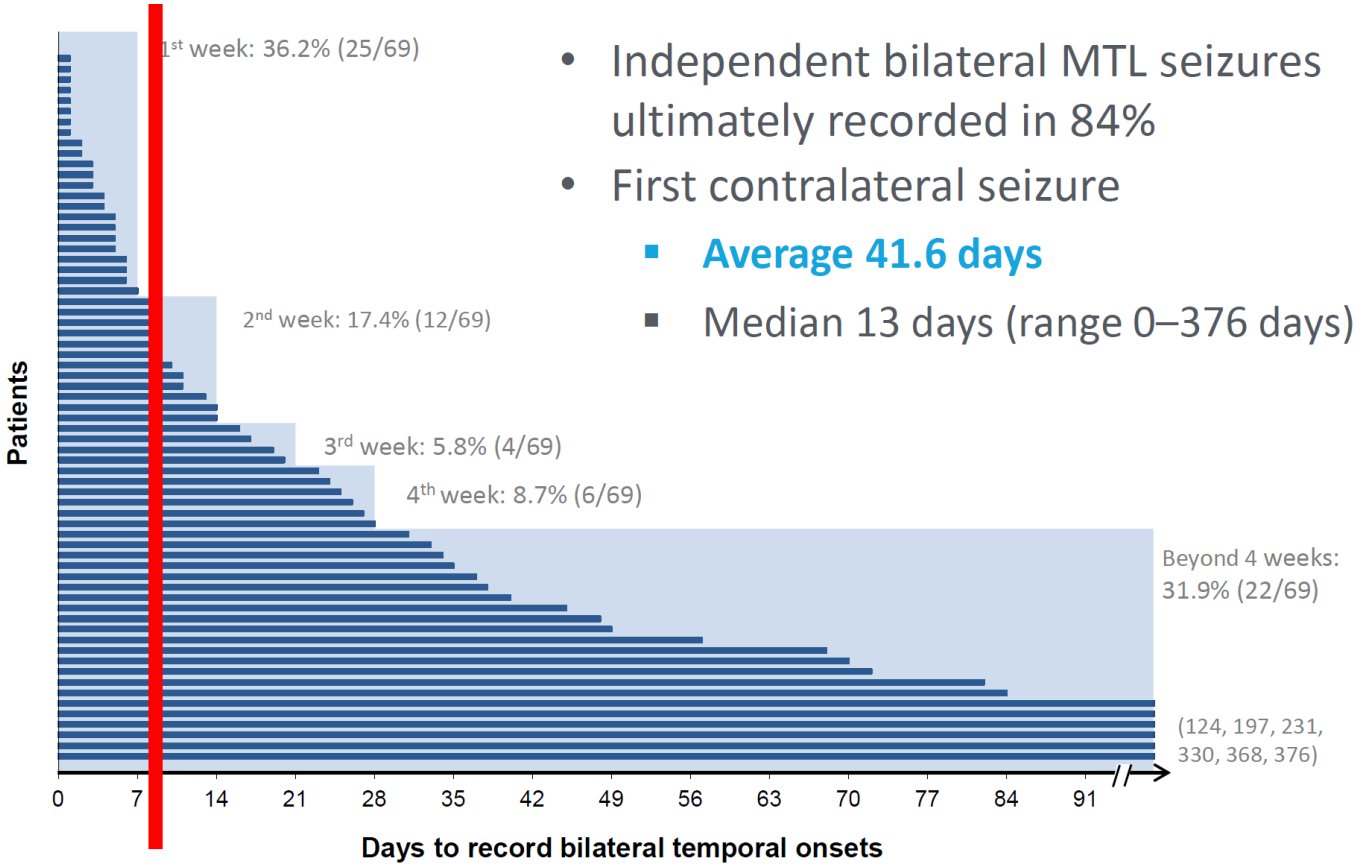
71 patients presumed bilateral;
9/71 (13%) had only unilateral electrographic seizures





King-Stephens et al., *Epilepsia* 2015

<u>Time to record first contralateral MTL seizure in patient with bilateral implants:</u>



- Independent bilateral MTL seizures ultimately recorded in 84%
- First contralateral seizure
  - **Average 41.6 days**
  - Median 13 days (range 0–376 days)

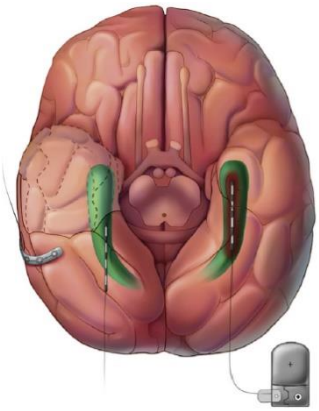
King-Stephens et al., *Epilepsia* 2015

Case series

Lawrence Hirsch et al. Outcomes after mesial temporal lobe resection following long-term ambulatory recording by the RNS System

- after bilateral MTL monitoring with RNS, 21 patients (at 17 epilepsy centers) had MTL resections.
- average RNS time before resection was 42 months (range: 8-117 months), and average post-resection follow-up was 37 months (range: 7-101 months).
- mean seizure reduction for all 21 patients was 90% (range: 50-100%).
- 15 of 21 patients (71%) were free of clinically reported disabling seizures.
- 8 of the 15 seizure free patients had only unilateral seizure onsets stored by the RNS System prior to resection, and the remaining 7 had bilateral seizures with an average of 90% from the resected side.
- 19/21 patients continued to be treated with the RNS.

Post right ATL with RNS System depth lead pulled back into the remaining hippocampus and subtemporal strip placed on the resection margin. The contralateral hippocampal RNS System depth lead left in place.



PROCEDURE – DEPTH ELECTRODE IMPLANTATION

HIPPOCAMPAL DEPTH

Trajectory (hippocampus cannulation) – see p. E15 >>

- prone in Leksell frame base (e.g. with special attachment to ROSA) or radiolucent Mayfield (but standard metal frame may have less wiggle than radiolucent frame) – make sure pins will not interfere with bur holes.
- guidance platform: Nexframe* or STarFix or ROSA**

*need O-arm registration (can be fiducialless)

**need O-arm registration (from frame pin ends, no need for bone fiducials)

CANNULA OPTIONS

A) conventional DBS cannula – see p. Op360 >>

If using *AlphaOmega* microdrive system with the bengun and cannulas:

- use "at target" cannula:
  - 1.81 mm outer diameter (each cannula slot on the bengun has diameter 1.8 mm)
  - 1.6 mm inner diameter
  - 192 mm length (set ROSA to "160 mm distance to target" - to accommodate the 30 mm height of non-XY CRW adapter).
- if outer table-target length is > 120 mm, cannot use *AlphaOmega* microdrive system as will not be able to drive ROSA to "160 mm distance to target", so rather use slotted cannula (see below).
- use 44 cm depth leads!!! (30 cm lead will have trouble securing in DBS lead holder); except if outer table-target length is ≤ 80 mm may use 30 cm RNS depth lead and "10 mm above target" cannula – when microdrive is dialed all the way down, the distance between cannula distal tip and the first lead snap is about 29 cm (be prepared to use only one clip on DBS lead holder and clip the lead at stylet plastic handle by pulling to a side) and the distance between the proximal tip of cannula and the first lead snap is about 8 cm (so just enough to pull the cannula up and see the exposed lead at the outer table); otherwise, use 44 cm depth lead.

B) slotted cannula is needed for STarFix or ROSA (unless using electrode holder when pulling regular non-slotted cannula up):

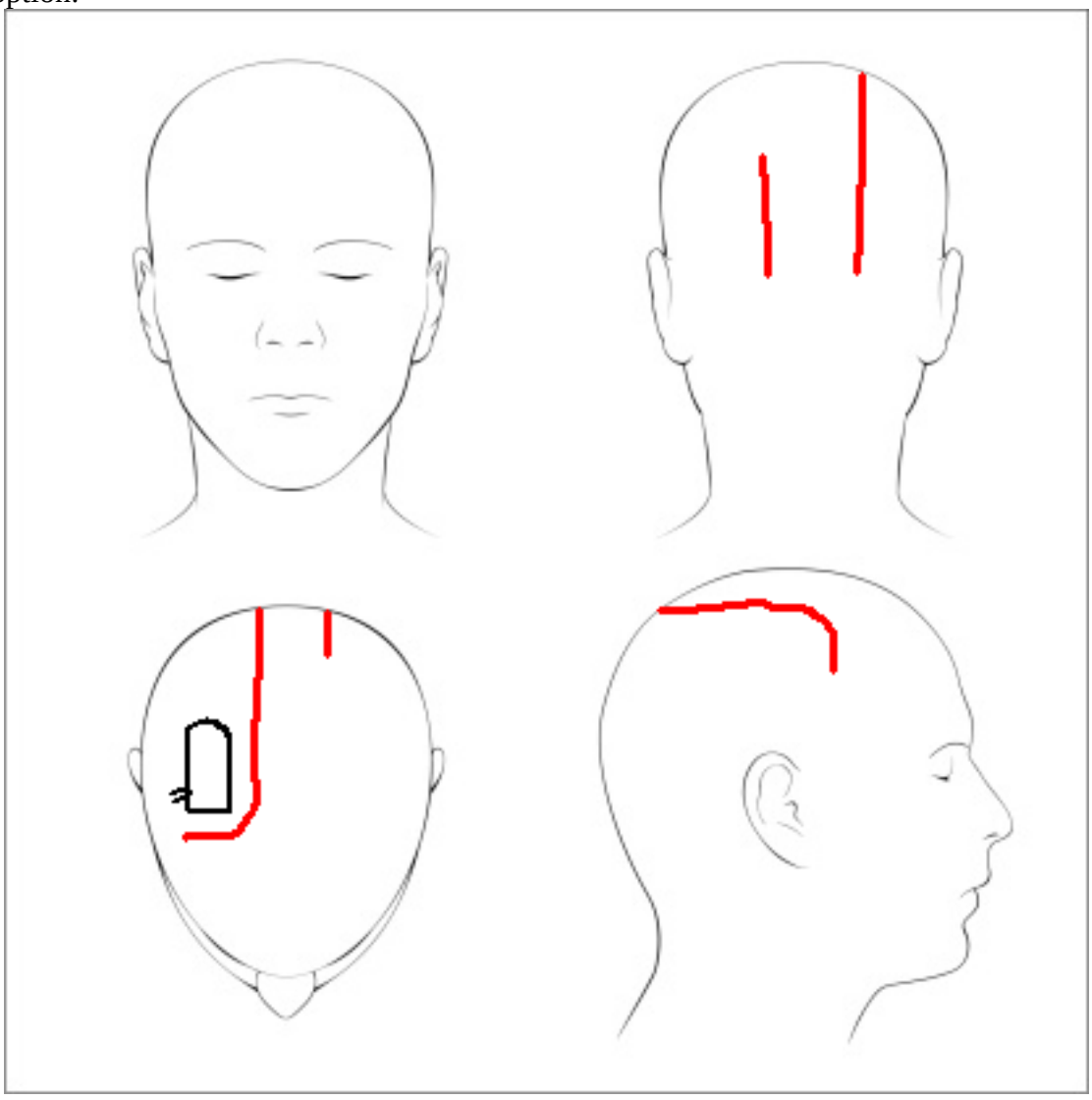
Two-piece slotted cannula (2SC-190X, *Ad-Tech Medical Instrument Corp*):

- 1,011 USD (re-usable).
- 190 mm length – set ROSA to "190 mm distance to target"
- 2.11 outer diameter.

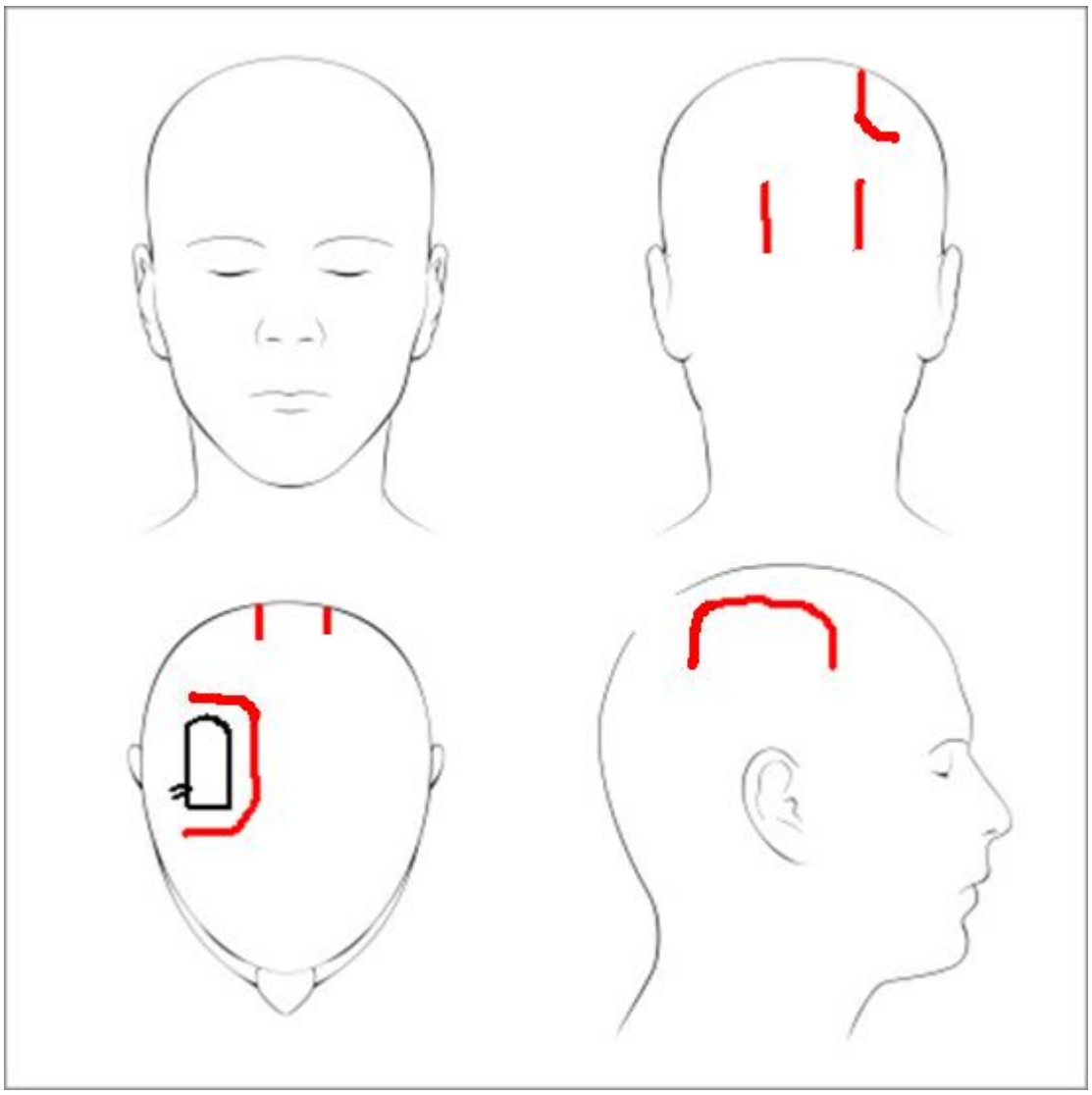
INCISIONS

for bilateral leads (keeping in mind scalp blood supply and the battery replacement surgeries):

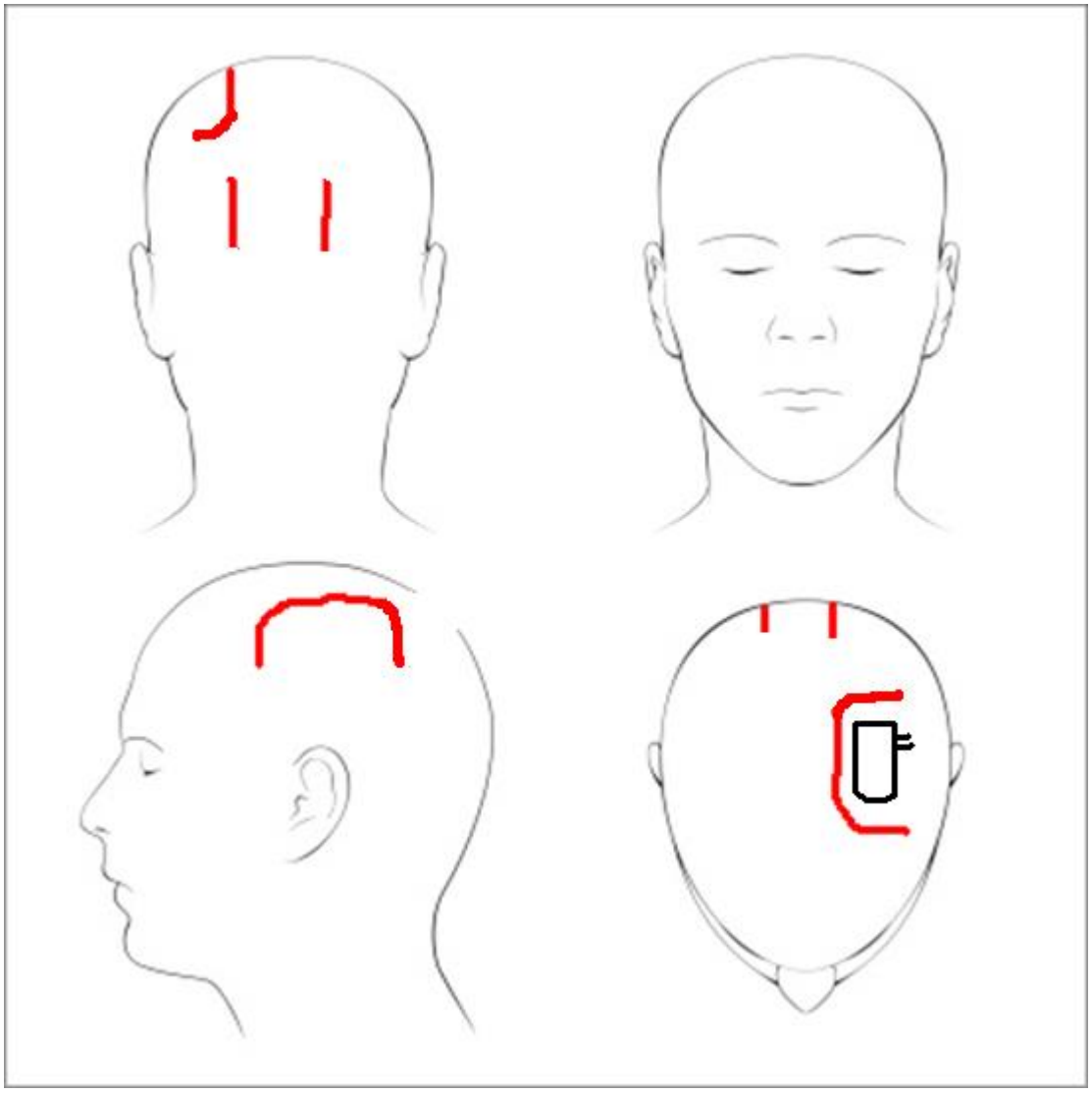
A option:



B option (device on the **right**):



B option (device on the **left**):



Implantation with ROSA

- O-arm registration.
- 3.2 mm drill hole.
- put a mark with permanent marker on a lead in two places:
    1) target to outer skull table
    2) length of cannula (i.e. top of ROSA platform) – not needed if using DBS lead holder

Implantation with Nexframe:

- Acra-Cut perforator (undercut laterally using M8 drill bit).
- Medtronic Nexframe needs double Silastic on lateral side (may even need offset bengun).
- if using Nexframe: "at target" DBS cannula with Neuropace electrode is placed into the center track to the full depth to the target.

- do CT and look for contact position (10 mm lead with 4 contacts spans 33 mm) – may need to pull lead back for the best coverage.

Lead anchoring options

a) Medtronic lead **burhole anchoring device (Stimloc)** – goes over standard bur hole 14 mm.
b) Neuropace lead **burhole anchoring device (Plunge)** – goes over standard bur hole 14 mm.

c) **Dogbone titanium plate** (advantage – skull twist hole can be very small; e.g. use 3.2 mm drill bit); to protect lead, slide a small piece of shipping tube over the lead where dogbone will sit (Neuropace formally recommends against using dogbone as lead fracture has been reported).

Implantation of 2 leads

- if implanting 2 leads in parallel (e.g. second lead in parahippocampal gyrus), aim to keep distance > 10 mm between leads so can stimulate in bipolar mode between contacts in separate leads.
- inner diameter of Neuropace bur hole cover is 10 mm (if using one bur hole for both leads, plan entry points ≤ 10 mm apart).

PROCEDURE - DEVICE IMPLANTATION

- two antibiotics: cefazolin, 2 g IV and vancomycin 1 g IV
- plan incision so generator is not under incision; may use pericranial flap of opposite direction.
- if incision is curved, plan generator implant so leads face away from incision; plan for future battery replacements – will need to open only scar at the flat end of device, curving a little bit on the side (opposite where leads exit).

CRANIECTOMY

N.B. partial thickness craniectomy is not recommended – time consuming, bone grows and pushes device out.

- consider pericranial flap.
- use template (e.g. ferule) to mark bone.
- location – anywhere where shape conforms to skull curvature, e.g. parietal area.
- one or two bur holes (some place it where ferule tab is going to be).
- discard bone flap.
- some place dural tack-ups along perimeter.

LEADS

- tunnel leads so the coil on the side (not above) the device, at the base of flap.
- electrodes are connected to Neuropace ports, e.g. the left hippocampal lead into port # 1, the left parahippocampal lead - into port # 2.
- normal lead impedance range 250-3500 Ohm.

Case report of implanting in infraclavicular position

A Novel Approach for Responsive Neural Stimulator Implantation With Infraclavicular Placement of the Internal Pulse Generator. Lucas R Philipp, Robert E Gross, MD, PhD Operative Neurosurgery, opy025, https://doi.org/10.1093/ons/opy025 Published: 14 March 2018

- band pass detection rates increased by 50%, while line length detection rates decreased by 50%.
- number of detections decreased from 1046 to 846, with a resultant decrease in stimulations.
- although there was some compromise of function due to the elevated noise floor, more than 2 yr following the procedure the patient remains free of seizures and infection.

Case report of implanting inside prosthetic skull implant

First In-Human Experience With Complete Integration of Neuromodulation Device Within a Customized Cranial Implant. Chad R Gordon, DO Gabriel F Santiago, MD Judy Huang,

MD Gregory K Bergey, MD Shuya Liu, MS Mehran Armand, PhD Henry Brem, MD William S Anderson, PhD, MD. Operative Neurosurgery, Volume 15, Issue 1, 1 July 2018, Pages 39–45

PROCEDURE - BATTERY REPLACEMENT

- enough to expose only very bottom (flat end) of generator → undo 2 screws (tab and connector cover), remove strain relief plate from leads, and reflect leads.
- use Bovie set at 6 if need to dissect leads (Dr. P. Weber); do not use Bovie when new battery is in.

BATTERY CHARGE LEVEL

- patient uploads daily report to PDMS – report contains battery voltage; when low voltage is detected, Neuropace informs neurosurgeon about the need to schedule IPG replacement.

	Model 320	Model 300
ERI (elective replacement indicated)	2.37 V	2.75 V
EOS (end of service)	2.30 V	2.70 V

PROCEDURE - EXPLANTATION

- explanting a chronically implanted cortical strip lead may cause cortical damage.

COMPLICATIONS

Infection (3.7-4.1%; 1.9% leading to explantations)
Hemorrhages (2.7%)

No chronic stimulation side effects!

POSTOPERATIVELY

MRI

https://www.neuropace.com/rns-system-mri-guidelines/

- device gives MRI artefacts.
- MRI may induce low levels of current through implanted leads (tingling sensation), vibration, heating.
- MRI scan may be safely performed on patients with the RNS® System only under the specific conditions:
  1) > 10 days after surgery.
  2) no fever > 37 degrees
  3) only 1.5 Tesla horizontal, closed-bore MRI systems with spatial field gradient ≤ 30 T/m (3,000 gauss/cm), gradient slew rate ≤ 200 T/m/s per axis.

4) stimulator has to be programmed into "MRI mode" (not detecting and not stimulating) and battery must not be in EOS.
   Note: neurostimulator ***uses more battery power in MRI Mode*** (neurostimulator can be in MRI Mode for up to approximately two days per year without affecting battery longevity)
5) only with model RNS-320 (RNS-300M is MRI unsafe) or incomplete RNS system (i.e. no IPG is implanted but other components still present):

MR Unsafe

Table 1: MR Unsafe Implantable RNS® System Components

Component	Model Number(s)
Neurostimulator	RNS-300M
Cranial Prosthesis[1]	P-01

[1] No longer distributed commercially and has not been evaluated for MRI safety.

MR Conditional

Table 2: MR Conditional Implantable RNS® System Components

Component	Model Number(s)
Neurostimulator	RNS-320
Depth Lead	DL-330-3.5 DL-330-10 DL-344-3.5 DL-344-10
Cortical Strip Lead	CL-315-10 CL-325-10 CL-335-10
Connector Cover, Connector Plug	CC-01, CP-01
Ferrule, Ferrule Clamp	F-01, FC-01

MR Safe

Table 3: MR Safe Implantable RNS® System Components and NeuroPace Products

Component	Model Number(s)
Lead Strain Relief, Lead Cap, Suture Sleeve	LSR-01, LC-01, SS-01

N.B. all Neuropace **lead** models are eligible for MRI.
- leads can be attached or unattached to the neurostimulator.
- unattached leads can be capped or uncapped.
- leads that are cut or broken (at any point along the length of the lead) are eligible for MRI.

6) do not use a head or extremity transmit coil
7) active scan ≤ 30 minutes per session; wait 30 minutes between sessions.

CONTRAINDICATED PROCEDURES

1. **Diathermy procedures** (any treatment that uses high-frequency electromagnetic radiation, electric currents, or ultrasonic waves to produce heat in body tissues); from RNS manual:
   "Patients absolutely CANNOT be treated with any type of shortwave, microwave, or therapeutic ultrasound diathermy device whether or not it is used to produce heat. These treatments should not be applied anywhere on the body."

2. **Electrosurgery** – conflicting info: some say not to use Bovie (use bipolar at > 2-3 cm away from device); others say it is OK to use **Bovie** (if close to device, it may reset the device – will need to reprogram). It is OK to use **Bovie** on old battery (if close to leads – use lowest settings on Bovie, e.g. 6).

3. **Electroconvulsive Therapy** (ECT).

4. **Transcranial Magnetic Stimulation** (TMS).

5. **Radiotherapy**
   Exposure to high levels of radiation may damage the RNS® System.
   The effects of high radiation sources (such as cobalt 60 or gamma radiation) on the RNS® System have not been studied - no studies to determine safe levels of irradiation for their device nor are there any recommendations for safe dose exposures. Neuropace suggests that the patient scan the device daily after each radiation fraction. This information can be transmitted to Neuropace who can determine if software repairs/re-programming can restore any lost functionality (if the device is damaged, it will try to reset itself. If unable to do that, it shuts down to a stable non-functioning state). Neuropace does not recommend prophylactically removing this device prior to radiation therapy.

ANALYSIS & PROGRAMMING

impedances - *see above >>*

- for 4-6 weeks postop - program just for recording as during this time recordings fluctuate and tend to gradually stabilize from surgical trauma.

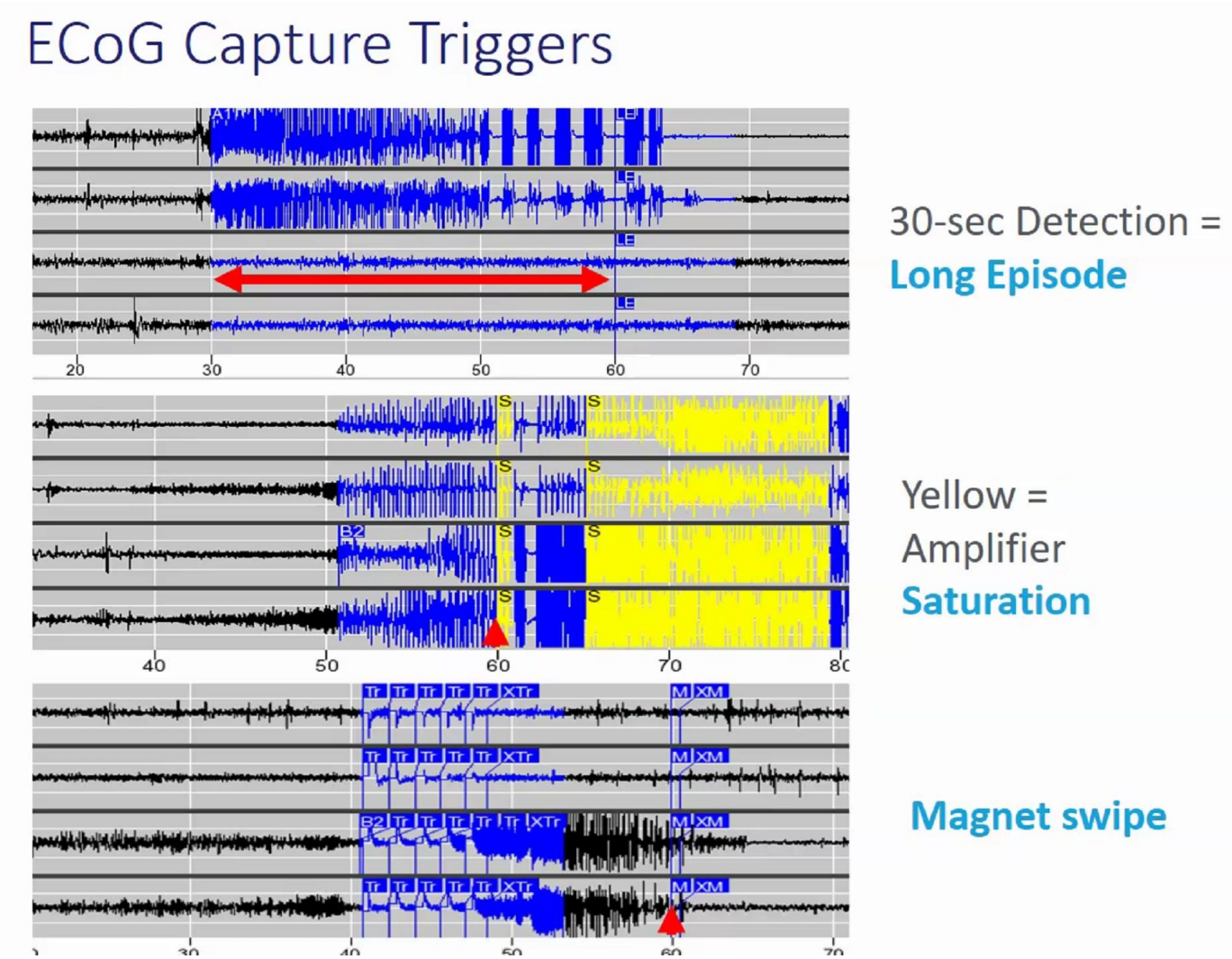
RNS device stores ECoG only at **certain triggers** (if no triggers, device stores ECoG at certain time every day - **scheduled**):

a) patient swipes **magnet** (e.g. if feels aura) – device stores 60 sec of preceding ECoG and 30 sec of subsequent ECoG
b) **amplifier saturation** (high amplitude)*
c) **long episodes** (spikes or fast activity run > set time, e.g. 10 sec)*

*device stores ECoG if triggered stimulation does not abort activity (i.e. device stores ECoG of stimulation failures)

RNS-320 stores 8 ECoGs (90 second duration each; device stores 60 sec of ECoG before trigger and 30 sec of subsequent ECoG after trigger); then it starts overwriting the oldest one without warning – so teach patient to regularly upload data to laptop – from RNS manual:

"The patient must collect data from the Neurostimulator once a day and send data to the PDMS once a week"



DETECTIONS

Detection counts: counts of irregular epileptiform activity detected by the RNS (mostly composed of brief interictal epileptiform events but also include a small number of electrographic seizure onsets).

Long episode counts: counts of a specific type of detection trigger (lasting longer than a pre-specified time period) that often represent electrographic seizures – could be a true objective *ECoG biomarker for seizure burden*.

> *David Spencer et al. Electrographic events recorded by a responsive neurostimulator may provide an objective assessment of clinical seizure burden.*

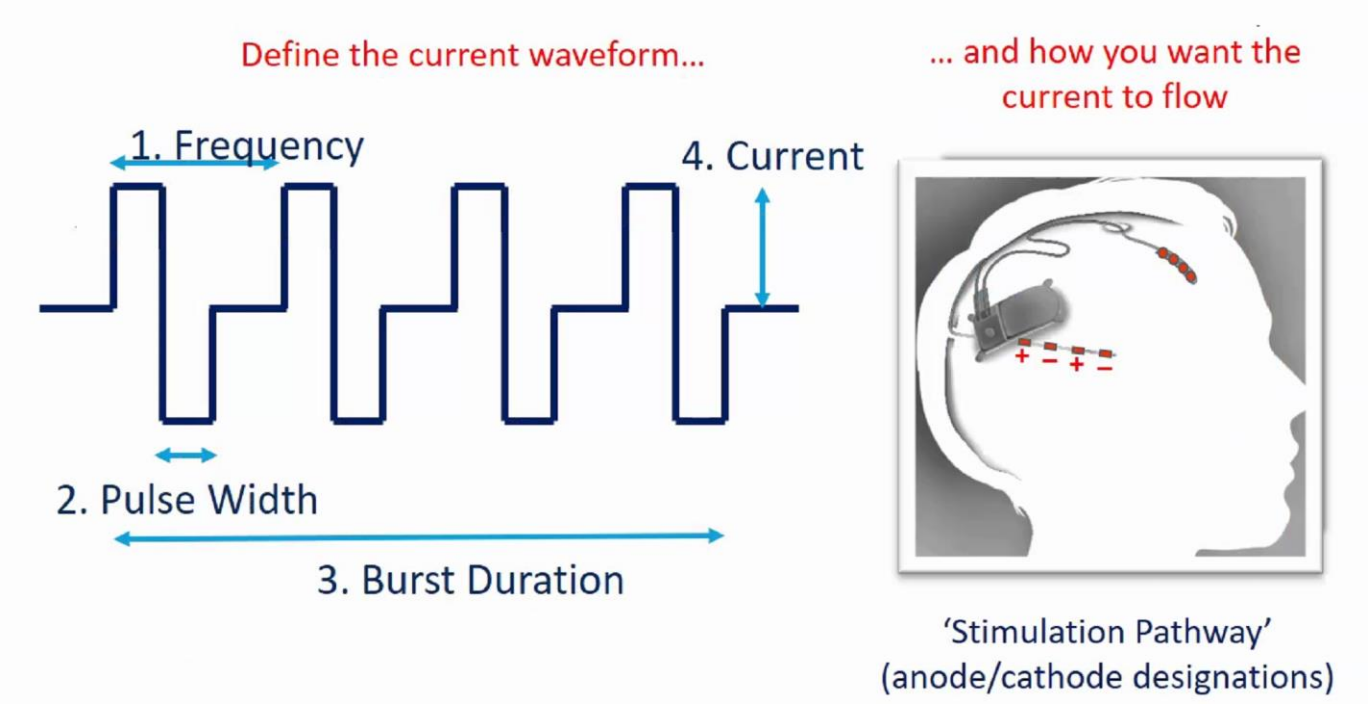
N.B. only 10% of RNS triggers are actual seizures! (thus, it is correct to say that "RNS detects electrographic activity" and not "electrographic seizures")

- interictal discharges – potential biomarkers.

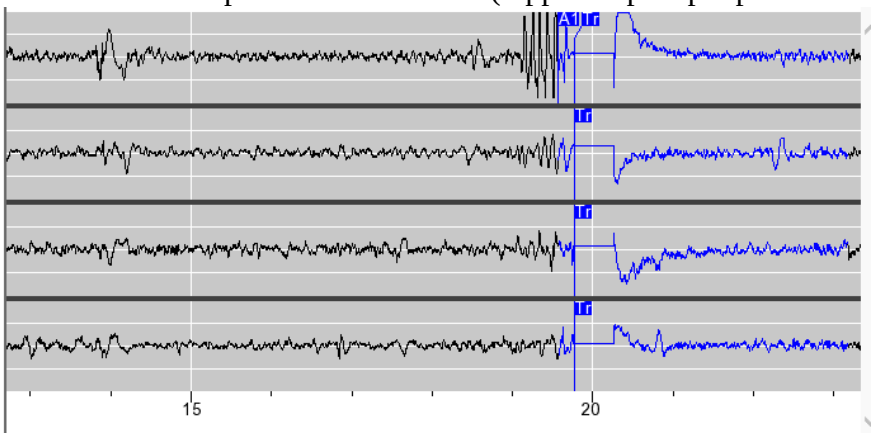
STIMULATION

Device stimulates up to 5 times (per FDA approval) if redetection happens right away.

- current: 1-3 mA
- pulse width: 160 μs
- frequency: 100-200 Hz
- burst duration: 100-200 ms



Detection and Responsive Stimulation (hippocampal epileptiform discharge):



OUTCOMES

NEUROPSYCHOLOGICAL

- some expert concerns that hippocampal (longitudinal) depth electrode placement may affect verbal memory – do neuropsychological testing 2 mos after implantation (before turning stim on).
- Loring et al. reported that there were no cognitive declines with responsive mesial temporal lobe stimulation and that there were improvements in verbal memory (small in magnitude but statistically

significant) vs. progressive memory decline in nonoperated patients who continue to be treated with AEDs.

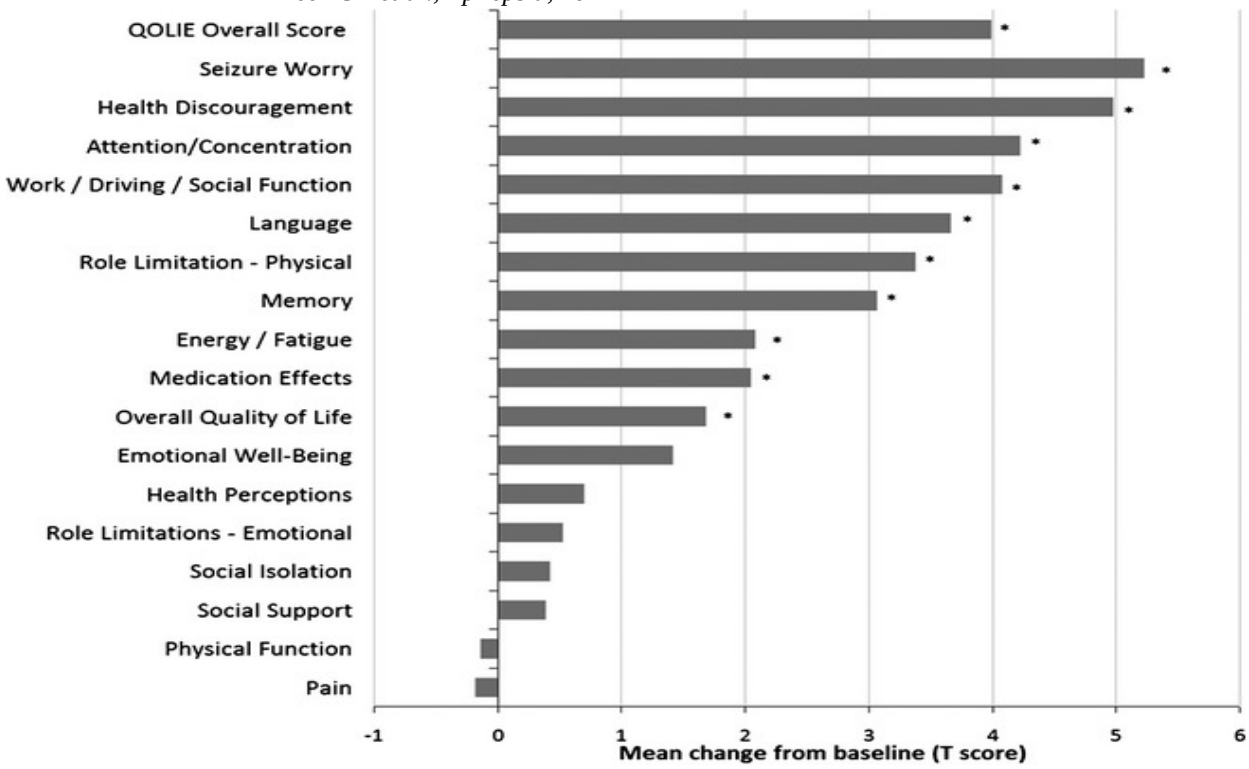
Loring DW et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia 2015;56:1836–1844.

- statistically significant improvements in:
  - **Naming** (BNT; p<0.001)
  - **Verbal learning** (AVLT; p=0.03)
  - **Visual memory** (BVMT-R total recall; p=0.03)
  - **Executive function** [D-KEFS design fluency (p<0.001), WAIS-III Block design (p<0.001); WAIS-III Information (p=0.009)]

QUALITY OF LIFE

- at 2 years of RNS treatment, there were clinically meaningful improvements in overall quality of life (QoL) in 41% of subjects, with only 16% reporting declines.
- Quality of Life Improvements:

Heck CN et al., Epilepsia, 2014



* Indicates significantly different from baseline at p<0.05.

- patients treated with RNS earlier in the course of their epilepsy exhibited significant improvements in multiple mood and quality-of-life measures that were not seen in patients treated later in the course of their disease, despite ***similar efficacy in seizure reduction***

Loring DW, Jarosiewicz B, Meador KJ, et al. Mood and quality of life in patients treated with brain-responsive neurostimulation: the value of earlier intervention. Epilepsy Behav 2021;117:107868.

SEIZURES

N.B. results improve over time!

- after RNS implantation, for 2 months postop seizure frequency may increase.
  Geller 2017. RNS for temporal epilepsy
- RNS uncovered that clinical seizures are only the tip of iceberg.

STUDIES

1. Feasibility Study

- n=65
- open-label
- assessed safety and followed adults over a 3-month preimplantation baseline and a 2-year postimplantation treatment period.

2. Pivotal Study

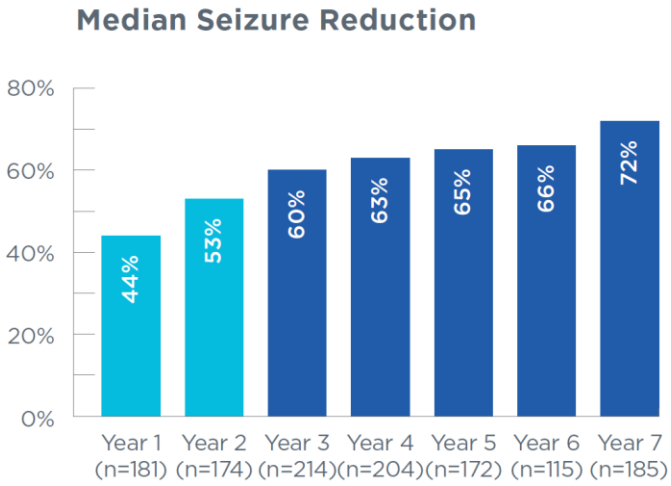
Heck CN, et al. Epilepsia. 2014 Mar;55(3):432-41

- randomized, controlled, double-blinded pivotal trial.
- enrolled adults with medically intractable partial epilepsy and an average of ≥ 3 partial seizures per month.
- n=191
- 3-month baseline was followed by a 1-month postimplantation stabilization period and then by a 4-month blinded period during which subjects were randomized 1:1 to receive active or sham stimulation.
- all subjects received active stimulation in a subsequent open-label period to collect safety and efficacy data to 2 years postimplantation.

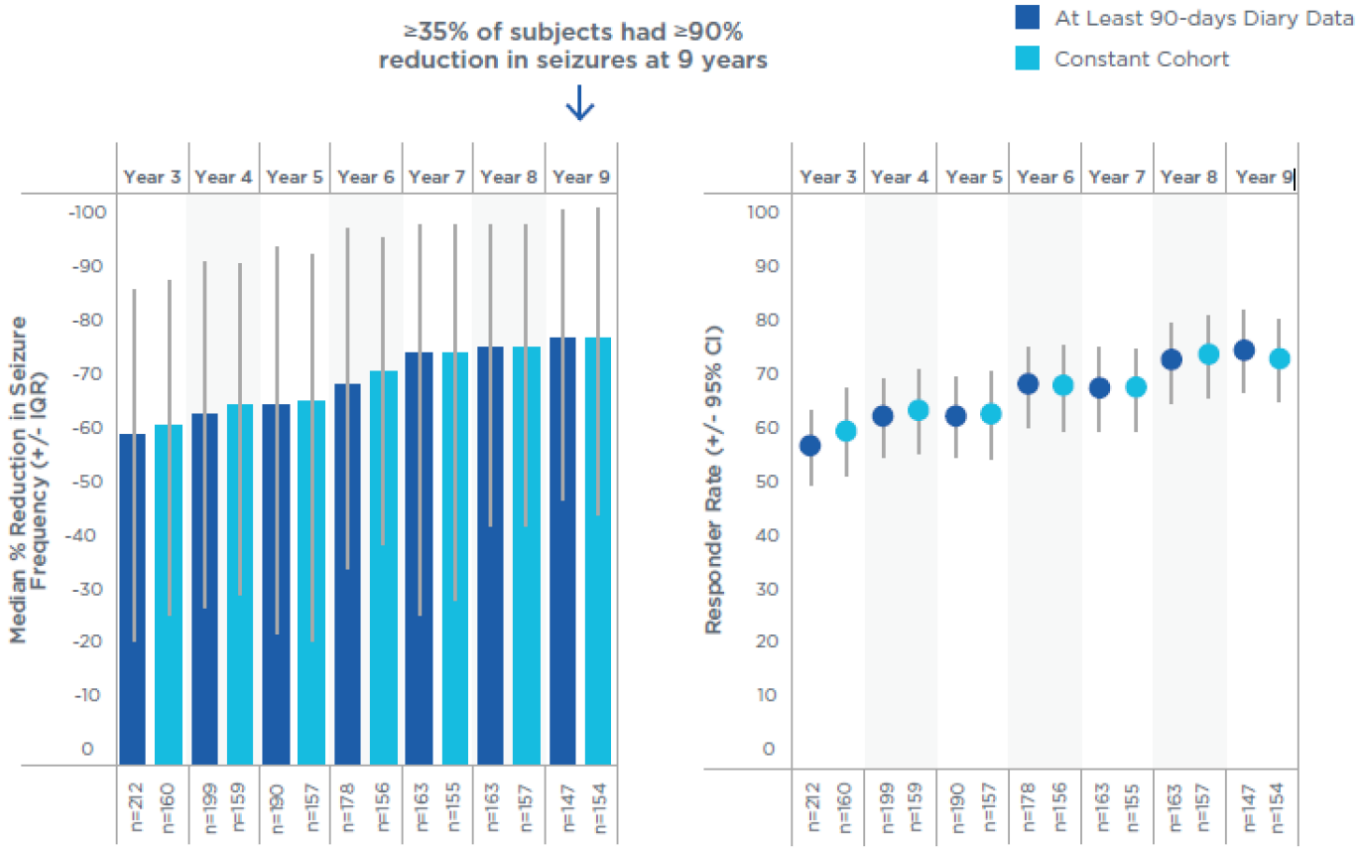
3. Long-term treatment (LTT) trial

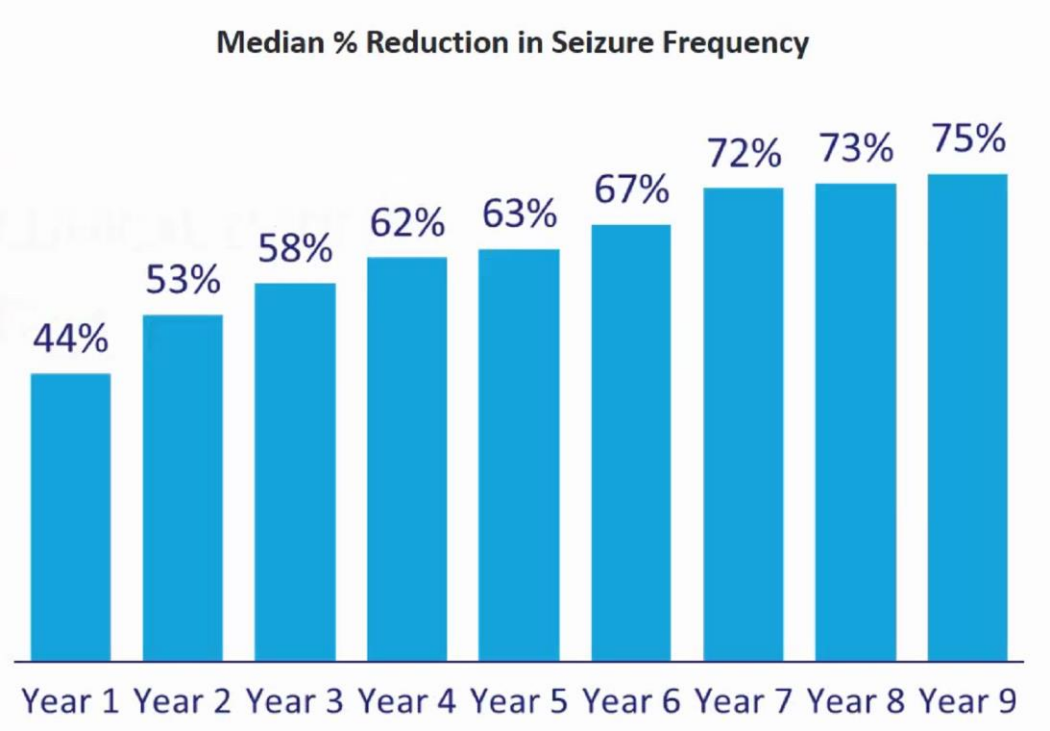
Bergey GK, et al. Neurology. 2015 Feb 24;84(8):810-7
Morrell et al. American Epilepsy Society. December 2016. Houston, TX.

- once subjects completed either the Feasibility or Pivotal study, they could continue in a follow-on Long-term Treatment (LTT) study.
- the study was ongoing as of the data cutoff on November 1, 2014.
- n=256
- <u>at 7 years</u>:
  72% median seizure reduction
  66% responder rate
  at least one seizure-free period lasting:
  ≥ 3 months - 39% of patients
  ≥ 6 months - 29% of patients
  ≥ 1 year - 16% of patients



- at 9 years (1895 patient years):
  75% median seizure reduction (35% of patients with ≥ 90% seizure reduction).
  73% responder rate (≥ 50% seizure reduction)
  at least one seizure-free period lasting:
    ≥ 6 months - 28% of patients
    ≥ 1 year - 18% of patients
  no chronic stimulation-related adverse effects, no adverse cognitive or neuropsychological effects



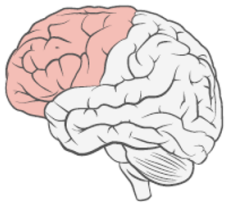


- responder rate:
  - By seizure type
    - CPS 27%
    - GTC 65%
  - By ictal onset
    - Hippocampus 74%
    - Neocortex 37%

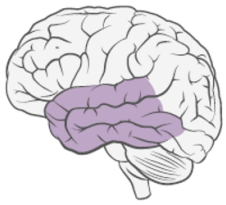
- responder rate by seizure focus:

MESIAL TEMPORAL
Median Change: -70%
Responder Rate: 66%
LOCF n=106

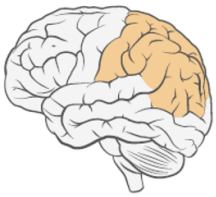
FRONTAL
Median Change: -70%
Responder Rate: 54%
LOCF n=37



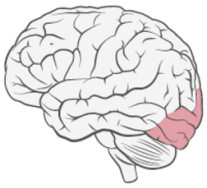
LATERAL TEMPORAL
Median Change: -58%
Responder Rate: 67%
LOCF n=27



PARIETAL
Median Change: -70%
Responder Rate = 58%
LOCF n=12



OCCIPITAL
Individual patient results:
-100%, -100%, -38%, -4%
LOCF n=4

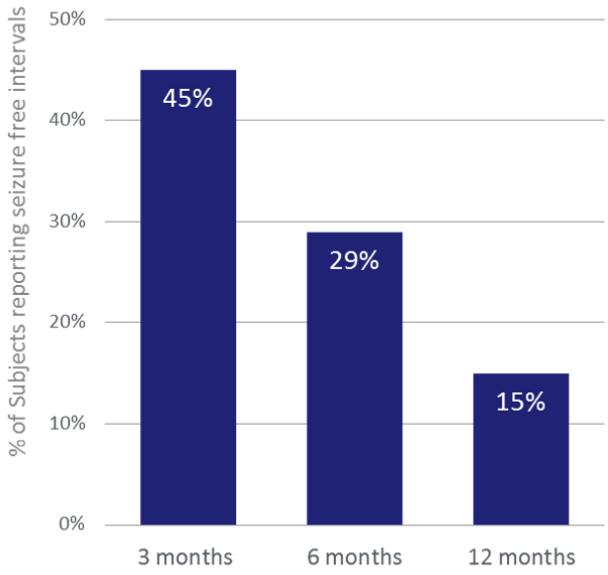


NEOCORTICAL MULTI-LOBAR
Median Change: -51%
Responder Rate: 52%
LOCF n=33

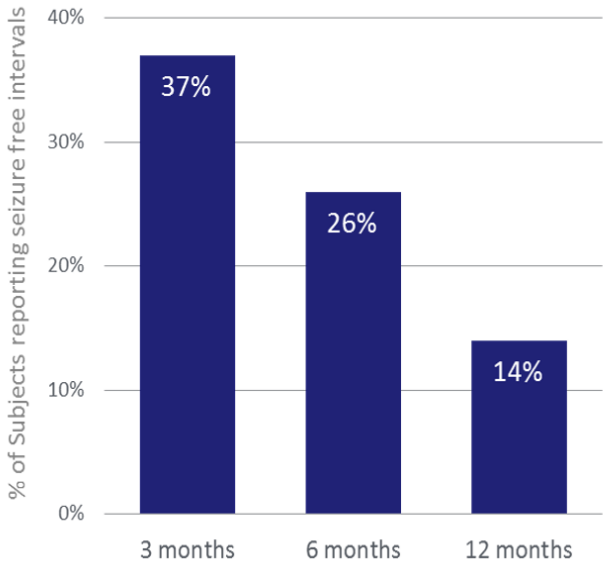
Geller et al., *Epilepsia*, 2017; Jobst et al., *Epilepsia*, 2017

- seizure free periods by onset zone:

Mesial Temporal Patients (n=111)



Neocortical Patients (n=126)



Geller et al., *Epilepsia*, 2017; Jobst et al., *Epilepsia*, 2017

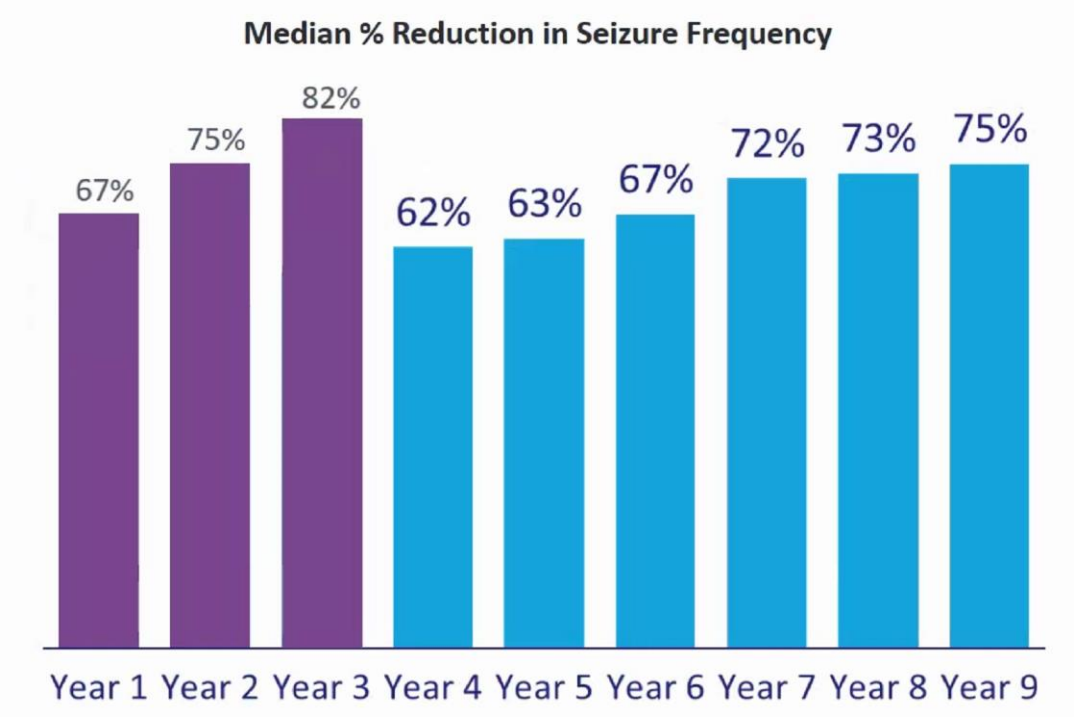
- effectiveness is similar for:
  - all ages and regardless of where the seizures started.
  - subjects with and without mesial temporal sclerosis (MTS), bilateral MTL onsets, prior resection, prior intracranial monitoring, and prior VNS*

*mechanisms by which VNS and RNS act are likely quite different, suggesting that a failure to respond to one does not predict response to the other.

4. Postmarketing studies (Post-approval study, Real-world study)

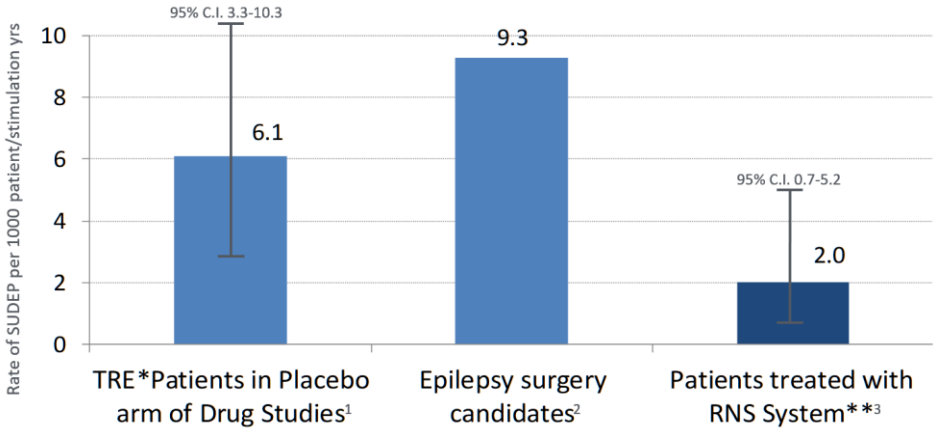
Did improvements in RNS therapy has accelerated in the field's post-marketing experience? The answer appears to be yes:

N.B. year 6 efficacy (of long-term study) achieved at year 1, year 9 efficacy – at year 2, superior efficacy at year 3



SUDEP

- SUDEP rate **decreased at least 3-fold** (2-3 per 1000 patient-years), compared with the expected rate in the DRE population (9 per 1000 patient-years).



Devinsky et al., Epilepsia. 2018: 1-7

*TRE = Treatment Resistant Epilepsy

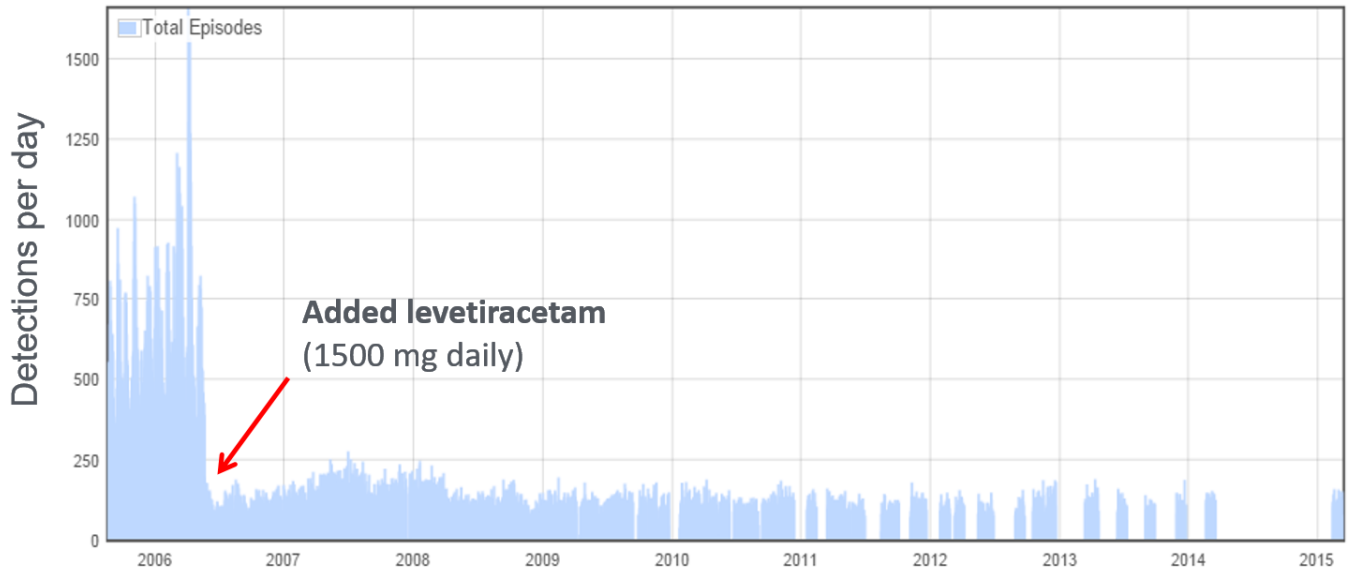
**RNS System data represents SUDEP rate per 1000 stimulation years.

[1] Ryvlin P, Cucherat M, Rheims S; Lancet Neurol. 2011; 10:961–8.

[2] Dasheiff, R.M., 1991. J Clin Neurophysiol 8, 216–222.
[3] Devinsky O, Friedman D, et al. Epilepsia. 2018; 1-7.

MEDICAL TREATMENT MONITORING

- typically, it takes many months to know whether a new AED will improve seizure control.
- electrographic data recorded by the RNS may be used to assess whether a new AED is likely to improve seizure frequency in as early as one month.



Clinical and electrocorticographic response to AED with RNS (correlations between device data and clinical seizure frequency)

Tara L. Skarpaas, Thomas K. Tcheng, Martha J. Morrell. Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation. Epilepsy & Behavior 83 (2018) 192–200

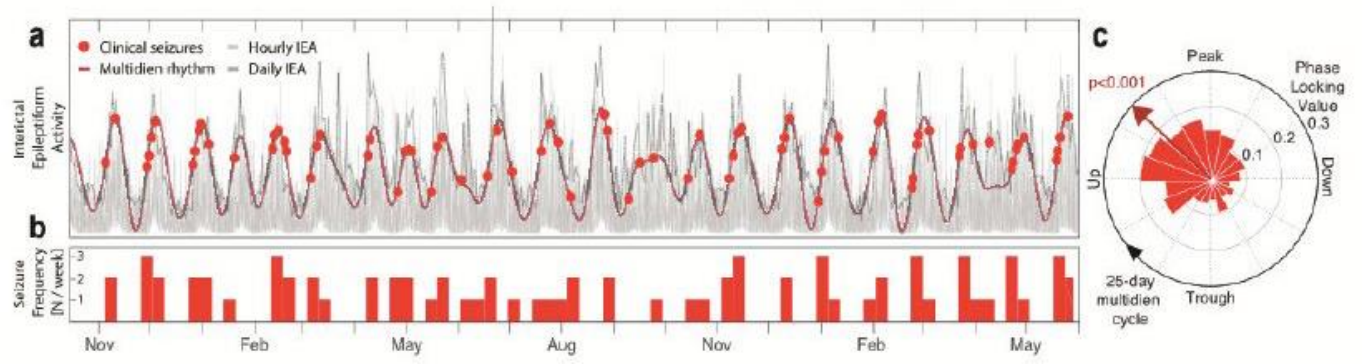
- in patients with RNS, adding clobazam or levetiracetam gave higher clinical benefit (seizure reduction) than starting lacosamide or pregabalin – that correlated with change in interictal spike rate.

SEIZURE PREDICTION

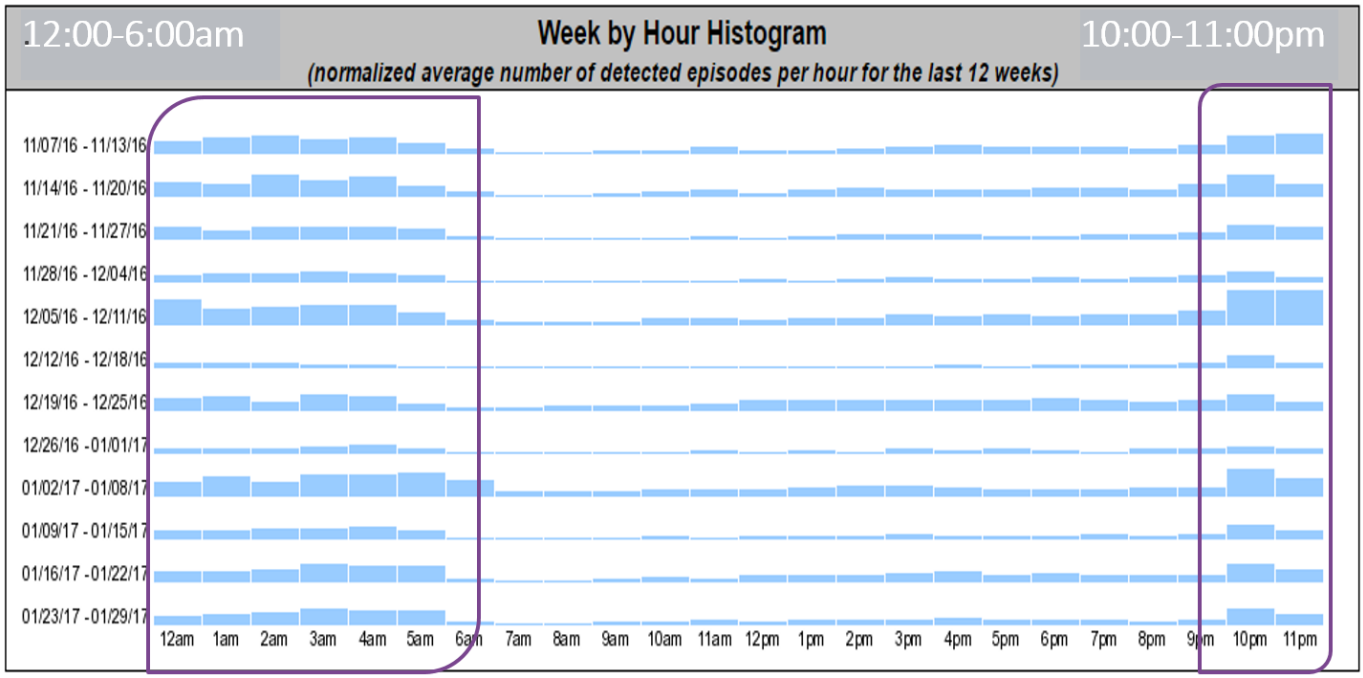
Clinical seizures cluster in relation to cycles of interictal epileptiform activity Maxime Baud, Thomas Tcheng, Vikram Rao

- epilepsy is a cyclical disorder.
- using chronic ECoG from RNS and clinical seizure diary reports, interictal epileptiform activity (IEA) cycles were analyzed for 16 patients - all patients were found to have circadian and multi-day ("multidien") IEA cycles with periodicities ranging from 7 to 33 days.
- an emerging view suggests seizures are not random events, and it may be possible to forecast clinical seizure risk on the scale of days with data obtained from the RNS.

12 months of RNS data from 1 patient – significant phase locking (clinical seizures occur in upward peak of IEAs):



Spencer et al. report circadian or ultradian patterns in 98% of subjects; data from 1 patient:



Spencer, Epilepsia, 2016.

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" → follow this LINK