Neuro-Modulation in Epilepsy

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Cleveland Clinic

Disclosures

Grant/Research Support:

- NIH RO1 (RO1NS089212) A Brain Atlas for Mapping Connectivity in Focal Epilepsy
- NIH RO1 (RNS097719A) Nomogram to Predict Seizure Outcome
- NeuroPace Long term Treatment Trial
- NeuroPace Post Approval Study
- Brain Sentinel

Speaker's Bureau:

NeuroPace, Inc.

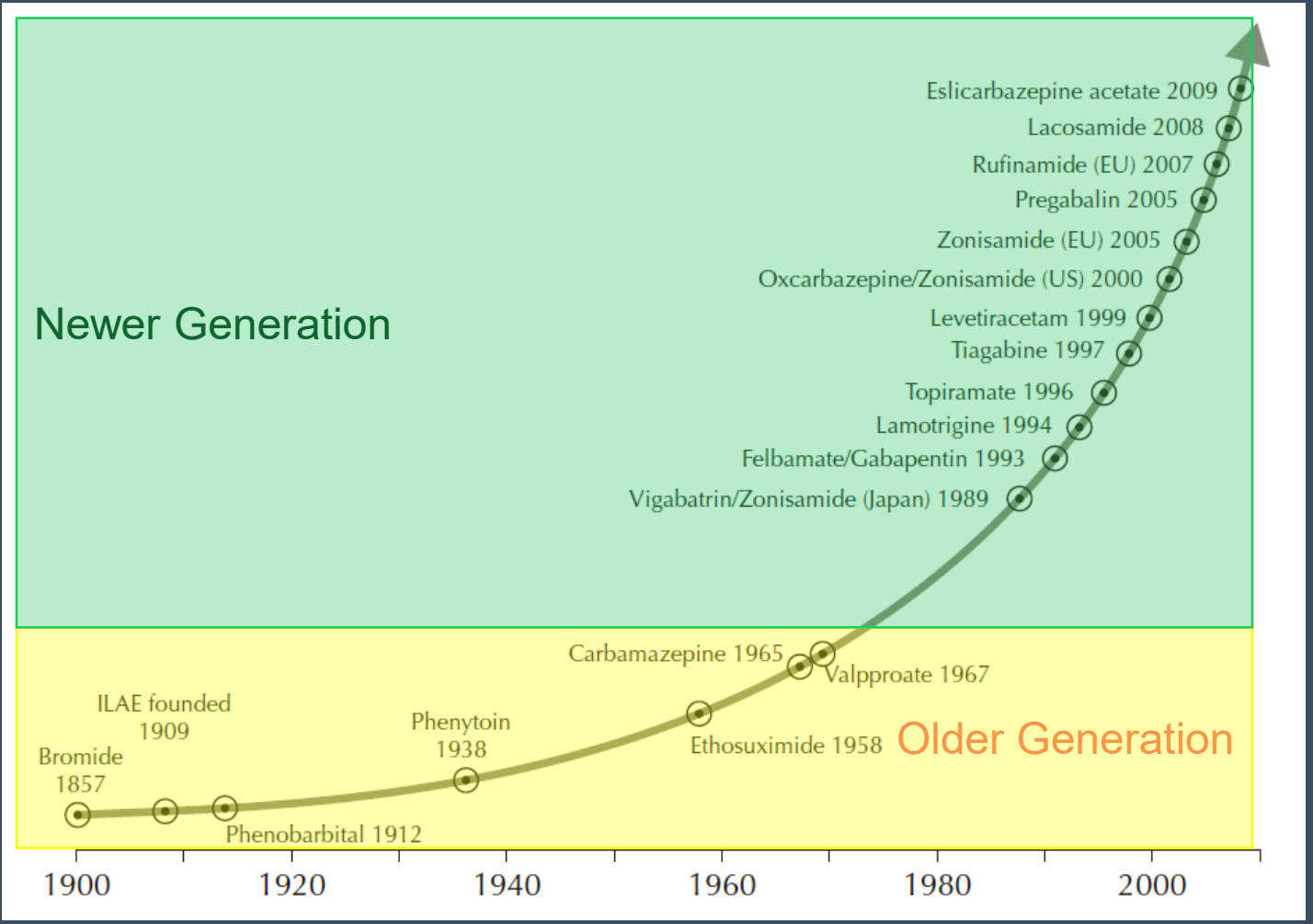
Consultant:

NeuroPace, Inc.

Major Shareholder:

None

Development & Evolution of Anti-Seizure Medications



Arzimanoglu A et al. Epileptic Disorders 2010

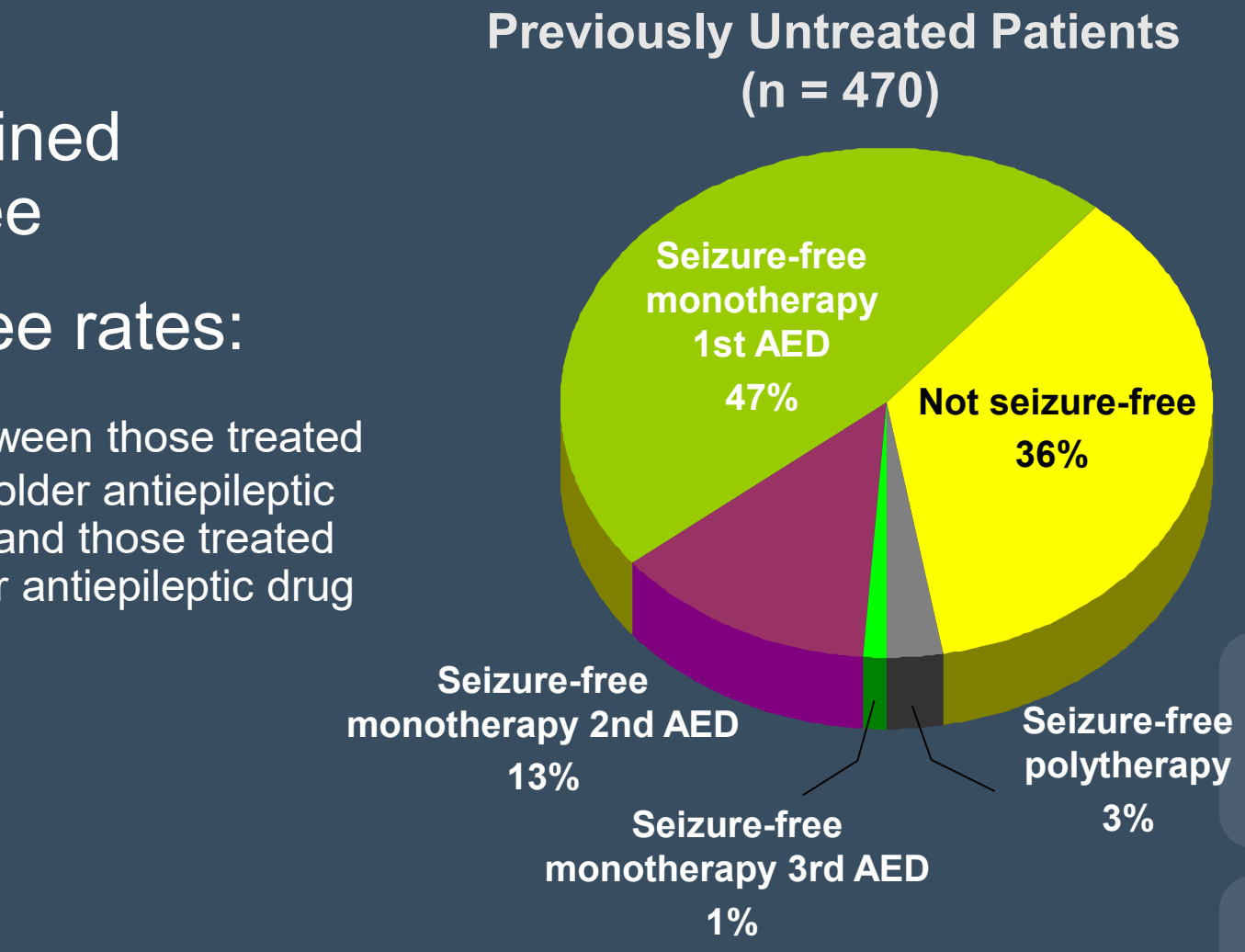
ILAE Definition of Drug-Resistant Epilepsy

- The failure of two appropriately chosen and tolerated AEDs (whether as monotherapies or in combination) to control seizures when used for an adequate period of time
- Defining the terms
  - Appropriateness:
    - Treatment should be proven (ideally in an RCT) to be effective for the patient's epilepsy and seizure type
    - Treatment used at adequate strength/dosage for a sufficient length of time
  - Tolerability:
    - Failure can not be assumed by tolerability by itself
  - Seizure outcome:
    - Categorized as seizure free, treatment failure, or undetermined
    - No seizures including auras for at least three times the longest pre-intervention inter-seizure interval or 12 months or longer, with any other outcome considered a treatment failure

Kwan P, et al. *Epilepsia* 2009

Seizure Free Rates Antiepileptic Drug Regimens

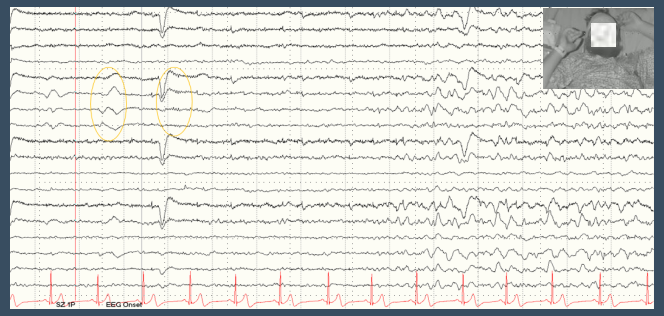
- 63% remained seizure-free
- Seizure-free rates:
  - Similar between those treated with single older antiepileptic drug (67%) and those treated with a newer antiepileptic drug (69%)



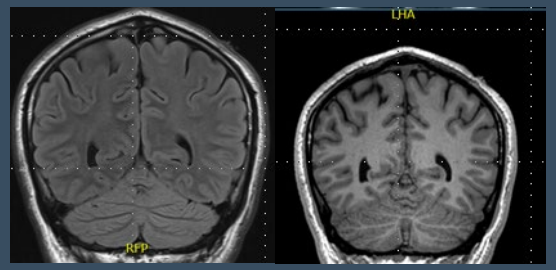
Kwan P, Brodie MJ. N Engl J Med. 2000;342:314-319.

Pre-surgical Evaluation

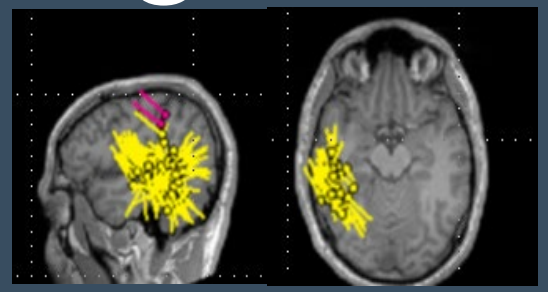
Epilepsy Center



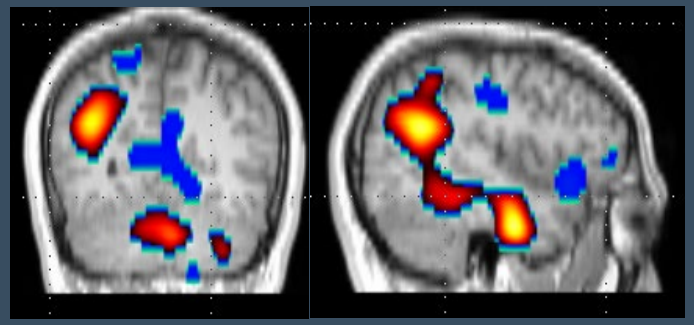
Video-EEG Monitoring



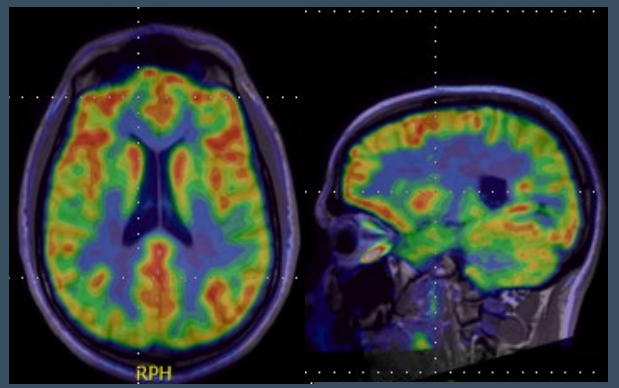
MRI Scan



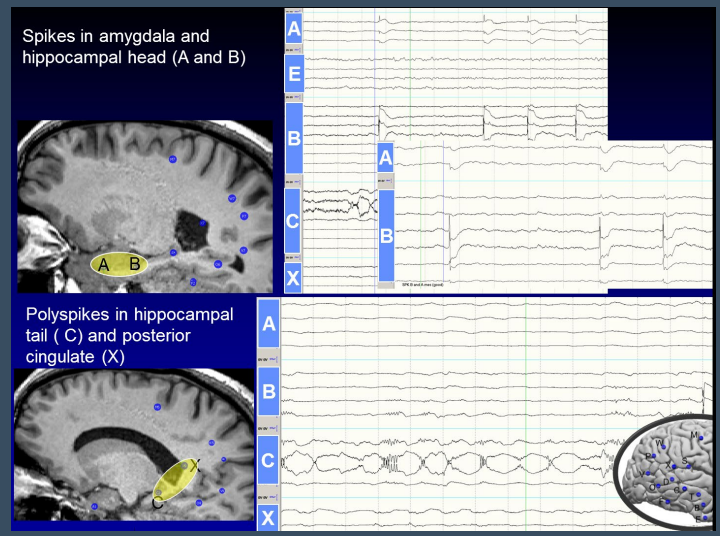
MEG



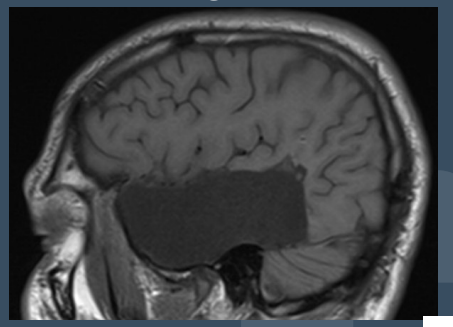
Ictal SPECT



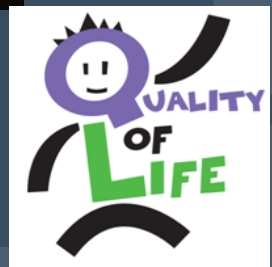
PET



Intracranial Recordings



Epilepsy Surgery



Epilepsy Surgery

Indications

- Medical intractability
- Tailored to the individual
- Concordance
  - Discrete MRI lesion
  - EEG and semiology
- Lack of concordance
  - More sophisticated pre-op testing
    - Ictal SPECT/PET/MEG
    - VBM/qPET
    - SEEG/Subdural/Depth

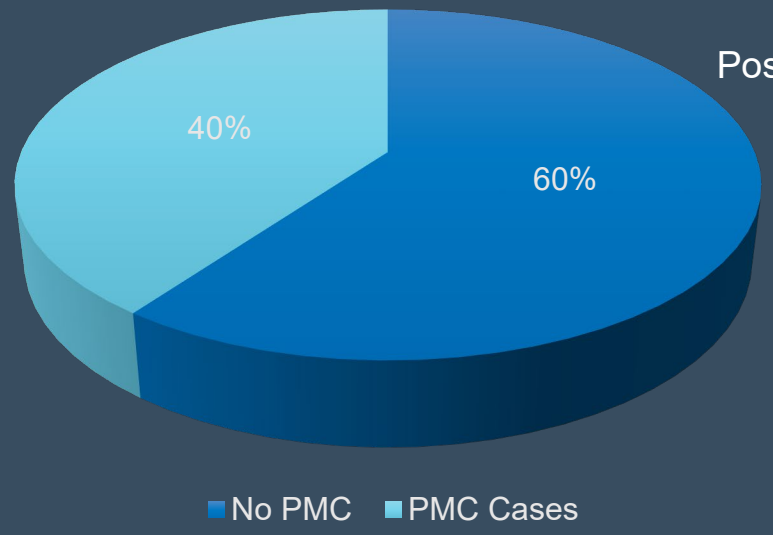
Contra-Indications

- Multiple seizure foci
- Poor localization
- Epileptic focus overlaps with eloquent cortex
- Medical conditions affecting tolerability of surgery

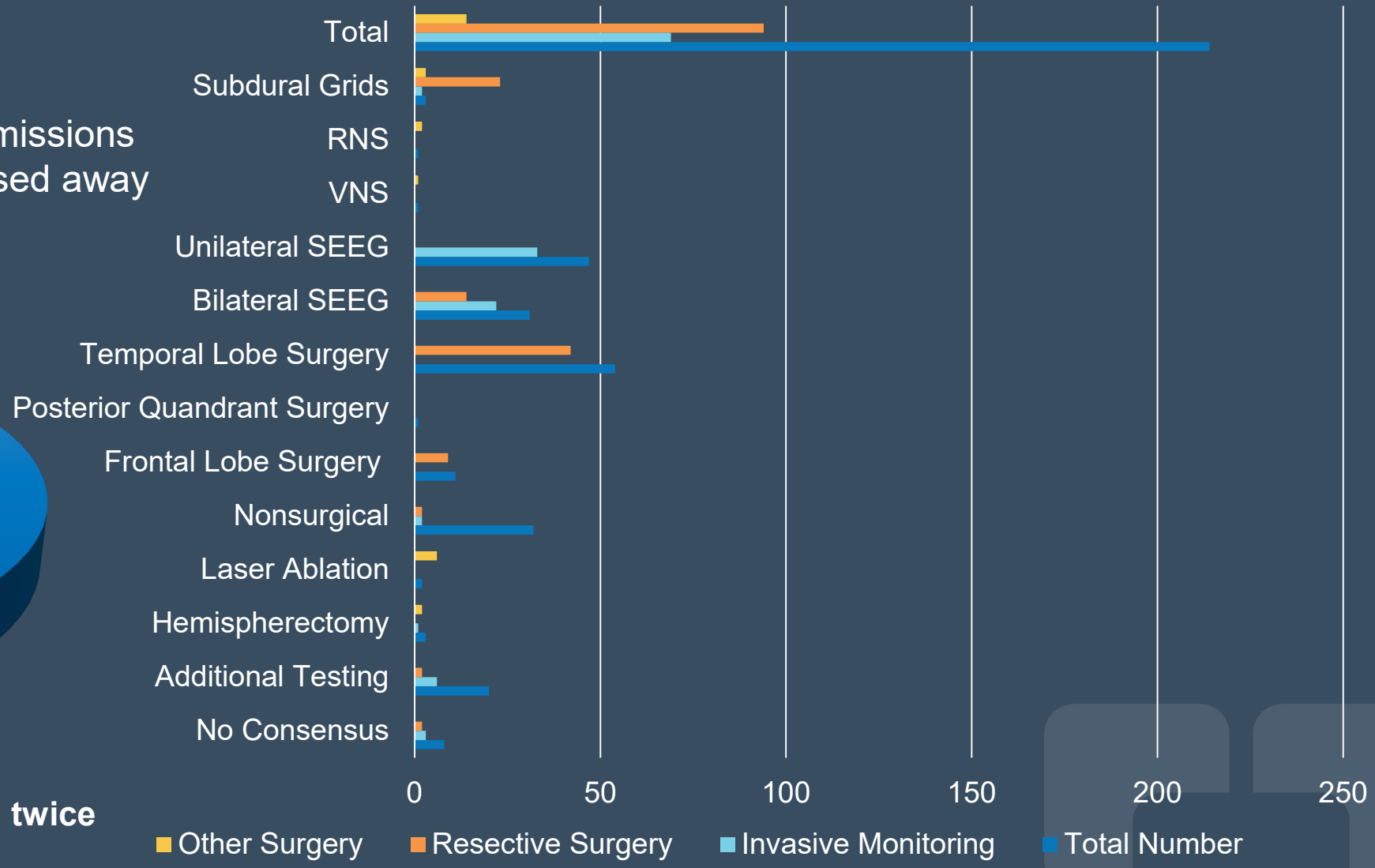
West S et al. Cochrane Database Syst Rev 2015

Cleveland Clinic Epilepsy Center 2017 Patient Management Discussions and Decisions

- 606 Total EMU Admissions
  - 52 patient with multiple admissions
- 15 patiented admitted who passed away



Total = 548 – 3 patient presented twice



Of 214 patients with surgical recommendations: 105 underwent either a resective or ablative surgery

Neuro-modulation in Epilepsy

- Vagus Nerve Stimulation
- Responsive Neurostimulation
- Deep Brain Stimulation

Neuromodulation

* FDA Approved Devices

Targets for Stimulation

- Cerebellum
- Hippocampus
- Subthalamic Nucleus
- Caudate Nucleus
- CentroMedian Nucleus
- Anterior Nucleus of the Thalamus*
- Various individualized cortical sites*
- Vagus Nerve*
- Trigeminal Nerve (External)

Types of Stimulation

- Open Loop vs Closed Loop
- Electrical vs Magnetic
- Invasive vs Noninvasive

Safety of Stimulation

- **Electrical stimulation of brain tissue**
  - **Less than 30μC/cm^2/phase**

Lin Y et al. Epilepsia Open 2017

Nune G et al. Curr Treat Opions Neurol 2012

Neuro-Modulation

Versus Medicine/Surgery

- Lack typical systemic or neurological sided effects
- Stimulation related side effects
  - Intracranial stimulation
  - VNS stimulation
- Surgically implanted
  - Surgical complications
  - Battery replacement
  - Less invasive
  - Reversible

Versus Medicine/Surgery

- Improvement of efficacy over time

Nune G et al. Curr Treat Opions Neurol 2012

Comparators: VNS, DBS & RNS

Similarities

- Parameters of Stimulation
  - Anode/Cathode contacts
  - Stimulation Frequency
  - Stimulation Duration
  - Stimulation Intensity
  - Stimulation Field
  - Pulse Duration

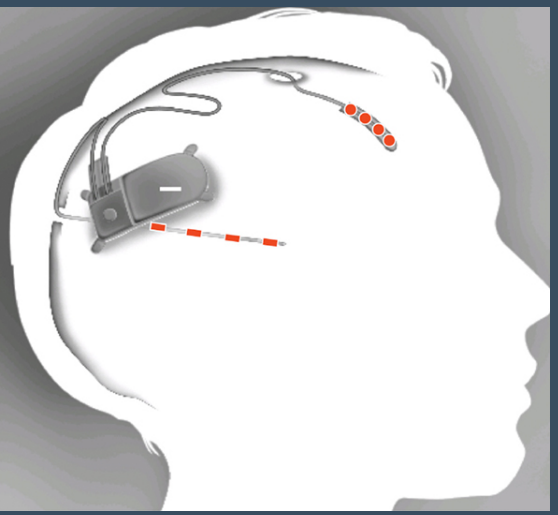
Differences

- Open vs Closed Loop
  - VNS (open) – heart rate feature
  - DBS (open)
  - RNS (closed)
- Magnets
  - Initiates stimulation –VNS
  - Initiates a storage of ECoG – RNS
- Stimulation
  - Determined by detection of ECoG pattern – RNS
  - Determined by ON time- VNS & DBS
- Placement of electrodes and device

Responsive Neural Stimulation (RNS)

Responsive Neural Stimulation

- Medically refractory focal epilepsy
  - 18 years or older
- FDA approved 2013
- Implantation
  - Device within the skull
  - Combination of 1-2 depths or subdural strips over seizure focus



- Closed loop
- Stimulation usually does not cause appreciable symptoms
- Stores ECoG
- Seizure detections algorithms programmed

Nune G et al. Curr Treat Opions Neurol 2012

RNS Stimulation Parameters

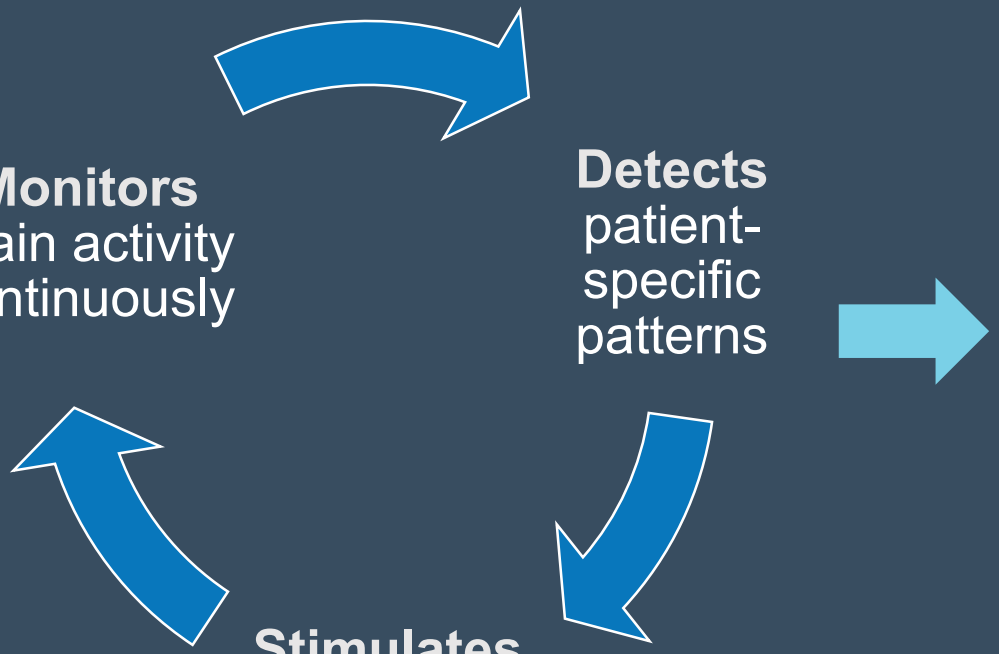
- Five sequential stimulations
  - Rapid succession
  - Each two bursts
- Starting 1mA
  - Adjust up to 3μC/cm^2/phase
- Pulse width 160μs
- Frequency 200 Hz
- Burst duration 100ms

- Polarity of electrodes can be configured
  - Close bipolar within electrode (+-+- and +-+-)
  - Wide bipolar across electrode (+++ and ----)
  - From electrode to generator cover

Nune G et al. Curr Treat Opions Neurol 2012

The RNS® System

The First Closed-Loop, Brain-Responsive Neurostimulation System



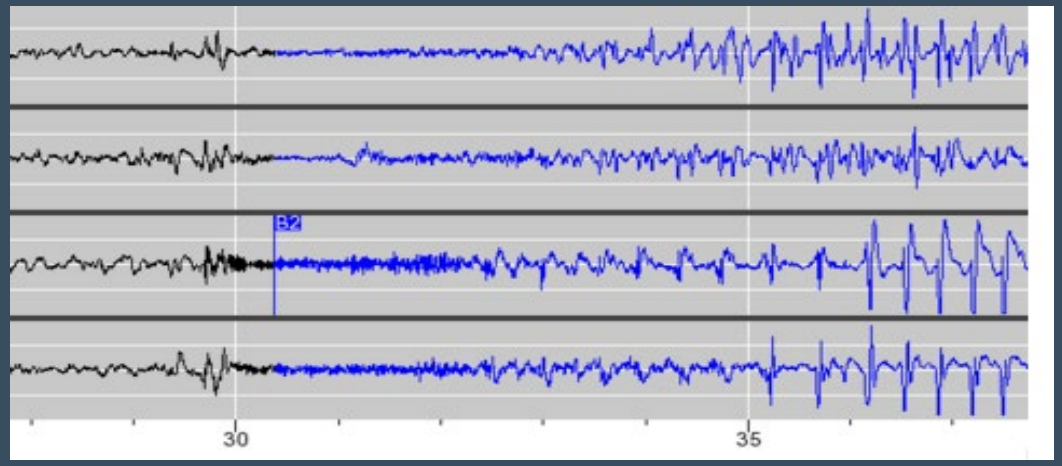
Records

- Frequency, timing, and location of electrographic activity
- Over months/years in a naturalistic setting

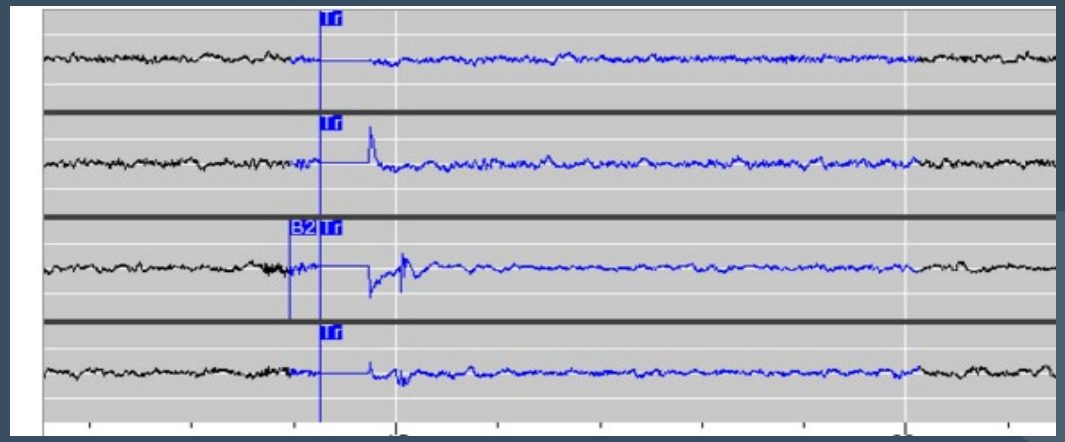
Responsive Neurostimulation

Personalized for each individual's seizure fingerprint

Step 1: Detection
Physician identifies and programs neurostimulator to detect patient-specific electrocorticographic patterns.

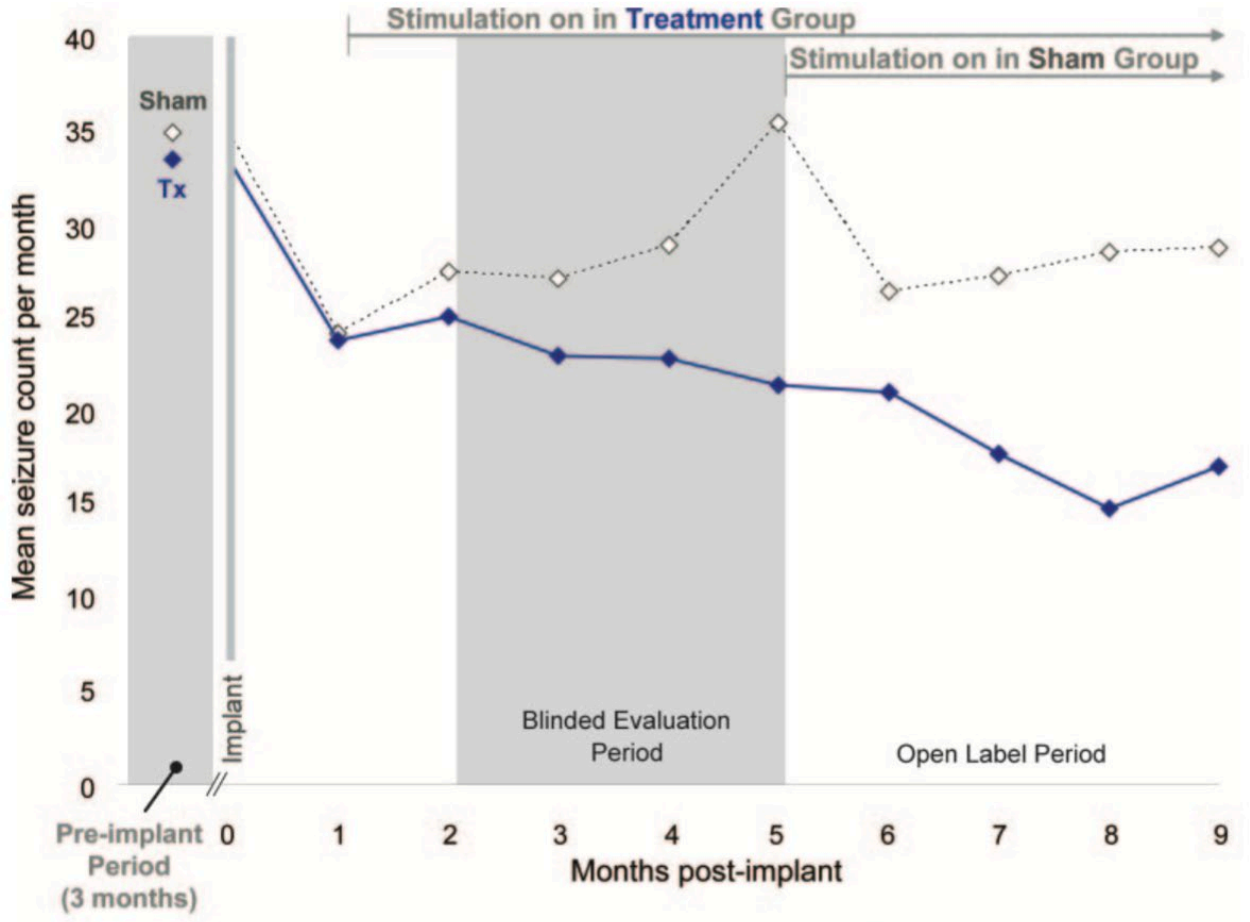


Step 2: Stimulation
Physician programs device to automatically stimulate in response to specific patterns, with the goal of preventing a clinical seizure.



Pivotal Study: Mean Disabling Seizures

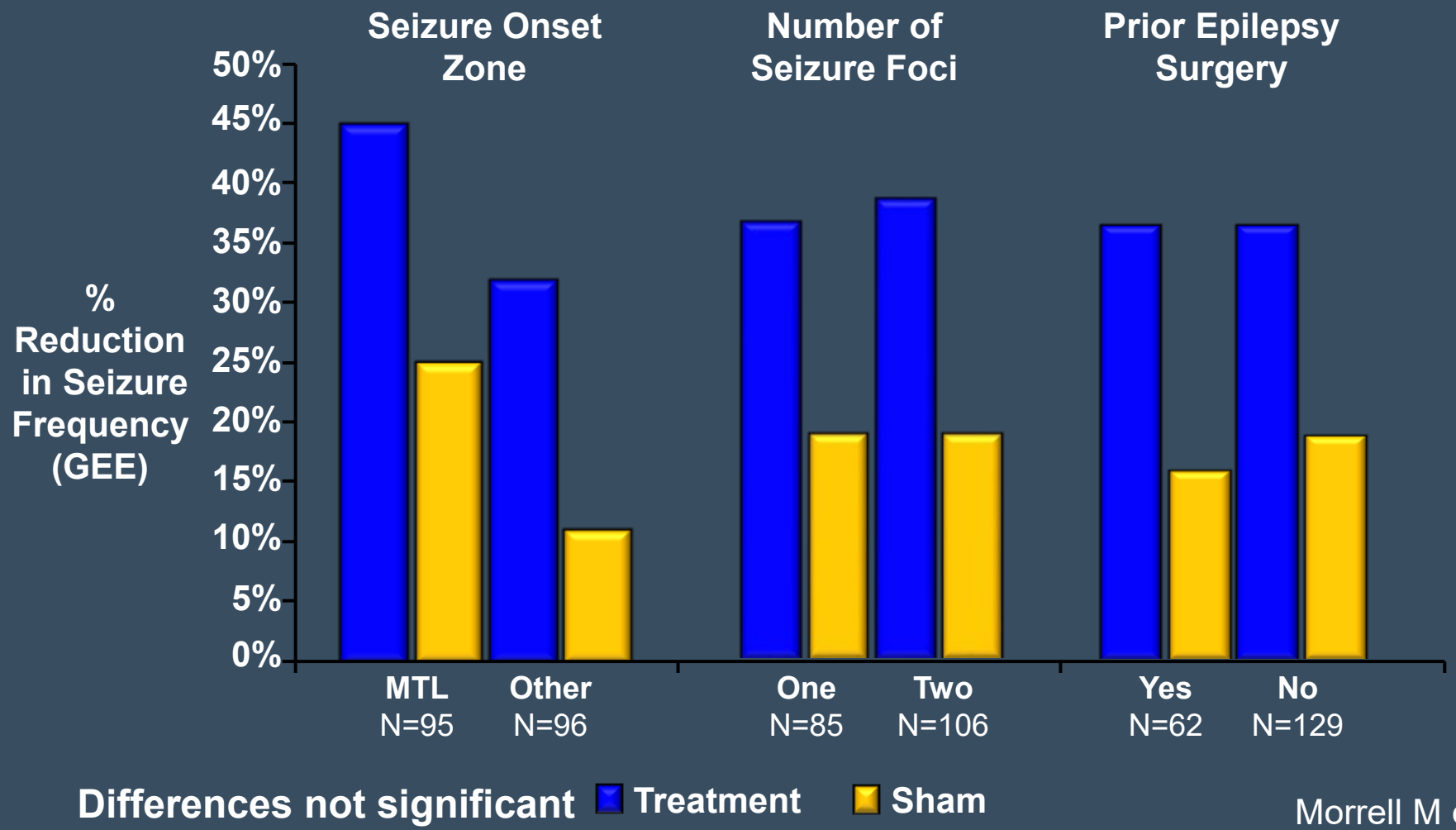
Figure 2 Mean disabling seizures by month, observed data



Treatment	n=97	96	96	96	95	95	94	95	93	93
Sham	n=94	94	93	93	90	91	91	91	89	88

Morrell M et al. Neurology 2011

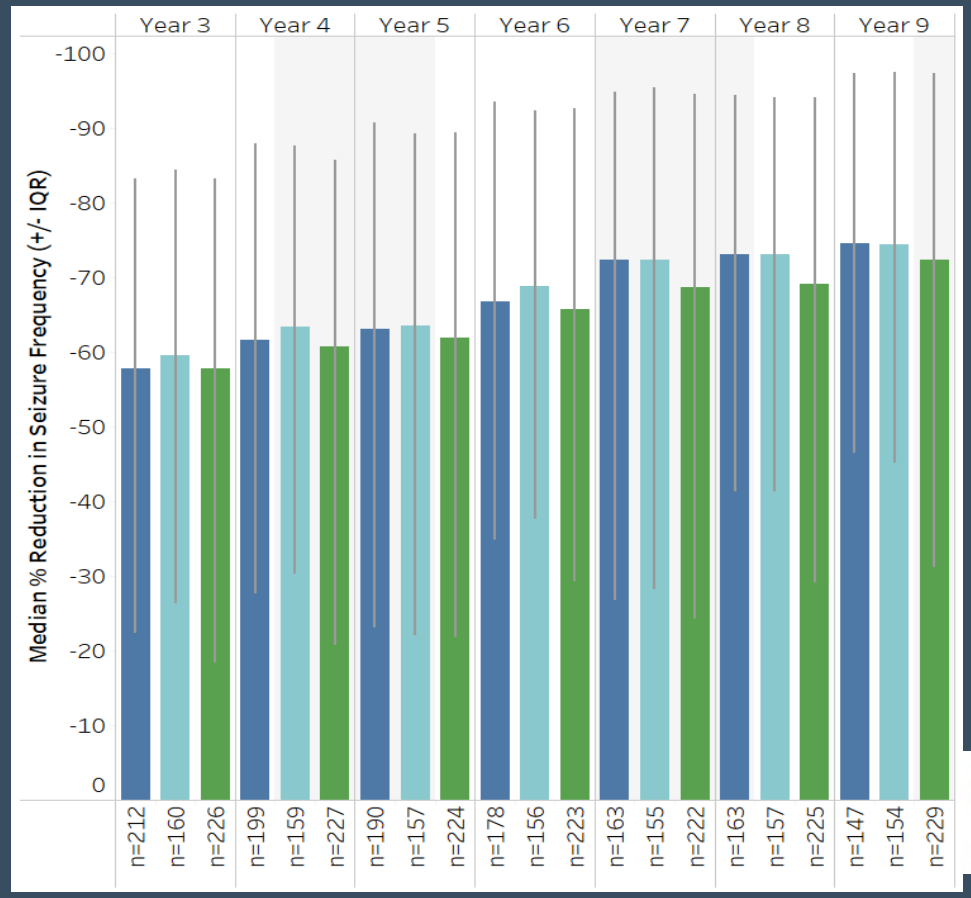
Pre-specified Subset Analyses (Randomization Characteristics)



Morrell M et al. Neurology 2011

Prospective Outcomes at Year 9

75% median seizure reduction at year 9



73% achieved ≥50% seizure reduction at year 9

35% achieved ≥90% seizure reduction in most recent 6 months

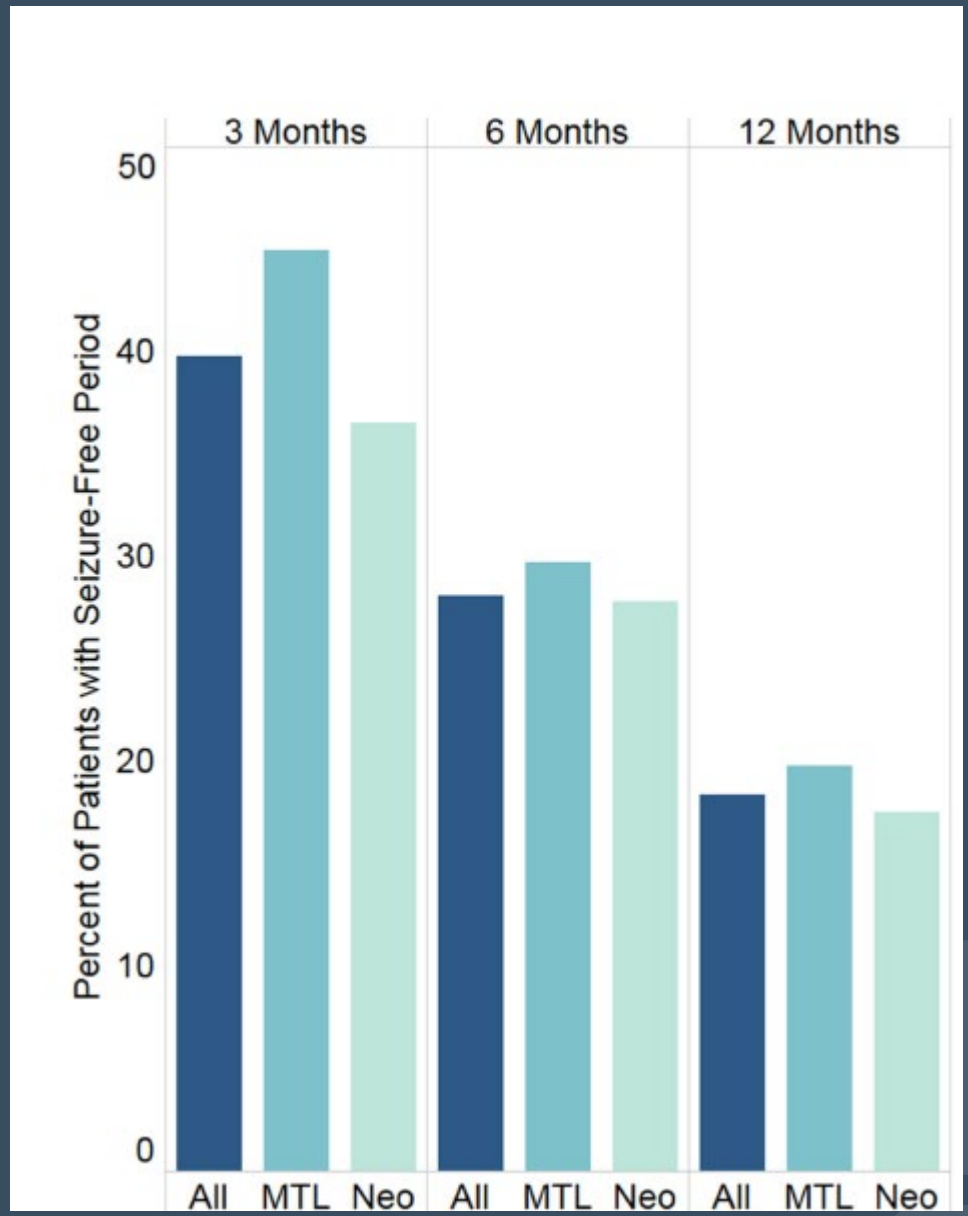
28% had at least 1 period of ≥6 months without seizures

Long-Term Treatment Trial was not powered to drive conclusions of clinical significance.

Nair et al., *submitted*

Seizure Freedom

- Approximately 1 in 4 patients (28%) had at least 1 seizure-free period of ≥ 6 months
- Approximately 1 in 6 patients (18%) had at least 1 seizure-free period of ≥ 1 year



Nair et al., *submitted*

Neuropsychological Benefits

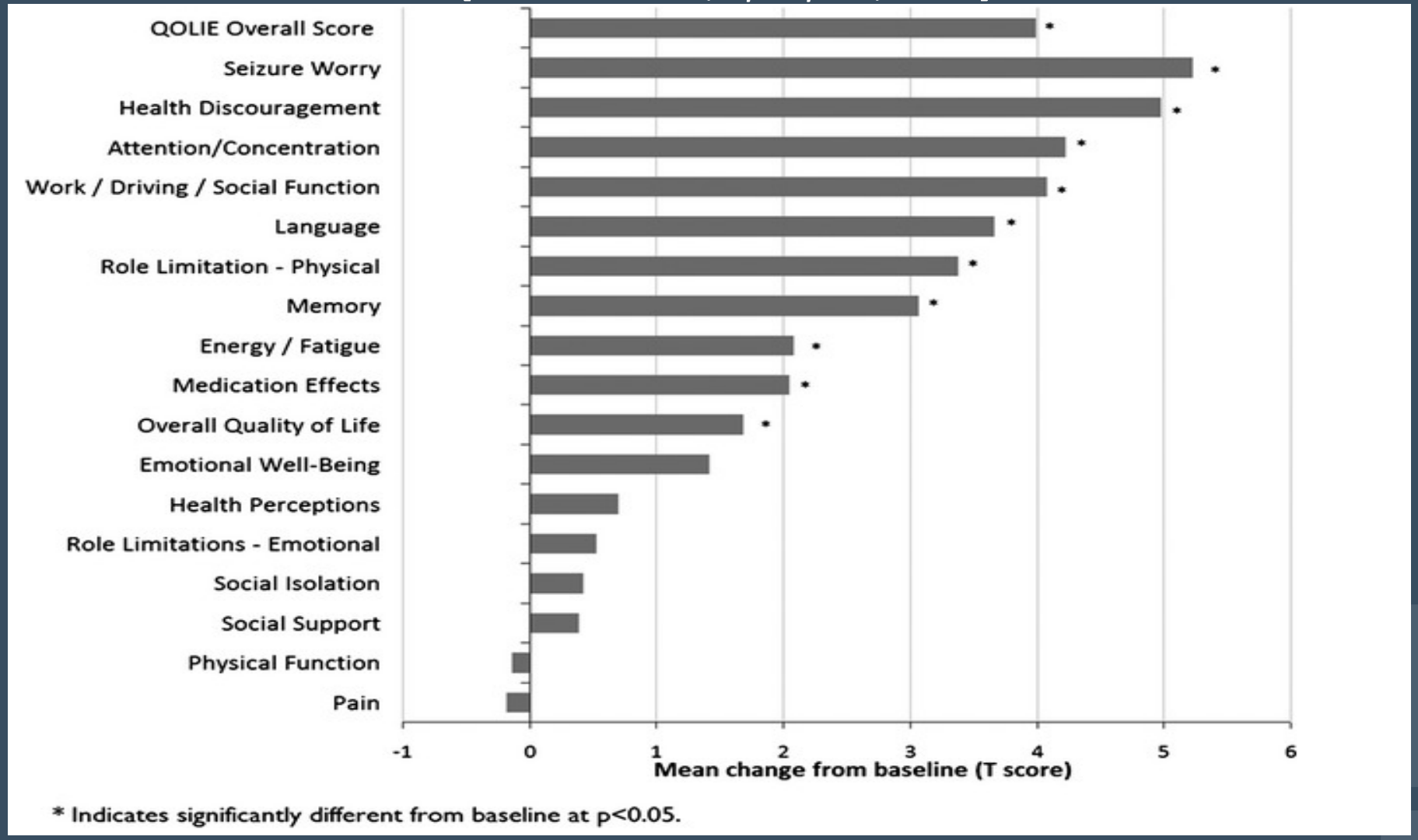
[Loring DW et al., *Epilepsia*, 2015]

- No group decline on any of 14 objective neuropsychological measures after blinded period or at 1 and 2 years (n=175)
- Statistically significant [1] 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 ($p=0.009$)]

[1] GEE

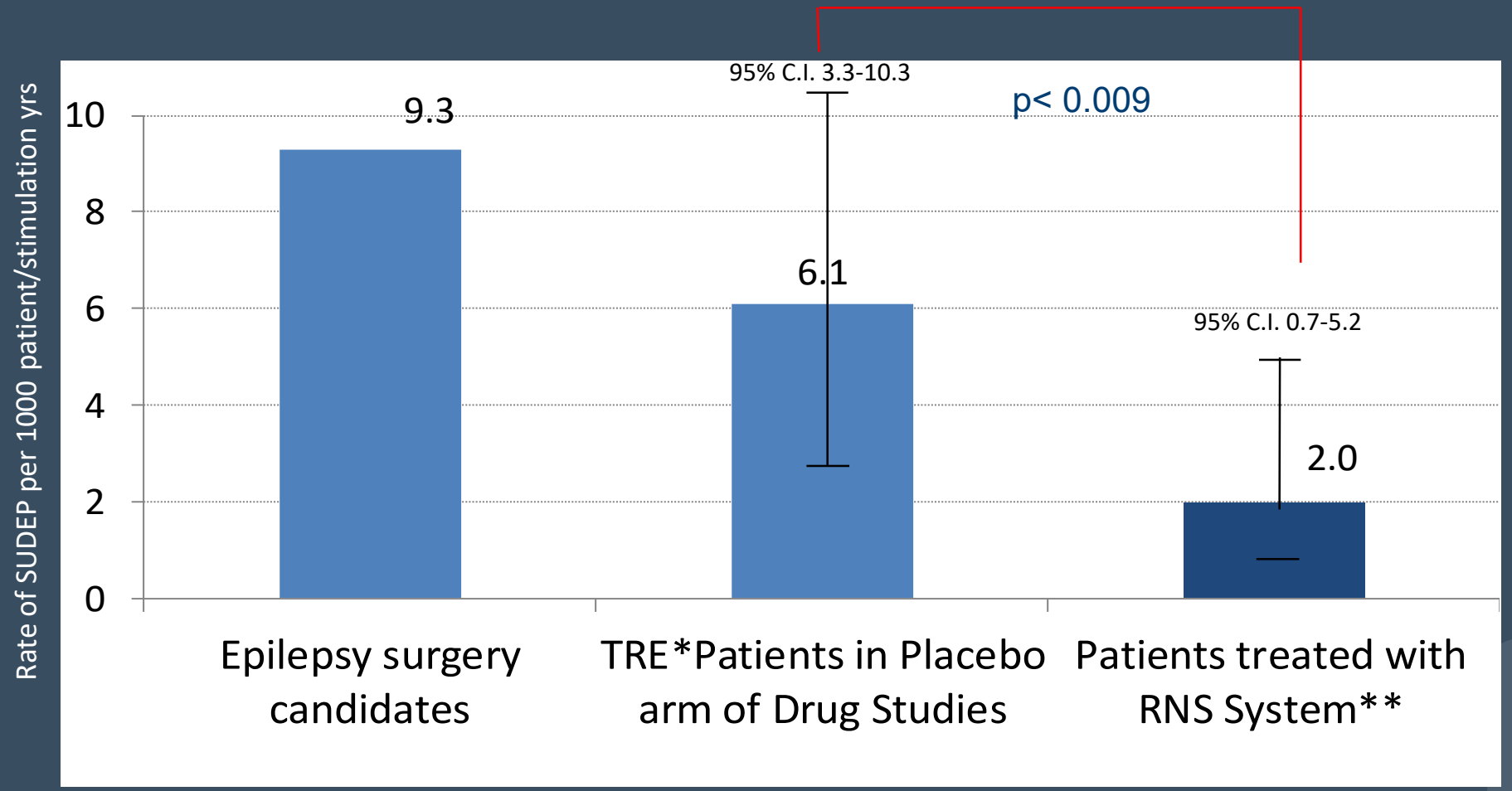
Quality of Life Improvements

[Heck CN et al., *Epilepsia*, 2014]



Outcomes reported at 2 years, n=191

Statistically significant reduction in SUDEP in patients treated with the RNS System



*TRE = Treatment Resistant Epilepsy

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

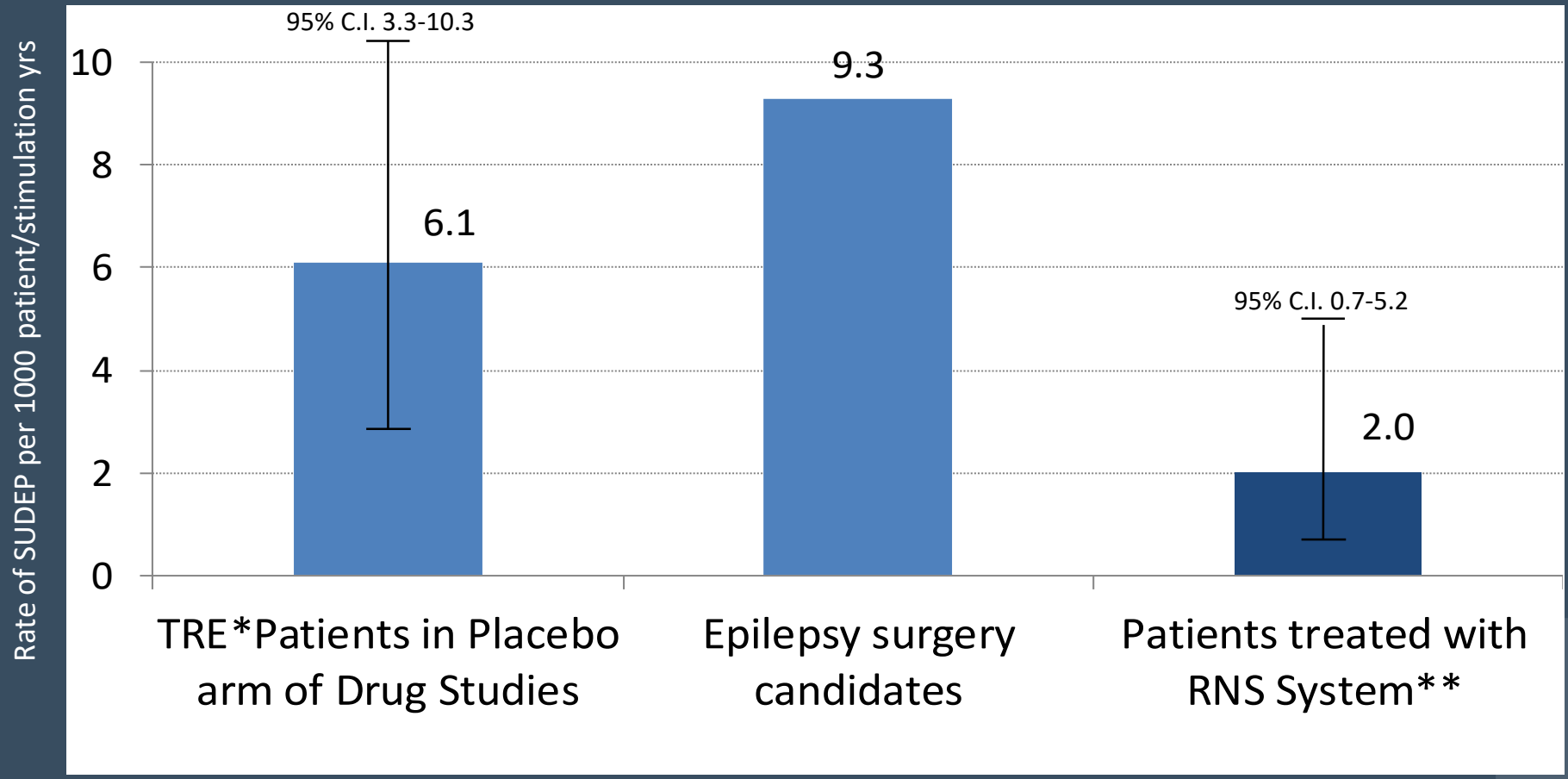
[1] Ryvlin P, Cucherat M, Rheims S; Lancet Neurol 2011; 10:961–8.

[2] Dasheiff, R.M., 1991. J Clin Neurophysiol 8, 216–222.

[3] Devinsky O, Friedman D, et al. Epilepsia. 2018; 1-7.

SUDEP Rates

[Devinsky et al., *Epilepsia. 2018: 1-7*]



*TRE = Treatment Resistant Epilepsy

**RNS System data represents SUDEP rate per 1000 stimulation years for the combined clinical trial and post-trial real-world experience.

[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.

Long-term Safety

- Clinical trial experience represents 256 patients with >1,895 implant years
- Safety outcomes from prospective clinical trials
  - No adverse cognitive effects[1]
  - No adverse mood effects[2]
  - No chronic stimulation side effects[3]
  - Rate of serious adverse events comparable to that of deep brain stimulation for movement disorders and epilepsy.[4,5]†
  - Device-related hemorrhage in 3.5% of subjects[6‡]
- Infection risk 4.1% per neurostimulator procedure

1. Loring DW, et al, *Epilepsia*, 2015
2. Meador K, et al, *Epilepsy Behav,* 2015
3. Heck, CN, et al, *Epilepsia*. 2014
4. Morrell, MJ, et al, *Epilepsia*, 2011
5. Salanova V, et al, *Neurology,* 2015
6. Bergey, GK, et al, *Neurology*, 2015

† Based on device related SAEs
‡ Not seizure related

Nair et al., *submitted*

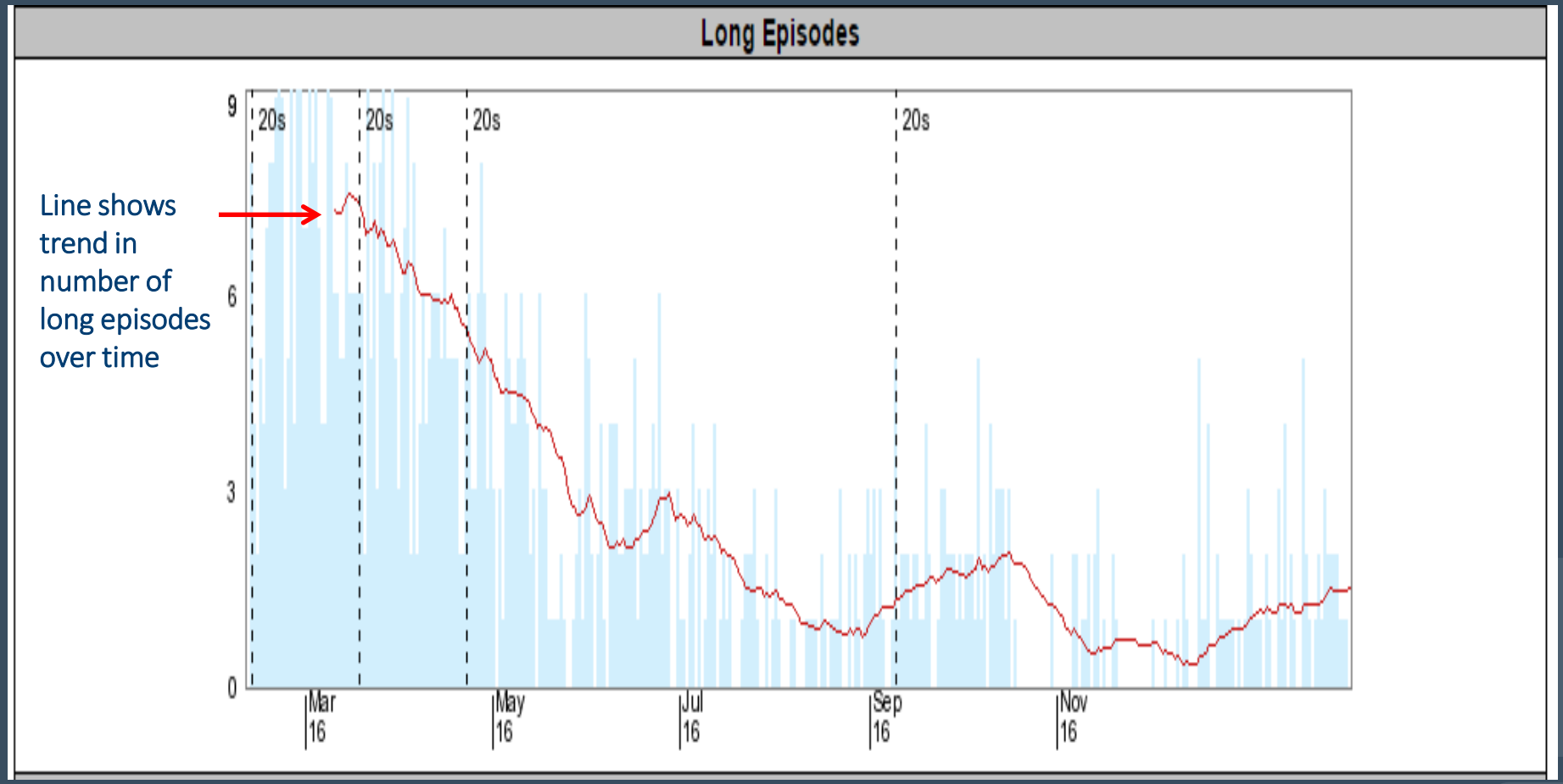
Conclusions

- Safe and effective over 9 years of prospective follow-up
- Efficacy reaches 75% at 9 years; similar in all brain regions
- Candidates for the RNS System include patients with:
  - Bilateral mesial temporal onsets
  - Unilateral mesial temporal onset with risks to memory or language with resection
  - Onset in eloquent (functional) cortex
  - Suboptimal response to VNS or epilepsy surgery
- Ongoing post-approval study will provide additional prospective safety and effectiveness data in 300 patients

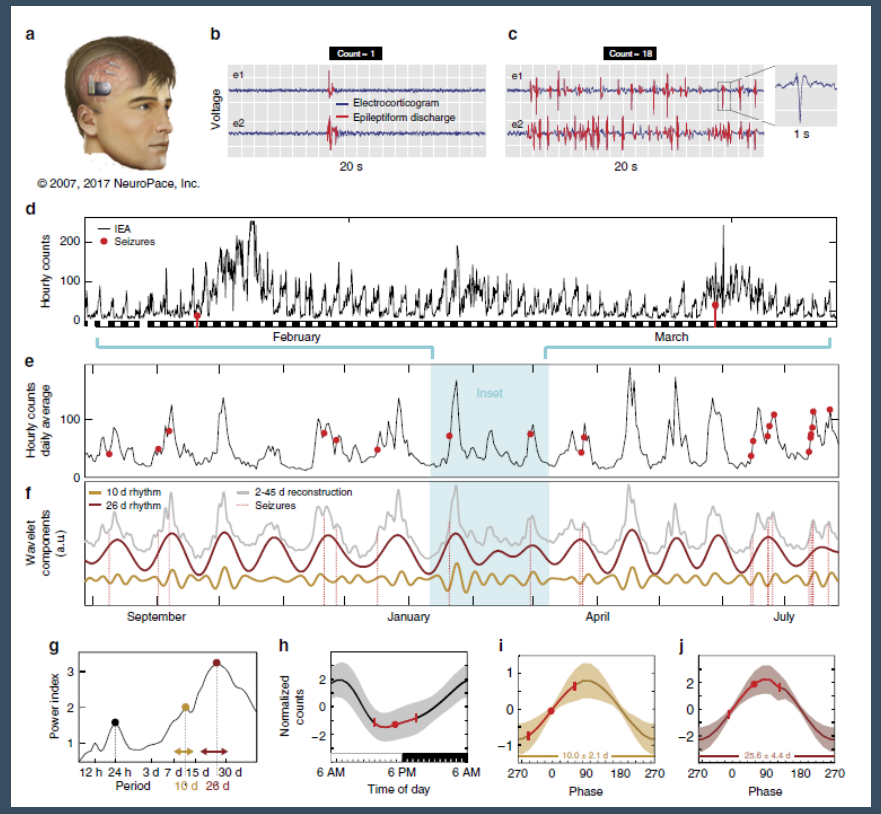
Nair et al., *submitted*

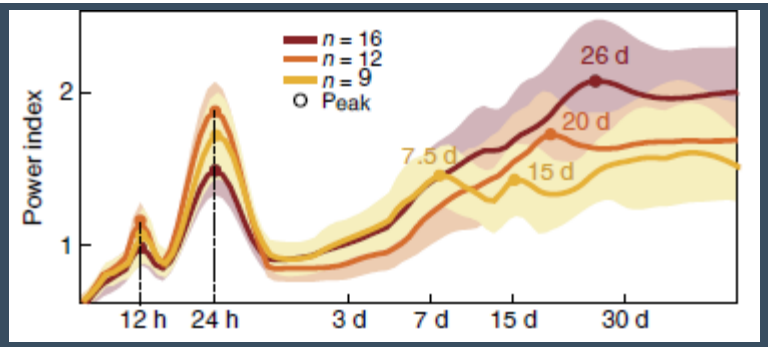
Supplement Clinical Seizure Reports

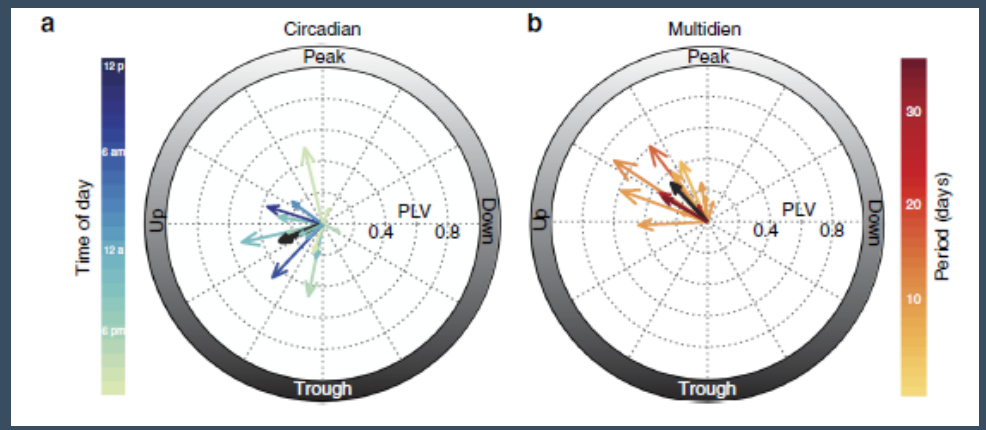
- RNS System data can reveal trends in long episodes over time

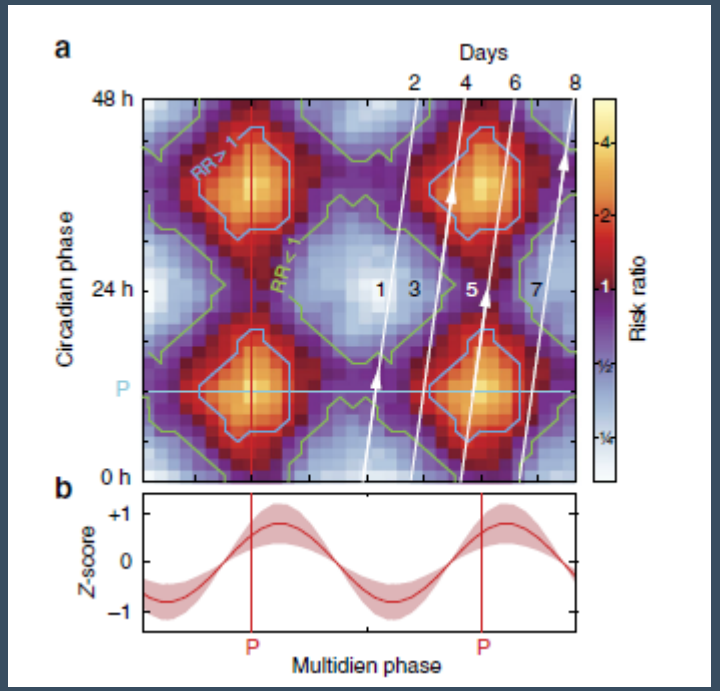


Multi-Day Rhythms Modulate Seizure Risk





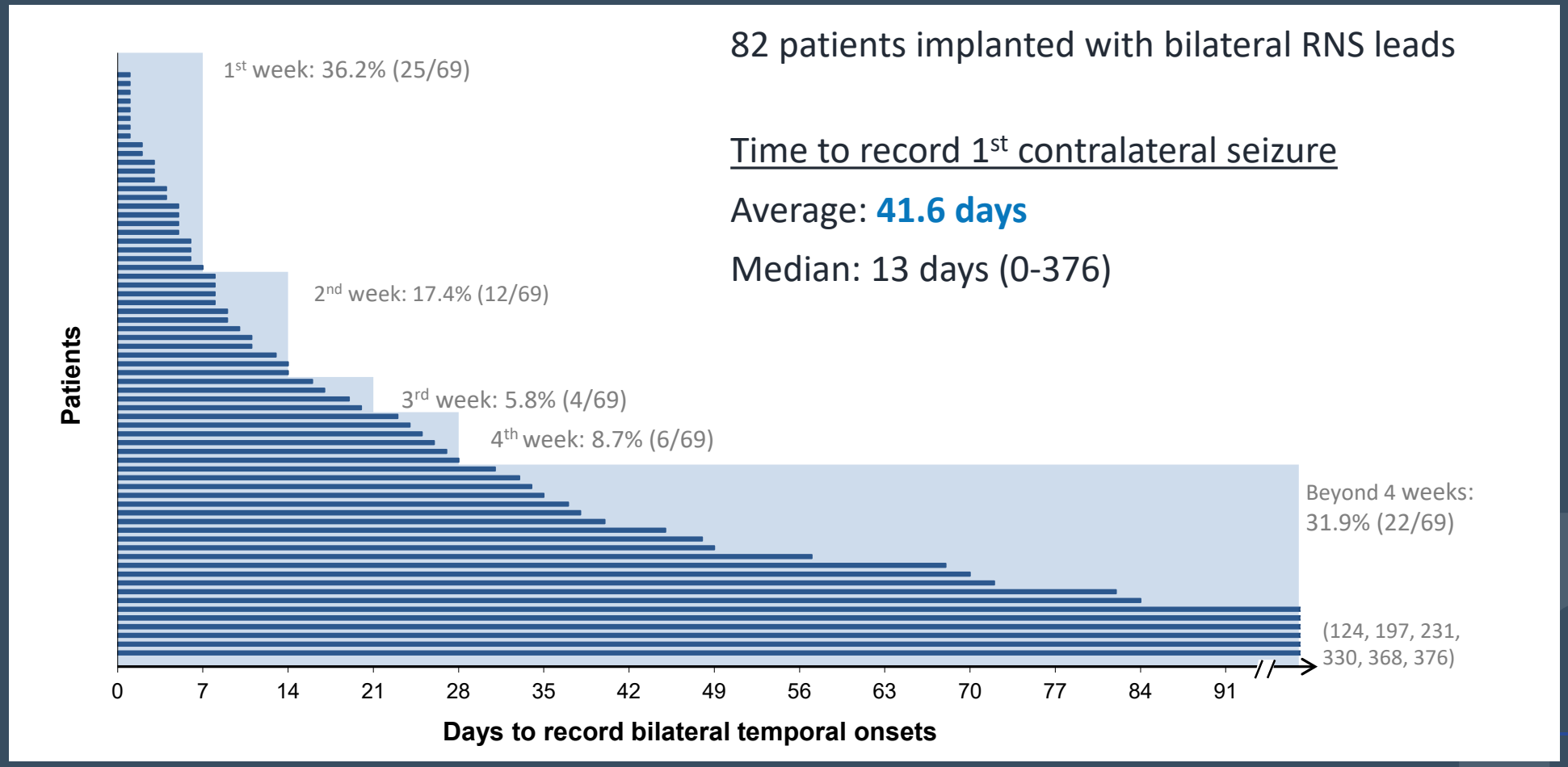




Baud MO et al. Nature Communications 2018

Lateralization of seizures of MTL onset

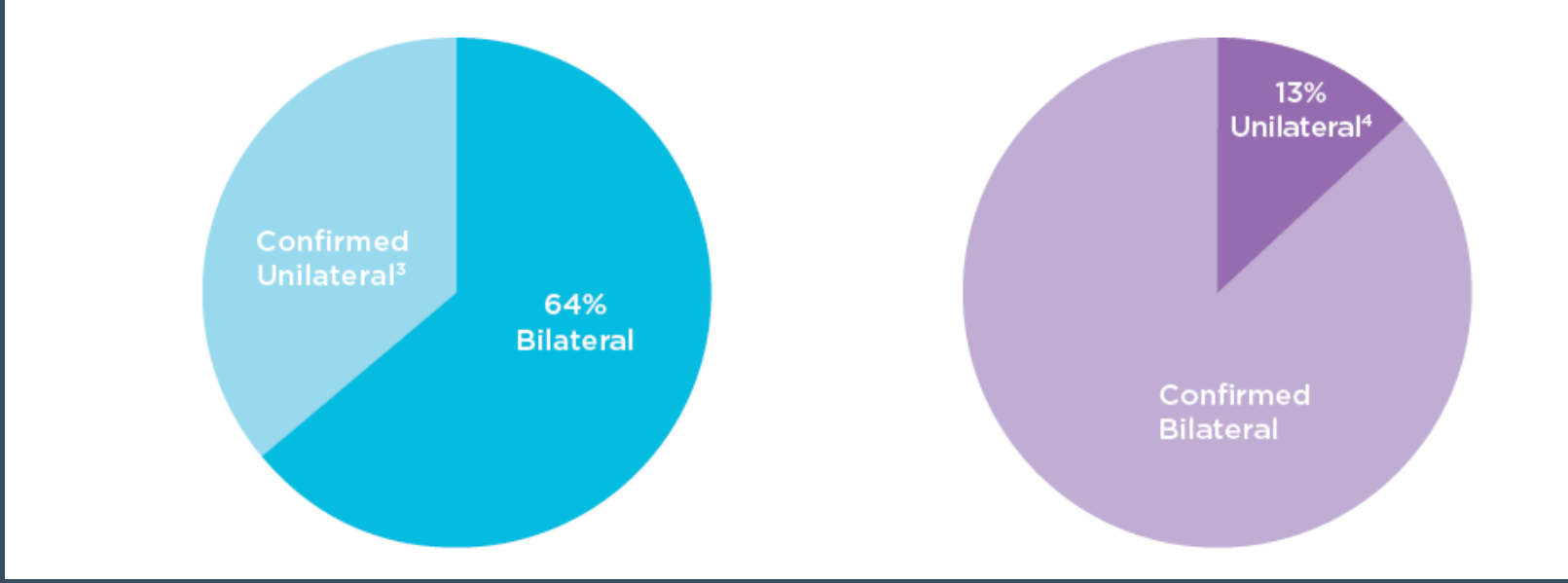
[King-Stephens et al., *Epilepsia*, 2015]



Lateralization of seizures of MTL onset

[King-Stephens et al., *Epilepsia*, 2015]

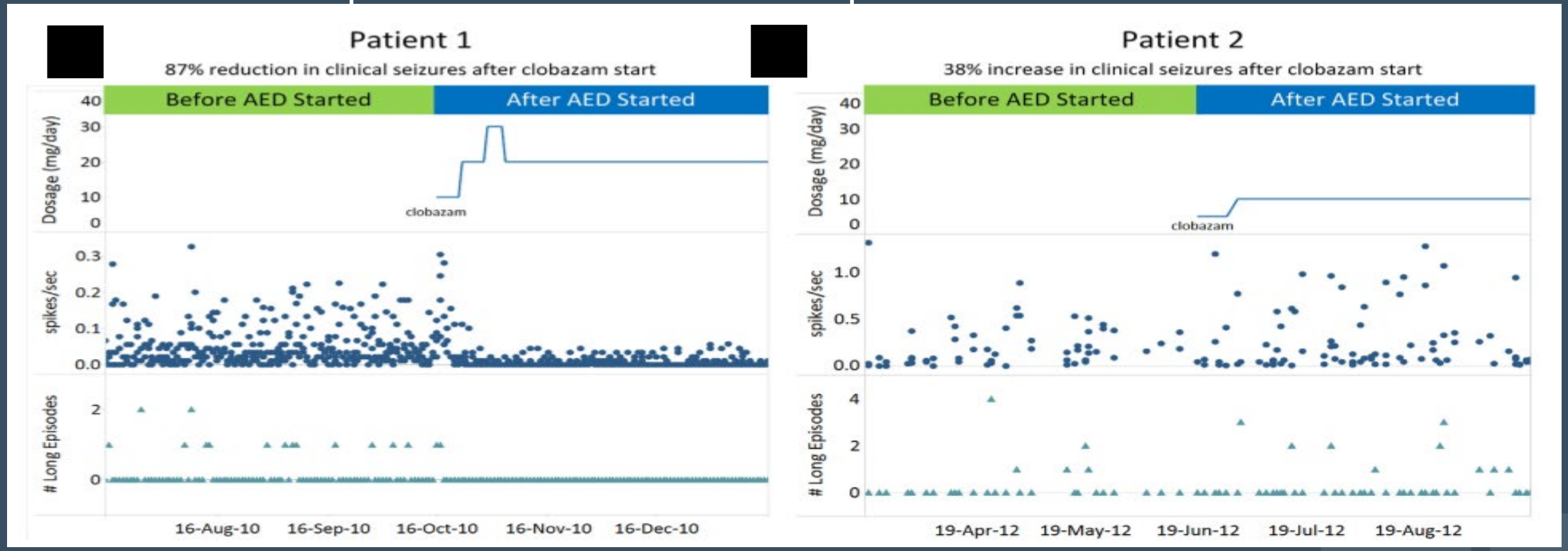
In **20% of patients**, the presumed lateralization determined by prior diagnostic testing changed after chronic ambulatory ECoG monitoring.



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

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

Changes in **interictal spikes** may serve as early indicators of patient's clinical response to AEDs



Use interictal biomarkers as a treatment endpoint to iterate device settings and AEDs

Skarpaas et. al., *2018, Epilepsy & Behavior*

Life Style Modification

- - Frequent episodes of status epilepticus (SE)
- - Episodes of SE occurred only on weekends

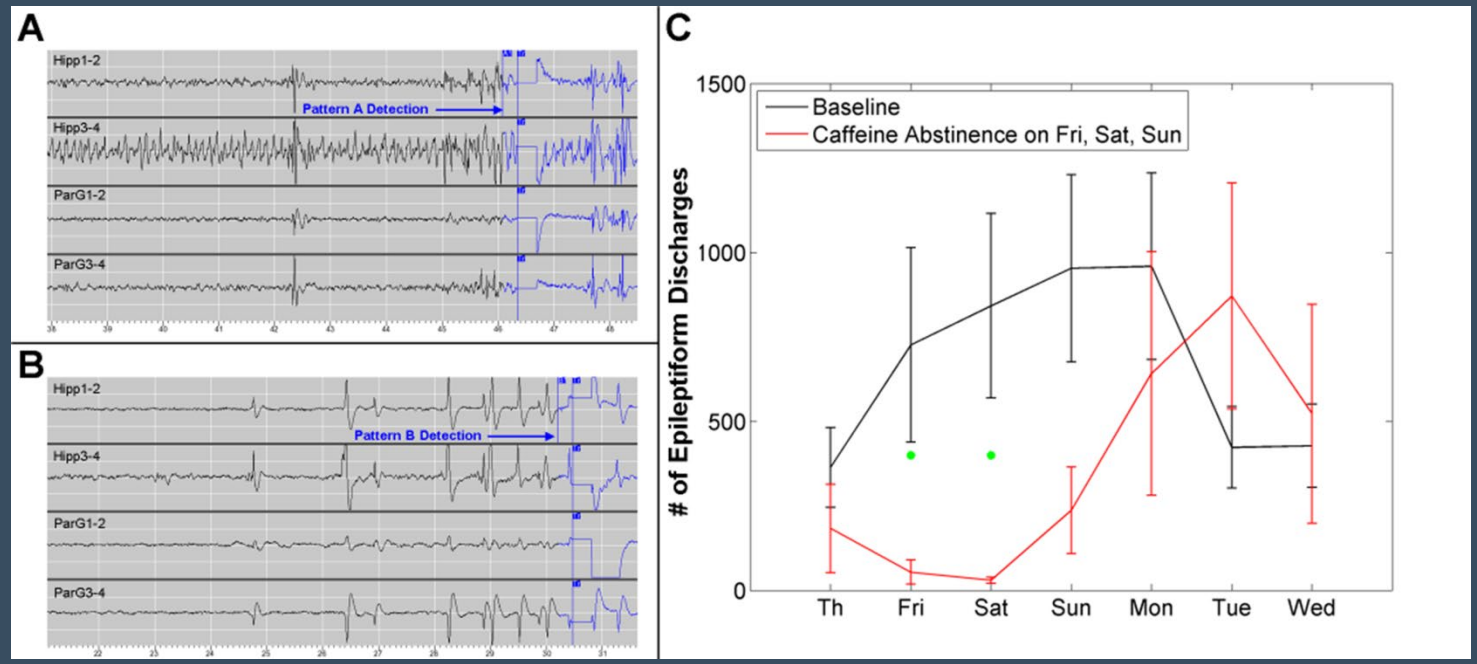
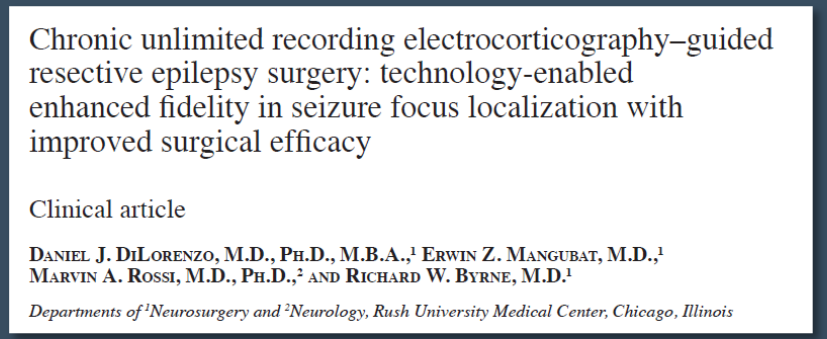


Figure. (A) Example of Pattern A detection. (B) Example of Pattern B detection. (C) Mean number of epileptiform discharges during control period, shown in black, compared to abstinence period, shown in red. Statistical significance ($p<0.05$) shown in green asterisk.

Source: Mackow, M., et al. (2016) *Clinical Neurophysiology, 127*(6), 2341-2342.

Long-term ECoG recordings with RNS® System may help identify resection candidates



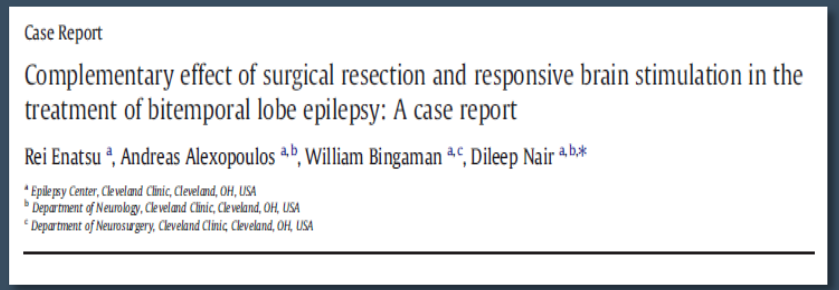
Chronic unlimited recording electrocorticography–guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy

Clinical article

DANIEL J. DILORENZO, M.D., PH.D., M.B.A.,[1] ERWIN Z. MANGUBAT, M.D.,[1] MARVIN A. ROSSI, M.D., PH.D.,[2] AND RICHARD W. BYRNE, M.D.[1]

Departments of [1]Neurosurgery and [2]Neurology, Rush University Medical Center, Chicago, Illinois

- Data obtained from the RNS System identified 4 patients who had not previously been considered for resective surgery as candidates.
- Patients subsequently underwent resective surgery
- All 4 are seizure free (2/4 continued w/ RNS System)



Case Report

Complementary effect of surgical resection and responsive brain stimulation in the treatment of bitemporal lobe epilepsy: A case report

Rei Enatsu [a], Andreas Alexopoulos [a,b], William Bingaman [a,c], Dileep Nair [a,b,*]

[a] Epilepsy Center, Cleveland Clinic, Cleveland, OH, USA
[b] Department of Neurology, Cleveland Clinic, Cleveland, OH, USA
[c] Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA

- RNS System data showed predominately right seizure onsets
- Right MTL resection and responsive stimulation on left, now seizure free

DiLorenzo, D. et al, *Journal of Neurosurgery*, 2014.
Enatsu, R et al, *Epilepsy & Behavior*, 2012.