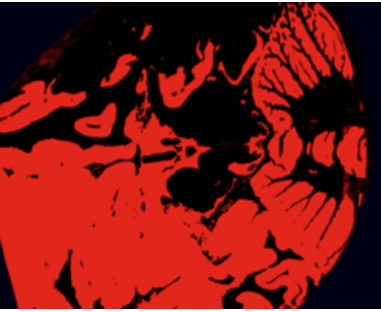


BRAINWEEK™ twenty 21 | Live Virtual Conference | MAY 7–9

Neurostimulation for Drug-Resistant Epilepsy

Dario J. Englot, MD, PhD

Title & Affiliation

Dario J. Englot, MD, PhD
Director of Surgical Epilepsy and Functional Neurosurgery
Assistant Professor
Vanderbilt University Medical Center

Disclosures

No relevant conflicts of interest.

Learning Objectives

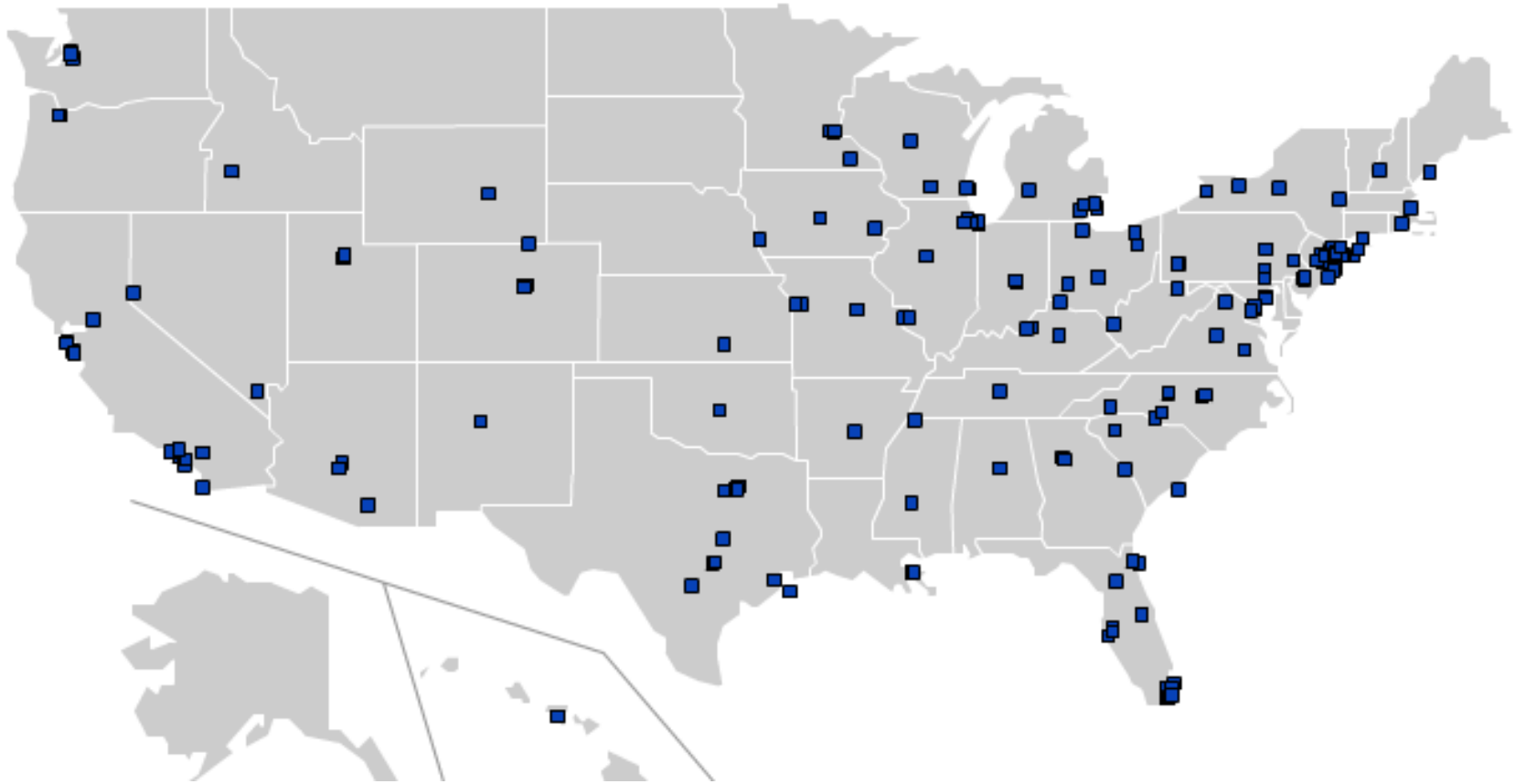
- Summarize the epidemiology and the global disease burden of epilepsy
- Describe nonpharmacological options available for treatment resistant epilepsy, including vagus nerve stimulation (VNS) and responsive neurostimulation (RNS)
- Review the short-term and long-term effects of brain responsive neurostimulation
- Discuss the effects of neuromodulation when utilized with antiepileptic drugs
- Summarize the MOA of deep brain stimulation for the treatment of epilepsy
- Outline future and emerging concepts surrounding neuromodulation for epilepsy

Epilepsy Background

- About 1% of the population suffers from epilepsy
- Seizures are refractory to anti-epileptic medications (AEDs) in 30% to 40% of patients
- The global burden of disease is similar to lung cancer in men and breast cancer in women
- Many patients with drug-resistant epilepsy can have significant improvement in seizures with epilepsy surgery or neurostimulation

National Association
NAEC
of Epilepsy Centers

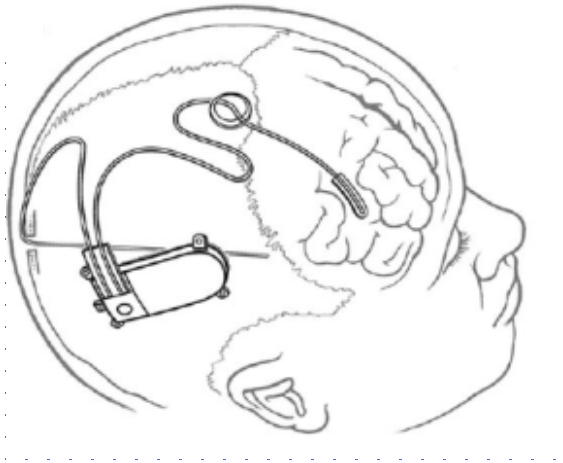
All US Epilepsy Centers



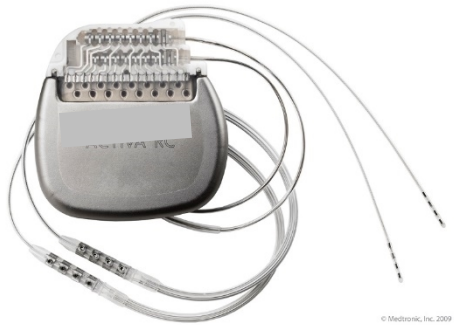
www.naec-epilepsy

Neuromodulation in Epilepsy

RNS



DBS



VNS

The New England Journal of Medicine

February 3, 2000 Volume 342 Number 5 · 315

EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

PATRICK KWAN, M.D., AND MARTIN J. BRODIE, M.D.

TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	NO. (%)
Response to first drug	222 (47)
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
Response to second drug	61 (13)
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
Response to third drug or multiple drugs	18 (4)
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

JAMA Neurology | Original Investigation

JAMA Neurology Published online December 26, 2017

Treatment Outcomes in Patients with Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

1795 patients, followed until October 2014

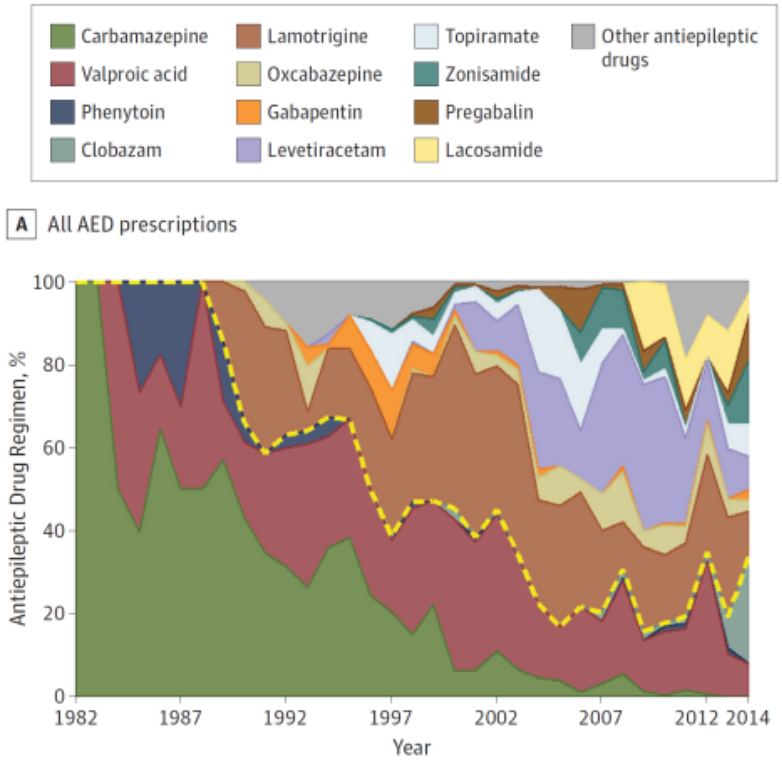
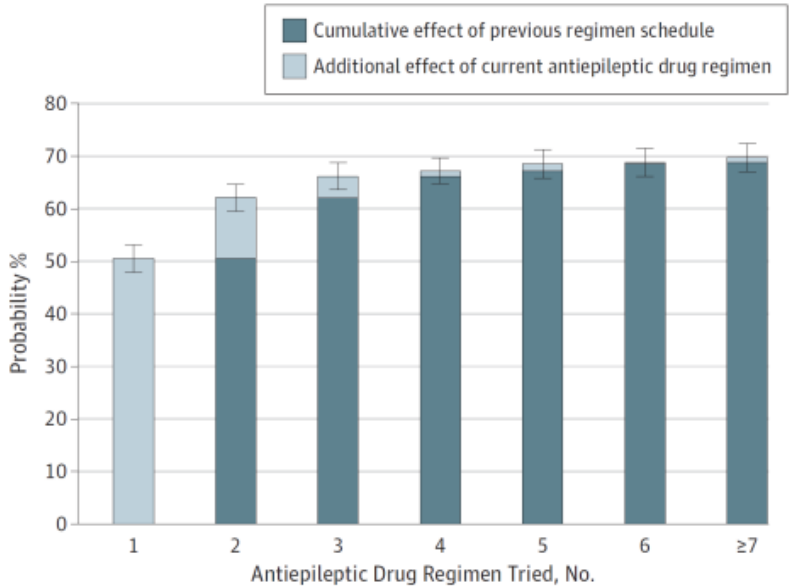


Figure 3. Increases in Probability of 1-Year Seizure Freedom for Each Additional Antiepileptic Drug Regimen Tried



The percentage of patients achieving seizure freedom via the first, second, third, fourth, fifth, sixth, and seventh AED regimens were 50.5%, 11.6%, 0.99%, 1.34%, 0.28%, and 0.94%, respectively. Please see Table 2 for numbers of patients achieving seizure freedom and total patients in each subgroup.

AMERICAN ACADEMY OF NEUROLOGY

Special Article

Practice parameter: Temporal lobe and localized neocortical resections for epilepsy

Report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons

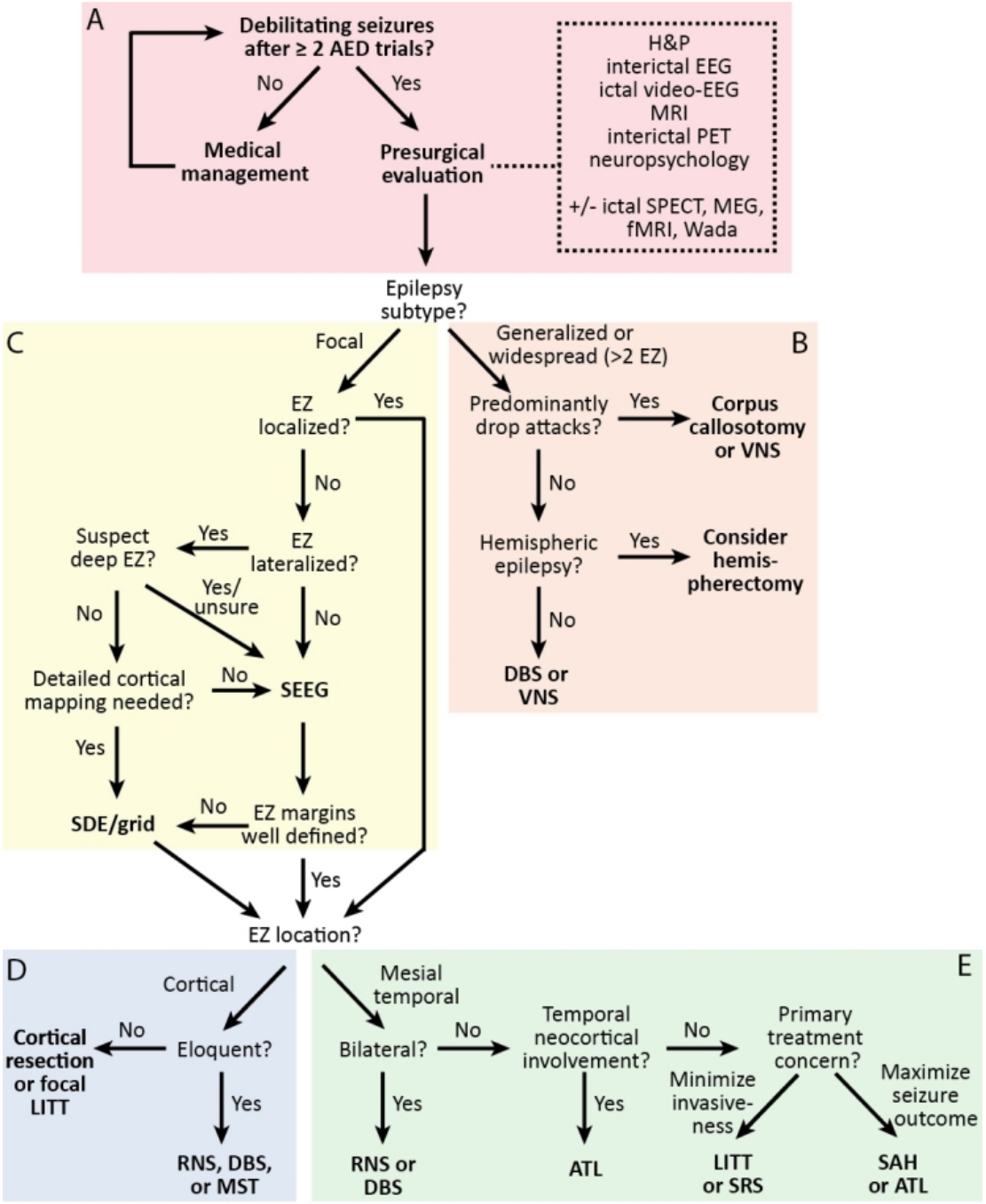
J. Engel, Jr., MD, PhD; S. Wiebe, MD; J. French, MD; M. Sperling, MD; P. Williamson, MD; D. Spencer, MD; R. Gumnit, MD; C. Zahn, MD; E. Westbrook, MD; and B. Enos, MD, PhD

NEUROLOGY 2003;60:538–547

Guideline: Patients who have failed ≥ 2 well-tolerated AED trials should be referred to a comprehensive epilepsy center for evaluation, including consideration of surgery

Epilepsy Surgery

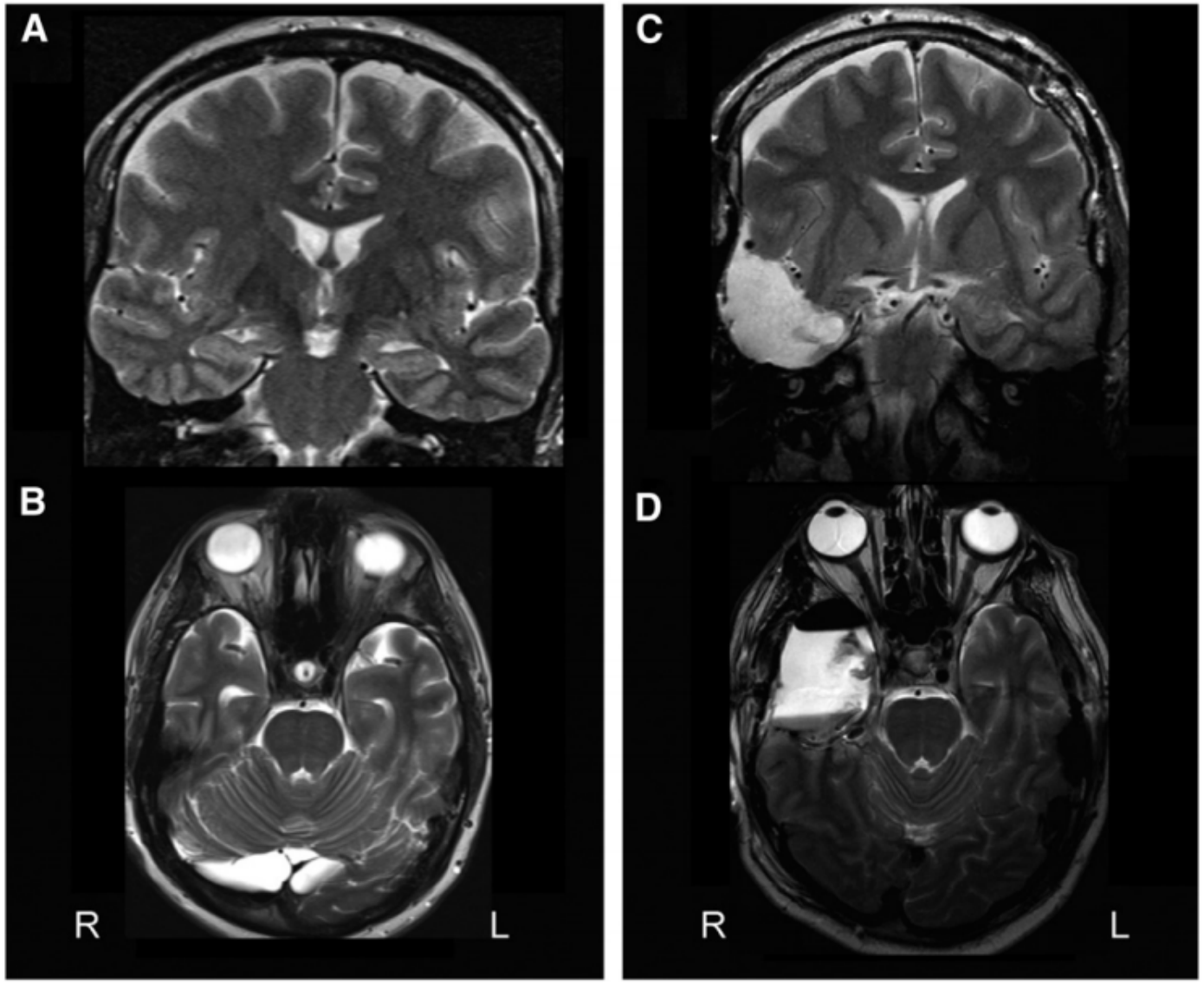
- **Ablative or destructive**
  - Resection
  - Ablation
    - Laser interstitial thermal therapy (LITT)
    - Radiofrequency ablation
  - Disconnection
    - Multiple subpial transections (MST)
    - Corpus callosotomy
    - Functional/anatomic hemispherectomy
- **Neuromodulation**
  - Vagus nerve stimulation (VNS) – FDA 1997
  - Responsive neurostimulation (RNS) – FDA 2013
  - Deep brain stimulation (DBS) – FDA 2018



One Possible *(Simplified)* Epilepsy Surgery Algorithm

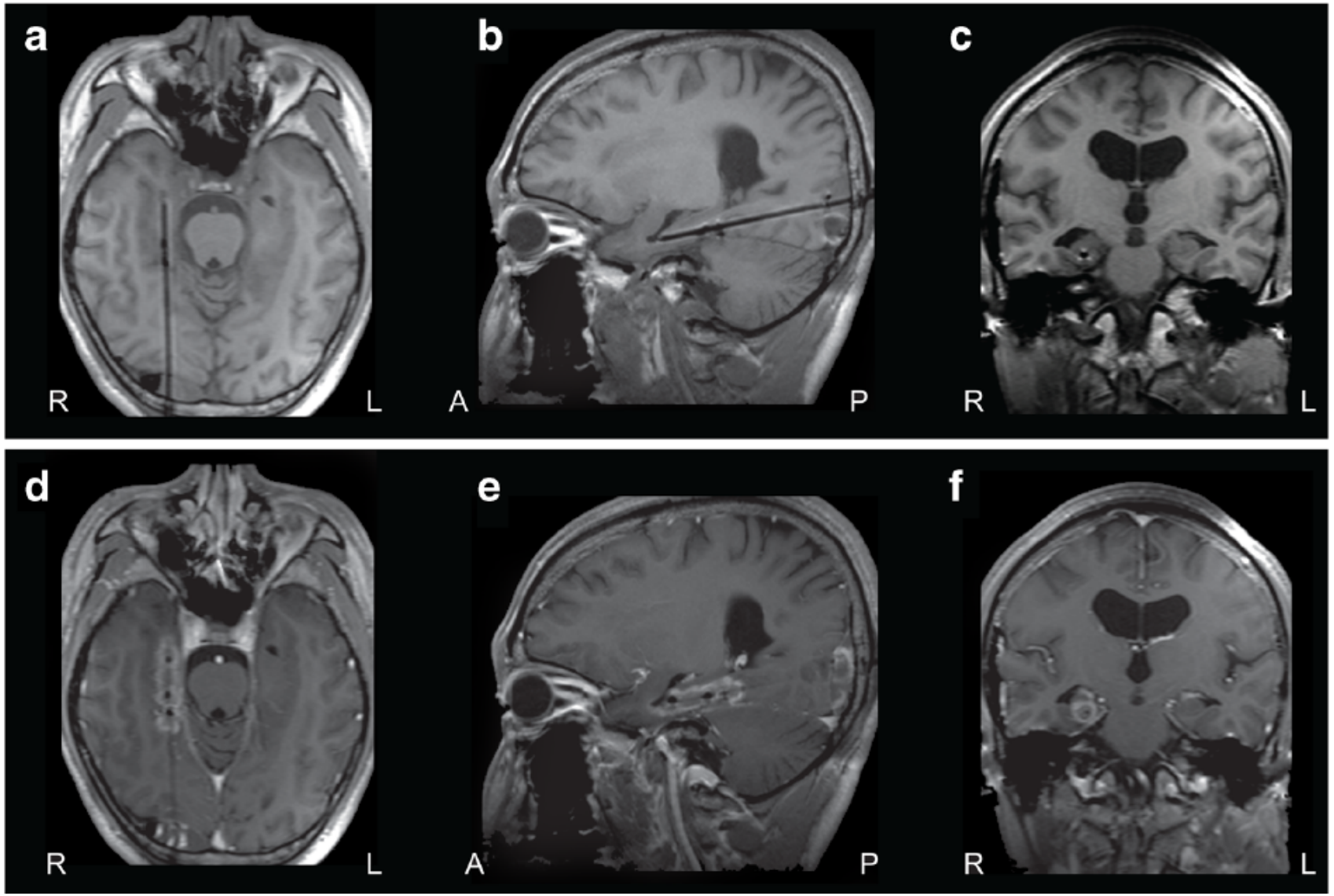
Modified from Englot, 2018, Epilepsy Behav

Example of Standard Anterior Temporal Lobectomy



Chang et al. Epilepsy Behav 2015 Jun;47:24-33.

LITT (Laser Interstitial Thermal Therapy)

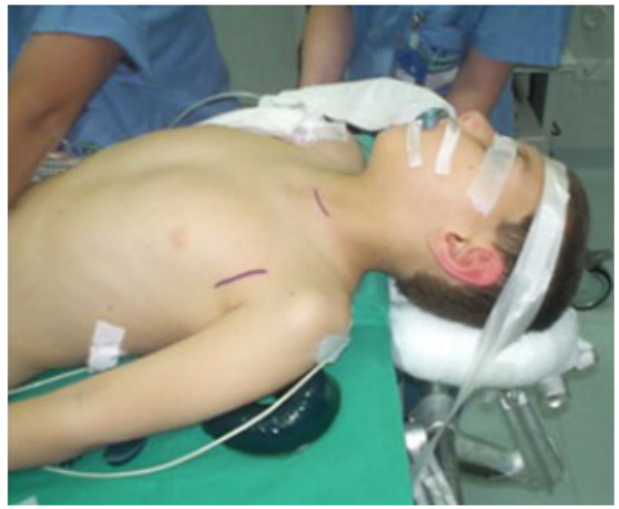


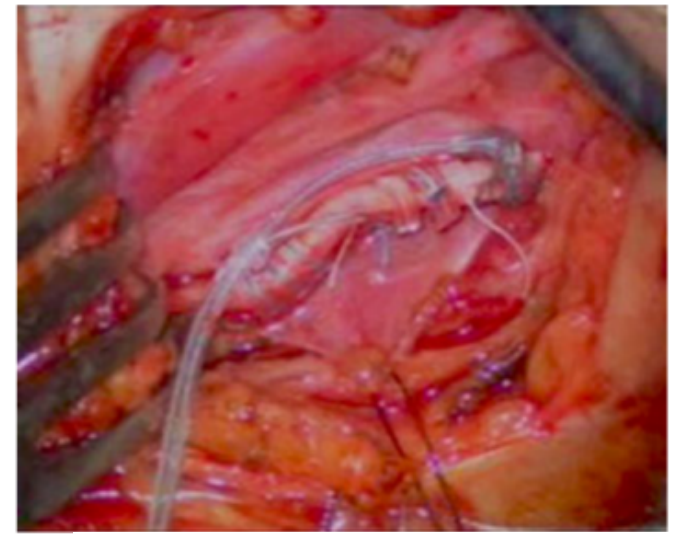
Englot et al., Neurosurg Rev. 2017 Apr;40(2):181-194.

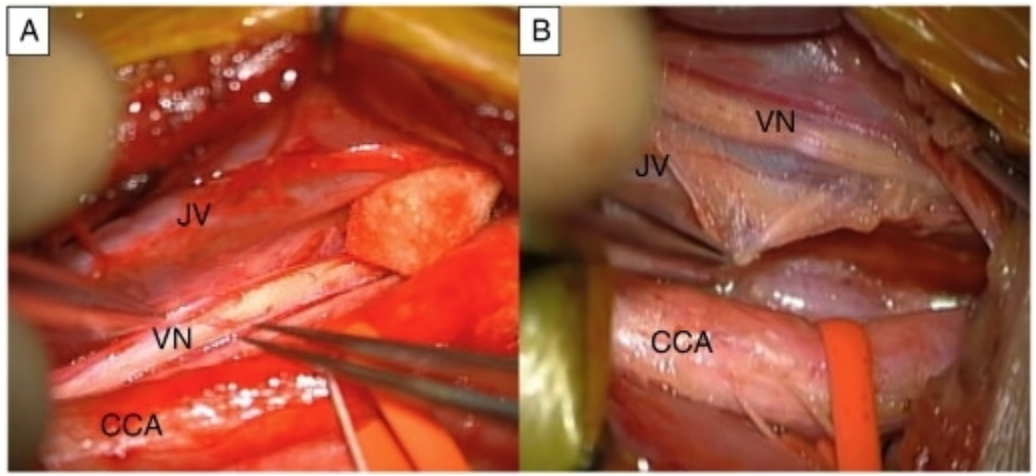
Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity

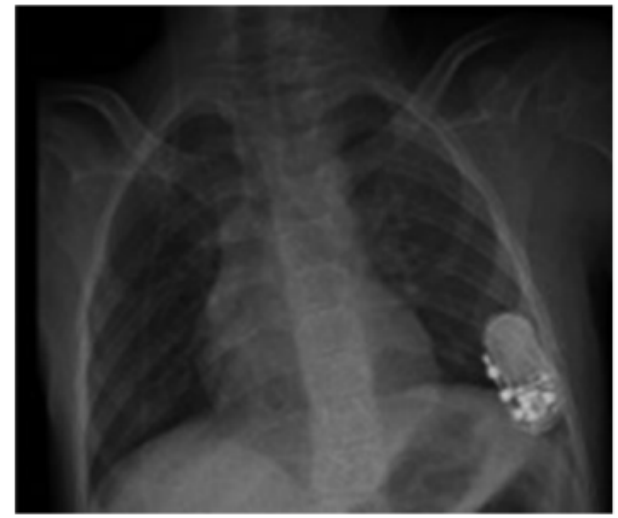
*Flavio Giordano, †Anna Zicca, ‡Carmen Barba, ‡Renzo Guerrini, and *Lorenzo Genitori

Epilepsia, 58(Suppl. 1):85–90, 2017
10.1111/epi.13678









Reference: ZANCHETTI, A., WANG, S. C. and MORUZZI, G. The effect of vagal afferent stimulation on the EEG pattern of the cat. *EEG Clin. Neurophysiol.*, **1952**, *4*: 357-361.

THE EFFECT OF VAGAL AFFERENT STIMULATION ON THE EEG PATTERN OF THE CAT [1]

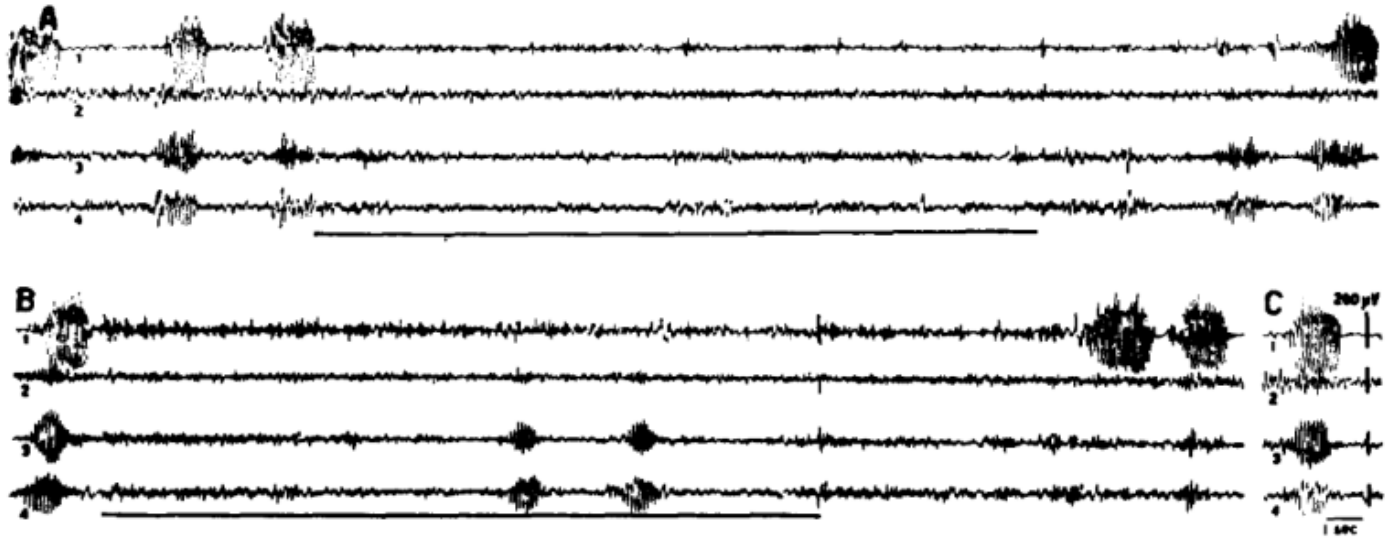
A. ZANCHETTI, M.D., S. C. WANG, M.D., Ph.D.[2] and G. MORUZZI, M.D.

Instituto di Fisiologia, Università di Pisa, Italy

A number of investigators have been interested in the influence of various visceral afferent impulses on spontaneous and induced movements (see Schweitzer and Wright 1937; for other references of the autonomic activities on EEG, see Darrow *et al.* 1946). Tournade and Malméjac (1929) found that shivering produced by cooling was inhibited by stimulating Hering's nerve, and Koch (1932) revealed that spontaneous movements were blocked following increased pressure in the carotid sinus. Different results were obtained by Danielopolu and his colleagues (1931, 1932, 1933), showing that after local strychninization of motor cortex an epileptiform seizure could be elicited by baroceptive or afferent

METHODS

Fifteen "encéphale isolé" preparations were prepared in cats under ether anesthesia, by transecting the spinal cord at C1 (Bremer 1937). The animal was then given artificial respiration and also an intravenous dose of ephedrine hydrochloride (10 mg. per kg.). Bipolar screw electrodes, about 1 cm. apart, were placed in the skull, corresponding to the frontal (sensori-motor), parietal and sometimes also occipital region. The frontal cortex was occasionally exposed for local application of dilute strychnine nitrate solutions (0.02 to 0.1 per cent; rarely 0.5 to 1.0 per cent) and its activity led off with saline wick electrodes. A Grass Model III electrenceph-



Randomized Controlled Trials Examining VNS

Class I evidence: blinded, randomized controlled trials							
Study	N	Seizure type	Comparison	Follow-up	No. centers	Mean % seizure reduction	% patients with >50% reduction
Ben-Menachem, 1994	114	partial	high vs low stim	3 months	multi	25 (high) vs 6 (low)	31
Handforth, 1998	196	partial	high vs low stim	3 months	multi	28 (high) vs 15 (low)	23

Nonblinded, randomized controlled trials							
Study	N	Seizure type	Comparison	Follow-up	No. centers	Median % seizure reduction	% patients with >50% reduction
Scherrmann, 2001	28	mixed	2 stim paradigms	NR	single	30 (overall)	45
DeGiorgio, 2005	61	partial	3 stim paradigms	3 months	multi	26 (overall)	29

Englot et al. J Neurosurg. 2011 Dec;115(6):1248-55.

JNS JOURNAL OF NEUROSURGERY
OFFICIAL JOURNALS OF THE AANS SINCE 1944

J Neurosurg 115:1248–1255, 2011

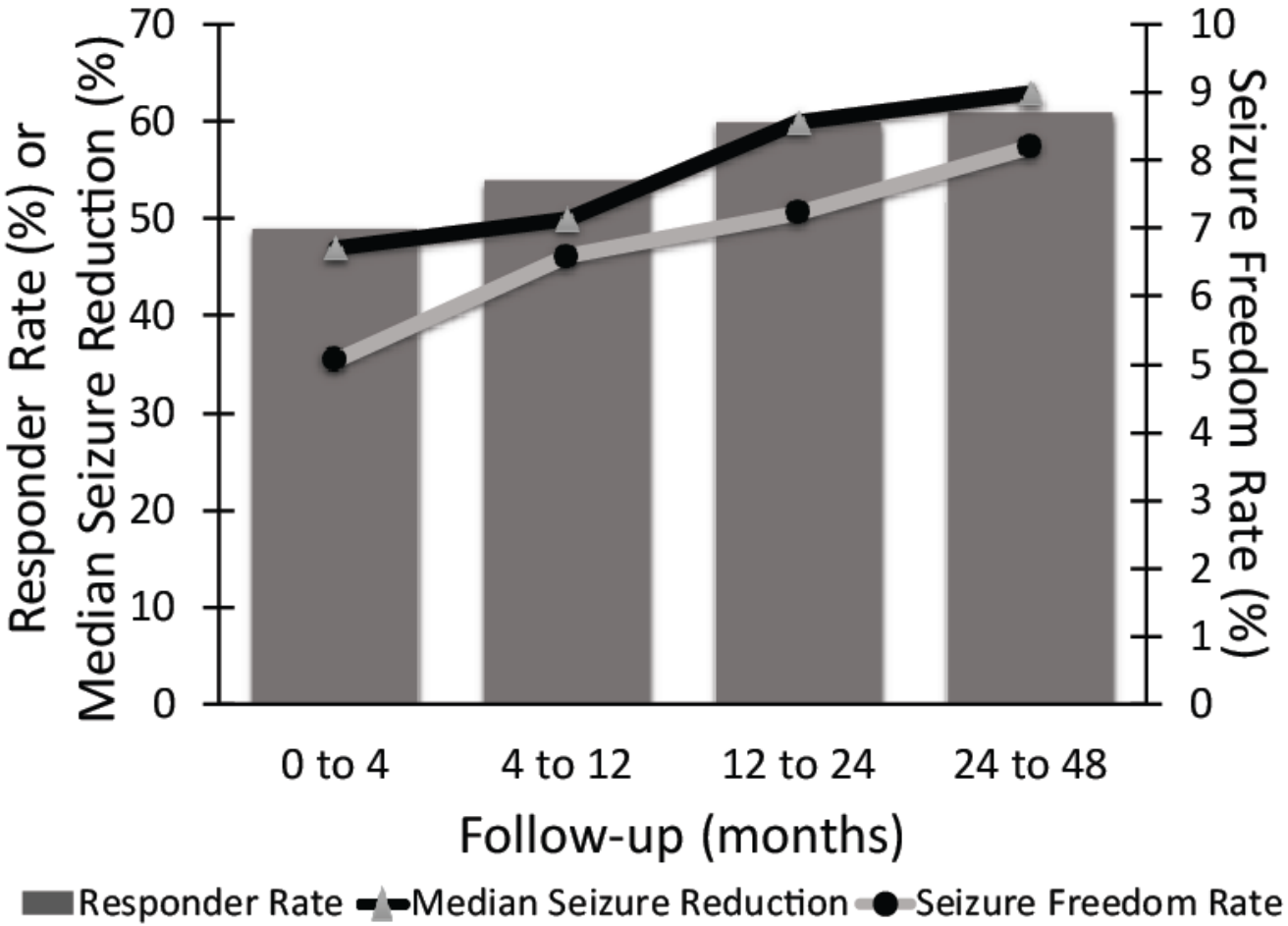
Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response

Dario J. Englot, M.D., Ph.D., Edward F. Chang, M.D., and Kurtis I. Auguste, M.D.

Department of Neurological Surgery, University of California, San Francisco, California

- 74 clinical studies with 3321 patients suffering from intractable epilepsy
- Seizure frequency reduced by average 45%, with 36% reduction in seizures at 3-12 months and 51% reduction after >1 year
- At the last follow-up, seizures reduced by ≥50% in approximately 50% of patients
- Complete seizure freedom rarely achieved, and one-quarter of patients experienced no benefit

Response and Seizure-freedom Rates with VNS from Manufacturer Registry Data



Data from 12,319 unique provider visits among 5,554 patients.

Englot et al., Neurosurgery. 2016 Sep;79(3):345-53.

NEUROSURGERY

Efficacy of Vagus Nerve Stimulation for Epilepsy by Patient Age, Epilepsy Duration, and Seizure Type

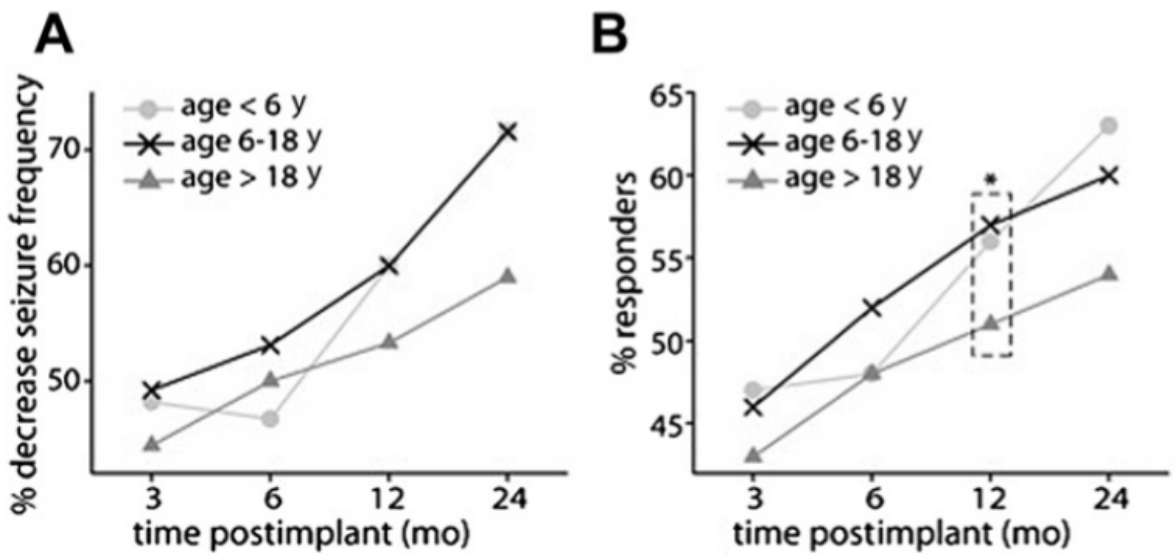
Clinics Review Articles

NEUROSURGERY CLINICS
OF NORTH AMERICA

Dario J. Englot, MD, PhD, Edward F. Chang, MD,
Kurtis I. Auguste, MD*

KEYWORDS

• Epilepsy • Outcomes • Seizures •
• Vagus nerve stimulation



Neurosurg Clin N Am 22 (2011) 443–448

Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy

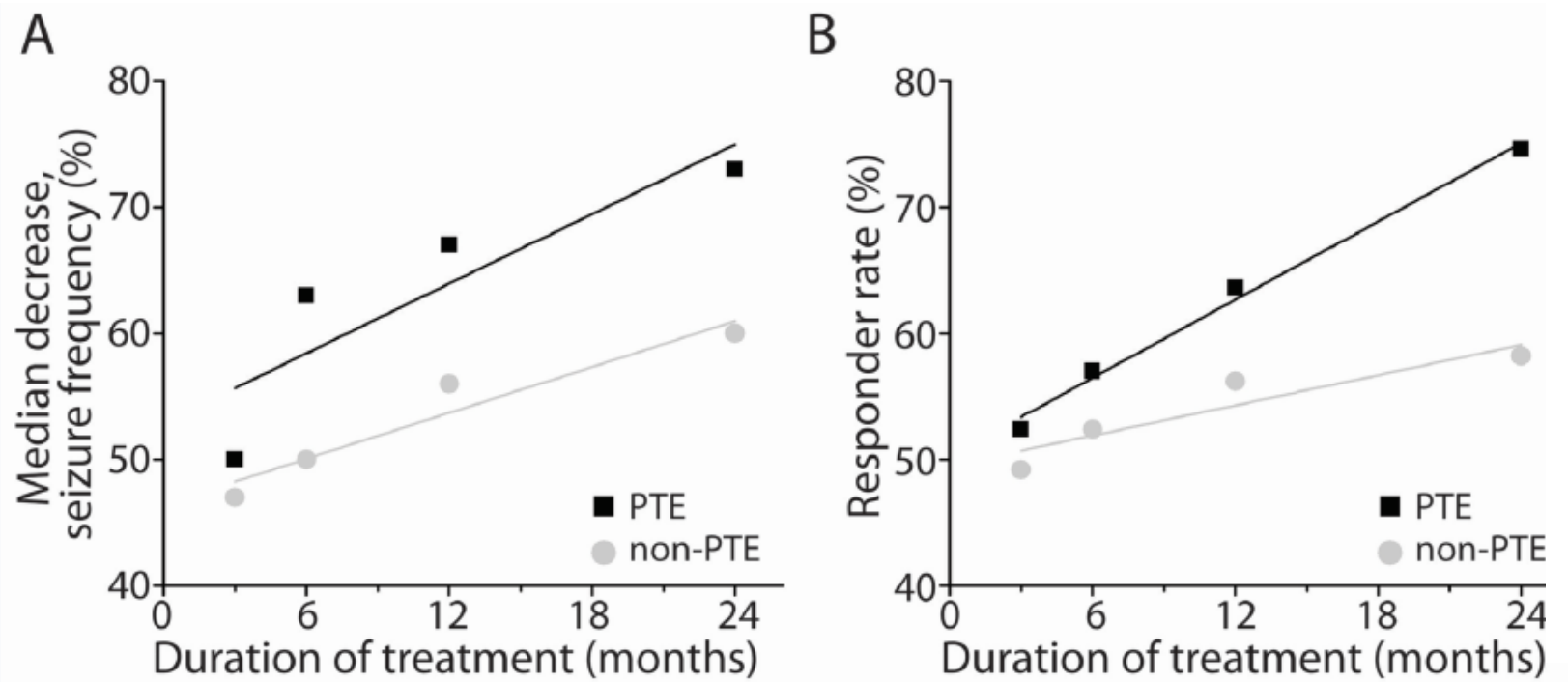
J Neurosurg 117:970–977, 2012

JNS JOURNAL OF NEUROSURGERY
OFFICIAL JOURNALS OF THE AANS SINCE 1944

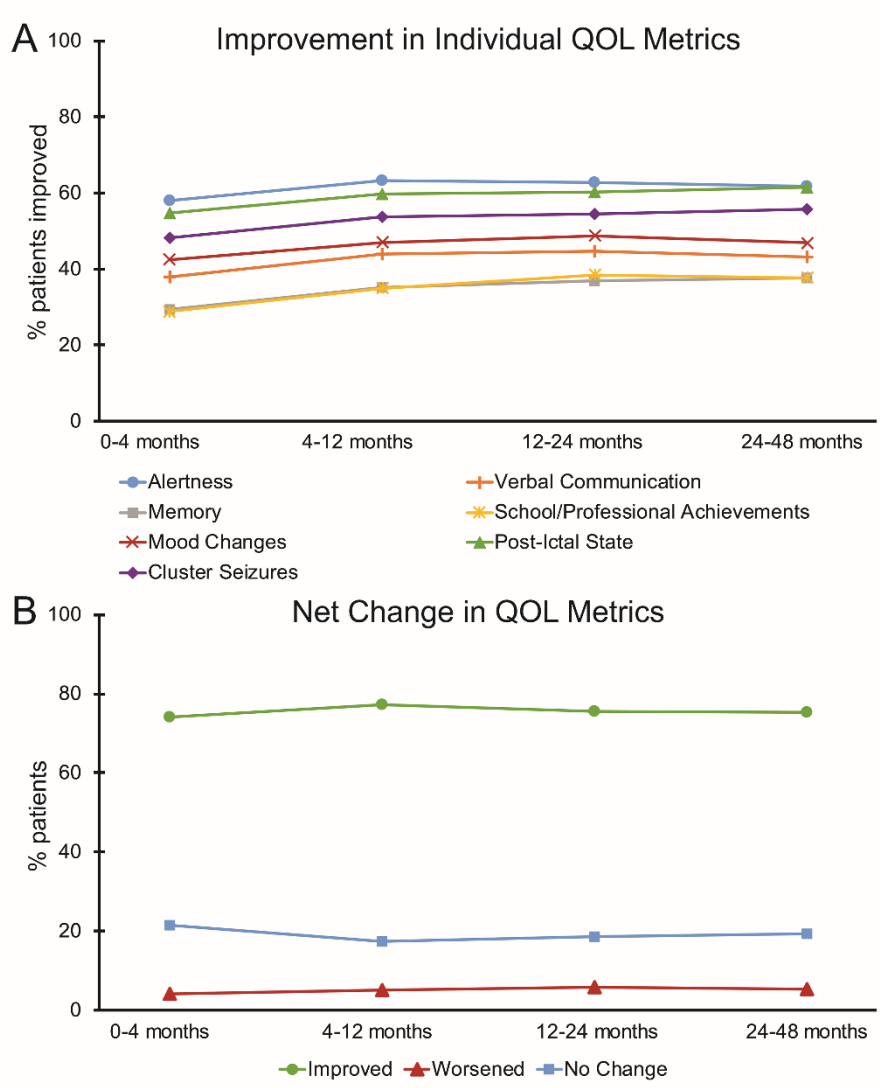
Clinical article

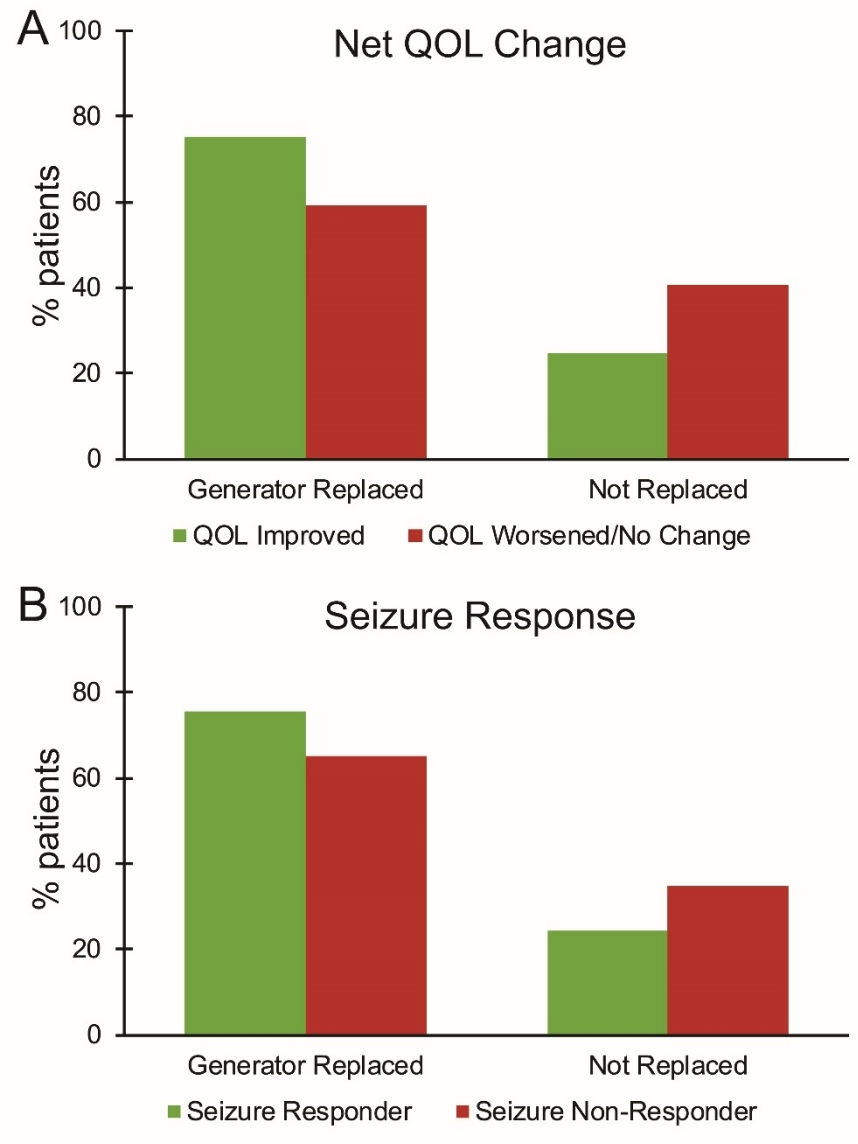
Dario J. Englot, M.D., Ph.D.,[1,2] John D. Rolston, M.D., Ph.D.,[1,2] Doris D. Wang, M.D., Ph.D.,[1,2] Kevin H. Hassnain, M.S.,[3] Charles M. Gordon, M.S.,[3] and Edward F. Chang, M.D.[1,2]

[1]Comprehensive Epilepsy Center and [2]Department of Neurological Surgery, University of California, San Francisco, California; and [3]Cyberonics, Inc., Houston, Texas



Quality of Life Metrics with VNS from Provider Survey Data





Englot et al., 2017 Epilepsy Behav.

Received: August 12, 2015 Revised: September 25, 2015 Accepted: October 11, 2015

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12376

Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance—The U.S. E-37 Trial

Robert S. Fisher, MD, PhD*; Pegah Afra, MD†; Micheal Macken, MD, MRCP‡; Daniela N. Minecan, MD§; Anto Bagić, MD, PhD¶; Selim R. Benbadis, MD; Sandra L. Helmers, MD, MPH††; Saurabh R. Sinha, MD, PhD‡‡; Jeremy Slater, MD§§; David Treiman, MD¶¶; Jason Begnaud, BS***; Pradheep Raman, MS***; Bita Najimipour, MS, CPM, CCRP*****

Epilepsy & Behavior 111 (2020) 107280

Contents lists available at ScienceDirect

Epilepsy & Behavior

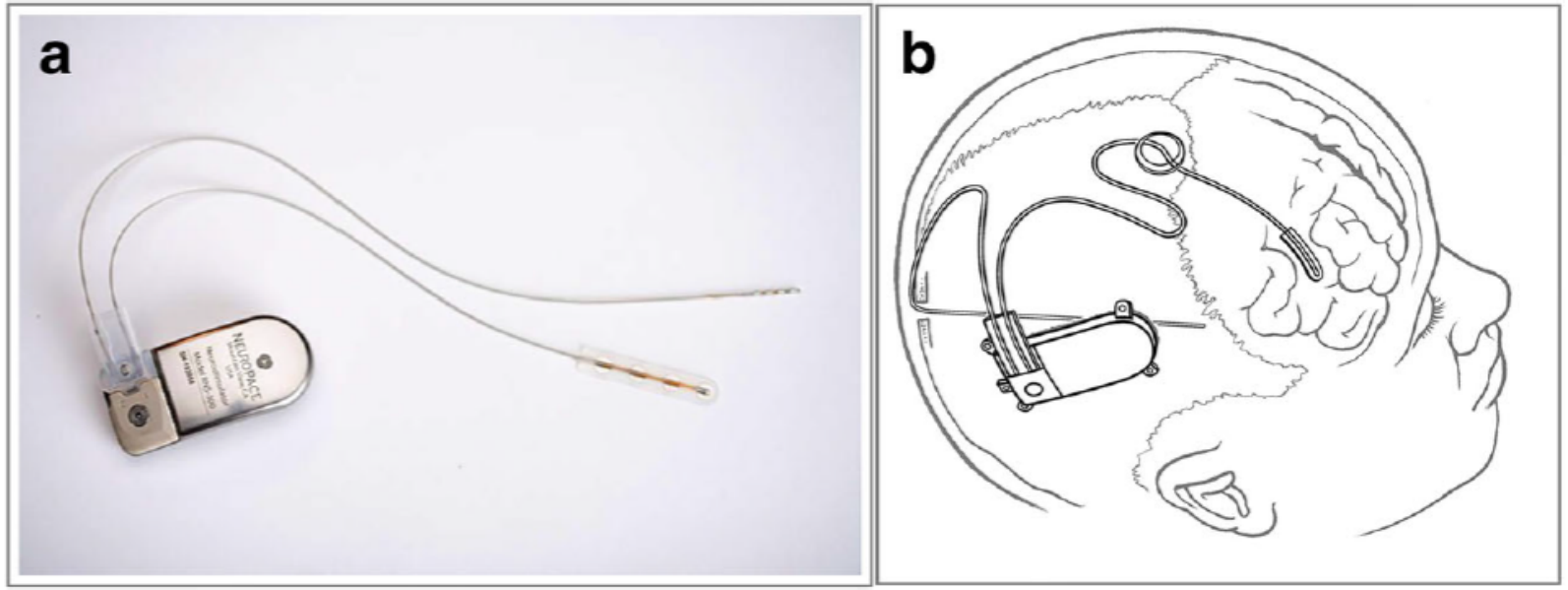
journal homepage: www.elsevier.com/locate/yebeh

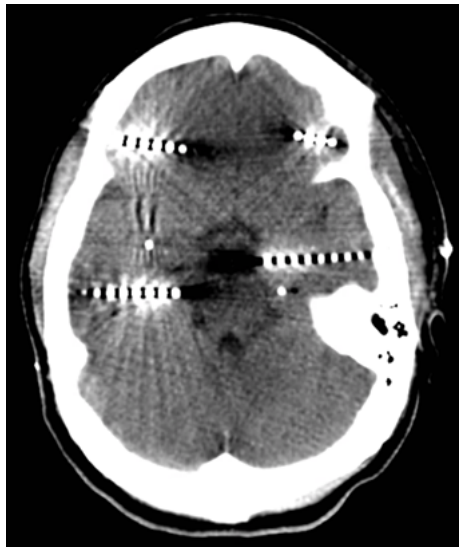
Vagus nerve stimulation with tachycardia detection provides additional seizure reduction compared to traditional vagus nerve stimulation

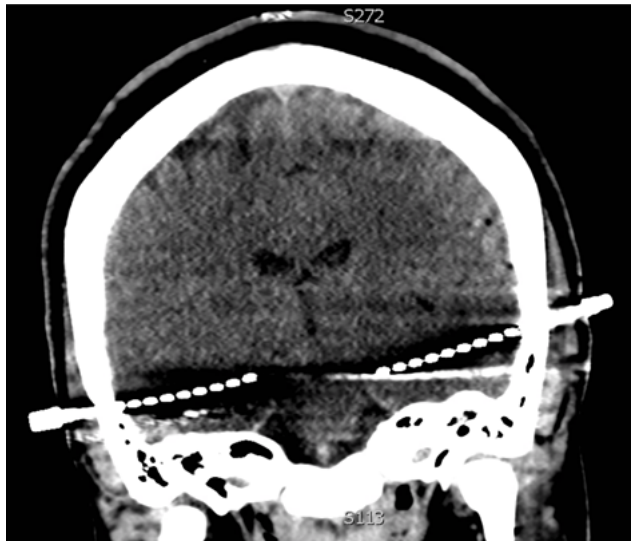
Proleta Datta [a,*], Krishna Mourya Galla [a], Kalyan Sajja [a], Christopher Wichman [b], Hongmei Wang [c], Deepak Madhavan [d]

[a] Department of Neurology, University of Nebraska Medical Center, Omaha, NE, United States of America
[b] Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE, United States of America
[c] Department of Health Service Research and Administration, University of Nebraska Medical Center, Omaha, NE, United States of America
[d] Boystown National Research Hospital, Boys Town, NE, United States of America

Responsive Neurostimulation (RNS)







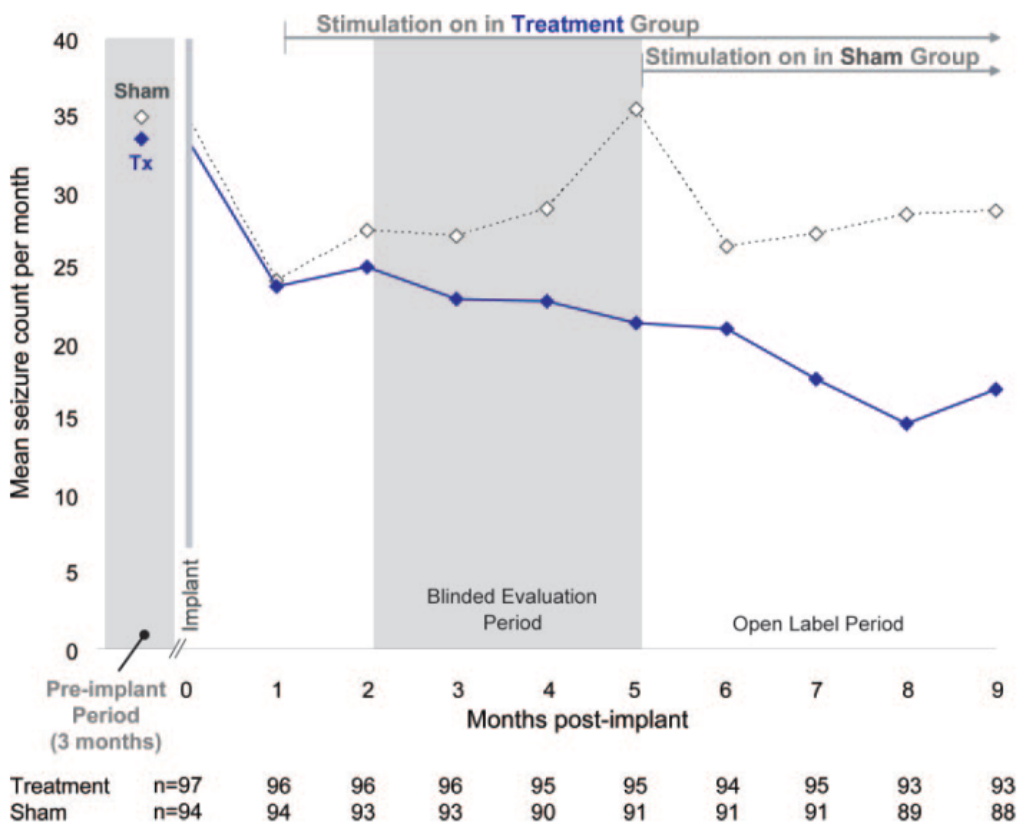
Responsive Neurostimulation (RNS)

Responsive cortical stimulation for the treatment of medically intractable partial epilepsy

Neurology 77 September 27, 2011

Martha J. Morrell, MD
On behalf of the RNS System in Epilepsy Study Group

Figure 2 Mean disabling seizures by month, observed data



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The Official Journal of the American Academy of Neurology

Long-term treatment with responsive brain stimulation in adults with refractory partial seizures

Gregory K. Bergey, MD
Martha J. Morrell, MD
Eli M. Mizrahi, MD
Alica Goldman, MD, PhD
David King-Stephens, MD
Dileep Nair, MD
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Gregory Worrell, MD, PhD
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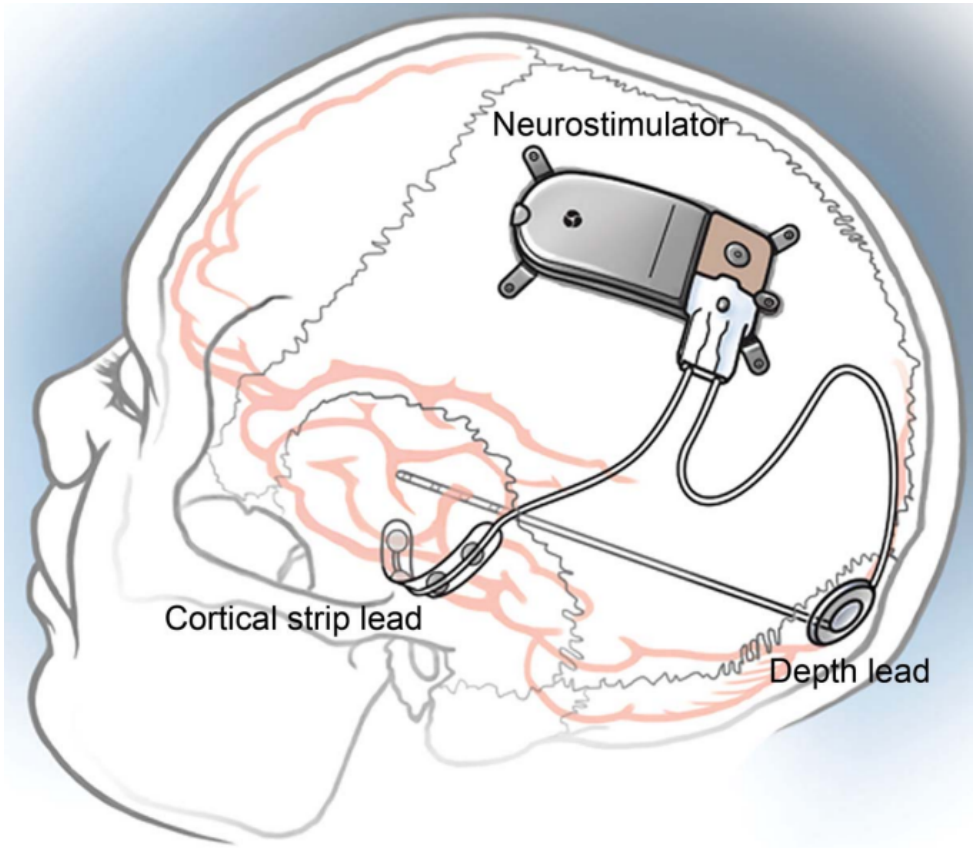

Jonathan Edwards, MD
Michael Duchowny, MD
David Spencer, MD
Michael Smith, MD
Eric Geller, MD
Ryder Gwinn, MD
Christopher Skidmore, MD
Stephan Eisenschenk, MD
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Neurology® 2015;84:810-817

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The Official Journal of the American Academy of Neurology

Long-term treatment with responsive brain stimulation in adults with refractory partial seizures

Methods: All participants were treated with a cranially implanted responsive neurostimulator that delivers stimulation to 1 or 2 seizure foci via chronically implanted electrodes when specific electrocorticographic patterns are detected (RNS System). Participants had completed a 2-year primarily open-label safety study (n = 65) or a 2-year randomized blinded controlled safety and efficacy study (n = 191); 230 participants transitioned into an ongoing 7-year study to assess safety and efficacy.

Results: The average participant was 34 (±11.4) years old with epilepsy for 19.6 (±11.4) years. The median preimplant frequency of disabling partial or generalized tonic-clonic seizures was 10.2 seizures a month. The median percent seizure reduction in the randomized blinded controlled trial was 44% at 1 year and 53% at 2 years ($p < 0.0001$, generalized estimating equation) and ranged from 48% to 66% over postimplant years 3 through 6 in the long-term study. Improvements in quality of life were maintained ($p < 0.05$). The most common serious device-related adverse events over the mean 5.4 years of follow-up were implant site infection (9.0%) involving soft tissue and neurostimulator explantation (4.7%).

Neurology® 2015;84:810-817

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The Official Journal of the American Academy of Neurology

Long-term treatment with responsive brain stimulation in adults with refractory partial seizures

- **Adverse events** in the trial included hardware site infection (5.2%), headache (10.5%), dysesthesia (6.3%), increase in generalized (4.7%) or complex-partial (5.8%) seizures. Other complications were rare.

- Serious adverse event rates did not differ between patients receiving therapeutic or sham stimulation.

Neurology® 2015;84:810-817

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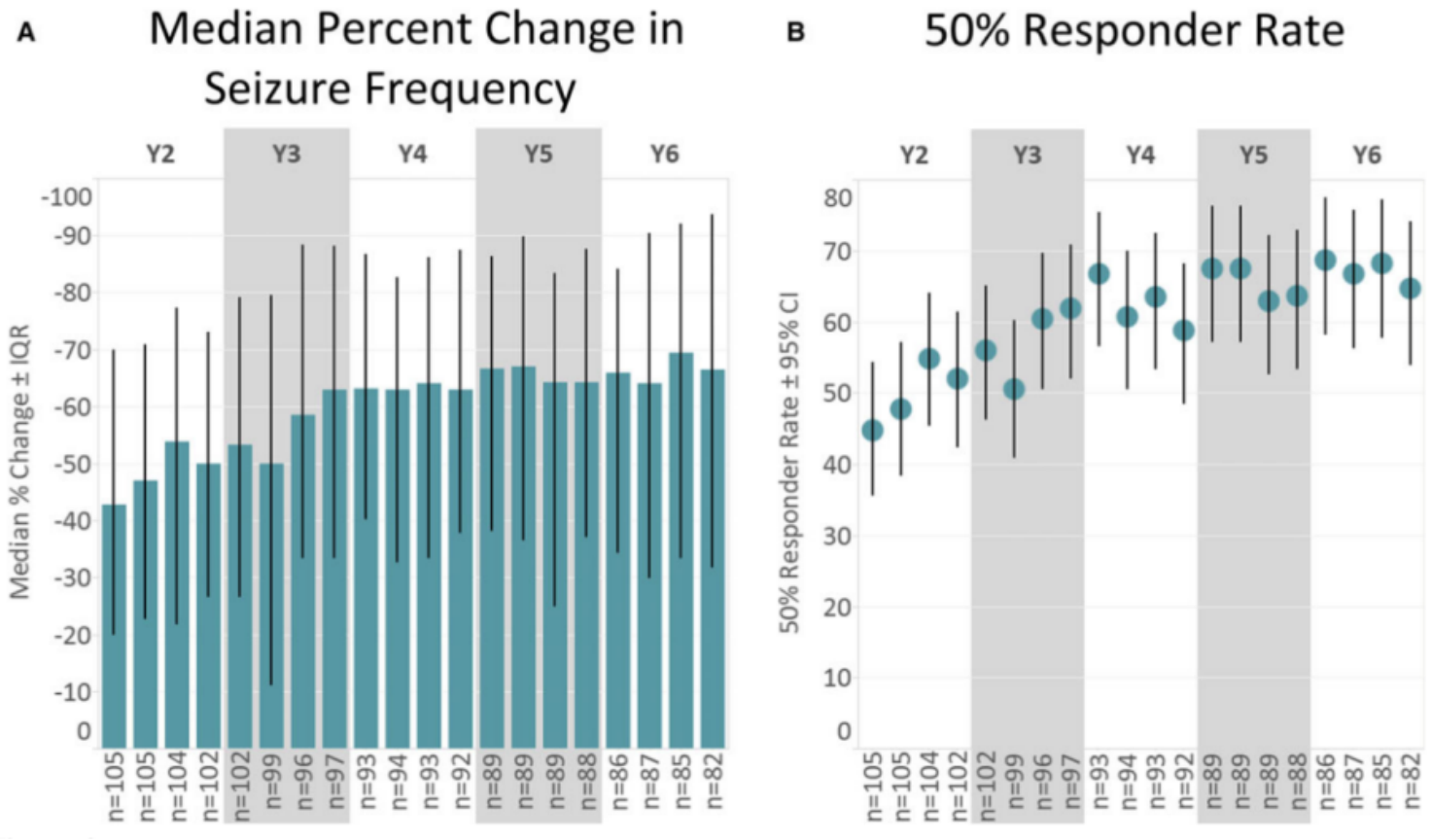
The Official Journal of the American Academy of Neurology

Epilepsia, 58(6):994–1004, 2017
doi: 10.1111/epi.13740

Epilepsia
Official Journal of the International League Against Epilepsy

Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy



111 patients, 72% bilateral. Median 70% seizure reduction at mean 6 years

Epilepsia, 58(6):1005–1014, 2017
doi: 10.1111/epi.13739

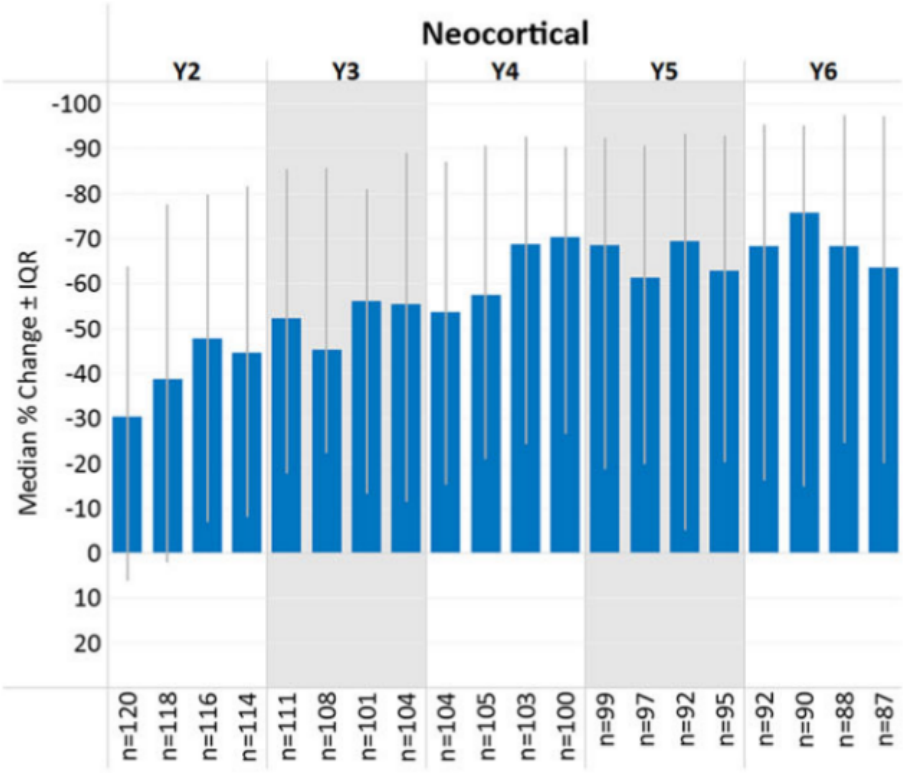
Epilepsia
Official Journal of the International League Against Epilepsy

Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas

126 patients

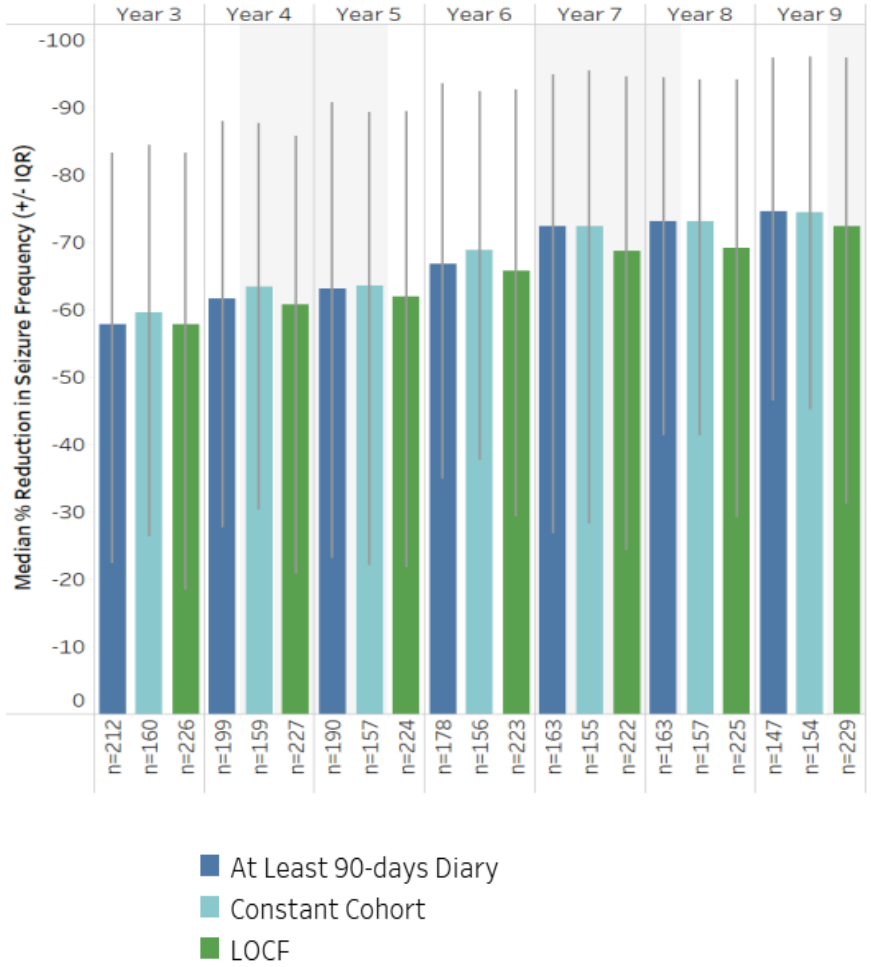
At mean 6 years, 70% seizure reduction with frontal/parietal, 58% temporal neocortical, 51% multilobar.

The rates of infection (0.017 per patient implant year) and perioperative hemorrhage (0.8%) similar to other neurostimulation devices.



Long-Term 9 Year RNS Outcomes

75% median seizure reduction at year 9



73% achieved ≥50% seizure reduction at year 9

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

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

Lobe	Median % Reduction	Responder Rate
MTL (n=66)	73% (58-96%)	77%
Neocortical (n=70)	81% (34-100%)	70%

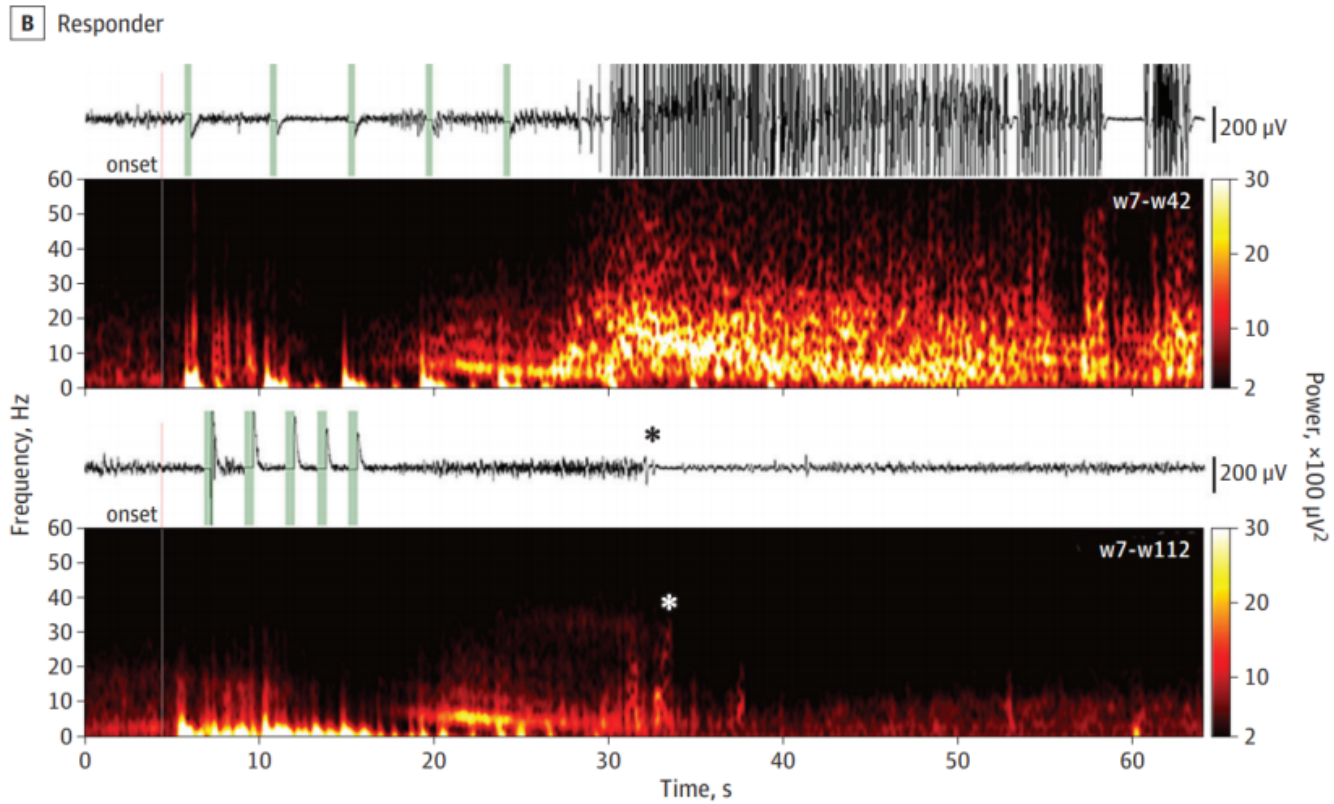
Nair D. et al, American Epilepsy Society Poster, 2018

JAMA Neurol. 2019;76(7):800-808. doi:10.1001/jamaneurol.2019.0658
Published online April 15, 2019.

JAMA Neurology | Original Investigation

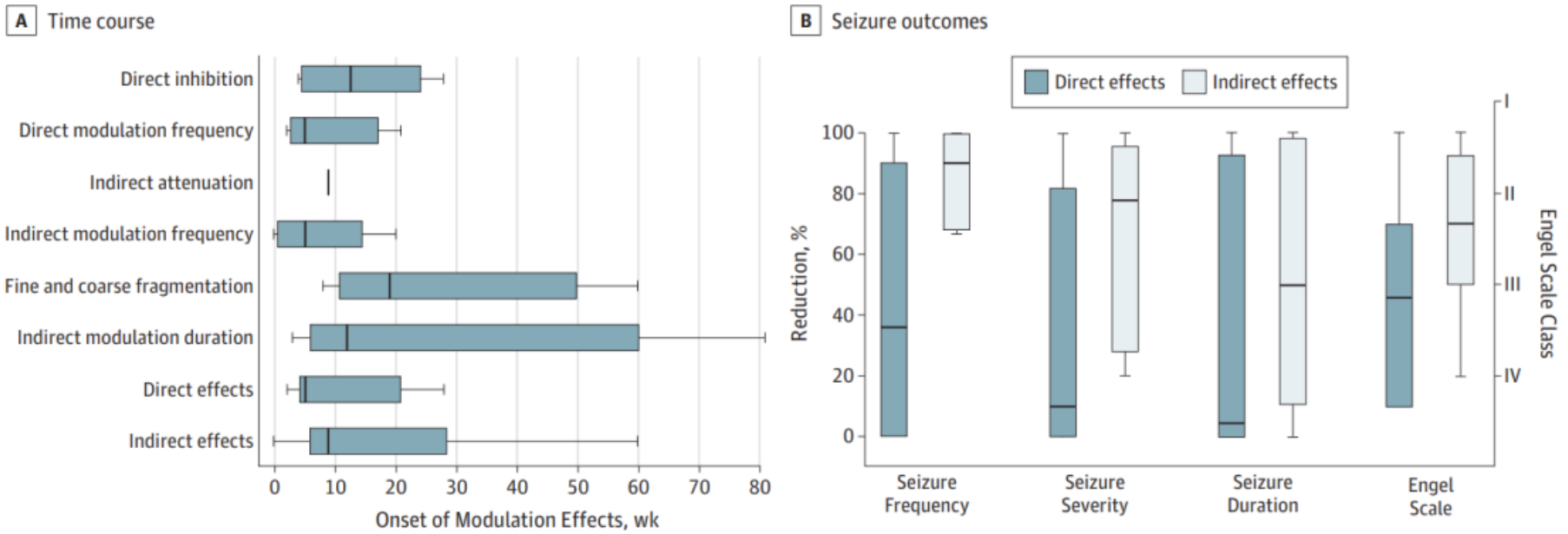
Association of Closed-Loop Brain Stimulation Neurophysiological Features With Seizure Control Among Patients With Focal Epilepsy

Vasileios Kokkinos, PhD; Nathaniel D. Sisterson, BA; Thomas A. Wozny, MD; R. Mark Richardson, MD, PhD



effect). B, Patient 11 (responder), whose typical ESP starts with a diffuse electro-decrement followed by the development of a theta-range (4-8 Hz) rhythm evolving into high–amplitude/power paroxysmal wide-band delta- to beta-range (2-30 Hz) rhythms overlaid with higher gamma (>30 Hz) frequencies (top). From weeks 7 to 112, a distinct number of ESPs were observed in which the development of the ongoing activity was spontaneously interrupted (bottom; asterisk) and the electrocorticography returned to normal background levels. Note that attenuation occurs more than 27 seconds after the first stimulation pulse and the bulk of stimulation ends almost 11 seconds before this spontaneous inhibition. Vertical lines represent ESP onsets (red) and stimulation events (green). w Indicates week of stimulation.

Figure 5. Electrographic Seizure Pattern Effects: Time Course and Association With Seizure Outcomes



These findings suggest that RNS effectiveness may be explained by long-term, stimulation-induced modulation of seizure network activity rather than by direct effects on each detected seizure.

Epilepsy & Behavior 83 (2018) 192–200

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation

Tara L. Skarpaas [a,*], Thomas K. Tcheng [a], Martha J. Morrell [a,b]

[a] NeuroPace, Inc., Mountain View, CA, Clinical and Research Departments, United States
[b] Stanford University School of Medicine, Stanford, CA, Neurology Department, United States

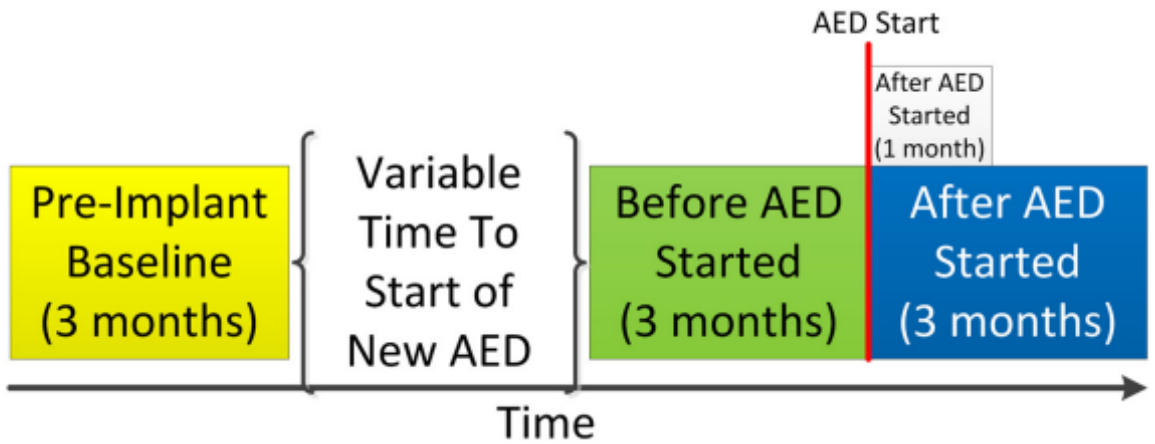
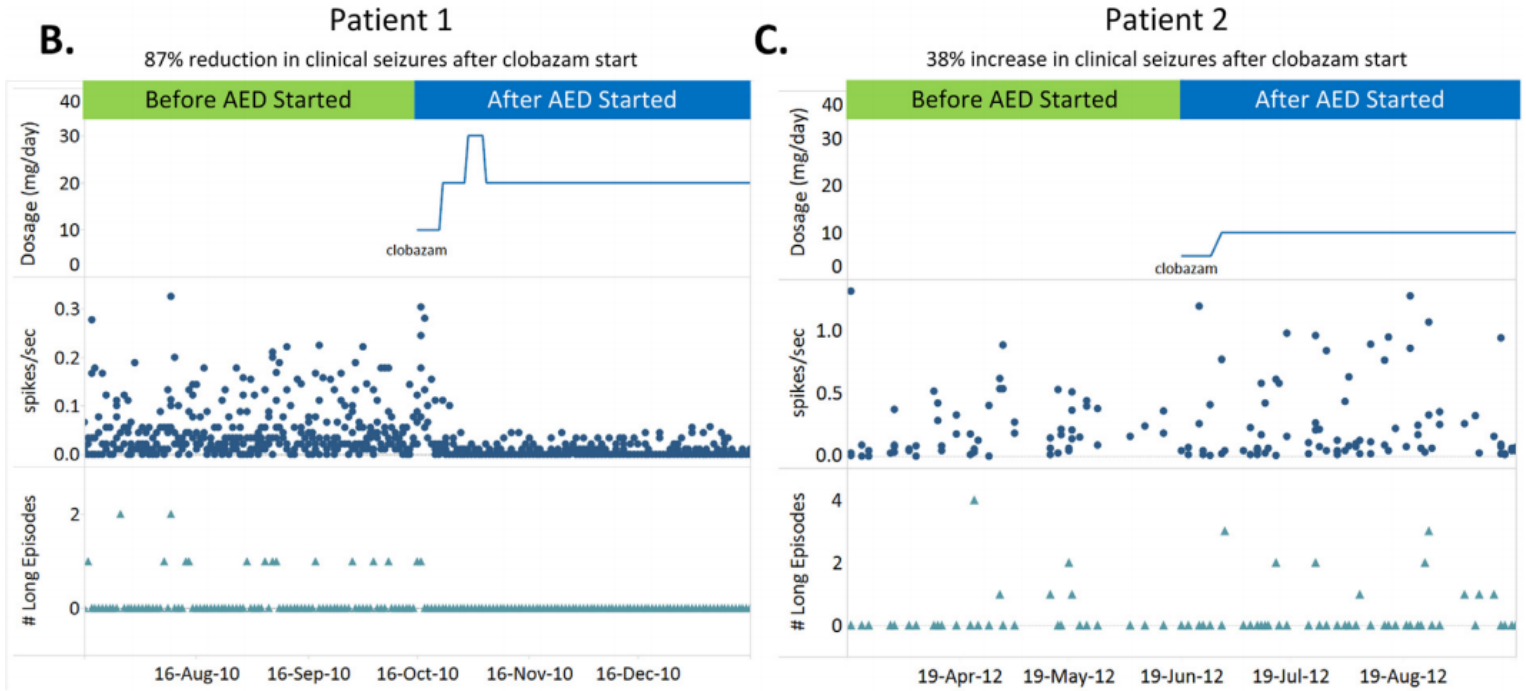
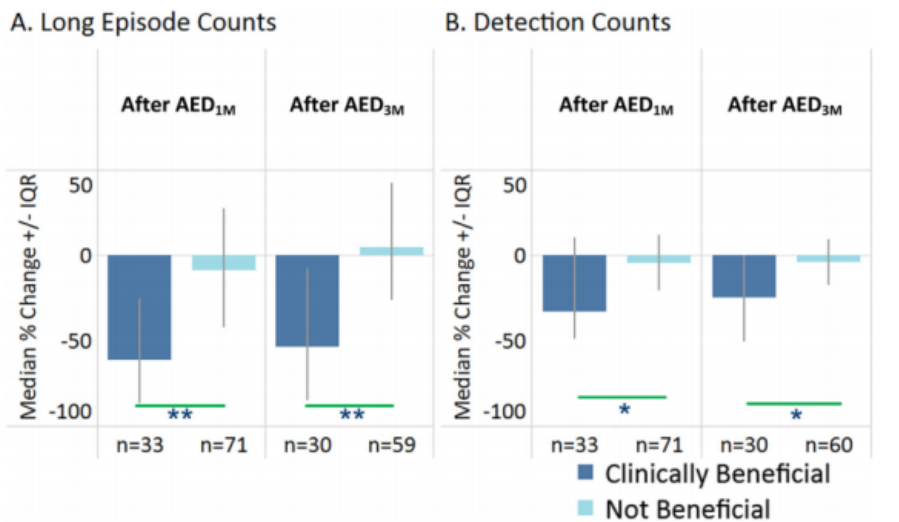
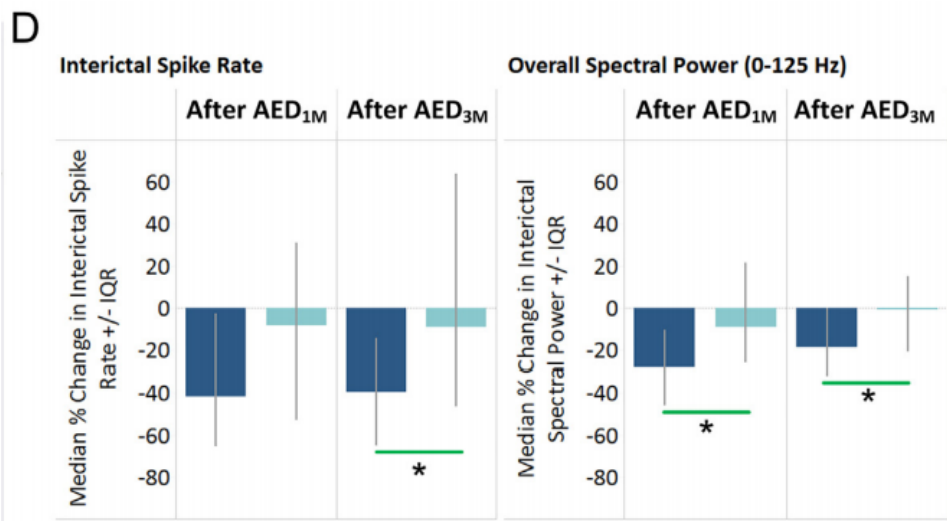


Table 1
Most common AEDs started.

AED	N
Clobazam	48
Lacosamide	111
Levetiracetam	35
Pregabalin	30


B.
Patient 1
87% reduction in clinical seizures after clobazam start
Before AED Started
After AED Started
Dosage (mg/day)
clobazam
spikes/sec
Long Episodes
16-Aug-10
16-Sep-10
16-Oct-10
16-Nov-10
16-Dec-10
C.
Patient 2
38% increase in clinical seizures after clobazam start
Before AED Started
After AED Started
Dosage (mg/day)
clobazam
spikes/sec
Long Episodes
19-Apr-12
19-May-12
19-Jun-12
19-Jul-12
19-Aug-12

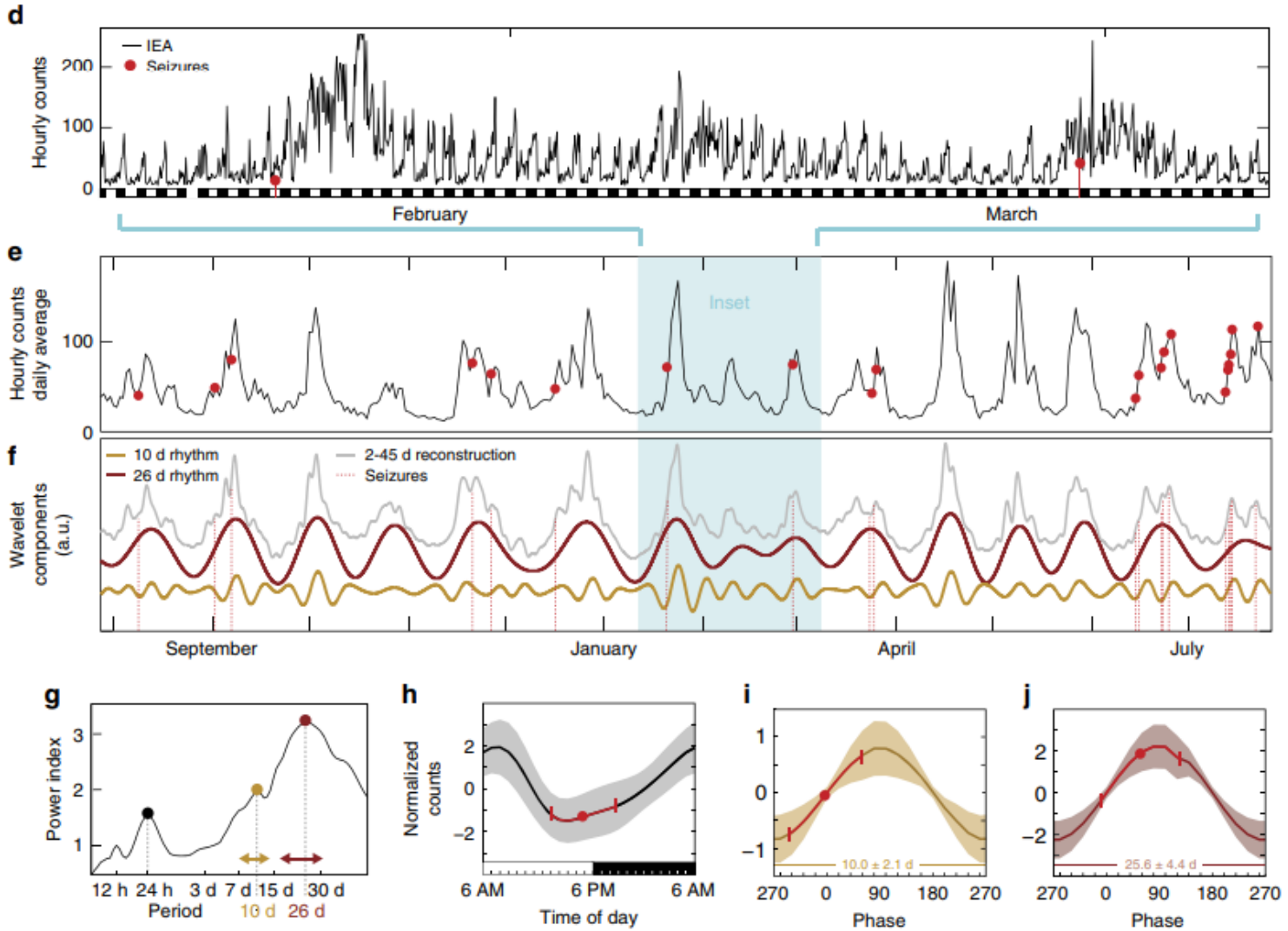

A. Long Episode Counts
B. Detection Counts
After AED1M
After AED3M
Median % Change +/- IQR
n=33
n=71
n=30
n=59
n=60
Clinically Beneficial
Not Beneficial


D
Interictal Spike Rate
Overall Spectral Power (0-125 Hz)
After AED1M
After AED3M
Median % Change in Interictal Spike Rate +/- IQR
Median % Change in Interictal Spectral Power +/- IQR

Multi-day rhythms modulate seizure risk in epilepsy

NATURE COMMUNICATIONS | (2018)9:88

Maxime O. Baud[1,2,3,4], Jonathan K. Kleen[1], Emily A. Mirro[5], Jason C. Andrechak[6], David King-Stephens[7], Edward F. Chang[8] & Vikram R. Rao[1]



AMERICAN EPILEPSY SOCIETY

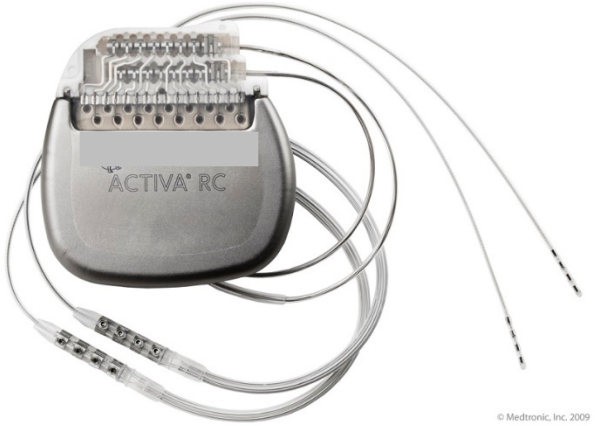
(Abst. 2.075), 2018

NINE-YEAR PROSPECTIVE SAFETY AND EFFECTIVENESS OUTCOMES FROM THE LONG-TERM TREATMENT TRIAL OF THE RNS® SYSTEM

Authors: Dileep R. Nair, Cleveland Clinic; RNS System Investigators; and Martha J. Morrell, Stanford University / NeuroPace, Inc.

- N = 256 implanted subjects, 1895 device years experience
- 75% median decrease seizure frequency at 9 years
- (67.2% using last observation carried forward)
- 30% with 6-month, 19% with 12-month seizure free period
- No device related serious adverse events

Deep Brain Stimulation (DBS)



Courtesy of Medtronic

1997: DBS for tremor symptoms in PD

2002: Advanced PD

2003: Dystonia: humanitarian device exemption

2016: Earlier PD

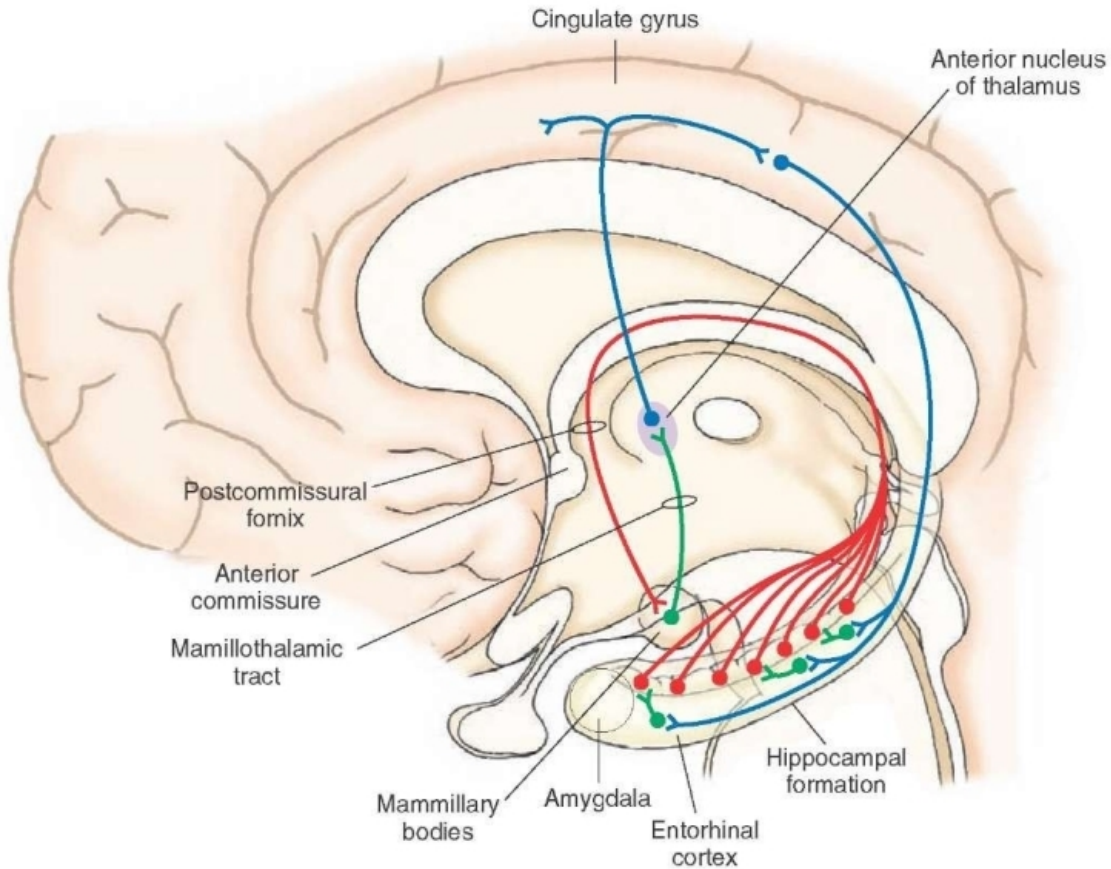
2018: Epilepsy

Int J Neurol. 1984;18:179-87.

Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man

I S Cooper, A R Upton, I Amin, S Garnett, G M Brown, M Springman

PMID: 6242978



FDA Approval: Medtronic Deep Brain Stimulation for Medically Refractory Epilepsy

Back

Tuesday, May 1, 2018

The U.S. Food and Drug Administration (FDA) granted approval for the use of Deep Brain Stimulation (DBS) therapy by Medtronic as add-on treatment for focal epilepsy. It is being approved for use in the following people:

- Age 18 years and older
- Have focal onset (also called partial) seizures
- Have medically refractory epilepsy (also called drug-resistant epilepsy). This means that their seizures have not been controlled with at least trials of 3 anti-seizure medications.

Epilepsia
Official Journal of the International League Against Epilepsy

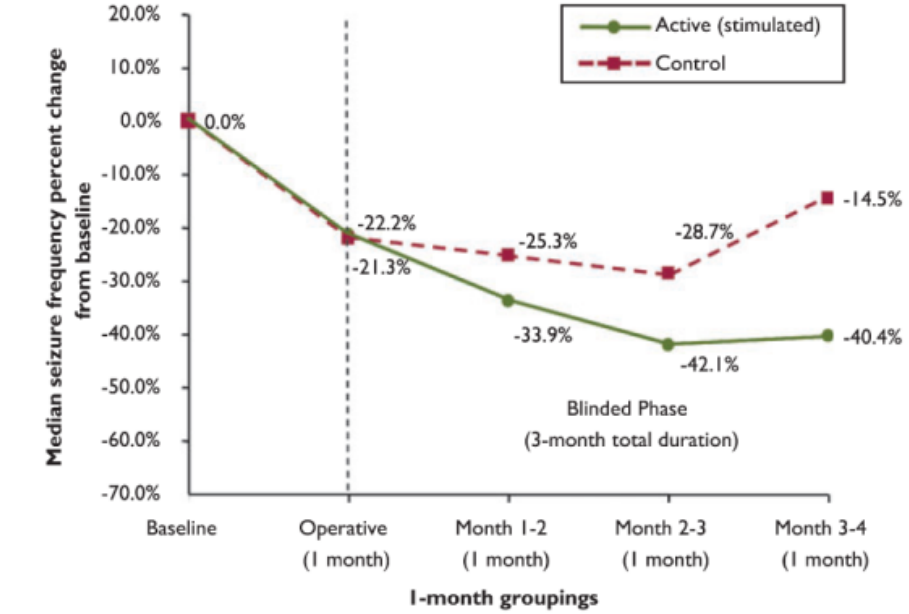
Epilepsia, 51(5):899–908, 2010
doi: 10.1111/j.1528-1167.2010.02536.x

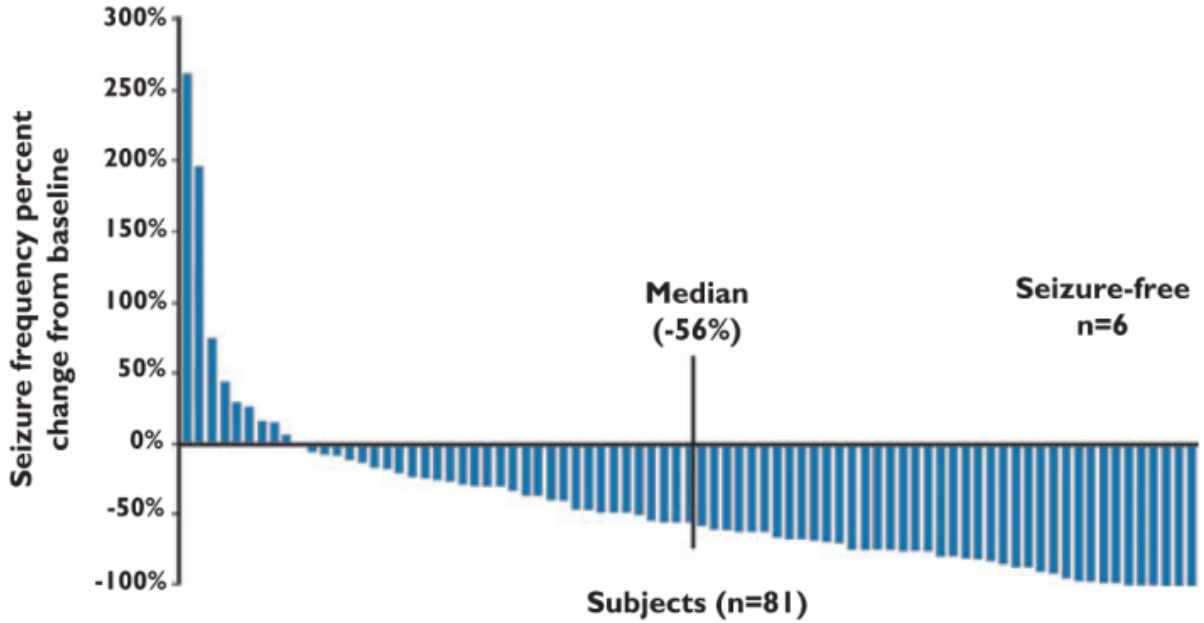
FULL-LENGTH ORIGINAL RESEARCH

Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy

*Robert Fisher, †Vicenta Salanova, †Thomas Witt, †Robert Worth, ‡Thomas Henry, ‡Robert Gross, §Kalarickal Oommen, ¶Ivan Osorio, ¶Jules Nazzaro, #Douglas Labar, #Michael Kaplitt, **Michael Sperling, ††Evan Sandok, ††John Neal, ‡‡Adrian Handforth, §§John Stern, ‡‡Antonio DeSalles, ¶¶Steve Chung, ¶¶Andrew Shetter, ##Donna Bergen, ##Roy Bakay, *Jaimie Henderson, ***Jacqueline French, ***Gordon Baltuch, †††William Rosenfeld, †††Andrew Youkilis, ‡‡‡William Marks, ‡‡‡Paul Garcia, ‡‡‡Nicolas Barbaro, §§§Nathan Fountain, ¶¶¶Carl Bazil, ¶¶¶Robert Goodman, ¶¶¶Guy McKhann, ###K. Babu Krishnamurthy, ###Steven Papavassiliou, ‡Charles Epstein, ***John Pollard, ****Lisa Tonder, ****Joan Grebin, ****Robert Coffey, ****Nina Graves, and the SANTE Study Group[!]

110 patients implanted and randomized to stimulation or no stimulation for 3 months, then all received stimulation for 2 years





Fisher et al., Epilepsia. 2010. 51(5):899-910.

Biggest impact on consciousness-impairing seizures (CPS, GTCS)

By 2 years, 56% median reduction in seizure frequency

54% of patients had a seizure reduction of at least 50%

AMERICAN EPILEPSY SOCIETY

LONG TERM OUTCOMES OF THE SANTE TRIAL: 7-YEAR FOLLOW-UP

Authors: Evan Sandok, Marshfield Clinic, Marshfield, Wisconsin; Michael Sperling, Thomas Jefferson University, Philadelphia, Pennsylvania; Robert E. Gross, Emory University, Atlanta, Georgia; and Robert Fisher, Stanford University School of Medicine

- N=50 of original 110
- 75% median seizure frequency decrease at 7 years
- 70% using last observation carried forward
- 74% responder rate (>50% decreased frequency)
- 18% with at least one 6-month seizure-free interval
- 9 subjects seizure free for preceding year
- Quality of life measure (QOLIE-31) showed significant improvements

Seizure 45 (2017) 133–141

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy

Alexander I. Tröster[a,*], Kimford J. Meador[b], Christopher P. Irwin[c], Robert S. Fisher[b], for the SANTE Study Group

- Improved scores on executive function and attention with stimulation
- No declines in cognitive or depression scores across a broad array of cognitive tests
- Some subjective memory and depression complaints

AMERICAN EPILEPSY SOCIETY

(Abst. 1.087), 2018

FINAL LONG-TERM SAFETY RESULTS OF THE SANTE STUDY: MORE THAN 10 YEARS OF FOLLOW-UP

Authors: Vincenta Salanova, Indiana University and Robert Fisher, Stanford University School of Medicine

- N = 110 implanted subjects, 938 device years experience
- No serious adverse events related to stimulation
- Two SUDEP deaths (2 per 1000 patient years), which is comparable to or better than historical controls

BRAIN
A JOURNAL OF NEUROLOGY

High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans

BRAIN 2018: 141; 2631–2643

Tao Yu,[1] Xueyuan Wang,[1] Yongjie Li,[1] Guojun Zhang,[1] Gregory Worrell,[2] Patrick Chauvel,[3] Duanyu Ni,[1] Liang Qiao,[1] Chang Liu,[1] Liping Li,[4] Liankun Ren[4] and Yuping Wang[4]

What are the mechanisms of ANT DBS?

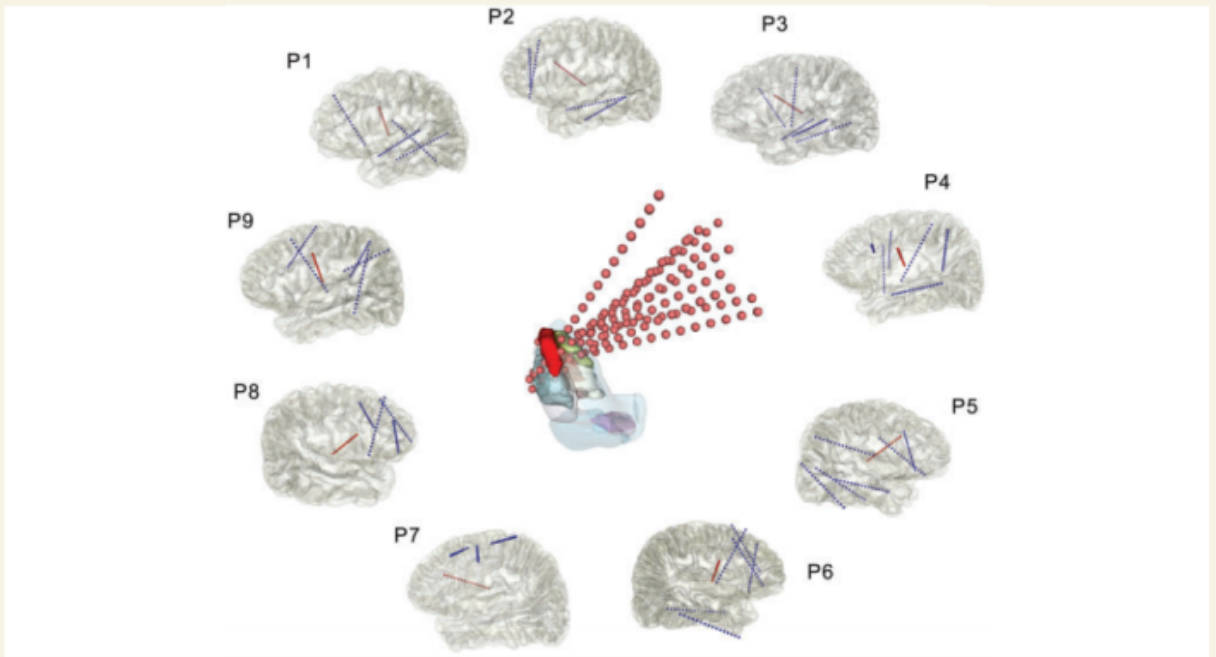
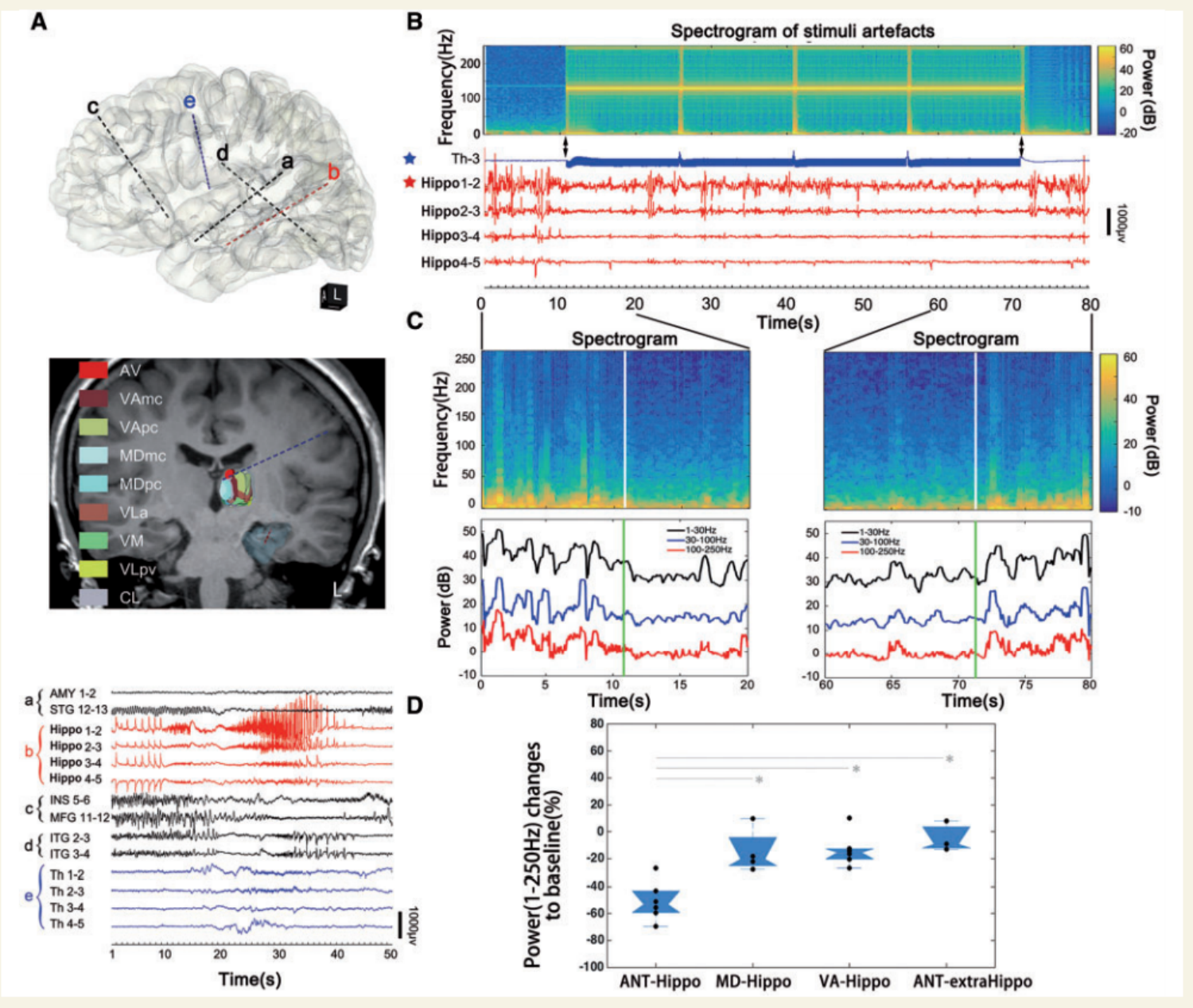


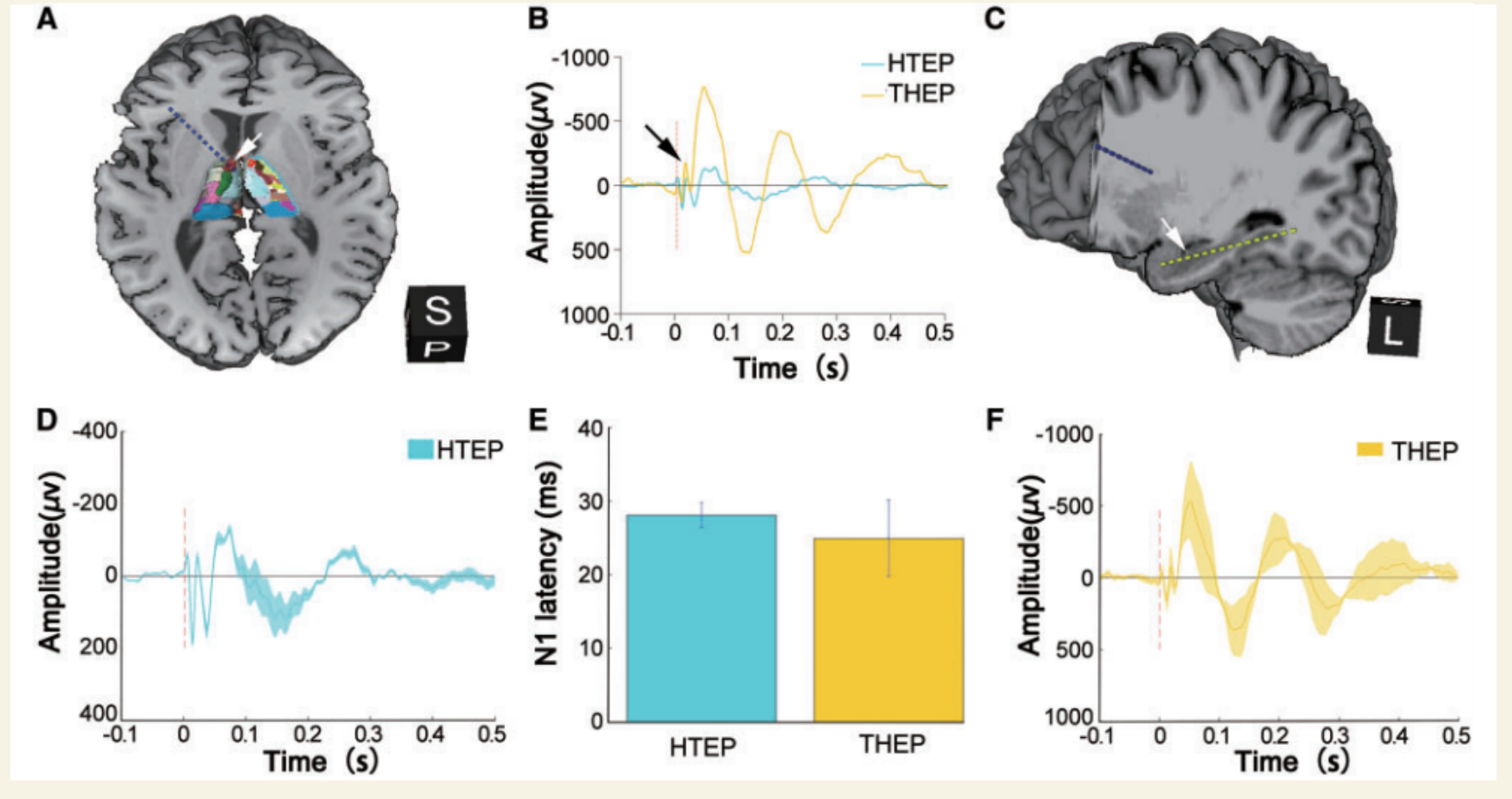
Figure 1 Reconstruction of depth electrodes. The peripheral images show reconstruction of depth electrodes into brain of all nine patients. The red colour-coded electrode was the electrode that was extended into thalamus. The *centre* image showed electrodes into thalamus of all patients overlaid onto the thalamic template (note, the electrodes on left side were flipped into the right side). The blue, red and green colour label the mediodorsal nucleus (MD), anteroventral (AV) of ANT and ventral anterior nucleus (VA), respectively.



15-45 Hz stim: synchronized hippocampal activity; >45 Hz stim: desynchronized.

Yu et al., Brain 2018. 141(9):2631-2643.

Reciprocal Connectivity Between Hippocampus and the Ipsilateral ANT



Yu et al., Brain 2018. 141(9):2631-2643.

FULL-LENGTH ORIGINAL RESEARCH

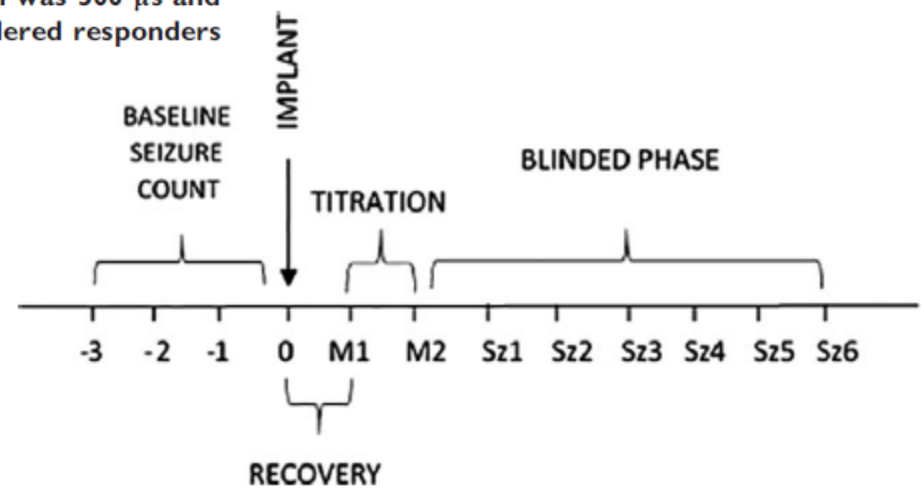
Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study

*†Arthur Cukiert, †Cristine Mella Cukiert, †Jose Augusto Burattini, †Pedro Paulo Mariani, and *Daniela Fontes Bezerra

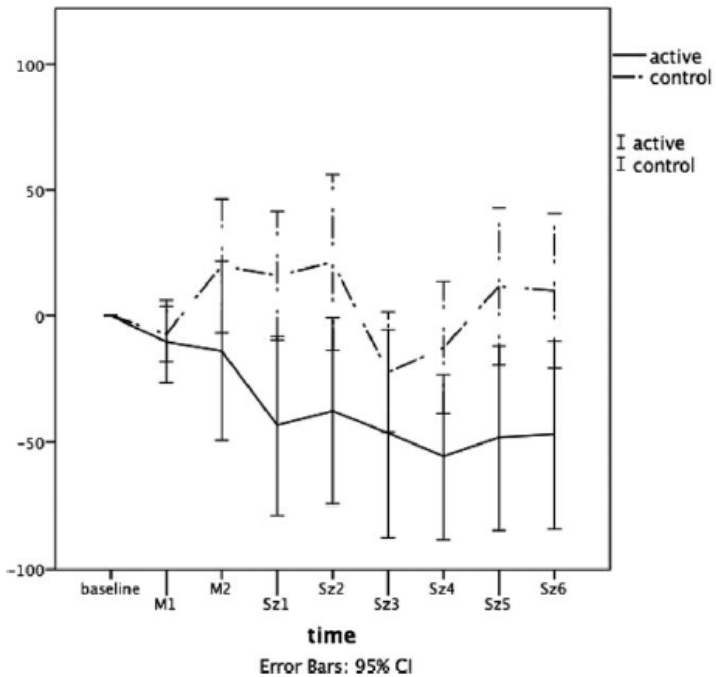
Epilepsia, **(*):1–6, 2017
doi: 10.1111/epi.13860

Objective: We designed a prospective, randomized, controlled, double-blind study to evaluate the efficacy of hippocampal deep brain stimulation (Hip-DBS) in patients with refractory temporary lobe epilepsy (TLE).

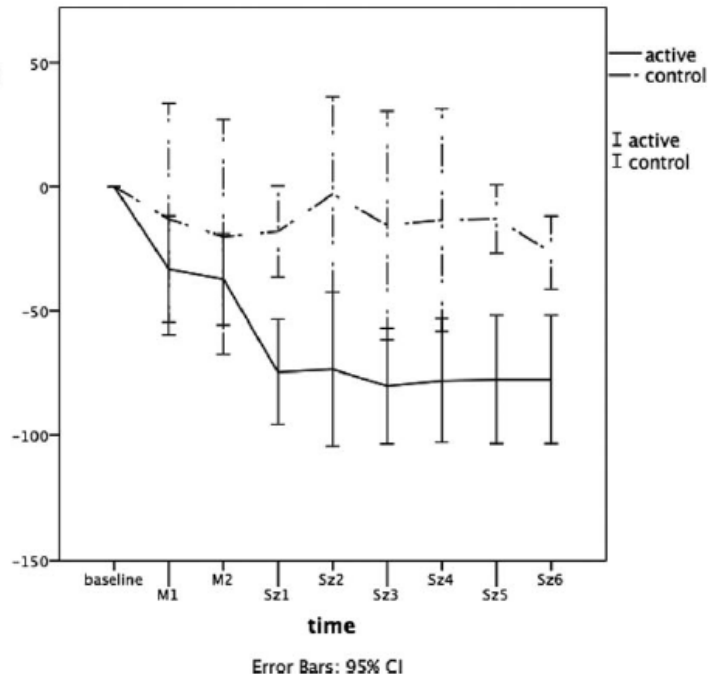
Methods: Sixteen adult patients with refractory TLE were studied. Patient's workup included medical history, interictal and ictal electroencephalography (EEG), and high-resolution 1.5T magnetic resonance imaging (MRI). Patients were randomized on a 1:1 proportion to an active (stimulation on) or to a control (no stimulation) arm. After implantation, patients were allowed to recover for 1 month, which was followed by a 1-month titration (or sham) period. The 6-month blinded phase started immediately afterward. A postoperative MRI confirmed the electrode's position in all patients. All patients received bipolar continuous stimulation. Stimulus duration was 300 μs and frequency was 130 Hz; final intensity was 2 V. Patients were considered responders when they had at least 50% seizure frequency reduction.



FAS



FIAS



Results: All patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). Mean preoperative seizure frequency was 12.5 $\pm$ 9.4 (mean $\pm$ standard deviation) per month. MRI findings were normal in two patients, disclosed bilateral mesial temporal sclerosis (MTS) in three, left MTS in five, and right MTS in six patients. An insertional effect could be noted in both control and active patients. In the active group (n = 8), four patients became seizure-free; seven of eight were considered responders and one was a nonresponder. There was a significant difference regarding FIAS frequency between the two groups from the first month of full stimulation ($p < 0.001$) until the end of the blinded phase ($p < 0.001$). This was also true for FAS, except for the third month of the blinded phase.

Significance: Hip-DBS was effective in significantly reducing seizure frequency in patients with refractory TLE in the active group, as compared to the control group. Fifty-percent of the patients in the active group became seizure-free. The present study is the larger prospective, controlled, double-blind study to evaluate the effects of Hip-DBS published to date.

Epilepsia
Official Journal of the International League Against Epilepsy

Full-Length Original Research | Free Access

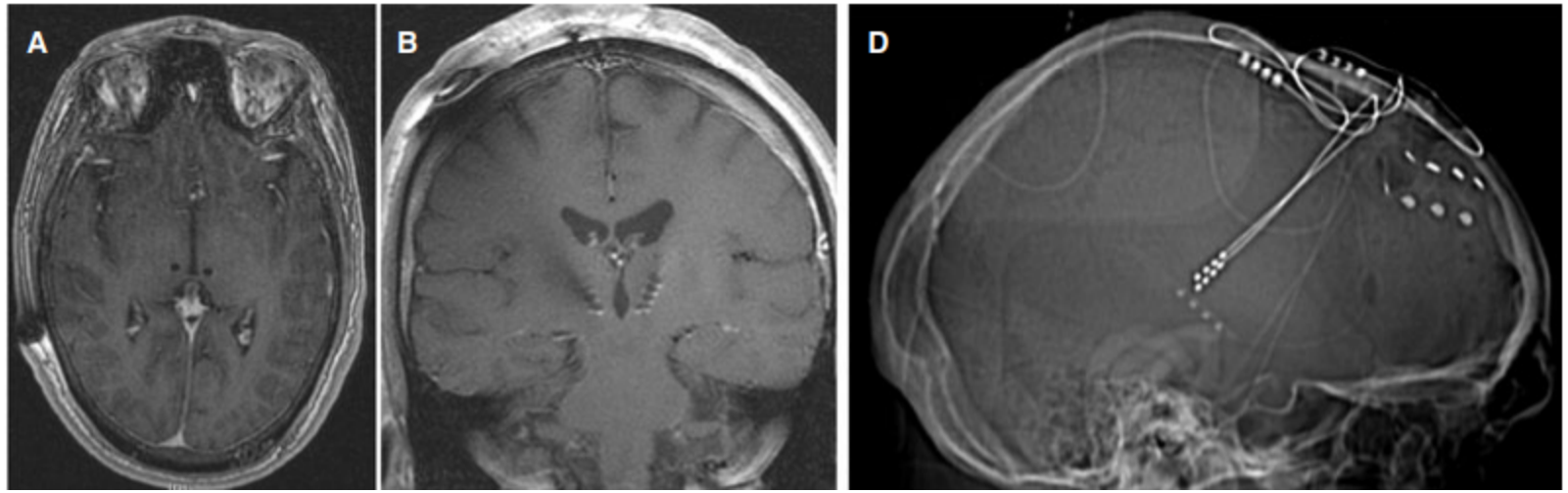
Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies

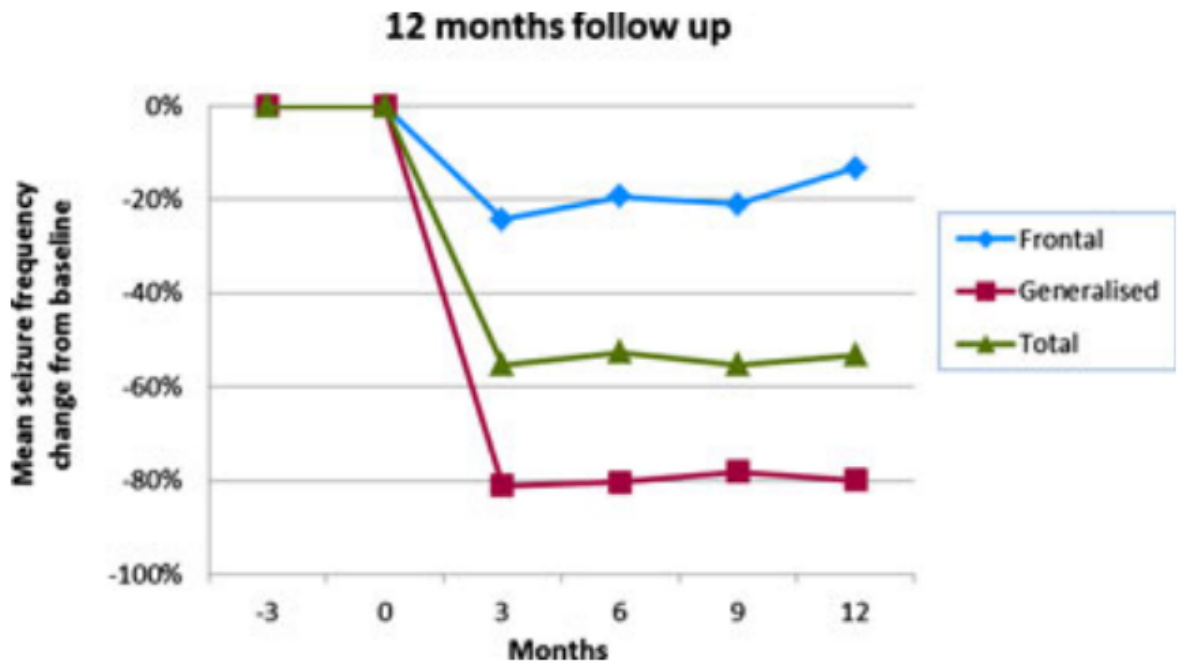
Antonio Valentín, Eduardo García Navarrete, Ramesh Chelvarajah, Cristina Torres, Marta Navas, Lelia Vico, Nerea Torres, Jesus Pastor, Richard Selway, Rafael G. Sola, Gonzalo Alarcon

First published: 13 September 2013 | https://doi.org/10.1111/epi.12352 | Cited by: 70

Purpose: **Deep brain stimulation (DBS) of the thalamus is an emerging surgical option for people with medically refractory epilepsy that is not suitable for resective surgery, or in whom surgery has failed. Our main aim was to evaluate the efficacy of bilateral centromedian thalamic nucleus (CMN) DBS for seizure control in generalized epilepsy and frontal lobe epilepsy with a two-center, single-blind, controlled trial.**

Methods: **Participants were adults with refractory generalized or frontal lobe epilepsy. Seizure diaries were kept by patients/carers prospectively from enrollment. The baseline preimplantation period was followed by a control period consisting of a blind stimulation-OFF phase of at least 3 months, a 3-month blind stimulation-ON phase, and a 6-month unblinded stimulation-ON phase. The control period was followed by an unblinded long-term extension phase with stimulation-ON in those patients in whom stimulation was thought to be effective.**





Key Findings: Eleven patients were recruited at King's College Hospital (London, United Kingdom United Kingdom) and at University Hospital La Princesa (Madrid, Spain). Among the five patients with frontal lobe epilepsy, only one patient had >50% improvement in seizure frequency during the blind period. In the long-term extension phase, two patients with frontal lobe epilepsy had >50% improvement in seizure frequency. All six patients with generalized epilepsy had >50% improvement in seizure frequency during the blind period. In the long-term extension phase, five of the six patients showed >50% improvement in the frequency of major seizures (one became seizure free, one had >99% improvement, and three had 60–95% reduction in seizure frequency). Among patients with generalized epilepsy, the DBS implantation itself appears to be effective, as two patients remained seizure free during 12 and 50 months with DBS OFF, and the remaining four had 50–91% improvement in the initial 3 months with DBS OFF.

Significance: DBS implantation and stimulation of the CMN appears to be a safe and efficacious treatment, particularly in patients with refractory generalized epilepsy. CMN stimulation was not as effective in frontal lobe epilepsy, which requires further studies. DBS of the CMN should be considered as a treatment option, particularly in patients with refractory generalized epilepsy syndromes.

Current and Future Directions

- Improved patient selection: not one-size fits all

- VNS (open loop)
  - Evaluation of closed-loop stimulation (?EEG driven)
  - Improved stimulation paradigms
- RNS
  - Improved detection and stimulation algorithms: Is it the responsive stimulation or cumulative stimulation?
  - Additional electrodes
  - Closed loop subcortical stimulation
- DBS
  - Improved targeting, relating outcomes to placement
  - Comparison of different targets
  - Study in generalized epilepsy syndromes
  - Further studies of mechanisms

VNS: Advantages and Disadvantages

- Advantages
  - Least invasive (not intracranial)
  - Shortest recovery
  - Relatively easy to program and easy to manage
  - Does not require localization
    - Efficacy in generalized and multifocal epilepsy

- Disadvantages
  - Seizure reduction rates appear lower
  - Most stimulation side effects, particularly at higher currents
  - Room for innovation may be more limited
  - No data output to improve therapy

DBS: Advantages and Disadvantages

- Advantages
  - Greater seizure reduction rates with brain stimulation
  - Relatively easy to program and easy to manage
  - Does not require localization
    - Efficacy in multifocal epilepsy (generalized?)

- Disadvantages
  - Less data vs RNS is recent studies
  - No data output to improve therapy
  - More invasive than VNS

RNS: Advantages and Disadvantages

- **Advantages**
  - Greater seizure reduction rates with brain stimulation
  - Data output provides feedback and guides therapy
  - Greater potential to innovate with closed-loop stimulation

- **Disadvantages**
  - Requires localization hypothesis
  - Requires more effort from patient and physician programmer
  - More invasive than VNS

Thanks!

Dario.Englot@vumc.org
@englot

BIEN lab