# Drug-Device Combinations for Epilepsy

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# M.I.: 32 year old woman

First generalized tonic clonic seizure (GTC) 5 years ago while studying for D.C. Bar

- 4 days later, admitted emergently with a series of GTCs
- Diagnosis: probable viral encephalitis

Now has seizure flurries every 3- 4 weeks; prodrome of doom that often evolves to GTC; amnestic for seizures

- Trials of 8 different antiseizure medications without control
- Not epilepsy surgery candidate- seizure foci include essential memory areas

Memory and concentration poor

- Unemployed, depressed and withdrawn; suicidal thoughts

# M. I.

Assessment:

- Medically intractable partial and secondarily generalized seizures which are life threatening
- Social and vocational disability
- Cognitive deficits and mood disturbance

Differential diagnosis:

- Brain injury from encephalitis
- Acute and chronic effects of multiple seizures
- Side effects from antiepileptic medications
- The loss of a normal life

***What am I treating?***

# Seizures and Epilepsy

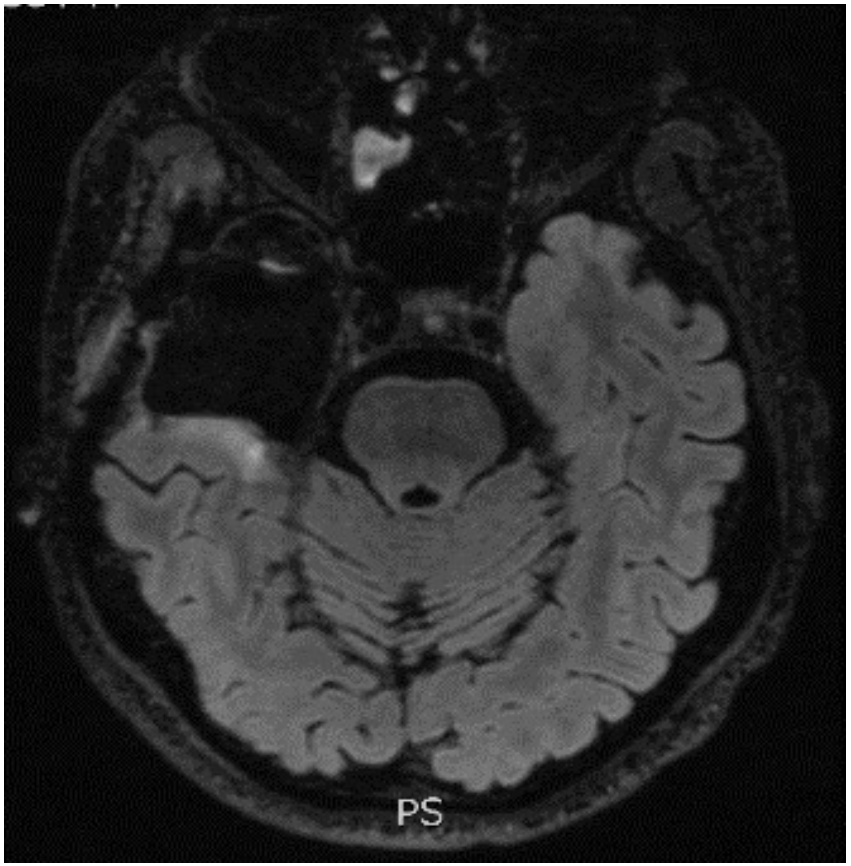
- Epilepsy: recurrent seizures caused by any of a number of brain conditions
  - ~ 1 in 100 people have epilepsy
- May affect a small focal area of the brain (partial) or the entire brain (generalized)
  - The area affected by the seizure loses its regular ability to function
- Comorbidities include missed educational and occupational opportunities, depression, anxiety, increased mortality
- Partial onset seizures are the most frequent type of uncontrolled epilepsy in adults

# FDA Approved Antiepileptic Medications

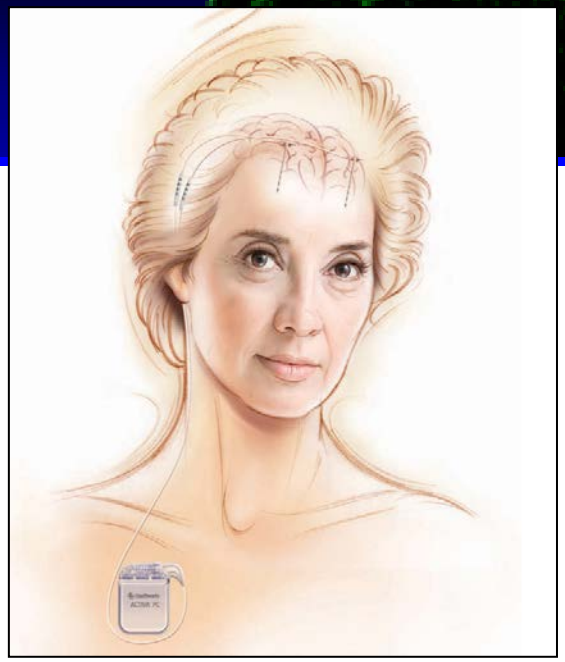
Despite new medications, ~30% of patients with partial onset seizures continue to have seizures

# Epilepsy Surgery

- ~ 15% of patients with intractable partial seizures are candidates for epilepsy surgery to remove or disconnect seizure focus
- Many are not candidates because of the risks of neurological deficits or the unlikelihood of a significant seizure reduction



# Devices for Epilepsy: Open Loop Stimulation for Partial Onset Seizures



Vagus Nerve Stimulation (VNS)

- RCTs demonstrated safety and efficacy
- Scheduled stimulation of the vagus nerve
- Approved by FDA in 1997 as adjunctive therapy for partial epilepsy

Deep Brain Stimulation (DBS)

- RCT for safety and efficacy in partial seizures
- Scheduled stimulation of the anterior nucleus of the thalamus
- Investigational in U.S; approved in > 30 countries outside U.S.

# Sensing Devices

MIT Watch: GSR

SmartWatch: Movement Monitor


Baby Monitor


Medpage MP5 Bed Seizure Detection Alarm

# Seizure Prediction and Alerting

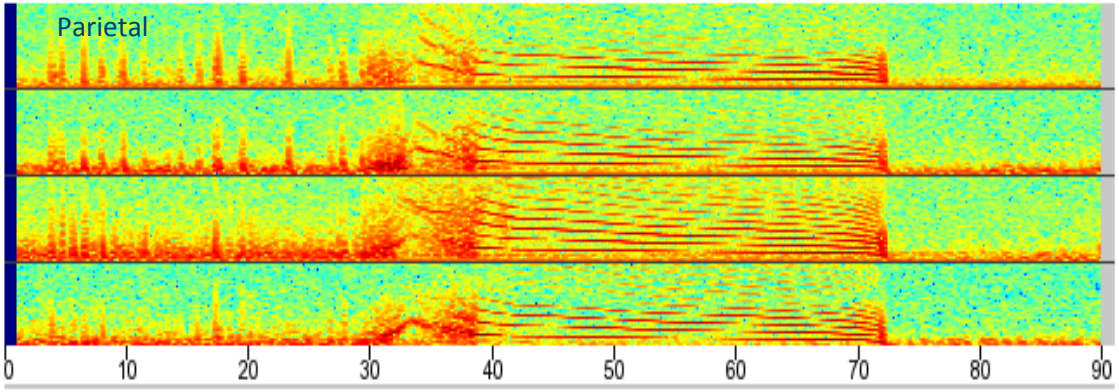
NeuroVista

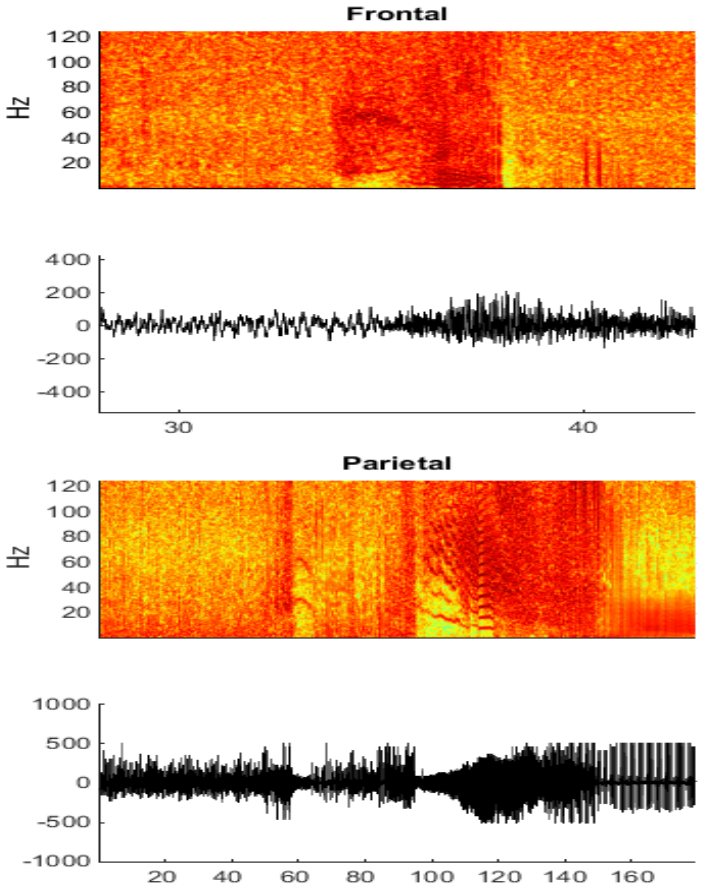
Investigational; not approved by U.S. FDA

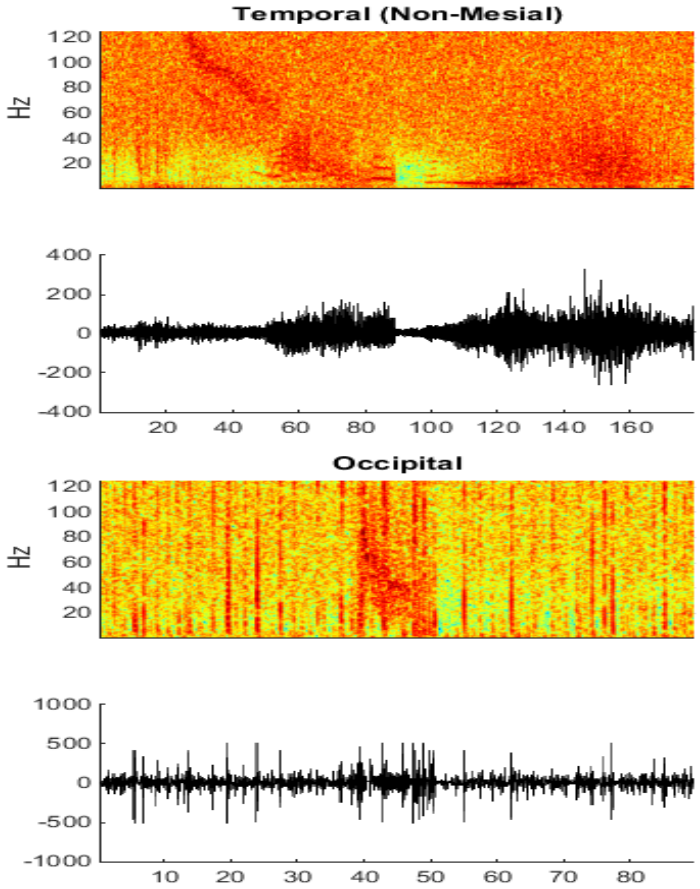
# Brain Responsive Neurostimulation: the RNS System

- Closed loop neurostimulation system approved by FDA for treatment for medically refractory, partial onset seizures for patients ≥ 18 years old
- 44% reduction in seizures at 1 year, 66% at 5 years
- Stimulation provided in response to detection of electrocorticographic patterns identified by physician
  - Detections individualized to patient
  - Total stimulation time < 6 minutes/day
  - Therapeutic stimulation not perceived by patient
- Long-term ambulatory ECoG data:
  - Physician reviews epileptiform activity, electrographic seizures and response to treatment

# Spectral Frequency and Electrocortico-graphic data displays: RNS System



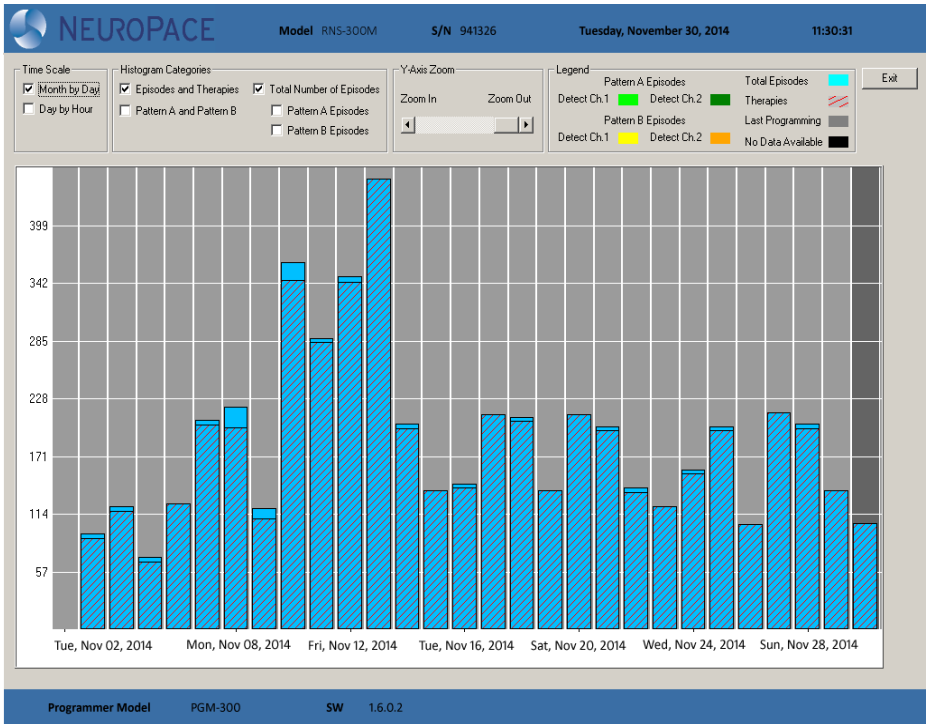



# Insights from Long-term Ambulatory Electrocorticographic (ECoG) Monitoring: the Power of Data

- Temporal patterns of seizures and epileptiform activity
- Biomarkers
- Individualized treatment
- Treatment synergies

# Temporal Patterns in Brain Epileptiform Activity as Recorded by RNS System

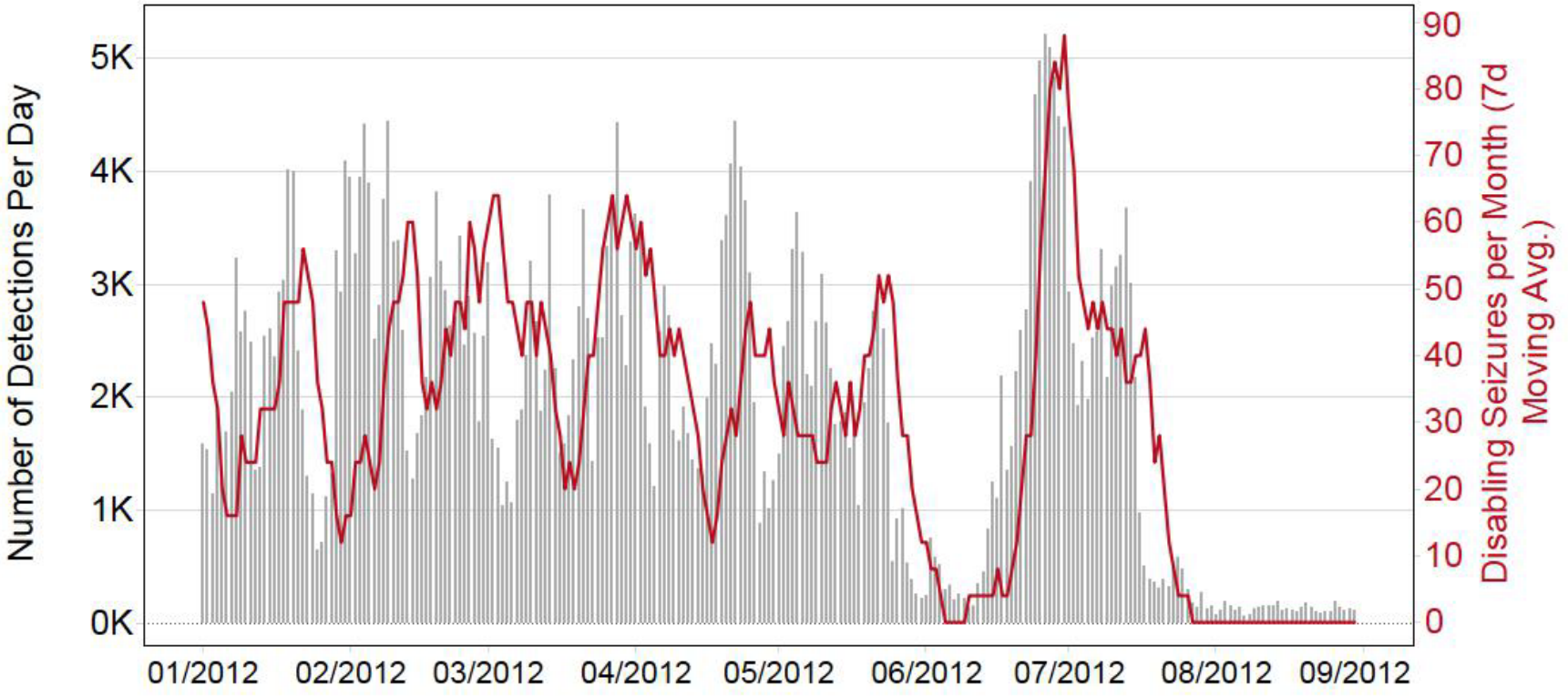





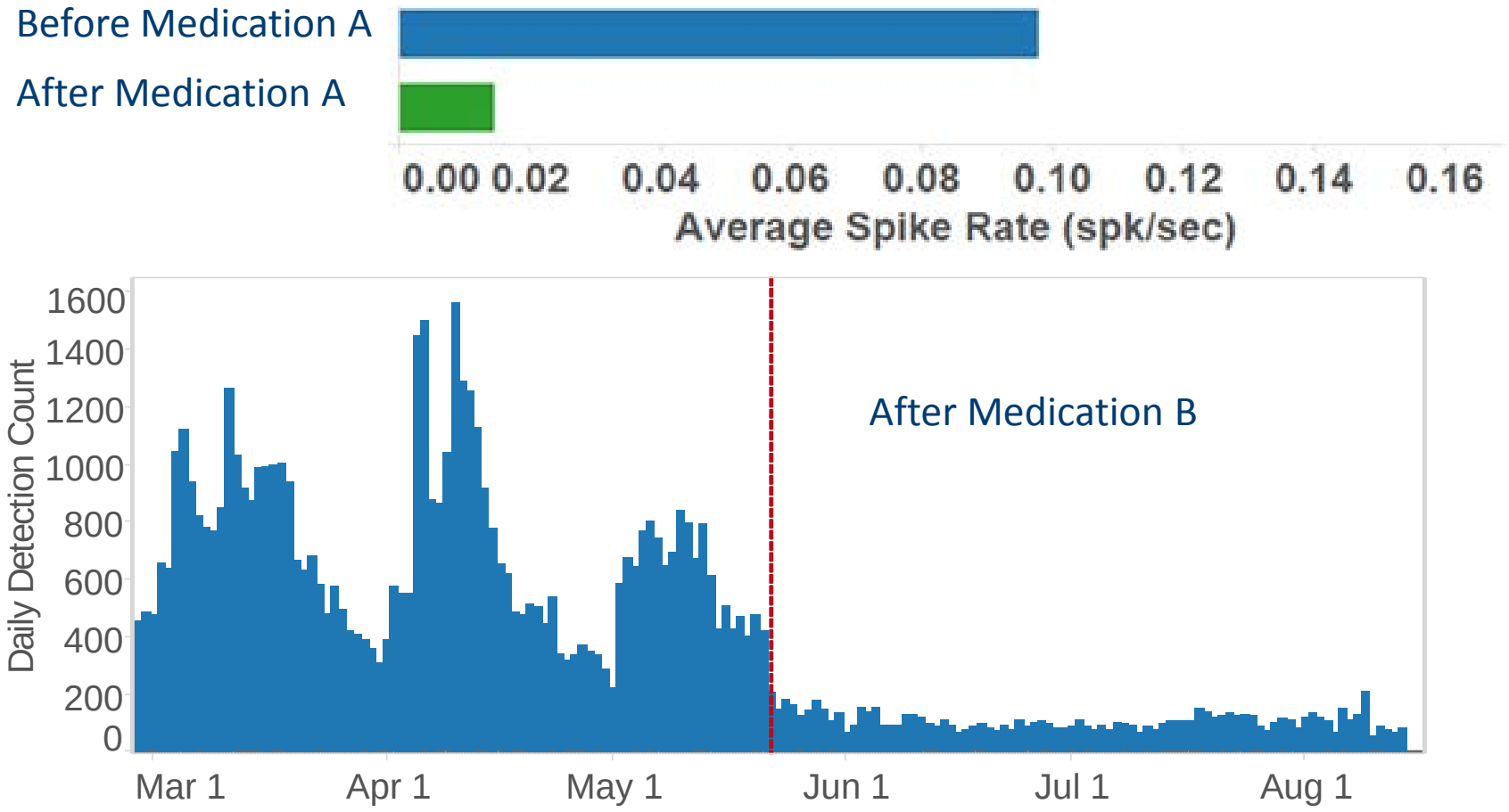

Daily Cycles
(Day by Hour)

Monthly Cycles
(Month by Day)

# Biomarkers: Correlation between Epileptiform Activity Recorded from the Brain and Clinical Seizures



# Electrographic Effects of Antiepileptic Medications as Recorded from RNS System




Detection of epileptiform abnormalities

Skarpaas et al., *American Epilepsy Society,* Dec 2013

# Drug and Device Epilepsy Therapies

- Effective antiepileptic medications with different MOA are available
- Safe and effective neurostimulation devices are available
  - MOA not known but clinical improvements acutely and over time suggest neuronal and network effects
- A responsive brain stimulation device is collecting clinical and long-term ambulatory ECoG data suitable for large scale data analytics
- Seizure alerting devices are proliferating as consumer products

# Drug-Device Combinations: Opportunities

Electrophysiological or behavioral event triggers:

- Targeted *temporal* delivery of drug
  - Alert sent to patient to use rescue medication
- Targeted *spatial* delivery of drug
  - Drug delivered from reservoir or lead, or activated at site by stimulation

Drugs selected to facilitate device effects:

- With cardiac devices, drugs that act by membrane stabilizing or use- dependent ion blockade are avoided– should this be the same with epilepsy devices?

# M. I.

- Treated with responsive stimulation at seizure foci in left and right temporal lobes
- Medications and stimulation settings adjusted based on clinical response and electrophysiological data
- Objective data indicates that increased epileptiform activity is correlated with increased suicidality
- Receiving multidisciplinary care from neurology, psychiatry and cognitive rehabilitation physicians
- Response being tracked over time

# Our Opportunity

*To go from this:*

*To this:*