Enhancing Epileptic Circuit Targeting for Optimizing Neurostimulation Therapy

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Driving Force for Innovation

• 3 million individuals in the U.S. (pop. 300,000,000)

• 50-60 million individuals world-wide with epilepsy

• About 20% have medication-resistant epilepsy
  o 500-800 thousand in the U.S.
  o About 10 million individuals globally
  o Over 12 billion U.S. dollars in healthcare costs every year
• 1% of the U.S. population is diagnosed with epilepsy (about 3 million individuals)

• About 500,000 individuals experience recurrent seizures resistant to pharmaco-therapy

• Approximately 5000 brain surgeries for epilepsy are performed in the U.S. every year

• The presurgical evaluation can be neuroimaging intensive
Treatment:

I. Medication

II. Diet

III. Surgery

1. Resection

2. Neurostimulation Therapy
   (Interfacing with Fragile Neural Networks)
For victims of paralysis, depression, and other diseases, new hope from exotic devices implanted like pacemakers.

By Michael Arndt (P. 74)

REWIRING YOUR BODY
### WHO'S WHO IN NEUROSTIMULATION

The market for implantable devices could double every five years. That’s attracting health-care giants and startups.

#### DIVERSIFIED GIANTS

| **BOSTON SCIENTIFIC (BSX)** | A leading maker of coronary stents, Boston Scientific jumped into the neurostimulation market last June. It paid $740 million for Advanced Bionics, a $100 million-a-year startup. More acquisitions may lie ahead.
| **JOHNSON & JOHNSON (JNJ)** | J&J got into cardiac devices through its takeover of Guidant, itself a newcomer to neurostimulation. J&J believes the market will grow quickly, and its marketing prowess and deep pockets could make it a winner.
| **MEDTRONIC* (MDT)** | The pioneer in pacemakers and defibrillators, Medtronic is also the leader in adapting this technology for other treatments. Its focus on implantable devices gives it an edge over rivals.

#### PURE PLAYS IN DEVICES

| **ADVANCED NEUROMODULATION SYSTEMS (ANSI)** | ANSI has been growing at a 30% clip or better. But while it is in tests for expanded uses of its neurostimulators, company execs concede they probably need the help of a diversified giant to continue growing.
| **CYBERONICS* (CYBX)** | A patent gives Cyberonics a near-monopoly on the market for vagus-nerve stimulation. One product treats epilepsy. And the FDA has conditionally approved a device for depression. The company could be a takeover play.

#### SMALL FRY

| **NEUROPACE** | Mountain View, Calif. The company is in clinical tests for brain stimulation to avert epileptic seizures. It hopes to be on the market by 2007.
| **NORTHSTAR NEUROSCIENCE** | Seattle. In clinical tests for brain stimulation to reverse stroke-related paralysis. Next up: tests on cerebral palsy and trauma victims.
| **TRANSNEURONIX** | Mt. Arlington, N.J. Has a product now being tested for stomach stimulation to treat obesity. It’s already on the market in Canada.

*Medtronic and Cyberonics results are for the twelve months ended Jan. 28, 2005.*

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*Business Week March 2005*
Definition of a Seizure:

Synchronous hyperactivity in a fragile neural network
(Pathological information processing)
Proposed Mechanisms of Neurostimulation Therapy:

Acute-onset efficacy of local neurostimulation therapy:

1. Conduction blockade
2. Synaptic inhibition
3. Synaptic depression
4. Overriding pathophysiologically network activity\(^1\)

Chronic exposure to direct neurostimulation has been associated with distant cortical synaptic proliferation\(^2\)

\(^1\)Rossi et al (2010). Predicting white matter pathways for direct neurostimulation therapy. Epilepsy Res

Neurostimulation in Epilepsy:

1. Vagus Nerve Stimulation (VNS)
2. Deep Brain Stimulation (DBS)
3. Responsive (Cortical) Neurostimulation (RNS)
VNS Implant Site

- Vogus nerve
- Electrodes
- Thin, flexible wire
- Pulse generator

- Negative electrode
- Positive electrode
- Anchor tether
Evolution of the Vagal Nerve Stimulator (VNS)

Model 100
- Thickness: 0.52” (13.2 mm)
- 31 cc

Model 101
- Thickness: 0.41” (10.3 mm)
- 26 cc

Pulse Model 102
- Thickness: 0.27” (6.9 mm)
- 14/16 cc

DemiPulse™ Model 103
- Thickness: 0.27” (6.9 mm)
- 8/10 cc
Proposed Mechanisms of Neurostimulation Therapy:

**Acute-onset efficacy** of local neurostimulation therapy

‘On demand’ magnetic switch triggering

**Chronic exposure** to direct neurostimulation therapy

Synaptic proliferation

Inhibitory (GABAergic?) upregulation
Neurostimulation in Epilepsy:

1. Vagus Nerve Stimulation (VNS)
2. Deep Brain Stimulation (DBS)
3. Responsive Cortical Stimulation (RNS)
Deep Brain Stimulator (DBS, Medtronic)

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) Trial

On March 12, 2010, a U.S. FDA advisory panel recommended approval of the DBS as being safe and effective for patients with severe and refractory partial-onset seizures with or without generalization.

Neurostimulation in Epilepsy:

1. Vagus Nerve Stimulation (VNS)
2. Deep Brain Stimulation (DBS)
3. Responsive (Cortical) Neurostimulation (RNS)
Overview of the NeuroPace® RNS® System

RNS® Neurostimulator and Leads
RNS® System: Clinical Studies

- Feasibility Study
  - 65 implanted

- Pivotal Study
  - 191 implanted

- Long-term Treatment Study (230 enrolled)

Responsive Neurostimulator (RNS, NeuroPace)

- Over the long-term, open label period of the Pivotal Clinical Trial, 47% of these subjects experienced a 50% or greater reduction in their seizure frequency when compared to their baseline.

- Data was submitted to the FDA in June 2010.

- FDA finally approved the device in Nov 2013.

Pivotal Study: Mean Disabling Seizures

<table>
<thead>
<tr>
<th>Pre-Implant</th>
<th>Post-Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment N:</td>
<td>97 97 97 96 96 95</td>
</tr>
<tr>
<td>Sham N:</td>
<td>94 94 94 94 93 90</td>
</tr>
</tbody>
</table>
Responsive ‘On-Demand’ Cortical Stimulator:

1. Detection
2. Stimulation

(A) 2.5 mA applied current
(B) 4.5 mA applied current
Electrocorticogram from Implantable RNS Buffer:
Charge-balanced and Symmetric Waveform used in Neurostimulation Therapy:
Proposed Mechanisms of Neurostimulation Therapy:

**Acute-onset efficacy** of local neurostimulation therapy

**Chronic exposure** to direct neurostimulation
Stimulation of the Ictal Onset Zone: Comparison of Grey versus White Matter

- Epileptogenic Zone
- Grey Matter Stimulation
- White Matter Stimulation
- Activation Field
- Grey Matter Activation
- White Matter Activation
Diffusion-Related MRI Abnormalities During Partial Status Epilepticus

15 year old with localization-related epilepsy & post-ictal hemiparesis

FLAIR MR sequence acquired within 24 hrs after brief stereotypic seizure & LUE Todd’s paresis

Diffusion Tensor Imaging:
Isotropic voxel
(FA = 0)
Anisotropic voxel - water diffusion has a preference in directionality (FA=1)
DTI
Chronic White Matter Changes (Following Years of Focal-Onset Seizures)

Intracranial EEG: Propagation to Contralateral Brain Regions Is Typically Slow
Single **Photon** Emission Tomography (SPECT)

1976-1984 Early tracers became available following development of first dedicated single head SPECT camera (Ronald Jaszczak)

~1984 Soon after, *interictal* SPECT scanning was incorporated into clinical practice.

~1986 *Ictal* SPECT was first attempted and compared with baseline *interictal* SPECT.
What is Gamma Camera SPECT?

• If images are taken at angular increments around a center of rotation, a 3-D cross-sectional image can be reconstructed.

• Multiple heads are used to increase the number of images per unit time.
SPECT

Static tracers

$^{99m}\text{Tc}$-HMPAO (Ceretec)
$^{99m}\text{Tc}$-ECD (Neurolite)

$^{123}\text{I}$-IMP (Spectamine)

$^{123}\text{I}$-HIPDM

Diffusible Tracers

$^{133}\text{Xe}, \; ^{127}\text{Xe}$
Peri-ictal Related Transient Blood Flow Changes

Interictal  Ictal  0-2 min Post-ictal  2-10 min Post-ictal

- Mild hypo-perfusion
- Marked hypo-perfusion
- Hyper-perfusion

rCBF changes during temporal lobe seizures
Spatial Resolution:

Subtraction Ictal SPECT Co-registered to MRI (SISCOM) 1998

Patient CH:

• CH is a 23 year old male with a 4 year history of complex partial seizures (localization related epilepsy/lesional epilepsy) prior to RNS.

• Initial seizure type began one day following being stung by a jellyfish or other aquatic animal at age 16.

• EEG at an outside hospital showed left temporal interictal activity. No seizures were captured.

• Seizures were resistant to multiple antiepileptic medications.

• Seizures worsened following closed head injury from a shot put and 1 week in a comatose state.

• Video/EEG monitoring revealed bilateral temporal lobe seizures.

• RNS implanted in June 2004.
High Res 1.6mm Gapless SPGR Sequence
Right Ictal Onset
Left Ictal Onset
SISCOM: Preoperative Stereotypic Seizure Onset

Hyperperfused regions

Concurrent hypoperfused regions
Subtracted Ictal SPECT (SISCOM) + Source Modeling
Right Ictal Onset
Post Implant CT

T20s
Mag: 3.2x
Comparison of Two Left Sided Detections

Response to 2.5 mA

Seizure that generalized

Response to 4.5 mA

Did not progress
Right Sided Seizure with No Stimulation
Stimulated Activated SPECT (SAS) Mapping

Deliver current & inject Tc-HMPAO

Tc-HMPAO equilibrates in brain

Dipole Source Modeling of EEG

Rossi et al (2005) AES Abstract
Subtracted Activated SPECT (SAS)

The SAS technique can demonstrate or validate changes in NEURONAL ACTIVITY at a significant distance from a stimulated depth electrode site.
Rossi et al., (2005)
- 20 year old female diagnosed with a right temporal/thalamic grade I astrocytoma at 13 months of age. The tumor was debulked at ages 14 months, 3 years, and 5 years.

- At ages 8-9 years of age she began experiencing vertigo/dizziness & nausea/vomiting.

- At age 13 (2003) an outside neuropsychologist witnessed a seizure during an neuropsychological evaluation.

**Seizure Frequency:** Every 4-14 days.

**Prodrome:** worsening nausea and vomiting lasting up to days prior to a ‘usual’ seizure, followed by headaches, dizziness and head tremors (titubations) within a day of her ‘usual’ seizures.

**Aura:** Intermittent worsening dizziness.

**Ictus:** staring with BUE automatisms lasting 30 sec-2 min.

**Postictal period:** severe nausea & vomiting, head tremors and inability to concentrate follows these seizures for 2-3 days. Denied significant confusion. All symptoms then resolved for 3-4 days.

- She was evaluated at: 1) Stanford, 2) Johns Hopkins, 3) Loyola (Chicago), 4) Children’s Memorial/Northwestern (Chicago).

Subtracted Post-Ictal DTI (spiDTI):
Post-Ictal Diffusion Tensor Imaging (spiDTI)

Pre-Implant Depth Electrode Stimulation Planning Model

RNS Pre-implant Model/Map
Diffusion Tensor Tractography
Using the Responsive Neurostimulation System (RNS) to Associate Real-World Closed-Circuit Video Monitoring with Implanted Ictal Electroconvulsiveography

Manuel Toledo, MD and Marvin A. Rossi, MD, PhD
Rush Epilepsy Center, Rush University Medical Center, Chicago, IL

AES, 2008
Chronic unlimited recording electrocorticography-guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy.

DiLorenzo DJ¹, Mangubat EZ, Rossi MA, Byrne RW
Graduation: 5/9/2015
SUMMARY

1. Next generation acute detection strategies for VNS

2. Possible reintroduction of DBS in the U.S. for intractable focal-onset epilepsy?

3. Further explore utility of interfacing with ‘on-ramps’ for NeuroPace RNS Therapy

4. Long-term ambulatory ECOG monitoring

5. Innovation of diagnostic neuroimaging modalities for identifying Fragile Neural Networks:
   a. SISCOM
   b. spiDTI
   c. SAS
KEY CONTRIBUTORS

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