Detecting and Aborting Seizures

Robert Fisher MD, PhD, Stanford University

- Discussion of technologies including external & intracranial stimulation, seizure detection algorithms, intracranial drug delivery, and hybrids.

Pros and Cons: Ivan Osorio MD (University of Kansas)

- Will these new devices fill the gap between drug therapy and surgery?
Devices for Epilepsy

Robert S. Fisher, M.D., Ph.D.
Stanford University
Department of Neurology

Editor-in-Chief
epilepsy.com
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<thead>
<tr>
<th>Name</th>
<th>Commercial Interest</th>
<th>Nature of Relationship</th>
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<tbody>
<tr>
<td>Robert S. Fisher, M.D., Ph.D.</td>
<td>NeuroVista, seizure prediction</td>
<td>Stock options, consulting</td>
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<td>IntelliVision, seizure detection</td>
<td>Stock options, consulting</td>
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<tr>
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<td>ICVRx, drug infusion to brain</td>
<td>Stock options</td>
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<td>SONY videogame seizures</td>
<td>Consulting</td>
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Note: No Medtronic or brain stimulation financial connections

No conflict relevant to this talk (except sponsored research to Stanford)
Therapeutic Devices for Epilepsy

The existing device

According to the Cyberonics website, more than 50,000 patients have been implanted.
Therapeutic Devices for Epilepsy

- Trigeminal stimulation
- SUDEP monitor
- Seizure notification
- Seizure prediction
- Cooling
- Optical Control
- Brain drug infusion
- Hybrid silicon neural implants
- Transcranial magnetic stimulation
- DBS in anterior thalamus
- Responsive neurostimulation
Therapeutic Devices for Epilepsy

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The Need
Identify responders for a VNS-like therapy, before invasive surgery
Trigeminal Nerve Stimulation

Can test externally
If helpful, implant

Supported by Epilepsy Therapy Project

0.0
0.5
1.0
1.5
2.0
2.5

Baseline
3 months

Daily Seizures

Christopher DeGiorgio
Neurology, April, 2009
Therapeutic Devices for Epilepsy

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The Need
Monitor for and prevent sudden unexpected death in epilepsy
**Monitor for SUDEP**

Epilepsia (Abst. 1.178), 2008
WEARABLE APNEA DETECTION DEVICE TO PREVENT SUDDEN DEATH
John Duncan, E. Villegas-Rodriguez, E. Aguilar-Pelaez and G. Chen

“breathing is monitored via acoustic sensing at the suprasternal notch. The system’s sensor consists of a miniature microphone placed within a small dome, which is fixed to the subject’s skin with a flexible medical adhesive . . . The sensitivity and specificity of the algorithm to detect apnea sections of over 25 seconds were 99.2% and 99.92% respectively.”

Microphone (1 mm)
Microchip (8 mm)
Radio transmitter
Base station
Hearing aid battery
Therapeutic Devices for Epilepsy

- Trigeminal stimulation
- SUDEP monitor
- Seizure notification → The need: Warn of an ongoing seizure
- Seizure prediction
- Cooling
- Optical Control
- Brain drug infusion
- Hybrid silicon neural implants
- Transcranial magnetic stimulation
- DBS in anterior thalamus
- Responsive neurostimulation
Smart Watch

- Sensors and intelligence built-in
- Alerts caregivers via wireless, mobile phones, PDAs
- As easy as wearing a “Watch”
Therapeutic Devices for Epilepsy

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The Need
Notify others when a seizure is taking place
Seizure Prediction Example

Seizure Prediction Approaches

- EEG component frequency analysis
- EEG nonlinear “chaos theory”
- EEG synchronicity and correlation
- EEG high-frequency oscillations
- Multiple unit responses (BrainGate/NeuroPort)
- Optical changes
- Patient behavior and awareness
- Other
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The Need
Reversible reduction of activity in a seizing region of brain
Cooling reduces neuronal bursting

Rat hippocampal slice in 10 µM bicuculline

From R.S. Fisher
BMI 2mM on left parietal cortex

After cooling to 30°C

After rewarming to 37°C

From R.S. Fisher
Will Cooling the Brain be Practical?

Review

Focal cooling for epilepsy: An alternative therapy that might actually work

Steven M. Rothman\textsuperscript{a,*}, Matthew D. Smyth\textsuperscript{b}, Xiao-Feng Yang\textsuperscript{a}, G.P. Peterson\textsuperscript{c}

- Gyri vs. sulci
- Heating dissipation
- Power demands
- Safety
- Other
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The Need
Controlling brain excitability by implanted fiber-optics
Work of Karl Deisseroth, Stanford

N. Pharonis contains a rhodopsin, light-sensitive protein, as in our retina. A family of rhodopsins opens various neuron channels. Make a viral vector and put the rhodopsin into neurons. Then light controls brain cell excitability.
Optical control of Excitability

- Mouse organotypic hippocampal culture slice
- Inject viral vector with halorhodopsin chloride pump gene
- Co-label vector with yellow fluorescent protein
- Orange light activates the rhodopsin and hyperpolarizes the transfected cells

Optical control of Excitability

1. Orange light activates rhodopsin gene
2. Opens chloride channel
3. Hyperpolarizes transfected neuron
4. Stops neuron firing

1. Organotypic hippocampal culture slices
2. Stimulus train induced bursting (STIB)
3. Orange light reversibly blocks bursting

Is Optical Control Feasible?

Need to localize seizure focus

Doubly invasive:
- Viral transfection
- Fiberoptic implant

Duration of transfection

How many cells transfected

Cost
Therapeutic Devices for Epilepsy

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The Need
Deliver drug to a seizure focus
Blocking Epileptiform Activity by AED Perfusion

Ictal EEG changes were defined as rhythmical spiking at a frequency greater than one per second, sustained for at least 10 seconds.

Subdural Infusion of AEDs

NYU Group: Nandor Ludvig, Hai M. Tang, Shirm L. Baptiste, Geza Medveczky, Jacqueline French*, Werner K. Doyle, Chad Carlson, Ruben I. Kuzniecky, Orrin Devinsky*

* Leaders of ETP
In a possible application, the infusion catheter is fully implanted with a transdermal port that is internally sealed and filtered to prevent bacterial ingress. At the time of treatment, an infusion pump would be attached to the port (shown for the T1 catheter only). … An individual patient could ordinarily have a single catheter.


* Leader of ETP
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The Need
Renewable release of an inhibitory compound to stimulation
Stimulation-Induced GABA Release

GABA releasing cells on electrodes

From Rickus & Irazoqui, Purdue University
1. continuous recording

2. output of recorded signal

3. seizure prediction

4. stimulation of device cells

5. Release GABA from "living electrodes"

From Rickus & Irazoqui, Purdue University
**Therapeutic Devices for Epilepsy**

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**The Need**

Noninvasive electromagnetic brain stimulation
24 people were randomly assigned to active (1 Hz for 15 min twice daily for 1 week at 120% of motor threshold) RTMS or placebo (the coil was angled away from the scalp). There was no significant effect of stimulation on seizure frequency, although in the first 2 weeks the active group had a 16% mean reduction; controls were unchanged. There was a non-significant tendency toward a greater effect in patients with neocortical foci than in those with mesial temporal foci. **This study suggests that a TMS effect, if there is one, is probably short-lived and weak.**

Electrical Stimulation for Epilepsy

CM = centromedian nucleus of thalamus.

From R.S. Fisher
Deep Brain Stimulation

OPEN-LOOP (Medtronic)

CLOSED-LOOP (NeuroPace)
Responsive Neurostimulation
SANTE Neurostimulation
Stimulation of the Anterior Nucleus of Thalamus for Epilepsy

p=0.002 for final month, including outlier

From R.S. Fisher & Medtronic, Inc., in press, Epilepsia
Improvement by Seizure Type
Double-Blind All patients, All 3 Months
(Not powered for seizure subtypes)

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Active</th>
<th>Control</th>
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<tr>
<td>Simple partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex Partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial-&gt;Generalized</td>
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<tr>
<td>&quot;Most Severe&quot; (from patient)</td>
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-60%  -40%  -20%  0%  Down is better

n=70  n=97  n=40  n=81

Note: All other data shown are total seizures

* p < 0.05
Money spent on the brain is never spent in vain.

Chinese Fortune Cookie
Uncle Lee's House of Szechuan
Baltimore, Maryland