New technologies for epilepsy treatment:

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The Classical Age
Clinical Neurophysiology/Epilepsy

Designed around technology of the day
Limited by frequency response of stylus
EEG machines designed and restricted to those frequencies (0.5-70 Hz)
Clinical definitions

EEG available for humans
Pattern classification
Normal vs abnormal
Based on observations
Technical limitations

All work done visually, using 1-70 Hz data

- Nothing higher was even recorded
The Modern Age
New technologies

Automated detectors
Seizure prediction
Implantable devices
Future research
Spike and Seizure detection

Early exploration: searching for the Northwest passage
Spike detection

Proprietary algorithms (the “black box”)

....often dubious results
Seizure detection

Rhythmic discharges, frequency power

Different people are different = hard to make a device for everyone

I usually ignore them when I read EEGs
A difficult journey

Can we do better???
we all hope so
Seizure Prediction

Patients can often sense that they are prone to seizures.

Some papers show changes in the hours preceding a seizure.

Can mathematical methods be used to predict seizures?
On the predictability of epileptic seizures

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Abstract

Objective: An important issue in epileptology is the question whether information extracted from the EEG of epilepsy patients can be used for the prediction of seizures. Several studies have claimed evidence for the existence of a pre-seizure state that can be detected using different characterizing measures. In this paper, we evaluate the predictability of seizures by comparing the predictive performance of a variety of univariate and bivariate measures comprising both linear and non-linear approaches.

Methods: We compared 30 measures in terms of their ability to distinguish between the interictal period and the pre-seizure period. After completely analyzing continuous intracranial multi-channel recordings from five patients lasting over days, we used ROC curves to distinguish between the amplitude distributions of interictal and preictal time profiles calculated for the respective measures. We compared different evaluation schemes including channelwise and seizurewise analysis plus constant and adaptive reference levels. Particular emphasis was placed on statistical validity and significance.

Results: Univariate measures showed statistically significant performance only in a channelwise, seizurewise analysis using an adaptive baseline. Preictal changes for these measures occurred 5–30 min before seizures. Bivariate measures exhibited high performance values reaching statistical significance for a channelwise analysis using a constant baseline. Preictal changes were found at least 240 min before seizures. Linear measures were found to perform similar or better than non-linear measures.

Conclusions: Results provide statistically significant evidence for the existence of a preictal state. Based on our findings, the most promising approach for prospective seizure anticipation could be a combination of bivariate and univariate measures.

Significance: Many measures reported capable of seizure prediction in earlier studies are found to be insignificant in performance, which underlines the need for statistical validation in this field.

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Methods tested


Results: there is a preictal state, it just might work
Int’l Workshop on Seizure Prediction

1\textsuperscript{st}: Bonn, 2002
- ~40 researchers, many promising claims

2\textsuperscript{nd} DC, 2005
- ~70 attendees, most claims from Bonn were refuted

3\textsuperscript{rd} Freiburg, 2007
- ~150 attendees, more focus on mechanisms and high frequency content

4\textsuperscript{th} Kansas City, 2009
- ~200 attendees: Prediction contest, 3 total entries (all newcomers), poor results
Int’l Workshop on Seizure Prediction

5th: Freiburg 2011
  150 attendees

6th: San Diego, 11/2013
  120 attendees

.........results
Seizure Prediction

Developed by private company, Neurovista

13 patients in Australia

Worked in about half

“Different patients are different”
Seizure Prediction

Company bankrupt 2013
Future of Seizure Prediction

Future trials

Big Data tools
Partner with industry?

New technology, new methods
Better EEG signals

Could Google figure it out now, or do we need better technology?
New ideas, new technology
Only 0.1 – 100 Hz?

No longer any limitation

EEG was defined at this range, so it was kept at this range
High Frequency Oscillations in Epilepsy

Berger bands 1-70
Fast gamma 70-150
Ripples 150-250
Fast Ripples 250-600
Units 1000-2000 *

Fig 2. An example of band pass filter settings used to detect specific electroencephalogram (EEG) activities recorded from microelectrodes. (A) Unfiltered EEG data, (B) ripple frequency (80–160Hz), (C) fast ripple frequency (250–500Hz), and (D) unit activity (600Hz–5kHz). Marker pulses shown in B and C indicate trigger points used for waveform averaging. ms = millisecond.

High Frequency Oscillations in Epilepsy

Berger bands 1-70
Fast gamma 70-150
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Fast Ripples 250-600
Units 1000-2000 *

High-frequency oscillations and seizure generation in neocortical epilepsy

Greg A. Worrell,1,3 Landi Parish,1 Stephen D. Cranstoun,1 Rachel Jonas,1 Gordon Baltuch2 and Brian Litt1
HFOs in epilepsy

Increased in SOZ

Increased 1 hour before seizure

Worrell et al. Brain 2008; Worrell et al Brain 2004
Using HFOs as a biomarker

**HFO characteristic**
- Localized to abnormal tissue
- More frequent than seizures
- Generated by epileptic pathology

**Implementation**
- Seizure localization
- Feedback for device
- Research epilepsy mechanisms
- Use to test antiseizure treatments
Curing Epilepsy

Fountain of Youth

A quest for longevity. Five hundred years ago, the Spanish explorer Ponce de León drank his way around the Florida coast during his expedition to find the legendary fountain of youth.
Surgical localization
Surgical localization

Dysplasia (Stealth)
Ictal onset zone
Rapid sz spread
Epileptogenic Zone
Broca’s area
HFOs

Brian Litt, Gordon Baltuch, University of Pennsylvania, 2004
Vagus Nerve Stimulator

“Open loop” stimulation:
Scheduled, recurring output

30% reduction in seizures
Less than 10% seizure free

20-30 Hz stimulus (artifact concerns in EMG)

Stacey and Litt, Nat Clin Prac Neurol 2008
Mechanism of VNS

Unknown

- Activation of Locus Ceruleus?
- Blood flow?
- EEG progression?

www.vnsthapy.com/.../mechanismofaction
SANTE Study: Medtronic DBS

Open loop stimulation

Promising results, 7:5 vote in FDA council, ultimately rejected

R. Fisher, AES Seattle 2008
Trigeminal stimulation

Very large nerve
Stimulation reduces seizures (like VNS)
Early clinical trials

DiGeorgio et al. Neurology 2003
DiGeorgio et al Neurology 2013
Neuropace Responsive Neurostimulator

“Closed loop” stimulation
stimulate only when needed
reduced power, possibly more effective
Promising results, FDA waited \textit{years}.....

AES Boston 2009, Neuropace, Inc.
Neuropace Responsive Neurostimulator

Detects seizure automatically

Delivers stimulus; aborts seizure - 600 times/day, < 1 sec each

Automated algorithms:
Analyze features
Individually trained

FDA approval

38% improvement
(Like another drug)

...19% placebo
Anti epilepsy devices

What we’ve learned:
- Electrical stimulation can abort seizures
- Devices are safe and effective
- Timing/location of stimulation is important

We still don’t know:
- Who will respond,
- What the devices do,
- When/Where/How to stimulate,
- Why they work/don’t work
Device deficiencies

Don’t know how/why they work
Never tested for “best stimulus”
Have not tested with prediction
Technology > 10 years old
No high frequency information
Next generation antiepilepsy devices
Current research: new tech

Better electrodes
Automated analysis
Computational modeling
Mix engineering with clinical experience
Faster sampling
Improved electrodes

Faster: 32 KHz
Smaller

Worrell et al. Brain 2008
New electrodes detect new signals

Worrell et al. 2008
Flexible and resorbable electrodes

800 lead flexible surface

J Viventi
Penn

J Rogers
UIUC

Viventi et al 2010 Sci Transl Med; Kim et al 2010 Nat Matls
Automated algorithms

Process terabytes of data per patient

J. Neurophys 10/10
Computer models of HFOs

How are HFOs produced?
Test epileptic pathologies
Test new treatments in computers first

Stacey et al 2009 J Neurophysiol
Human trials?

How will these affect clinical decisions?

Higher resolution
Frequency
Spatial
Testing electrical stimulation

Current method: “first guess”
Many new possibilities—active research
Test in computer, then animal, then humans
Mapping the brain: a bright future ahead
Thank You