EPILEPTIC BIOMARKERS: HUMAN AND EXPERIMENTAL SYSTEMS

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An alternative and accessible version of this presentation is available at 3:30 pm in the Videocast of Day One

We do have significant “potential” financial interest related to this conference:

Intellectual properties:

1. Patent #PCT/US2006/010334 (JE)

Assignee: UCLA

“Functionalized Magnetic Nanoparticles and Methods of Use Thereof”

2. Patent submitted# 60/900,487 (SLM)

Assignee: AECOM

“A model of infantile spasms”

EPILEPSY BIOMARKERS/ SURROGATE MARKERS

- Risk factors
- Markers of epileptogenesis
- Markers of epileptogenicity
- Markers of serious adverse events

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  Development and extension of tissue capable of generating spontaneous behavioral and/or electrographic seizures

  - Development of an epileptic condition
  - Progression after the condition is established
- Markers of epileptogenicity

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  - Progression after the condition is established

- Markers of epileptogenicity

  Tissue capable of generating spontaneous, behavioral and/or electrographic seizures

  - Localization of the epileptogenic region
  - Measure of severity

USES OF BIOMARKERS

- Predict what people with epilepsy risk factors (e.g., cerebral insult, isolated seizures, febrile status, epilepsy gene) will develop chronic seizures for anti-epilepsy intervention
- Predict what people with epilepsy will have pharmacoresistant seizures and/or irreversible disability for early identification of surgical therapy
- Delineate brain areas to be resected for surgical therapy
- Determine the efficacy of a therapeutic intervention before another seizure occurs
  - Tailor individual therapy
  - Streamline clinical trials
- Create cost-effective rapid throughput animal models for screening potential antiepileptic drugs

TARGET MECHANISMS

- Cell loss (e.g., hippocampal atrophy)
- Axonal sprouting
- Synaptic reorganization
- Altered neuronal function (e.g., gene expression profiles, protein products
- Neurogenesis
- Altered glial function and gliosis
- Inflammatory changes
- Angiogenesis
- Altered excitability and synchrony

POTENTIAL BIOMARKERS

- Hippocampal changes on MRI
- Interictal spike features, including fMRI
- Fast Ripples (FR)
- Excitability – TMS
- AMT imaging
- Gene expression profiles

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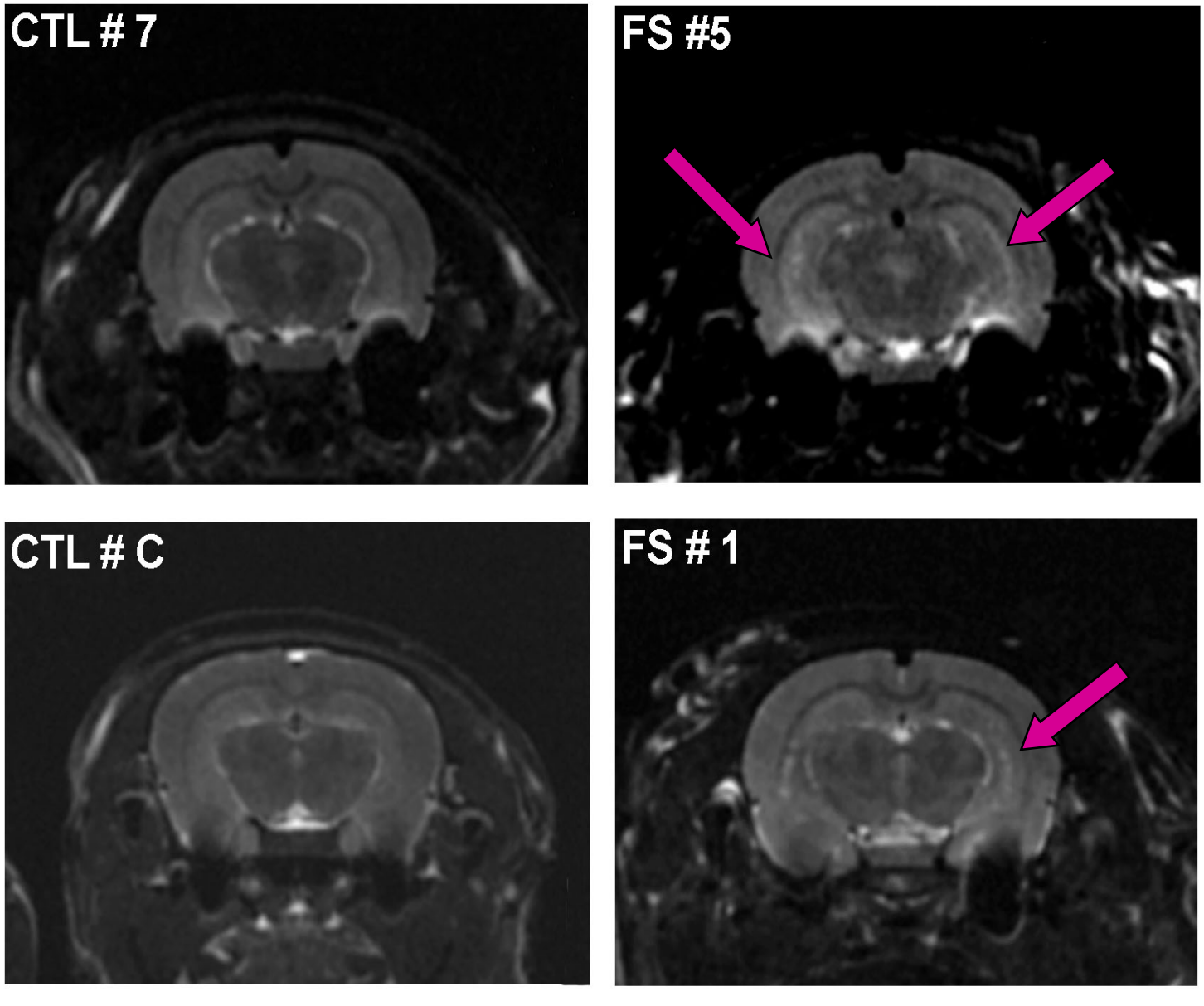
Hippocampal T2 changes after prolonged experimental febrile seizures



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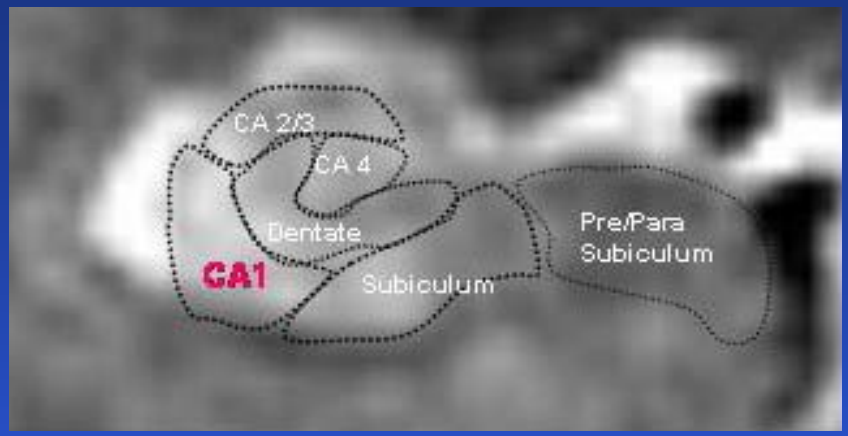
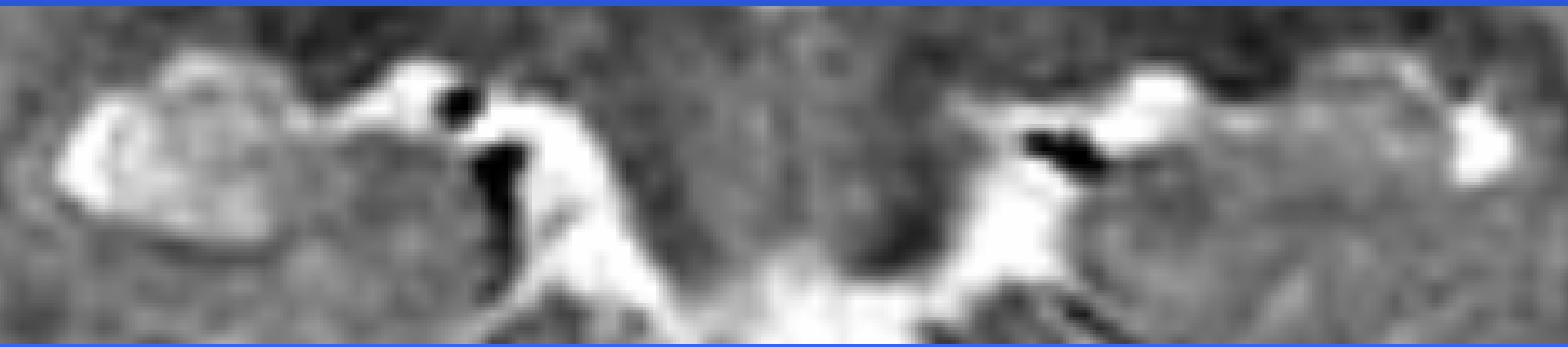
Dube & Baram

Distribution of T2 Signal Abnormality in Acute Hippocampal Injury



Miller et al. AJNR 17:23-26, 1996



Is hippocampal T2 hyperintensity after febrile status epilepticus a biomarker for MTS orTLE?

8 hot hippocampi have follow-up (ave. 3.5 yrs., range 1 mo.-10 yrs.)

- 6 of 7 with volume data have lost volume
- all 8 have abnormal signal
- 2 of 8 have already developed TLE

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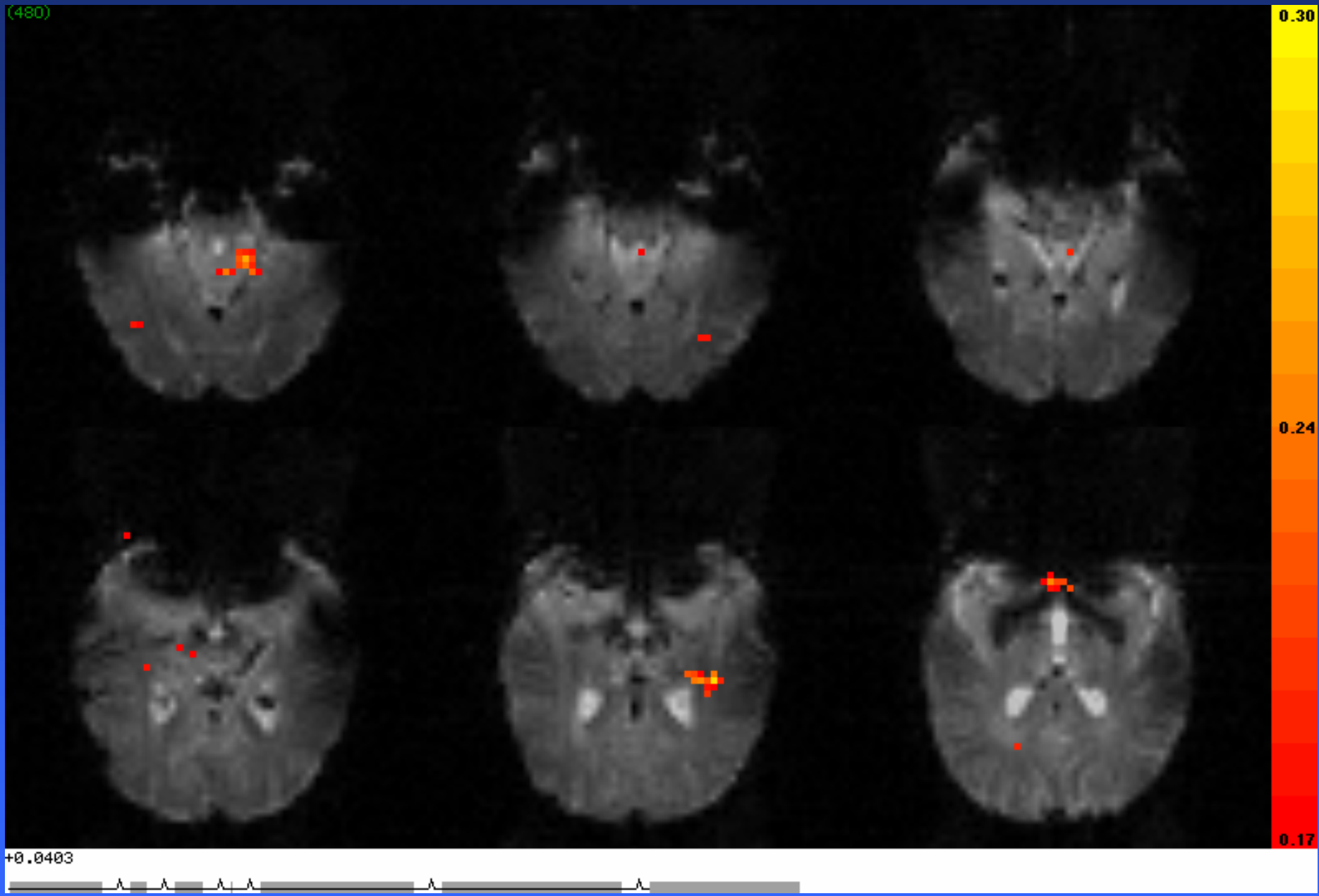
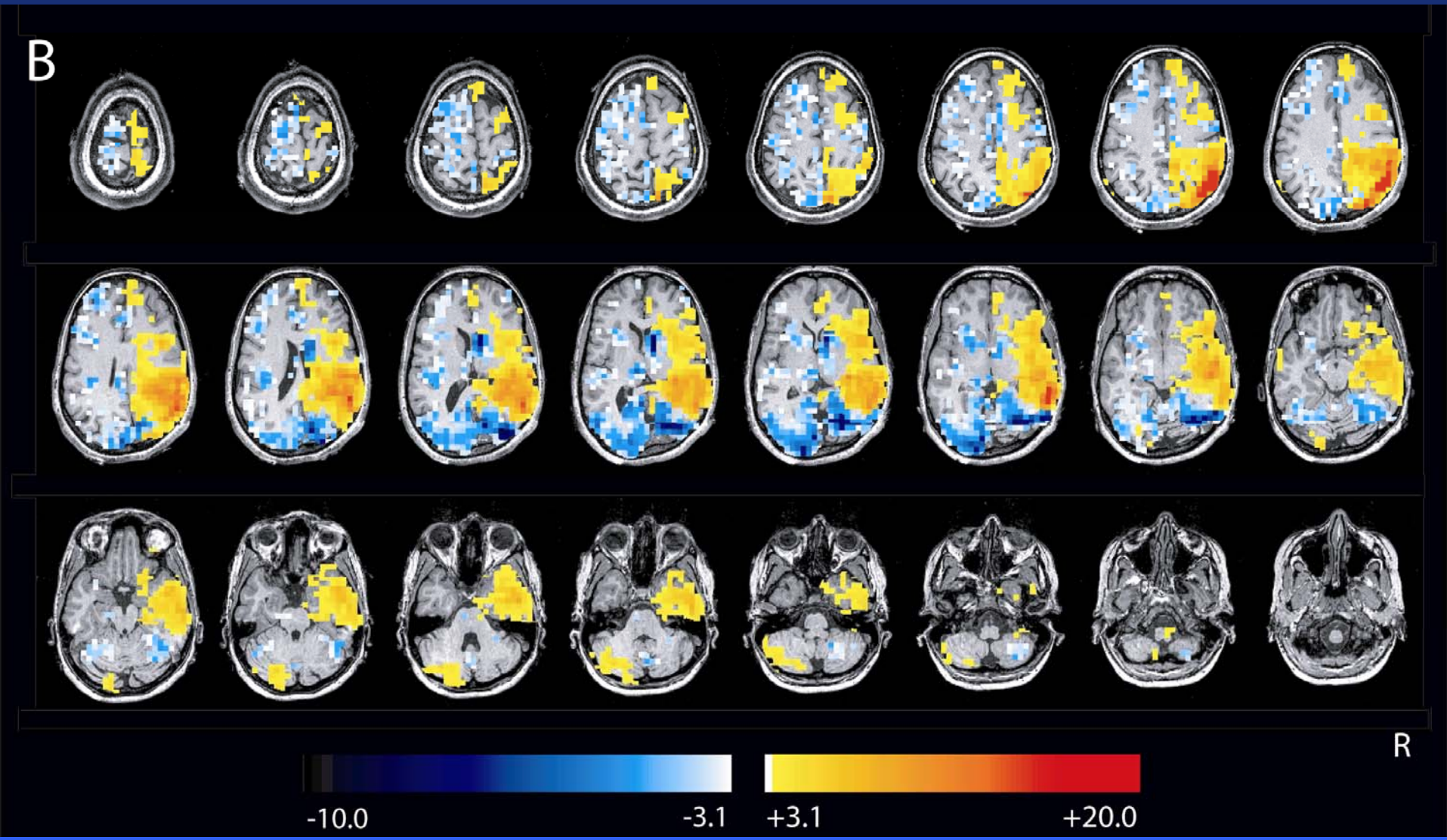


J Stern and M Cohen



BOLD activation is maximum in the angular gyrus (far from EEG focus) and involves a large fraction of the hemisphere: important discrepancy with EEG, for focus and extent.

Kobayashi, Hawco, Grova, Dubeau & Gotman, *Neurology, 2006*

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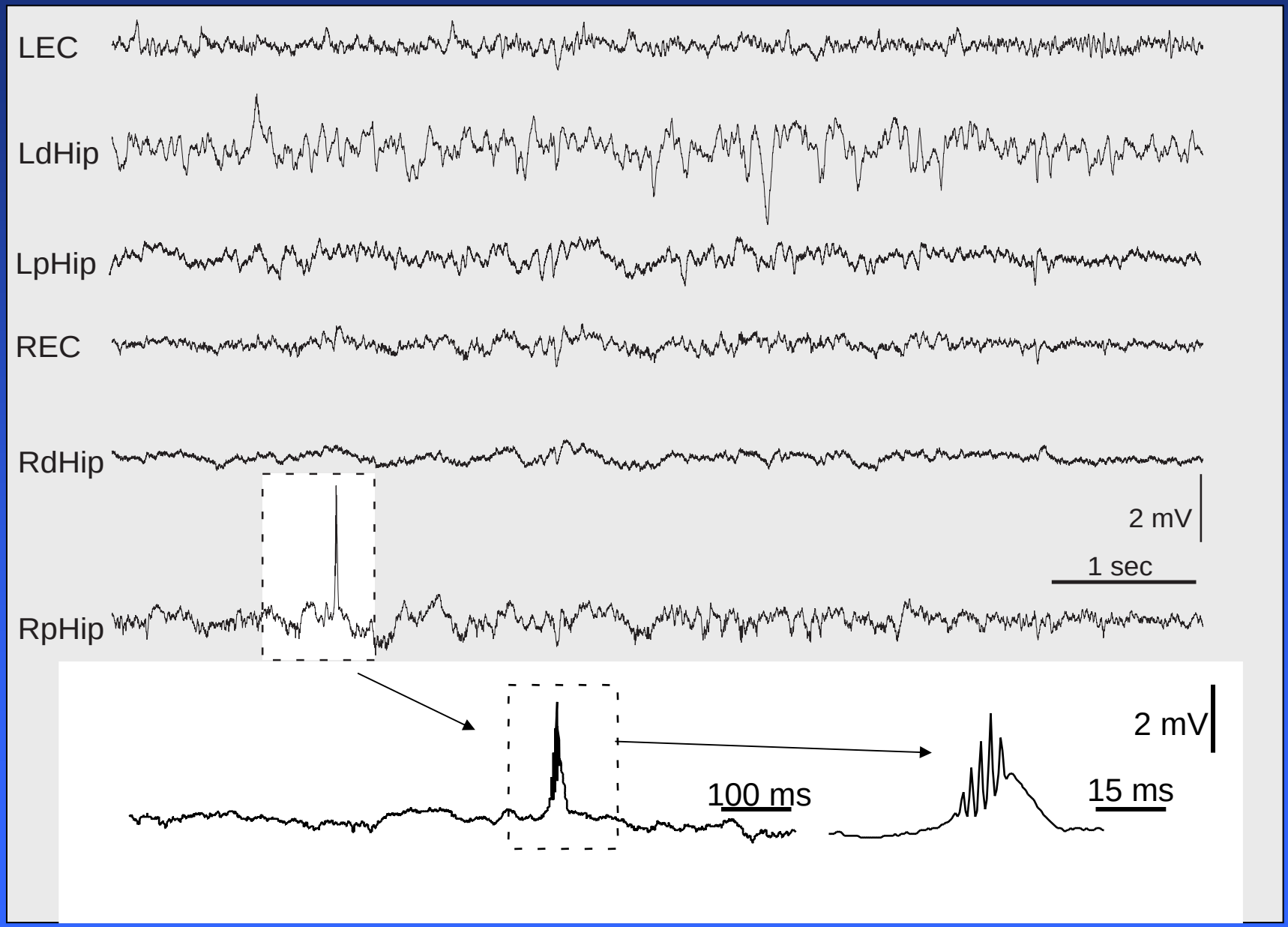
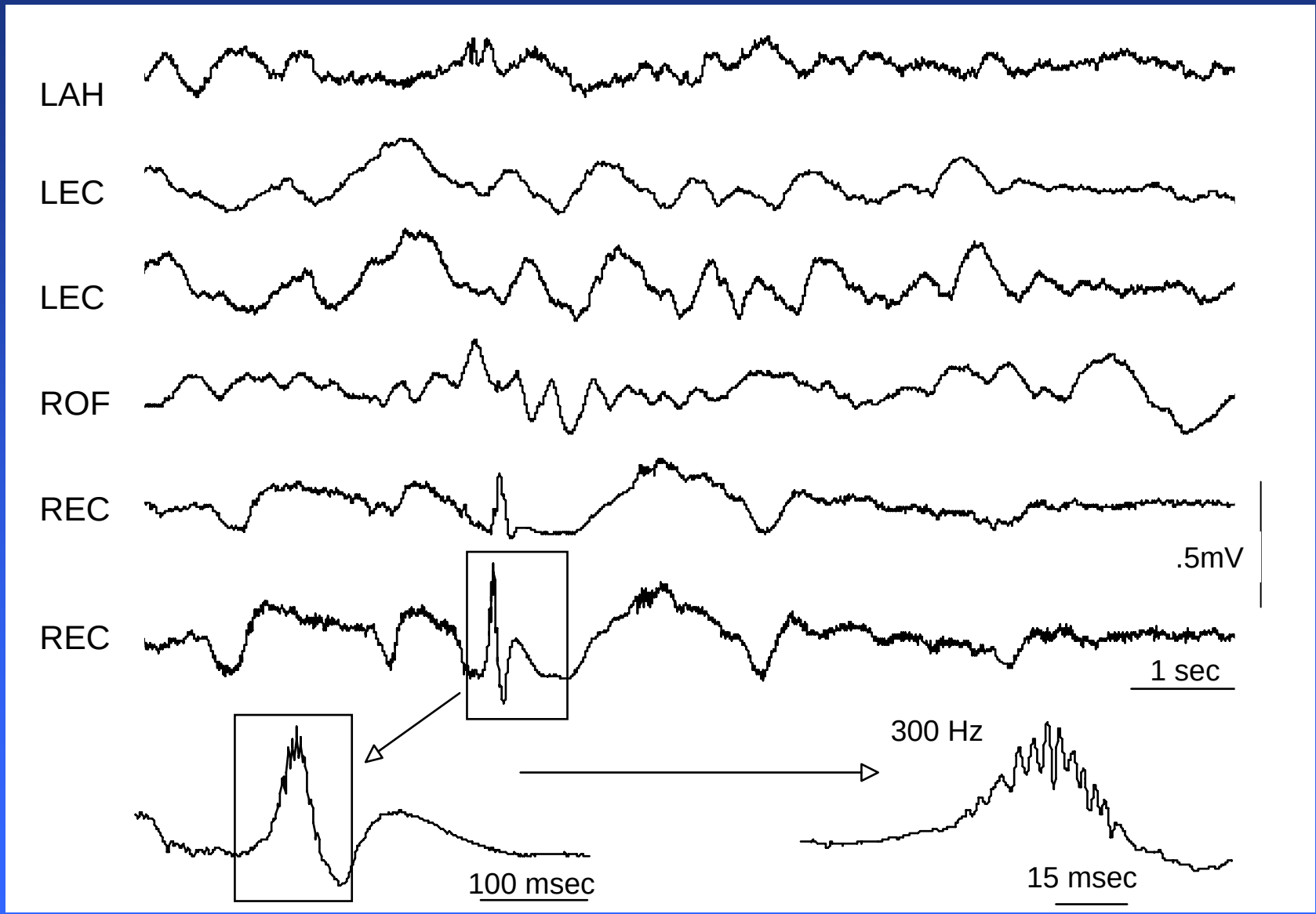
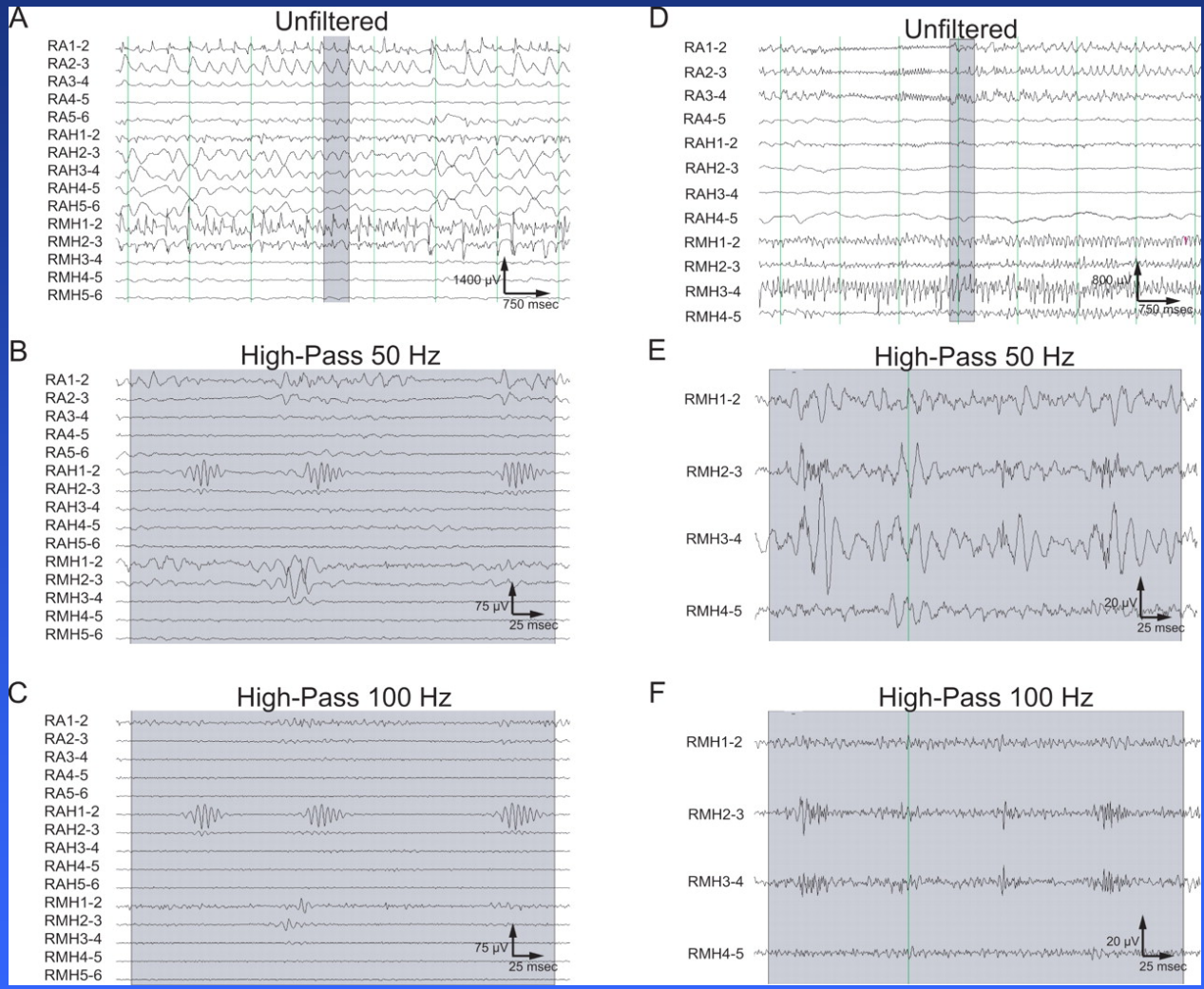
Rat



Human



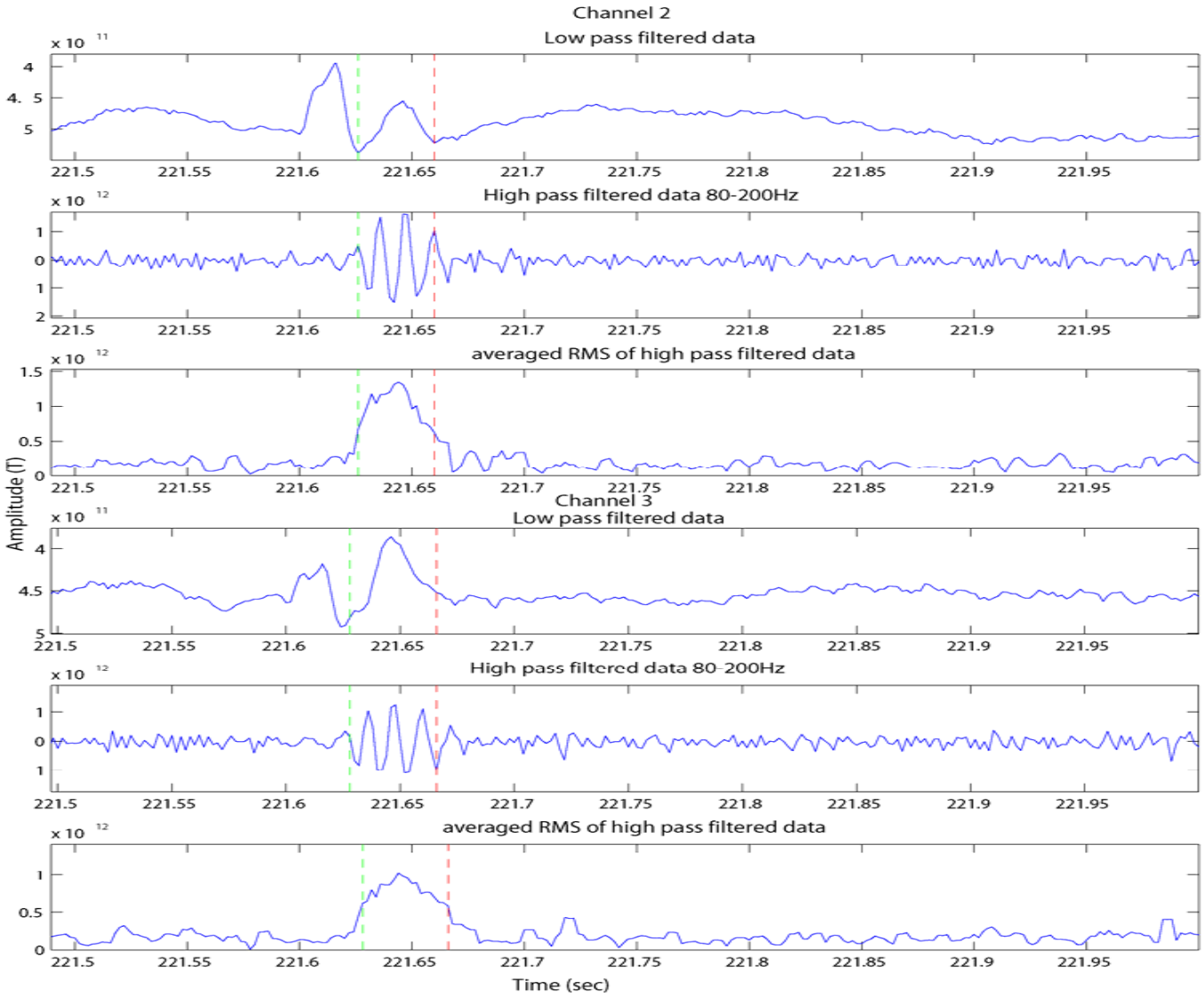
Discrete HFOs are identified in the EEG through visual inspection of the digitally filtered signal



Jirsch, J. D. et al. Brain 2006 129:1593-1608; doi:10.1093/brain/awl085

BRAIN
A journal of neurology

HFOs recorded with MEG



Y. Okada

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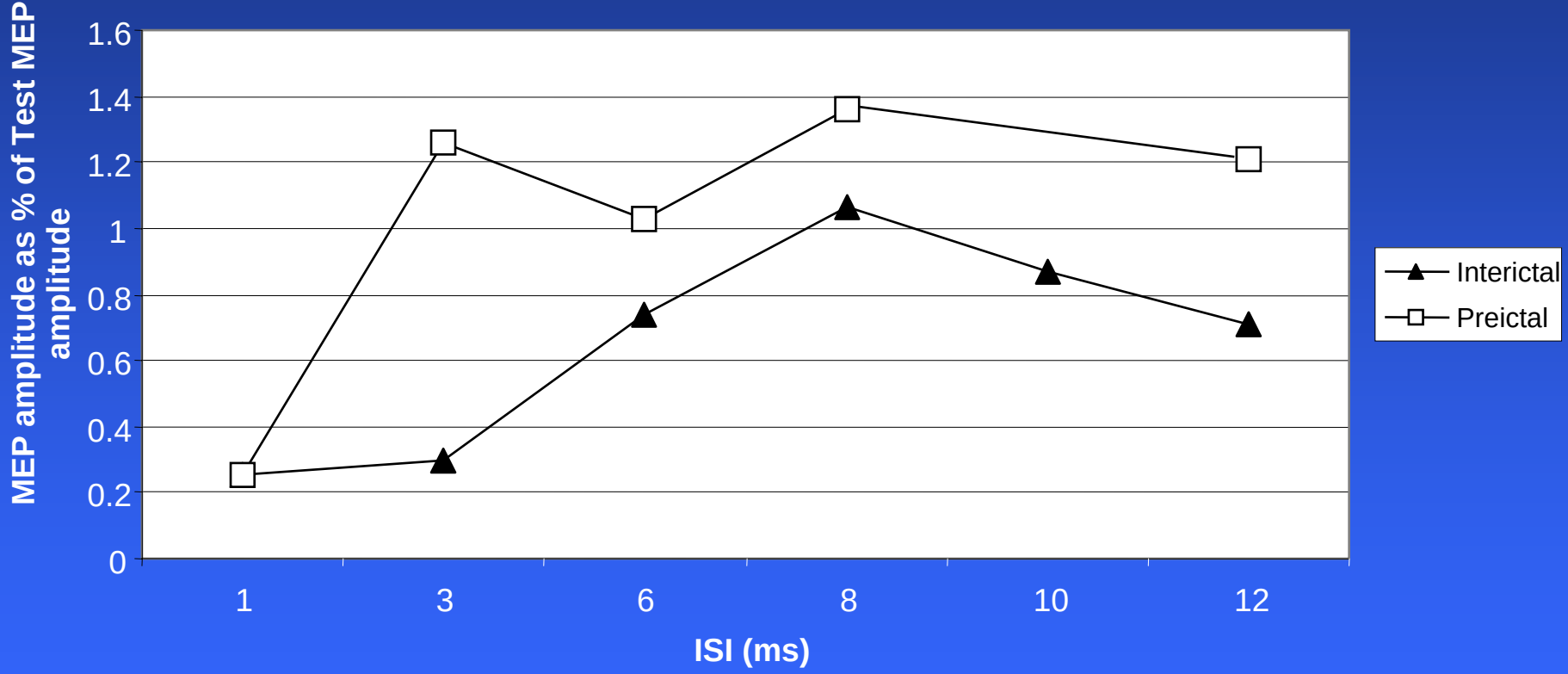
Subject 2 - Large Hemispheric Cortical Dysplasia

Hemisphere Ipsilateral To Epileptogenic Region

Paired Pulse Curve



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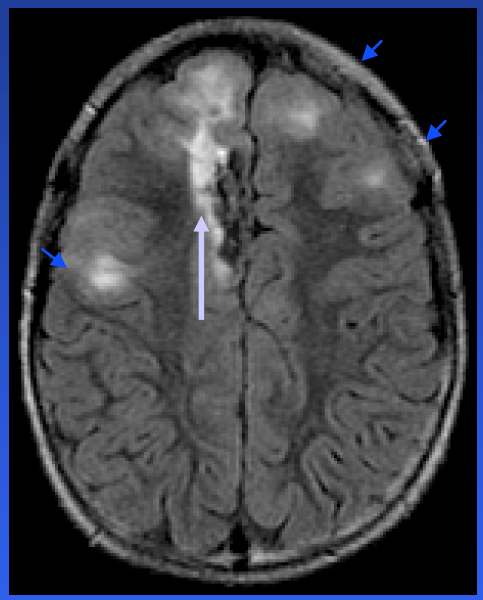
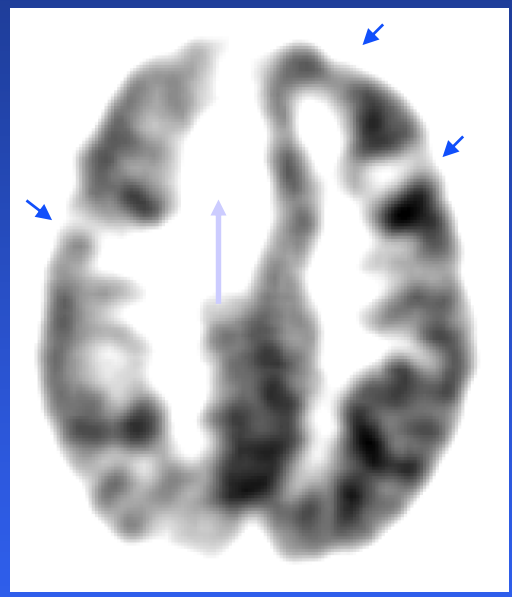
Alpha[C-11]methyl-L-tryptophan PET selectively identifies the epileptogenic tuber in a 7-year-old boy with tuberous sclerosis complex

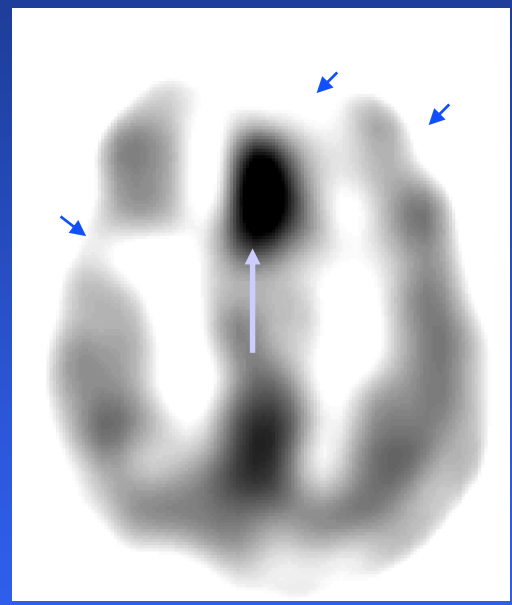
FLAIR MRI



FDG

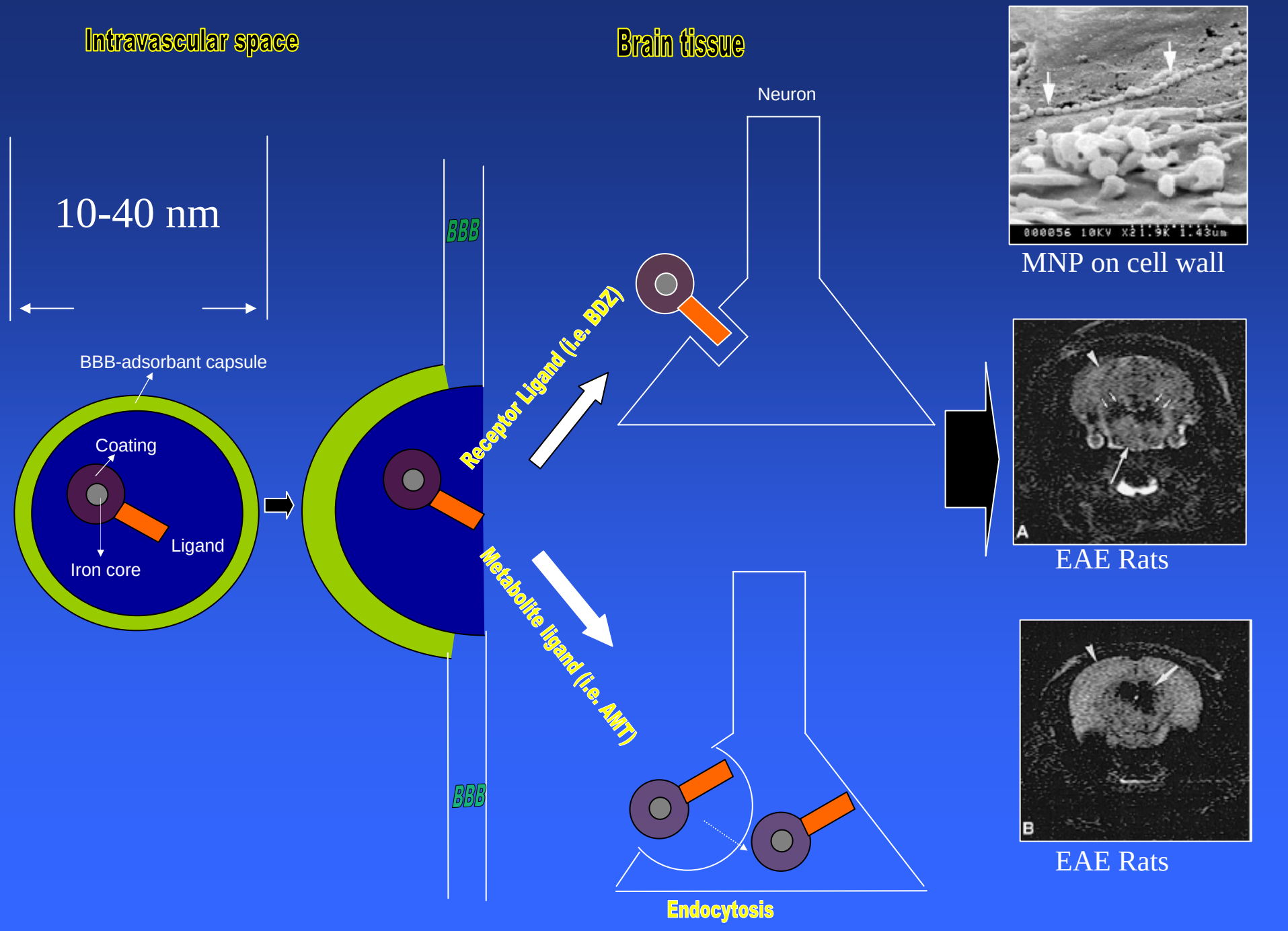


AMT



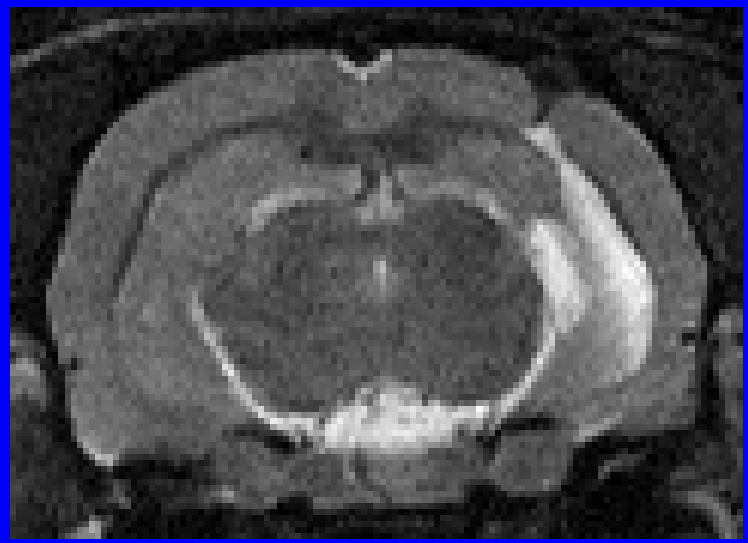
EEG showed spike and wave activity in the right frontal region.

Asano, Chugani et al. 2000
PET Center/Pediatric Neurology,
Children's Hospital of Michigan
Wayne State University, Detroit, MI

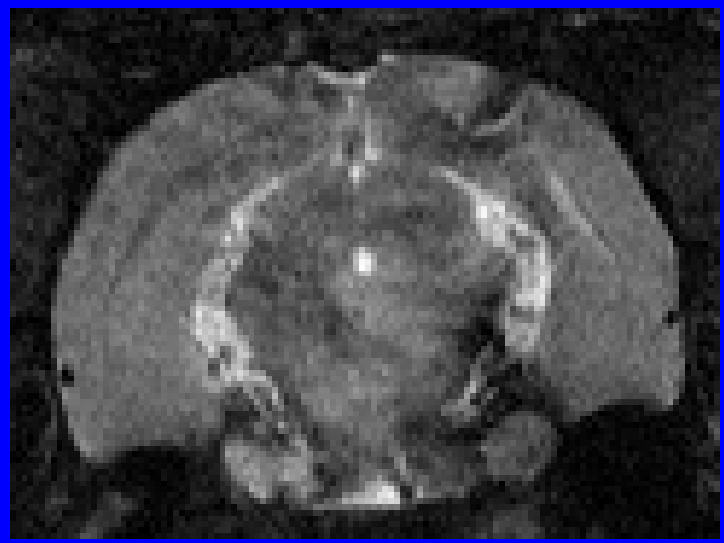

Intravascular space
Brain tissue
Neuron
10-40 nm
BBB
BBB-adsorbant capsule
Coating
Ligand
Iron core
Receptor Ligand (i.e. BDZ)
Metabolite ligand (i.e. AMT)
Endocytosis
MNP on cell wall
EAE Rats
EAE Rats

Kainate Injection Right Hippocampus

No Seizures



Seizures



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In Summary

Establishment of reliable markers for epileptogenicity and epileptogenesis would greatly facilitate diagnosis and treatment by:

- Predicting epilepsy before it develops
- Predicting pharmacoresistance and localizing surgically resectable lesions
- Eliminating the trial-and-error factor in determining effective therapies
- Providing an experimental means to cheaply identify potential antiepileptogenic and antiepileptic compounds