BIOMARKERS IN EPILEPSY

Why do we need them, what will they tell us, and where will they come from?

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LEARNING OBJECTIVES

- Why are biomarkers of epilepsy necessary?
- How could biomarkers of epilepsy facilitate discovery and validation of antiepileptogenic and antiseizure therapies?
- What potential biomarkers currently exist?

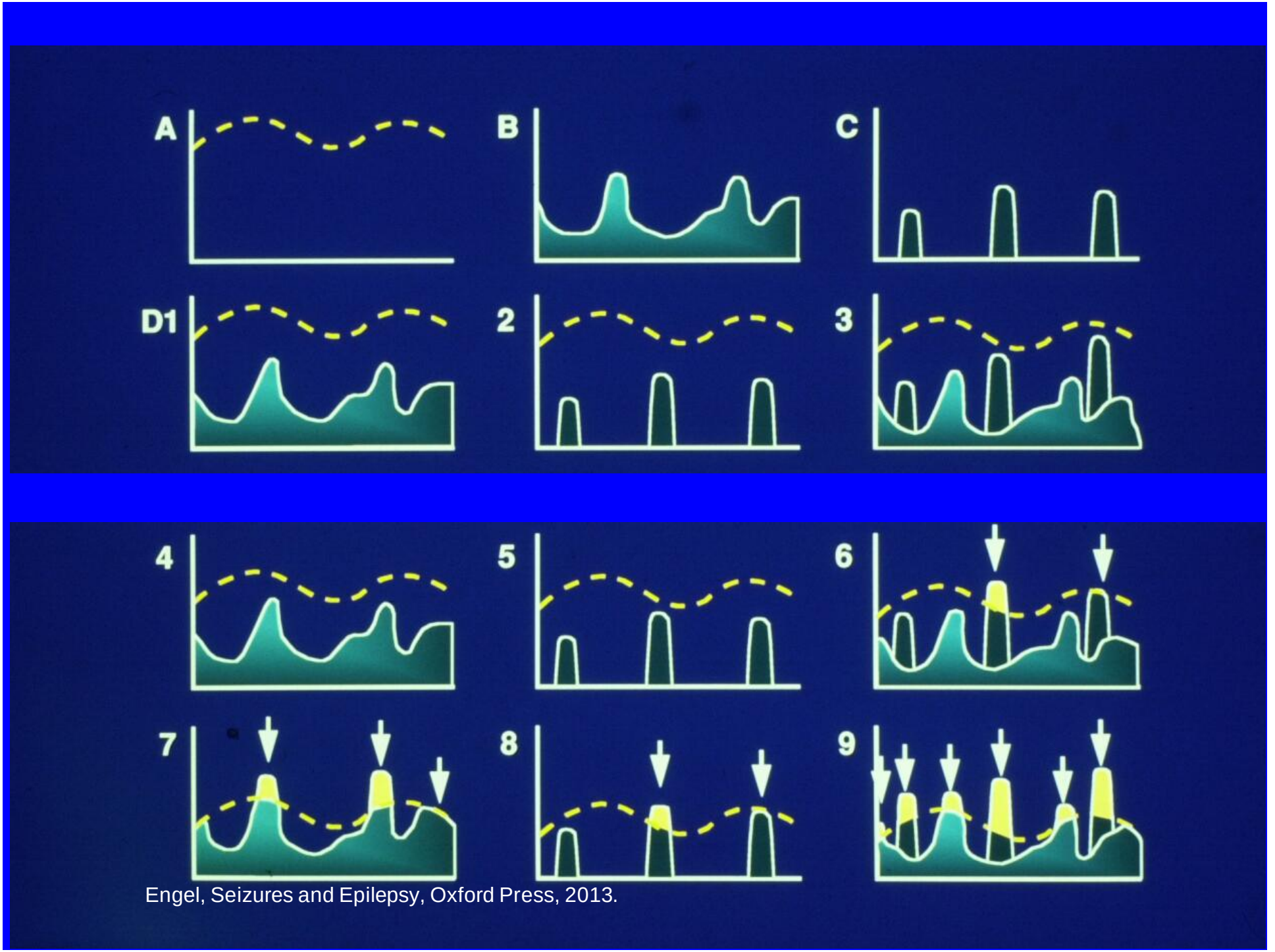
BIOMARKERS

Dynamic changes that indicate the presence of an epileptogenic process with a sufficiently high degree of reliability to warrant intervention

- Biomarkers of epileptogenesis
- Biomarkers of epileptogenicity

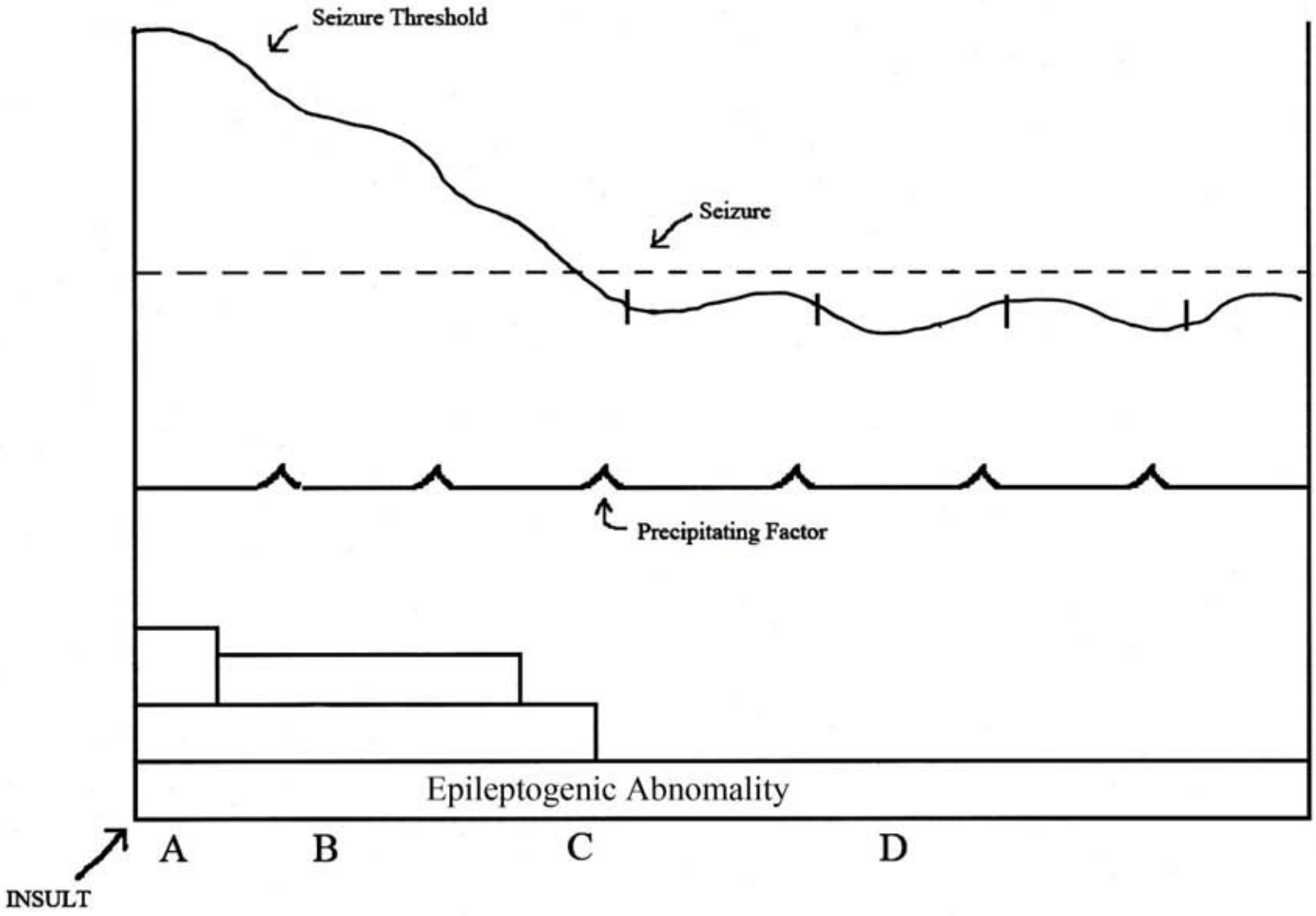
MARKERS OF CLINICAL EPILEPSY

- Risk factors
- Precipitating factors
- Seizure prediction and detection
- Outcome measures
- Surrogate markers
- Biomarkers

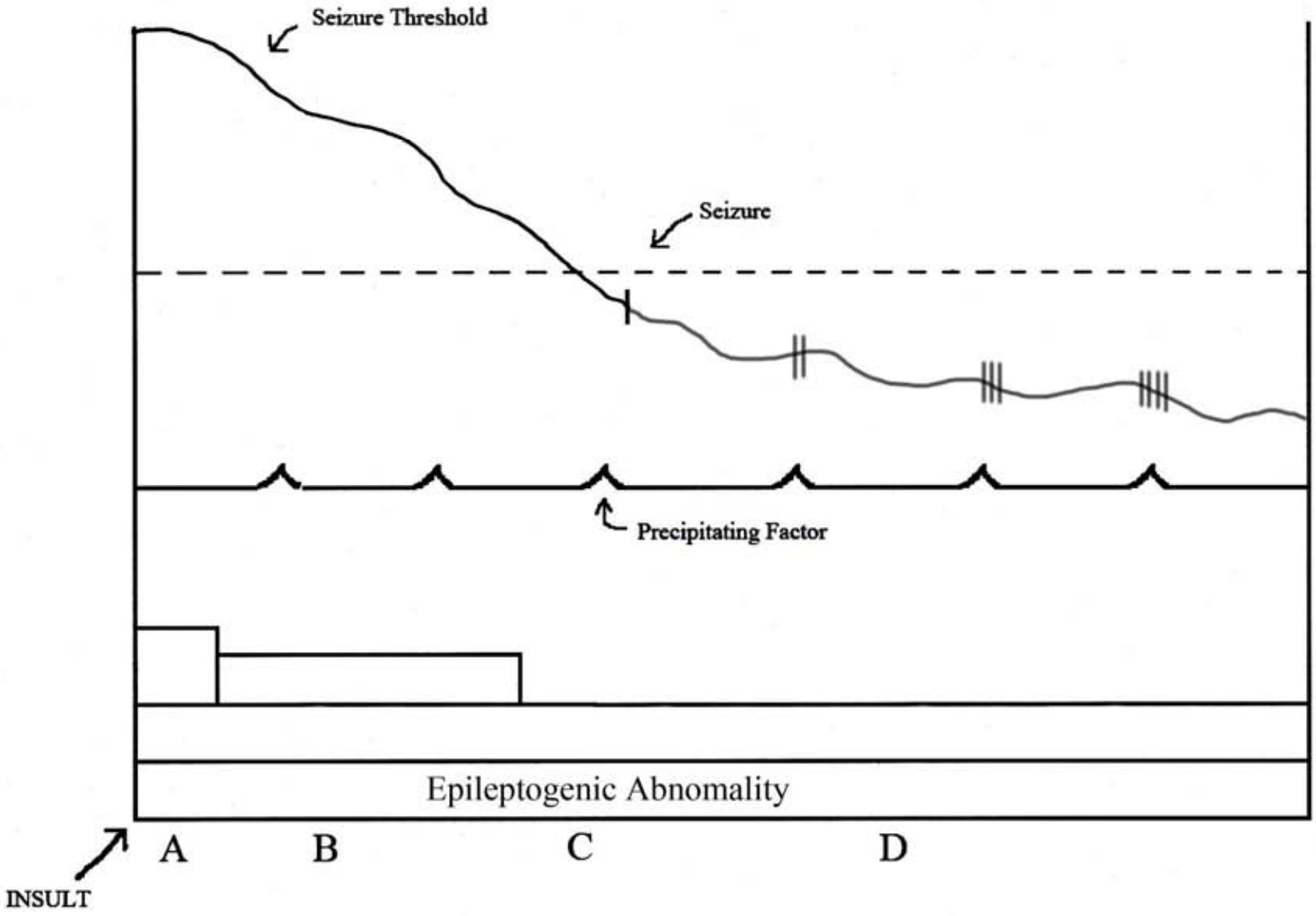


Engel, Seizures and Epilepsy, Oxford Press, 2013.

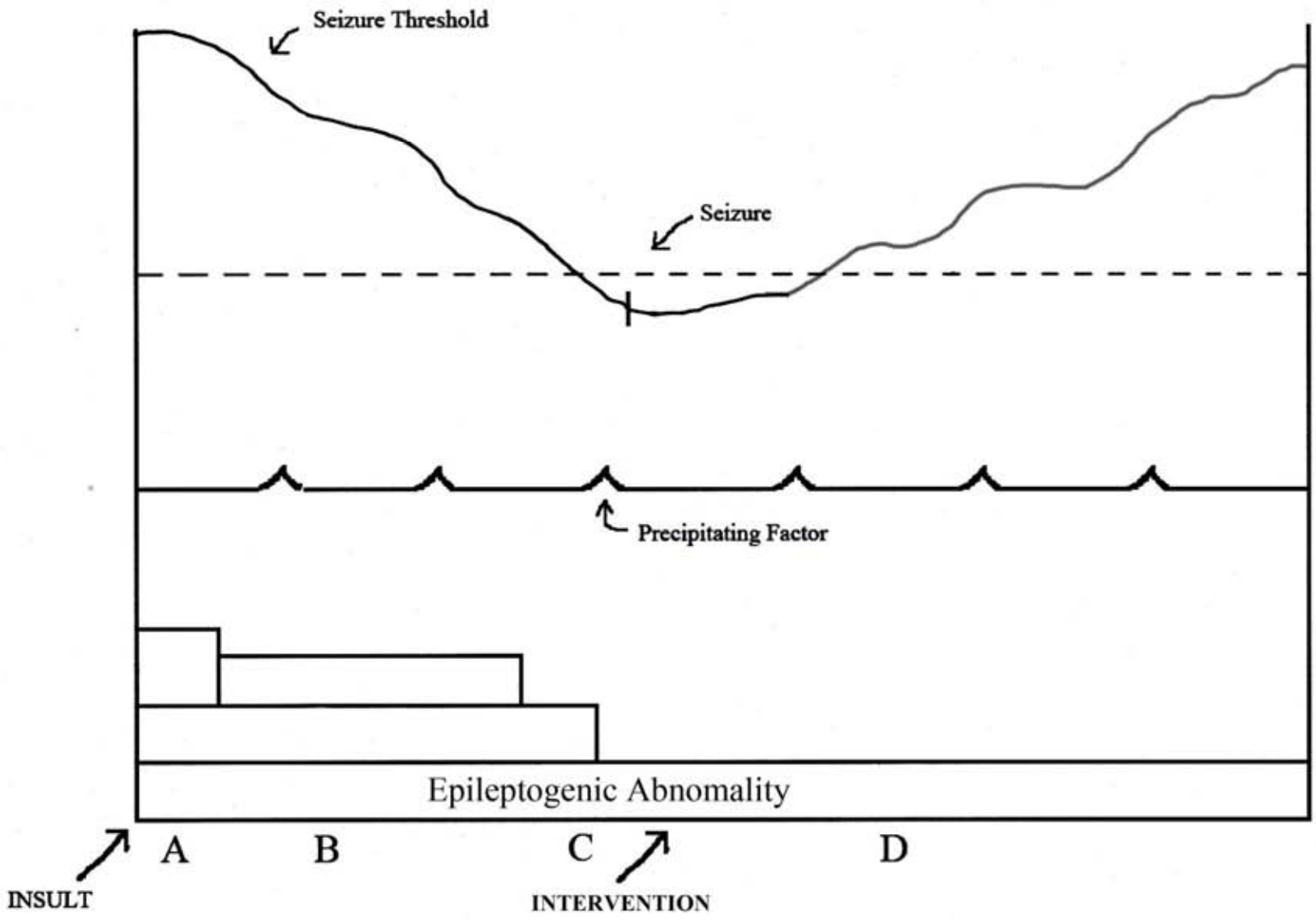
Epileptogenesis



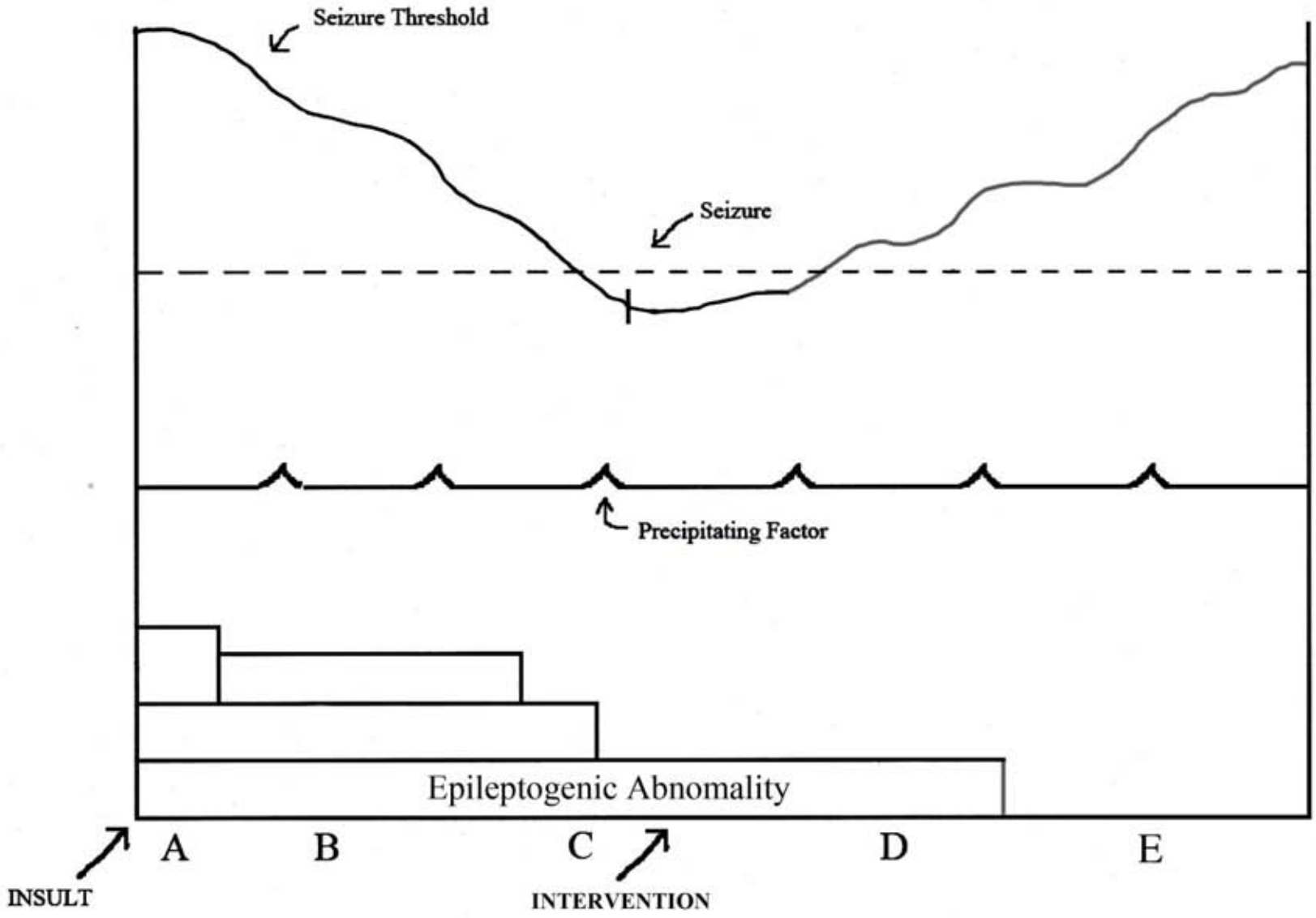
Progression



Remission


Seizure Threshold
Seizure
Precipitating Factor
Epileptogenic Abnomality
A
B
C
D
INSULT
INTERVENTION

Cure


Seizure Threshold
Seizure
Precipitating Factor
Epileptogenic Abnomality
A
B
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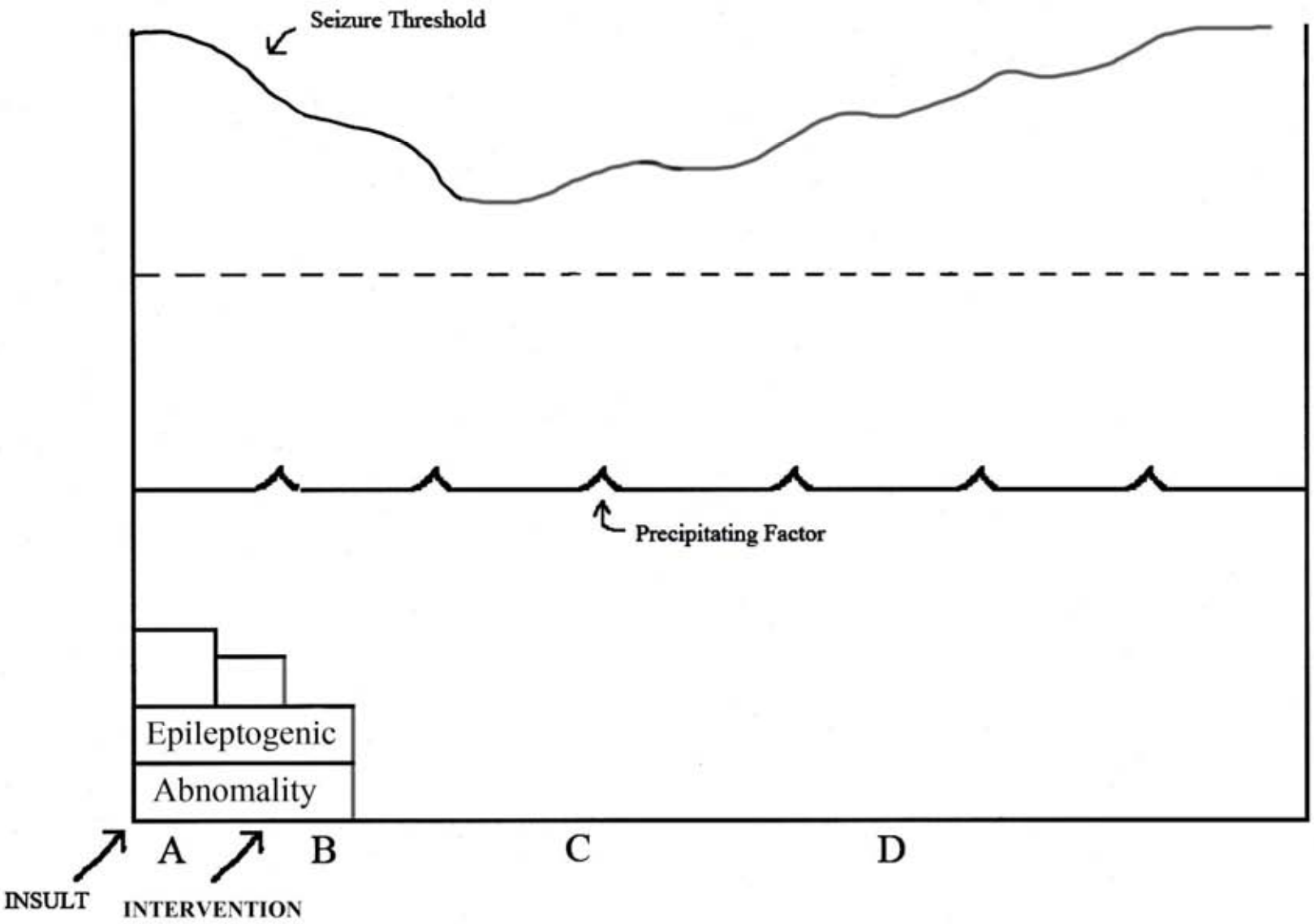
D
E
INSULT
INTERVENTION

Prevention


Seizure Threshold
Precipitating Factor
Epileptogenic
Abnomality
A
B
C
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INTERVENTION

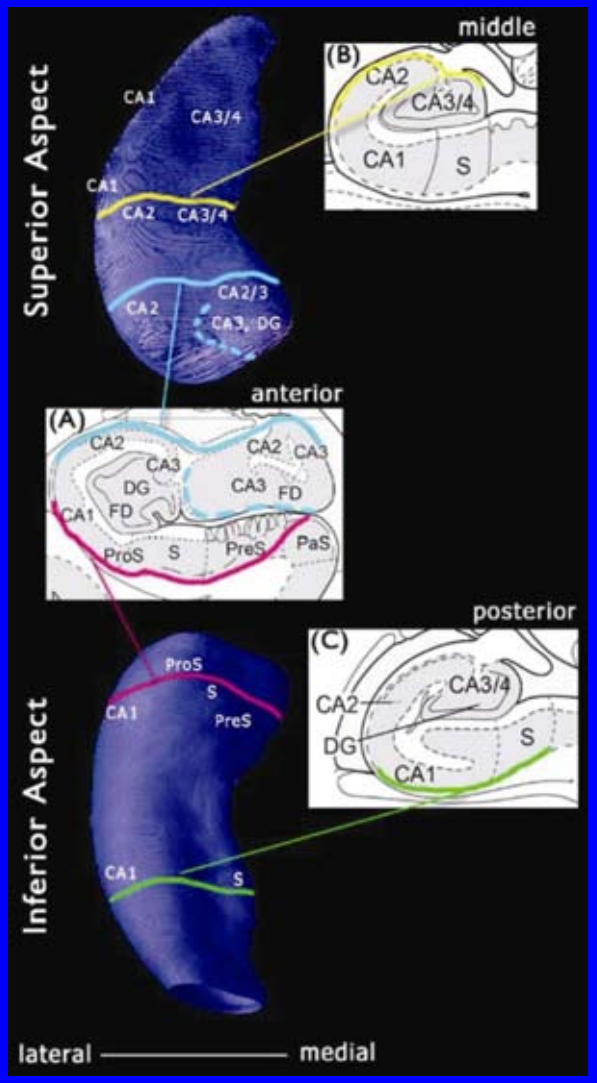
TARGET MECHANISMS

- 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

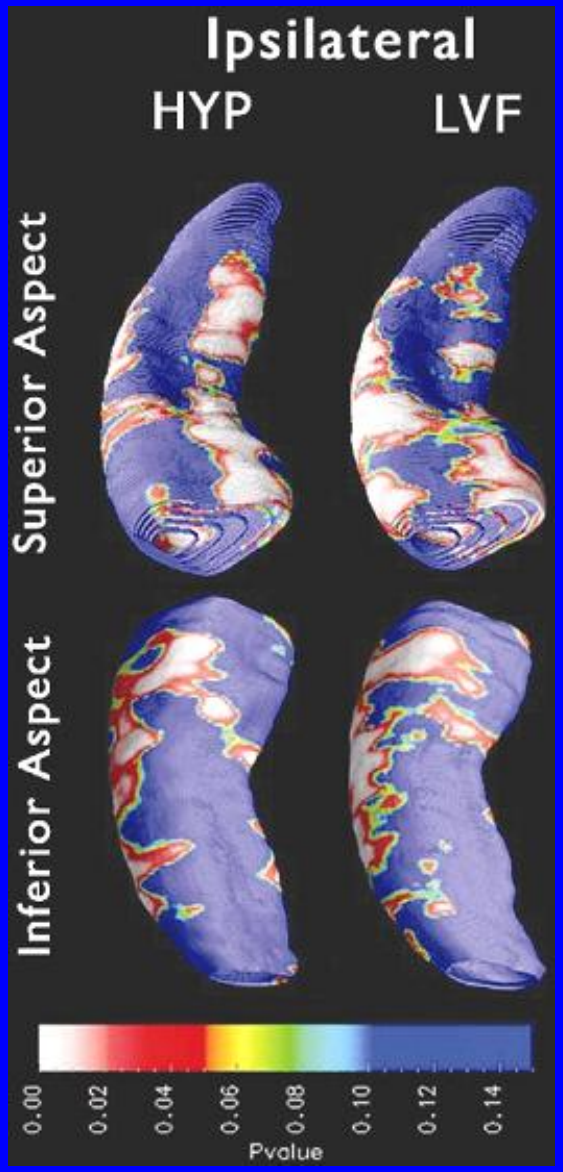
POTENTIAL BIOMARKERS

- Hippocampal changes on MRI
- Interictal spike features, including fMRI
- Pathological high-frequency oscillations (pHFOs)
- Excitability – TMS
- AMT-PET imaging
- Gene expression profiles

HYP & LVF seizure onsets associated with unique patterns of damage



Ogren et al. In press

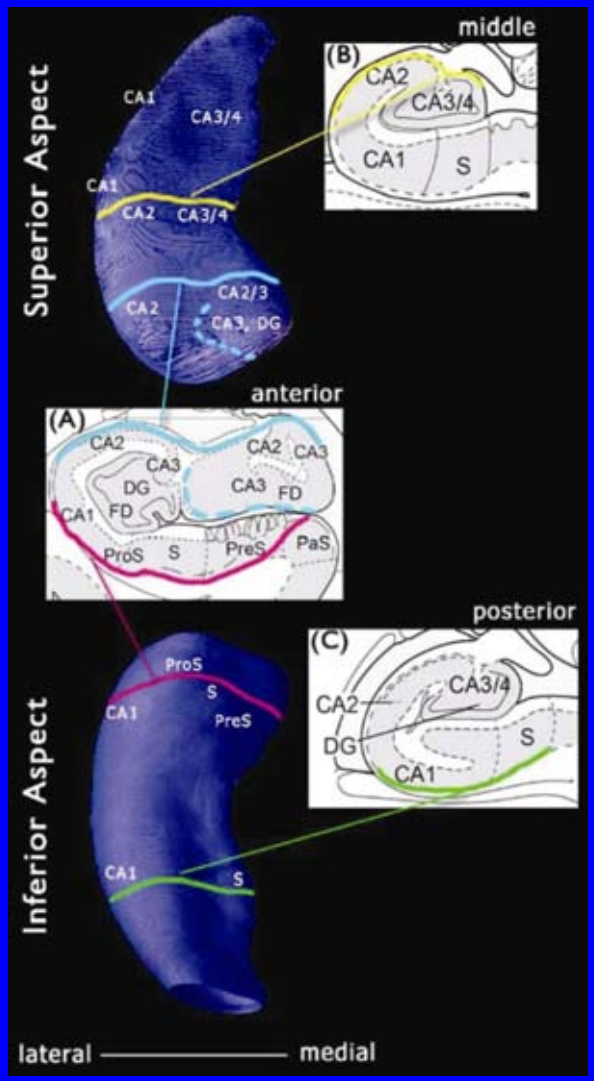


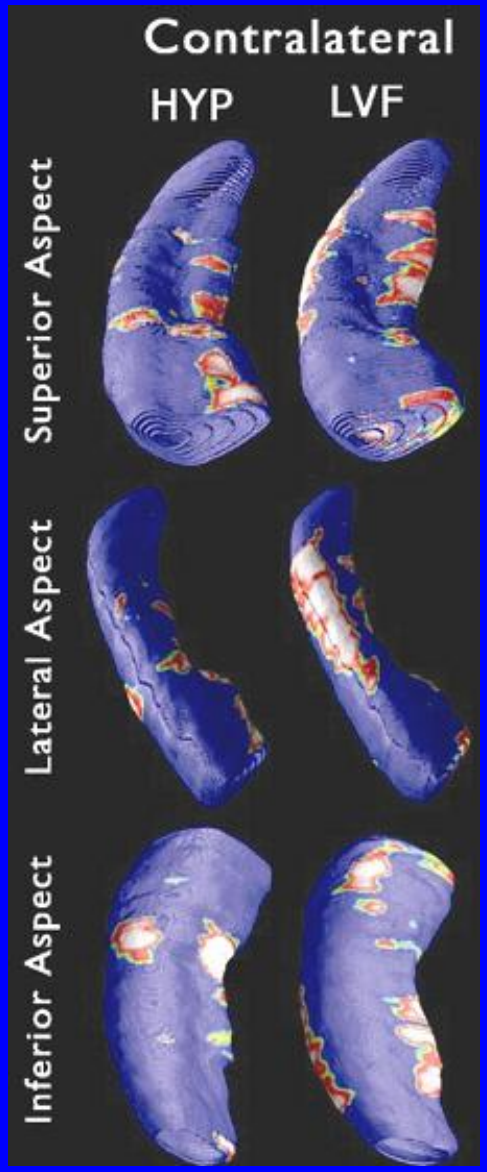
HYP or LVF seizure onsets associated with significant atrophy.

Atrophy in patients with HYP onset resembles classical hippocampal sclerosis.

Atypical pattern of atrophy associated with LVF onsets compared to HYP onsets.

Contralateral damage in patients with LVF seizure onsets

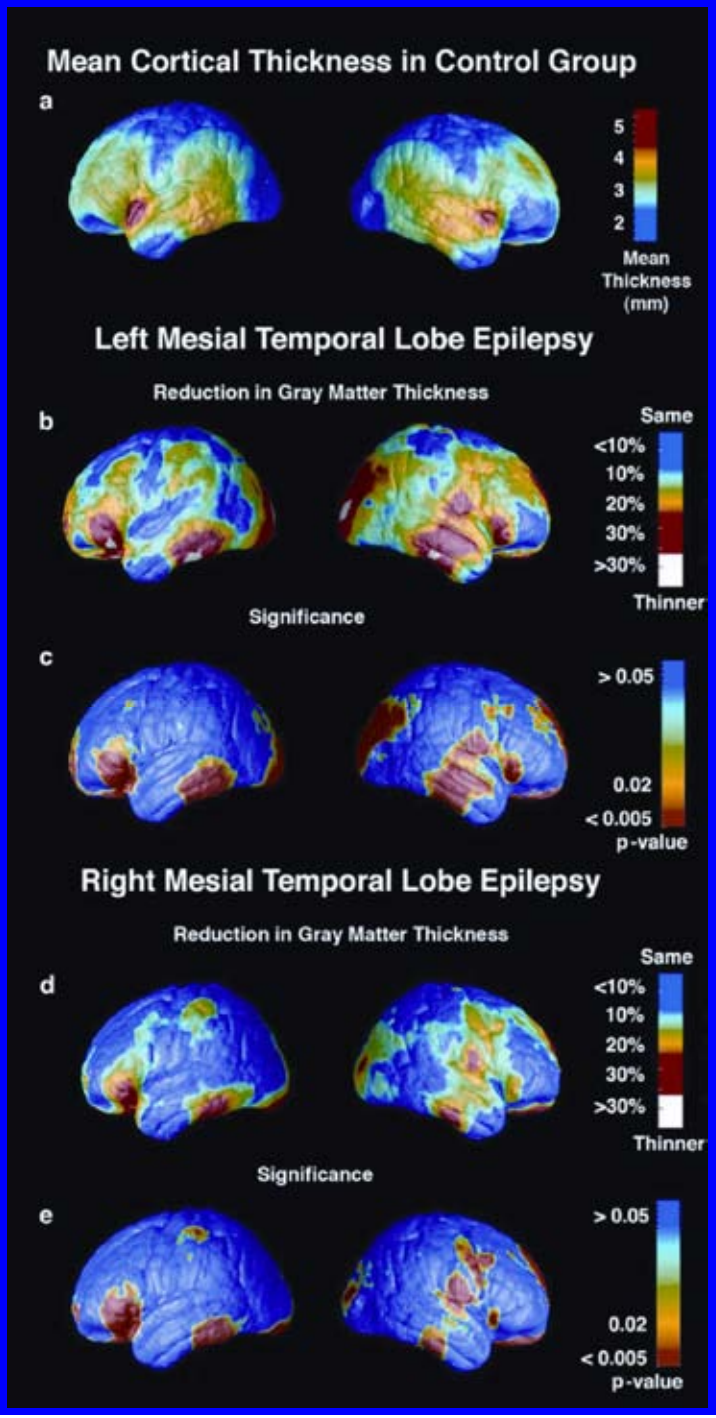




HYP onsets associated with isolated areas of damage, but overall not significantly different with respect to control subjects.

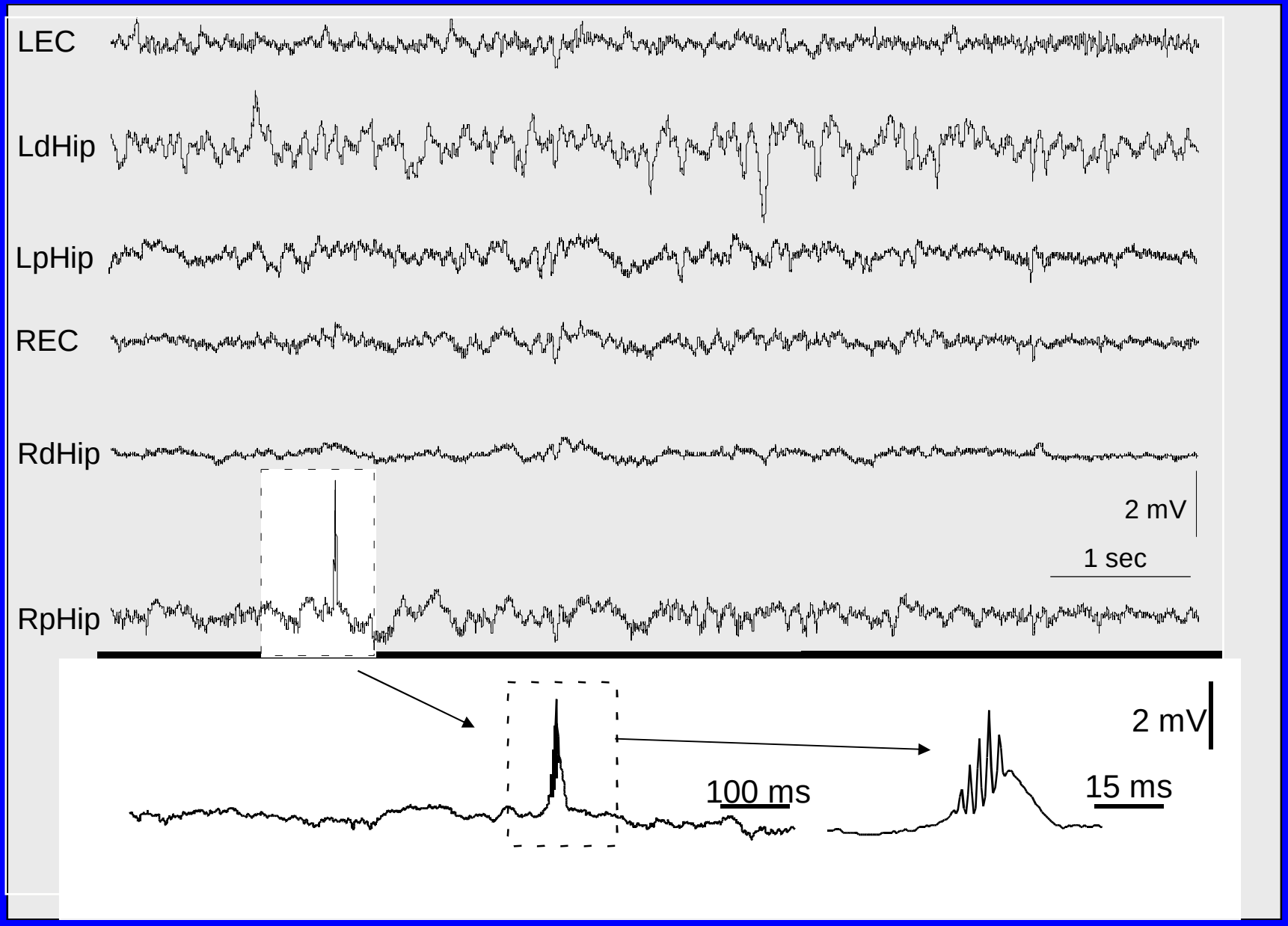
Significant contralateral atrophy in patients with LVF onsets.

Ogren JA, Bragin A, Wilson CL, Hoftman GD, Lin JJ, Dutton RA, Fields TA, Toga AW, Thompson PM, Engel J, Jr., Staba RJ. Three-dimensional hippocampal atrophy maps distinguish two common temporal lobe seizure-onset patterns. Epilepsia, 2009; 50: 1361-70.

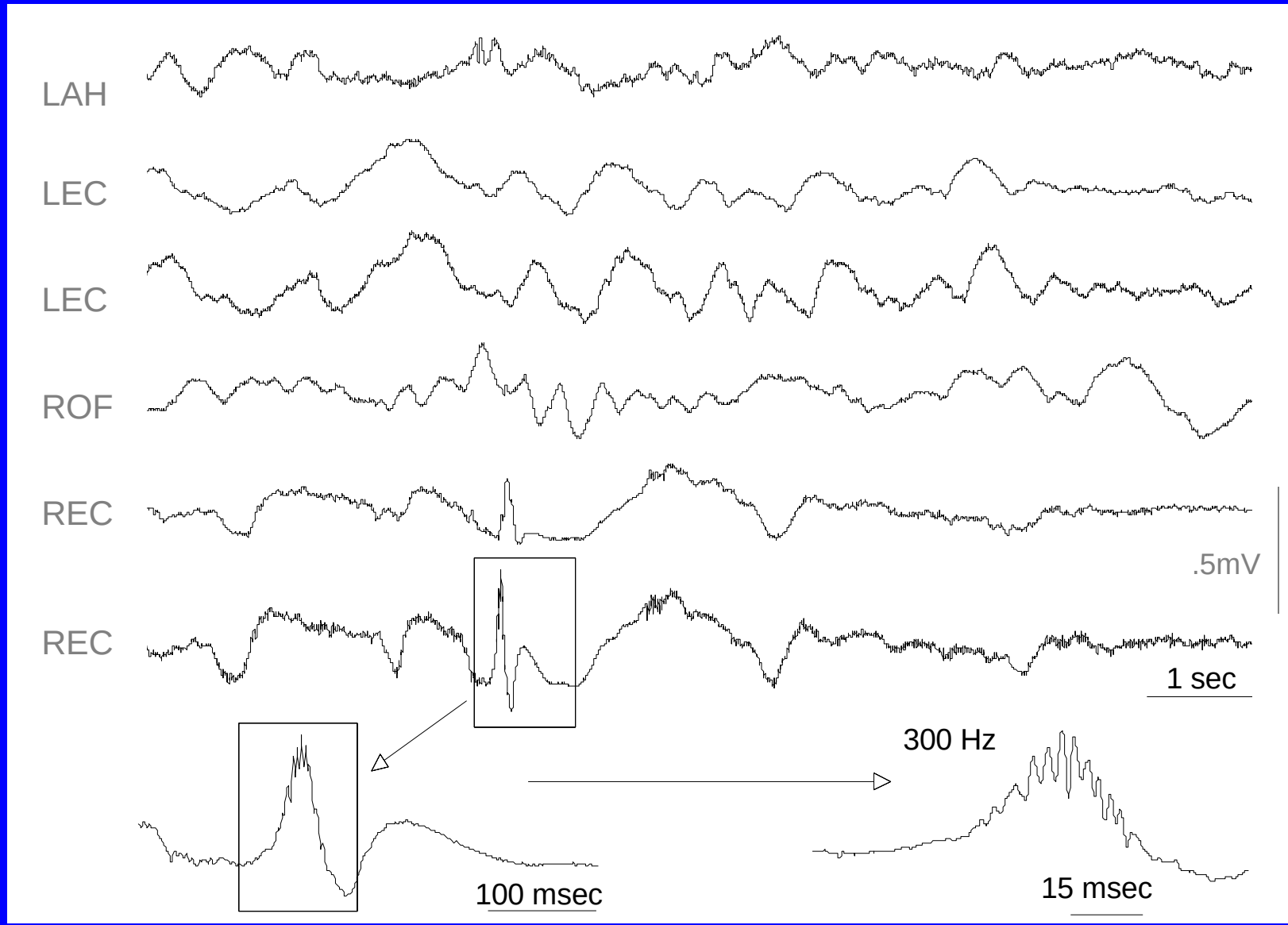


Lin JJ, Salamon N, Lee AD, Dutton RA, Gaeaga JA, Hayashi KH, Luders E, Toga AW, Engel J, Jr., Thompson PM. Reduced neocortical thickness and complexity mapped in mesial temporal lobe epilepsy with hippocampal sclerosis. Cereb Cortex, 2007; 17: 2007-18.

Rat

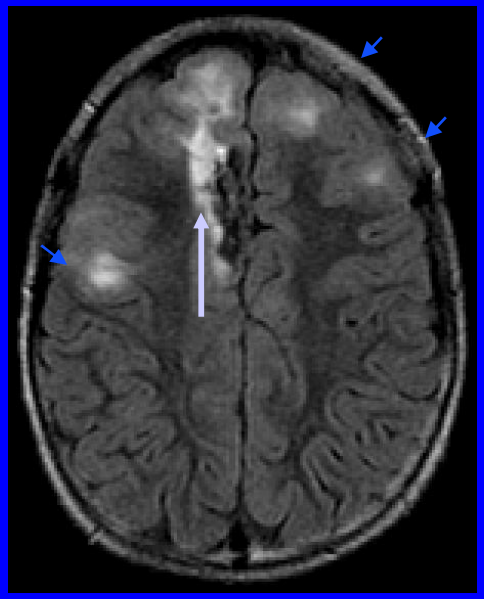


Human

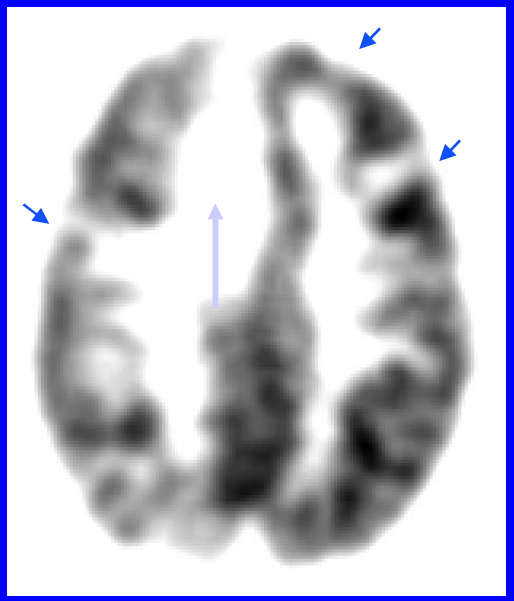


Alpha[C-11]methyl-L-tryptophan PET selectively identifies the epileptogenic tuber in a 7-year-old boy with tuberous sclerosis complex

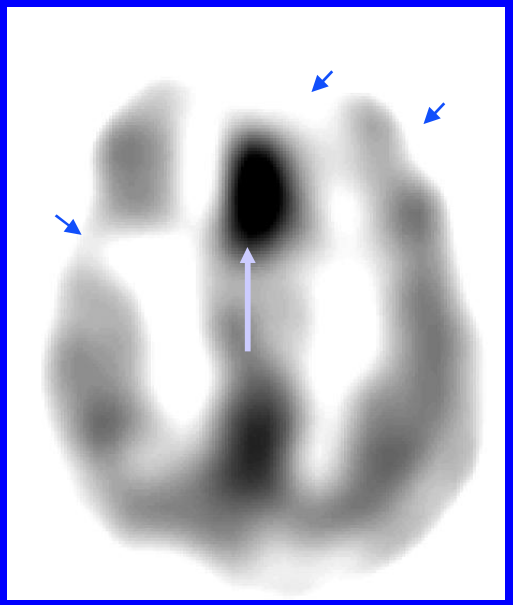
FLAIR MRI



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

Epileptogenesis: The development and extension of tissue capable of generating spontaneous seizures. This includes:

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

Ictogenesis: Tissue capable of generating spontaneous behavioral seizures.

BIOMARKERS OF EPILEPTOGENESIS

- Identify the development of brain tissue capable of generating spontaneous epileptic seizures.
- Identify the progression of an epileptic condition after it has developed.

BIOMARKERS OF EPILEPTOGENICITY

- Identify the existence of brain tissue capable of generating spontaneous seizures.
- Measure the severity of an epileptic condition.
- Determine pharmacoresistance.
- Localize brain tissue capable of generating spontaneous seizures.

BIOMARKERS OF EPILEPSY DEVELOPMENT

- Predict epilepsy in patients with risk factors
  - genetic predisposition
  - prolonged febrile seizure
  - head trauma
  - intracranial infection
  - brain lesion
- Institute antiepileptic intervention

BIOMARKERS OF EPILEPSY PROGRESSION

- Diagnose progression in patients with epilepsy
- Early aggressive treatment is essential to prevent irreversible social and psychological disabling consequences of recurrent seizures
- Determine when to refer patients for surgical therapy
- Identify patients who might benefit from experimental treatments

BIOMARKERS OF THE EXISTENCE OF EPILEPSY

- Predict which people have epilepsy after a single seizure, in order to begin AED treatment immediately and not wait for a second seizure, which could cause injury or death.
- Diagnose epilepsy definitely in patients with equivocal events without the need for inpatient video-EEG monitoring.
- Confirm that a patient with epilepsy has been cured.

BIOMARKERS OF EPILEPSY SEVERITY

- Determine the efficacy of therapeutic interventions without the need to wait for another seizure to occur
  - test pre intervention
  - test post intervention
- Tailor individual pharmacotherapy
  - rapid drug screening to identify the best pharmacotherapy regimen for each individual patient

BIOMARKERS THAT LOCALIZE EPILEPTIC BRAIN TISSUE

- Localize the epileptogenic region for surgical resection without the need for expensive presurgical evaluation.
- Identify epileptogenic brain tissue for basic research on fundamental mechanisms of epilepsy.

BIOMARKERS OF PHARMACORESISTANCE

- Identify pharmacoresistance in individual patients without the need to conduct multiple drug trials
- Early aggressive treatment is essential to prevent irreversible social and psychological disabling consequences of recurrent seizures
- Determine when to refer patients for surgical therapy
- Identify patients who might benefit from experimental treatments

BIOMARKERS OF PHARMACORESISTANCE

- Facilitate clinical trials of interventions intended to prevent or treat pharmacoresistance
  - new antiepileptic drugs
  - rational polytherapy with rapid course change, e.g., I-SPY
- Create cost-effective rapid throughput animal models of pharmacoresistance to identify
  - antiepileptic compounds
  - antiepileptic devices

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