Highlight in Epilepsy 2015

Outline

Clinical Practice

: Management of an unprovoked 1st in adult

: New AED: parampanel

: Co-morbid in epilepsy

Biomarker

Epileptic surgery

Personalized

Basic science

Biomarker: electrophysiological

SUDEP

Epilepsy network

SPECIAL ARTICLE

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Evidence-based guideline: Management of an unprovoked first seizure in adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

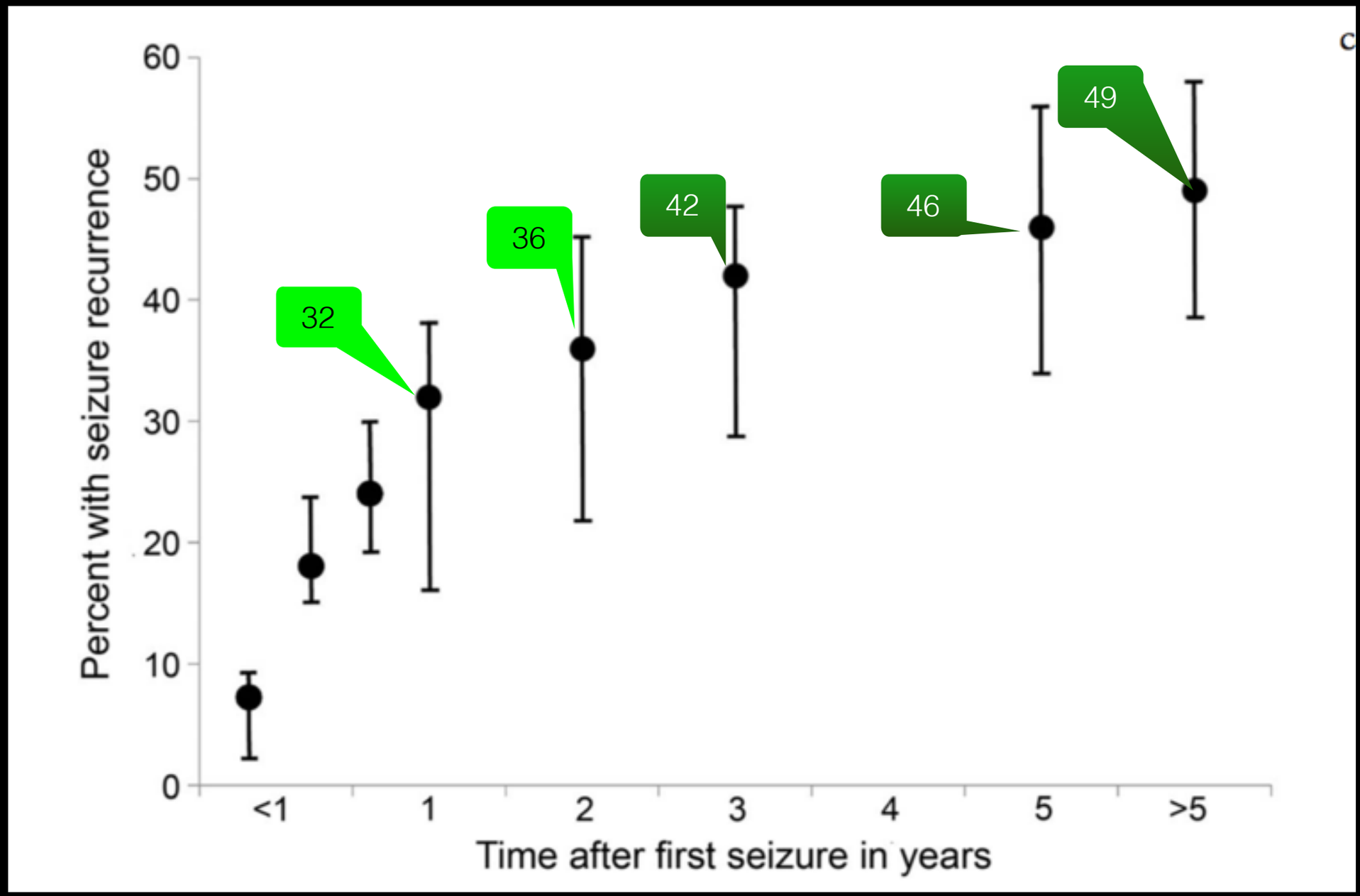
Neurology® 2015;84:1705-1713

1. **What are the risks for seizure recurrent?**

2. **Dose immediate treatment with an AED as compared with delay pending a seizure recurrent influence prognosis, such as the potential for seizure remission over the long term (> 3 years)?**

3. **What are the nature and frequency of AEs with AED treatment?**

What are the risks for seizure recurrent?



What are the risks for seizure recurrent?

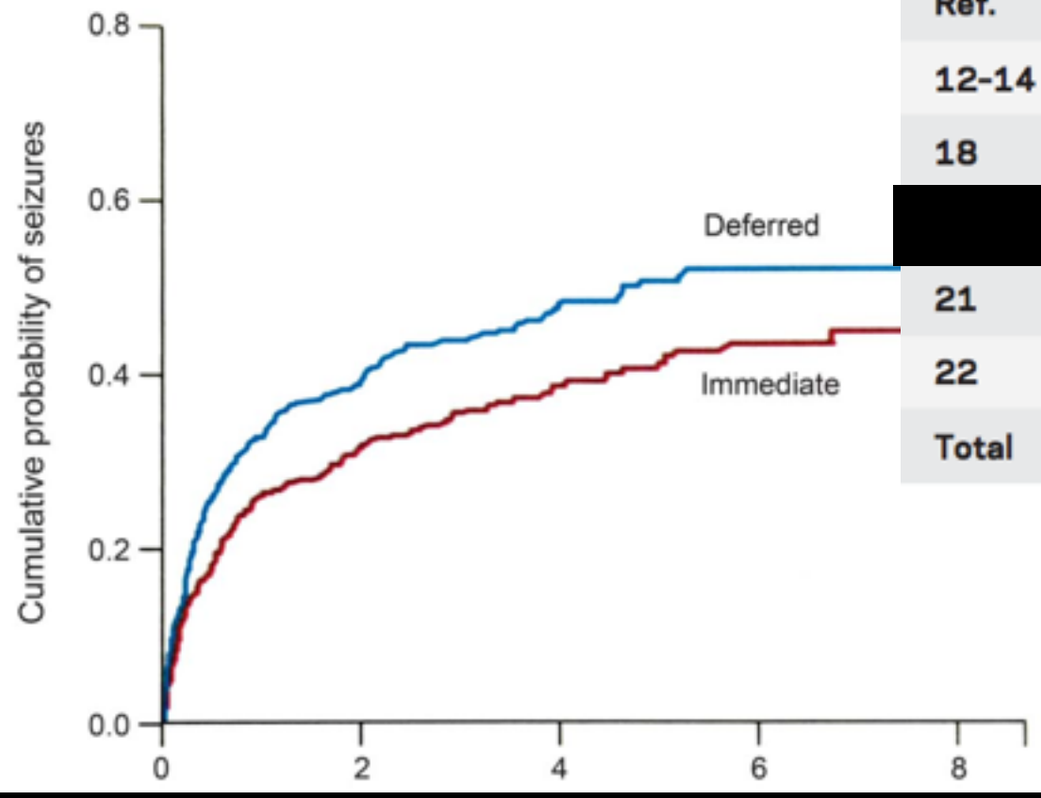
Risk factors	Relative rate
Prior brain lesion or insult causing seizure:	2.55 (95%CI 1.44-4.51)
An EEG with epileptiform abnormalities	2.16 (%%CI 1.07-4.38)
A significant brain-imaging abnormality	2.44 (95%CI 1.09-5.44)
Nocturnal seizure	2.1 (95%CI 1.0-4.3)

What are the risks for seizure recurrent?

1. An adult with an unprovoked first seizure is at greatest risk of a recurrence relatively early, within the first 2 years (21%–45%), and especially in the first year (2 Class I studies, 8 Class II studies).
2. The risk of seizure recurrence increases in certain clinical circumstances.

- a prior brain lesion or insult causing the seizure (2 Class I studies, 2 Class II studies)
- an EEG with epileptiform abnormalities (2 Class I studies, 4 Class II studies)
- a significant brain-imaging abnormality (2 Class II studies, 1 Class III study)
- a nocturnal seizure (2 Class II studies).

Dose immediate treatment with an AED as compared with delay pending a seizure recurrent influence prognosis, such as the potential for seizure remission over the long term (> 3 years)?



Ref.	Class	No.	Treated, n (%)	Recur. rate treated, n (%)	Recur. rate untreated, n (%)	Length of follow-up, y
12-14	I	397	204 (51)	36 (18)[a]	75 (39)	2
18	II	76	36 (47)	4 (11)[a]	18 (45)	1
21	II	228	113 (50)	5 (4)[a]	63 (55)	1
22	II	87	45 (52)	9 (20)[a]	28 (66)	2
Total		1,600	804 (50)	183 (23)	343 (43)	1 or 2

absolute risk reduction in seizure recurrence of 35% (95% CI 23%–46%)

no significant differences in standard, validated 2-year QOL measures.

Dose immediate treatment with an AED as compared with delay pending a seizure recurrence influence prognosis, such as the potential for seizure remission over the longer term (>3 years)?

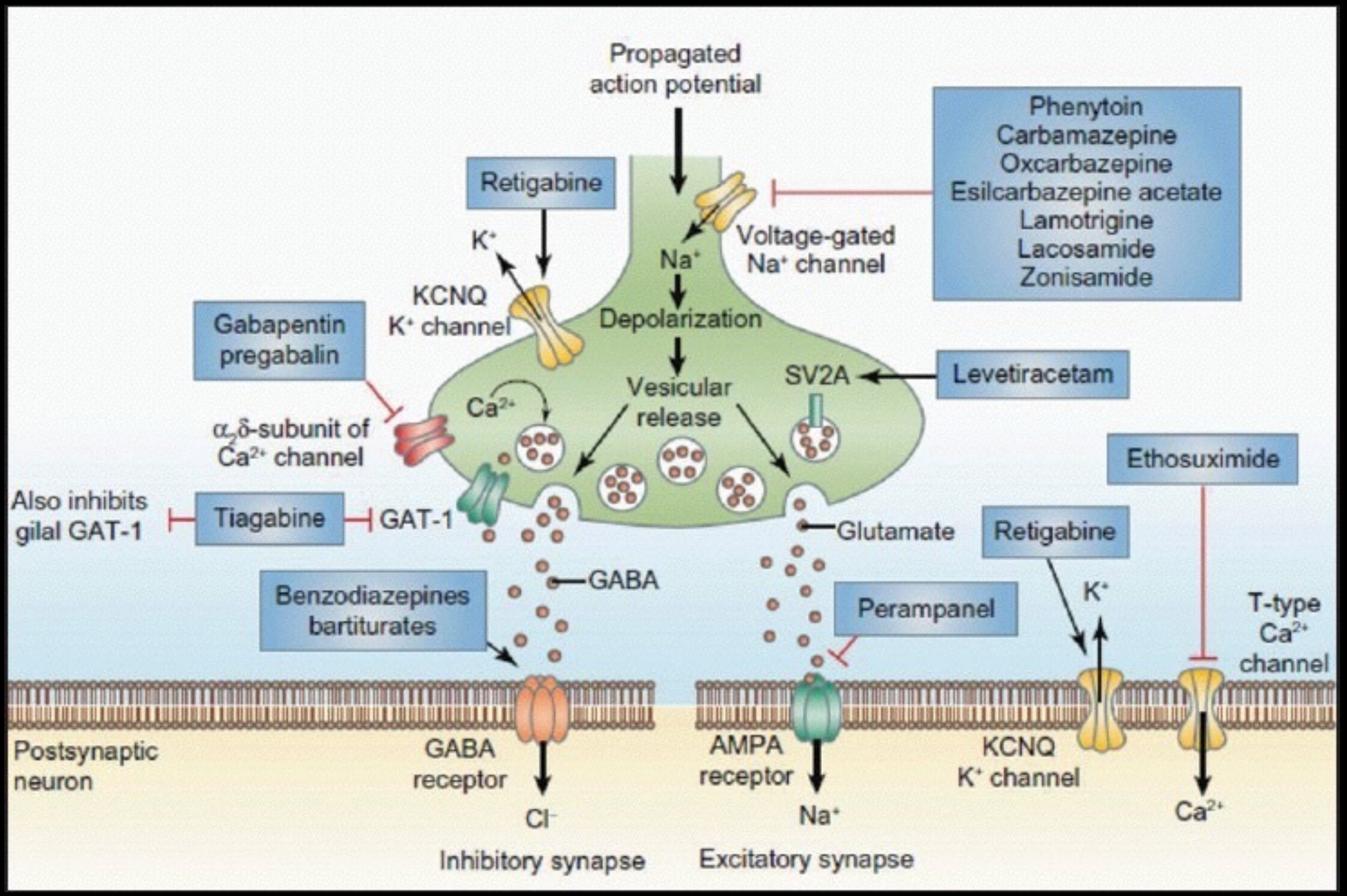
Ref.	Class	No.	Immediate treatment, n (%)	Remission, immediate treatment, n (%)	Remission, deferred treatment, n (%)	Length of follow-up
12-14	I	419	215 (51)	174 (81), NS	159 (78)	More than 3 y[a]
15	II	812	404 (50)	372 (92), NS	375 (92)	5 y[b]
Total		1,231	619 (50)	546 (88)	534 (87)	

What are the nature and frequency of AEs with AED treatment?

- The incidence of AEs from AEDs is reported to range from 7%-31% for a variety with AEDs
- Reported AEs in these studies appear to be mild and reversible when an affect patient is switched to another AED
- No AED-related deaths or lift-threatening allergic reactions were described.

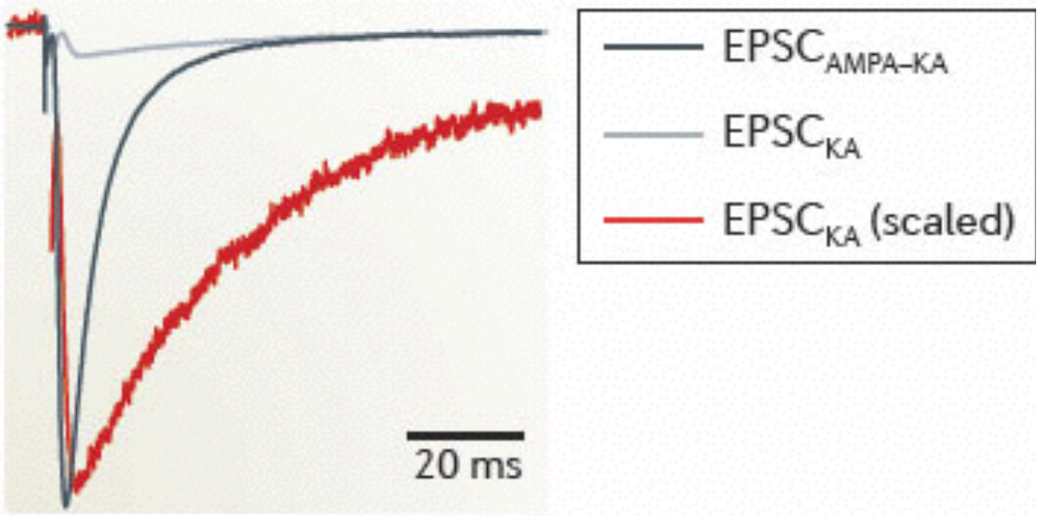
Ideal AED

1. Antiepileptogenicity
2. Efficacy and Effectiveness
3. Adverse drug reaction
4. Pharmacokinetic
5. Special population
6. Cost

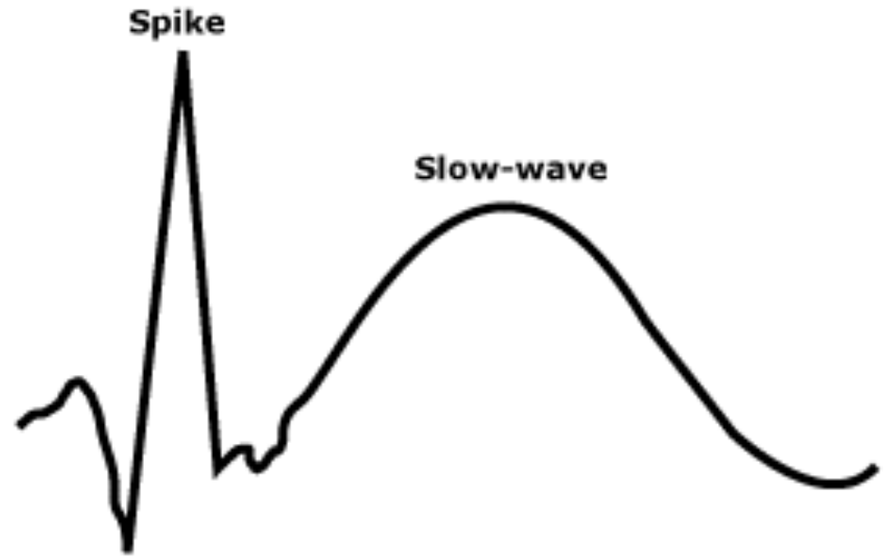


Nat Rev Neurol 2012;8:611-2

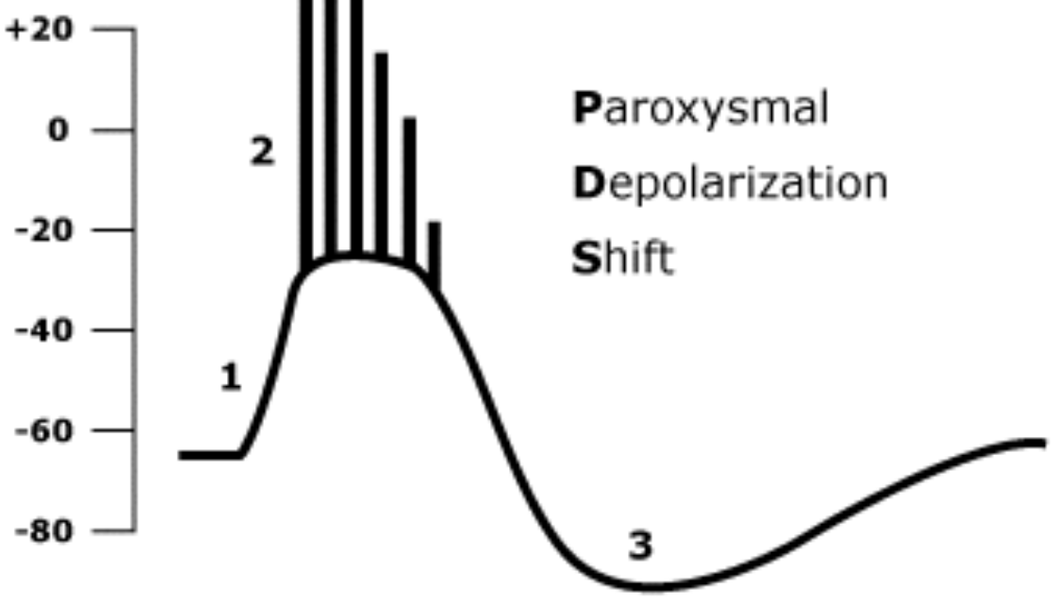
a $EPSC_{AMPA–KA}$ **versus isolated** $EPSC_{KA}$



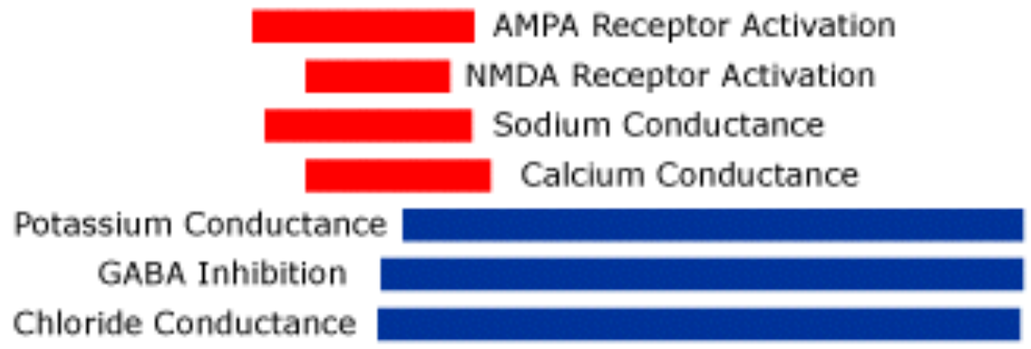
EEG



Intracellular recording



Ion channels



Ideal AED

1. Antiepileptogenicity
2. Efficacy
3. Adverse drug reaction
4. Pharmacokinetic
5. Formulation
6. Easy to use
7. Special population
8. Cost

Adverse drug reactions

		Perampanel			
Adverse event, n (%)	Placebo (n=442)	2 mg/day (n=180)	4 mg/day (n=172)	8 mg/day (n=431)	12 mg/day (n=255)
Any TEAE	294 (67%)	111 (62%)	111 (65%)	350 (81%)	227 (89%)
Dizziness	40 (9%)	18 (10%)	28 (16%)	137 (32%)	109 (43%)
Somnolence	32 (7%)	22 (12%)	16 (9%)	67 (16%)	45 (18%)
Headache	50 (11%)	16 (9%)	19 (11%)	49 (11%)	34 (13%)
Fatigue	21 (5%)	8 (4%)	13 (8%)	36 (8%)	31 (12%)
Irritability	13 (3%)	7 (4%)	7 (4%)	29 (7%)	30 (12%)
Nausea	20 (5%)	4 (2%)	5 (3%)	25 (6%)	20 (8%)
Fall	15 (3%)	2 (1%)	3 (2%)	22 (5%)	26 (10%)
Nasopharyngitis	18 (4%)	7 (4%)	9 (5%)	23 (5%)	11 (4%)
Upper RTI	12 (3%)	11 (6%)	6 (4%)	14 (3%)	10 (4%)
Ataxia	0	0	1 (<1%)	14 (3%)	21 (8%)
Balance disorder	2 (<1%)	0	0	22 (5%)	8 (3%)

TEAE, treatment-emergent adverse event; RTI, respiratory tract infection

Table 1. *Treatment-emergent adverse events reported in ≥5% of patients in any treatment group: results from a pooled analysis of phase 3 studies*[9]

Ideal AED

1. Antiepileptogenicity
2. Efficacy
3. Adverse drug reaction
4. Pharmacokinetic
5. Formulation
6. Easy to use
7. Special population
8. Cost

Stereotagticelectroencephalography

: Practice of recording EEG signals via depth electrodes

: Aim to conceptualized the three-dimentional spatial-temporal organisation of epileptic discharge

: Base on anatomo-electro-clinical correlation

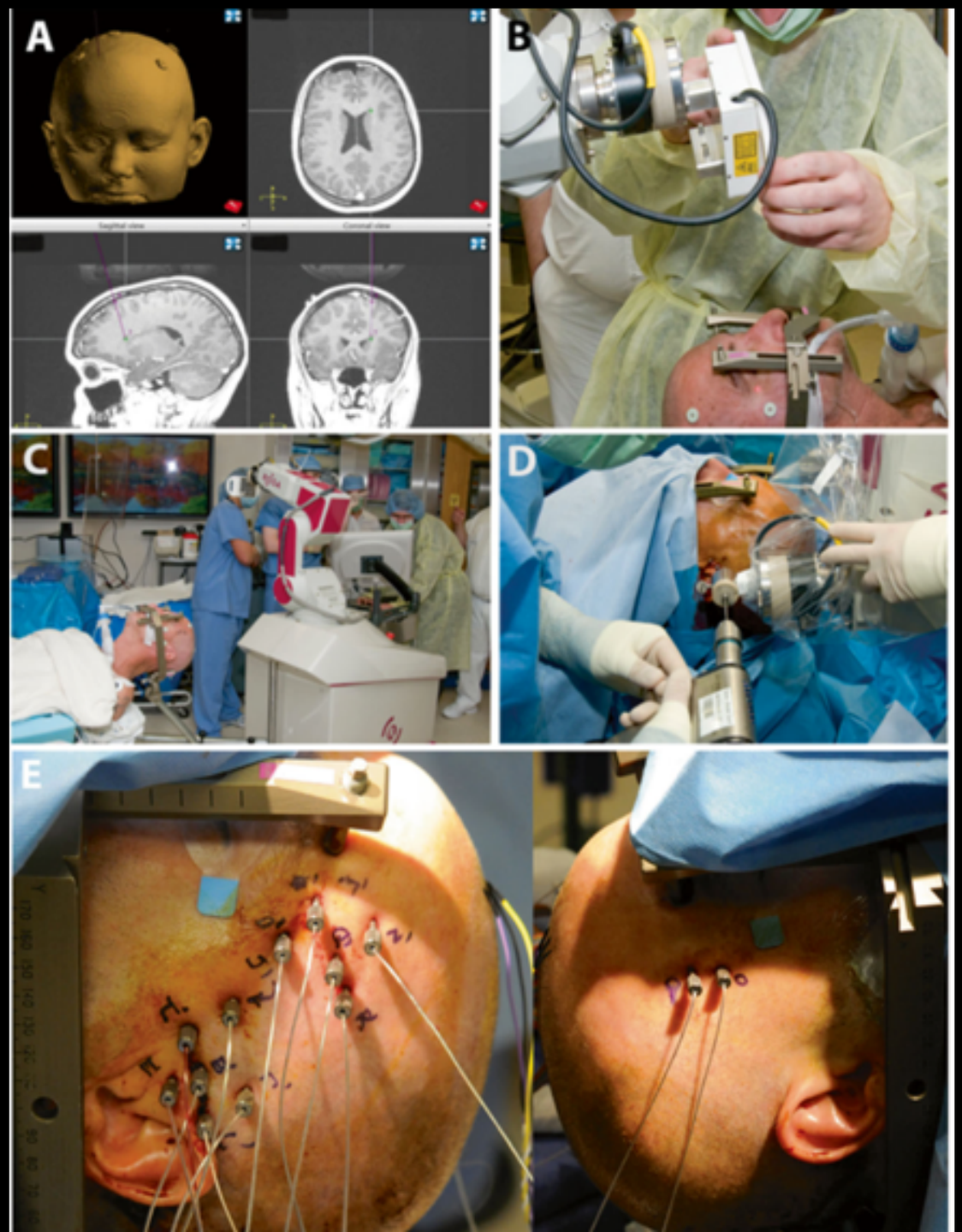
: The only technique that provides direct access to electrophysiological recording in the seizure onset zone, when located in deep brain structures

Stereotagticelectroencephalography

: 3D coordinate system to locate brain structures

: Requires a stereotactic positioning device

: Multimodal imaging (CT, MRI, Angiography etc.) that allows visualisation of patient anatomy and co-registration with stereotactic frame



Stereotagticelectroencephalography

- noninvative evaluation fail to correctly localise the EZ
- With no definite anatomical abnormality
- A wide involvement of extralesional ares
- Large focal, hemispheric, multifical or bilateral MRI abnormality
- Presurgical evaluation suggestive of functional network involvement in the setting of normal MRI

Biomarkers in Epilepsy

Engel J. Biomarkers in epilepsy: introduction. Biomarkers Med. 2011

- Biomarkers: An objectively measured signal associated with a normal or pathological process.

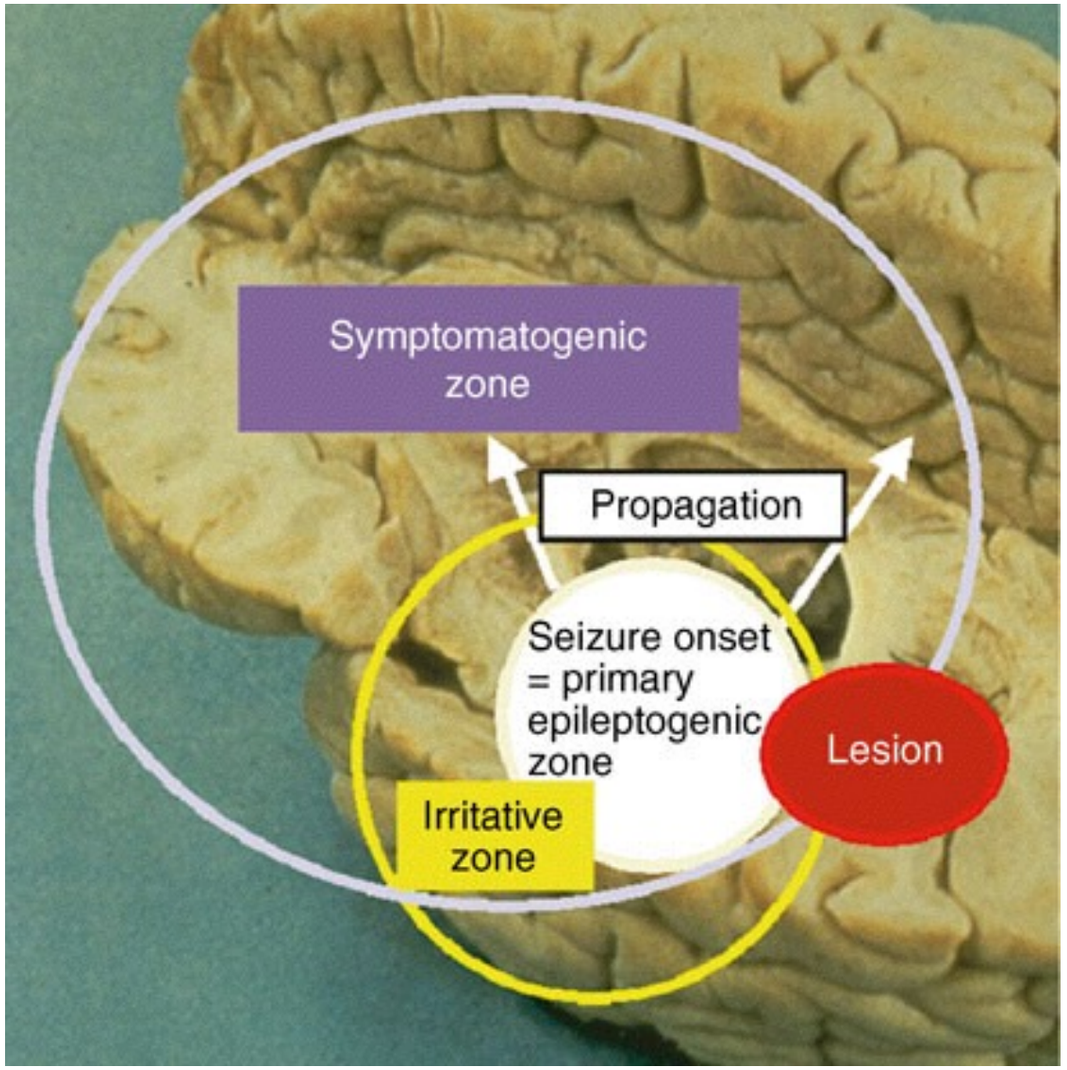
- Surrogate Biomarker: An indirect measure of disease presence or progression

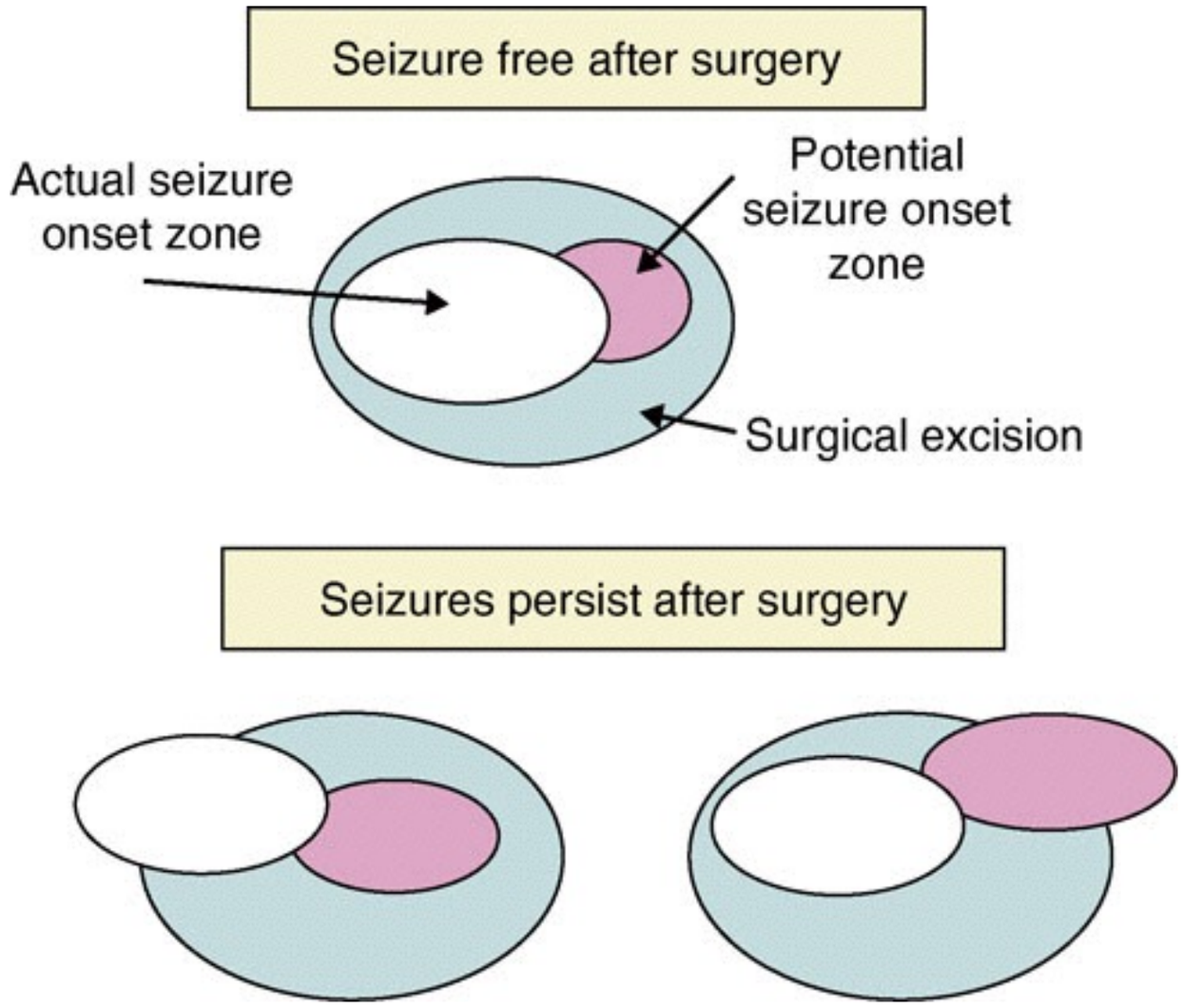
Biomarkers in Epilepsy

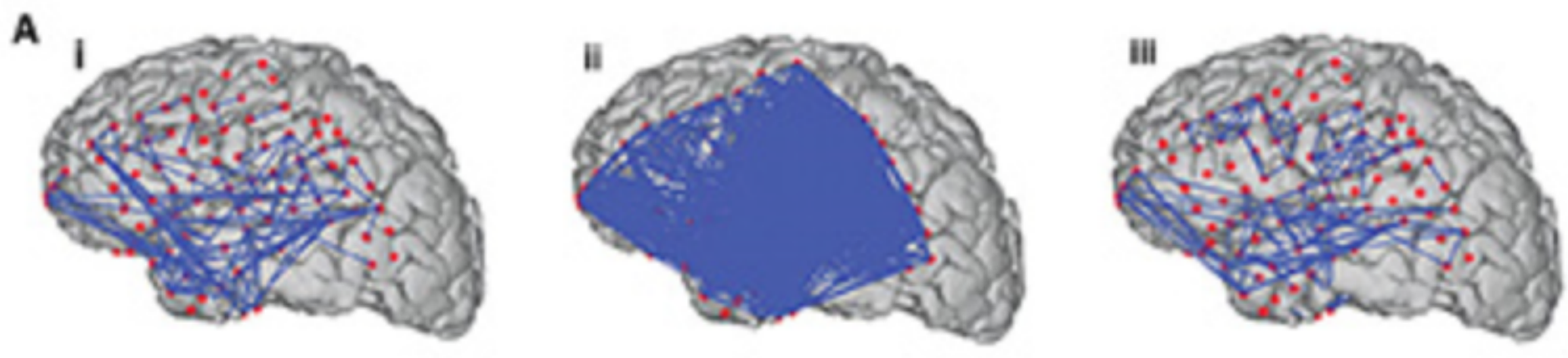
Engel J. Biomarkers in epilepsy: introduction. Biomarkers Med. 2011

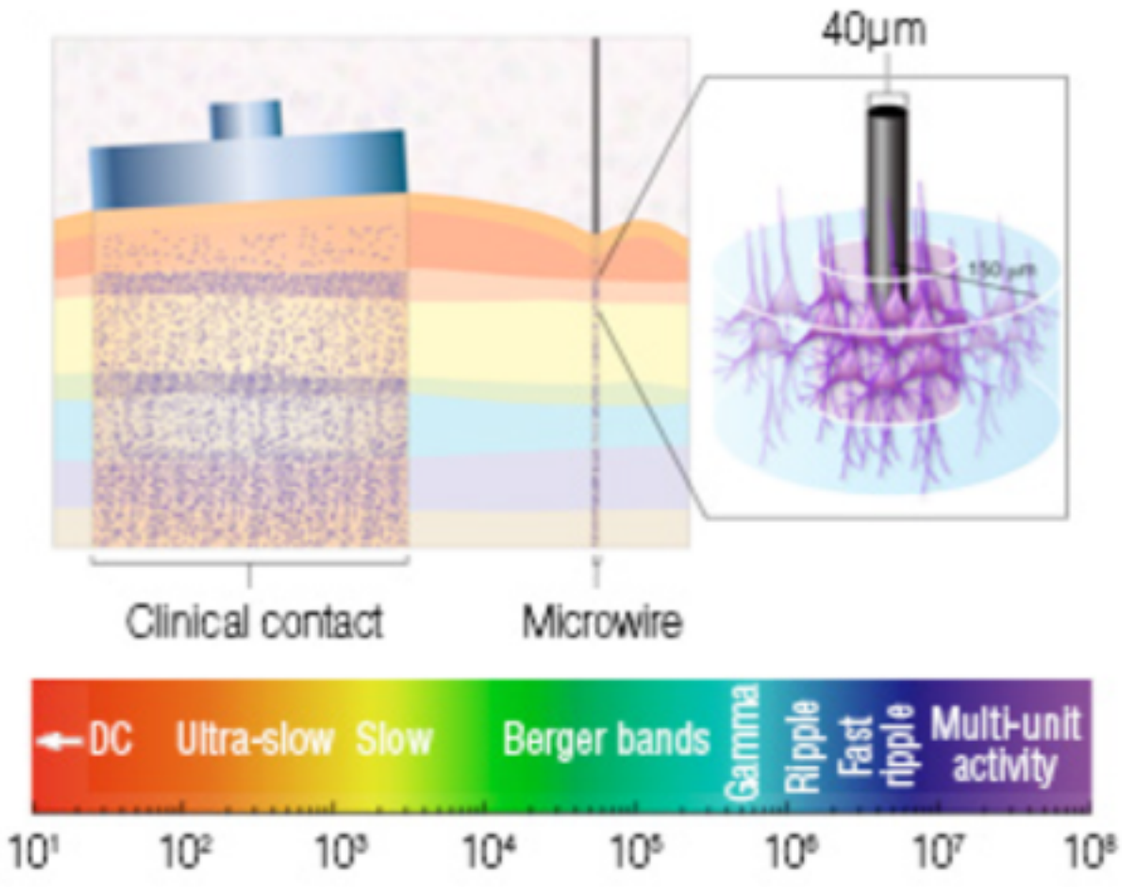
Table 3. Electrophysiologic and imaging epilepsy biomarkers

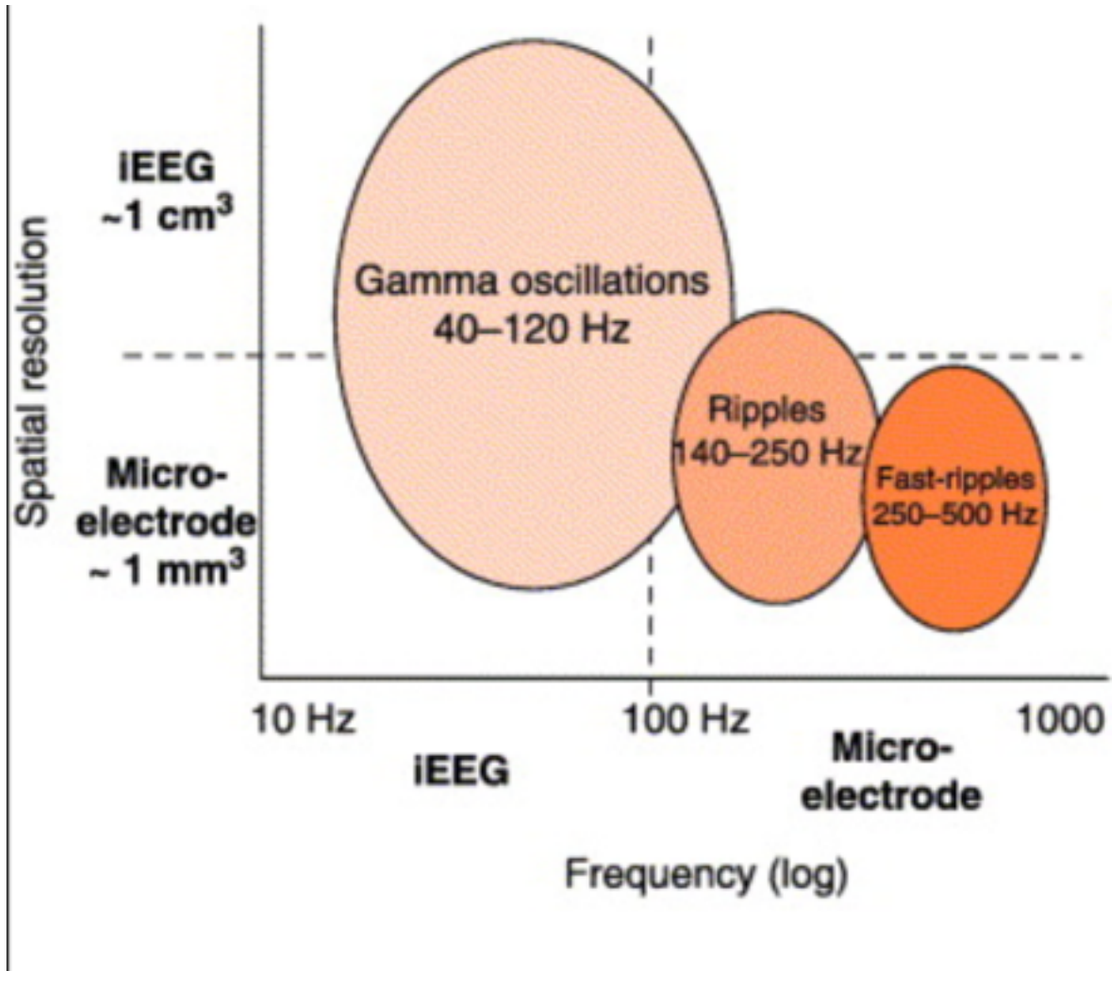
Electrophysiology			Imaging	
Ictal pattern and interictal spikes			MRI (magnetic resonance imaging)	
Frequencies	Duration	Morphology	Routine MRI measures	Enhancement
Field size	Source localization		Functional (fMRI)	Spectroscopy
			Diffusion tensor (DTI)	Susceptibility
High frequency oscillations (HFOs)			PET	
provocative maneuvers			(positron emission tomography)	
Photic stimulation	Hyperventilation		FDG (deoxyglucose)	FMZ (flumazenil)
Sleep deprivation	Drug induction		AMT (α-methyl-tryptophan)	PK (inflammation)
Excitability			SPECT	
TMS (transcranial magnetic stimulation)	Direct electrical stimulation (part of surgical workup)		(Single photon emission computed tomography)	


Symptomatogenic zone
Propagation
Seizure onset = primary epileptogenic zone
Lesion
Irritative zone


Seizure free after surgery
Actual seizure onset zone
Potential seizure onset zone
Surgical excision
Seizures persist after surgery


A
I
II
III


40µm
150 µm
Clinical contact
Microwire
DC
Ultra-slow
Slow
Berger bands
Gamma
Ripple
Fast ripple
Multi-unit activity
10¹
10²
10³
10⁴
10⁵
10⁶
10⁷
10⁸


Spatial resolution
iEEG
~1 cm³
Micro-
electrode
~ 1 mm³
Gamma oscillations
40–120 Hz
Ripples
140–250 Hz
Fast-ripples
250–500 Hz
10 Hz
100 Hz
1000
iEEG
Micro-
electrode
Frequency (log)

Mapping the brain

Electrophysiological Biomarkers

AES 2014: President's symposium

Physiological activity

Oscillations: …. Theta, Alpha, Gamma, Ripples,….

Nesting, Synchrony, Connectivity

Task evoked & induced activity

Pathological activity

Ictal: Habitual spontaneous seizure

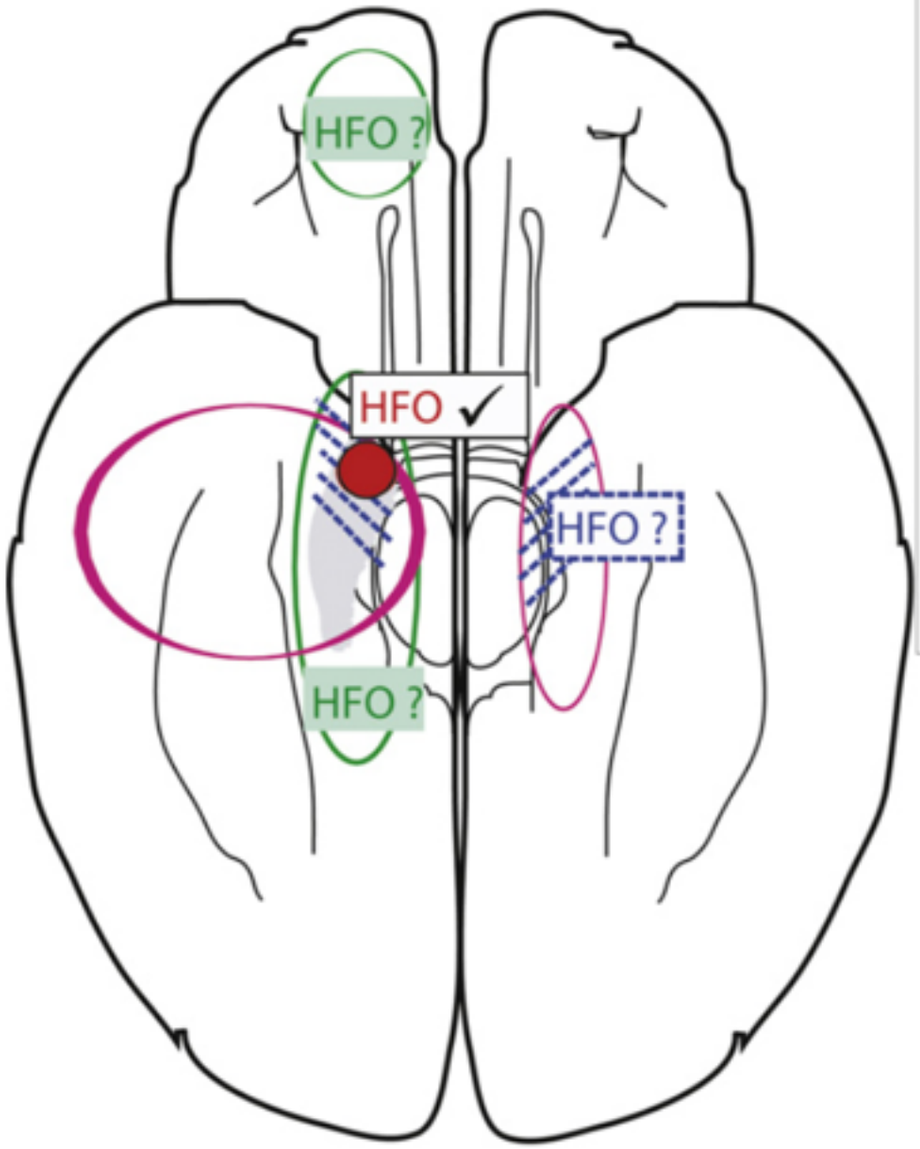
Interictal:

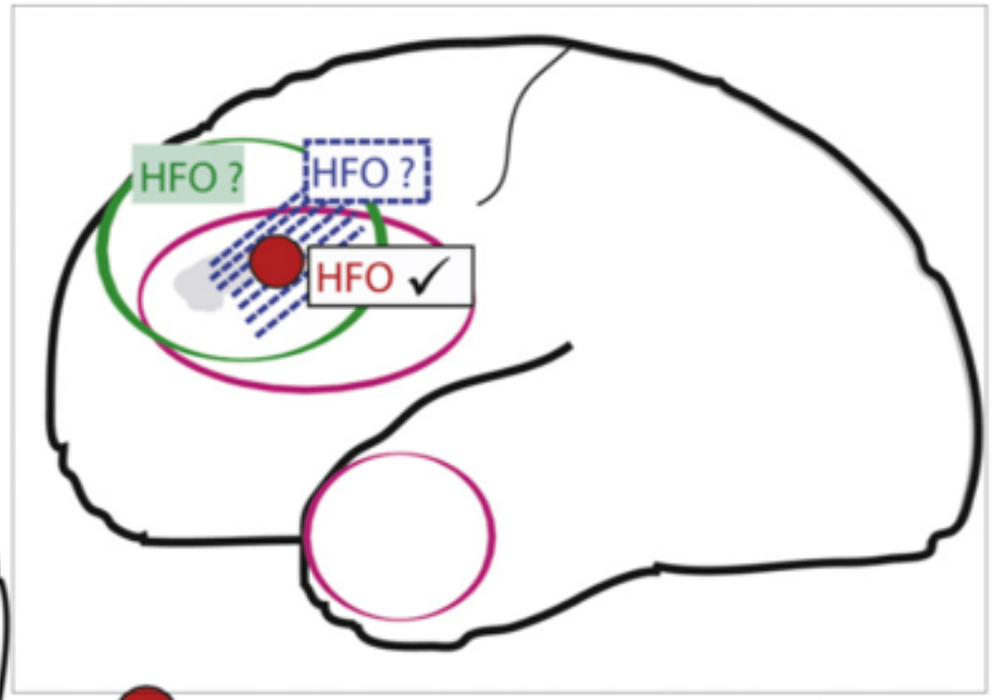
Epileptiform spike: Staley et al. 2011 Pearce et al. 2014

Focal slow oscillations: Gloor et al. 1977 Nordli et al. 2012

Microdomain seizures: Schevon et al. 2008 Stead 2010

High Frequency Oscilations: Bragin et al. 1999





Seizure onset zone (SOZ), gold standart of the presurgical evaluation.
Clear corelation between the occurence of HFOs and the SOZ.

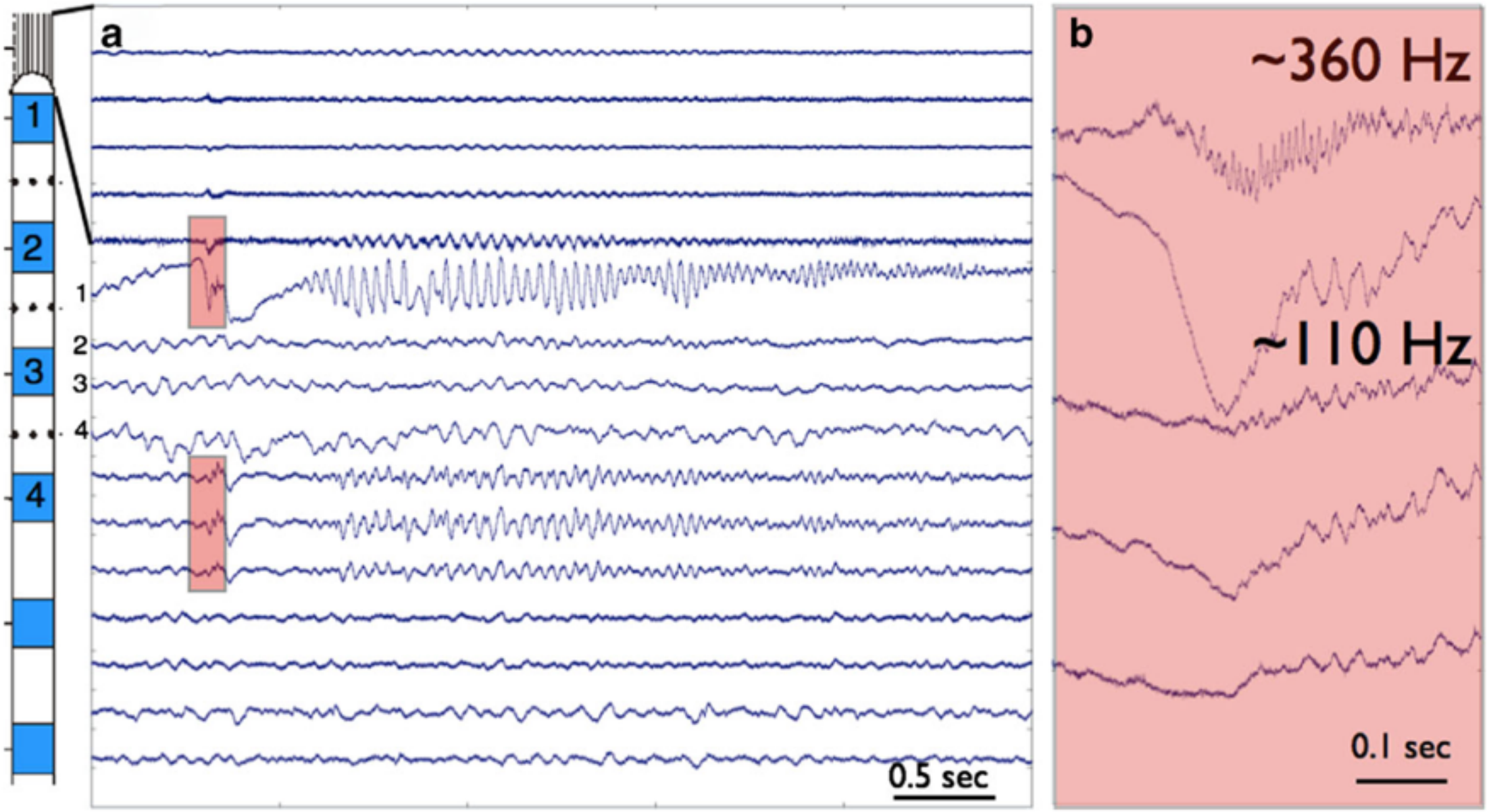
Epileptogenic zone, HFO could be biomarkers of this area.

Irritative zone, area which generates interictal epileptic spikes.
It usually shows only partial overlap with the SOZ and HFO areas.

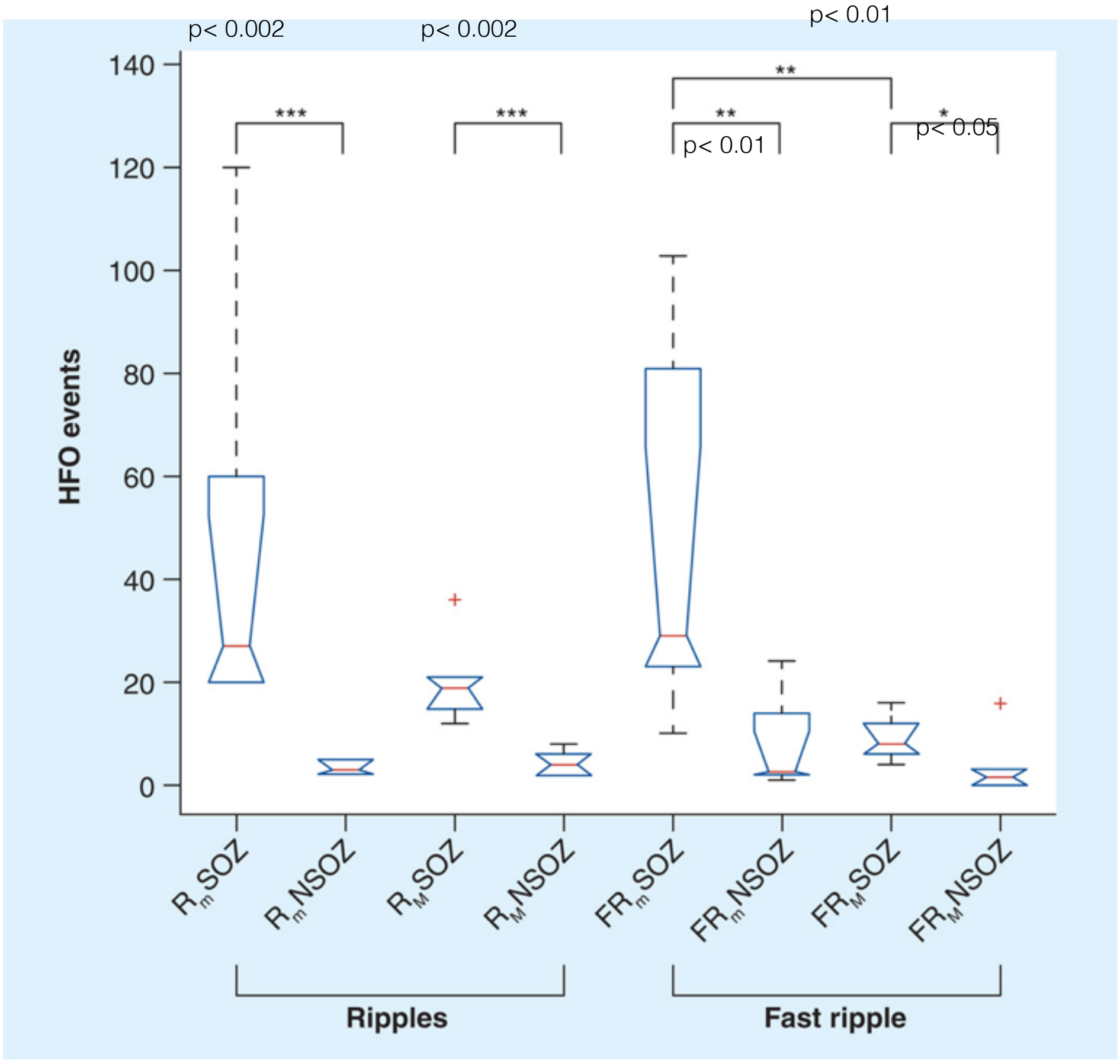
Area of the neuropsychological deficit.
Physiological HFO could help to define this area in the future.

Radiologically defined lesion,
often with some but not complete overlap with the epileptogenic areas

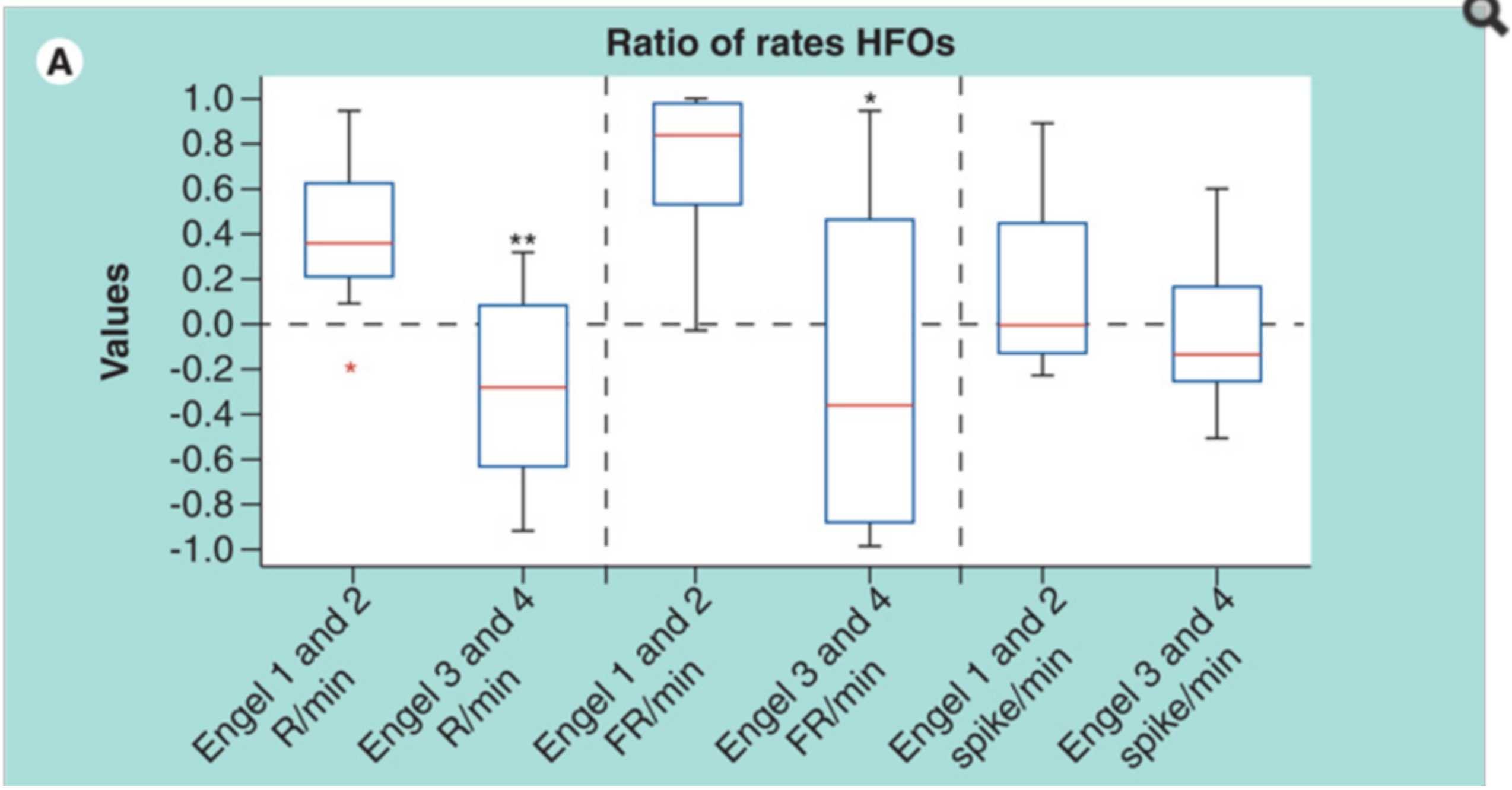
Jacobs et al. Prog Neurobiol 2012:98;302-15



Staba et al., Neurotherapeutics 2014;11:334-46.

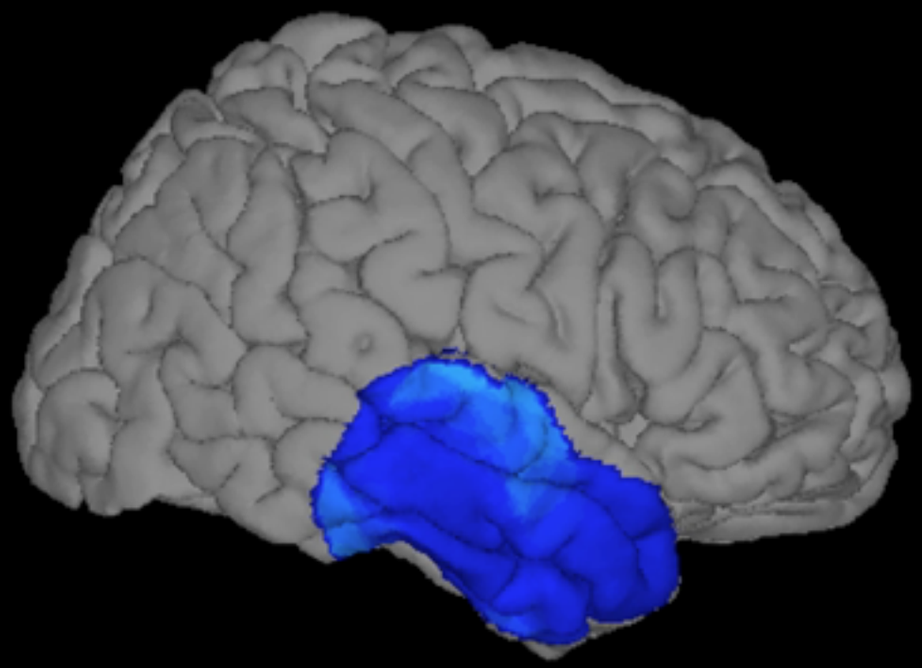


Worrell et al. Brain 2008;131:928-37

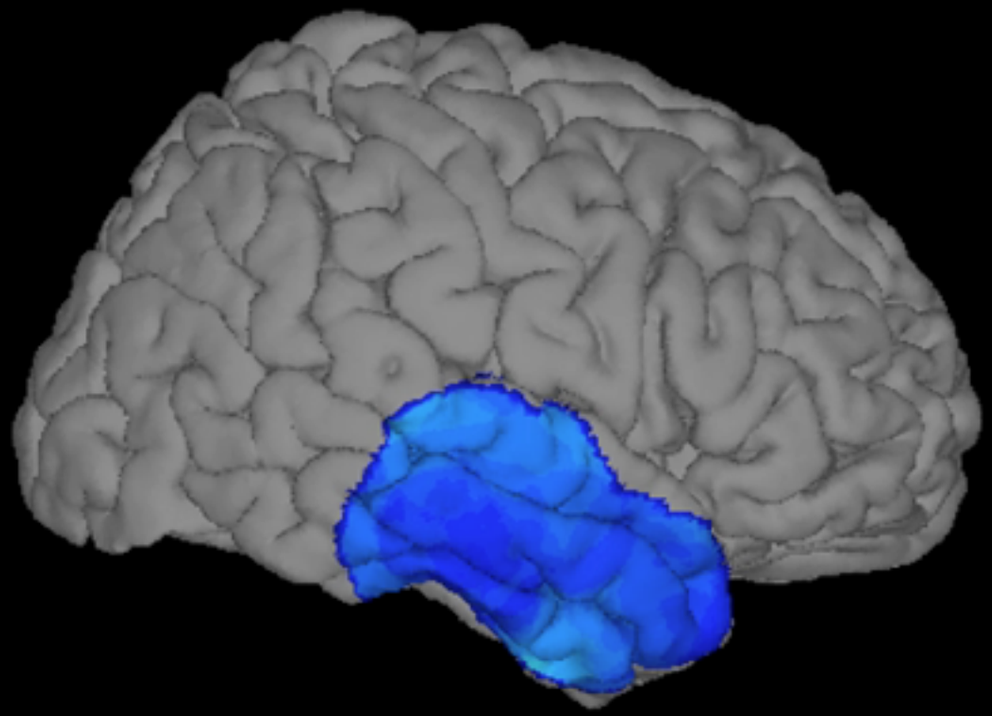


Jacobs et al. Ann Neurol 2010;67:209-20

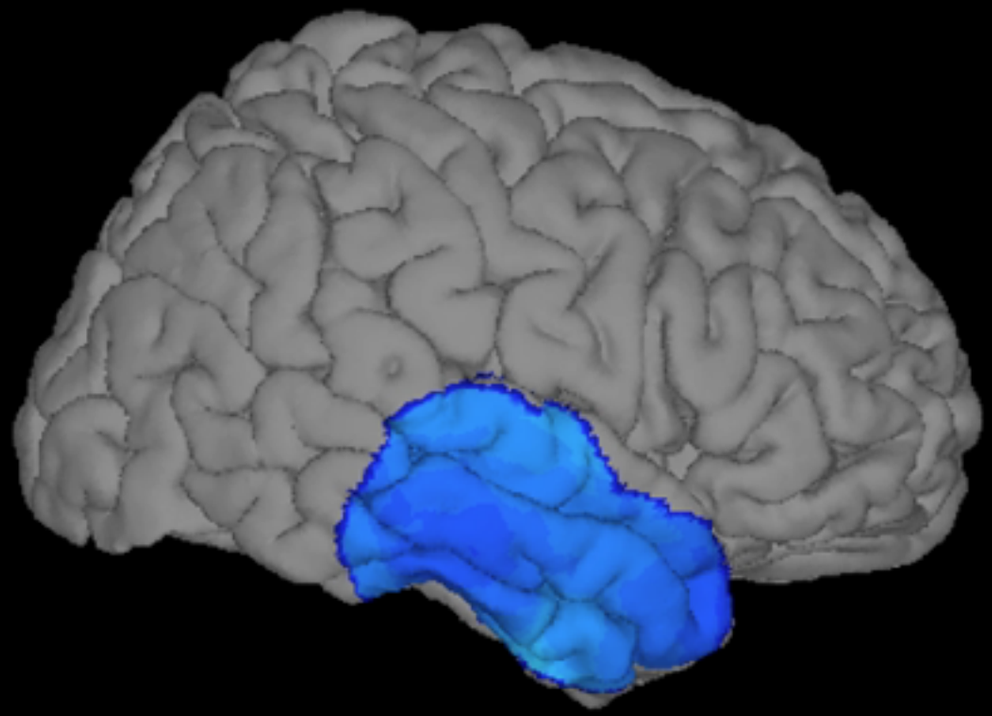
Gamma (50-125Hz)



Ripple (125-250Hz)



Fast ripple (250-500Hz)



Kucewich et al. Brain 2014;137:2231-44.

PROGRAM PREVIEW

69TH ANNUAL MEETNG

DECEMBER 4 - 8, 2015

PENNSYLVANIA CONVENTION CENTER
PHILADELPHIA, PA

8:45 a.m. – 10:45 a.m.

Hot Topics Symposium: Epilepsy Updates

OVERVIEW

The Hot Topic Symposium offers the latest in epilepsy research, diagnosis and treatment. Review of the most relevant topics is underway and the session descriptions will be updated as finalized.

LEARNING OBJECTIVES

- Utilize diagnostic testing for genetic and autoimmune disorders more effectively, to better diagnose and treat these conditions
- Prescribe valproate more effectively to improve medical management of women with epilepsy
- Discuss the latest information regarding cannabis and epilepsy to provide better advice for patients

TARGET AUDIENCE

Intermediate and Advanced (See page 4 for details)

PROGRAM

Chair: Michael Sperling, M.D.

When Should Genetic Testing Be Performed?
TBA

When Should Autoantibody Testing Be Performed?
TBA

Update on Valproate Prescription for Women
TBA

Cannabis Update
TBA