Highlight in Epilepsy 2013

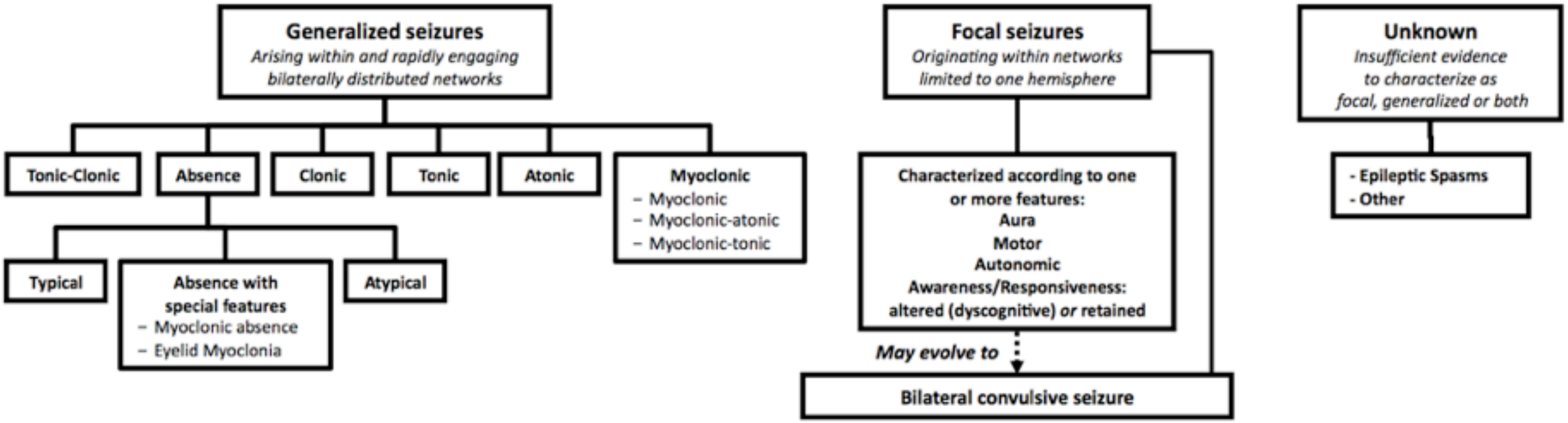
รศ.นพ. คณิตพงษ์ ปราบพาล

Topic cover

- Classification
- Definition
- Update ILAE evidence review : AEDs monotherapy
- Antiepileptic drugs and suicidal
- Antiepileptic drug and pregnancy
- Adverse drug reaction
- International consensus: classification of hippocampal sclerosis in TLE
- mTOR
- Epileptic surgery: New biomarker
- Epileptic encephalopathy
- Borderland and epilepsy

ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Classification of Seizures



Changes in terminology and concepts

New Term and Concept	Examples	Old Term and Concept
Etiology		
Genetic: *genetic defect directly contributes to the epilepsy and seizures are the core symptom of the disorder*	*Channelopathies, Glut1 deficiency, etc.*	**Idiopathic:** *presumed genetic*
Structural-metabolic: *caused by a structural or metabolic disorder of the brain*	*Tuberous sclerosis, cortical malformations, etc.*	**Symptomatic:** *secondary to a known or presumed disorder of the brain*
Unknown: *the cause is unknown and might be genetic, structural or metabolic*		**Cryptogenic:** *presumed symptomatic*
Terminology		**Terms no longer recommended**
Self-limited: *tendency to resolve spontaneously with time* **Pharmacoresponsive:** *highly likely to be controlled with medication*		**Benign** **Catastrophic**
Focal seizures: *seizure semiology described according to specific subjective (auras), motor, autonomic, and dyscognitive features*		**Complex partial** **Simple partial**
Evolving to a bilateral convulsive seizure: *eg. tonic, clonic, tonic-clonic*		**Secondarily generalized**

References: 1.Berg AT et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-685. 2.Berg AT, Cross JH. *Lancet* 2010:9;459-61. 3.Blume WT et al. Glossary of descriptive terminology for ictal semiology: Report of the ILAE task force on classification and terminology. *Epilepsia* 2001:42;1212-1218.

ILAE Proposal for Revised Terminology for Organization of Seizures and Epilepsies 2010

Electroclinical Syndromes and Other Epilepsies Grouped by Specificity of Diagnosis

Electroclinical syndromes

One example of how syndromes can be organized: Arranged by typical age at onset*

Neonatal period
- Benign neonatal seizures^
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures^, Febrile seizures plus (FS+)
- Benign infantile epilepsy
- Benign familial infantile epilepsy (BFIE)
- West syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy (MEI)
- Myoclonic encephalopathy in nonprogressive disorders
- Epilepsy of infancy with migrating focal seizures

Childhood
- Febrile seizures^, Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Childhood absence epilepsy (CAE)
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)+
- Landau-Kleffner syndrome (LKS)

Adolescence – Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Variable age at onset
- Familial focal epilepsy with variable foci (childhood to adult)
- Progressive myoclonus epilepsies (PME)
- Reflex epilepsies

Distinctive constellations/surgical syndromes

Distinctive constellations/Surgical syndromes
- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy

Nonsyndromic epilepsies**

Epilepsies attributed to and organized by structural-metabolic causes
- Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
- Tumor, infection, trauma, angioma, antenatal and perinatal insults, stroke, etc

Epilepsies of unknown cause

* The arrangement of eletroclinical syndromes does not reflect etiology,
^ Not traditionally diagnosed as epilepsy
+ Sometimes referred to as Electrical Status Epilepticus during Slow Sleep (ESES)
** Forms of epilepsies not meeting criteria for specific syndromes or constellations

Special Article

Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)

Epilepsia 2005; 46: 470-2

*Robert S. Fisher, †Walter van Emde Boas, ‡Warren Blume, §Christian Elger, ||Pierre Genton, ¶Phillip Lee, and **Jerome Engel, Jr.

Epilepsy is a disorder characterized by an enduring predisposition to generate epileptic seizure, and by the neurological cognitive, psychological, and social consequences of this condition.

The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following condition:

1. At least two unprovoked seizures occurring more than 24 hours apart.

2. One unprovoked seizure and probability of further seizures similar to the general recurrence risk after two unprovoked seizure (approximately 75%) or more).

3. At least two seizures in a setting of reflex epilepsy.

Epilepsy is considered to be no longer present for individual who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for at least 10 years off anti-seizure medicines, provided that there are no known risk factors associated with a high probability of further seizure

Robert Fisher; IEC 2013

Operational (practical) clinical definition of epilepsy

A 25 year-old man has two unprovoked seizures one year apart

Old definition

Yes No

New definition

Yes No

Operational (practical) clinical definition of epilepsy

A 65 year-old man had a left middle cerebral artery stroke

6 weeks ago and now presented with an unprovoked seizure

With a seizure in this time relation to stroke (or brain infection or brain trauma) literature **(Hesdorffer et al. 2009)** suggests a high (~ 75%) risk of another unprovoked seizure. Therefore, in the new (but not the old) definition, this man would have epilepsy.

Old definition

Yes No

New definition

Yes No

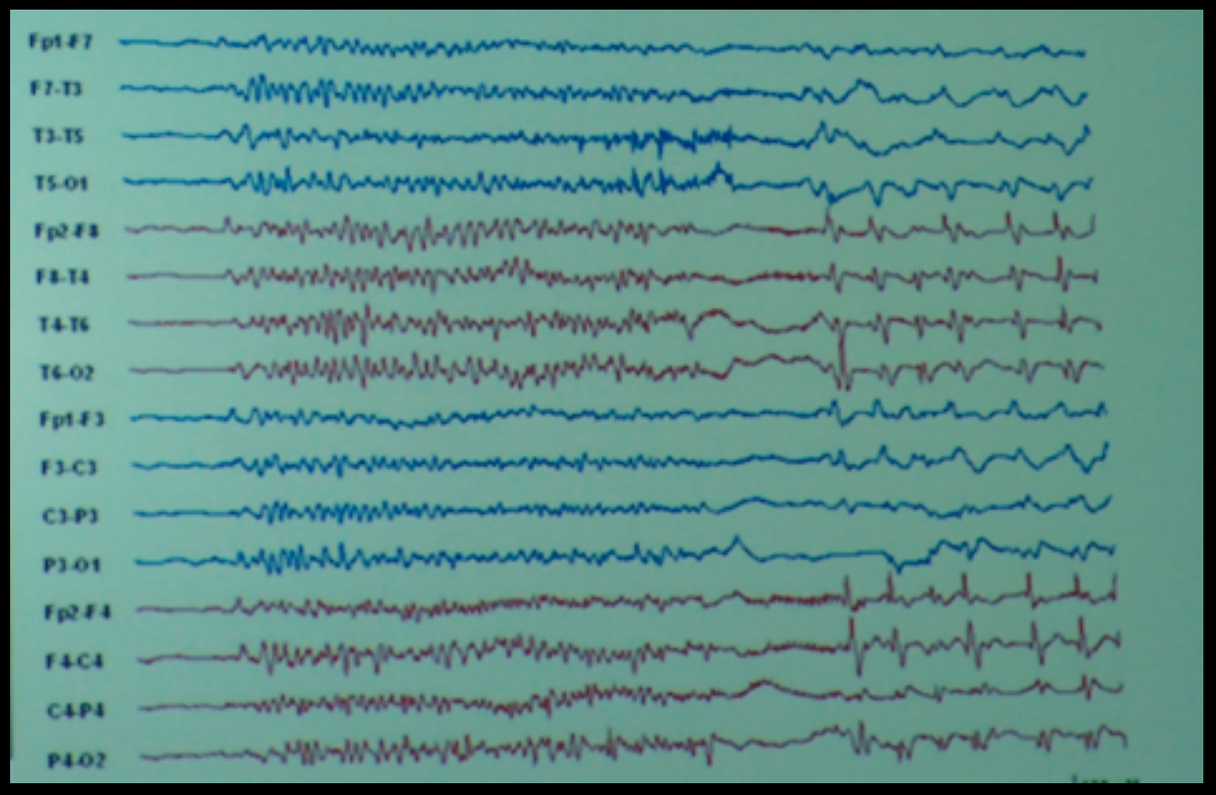
Operational (practical) clinical definition of epilepsy

A 20 year-old man has had 2 seizures 3 day apart while playing a video-game involving flashing lights. There have been no other seizures. EEG shows an abnormal photoparoxysmal response

Old definition		New definition	
Yes	No	Yes	No

This man has epilepsy according to the new definition (but not the old), even through the seizures are provoked by lights, since there is an abnormal enduring predisposition to have seizures with light flashes

Photic-induced seizure



Operational (practical) clinical definition of epilepsy

A 21 year-old man has a focal seizure at age 2 and another at age 3 years.

EEG, MRI, blood test and family history were all unrevealing. He received

antiepileptic drugs from age 3 to age 7 years, when they were discontinued.

There have been no further seizures

Old definition

Yes No

New definition

Yes No

According to the new definition, epilepsy is no longer present, since he has more than 10 years seizure-free and off seizure medication. This is not a guarantee against further seizures, but he has a right to be viewed as someone who dose not currently have epilepsy

Possible consequences

Pros

Closer to clinician view
Support for earlier diagnosis
Encourage disease-modifying therapy
Allows for epilepsy no longer present

Cons

May upset those diagnosed sooner
May increase stigma for some
Makes diagnosis more complex

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

Seizure type/epileptic syndrome	Level of efficacy and effectiveness evidence	Antiepileptic drug
Adult with partial-onset seizure	A	Carbamazepine, Levetiracetam, Phenytoin, Zonisamide
	B	Valproate
	C	Gabapentin, Lamotrigine, Oxcarbazepine, Phenobarbital, Topiramate, Vigabatrin
	D	Clonazepam, Primidone
Adult with generalized-onset tonic-clonic seizure	A	None
	B	None
	C	Carbamazepine, Lamotrigine, Oxcarbazepine, Phenobarbital, Topiramate, Valproate
	D	Gabapentin, Levetiracetam, Vigabatrin
Elderly adult with partial-onset seizure	A	Gabapentin, Lamotrigine
	B	None
	C	Carbazepine
	D	Topiramate, Valproate
Children with generalized-onset tonic-clonic seizure	A	None
	B	None
	C	Carbamazepine, Phenobarbital, Phenytoin, Topiramate, Valproate
	D	Oxcarbazepine
Children with partial-onset seizure	A	Oxcarbazepine
	B	None
	C	Carbazepine, Phenobarbital, Phenytoin, Topiramate, valproate, vigabatrin
	D	Clobazam, Clonazepam. Lamotrigine, Zonisamide

Epilepsia, 54(3):551–563, 2013
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SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

Seizure type/epileptic syndrome	Level of efficacy and effectiveness evidence	Antiepileptic drug
Children with absence seizure	A	Ethosuximide, Valproate
	B	None
	C	Lamotrigine
	D	None
Benign epilepsy with centrotemporal spike	A	None
	B	None
	C	Carbamazepine, Valproate
	D	Gabapentin, Levetiracetam, Oxcarbazepine Sulthiame
Juvenile myoclonic epilepsy	A	None
	B	None
	C	None
	D	Topiramate, Valproate

SPECIAL REPORT

Epilepsia, 54(1):199–203, 2013
doi: 10.1111/j.1528-1167.2012.03688.x

Antiepileptic drugs and suicidality: An expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology

*Marco Mula, †Andres M. Kanner, ‡Bettina Schmitz, and §Steven Schachter

*Amedeo Avogadro University, Novara, Italy; †Rush Medical College at Rush University, Chicago, Illinois, U.S.A.; ‡Vivantes Humboldt-Klinikum, Berlin, Germany; and §Beth Israel Deaconess Medical Center, Harvard University, Boston, Massachusetts, U.S.A.

FDA	ILAE
A increased risk of suicide with all AEDs, despite the fact that statistical significance was found in only 2 of the 11 AED studies.	Some not all cab be associated with treatment-emergent psychiatric problems that can lead to suicidal ideation and behavior, the actual suicidal risk is yet to be established, but it seem to be very low.
Most epilepsy trial included patients taking adjunctive therapy	Clinician should investigate the existence of such risk factors and if necessary , refer the patient for a psychiatric evaluation, but not withhold treatment event in patients with positive suicidal risk
The assessment of suicidality was based on "spontaneous" reports of patients.	The C-SSRS represents a suitable and reliable instrument to evaluate suicidality.
Suicidal behavior was greater in certain geographic region.	Data on treatment-emergent psychiatric adverse events need to be collected

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Table 1. Treatment-emergent psychiatric adverse events of AEDs in patients with epilepsy

Depression	Psychoses	Irritability/Emotion lability
Barbiturates	Ethosuximide	Felbamate
Tiagabine	Levetiracetam	Lamotrigine
Topiramate	Phenytoin (toxic levels)	Levetiracetam
Vigabatrin	Topiramate	
Zonisamide	Vigabatrin	
	Zonisamide	

Adverse effects of antiepileptic drugs

Piero Perucca, Frank G Gilliam

Lancet Neurol 2012; 11: 792–802

This online publication has been corrected. The corrected version first appeared at thelancet.com/specialty on August 13, 2012

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http://dx.doi.org/10.1016/S1474-4422(12)70153-9

	Description	Examples	Prevention	Management
Type A	Related to the known mechanism of action of the drug; common (1–10%) or very common (>10%); acute; dependent on dose or serum concentration; predictable; reversible	Drowsiness, lethargy, tiredness, fatigue, insomnia; dizziness, unsteadiness, vertigo, imbalance, ataxia, diplopia, tremor; cognitive impairment; irritability, aggressive behaviour, depression; gastrointestinal symptoms; hyponatraemia; paresthesias	Select an antiepileptic drug with a profile of tolerability suitable to the characteristics and preferences of the patient; start at low doses; up-titrate gradually; target the lowest effective maintenance dose	Reduce dose; modify the dosing scheme; discontinue antiepileptic drug if measures to prevent or ameliorate toxicity are ineffective
Type B	Related to the individual vulnerability (immunological, genetic, or other mechanism); uncommon (0·1–1%) or rare (<0·1%); develop during the first few weeks of treatment; unpredictable; high morbidity and mortality; reversible	Skin rashes, severe mucocutaneous reactions (drug rash with eosinophilia and systemic symptoms, toxic epidermal necrolysis, Stevens-Johnson syndrome); aplastic anaemia, agranulocytosis; hepatotoxic effects, pancreatitis; angle closure glaucoma; aseptic meningitis	Avoid (or use very cautiously) specific antiepileptic drugs in high-risk groups; start at low doses; up-titrate gradually	Discontinue antiepileptic drug promptly; symptomatic or supportive management; substitute antiepileptic drug with least risk for cross-reactivity reactions or worsening of underlying condition
Type C	Related to the cumulative dose of the drug; common (1–10%); chronic; mostly reversible	Decreased bone mineral density; weight gain, weight loss; folate deficiency; connective tissue disorders; hirsutism, gingival hypertrophy; alopecia; visual field loss	Select an antiepileptic drug with a tolerability profile suitable to the characteristics and preferences of the patient	Symptomatic or replacement treatment (eg, calcium, vitamin D, folic acid) as needed; discontinuation of antiepileptic drug if required
Type D	Related to prenatal exposure to the drug (eg, teratogenesis) or carcinogenesis; uncommon (0·1–1%); delayed; dose dependent; irreversible	Birth defects; neurodevelopmental delay in the offspring; pseudolymphoma	If possible, avoid valproate, phenobarbital, and polytherapy in women of childbearing potential; aim at low-risk monotherapies at the lowest effective dose before pregnancy; avoid discontinuation or major treatment changes during pregnancy	..
Type E	Adverse drug interactions; common (1–10%); predictable; reversible	Increased risk of skin rash after adding lamotrigine to valproate; reduced seizure control after adding the combined contraceptive pill to lamotrigine; reduced effectiveness of warfarin after adding carbamazepine; increased risk for CNS neurotoxicity after combination of sodium-channel-blocking antiepileptic drugs	Avoid unnecessary polytherapy; choose concurrent drugs with low potential for adverse drug interactions	Adjust doses according to clinical response and, if necessary, drug concentrations in serum

Table 3: **Adverse effects of antiepileptic drugs based on a modified version of the WHO classification**

Epilepsia, 54(7):1315–1329, 2013
doi: 10.1111/epi.12220

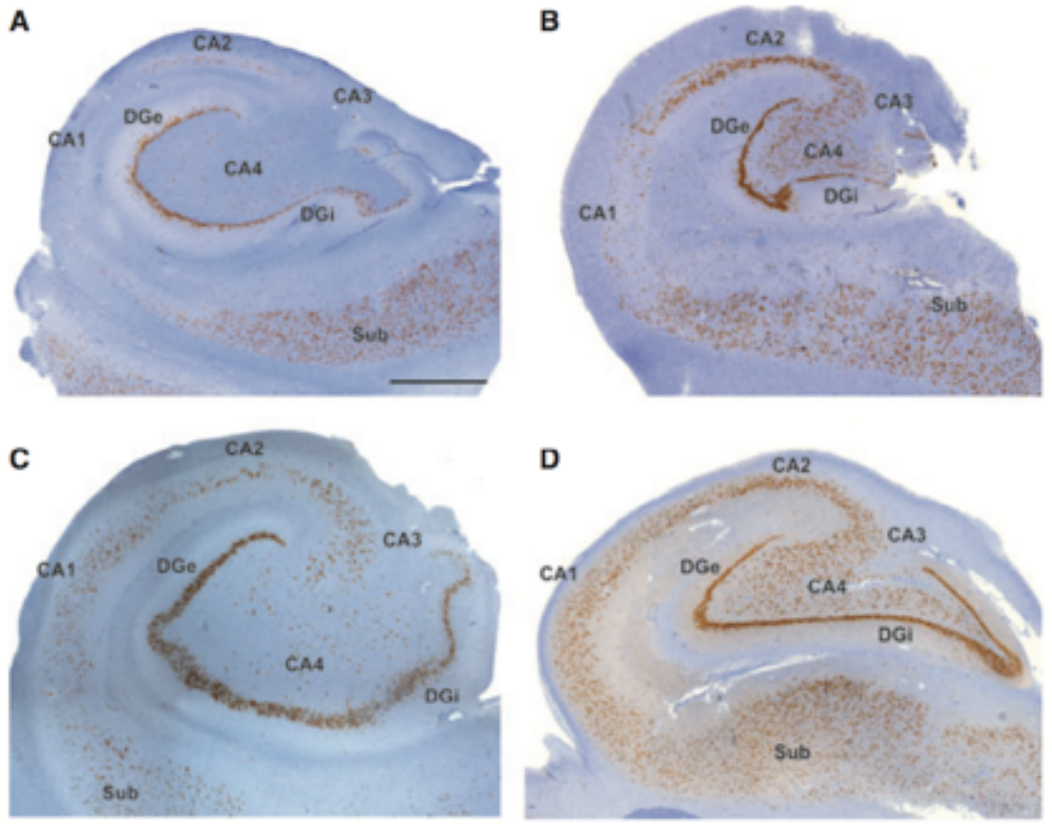
SPECIAL REPORT

International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods

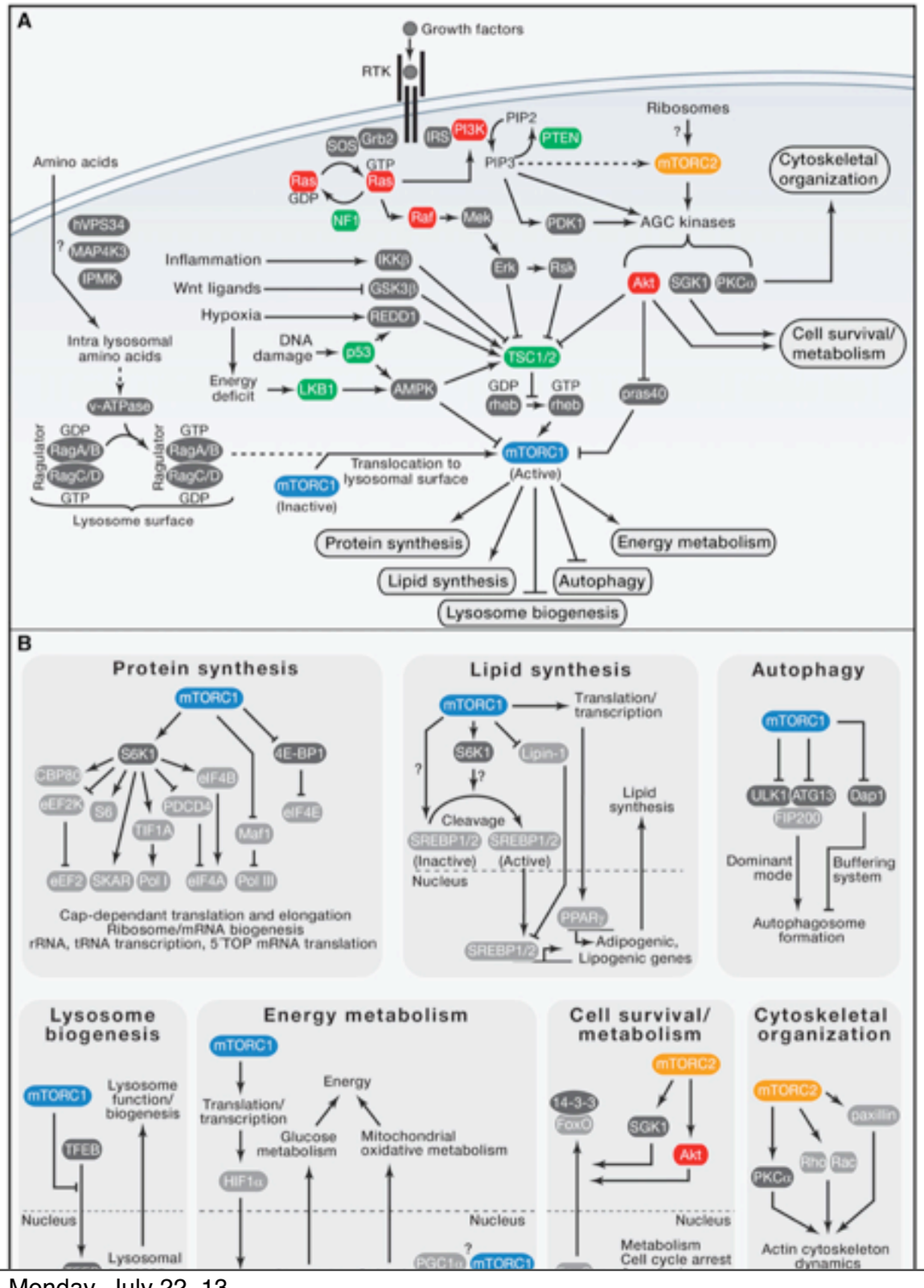
***Ingmar Blümcke, †Maria Thom, ‡§Eleonora Aronica, ¶Dawna D. Armstrong, #Fabrice Bartolomei, **Andrea Bernasconi, **Neda Bernasconi, ††Christian G. Bien, ‡‡Fernando Cendes, *Roland Coras, §§J. Helen Cross, ¶¶Thomas S. Jacques, ##Philippe Kahane, ***Gary W. Mathern, †††Haijme Miyata, ‡‡‡§§§¶¶¶Solomon L. Moshé, ###Buge Oz, ****Çiğdem Özkara, †††††‡‡‡‡Emilio Perucca, §§§§Sanjay Sisodiya, ¶¶¶¶Samuel Wiebe, and ####Roberto Spreafico**

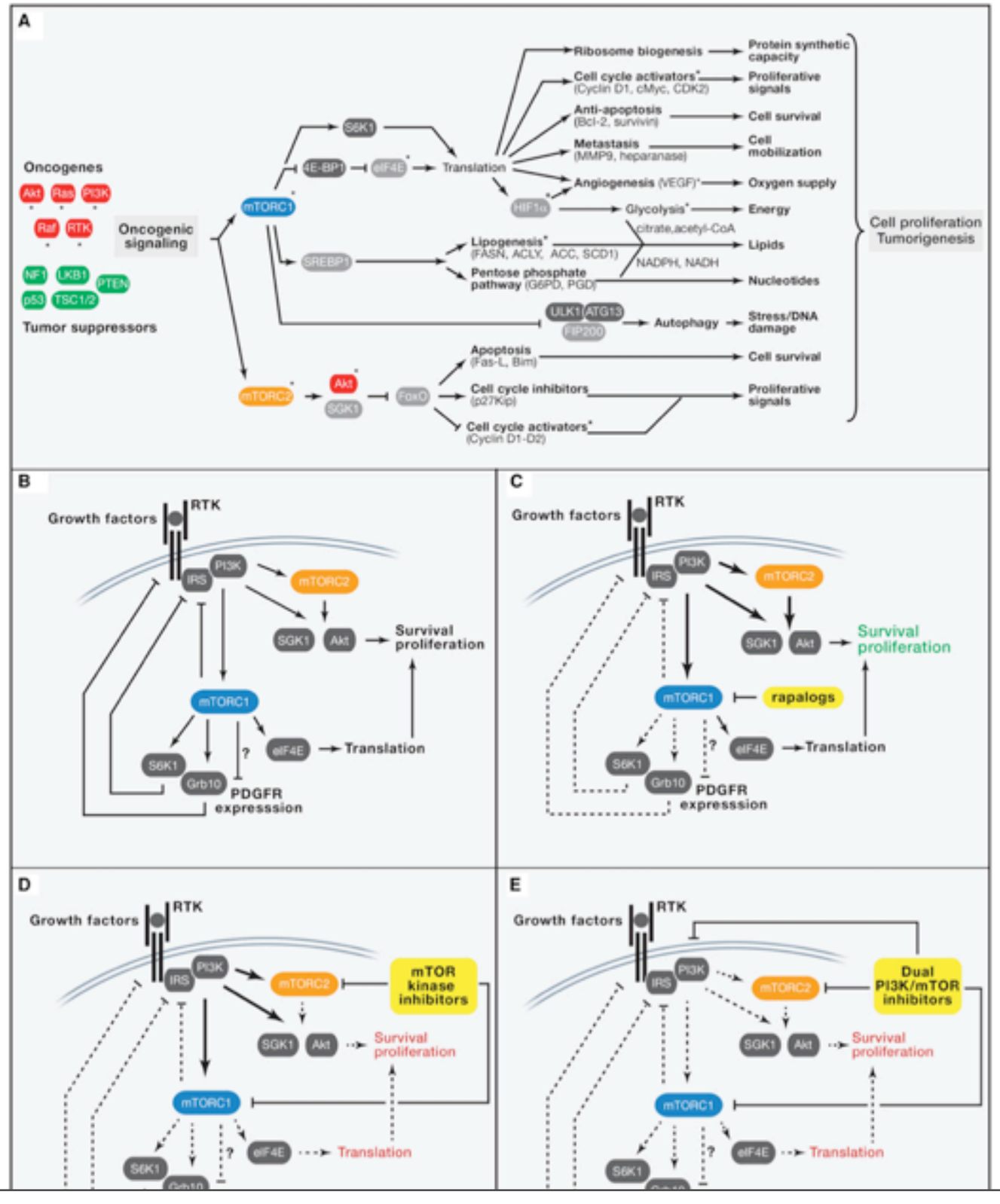
Table 1. ILAE consensus classification of hippocampal sclerosis

	Subfield pathology patterns of neuronal cell loss and gliosis (in *en bloc* resected samples)			
Class.[a]	HS ILAE Type 1	HS ILAE Type 2 "CA1 Predominant"	HS ILAE Type 3 "CA4 Predominant"	No-HS / Gliosis only
CA1 [b]	2	1 - 2	0 - 1	0
CA2 [b]	0 - 2	0 - 1	0 - 1	0
CA3 [b]	0 - 2	0 - 1	0 - 1	0
CA4 [b]	2	0 - 1	1 - 2	0
DG [c]	0 - 2	0 - 1	0 - 2	0 - 1



mTOR signaling in growth control and disease





PI3K

STRADα

PTENopathies

Akt

RAS

NF1

MAPK

PMSE

MO25

STRADα

LKB1

AMPK

Hamartin/TSC1

Tuberin/TSC2

Tuberous sclerosis
FCD type II

Rheb-GP

?

?

mTORC1

PRAS40

Gbl

SK6

Ribosomal S6

4E-BP1

eIF4E

mTOR inhibitors as antiseizure

mTOR inhibitors as anti-epileptogenesis

Protein synthesis, metabolism, cell growth, cell proliferation, synaptic plasticity
ion channel expression and neurogenesis/neuronal death

mTOR inhibitor as Antiseizure

Involved in regulating the ion channel expression

Decrease seizure in TSC, Pten models (Zeng et al, 2008; Kwon et al., 2003; Ljungberg et al., 2009; Sunnen et al., 2011)

pilocarpine, electrical stimulation, kainic acid and symptomatic IS (Huang et al, 2010; Raffo et al., 2011; Harffo et al., 2012)

A coup case report decrease in seizure frequency in TSC patients (Muncy et al, 2009; Perek-poinik et al., 2012)

secondary outcome measure treatment SERGAs (Krueger et al, 2010)

Preliminary result 53% (50% seizure reduction), 3/17 seizuree free (Wilfong et al, 2011)

mTOR inhibitor as anti-epileptogenesis

TSC model

Rapamycin before onset seizure can prevent the development of epilepsy of epilepsy and many of the associated pathological and cellular abnormalities, consist with a true anti-epileptogenesis (Zeng et al, 2008; Meikle et al., Goto et al, 2011; Zeng et al., 2011Carson et al., 2012)

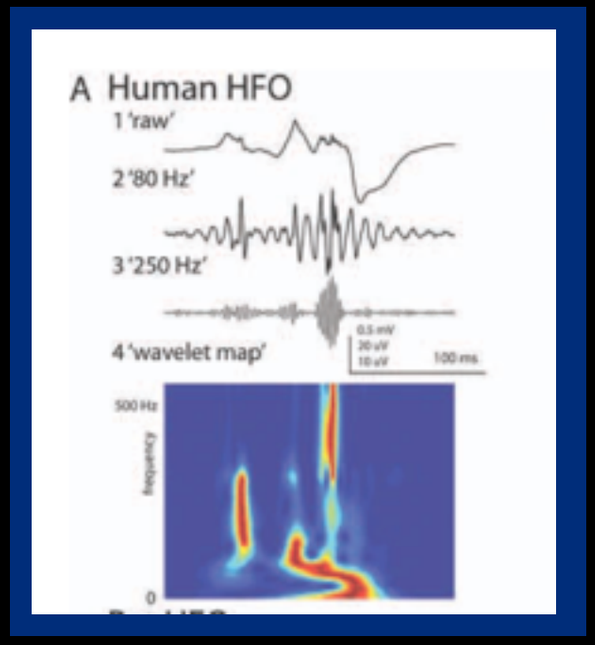
Beyond TSC model

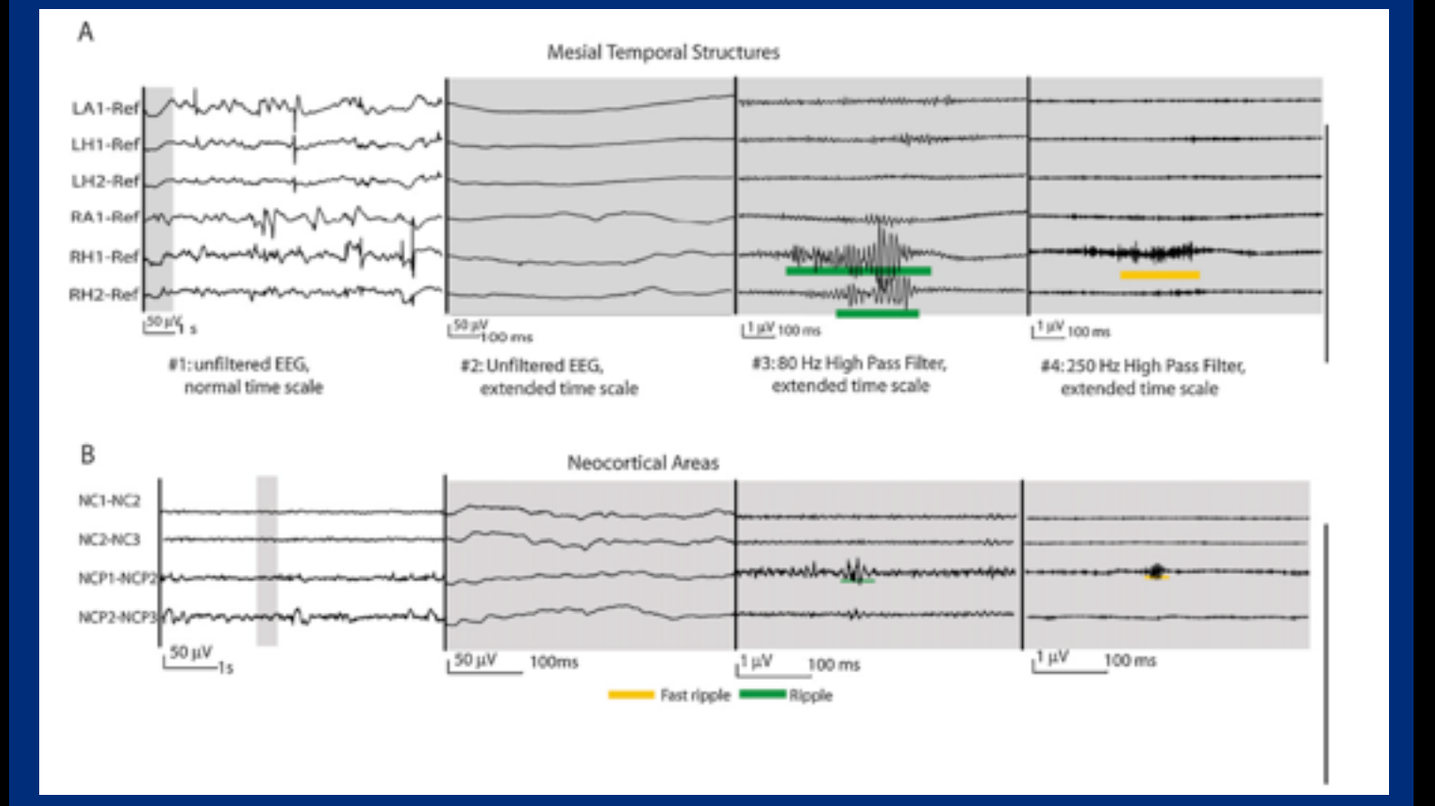
Brain injury following SE: inhibit mossy fiber

Traumatic brain injury: neuroprotective effects against neuronal death

High-frequency oscillations

- New biomarker: epileptogenicity, epileptic surgery (Zijlmans et al, 2012; Jabobs 2012)
- predict good surgical outcome, even better than removal of the ictal onset zone (Jacobs et al, 2010; Haegelen et al., 2013; Fujiwara et al., 2012; Jette et al., 2013))
- iEEG, MEG, EEG
- ripple (80-250 Hz); fast ripple (250-600 Hz)





High-frequency oscillation

- Is it importance to differentiate between ripples and fast ripple?

  microelectrodes: fast ripples are most specific for the epileptogenic zone

  macoelectrode: both ripple and fast ripple in the evaluation of potential epileptogenic zone

- HFOs and the irritative zone

  not known whether it is beneficial to distinguish HFOs with and without spike

- HFOs and the seizure onset zone

  interictal HFOs is that they have been shown to be reliable markers of the seizure onset zone, better than epileptic spike

- HFOs and the epileptogenic lesion: tissue's intrinsic epileptogenicity

High-Frequency Electroencephalographic Oscillations

Epilepsia, 53(9):1607–1617, 2012
doi: 10.1111/j.1528-1167.2012.03629.x

FULL-LENGTH ORIGINAL RESEARCH

Resection of ictal high-frequency oscillations leads to favorable surgical outcome in pediatric epilepsy

***Hisako Fujiwara, *Hansel M. Greiner, †Ki Hyeong Lee, *Katherine D. Holland-Bouley, †Joo Hee Seo, *Todd Arthur, ‡Francesco T. Mangano, §James L. Leach, and *Douglas F. Rose**

Epilepsia, 54(5):848–857, 2013
doi: 10.1111/epi.12075

FULL-LENGTH ORIGINAL RESEARCH

High-frequency oscillations, extent of surgical resection, and surgical outcome in drug-resistant focal epilepsy

***†Claire Haegelen, *Piero Perucca, *‡Claude-Edouard Châtillon, §Luciana Andrade-Valença, *Rina Zelmann, *Julia Jacobs, †D. Louis Collins, ‡François Dubeau, ‡André Olivier, and *Jean Gotman**

ขอบคุณที่ตั้งใจฟังครับ