2023 GW Epilepsy Board Review & Best Practices

Mechanisms of Epilepsy

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DISCLOSURES

- **Disclosure of Financial Relationships**
  Consultant – Neurocrine Biosciences
  Speaker Bureau – Zogenix, Inc and Marinus Pharmacueticals

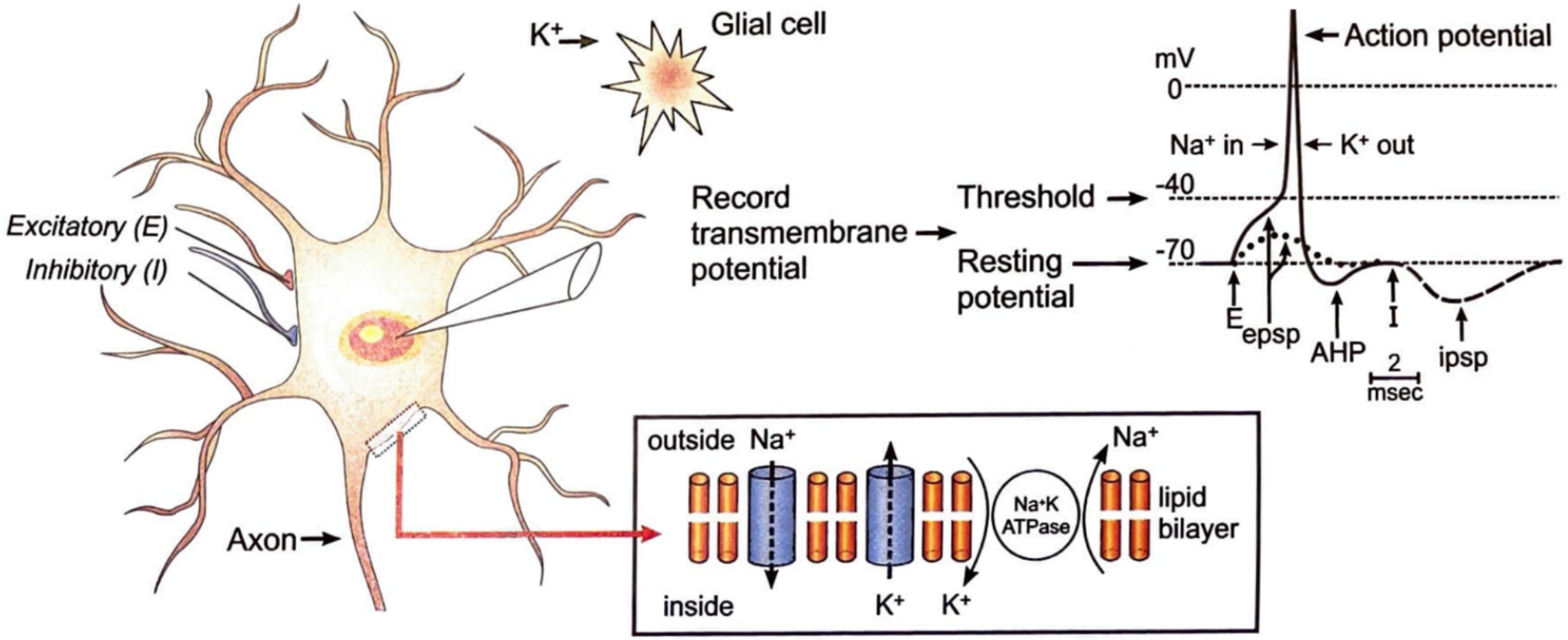
- **Off-Label Usage**
  None

Objectives

- Examine the cellular basis of neurophysiology
- Describe how cellular events contribute to EEG signal
- Recognize pathology and pathophysiology of different types of epilepsy
- Illuminate different pathways of epileptogenesis and corresponding clinical evidence

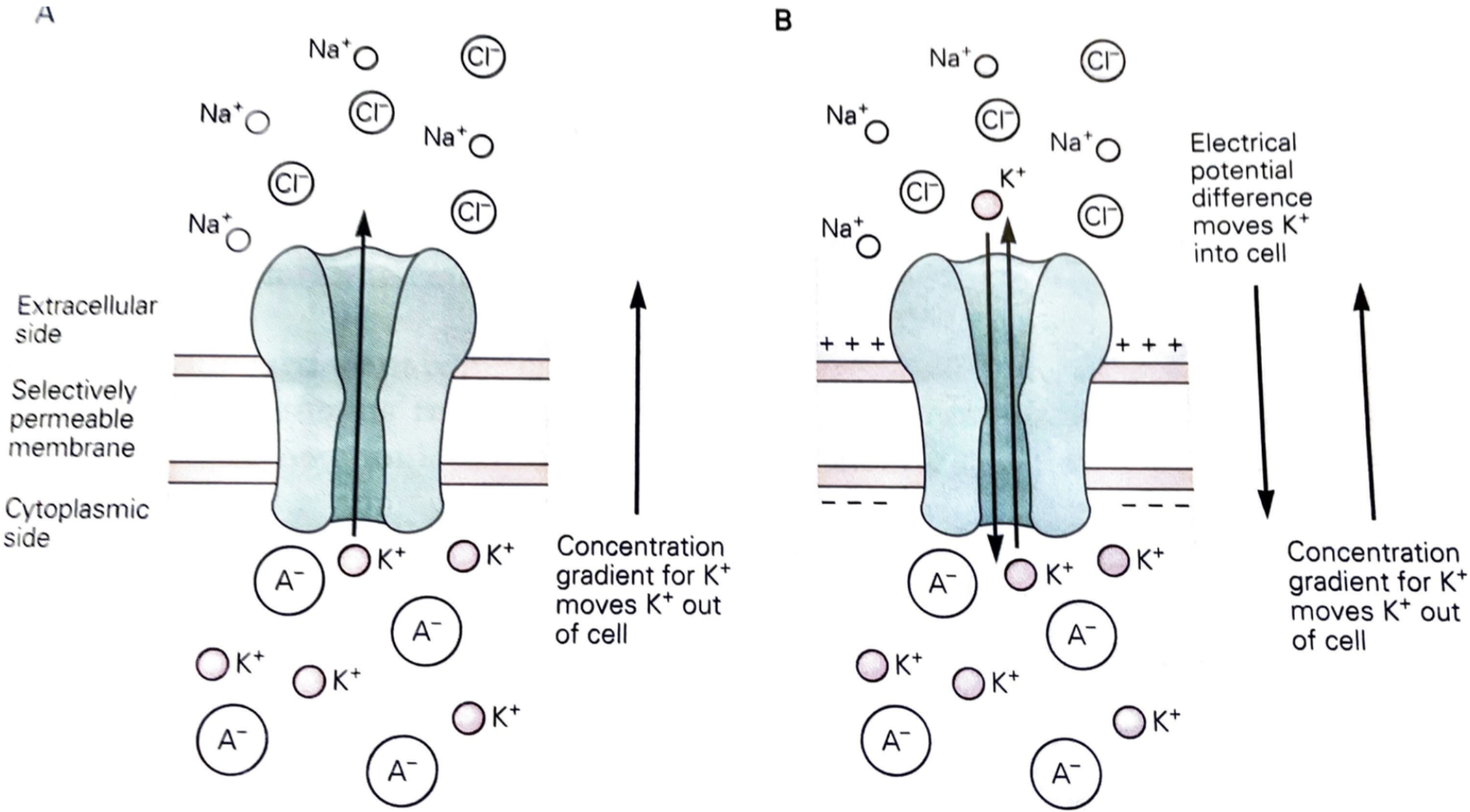
Cellular Neurophysiology and EEG Signal

Neurons are the fundamental unit



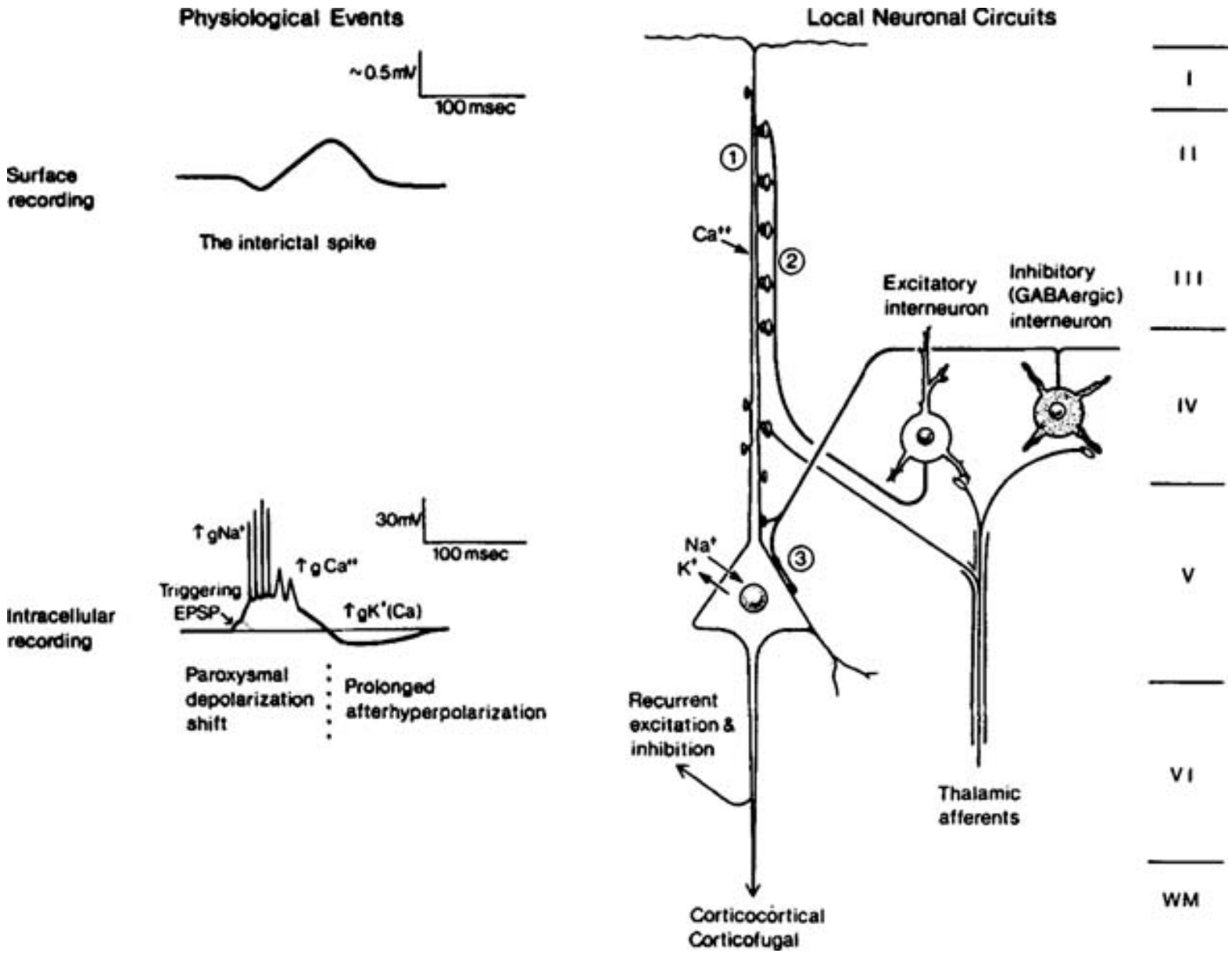
From: White and Rho, Mechanism of Antiepileptic Drug Action

C/o Forcelli



C/o Forcelli

From: Kandel et al., Principles of Neural Science

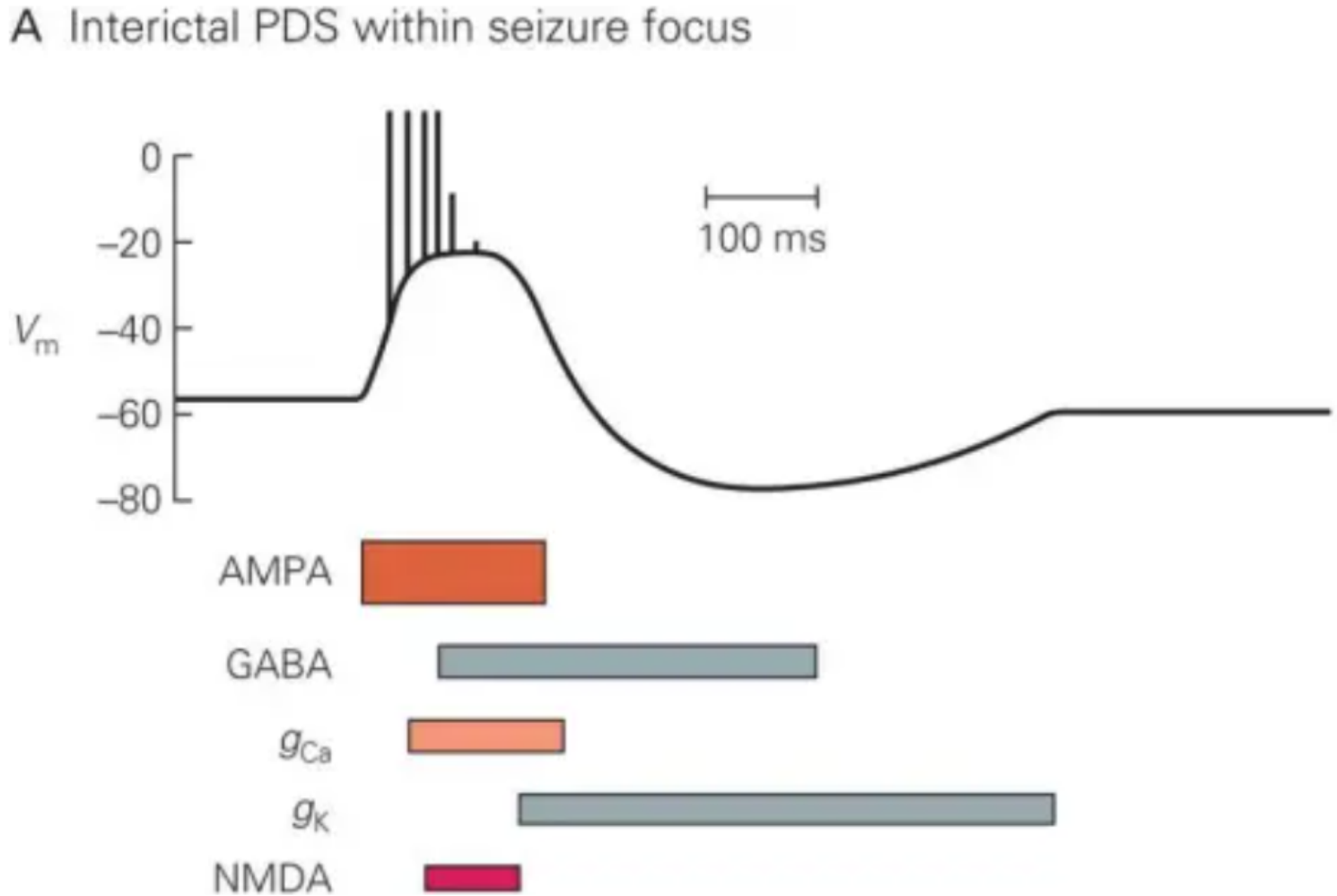

Physiological Events
~0.5mV
100 msec
Surface recording
The interictal spike
30mV
100 msec
↑gNa+
↑g Ca++
Triggering EPSP
↑gK+(Ca)
Intracellular recording
Paroxysmal depolarization shift
Prolonged afterhyperpolarization
Local Neuronal Circuits
Ca++
Na+
K+
Excitatory interneuron
Inhibitory (GABAergic) interneuron
Recurrent excitation & inhibition
Thalamic afferents
Corticocortical
Corticofugal
I
II
III
IV
V
VI
WM

Paroxysmal Depolarizing Shift

- Spikes = primarily PDS leading to sustained action potential firing and sometimes followed by robust hyperpolarization
- Depolarization results primarily from activation of AMPA and NMDA receptors and voltage-gated calcium channels (spike)
- After-hyperpolarization is generated primarily by calcium- and voltage-dependent potassium channels and GABA-A (Cl-) and GABA-B (K+) conductances (wave)

Slow waves

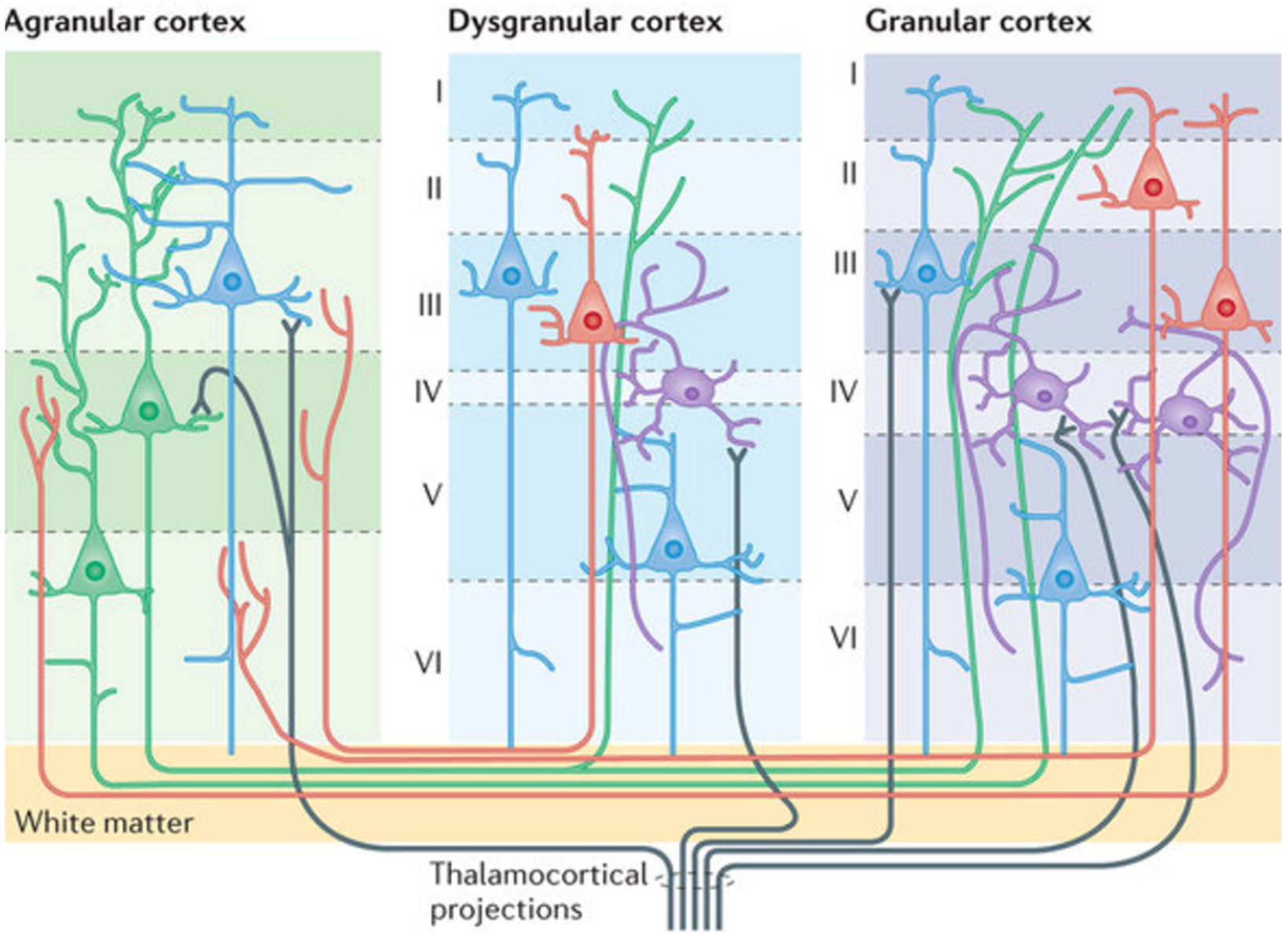
- 0.5-1 second refractory period (to single-shock stimulation) after an interictal spike is observed in the irritative zone surrounding the EZ, but not within the seizure-onset zone (fast activity may even be enhanced here)
- Possible mechanisms
  - GABA-A (100 ms)
  - GABA-B (nearly 1 second)
  - pH changes (> 1 second) -> decoupling gap junctions



https://neupsykey.com/seizures-and-epilepsy-4/

Synaptic and Non-synaptic Activity Contribute to EEG signal

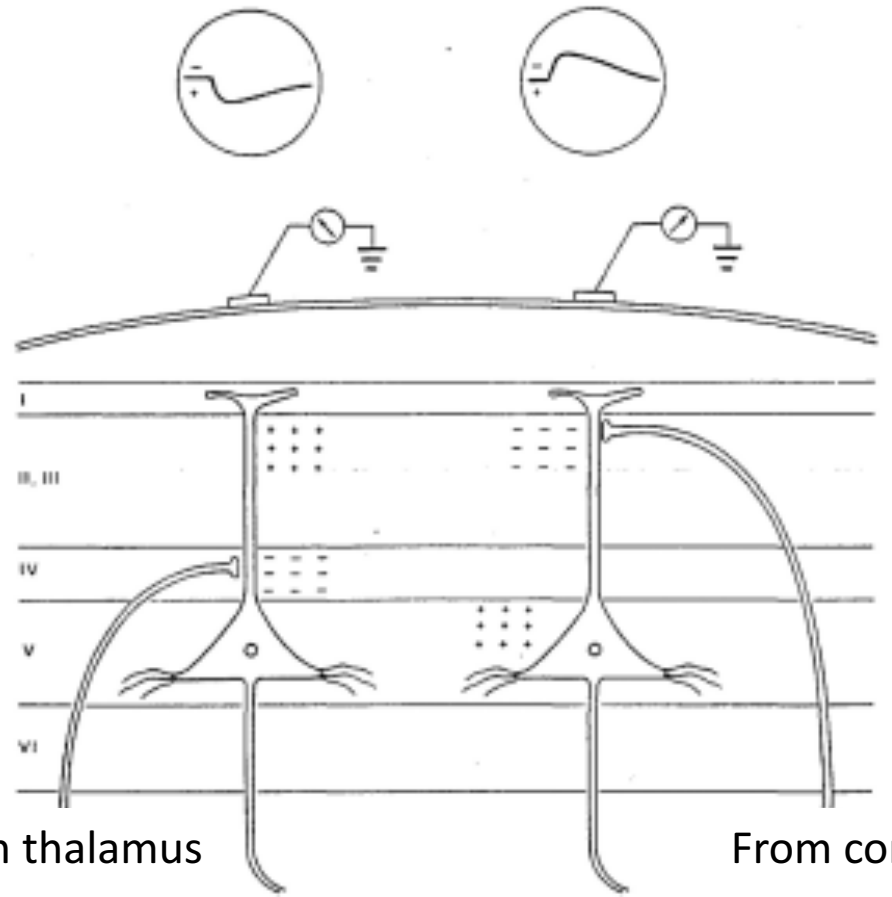
- Action potentials do not contribute significantly to scalp-recorded EEG potentials, mainly because of their short duration (<2 milliseconds)
- Primary source – EPSPs and IPSPs (as viewed from the extracellular space):
  - Sink – current flows IN to the cell (loss of + charge) – EPSPs, extracellular negative
  - Source – current flows OUT of the cell (return of + charge)
- Other:
  - Calcium spikes generated in dendrites (voltage-dependent) also contribute to EEG signal (non-synaptic)
  - Voltage-dependent intrinsic oscillations
  - Spike after-hyperpolarizations
  - Neuro-glia communication – may contribute to spreading depression
  - Ultrafast cortical rhythms (ripples) may be detected on intracranial EEG



Supragranular layers	Intrahemispheric connections
Granular Layer	Thalamic input, Intrahemispheric input
Pyramidal layer	Subcortical efferents
Polymorphic layer	Thalamic efferents

From: Feldman Barrett and Simmons, Nat Rev Neuro

C/o Forcelli



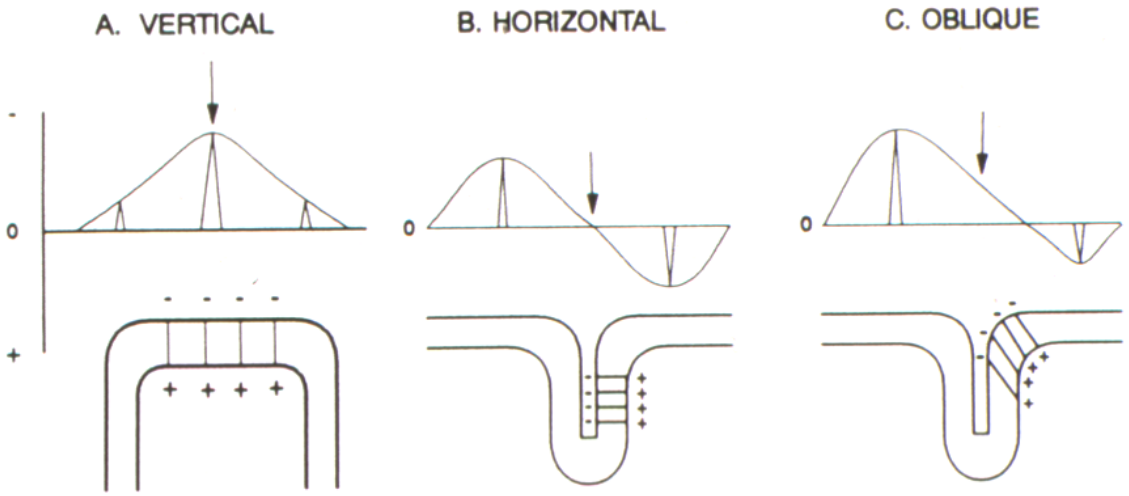
From thalamus

From cortex*

FIGURE 2. Generation of extracellular voltage fields from graded synaptic activity (from Martin, 1991). Relationship between polarity of surface potentials and site of dendritic postsynaptic potentials.

*somatic inhibition would have same effect

Dipole



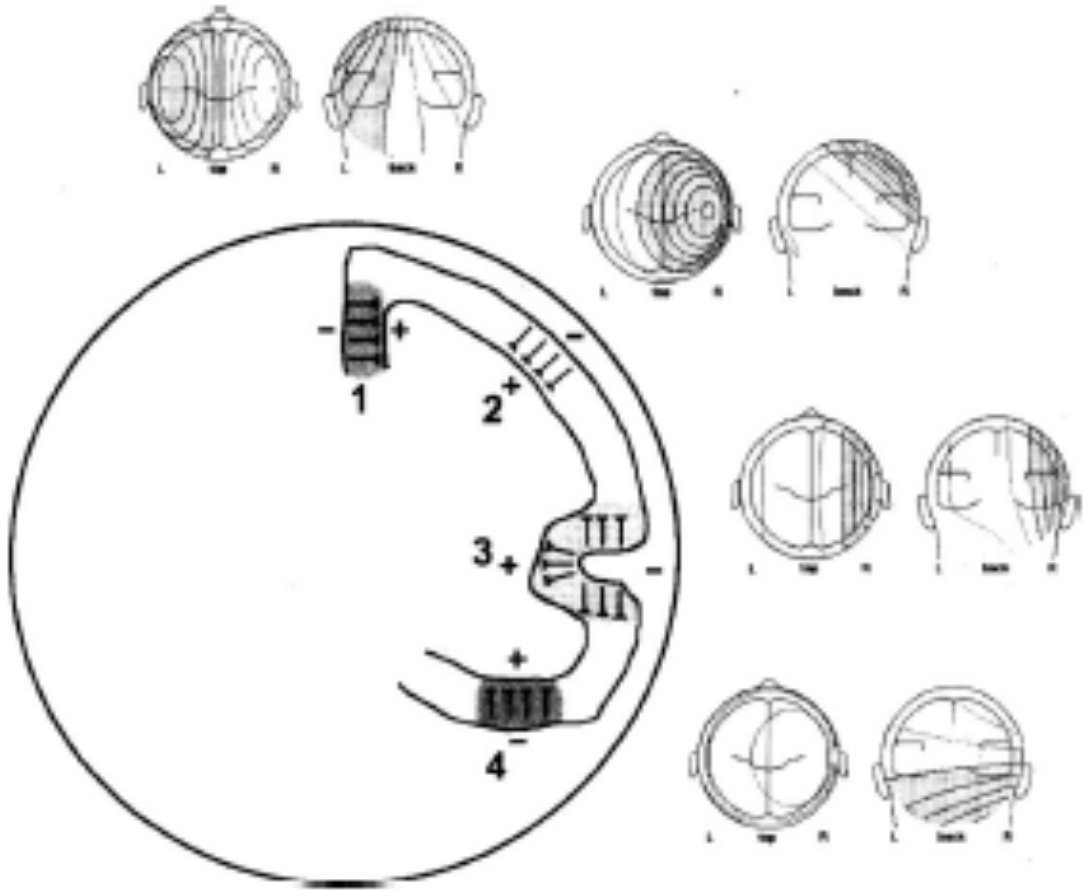
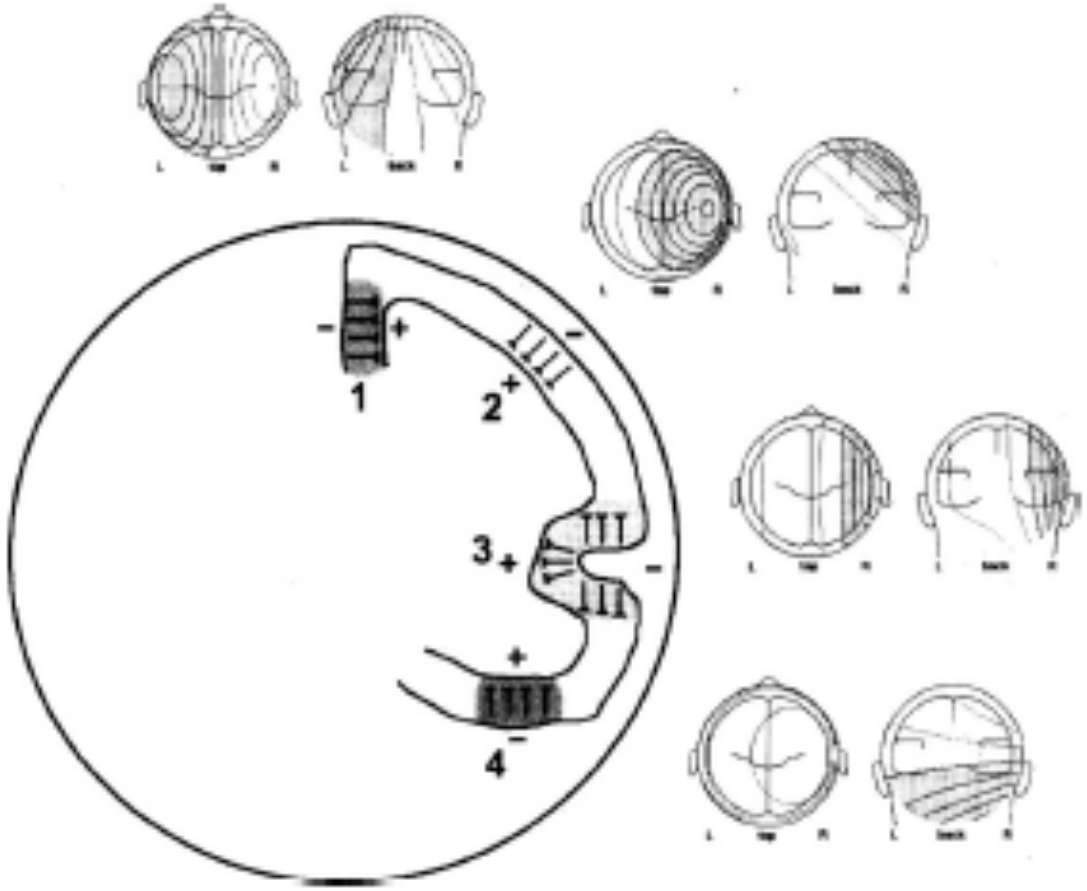


FIGURE 3. Schematic of a brain cross section, illustrating four representative cortical EEG sources (from Ebersole, 2003). Sources 2 and 3 produce radial fields, so the negative, so the negative voltage maximum is directly above them. Sources 1 and 4 produce tangential fields and both negative and positive voltage maxima are displaced to either side.

Olejniczak 2006, *J Clin Neurophys*



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Olejniczak 2006, *J Clin Neurophys*

Epileptiform Discharge Definition

- “Distinctive waves or complexes, distinguished from background activity, and resembling those recorded in a proportion of human subjects suffering from epileptic disorders.”

Some terminology

- Spike 20-70 ms
- Sharp wave 70-200 ms
- ± slow wave
- Morphology - monophasic, biphasic, triphasic
- Polarity

- Location – focal, unilateral, bilateral, multifocal, generalized, etc.

Neurophysiology

- Electrical activity detected by scalp EEG largely reflects summated post-synaptic potentials of cortical pyramidal neurons
- Synchronized cortical activity from a minimum of 6 cm^2 and more typically 20 cm^2
- Spread
  - Volume conduction – passive, attenuated
  - Propagation – may differ in morphology and polarity

J.S. Ebersole, Defining epileptogenic foci: past, present, future J Clin Neurophysiol 14 (1997) 470-483.
S.V. Pacia, J.S. Ebersole, Intracranial EEG substrates of scalp ictal patterns from temporal lobe foci Epilepsia 38 (1997) 642-654.

Risk of Recurrence after Unprovoked Seizure (Pediatric)

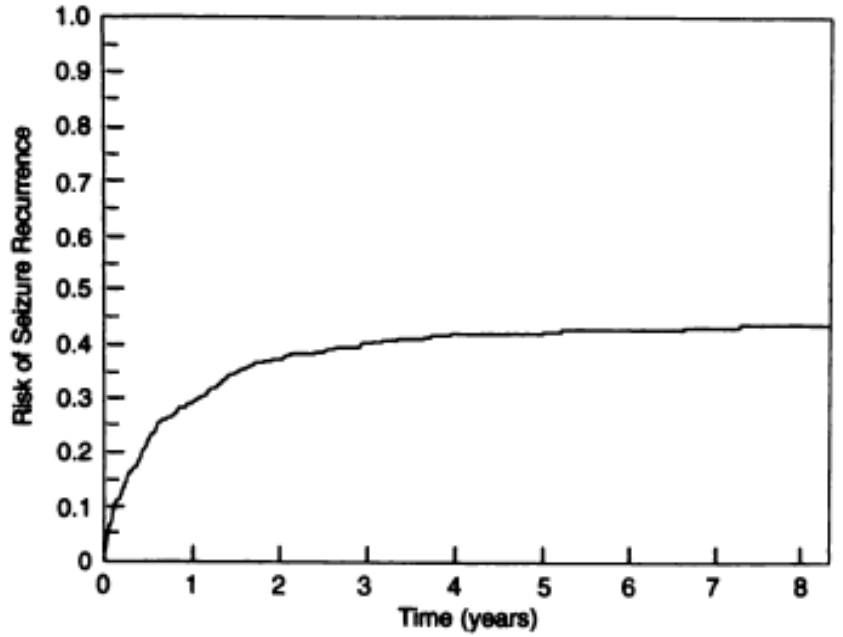


Fig 1. Probability of seizure recurrence after a first unprovoked seizure (n = 407): Kaplan-Meier curve.

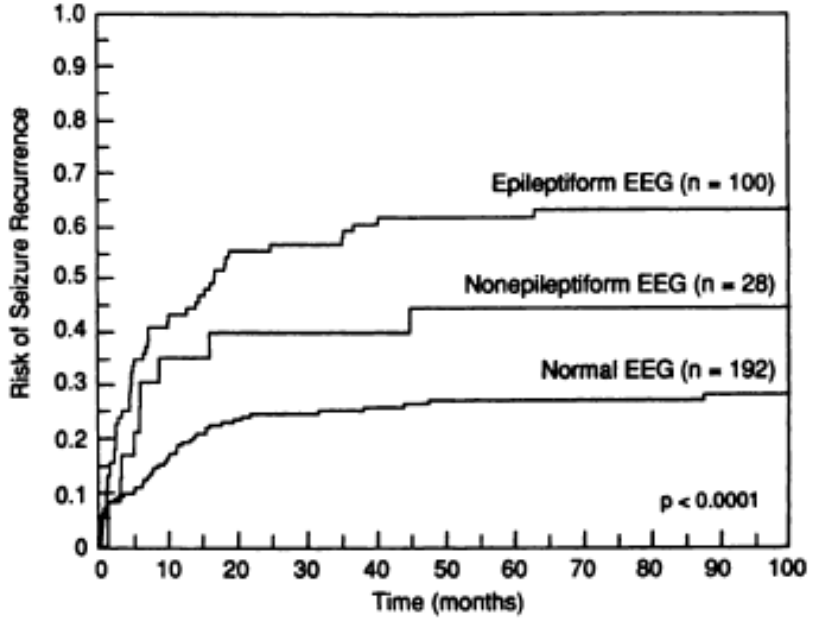


Fig 3. Probability of seizure recurrence after a cryptogenic first seizure as a function of the electroencephalogram (n = 320): Kaplan-Meier curve.

Shinnar et al. ***Pediatrics*** **1996;98:216–225**

Significance of epileptiform activity

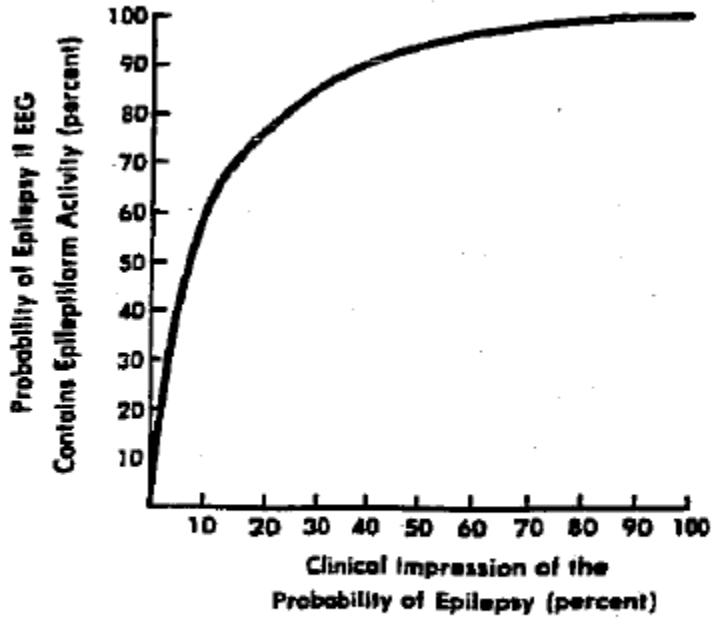


FIG. 1. The relationship between the diagnostic specificity of interictal epileptiform activity and the percentage of individuals with epilepsy in the population being tested. With permission from D.S. Goodin and M.J. Aminoff, Lancet 1:837—8, 1984.

TABLE 2. *IEA most likely to be encountered as the only EEG abnormality in individuals undergoing EEG without a complaint of seizures*

Photoparoxysmal responses
Occipital dominant, generalized irregular spike and wave
Centromidtemporal spikes in childhood and adolescence
Occipital spikes in blindness

TABLE 3. *IEA most likely to be associated with seizures regardless of the complaint of seizures*

3 Hz spike and wave
Localized anterior and mid-temporal spikes
Temporal intermittent rhythmic delta activity
Localized frontal lobe spikes
Pseudoperiodic lateralized epileptiform discharges

Fisch BJ. Interictal epileptiform activity: Diagnostic and behavioral implications. J Clin Neurophys 2003, 20: 155-162.

Seizure

- Loss/ failure of inhibition leads to increased synchronization and seizure propagation

NATURE COMMUNICATIONS | 3:1060 | DOI: 10.1038/ncomms2056

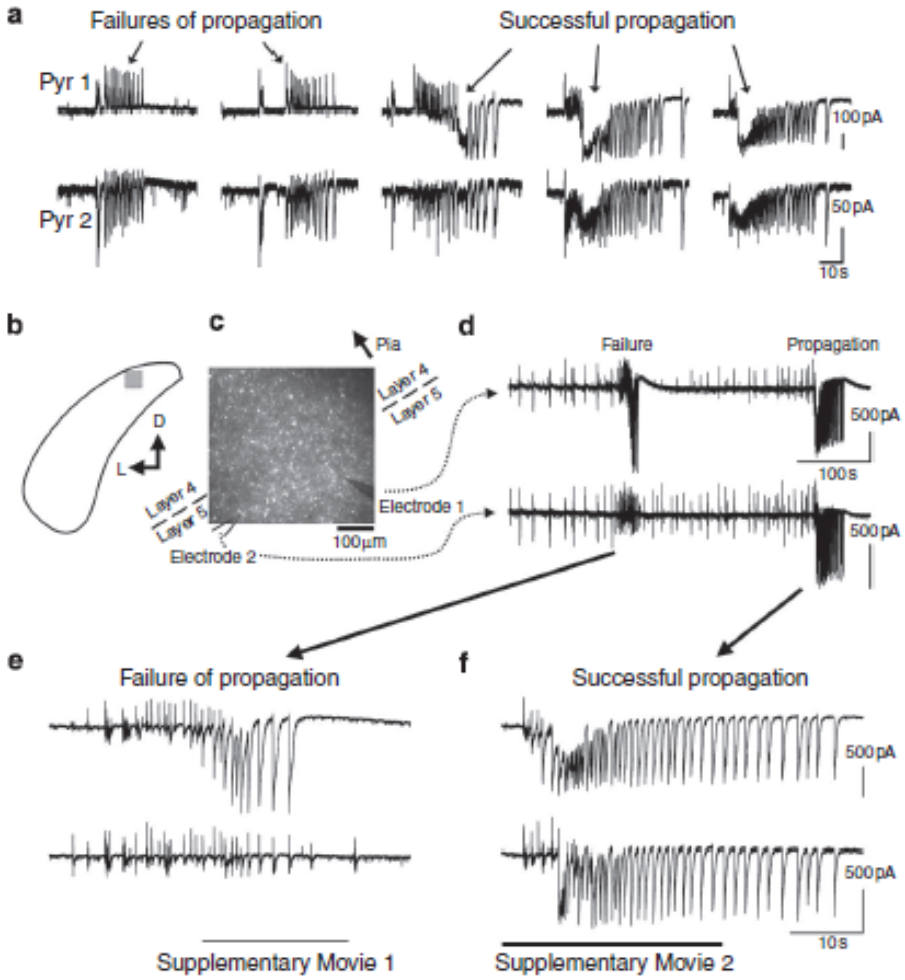
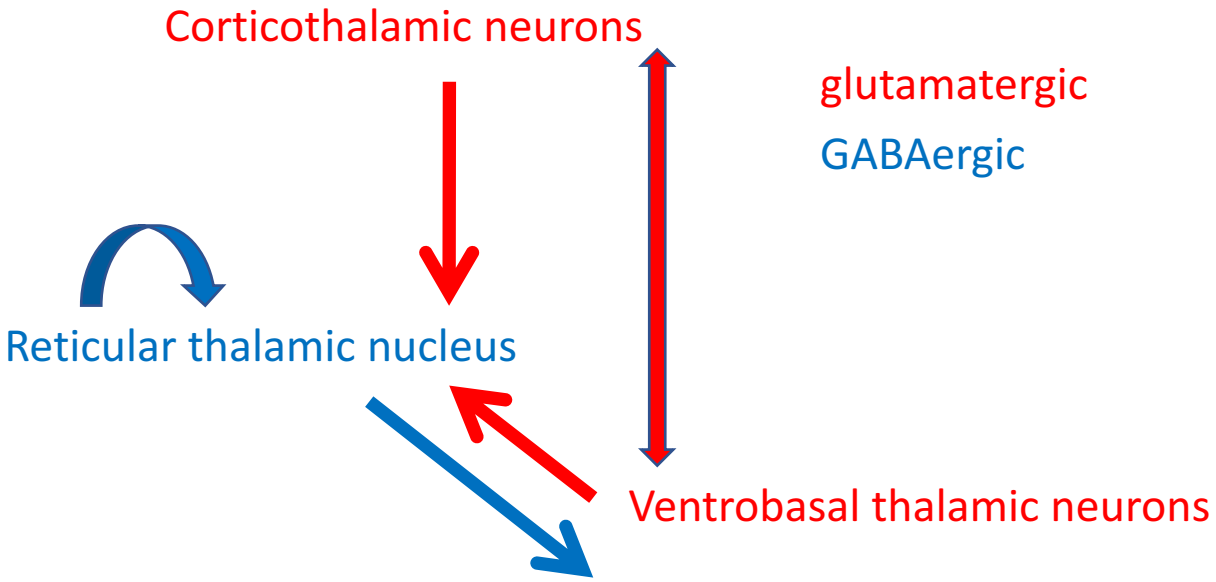


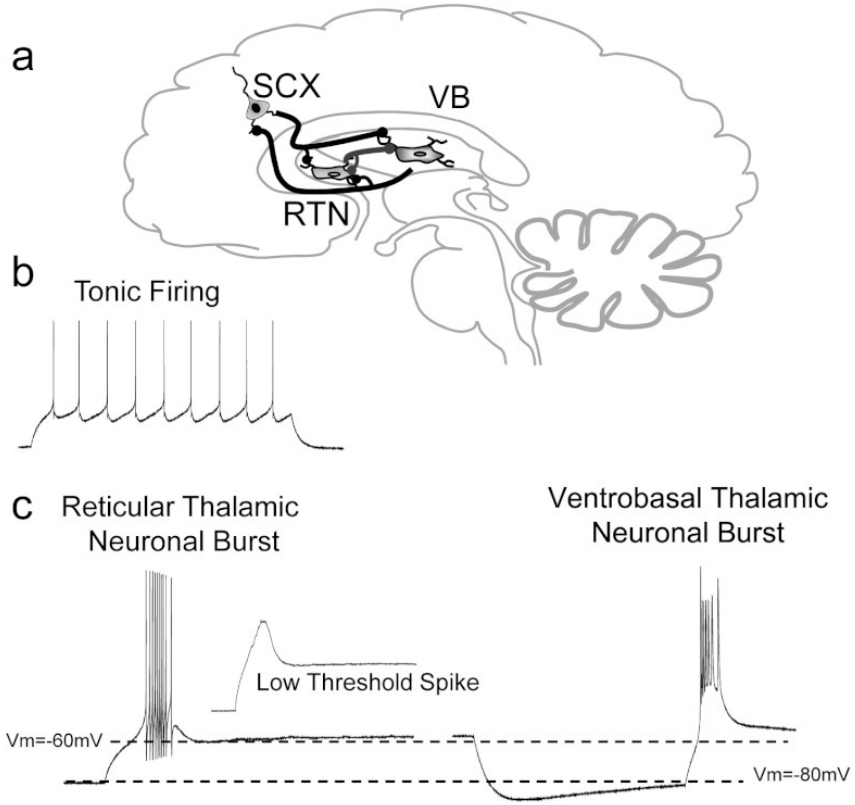
Figure 1 | Failure of propagation of full ictal events in mouse brain slices. (**a**) Five successive ictal events (shown left to right) recorded in two layer 5 pyramidal cells (PCs) 600 µm apart. Only in the last three events, does PC 1 make the transition from inhibitory to excitatory barrages, which is indicative of being incorporated into the ictal event. A very important point arising from a previous study[10] is that the upward deflections are not purely inhibitory, merely predominantly so. The level of inhibition simply occludes the very large concurrent excitatory drive at this time, which can be seen instead if the cell is clamped close to the GABAergic reversal potential. (**b**–**f**) Another example of δ-frequency, interictal-like activity, with concurrent low magnification Ca^{2+} network imaging. The more extended field of view allows us to visualize the failure of propagation, as the view incorporates territories that are recruited to the ictal event and other regions that resist recruitment. (**b**) Schematic showing the field of view in the brain slice. (**c**) Field of view; the two electrodes are visible, located in layer 5. (**d**) Eight minute recording showing two full ictal events, the first of which is only manifest as δ-frequency interictal activity in electrode 2. (**e**,**f**) Detailed views of the two ictal events, showing the time period of two Ca^{2+} network imaging movies (Supplementary Movies 1 and 2).

Seizure Network: Cortico-thalamic-cortical circuit

- Neurons involved:
  - Cortical glutamatergic neurons (from layer VI) projecting to reticular nucleus
  - GABAergic reticular nucleus that projects on itself and thalamic relay
  - Thalamic relay neurons with excitatory projections to cortical pyramidal neurons
- Reticular neurons can fire in oscillatory pattern (spindles or seizures) or continuously (tonic during wakefulness)
- Mediated by low-threshold T-type calcium channel currents
  - Depolarization allows transient calcium inflow before inactivation
  - Reactivation requires relatively long hyperpolarlization (facilitated by GABA-B receptors, which is why drugs that increase GABA-B activity like vigabatrin and gabapentin can worsen absence)
- End of inhibition triggers rebound low threshold spike with a high frequency burst of action potentials, which again excites the target RE cells

Jasper, Basic Mechanisms of the Epilepsies





Wakefulness/ seizure free: tonic firing

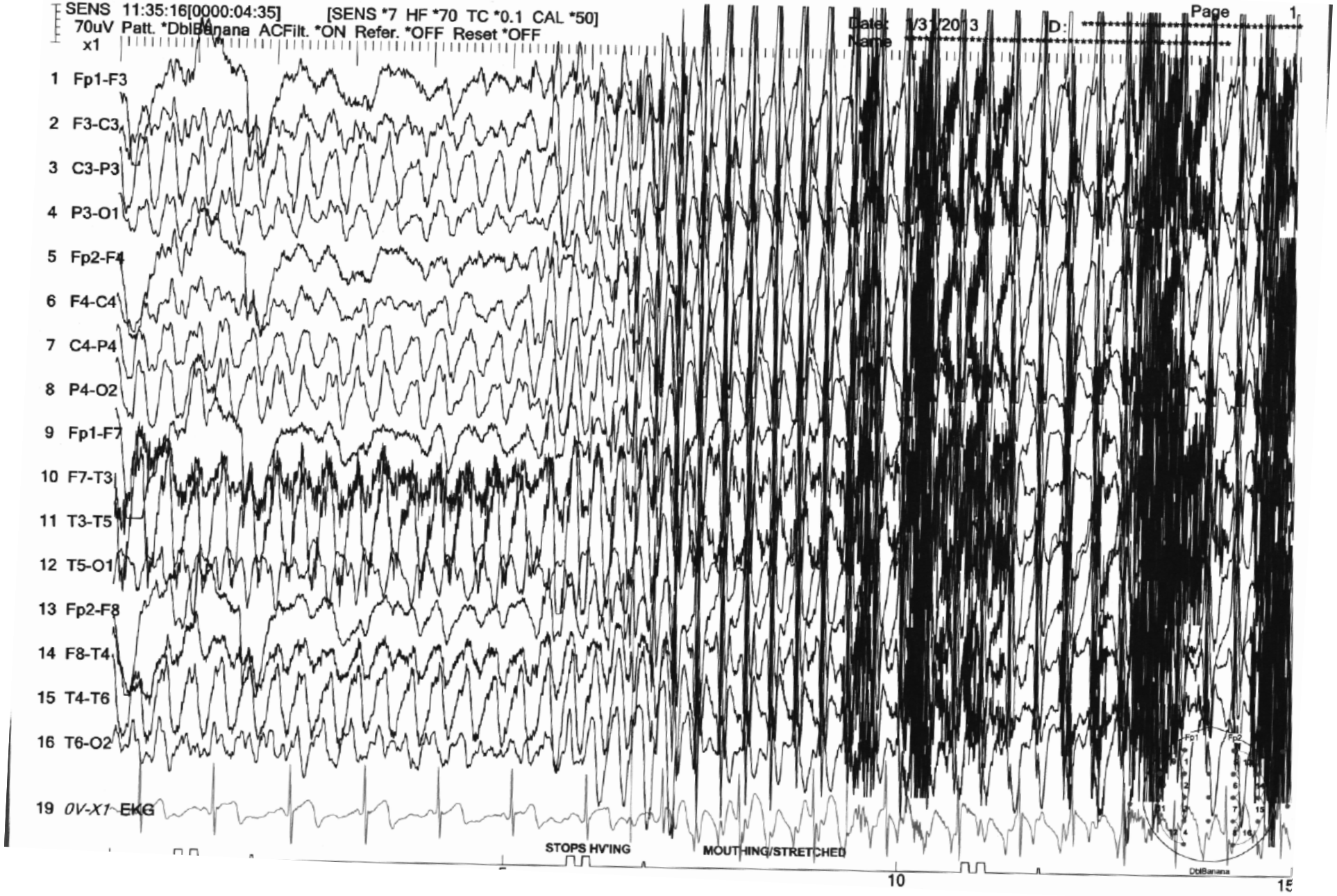
-thalamic neurons are relatively depolarized and T-type calcium channels are inactivated

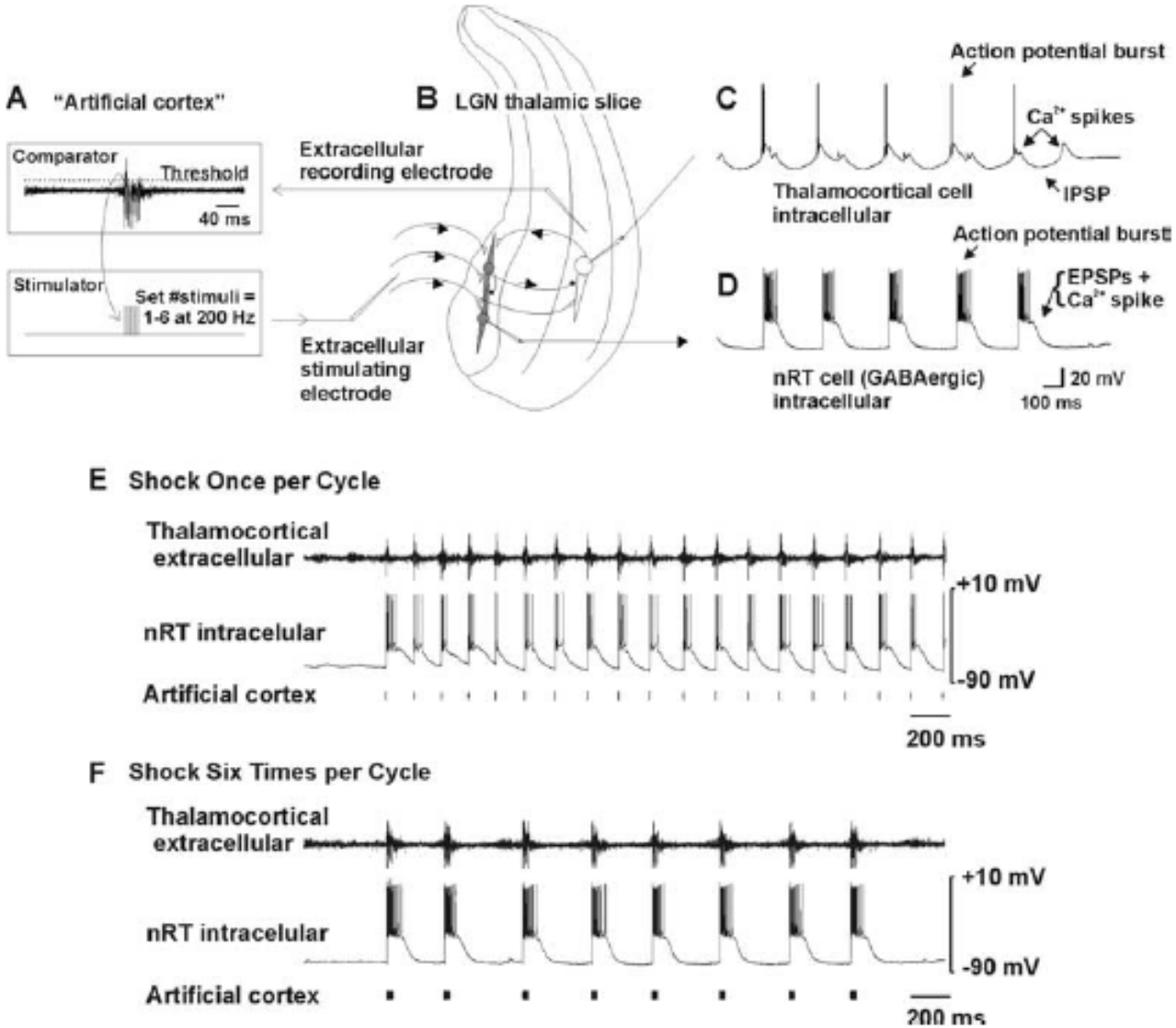
Sleep/ seizure: phasic, oscillatory loop

-RTN neurons are more hyperpolarized, allowing burst-firing via de-inactivation of T-type calcium channels in response to depolarization (from cortex and VB)

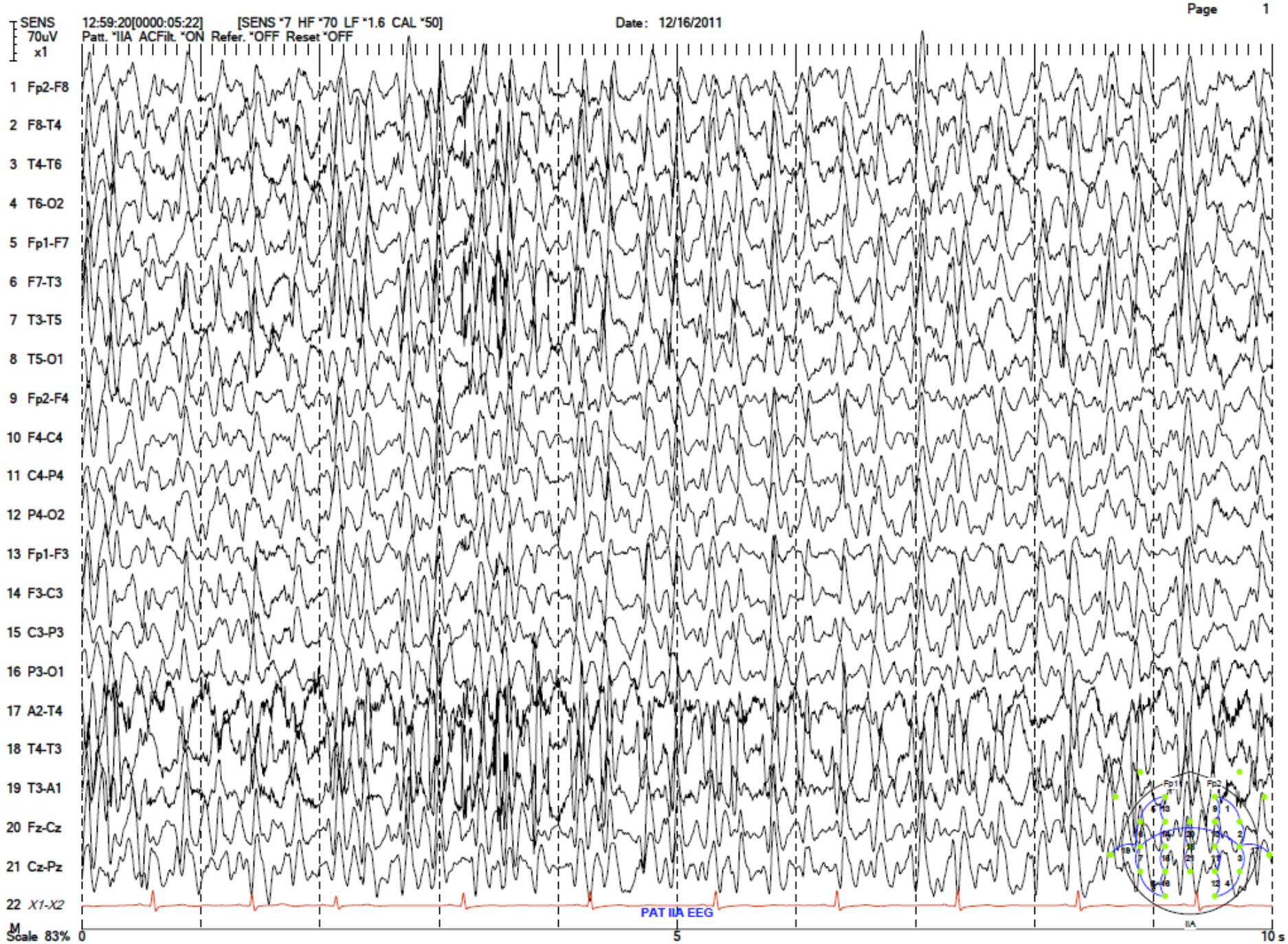
-Burst firing of RTN induces hyperpolarization of VB neurons (via $GABA_AR$ or $GABA_BR$)

-De-inactivates T-type calcium channels in VB which then excite cortical neurons (and then reactivates the RTN)


SENS 11:35:16[0000:04:35] [SENS *7 HF *70 TC *0.1 CAL *50]
70uV Patt. *DblBanana ACFilt. *ON Refer. *OFF Reset *OFF
x1
Date: 1/31/2013 ID:
Name:
Page 1
1 Fp1-F3
2 F3-C3
3 C3-P3
4 P3-O1
5 Fp2-F4
6 F4-C4
7 C4-P4
8 P4-O2
9 Fp1-F7
10 F7-T3
11 T3-T5
12 T5-O1
13 Fp2-F8
14 F8-T4
15 T4-T6
16 T6-O2
19 0V-X1 EKG
STOPS HV'ING
MOUTHING/STRETCHED
10
DblBanana



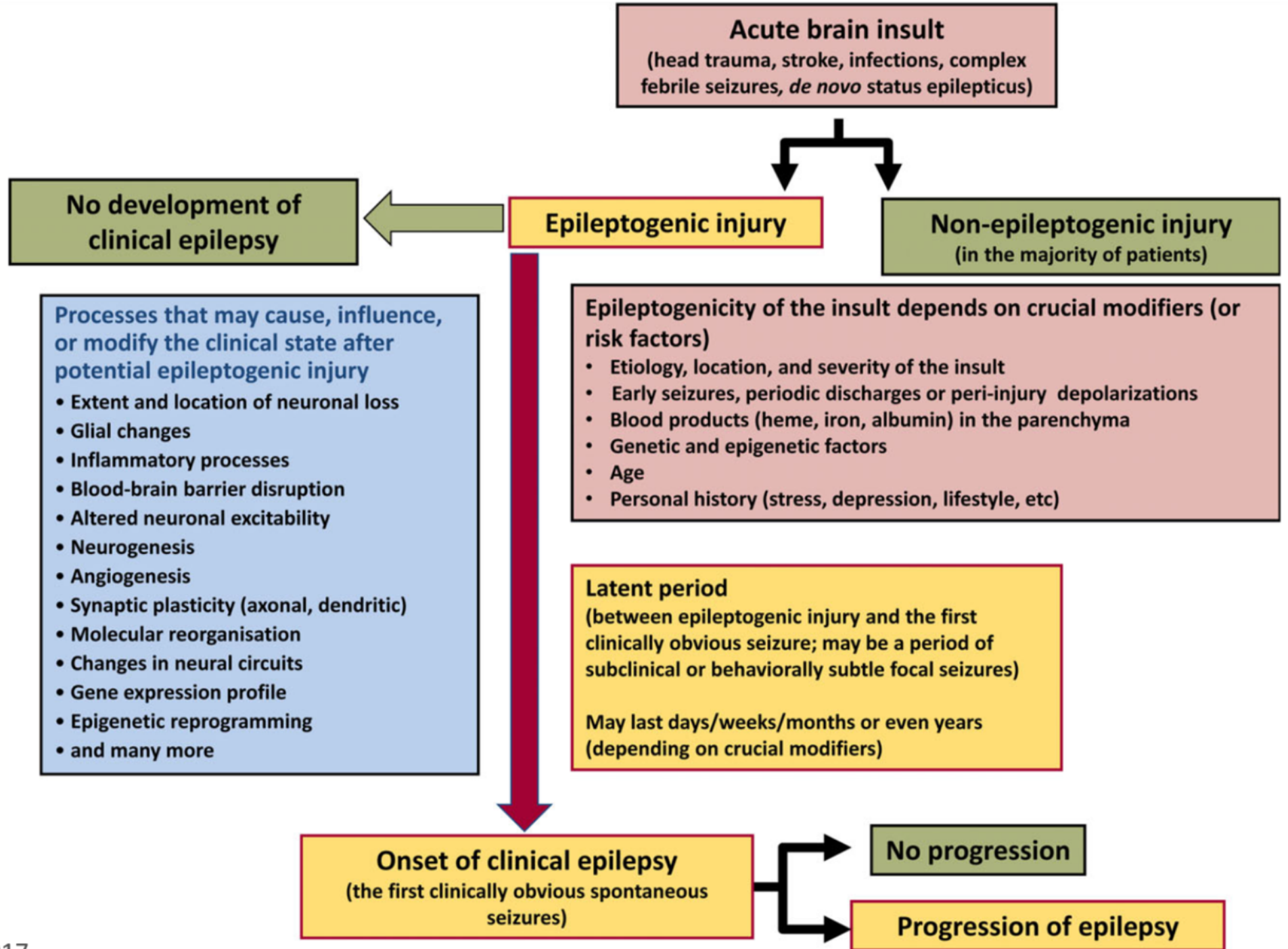
Epilepsia, 2005, 46, S9: 21-33


Page 1
SENS 12:59:20[0000:05:22] [SENS *7 HF *70 LF *1.6 CAL *50]
Date: 12/16/2011
70uV Patt. *IIA ACFilt. *ON Refer. *OFF Reset *OFF
x1
1 Fp2-F8
2 F8-T4
3 T4-T6
4 T6-O2
5 Fp1-F7
6 F7-T3
7 T3-T5
8 T5-O1
9 Fp2-F4
10 F4-C4
11 C4-P4
12 P4-O2
13 Fp1-F3
14 F3-C3
15 C3-P3
16 P3-O1
17 A2-T4
18 T4-T3
19 T3-A1
20 Fz-Cz
21 Cz-Pz
22 X1-X2
M
Scale 83%
0
5
10 s
PAT IIA EEG
IIA

Epileptogenesis and Pathology

Neonatal seizures
Status epilepticus
Hippocampal sclerosis
Traumatic brain injury
Malformations of cortical development
Tumor
Genetic/ metabolic (see prior lectures)

c/o Forcelli



Klein et al., 2017

Neonatal seizures – etiology and effects

- Hypoxia-ischemia
- Intracranial hemorrhage
- CNS infection
- Infarction
- Metabolic (hypoglycemia, hypocalcemia, hypomagnesemia)
- Chromosomal/ genetic anomalies
- Congenital abnormalities of the brain
- IEM
- Drug withdrawal or intoxication

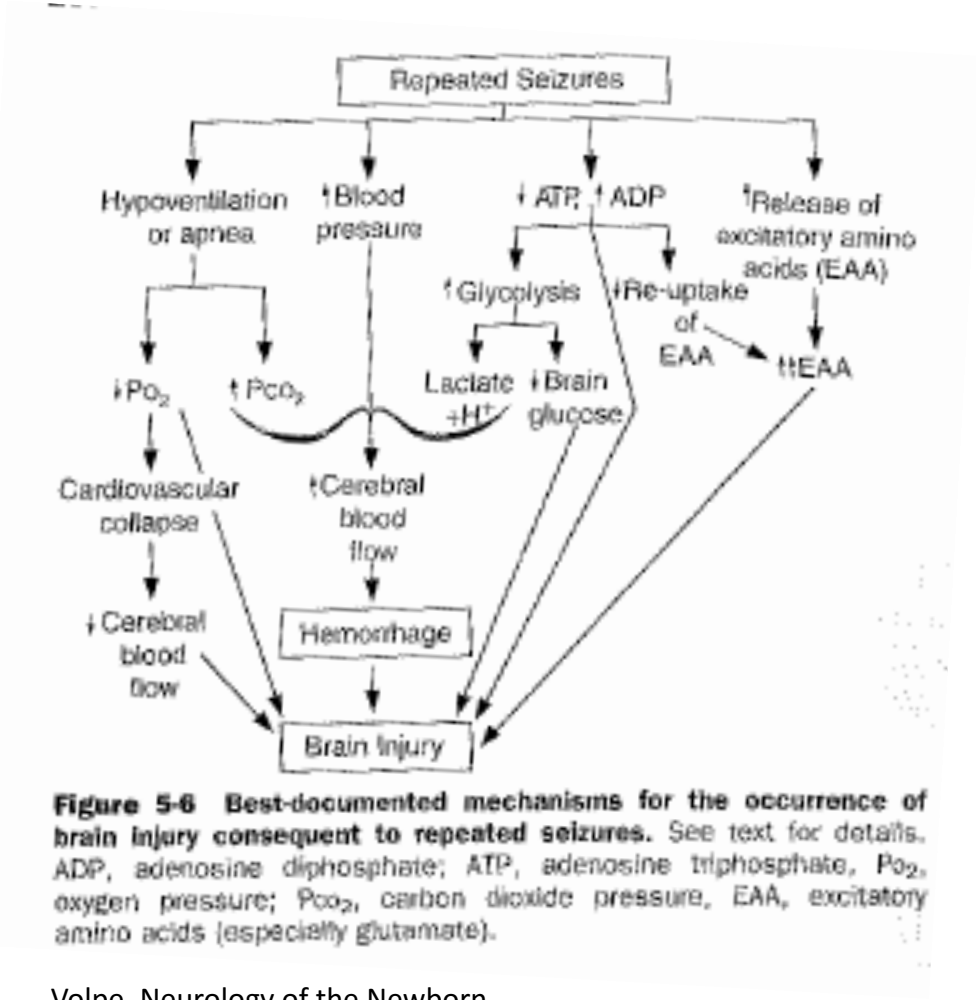
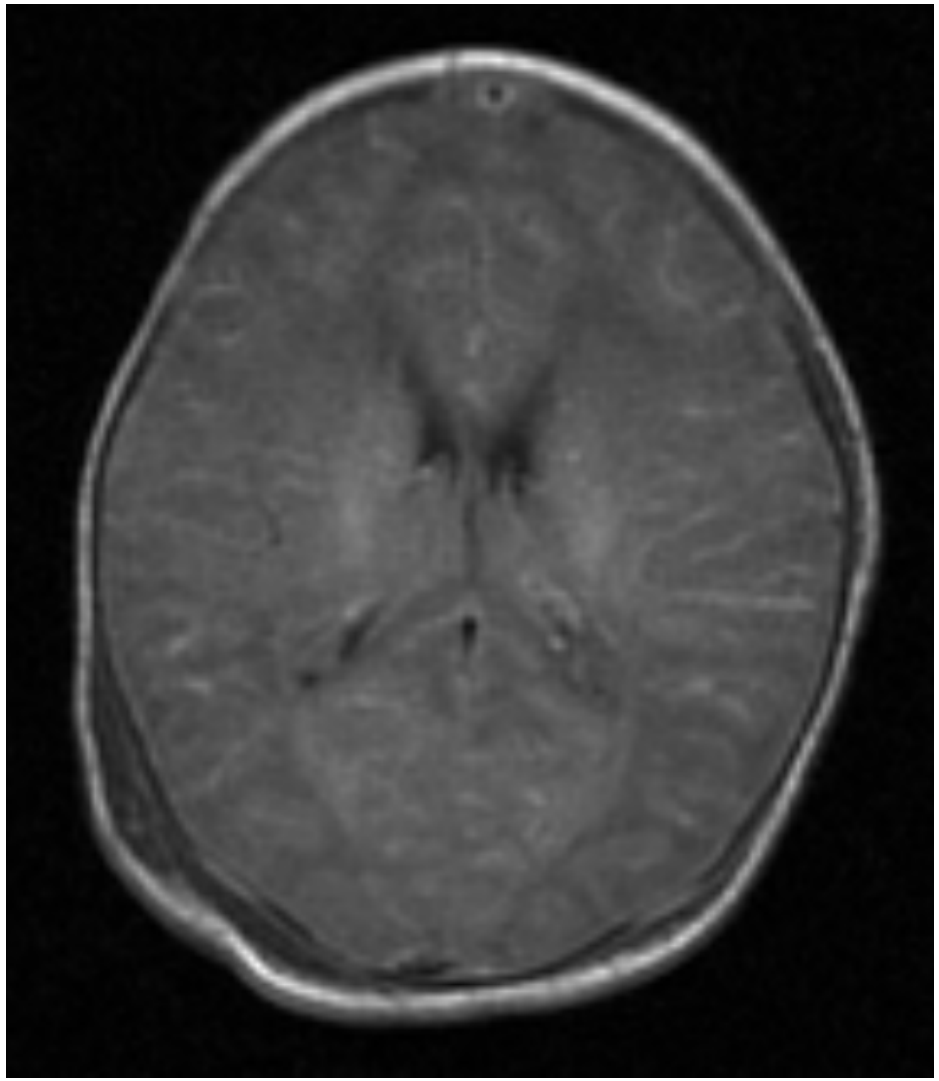


Figure 5-6 Best-documented mechanisms for the occurrence of brain injury consequent to repeated seizures. See text for details. ADP, adenosine diphosphate; ATP, adenosine triphosphate, Po_2, oxygen pressure; Pco_2, carbon dioxide pressure, EAA, excitatory amino acids (especially glutamate).

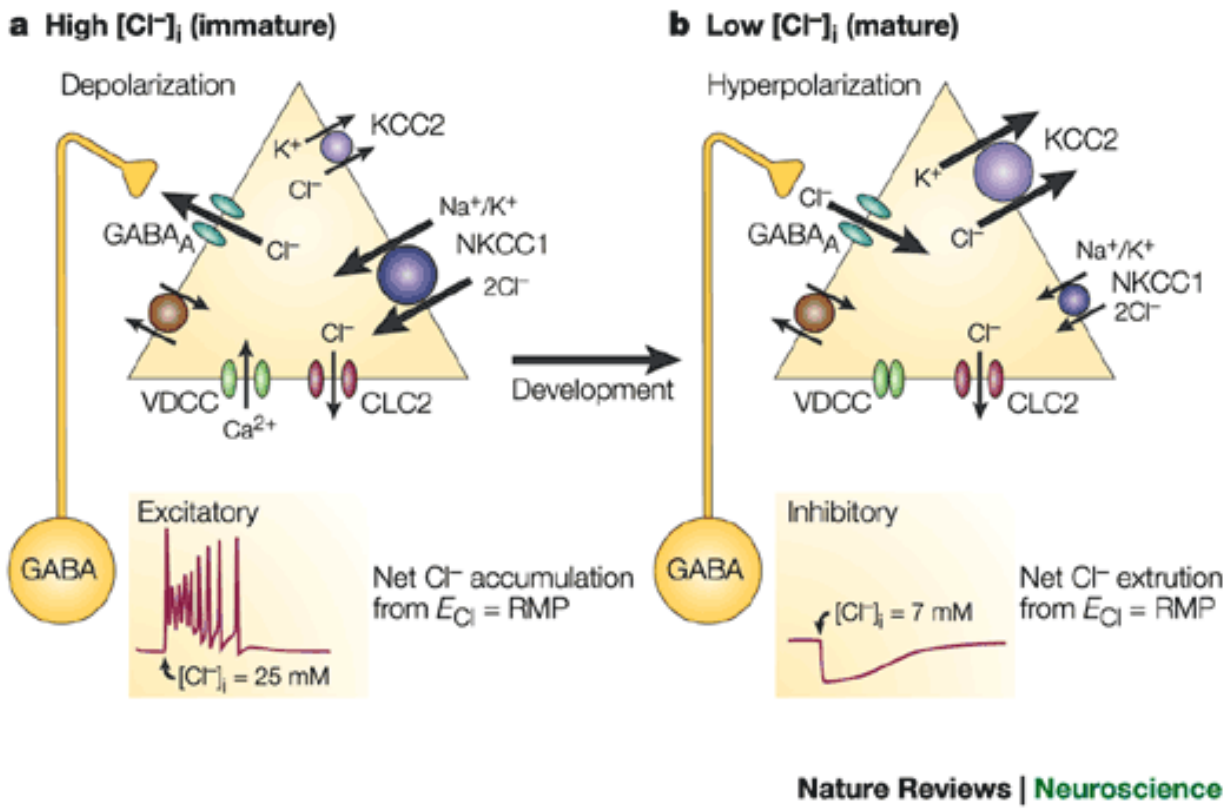
Volpe, Neurology of the Newborn

HIE



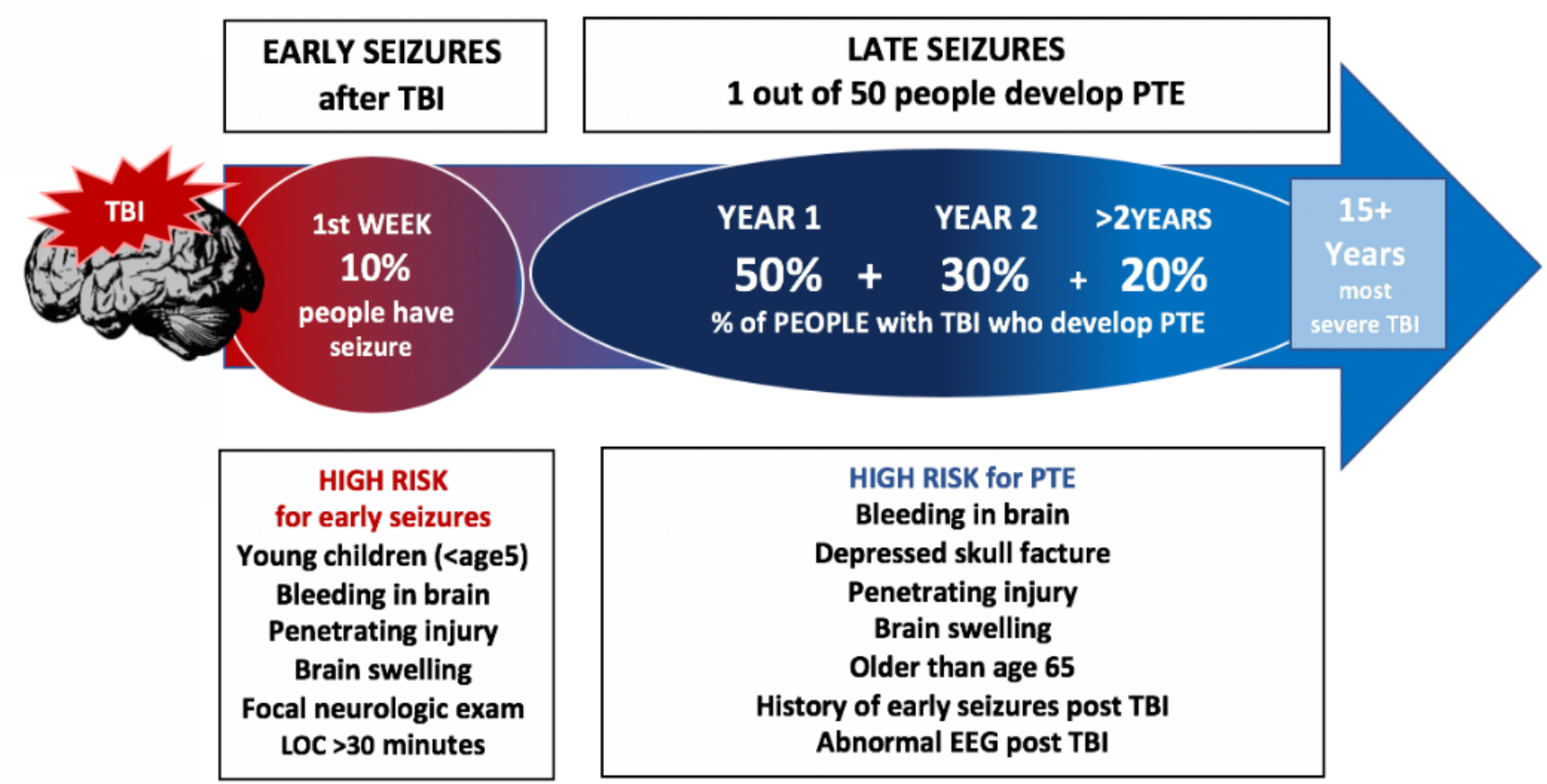
- **The K^+/Cl^- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation (Rivera et al.)**

- Decreased Seizure Activity in a Human Neonate Treated With Bumetanide, an Inhibitor of the Na^+-K^+-$2Cl^-$ Cotransporter NKCC1 (2009)
- Bumetanide enhances phenobarbital efficacy in a neonatal seizure model - VI Dzhala, AC Brumback, KJ Staley
- More recent studies are yet unclear (NEMO, RCT)



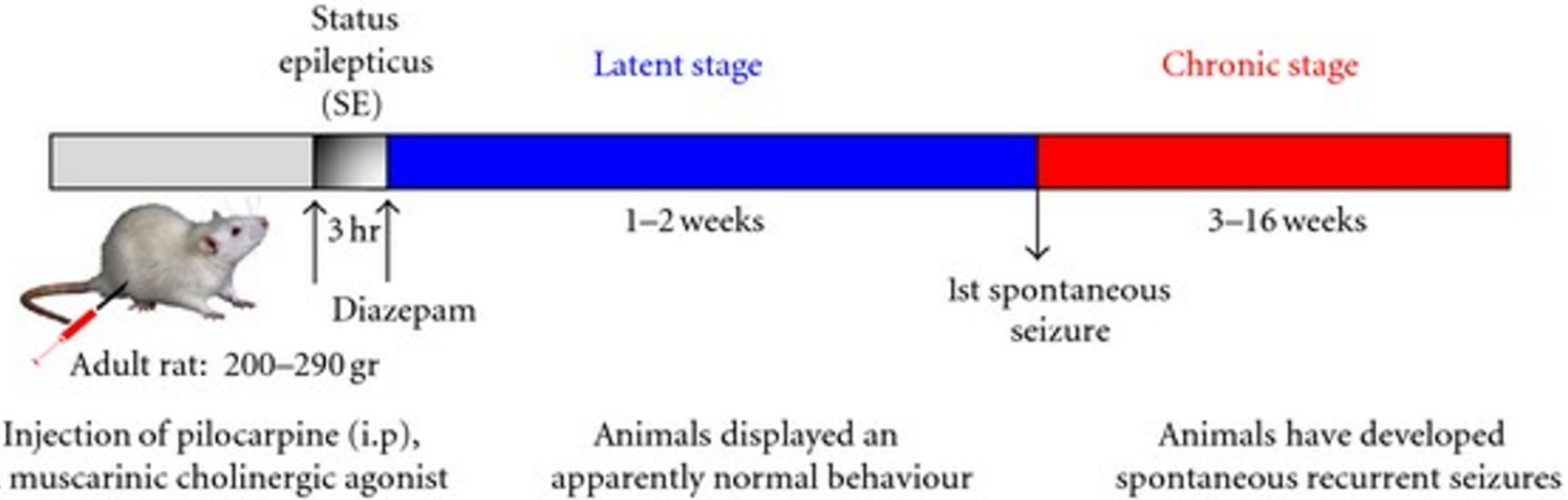
Seizures after TBI

- Early (< 1 week)
- Late (> 1 week)



c/o Forcelli

Status Epilepticus Model



Status models:

Olney and colleagues demonstrated that kainate kills cells in the brain (1974)

Ben-Ari and Lagowska demonstrated that kainate induces status epilepticus (1978)

Cavalheiro and colleagues demonstrate that kainate-induced status epilepticus results in spontaneous seizures (1983)

Turski et al. demonstrate that pilocarpine causes status epilepticus and a syndrome similar to that seen with kainate (1984)

Sloviter demonstrates that electrically evoked status epilepticus (caused by stimulating hippocampal afferents) causes a similar syndrome (1987)

c/o Forcelli

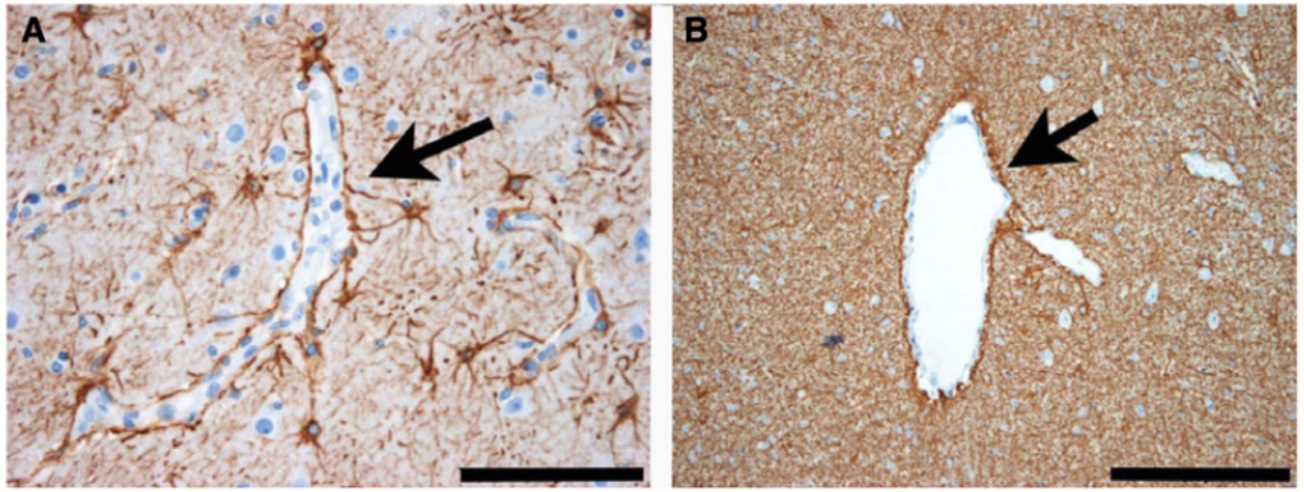
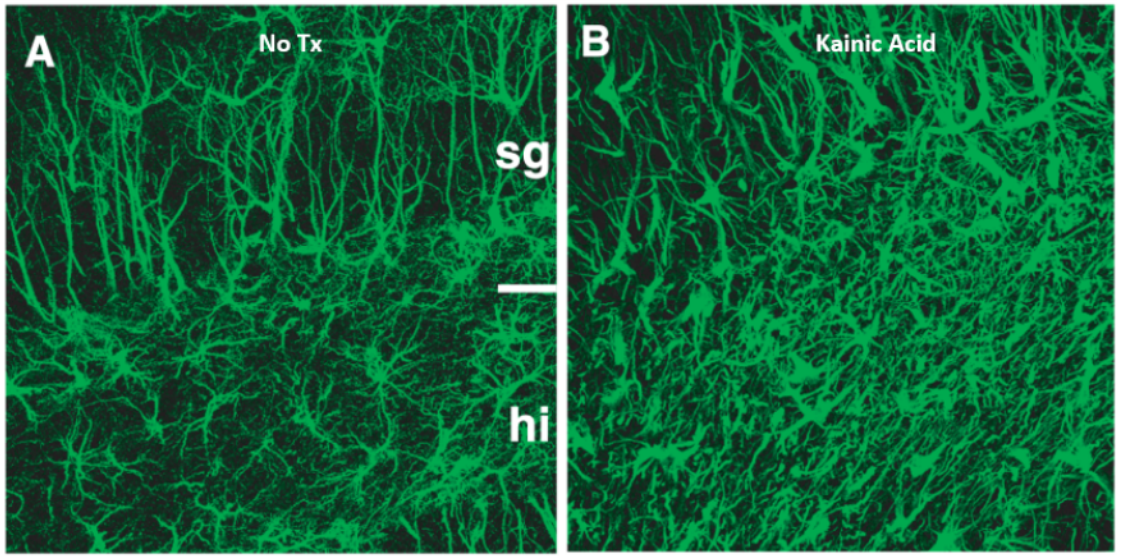


FIGURE 2 Common patterns of astrogliosis in epileptic human brain tissue. A, Reactive astrogliosis in the neocortex of human epilepsy surgery brain specimens is commonly seen along cortical capillaries (arrow). B, In white matter, there is another common pattern of astrogliosis built by a dense glial fibrillary meshwork. The arrow points toward an enlarged venous vessel. Scale bar in A = 100 μm, in B = 200 μm. Glial fibrillary acidic protein immunohistochemistry (brownish color) with bluish hematoxylin counterstaining [Color figure can be viewed at wileyonlinelibrary.com]

- Epilepsy induces astrogliosis. Reactive astrocytes are detected after both acute and long-duration seizures
- Occurs in many brain areas

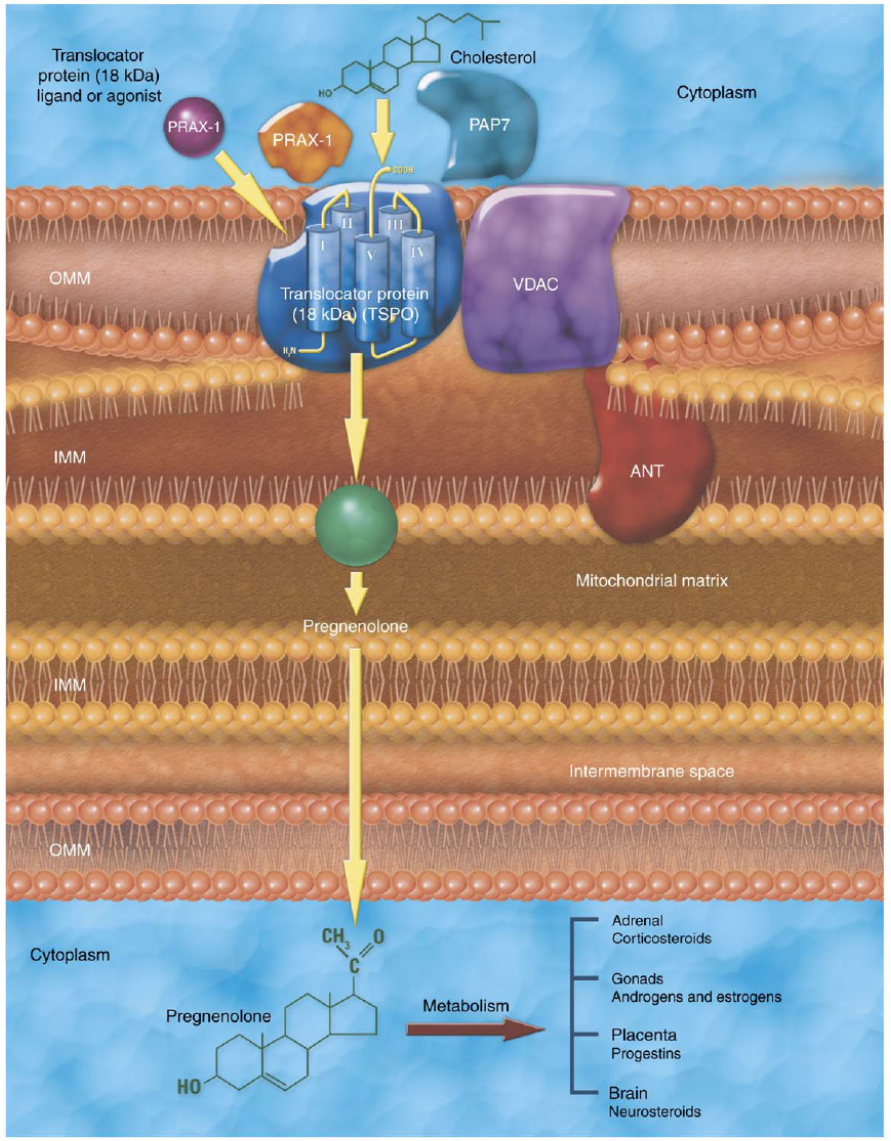


GFAP immunofluorescence in hippocampus of mice is increased by status epilepticus

Fedele et al., 2005

Translocator protein 18 kDa (TSPO)

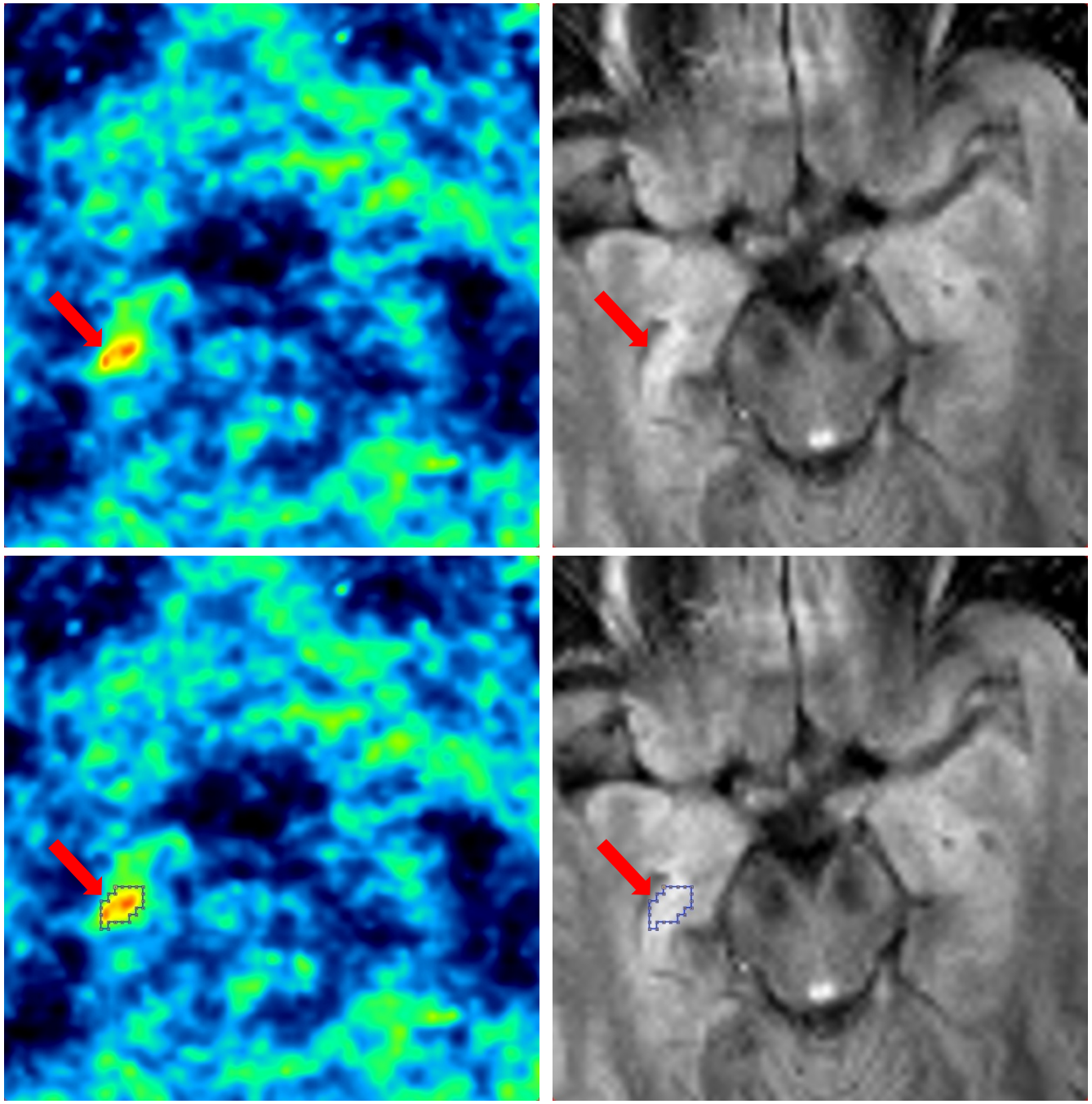
- Heterotrimers with isoquinoline binding protein, voltage-dependent anion channel, adenine nucleotide transporter
- located on mitochondrial membranes
- Activated microglia and astrocytes overexpress TSPO in inflammation



Veenman & Gavish *Pharmacol Ther* 2006;110:503-524

Papadopoulos et al. *Trends Pharmacol Sci* 2006;27:402-409

Mesial Temporal Sclerosis: Increased PET 11C-PBR28 binding



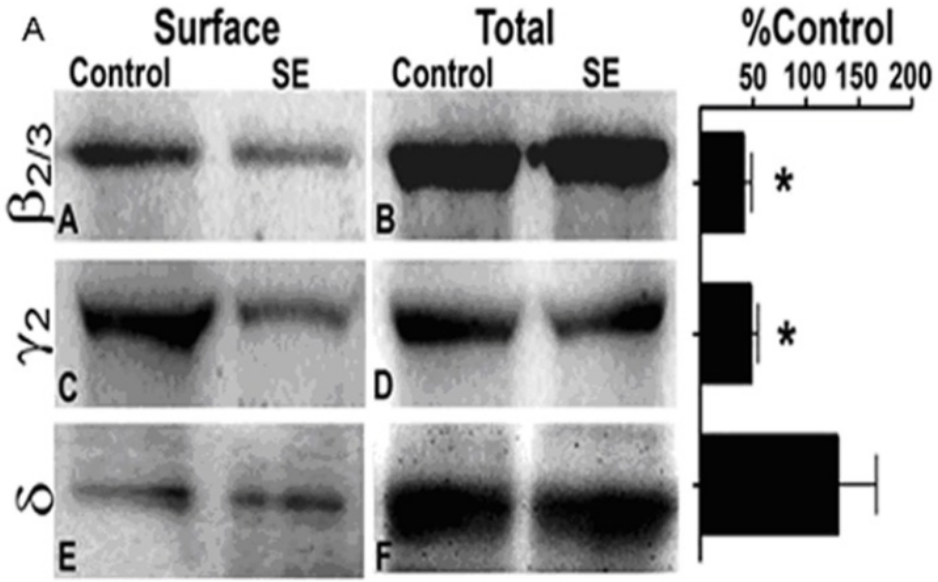
Hirvonen, Innis and Theodore

^{11}C-PBR28 PET (TLE_04)

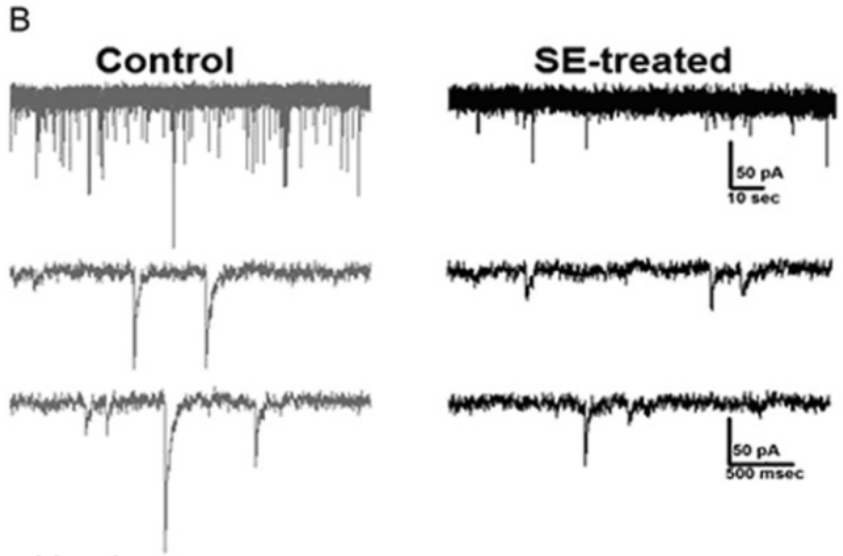
FLAIR MRI (TLE_04)

c/o Forcelli

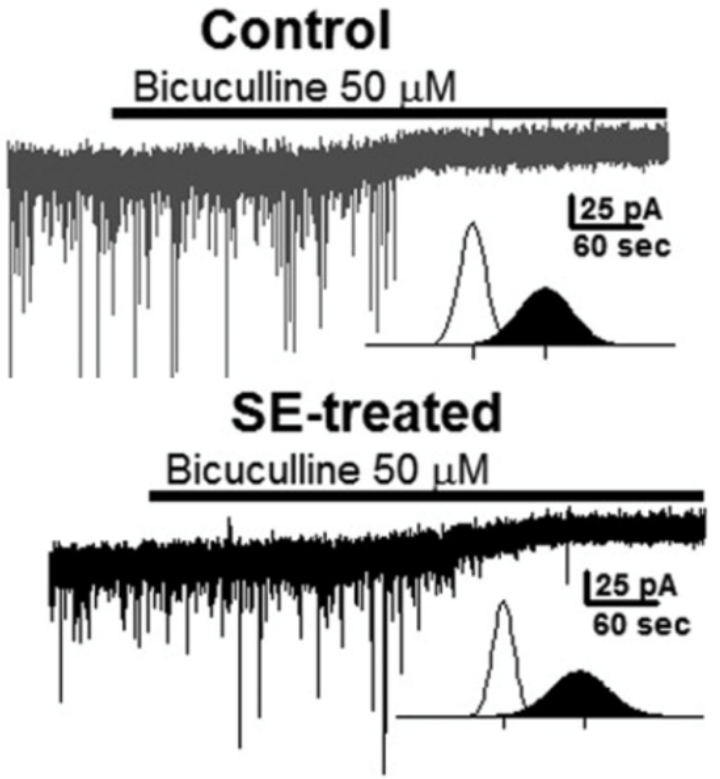
Status Epilepticus leads to rapid internalization of GABA-A receptors



This means less GABAergic synaptic inhibition



Joshi and Kapur, 2012



But no change in TONIC inhibition

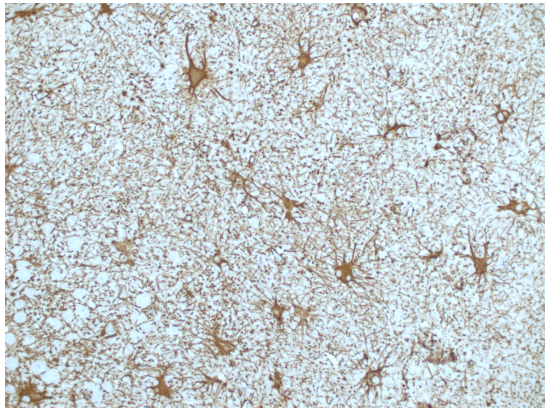
Tonic inhibition is mediated by a different population of GABAa receptors than phasic (synaptic inhibition. This is due to different subunit composition of these receptors. How might you use this info to treat "refractory" status that doesn't respond to standard benzodiazepines (which activate "phasic" inhibition?

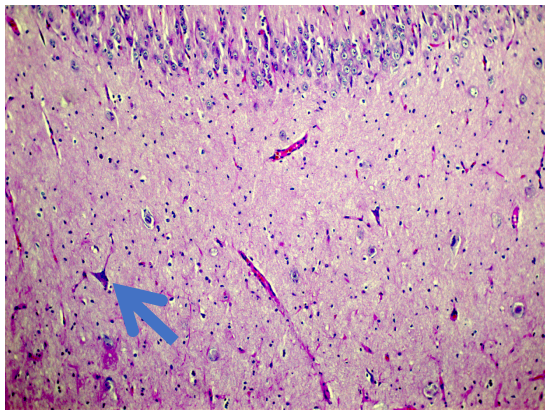
History of Hippocampal Sclerosis

- HS is the most common pathologic finding in adult epilepsy surgery
- Ammon's horn sclerosis linked to epilepsy – Sommer (1880) and Bratz (1899)
  - Neuronal loss largely restricted to CA1 (*cornu ammonis*)
- Jackson & Beevor (1889) – associated clinical symptoms of TLE with focal lesions in hippocampus
- Sano and Malamud (1953) – associated HS with EEG evidence of TLE
- Jackson et al., 1990; Berkovic et al., 1991 – recognized that MRI can detect HS

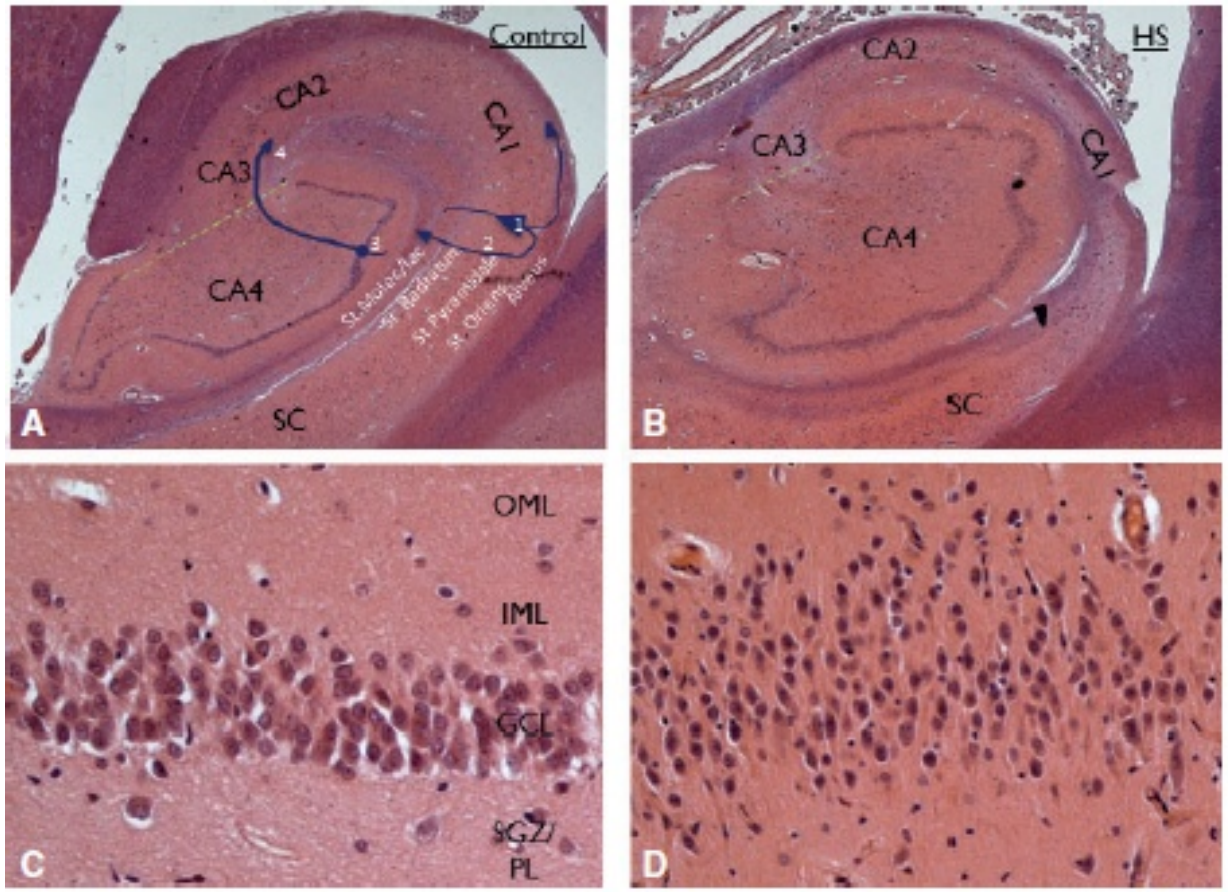
Hippocampal Sclerosis Pathology

- Neuronal loss in the pyramidal cell layer
  - Classical HS – neuronal loss primarily involving CA1 > CA4 with relatively preserved subiculum and CA2 and variable loss from CA3
  - Severe/ Total HS – neuronal loss also involves CA2 and granule cells of dentate gyrus
  - End-folium HS – restricted to CA4
  - CA1 HS – restricted to CA1
- Granule cell dispersion
- Mossy fiber sprouting
- Chronic fibrillary gliosis
- Altered interneurons
- “HS Plus”/ MTS
- “Dual” pathology – FCD IIIa, low-grade tumors (DNETs, gangliogliomas), vascular and cortical malformations





Histology



Malmgren & Thom, 2012

Hippocampal Sclerosis in Temporal Lobe Epilepsy Demonstrated by Magnetic Resonance Imaging

Samuel F. Berkovic, MD, Frederick Andermann, MD, André Olivier, MD, Roméo Ethier, MD, Denis Melanson, MD, Yvon Robitaille, MD, Ruben Kuzniecky, MD, Terence Peters, PhD, and William Feindel, MD

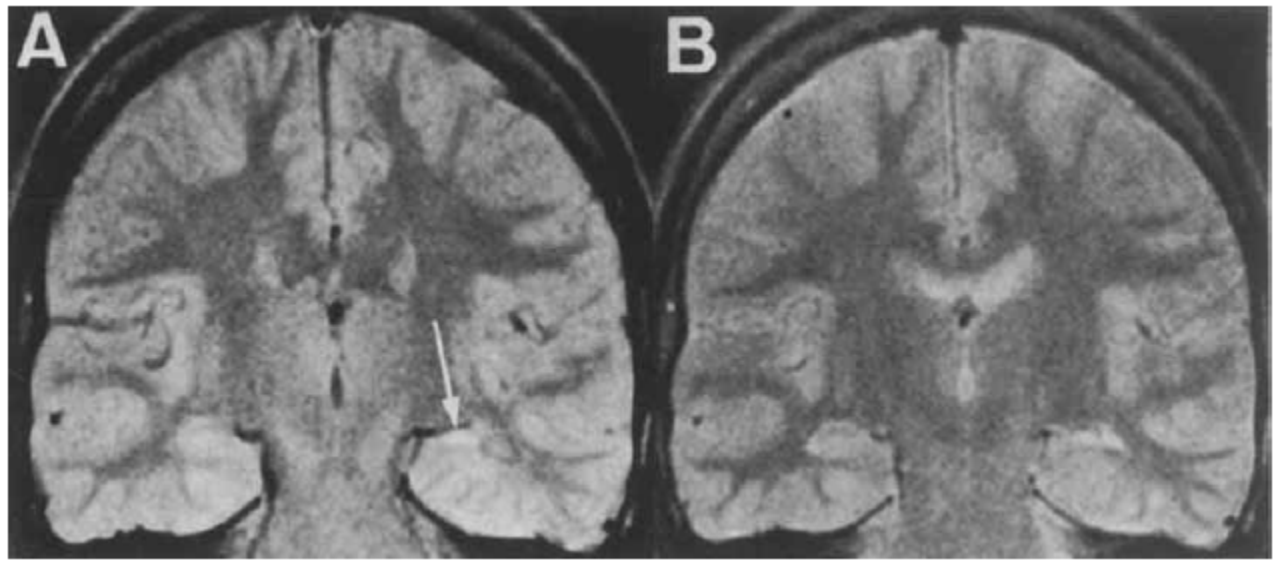


Fig 3. Magnetic resonance imaging, Patient 10. (A) First echo image. The left hippocampus (arrow) *is severely shrunken with slightly increased signal compared with the left. (B) Second echo image. The asymmetry in the hippocampal signals is better appreciated; the abnormal left hippocampus can be resolved from the adjacent high signal of the temporal horn.*

MRI features of HS

- T2 hyperintensity (hippocampal hyperintense FLAIR signal occurs in about 1/3 of normal controls (Labate et al., 2010) but is not associated with hippocampal atrophy
- Reduced hippocampal volume
- Disturbed internal architecture
- Others
  - Temporal lobe atrophy
  - Dilatation of the temporal horn
  - Blurring of the gray-white junction

Potential Etiologies

- Febrile seizures/ febrile status epilepticus
- Infection
- Inflammation
- “Dual” pathology
- Seizures
- Traumatic brain injury
- Genetic

Animal models: Induced seizures → HS

- Pilocarpine-induced SE in the rat (Chakir et al., 2006; Covolan & Mello, 2000)
- Kainic acid-induced SE (Covolan & Mello, 2000)
- Fluid-percussion injury (Lowenstein et al., 1992)
- Hippocampal kindling (Bengzon et al., 1997)
- Cell loss, hyperexcitability, structural changes, apoptosis and proliferation in various regions
- Hyperthermic seizures (Baram)

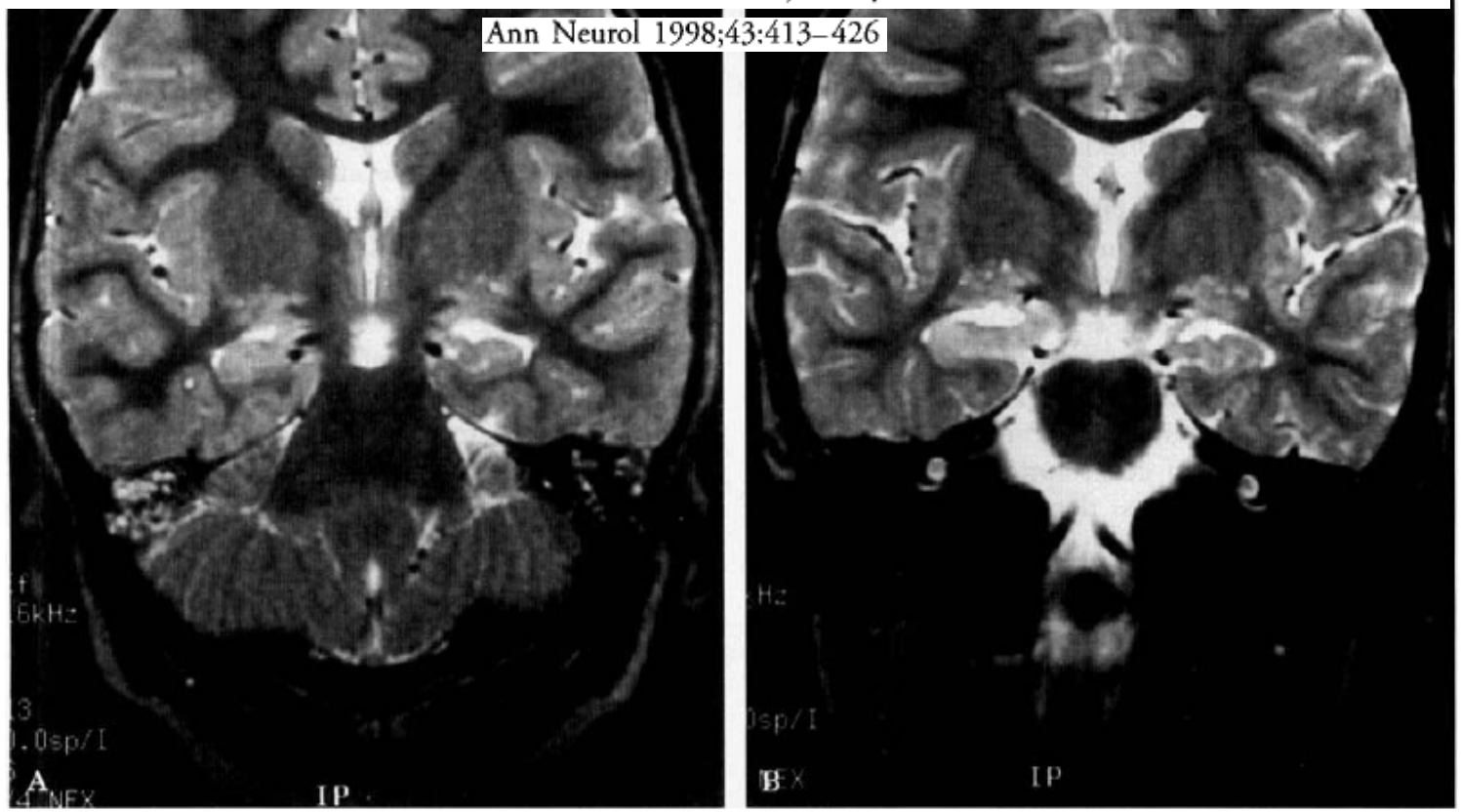
Febrile Seizures/ Status Epilepticus and TLE/Hippocampal Sclerosis

- Retrospective studies report a history of prolonged or complex FS during childhood in patients with intractable MTLE ± HS more often than would be expected by chance (Falconer et al., 1964; Abou-Khalil et al., 1993; Cendes et al., 1993; French et al., 1993)
- Prospective studies of FS yield mixed results regarding seizure risk
  - Nelson & Ellenberg, 1976 (1706 with FS to age 7 yrs) – 18x risk if neurologically abnormal and complex FS; none developed intractable CPS
  - Camfield et al., 1994 (504 epilepsy) – PFC associated with *intractable* epilepsy of *any* type
  - Annegers et al., 1987 (687 with FS to age 25 yrs) – additive risk for subsequent *partial* unprovoked seizure with complex features
  - Berg et al., 1999 (524 with epilepsy) – 73 (13.9%) had antecedent FS; similar proportion with TLE and other epilepsy types (except absence)
- FEBSTAT study – ongoing, 199 children enrolled
- The mean latency to develop mTLE after FS is 8-11 years (French et al., 1993; Mathern et al., 1995); mean latency to become intractable 9 years (Berg et al., 2003)

Magnetic Resonance Imaging Evidence of Hippocampal Injury after Prolonged Focal Febrile Convulsions

Kevan E. VanLandingham, MD, PhD,* E. Ralph Heinz, MD,† Jose E. Cavazos, MD, PhD,§ and Darrell V. Lewis, MD‡

Ann Neurol 1998;43:413–426



DOI: 10.1093/brain/awg262 *Brain* (2003), **126,** 2551–2557

Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study

Rod C. Scott,[1,2,3] Martin D. King,[2,3] David G. Gadian,[2,3] Brian G. R. Neville[1,3] and Alan Connelly[2,3]

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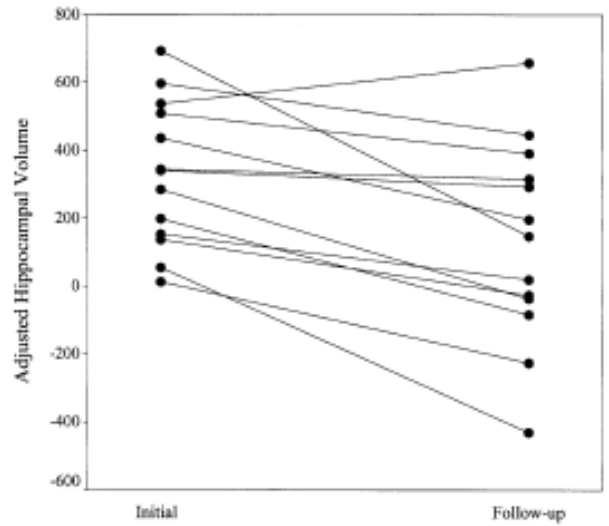

Fig. 2 Adjusted hippocampal volume (adjustment defined as the difference between the predicted hippocampal volume for a given age and intracranial volume in control subjects, and the patient hippocampal volume; see Statistical analysis section) in patients investigated within 5 days of a prolonged febrile convulsion (initial) and 4–8 months later (follow-up). Each pair of dots joined by a line represents a single patient.

MRI abnormalities following febrile status epilepticus in children

The FEBSTAT study

Neurology® 2012;79:871-877

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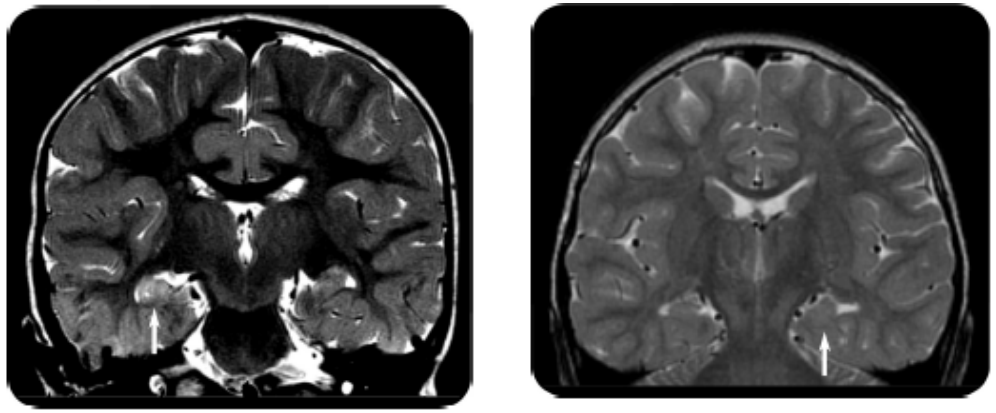
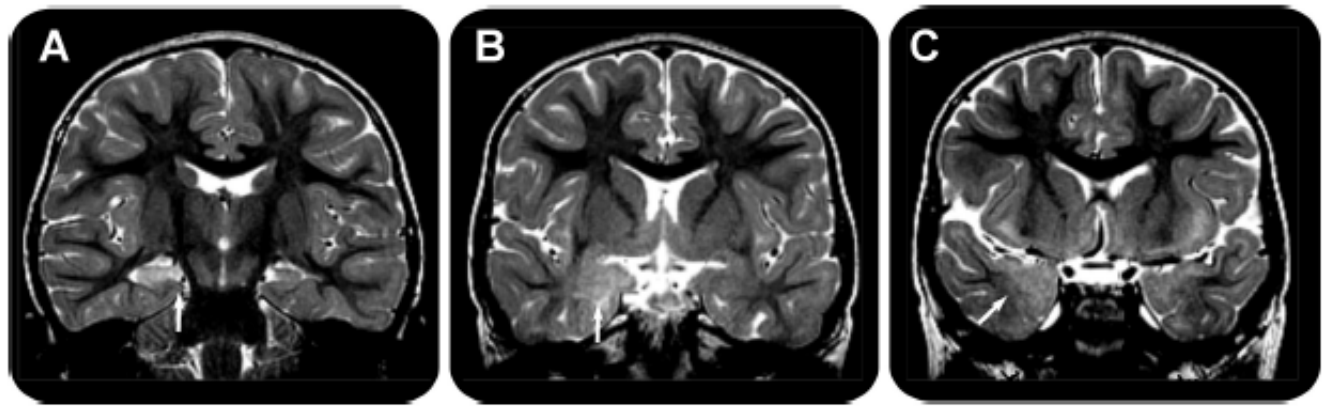


Figure 2 Extrahippocampal temporal lobe abnormality following febrile status epilepticus (FSE)

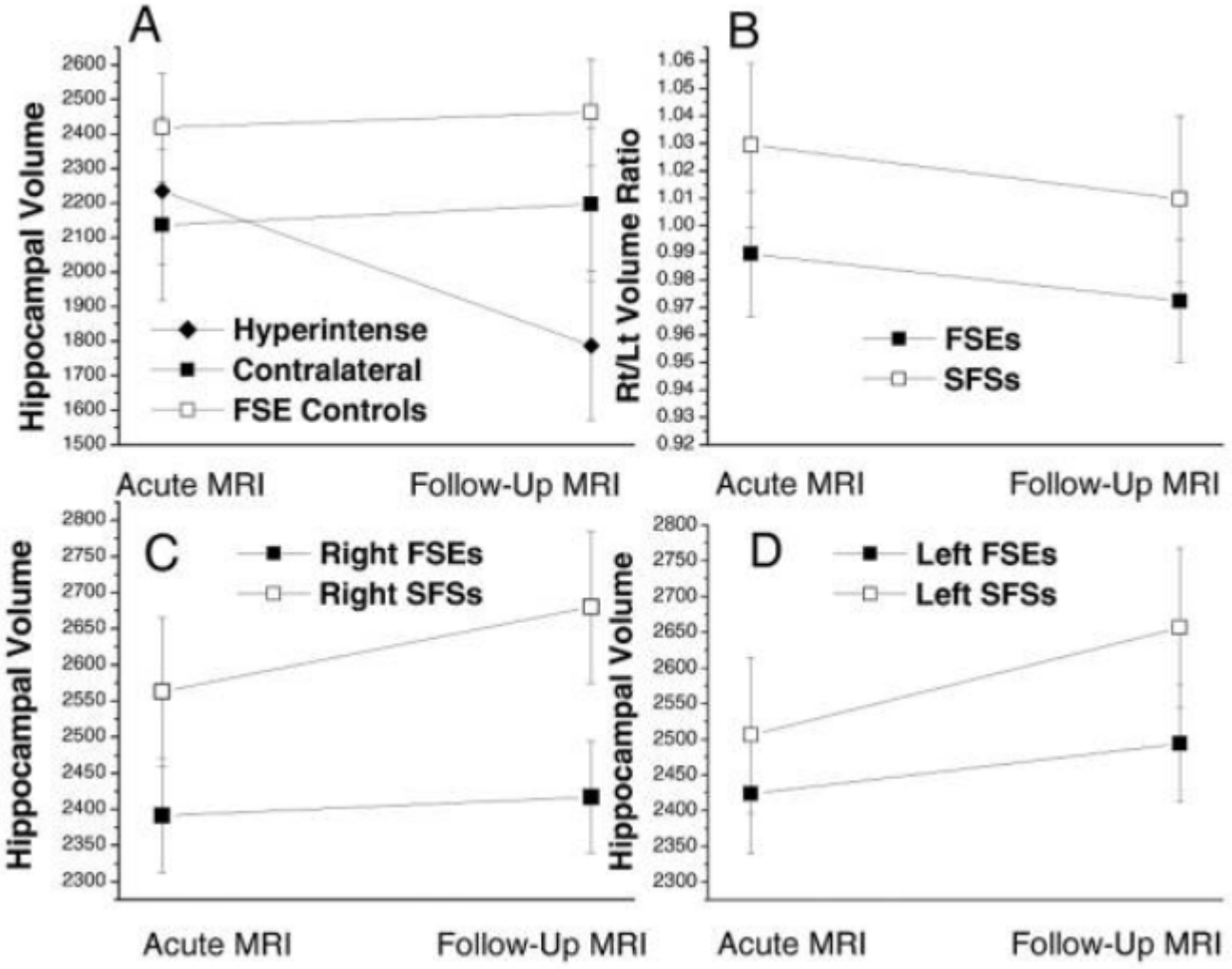


MRI of 11-month-old child with focal FSE. Seizure was continuous and lasted 120 minutes. MRI performed 3 days after the episode of FSE. Note increased T2 signal and enlargement of the right hippocampus (arrow in A), accompanied by increased T2 signal in the right amygdala (B) and right mesial temporal cortex (C).

Hippocampal Sclerosis After Febrile Status Epilepticus: The FEBSTAT Study

- 22/226 had acute increased T2 signal and hippocampal volume
- 1 year follow up MRI in 14 of these 22 showed HS in 10 and reduced hippocampal volume in 12
- Only 1/116 without acute T2 hyperintensity developed HS (after another FSE)

SFS (simple febrile seizure)



Hippocampal sclerosis and a second focal lesion—How often is it ipsilateral?

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*Department of Radiology, University Hospital Maastricht, Maastricht, The Netherlands; †Brain Research Institute, Austin Health, Heidelberg West, Victoria, Australia; ‡Department of Radiology, Austin Health, Melbourne, Victoria, Australia; §Department of Medicine, University of Melbourne, Parkville, Victoria, Australia; and ¶Department of Radiology, University of Melbourne, Parkville, Victoria, Australia

Table 1. Types of EHL

	MRI diagnosis
Acquired	31 (54%)
Stroke	11
Trauma	8
Atrophy	9
Postoperative	2
Neoplasm	1
Developmental	21 (36%)
MCD	17
Cavernoma	2
TS	1
Sturge-Weber	1
Not clear	6 (10%)

"Not clear" means a clear abnormality but unclear diagnosis. MCD, malformation of cortical development; TS is tuberous sclerosis.

Table 3. Side of HS and EHL (A), and lobar distribution of the EHLs in patients with HS and EHL on the same side (N = 57) (B). The second column in table 3B shows the number of patients with unique involvement of a lobe; the third column lists the number of patients with a combined involvement of lobes

A

Side of HS and EHL	
R – R	17
L – L	24
Bilateral HS – R/L EHL	6
R/L HS – Bilateral EHL	10
L – R	1

98% ipsilateral

B

Lobe	Unique	Combined	Total (%)
Temporal	8	27	35 (61)
Frontal	6	27	33 (58)
Occipital	7	23	30 (53)
Parietal	2	22	24 (42)

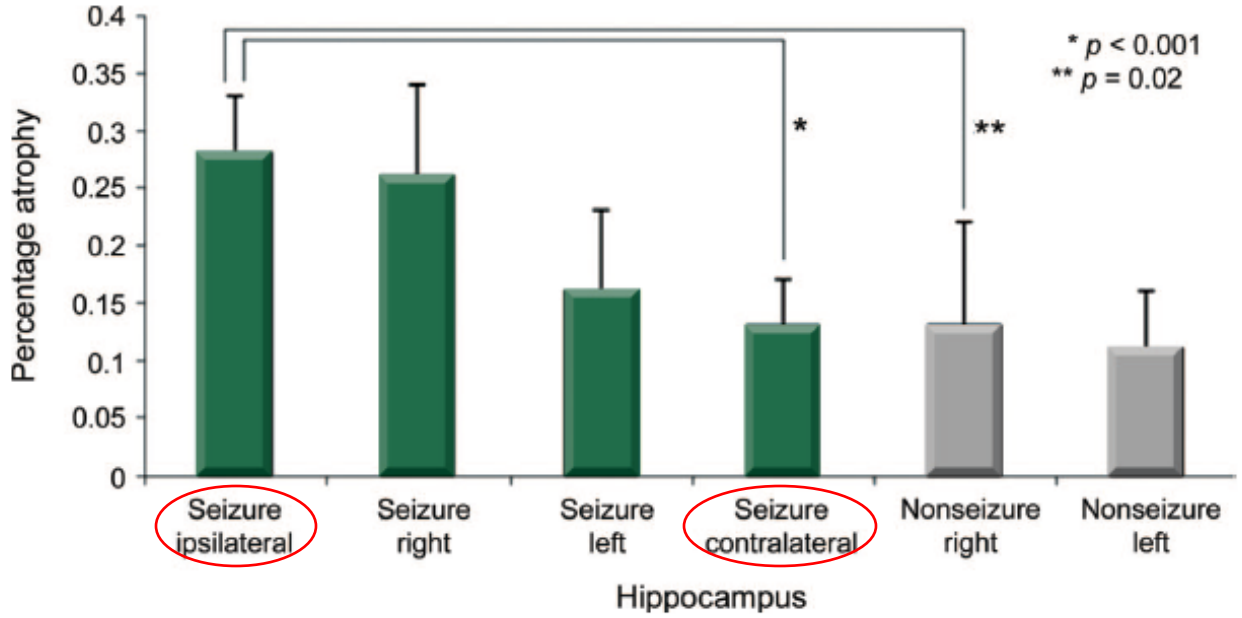
Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy

Neurology® 2010;75:792-798

Table 2 Global and hippocampal brain atrophy by group

Atrophy	Seizure	Nonseizure	*p* Value
Hippocampal	0.21 ± 0.09	0.12 ± 0.06	0.007
Global	0.08 ± 0.05	0.08 ± 0.03	0.907

Figure 2 Long-term brain atrophy in hippocampal regions are shown for the seizure and nonseizure groups



Bars are labeled by group (seizure, black; nonseizure, white) and by hippocampus location (right, left, ipsilateral or contralateral to the EEG seizure focus). There is greatest hippocampal atrophy in the seizure patients' hippocampi ipsilateral to the EEG seizure focus. The right hemisphere was ipsilateral to seizures more commonly than the left. Late hippo atrophy = percentage atrophy at 6 months as compared with the acute image.

P.M. Vespa, MD, FCCM, FAAN
D.L. McArthur, PhD
Y. Xu, MD
M. Eliseo, BS
M. Etchepare, BSN, RN
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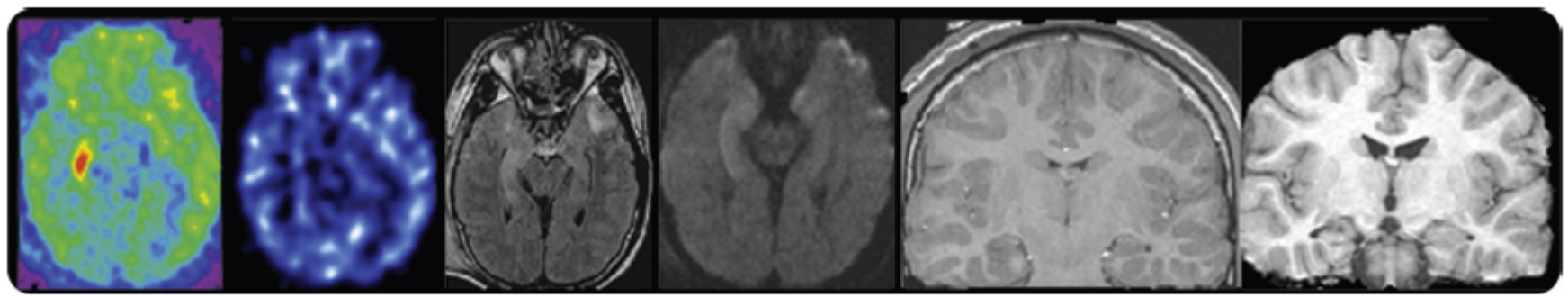
T.P. Glenn, PhD
D. Hovda, PhD

Figure 3 **Hippocampal atrophy ipsilateral to the seizure focus**



Composite of acute PET scan and acute and chronic MRI volumetric scans on seizure subject 4. The patient has increased glucose metabolism in the right hippocampus without a similar increase in CMRO2. The hyperintensity on the fluid-attenuated inversion recovery (FLAIR) sequence was due to acute seizure activity and not traumatic hemorrhage. MRI at 6 months shows right hippocampal atrophy and also right temporal lobe atrophy. CMRO2 = oxidative metabolism PET; FDG = fluorodeoxyglucose PET; PIH = postinjury hour.

Recurrent seizures may cause hippocampal damage in temporal lobe epilepsy

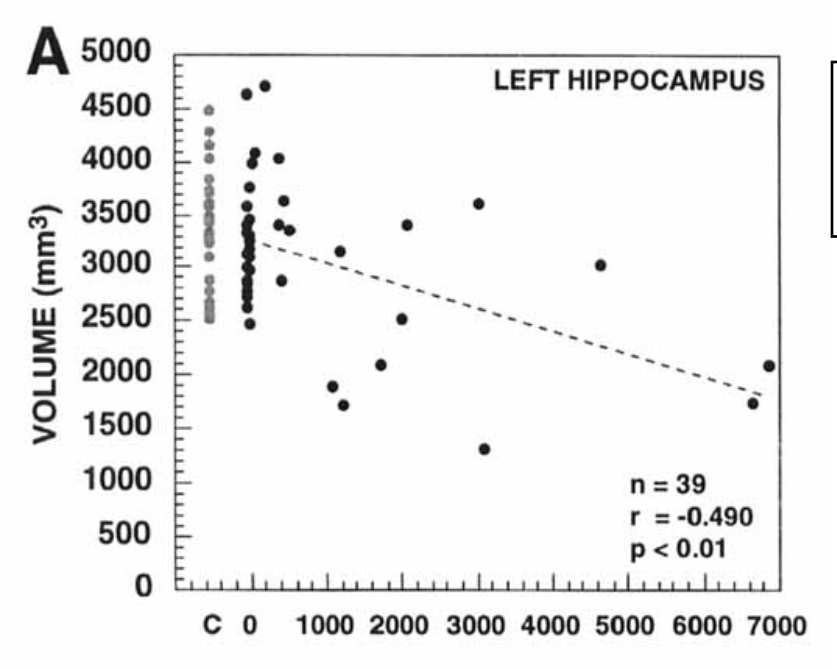
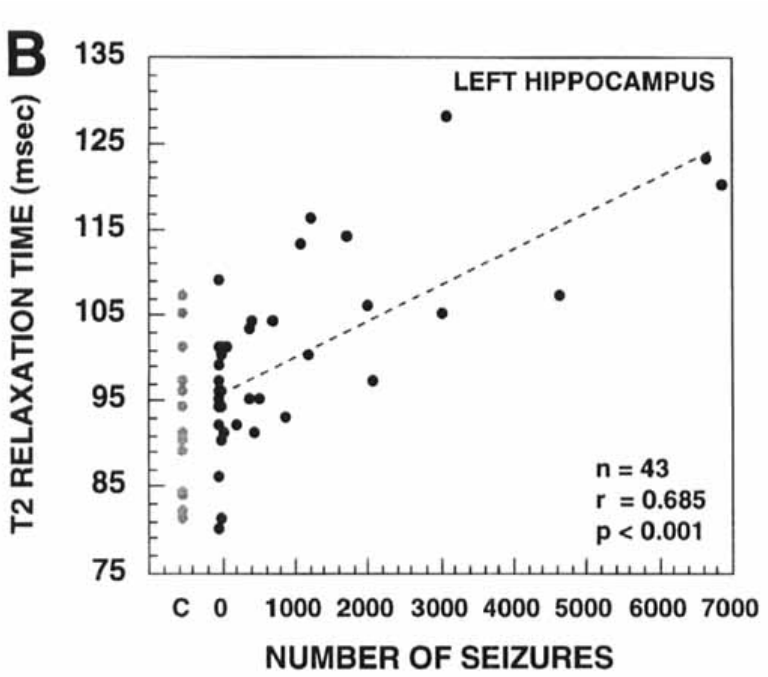


Figure. (A) Correlation between the lifetime number of seizures (both partial and secondary generalized) and the volume of the left hippocampus in patients with left-sided focus. After logarithmic transformation of volumes: r = -0.391, p < 0.01. (B) Correlation between the lifetime number of seizures and T2 relaxation time with left-sided focus. c = controls; n = number ofpatients; r = correlation coefficient (Pearson).

R. Kalviainen, MD, PhD; T. Salmenpera, MD; K. Partanen, MD, PhD; P. Vainio, Msci;P. Riekkinen, SrMD, PhD; and A. Pitkanen, MD, PhD

NEUROLOGY 1998;50: 1377-1382



Cerebral Cortex Embryology

- Week 7: proliferation of neuroblasts in the germinal matrix
- Week 8: radial migration begins
- Migration along radial glial cells (dependent on recognition, attachment, and calcium entry/ NMDA activation)
- Neurons migrate in an inside out sequence (except for layer 1 – molecular layer)

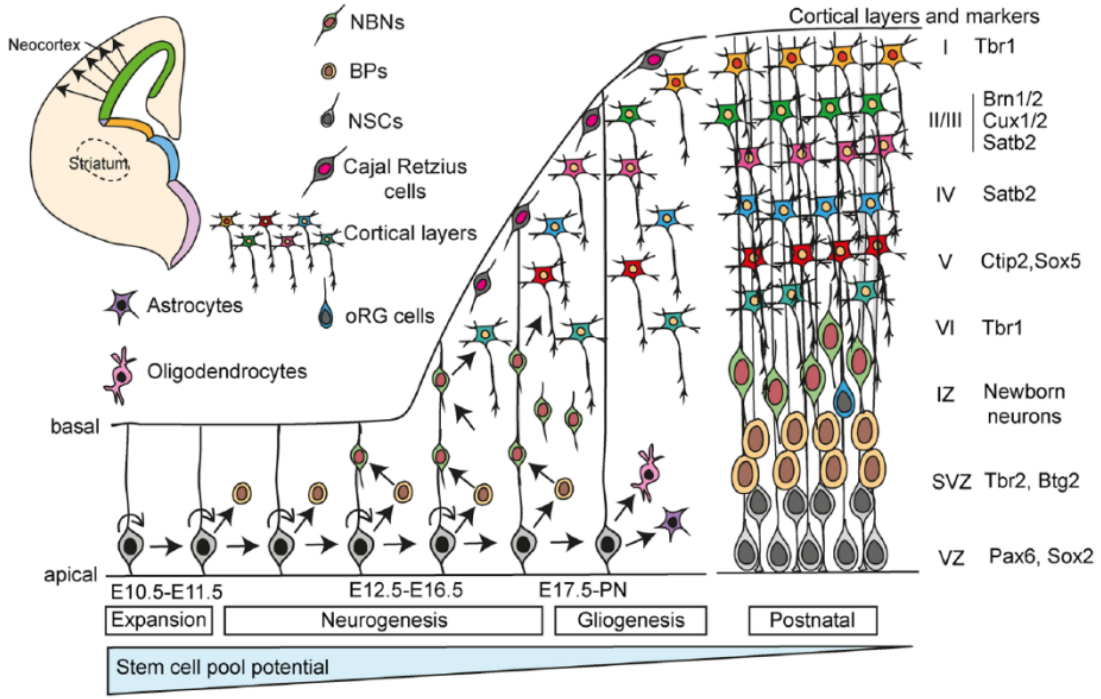


Figure 5. Systematic formation of isocortex layers in the dorsal telencephalon. During early stages of cerebral cortical development (embryonic days E10.5-E11.5), NSCs predominantly undergo symmetric cells divisions to expand the NSC pool. This phase is referred to as the expansion phase. The first neurons to be formed are generated by direct neurogenesis of the NSCs. The Cajal-Retzius cells populate layer I of the isocortex and play important roles in establishing cortical architecture. During late embryogenesis (E12-E16.5), NSCs undergo increasingly more asymmetric divisions to generate 1 NSC (self-renewal) and 1 BP. The BPs generate the neurons. This is the neurogenic phase. Neurons are generated in a sequential, inside-out fashion and are specified by different transcription factors, some of which are shown. At later stages of development, NSCs generate the other cell types of the brain including astrocytes, oligodendrocytes, and ependymal cells (not shown). This is referred to as the gliogenic phase. The potential of the NSC pool reduces over time during development. This does not exclude that multiple restricted stem cells become activated and are lost at different times during cortical development. BPs indicate basal progenitors; IZ, intermediate zone; NBNs, newborn neurons; NSCs, neural stem cells; SVZ, subventricular zone; VZ, ventricular zone.

Mukhtar and Taylor, 2018

Malformations of Cortical Development

- 23-26% of intractable epilepsies in children and young adults (*Neurology* 1993; 43:681-687, *Ann Neurol* 1998; 44:740-748, *Acta Neuropathol* 1992; 83:246-259, *Arch Pathol Lab Med* 2000; 124:545-549, *Epileptic Disord* 2002; 4:99-119)
- Mutations
  - Stem cell production
  - Radial glial fascicle development
  - Neuronal migration
  - Ability to disengage from radial glial fascicle and organize
- Destructive events
  - Infection
  - Ischemia
- Exogenous/ endogenous toxins
  - Drugs/ alcohol
  - Metabolic disorders (PDH deficiency, NKH)

FCD and epileptogenesis

- Altered cell morphology
- Altered synaptic connectivity/ disrupted cytoarchitecture
- Changes in ion channel or neurotransmitter receptor expression

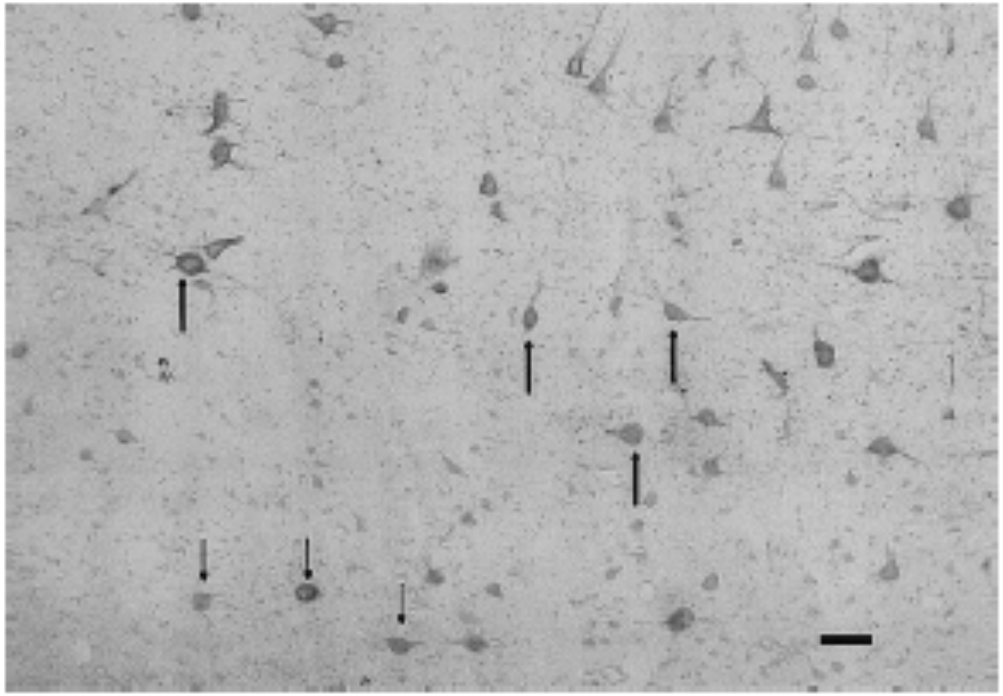
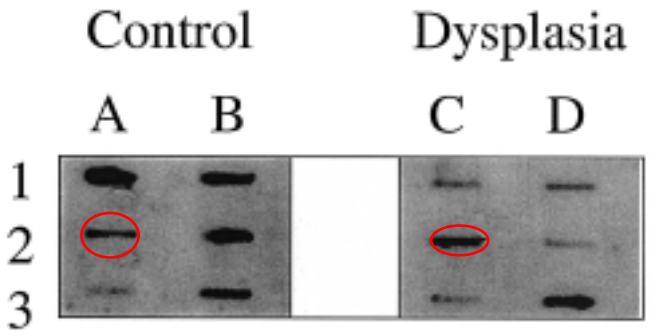


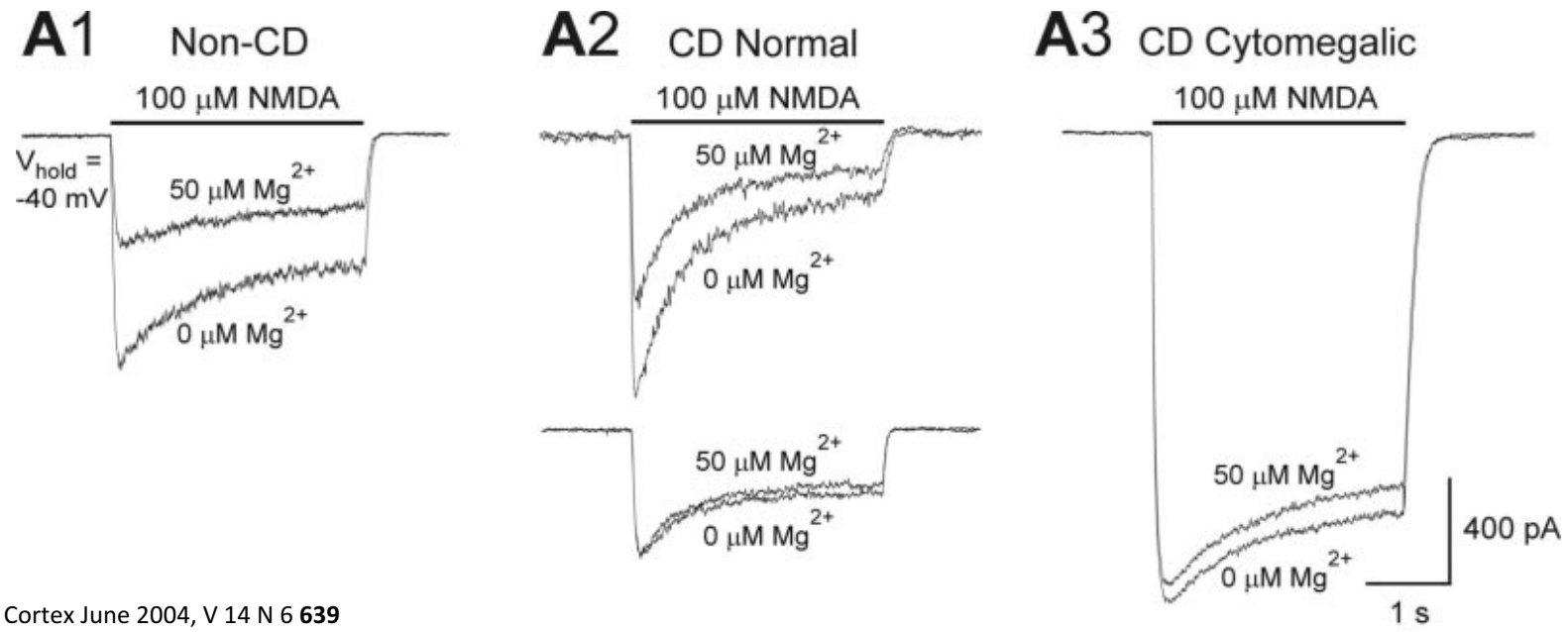
Figure 1. Focal cortical dysplasia specimen immunolabeled with the NeuN antibody. Note large dysplastic neurons (upward arrows) exhibiting disorganized radial and laminar organization, and heterotopic neurons (downward arrows) within the subjacent subcortical white matter. Bar = 150 μm.

NEUROLOGY 2001;56:906–913



A1	$GABA_A$ α1	C1
B1	$GABA_A$ α2	D1
A2	GluR4	C2
B2	$GABA_A$ β1	D2
A3	PBS	C3
B3	α internexin	D3

Figure 4. Representative reverse Northern blots probed with amplified messenger RNA (aRNA) from single control or dysplastic neuron. Note different hybridization intensities to individual complementary DNA (cDNA) on the blot. Compare background hybridization to pBlueScript (slot A3 and C3) to the high-abundance messenger RNA γ-aminobutyric acid A receptor β1 ($GABA_AR\beta_1$) (slot B2). Hybridization to α-internexin cDNA (slots B3 and D3) confirm the neural phenotype of the assayed cells. Legend below blot identifies glutamate receptor (GluR) and $GABA_AR$ cDNA in each slot.



Epidemiology

- Proportion of incident epilepsy cases with brain tumors – 4-6%[1, 2]

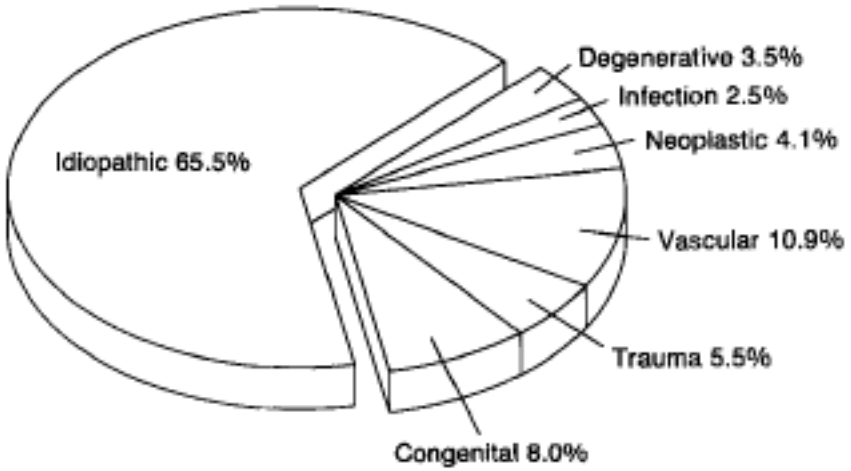


FIG. 2. Proportion of incidence cases (1935–1984) by etiology of epilepsy (all ages).

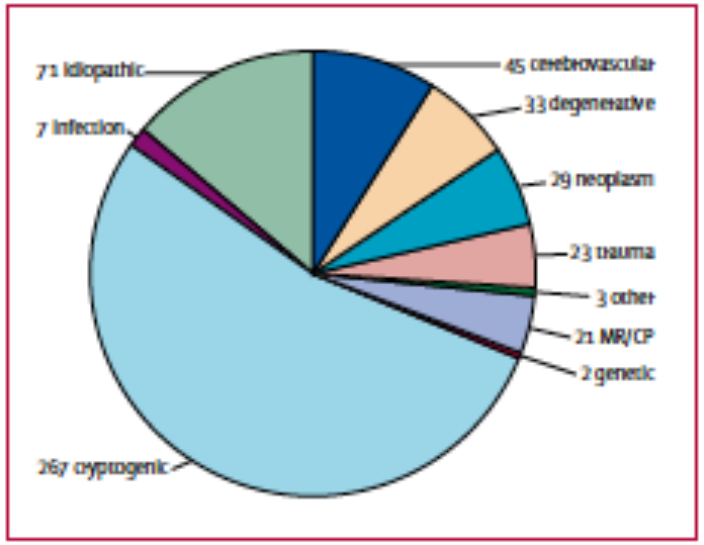


Figure 3: Distribution of causes of and risk factors for all (501) unprovoked seizures in Iceland from 1995 to 1999
MR/CP=mental retardation/cerebral palsy.

1. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993, 34: 453-68.
2. Olafsson E, Ludvigsson P, Gudmundsson G, et al. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol 2005, 4: 627-34.

Etiology according to age

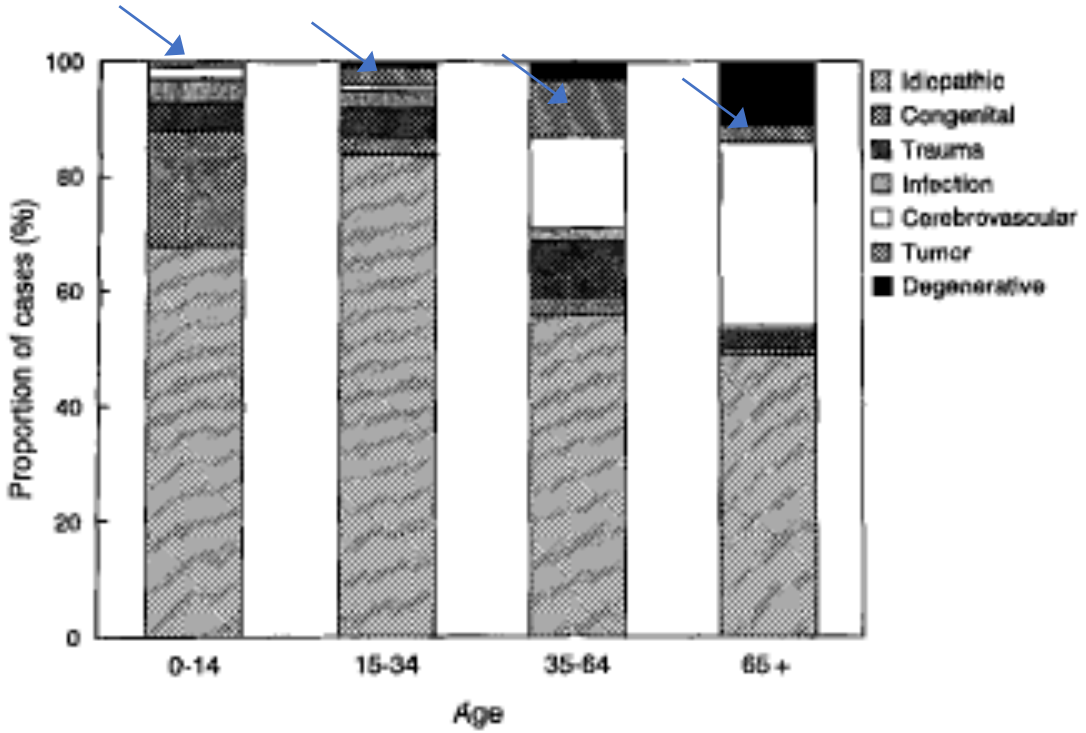


FIG. 10. Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories within age groups, including idiopathic/cryptogenic category. Area: idiopathic (gray cross-hatched), congenital (dashed), trauma (dotted), trauma (widely dotted), infection (hatched), cerebrovascular (closely dotted), tumor (black), degenerative (light cross-hatch).

Seizure frequency according to tumor type

	Seizure frequency
Dysembryoblastic neuroepithelial tumour[5,11]	100%
Ganglioglioma[5,12]	80–90%
Low-grade astrocytoma[12,13]	75%
Meningioma[5,12]	29–60%
Glioblastoma multiforme[5,13]	29–49%
Metastasis[5,12]	20–35%
Leptomeningeal tumour[24,25]	10–15%
Primary CNS lymphoma[14]	10%

Table 1: **Association between tumour type and seizure frequency**

Van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 2007, 6: 421-30.

Seizure frequency according to tumor location

- Supratentorial 22-68% vs. infratentorial 6%
- Superficial/ cortical 63% vs. non-cortical/ deep 29%
- Parietal, temporal, frontal > occipital
- Increased seizure incidence with proximity to rolandic fissure

1. Recht LD, Glantz M. Neoplastic diseases. In: Engel J, Pedley TA, eds. Epilepsy: A Comprehensive Textbook. Philadelphia: Lippincott-Raven, 1998: 2579-85 (vol 3).
2. Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors: A retrospective review. ClinNeurolNeurosurg 2007, 109: 634-8.

Epileptogenesis

- Lesions are often electrically inert; epileptogenic activity probably arises from perilesional tissue
- Mirror focus – actively discharging epileptiform region may induce similar activity in a homologous site

1. Wolf HK, Roos D, Blumcke I, et al. Perilesionalneurochemical changes in focal epilepsies. ActaNeuropathol 1996, 91: 376-84.
2. Gilmore R, Morris H 3rd, Van Ness PC, Gilmore-Pollak W, Estes M. Mirror focus: function of seizure frequency and influence on outcome after surgery. Epilepsia 1994, 35: 258-63.

DNETs

- First described as a distinct entity in 1988
- Supratentorial, cortical
- Multinodular architecture
- Presence of neurons (mixture of glial and neuronal elements)
- Components resembling astrocytoma, oligodendroglioma, or oligoastrocytoma
- Columnar structure oriented perpendicular to cortical surface
- MRI – ↓T1, ↑T2; variable patchy enhancement; variable adjacent skull molding

1. Daumas-Duport C. Dysembryoplasticneuroepithelialtumours. Brain Pathol 1993, 3: 283-295.

DNET

- Usually intracortical, temporal
- Often presents with childhood-onset epilepsy
- May be associated with peritumoral changes (hypercellularity, satellite nodules) and other pathology (HS, FCD)

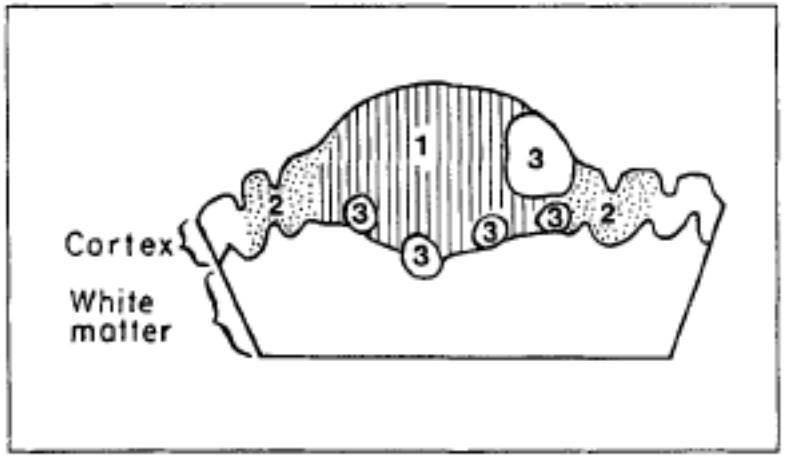


Figure 4 Schematic representation of complex form of DNTs. 1, Specific glioneuronal element; 2, Cortical dysplasia; 3, Glial nodules. Reproduced with permission from *Neursurgery* 23: 545-556, 1988, reference 2.

1. Daumas-Duport C. Dysembryoplasticneuroepithelialtumours. Brain Pathol 1993, 3: 283-295.
2. Burneo JG, Tellez-Zenteno J, Steven DA, et al. Adult-onset epilepsy associated with dysembryoplasticneuroepithelial tumors. Seizure 2008, 17: 498-504.
3. Thom M, Toma A, An S, et al. One hundred and one dysembryoplasticneuroepithelial tumors: An adult epilepsy series with immunohistochemical, molecular genetic, and clinical correlations and a review of the literature. J Neuropathol Exp Neurol 2011, 70: 859-878.
4. Takahasi A, Hong SC, Seo DW, et al. Frequent association of cortical dysplasia in dysembryoplasticneuroepithelial tumor treated by epilepsy surgery. SurgNeurol 2005, 64: 419-427.

EEG in patients with DNET

- MEG demonstrated spike-dipoles in a marginal area surrounding the lesion or a distant area of cortex in the same lobe
- Scalp EEG is not always focal or concordant with the lesion
- Intracranial recording is often employed to find the epileptogenic lesion

Table 1 Demographic and clinical characteristics

Characteristics	
Number of patients	23
Demographics	
Mean age (range)	33.4 (5–56)
Male:female ratio	1.1
Age at seizure onset (range)	17.4 (1–43)
Seizure type, *n* (%)	
Simple partial	13 (57)
Complex partial	21 (91)
Secondary generalization	16 (70)
Tumor location (based on MRI), *n* (%)	
Temporal	18 (86)
Frontal	4 (17)[a]
Parietal	2 (9)
EEG, *n* (%)	
Congruent interictal EEG	13 (57)
Congruent ictal EEG	17 (85)
Intracranial EEG	5
Seizure free after surgery, *n* (%)	
Engel I	17 (85)
Engel II	2 (9)
Engel III/IV	2 (9)
Information not available	2 (9)

[a] One patient counted twice because of overlapping frontal–temporal location.

1. Fukao K, Watanabe Y, Shiraishi H, et al. Magnetoencephalographic findings on patients having symptomatic localization-related epilepsy with dysembryoplasticneuroepithelial tumor as the epileptogenic lesion. Epilepsia 2000, 41 (Suppl 9): 61-2.
2. Burneo JG, Tellez-Zenteno J, Steven DA, et al. Adult-onset epilepsy associated with dysembryoplasticneuroepithelial tumors. Seizure 2008, 17: 498-504.
3. Lee MC, Kang JY, Seol MB, et al. Clinical features and epileptogenesis of dysembryoplasticneuroepithelial tumor. Childs NervSyst 2006, 22: 1611-8.

Objectives

- Examine the cellular basis of neurophysiology
- Describe how cellular events contribute to EEG signal
- Recognize pathology and pathophysiology of different types of epilepsy
- Illuminate different pathways of epileptogenesis and corresponding clinical evidence