4ª. ESCOLA LATINO-AMERICANA DE VERÃO DE EPILEPSIA
4ª. ESCUELA LATINO-AMERICANA DE VERANO DE EPILEPSIA
4th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 1-10 DE FEVEREIRO DE 2010
Centro de Convenções Santa Mônica

COORDENAÇÃO GERAL: Prof. Dr. Esper A. Cavalheiro

REPRESENTANTE LATINO-AMERICANA NA COMISSÃO DE EDUCAÇÃO DA INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE):
Profa Dra Elza Márcia Yacubian – Universidade Federal de São Paulo

PRESIDENTE DA LIGA BRASILEIRA DE EPILEPSIA (LBE):
Prof. Dr. Wagner Teixeira – Hospital de Base, Brasília, DF

PRESIDENTE DA ILAE: Prof. Dr. Solomon Moshé - Albert Einstein College of Medicine - New York, USA

GERENTE EXECUTIVO DA ACADEMIA LATINO-AMERICANA DE EPILEPSIA (ALADE):
Prof. Dr. Fulvio Alexandre Scorza – Universidade Federal de São Paulo

COMISSÃO ORGANIZADORA:
Américo Sakamoto – USP-Ribeirão Preto
Elza Márcia Yacubian - UNIFESP
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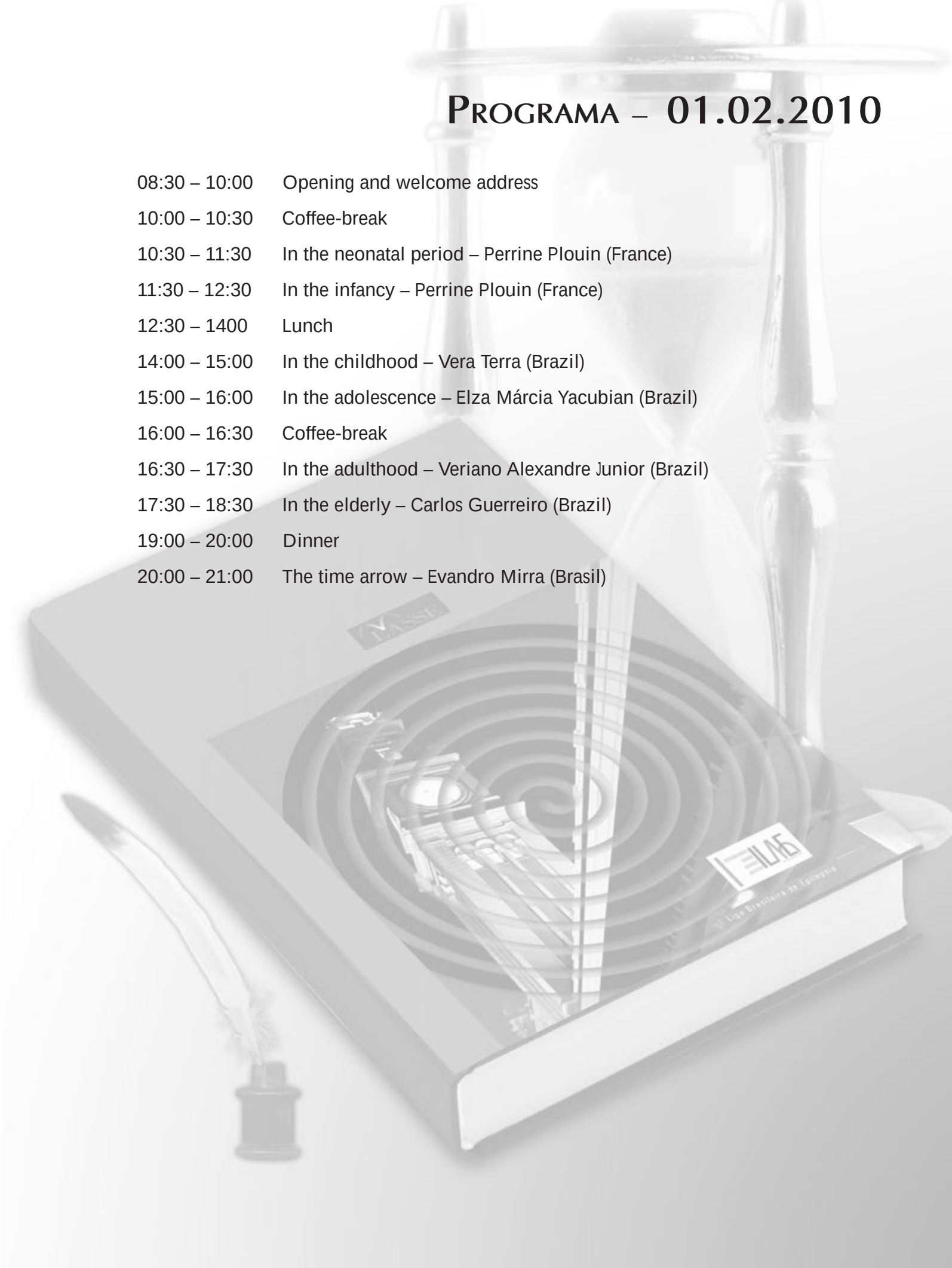
João Pereira Leite – USP-Ribeirão Preto
Luiz Eugênio Mello – UNIFESP
Marly de Albuquerque - UMC

Epilepsia e Tempo

A IV Escola Latino-Americana de Verão de Epilepsia (LASSE IV) será dedicada à compreensão dos processos ligados à epilepsia de forma sequencial e ordenada, segundo sua evolução temporal. O programa vai dar especial ênfase às alterações moleculares e sistêmicas em seu contexto temporal, de modo a permitir o entendimento dos mecanismos fisiopatológicos subjacentes ao estabelecimento e à evolução das síndromes epilépticas. Em virtude dos eventos temporais se manifestarem de forma contínua ou episódica, será enfatizada a relação desses processos com aqueles ligados mais diretamente com à expressão das crises epilépticas ou às características da epilepsia ao longo da vida. Assim, as aulas irão direcionar-se aos fenômenos relacionados ao desenvolvimento, à maturação e ao envelhecimento do sistema nervoso central e aos ritmos que governam a vida e sua influência sobre os mecanismos icto e epileptogênicos, tais como o ciclo vigília-sono e outros processos de regulação circadiana ou sazonal.

Programa – 01.02.2010

08:30 – 10:00	Opening and welcome address
10:00 – 10:30	Coffee-break
10:30 – 11:30	In the neonatal period – Perrine Plouin (France)
11:30 – 12:30	In the infancy – Perrine Plouin (France)
12:30 – 1400	Lunch
14:00 – 15:00	In the childhood – Vera Terra (Brazil)
15:00 – 16:00	In the adolescence – Elza Márcia Yacubian (Brazil)
16:00 – 16:30	Coffee-break
16:30 – 17:30	In the adulthood – Veriano Alexandre Junior (Brazil)
17:30 – 18:30	In the elderly – Carlos Guerreiro (Brazil)
19:00 – 20:00	Dinner
20:00 – 21:00	The time arrow – Evandro Mirra (Brasil)



In the neonatal period / In the infancy
Perrine Plouin (France)

Epileptic seizures in newborns and infants

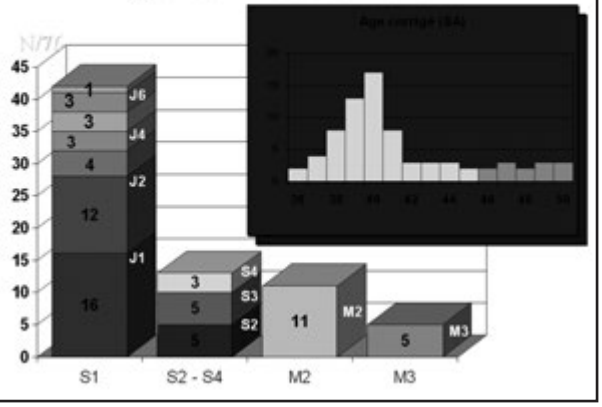
Perrine Plouin
Hôpital Necker Enfants Malades, Paris

SVP patients (E.Raffo, 2003)

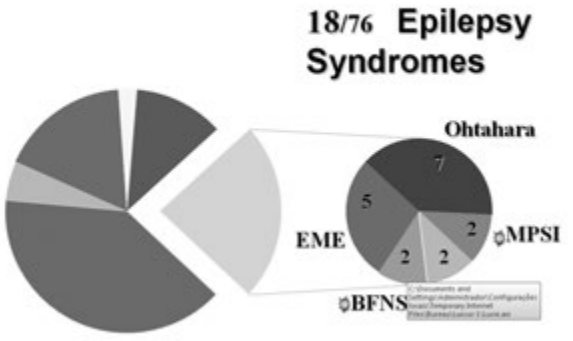
- 1994 - 2001
- Neonatal seizures ?
- Video EEG > 3 hours
- 90 cases

- Follow-up 6 months

Age at first seizure



Neonatal seizures in neuropediatry

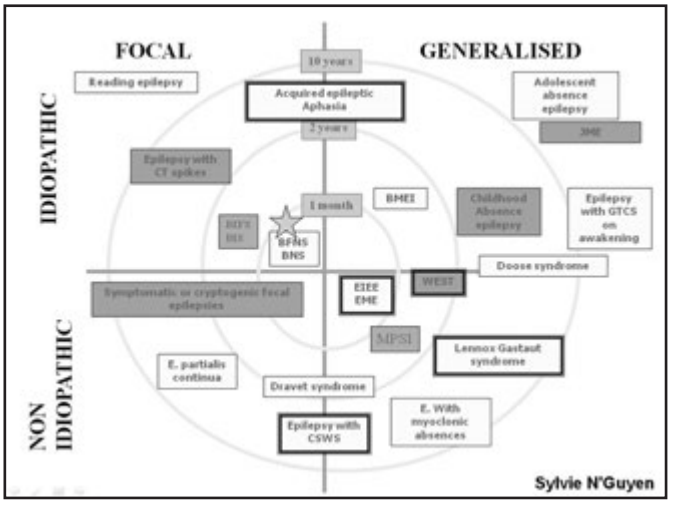


Criteria for evaluating epilepsy syndromes

1. Epileptic seizure type
2. Age of onset
3. Progressive nature
4. Interictal EEG
5. Associated interictal signs and symptoms
6. Pathophysiologic mechanisms, anatomical substrates, and etiologies
7. Genetic basis

Epileptic seizure type

- Focal seizures, clonic, tonic
- Myoclonic seizures focal, segmentary, generalized
- Epileptic spasms



Benign Familial Neonatal Seizures

- Rett & Teubel (1964) reported the first BFNS family, with 8 cases over 3 generations.
- On the third day of life the male proband developed an **initial tonic phase with cyanosis followed by clonic movements of the whole body including the face and eye muscles,** and he had 15-20 seizure events on the following day.
- A brother born 16 months later had a similar experience.
- Several normal interictal EEGs were reported for these two boys and single EEGs for three other affected relatives.
- The authors noted the familial history, the normality of the interictal EEG and the favorable outcome.

Benign Familial Neonatal Seizures

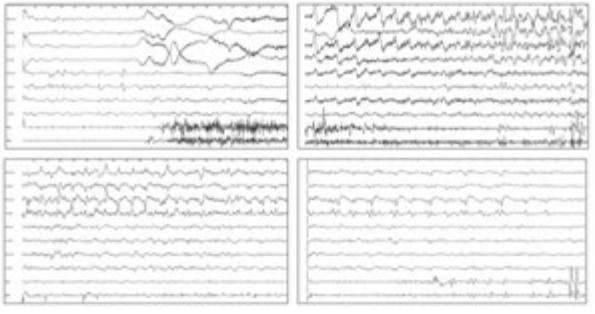
- Incidence estimated as 14.4 /100.000 live births (Ronen et al, 1993)
- 44 reported families, 355 cases
- Onset on D2 and D3 (80% of cases)
- Normal neurological examination
- Normal interictal EEG
- Normal biological work up
- **Positive familial history**
- Treatment selection?

Benign Familial Neonatal Seizures

- All seizures start with a tonic component, uni or bilateral, but assymetrical, changing side from one seizure to the next in a given baby
- Autonomic, oculofacial features and/or clonic movements follow
- Duration is around one minute
- Ronen et al, 1993, Hirsch et al, 1993, Bye 1994, Plouin and Anderson, 2002

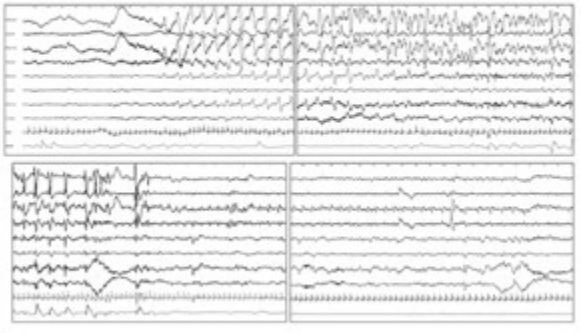
No myoclonic sz, no epileptic spasm, no GTCSz

BFNS Seizure



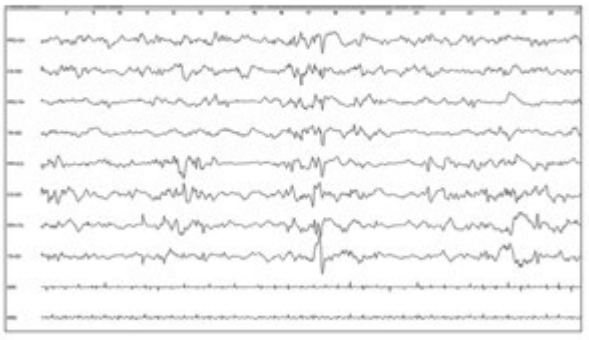
ELG…D8 SVP

BFNS Seizure



DEL…Maxime 4 days NEM

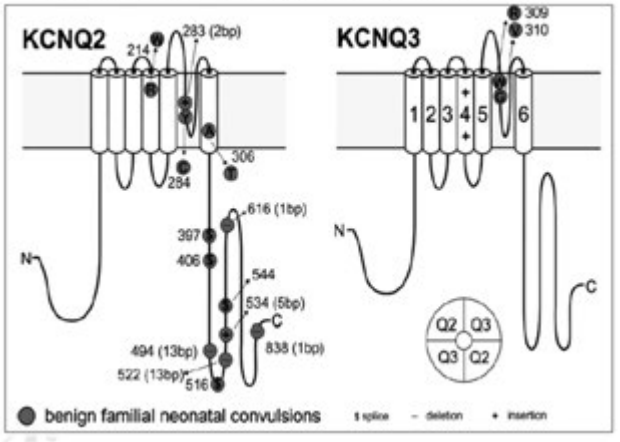
BFNS interictal sleep



BFNS genetics

Syndrome		Gene
name	locus	name
EBN 1	20q13.3	KCNQ2
EBN 2	8q24	KCNQ3

Mutations in genes *KCNQ2* and *KCNQ3* in BFNS



Recent data

- New families have been reported with
  - Association of Infantile seizures and BECT (Singh et al, 2003)
  - Association with CT spikes at age 3 years (Coppola et al,2003)
  - Resistant seizures from birth (Dedeck et al, 2003, Borgatti et al, Tang et al, 2004)
  - Association of other epilepsy syndromes (Pereira et al, 2004)

- **A novel mutation of KCNQ3 gene in a Chinese family with benign familial neonatal convulsions.**
  - Li H, Li N, Shen L, Jiang H, Yang Q, Song Y, Guo J, Xia K, Pan Q, Tang B.
  - Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, PR China. : Epilepsy Res. 2008 Mar;79(1):1-5.
  - Benign familial neonatal convulsions (BFNC, also named benign familial neonatal seizures, BFNS) is a rare autosomal dominant inherited epilepsy syndrome with clinical and genetic heterogeneity. Two voltage-gated potassium channel subunit genes, KCNQ2 and KCNQ3, have been identified to cause BFNC1 and BFNC2, respectively. To date, only three mutations of KCNQ3, all located within exon 5, have been reported. By limited linkage analysis and mutation analysis of KCNQ3 in a Chinese family with BFNC, we identified a novel missense mutation of KCNQ3, c.988C>T located within exon 6. c.988C>T led to the substitution Cys for Arg in amino acid position 330 (p.R330C) in KCNQ3 potassium channel, which possibly impaired the neuronal M-current and altered neuronal excitability. Seizures of all BFNC patients started from day 2 to 3 after birth and remitted during 1 month, and no recurrence was found. One family member who displayed fever-associated seizures for two times at age 5 years and was diagnosed as febrile seizures, however, did not carry this mutation, which suggests that febrile seizures and BFNC have different pathogenesis. To our knowledge, this is the first report of KCNQ3 mutation in Chinese family with BFNC.

- **A novel missense mutation (N258S) in the KCNQ2 gene in a Turkish family afflicted with benign familial neonatal convulsions (BFNC).**
  - Yalçin O, Cağlayan SH, Saltik S, Cokar O, Ağan K, Dervent A, Steinlein OK.
  - Department of Molecular Biology and Genetics, Boğaziçi University, Istanbul, Turkey.
  - Turk J Pediatr. 2007 Oct-Dec;49(4):385-9
  - Benign familial neonatal convulsions (BFNC) is a rare monogenic subtype of idiopathic epilepsy exhibiting autosomal dominant mode of inheritance. The disease is caused by mutations in the two homologous genes KCNQ2 and KCNQ3 that encode the subunits of the voltage-gated potassium channel. Most KCNQ2 mutations are found in the pore region and the cytoplasmic C domain. These mutations are either deletions/insertions that result in frameshift or truncation of the protein product, splice-site variants or missense mutations. This study reveals a novel missense mutation (N258S) in the KCNQ2 gene between the S5 domain and the pore of the potassium channel in two BFNC patients in a Turkish family. The absence of the mutation both in the healthy members of the family and in a control group, and the lack of any other change in the KCNQ2 gene of the patients indicate that N258S substitution is a pathogenic mutation leading to epileptic seizures in this family.

Infantile seizures and other epileptic phenotypes in a Chinese family with a missense mutation of KCNQ2

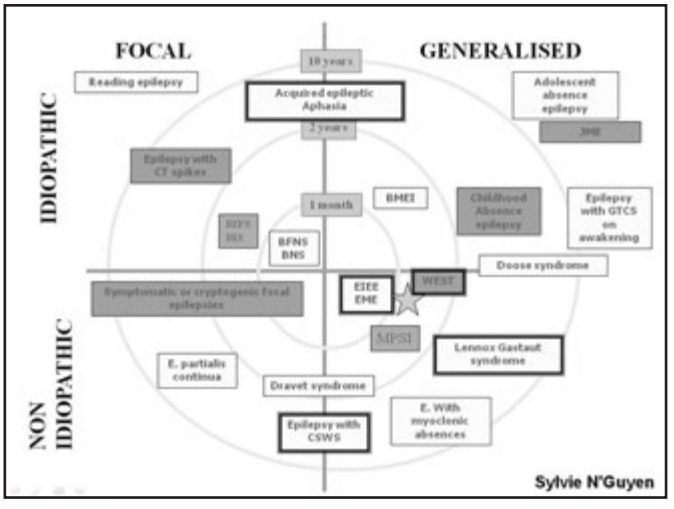
Zhou X, Ma A, Liu X, Huang C, Zhang Y, Shi R, Mao S, Geng T, Li S

A large Chinese family in which all 17 affected members had had infantile seizures with onset at age 2-4 months,.

Linkage analysis in this family confirmed a previous report of genetic heterogeneity in BFIS - since linkage was excluded at the above-mentioned known BFIS loci - and suggested a possible linkage to the KCNQ2 gene, which is believed to be a voltage gated potassium channel gene responsible for BFNS.

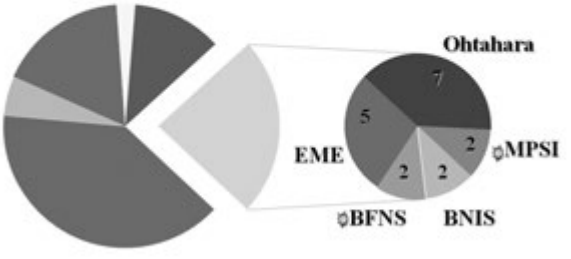
- Sequencing of the KCNQ2 gene revealed that all 17 affected family members carried a heterozygous Gly-to-Val (G271V) mutation in the conserved pore region that resulted from a guanine-to-thymine transition in exon 5 of KCNQ2. **The same mutation with a comparable localization in the KCNQ3 (G310V) gene has been found in BFNS patients.** The same conserved amino acid was also found to be mutated in the KCNQ1 gene in a family with Long QT Syndrome.

Eur J Pediatr. 2006 May 12



Neonatal seizures in neuropediatry

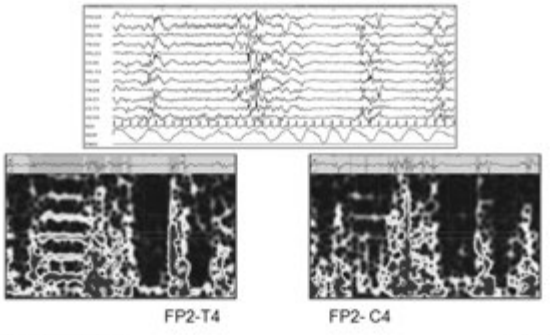
18/76 Epilepsy Syndromes



Neonatal epileptic encephalopathies with Suppression-Burst pattern

- complex bursts of spikes and irregular, arrhythmical sharp waves and slow waves lasting from 1 to 5 seconds and alternating with flat periods of 3 to 10 seconds.The complex burst can occur either synchronously or independently in the two hemispheres
- the normal background activity is absent.
- there may be no difference between wakeness and sleep
- Hidden focal sz during suppressions…(Al Futaisi et al, 2005)

Neonatal epileptic encephalopathy



GHE… Ilhane D11 NEM

Early Myoclonic Encephalopathy: EME « Neonatal myoclonic encephalopathy »

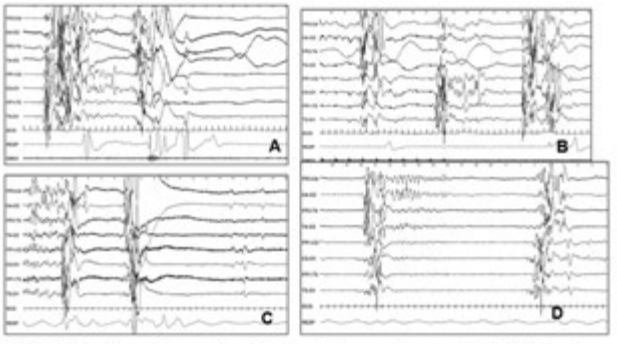
Aicardi and Goutieres, 1978

- Massive myoclonic sz, erratic myoclonia, focal seizures
- Onset before D28
- Abnormal neurological exam
- Suppression Bursts EEG pattern
- Normal work up
- Possible familial history
- Treatment selection?

EME: outcome

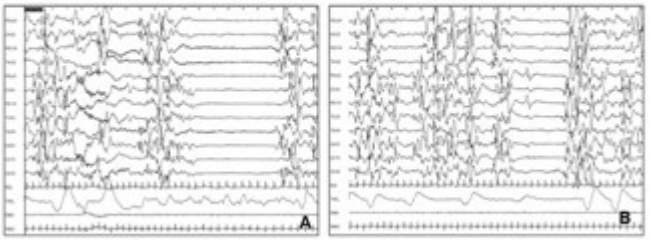
- 50% of death before the age of 2 years was already reported in the first publication, with no normal outcome in the other 50%
- Since 1990 20 cases have been reported, half of them died before the age of one year

Early Myoclonic Encephalopathy
suppression burst pattern



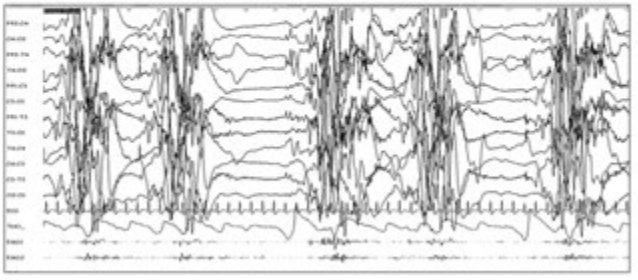
NOE…Geoffrey 1 month A, B: wakeness; C: myoclonic jerk D: sleep

Early Myoclonic Encephalopathy
suppression burst pattern



NOE…Geoffrey 3 months A: wakeness; **B** : sleep

Early Myoclonic Encephalopathy



CHA…Merva 15 days NEM

Impaired Mitochondrial Glutamate Transport in Autosomal Recessive Neonatal Myoclonic Epilepsy Am J Hum Genet. February 2005; 76(2): 334–339.

Florence Molinari, Annick Raas-Rothschild, Marlène Rio, Giuseppe Fiermonte, Ferechté Encha-Razavi, Luigi Palmieri, Ferdinando Palmieri, Ziva Ben-Neriah, Noman Kadhom, Michel Vekemans, Tania Attié-Bitach, Arnold Munnich, Pierre Rustin, and Laurence Colleaux

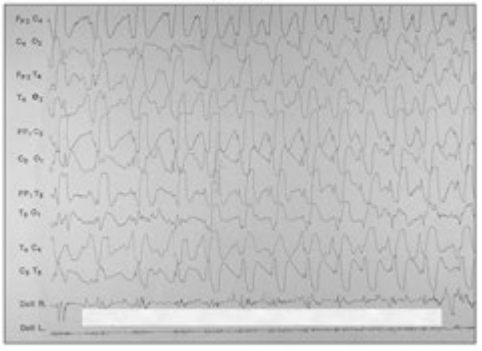
- Here, we report the genetic mapping of an autosomal recessive form of EME on to chromosome 11p15.5 and the identification of a missense mutation (p.Pro206Leu) in the gene encoding one of the two mitochondrial glutamate/H+ symporters (*SLC25A22*, also known as "*GC1*").
- **Moreover, expression studies showed that, during human development, *SLC25A22* is specifically expressed in the brain, within territories proposed to contribute to the genesis and control of myoclonic seizures.**
- These findings provide the first direct molecular link between glutamate mitochondrial metabolism and myoclonic epilepsy and suggest potential insights into the pathophysiological bases of severe neonatal epilepsies with suppression-burst pattern

PYRIDOXINO DEPENDANCY

- Myoclonic fits, epileptic spasms, focal seizures
- Onset from firsts days of life
- Hyperexcitability
- Abnormal EEG patterns
- Normal Work up
- Possible familial history
- Specific treatment

Vit B6 dependency

interictal



PER…Nicolas 1 month

Glycine encephalopathy

Nonketotic Hyperglycinemia

- initial symptom-free interval of 1 to 42 days.
- lethargy, poor feeding, apneic spells, altered muscular tone, and intermittent ophthalmoparesis
- Segmental **myoclonic jerks**, hiccups, and coma follow.. **axial myoclonia,** infantile spasms and focal seizures
- EEG demonstrates **a suppression-burst pattern.**
- **Elevated glycine** concentrations in the cerebrospinal fluid (CSF)

Early Infantile Encephalopathy with Epilepsy: EIEE Ohtahara et al 1976

- Epileptic Spasms, , tonic spasms, focal seizures
- Onset from D1, up to 2 or 3 months
- Abnormal neurological examination
- Suppression-Bursts EEG pattern
- Abnormal findings on Neuro radiology
- No familial history

EIEE: etiology

Malformations, are often found:

- Porencephaly,
- Aicardi syndrome
- cerebral dysgenesis
- olivary-dentate dysplasia
- hemimegalencephaly
- linear sebaceous nevus
- Leigh's encephalopathy
- subacute diffuse encephalopathy
- A few cryptogenic cases have also been reported

EIEE: outcome

- 1982-2004: more than 100 reported cases
- Among 61 cases in 7 series:
  - 23 deaths < age of one year (38%)
  - Severe sequellae among others: severe epilepsy (spasms), hypsarhythmia and mental retardation
- Four children underwent surgery: 2 FCD and 2 hemimegalencephaly with a dramatic improvement on sz

Successful treatment of Ohtahara syndrome with chloral hydrate.

Pediatr Neurol. 2002 Nov;27(5):388-91

Krsek P, Sebronova V, Prochazka T, Maulisova A, Komarek V.

We present a patient with early infantile epileptic encephalopathy with suppression bursts (Ohtahara syndrome) with an excellent response to chloral hydrate to draw attention to a possible role of the "old" drug in the treatment of intractable epilepsy. Chloral hydrate (58 mg/kg/day) was used for a short-term administration in a 5-week-old female with typical features of cryptogenic Ohtahara syndrome after the failure of conventional antiepileptic drugs. Seizures disappeared in the course of 24 hours after the launch of chloral hydrate therapy and have not recurred. Results of electroencephalogram studies of the child demonstrate marked improvement. Psychomotor development is significantly delayed. Detailed diagnostic tests have not revealed any metabolic or structural abnormalities of the brain.

REPORT

A Longer Polyalanine Expansion Mutation in the *ARX* Gene Causes Early Infantile Epileptic Encephalopathy with Suppression-Burst Pattern (Ohtahara Syndrome)

Mitsuhiro Kato, Shinji Saitoh, Atsushi Kamei, Hideaki Shiraishi, Yuki Ueda, Manami Akasaka, Jun Tohyama, Noriyuki Akasaka, and Eiyoshi Hayasaka

Early infantile epileptic encephalopathy with suppression-burst pattern (EIEE) is one of the most severe and earliest forms of epilepsy, often evolving into West syndrome; however, the pathogenesis of EIEE remains unclear. *ARX* is a crucial gene for the development of interneurons in the fetal brain, and a polyalanine expansion mutation of *ARX* causes mental retardation and seizures, including those of West syndrome, in males. We screened the *ARX* mutation and found a hemizygous, de novo, 33-bp duplication in exon 2, 298_330dup(GCGGCA(GCG)$_{10}$), in two of three unrelated male patients with EIEE. This mutation is thought to expand the original 16 alanine residues to 27 alanine residues (A110_A111insAAAAAAAAAAA) in the first polyalanine tract of the ARX protein. Although EIEE is mainly associated with brain malformations, *ARX* is the first gene found to be responsible for idiopathic EIEE. Our observation that EIEE had a longer expansion of the polyalanine tract than is seen in West syndrome is consistent with the findings of earlier onset and more-severe phenotypes in EIEE than in West syndrome.

The American Journal of Human Genetics Volume 81 August 2007

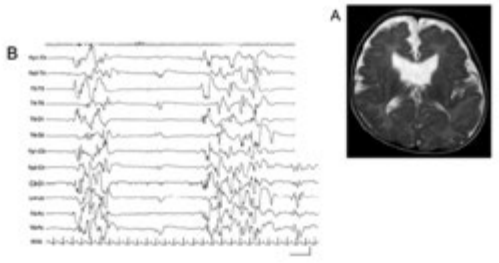
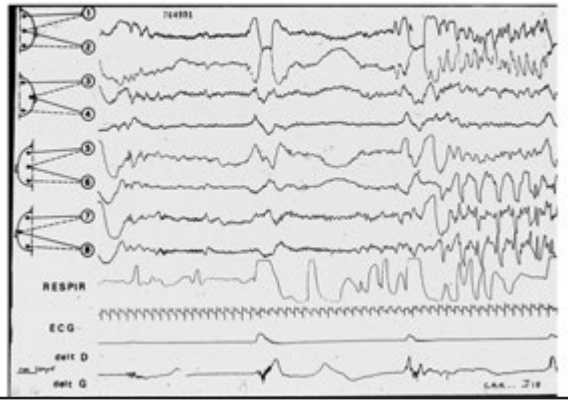
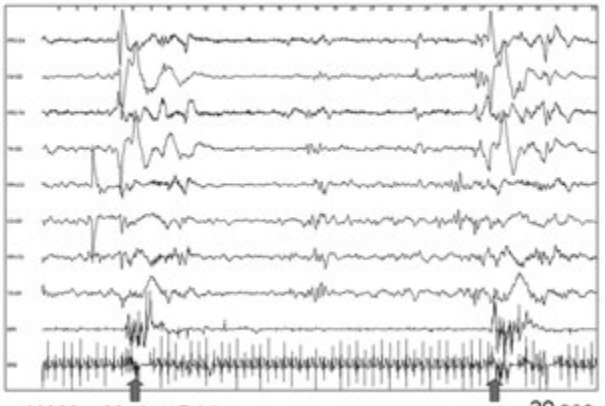


Figure 2. *A*, Brain MRI of patient 1 at the age of 8 Wk shows dilatation of the anterior horns of the lateral ventricles and normal gyri. *B*, Interictal EEG of patient 2 shows a marked depression of background activity, interrupted with eye bursts.

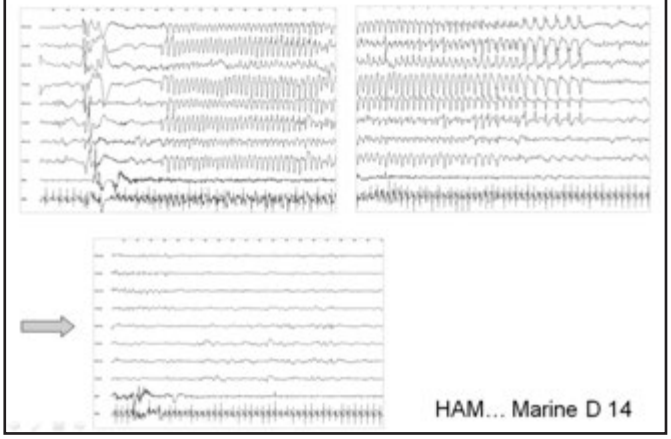
EIEE syndrome d'OHTAHARA



Right frontal Dysplasia: spasms



Right frontal Dysplasia:focal seizure



Neonatal Epilepsy and "SUPPRESSION-BURSTS"

Schlumberger et al 1992

Retrospective study of 23 neonates, 1978-1990

Type of seizures

- erratic myoclonias: 10 cases
- spasms: 8 cases
- focal seizures: 22 cases, with spasms (7), myoclonias (9), or spasms plus myoclonias (2).

Neonatal Epilepsy and "SUPPRESSION-BURSTS"

15 infants could be classified between EME and EIEE

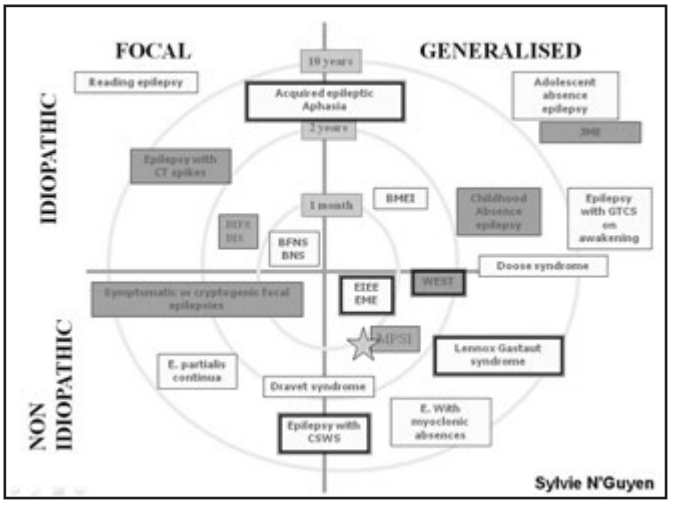
3rd group: 8 unclassified cases

- no evidence of brain malformation
- different from EME

Neonatal Epileptic Encephalopathies and "SUPPRESSION-BURSTS"

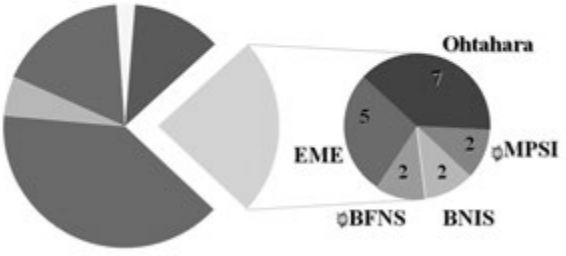
EME and EIEE are two different syndromes. Clinical and EEG data allow to recognize them.

However some neonates with epilepsy and "S-B" EEG cannot be classified among these two syndromes.



Neonatal seizures in neuropediatry

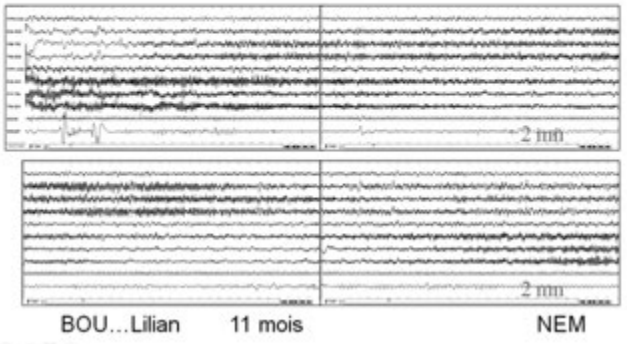
18/76 Epilepsy Syndromes



Infantile epilepsy with migrating partial seizures (Coppola et al 1995) Definition

Nearly continuous activity of focal seizures affecting randomly various parts of both hemispheres, and beginning in early infancy

Migrating Focal Seizures in Infancy



Course

Between 24 days and 10 months (mean 4.5 months), seizures become

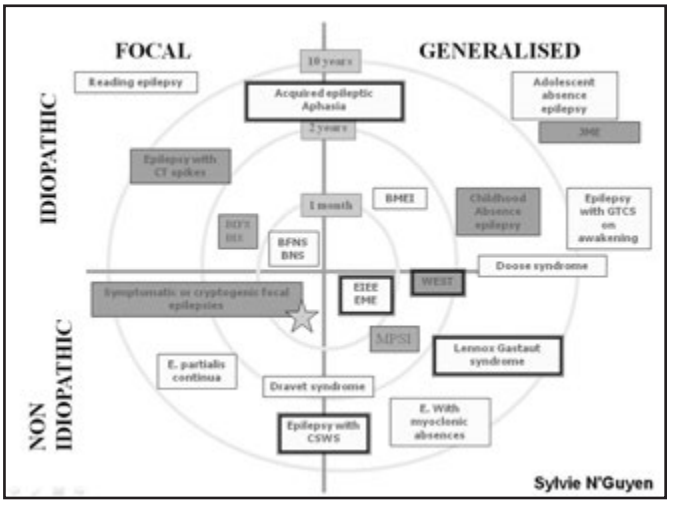
- nearly continuous
- with major deterioration
- alternating with seizure-free periods

Ictal characteristics

- Good clinical/EEG correlation according to topography of the discharge
- Very complex combination of simultaneous focal seizures
- Without video/EEG, seizures are often overlooked
- Seizures can affect a single hemisphere for several months

1995-2005

- 27 cases reported (+ 6 in our population)
- From the most recent cases prognosis seems to be less severe although intractable seizures lasted for months
- Hypotonia and psycho-motor retardation are constant



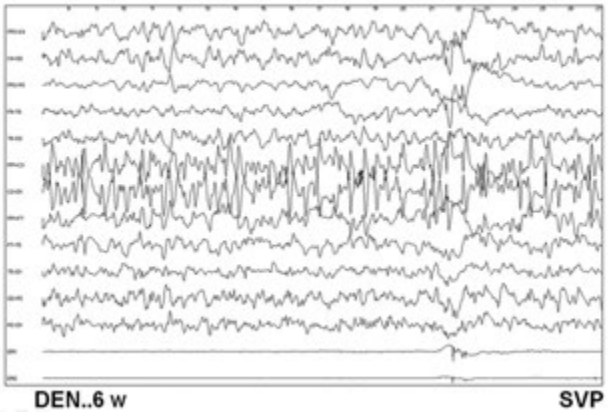
DEN.. Nicolas

- D2 : 1st seizure, upper limbs and head clonic jerks
- D3 : idem, EEG : left central focus of spikes
- CTScan : left hemisphere abnormalities
- PB+VPA : no seizure during 1 month
- M1: reappraisal of seizures : GVB, CBZ, CLB, STP, ketogenic diet :no efficacy
- Normal development, right hemiparesis
- MRI : left temporo-parieto-occipital cortical dysplasia

⇨ Surgery

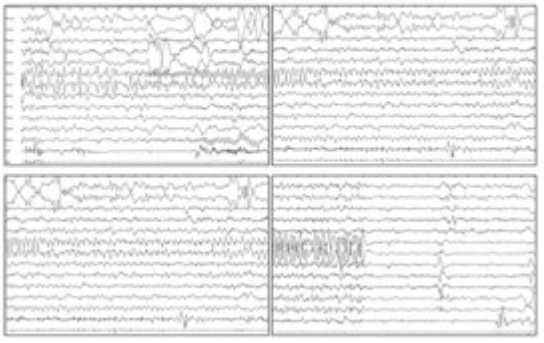
SVP

Left central CD: interictal



DEN..6 w **SVP**

Left central CD: seizure

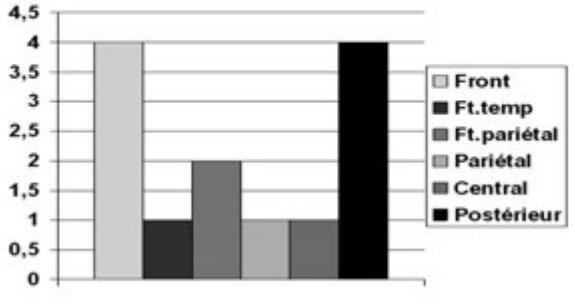


DEN.. 6w SVP

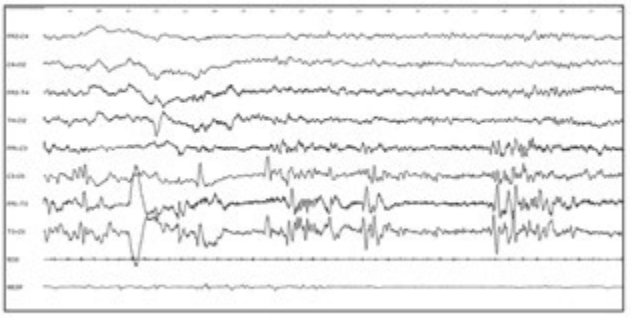
Neonatal epilepsy and FCD (Ville et al)

- Epilepsy :
  - 7: focal seizures associated with spasms
  - 5: focal seizures only
  - 1: no precise data
- Early EEG data in 6 children

  All tracings are asymmetrical, with an interictal lateralized focus of slow waves and spikes

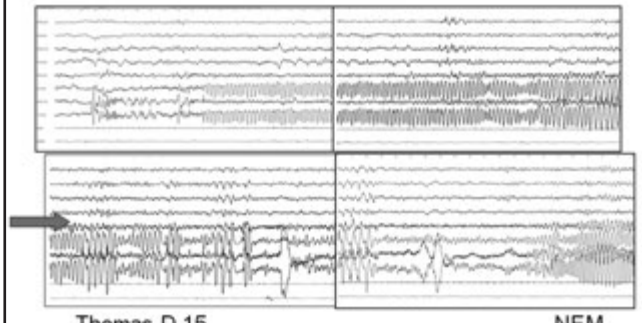


Left Hemimegalencephaly: interictal



Thomas D 15 NEM

Left Hemimegalencephaly: seizure



Thomas D 15 NEM

FULL-LENGTH ORIGINAL RESEARCH

The three stages of epilepsy in patients with *CDKL5* mutations

•†Nadia Bahi-Buisson, ‡‡Anna Kaminska, §aNathalie Boddaert, ¶Mariana Rio, **Alexandra Afenjar, §¶Marion Gérard, ††Fabienne Giuliano, ‡‡‡Jacques Motte, §§Delphine Héron, ¶¶Maria Anga N'Guyen Morel, ‡‡Perrine Plouin, ¤¤Christian Rivalsina, ***Vincent des Portes, *‡‡Olivier Dulac, ‡‡‡Christophe Philippe, *‡‡Catherine Chiron, *‡‡Rima Nabbout, and ‡‡‡Thierry Bienvenu

SUMMARY

Epilepsy syndromes in infancy

(2001: n=11)

- 5 of these syndromes concerning focal epilepsies
  - Idiopathic focal epilepsies
    - benign infantile seizures
    - Panayiotopoulos syndrome
  - Familial focal epilepsies
    - benign familial infantile seizures
  - Focal symptomatic epilepsies
    - HH syndrome
    - Migrating focal seizures in infancy

Epilepsy syndromes in infancy

(2001: n=11)

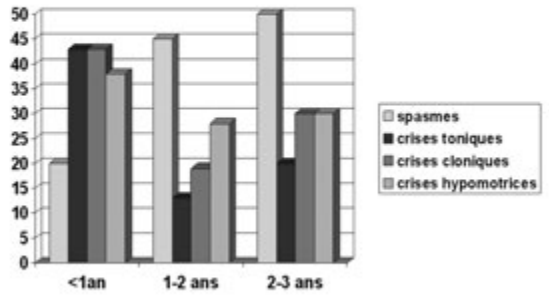
- Idiopathic generalized epilepsies
  - Benign myoclonic epilepsy of infancy (reflex or not)
- Epileptic encephalopathies
  - West syndrome
  - Lennox Gastaut syndrome
  - Dravet syndrome
  - Myoclonic status of non progressives encephalopathies

Seizure types in these epilepsy syndromes of infancy

- **Epileptic spasms**
- Myoclonic seizures
- Focal seizures
- Generalized tonic seizures

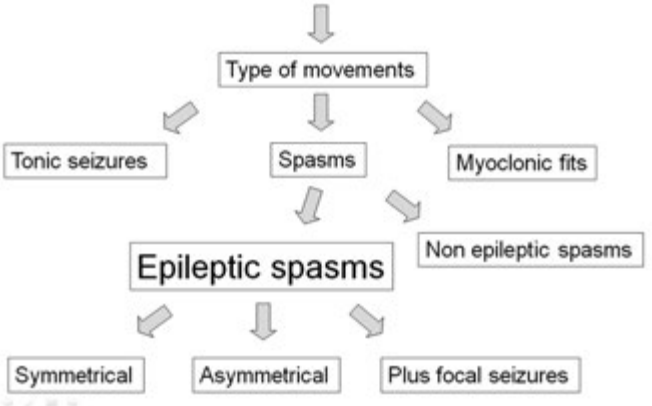
- Generalized tonic clonic seizures
- absences

Seizure types according to age



Hamer et al. 1999

Report of abnormal serial movements in an infant

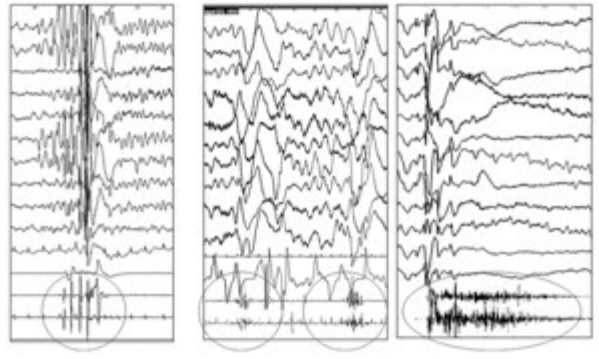


Epileptic spasms

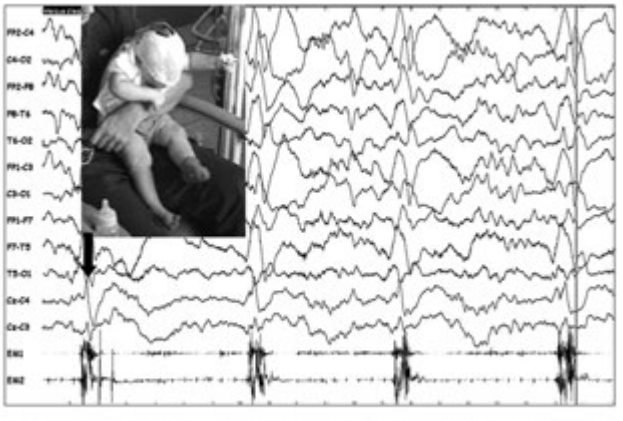
- Epileptic spasms consist of axial contraction that may occur in flexion, extension, or both, and that may be symmetric or asymmetric.
- Asymmetry may involve the upper limbs, head, or eyes, and video recording is often required for detailed analysis.
- The contractions are usually brief and differ from myoclonic and tonic fits.
- They occur in clusters, occasionally combined with a focal discharge.(Dulac)

Epileptic spasms

- The true spasm consists of a characteristic muscular contraction that lasts from 1 to 2 seconds and reaches a peak more slowly than a myoclonic jerk, but more rapidly than a tonic seizure.(Vigevano)



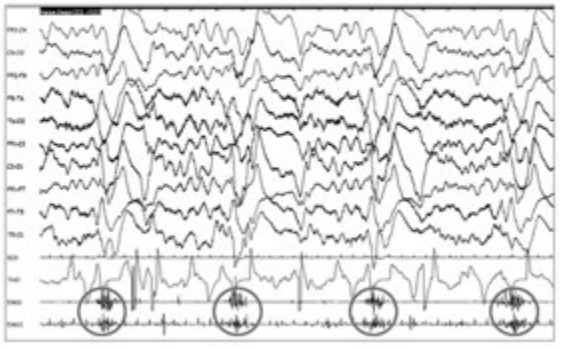
Myoclonia Spasm Tonic seizure



Cluster of epileptic spasms: right and left deltoid surface EMG

Epileptic Spasms

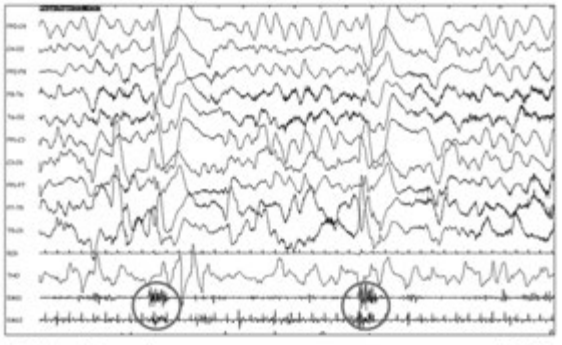
CDG syndrome



DEN… Yvon 1 year NEM

Epileptic Spasms

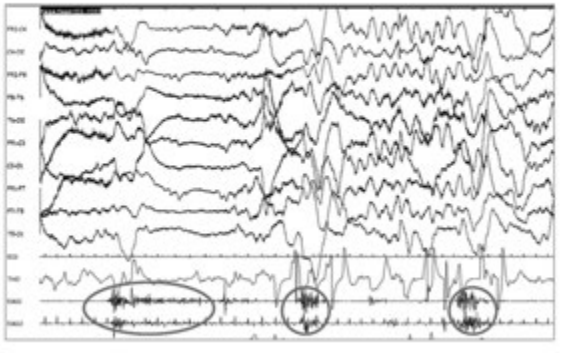
CDG syndrome

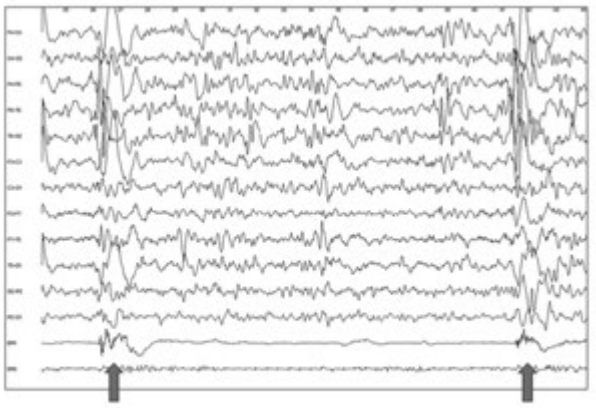


DEN… Yvon 1 year NEM

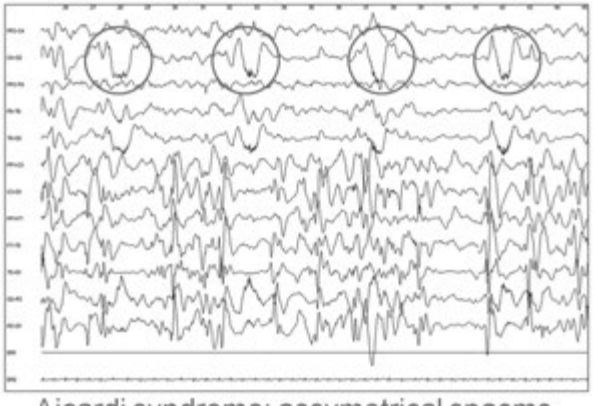
Tonic seizure + ES

CDG syndrome





Asymmetrical epileptic spasms right temporal FCD



Aicardi syndrome: assymetrical spasms

Epileptic Spasms

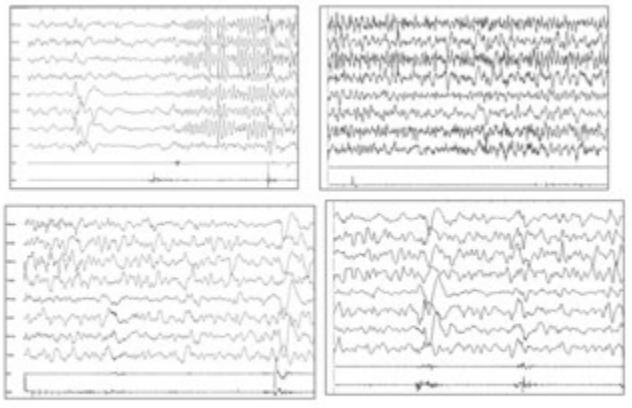
Focal seizure → **cluster of spasms**

Spasm → **focal seizure** → **cluster of spasms**

Cluster of spasms → focal seizure → **cluster of spasms**

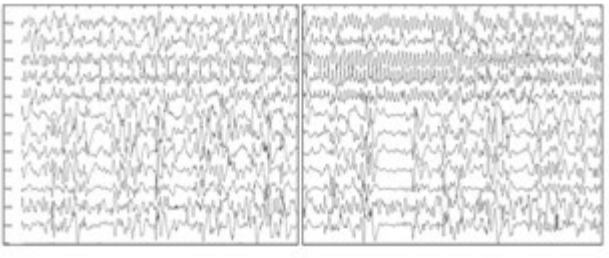
Non concomitant clusters of spasms and **focal seizures**

SVP



Focal seizure followed by a cluster of spasms

Spasms + PS
Agenesis of Corpus Callosum



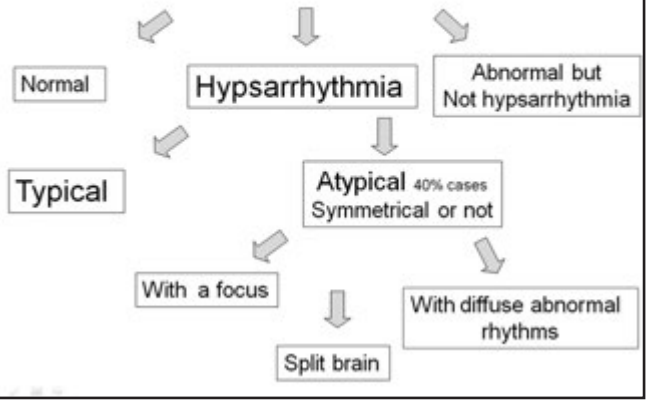
BLA...6 months SVP

West Syndrome

- West syndrome :
  - infantile spasms
  - Hypsarrhythmia
  - Lack of development or regression

  - infantile spasms with a spike focus
  - partial epilepsy +/- hypsarrhythmia

Interictal EEG



Hypsarrhythmia

- random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location... The abnormality is almost continuous, and in most cases it shows as clearly in the waking as in the sleeping record.
- It is referred as hypsarrhythmia (Gibbs and Gibbs, 1952)

Hypsarrhythmia atypical or modified

- Gastaut et al. 1970
  - fragmented awake
  - excessive slowing
  - rapid activity
  - asymmetrical
  - with a focus
- Hrachovy et al. 1984
  - with increased interhemispheric synchronization
  - asymmetrical
  - a consistent focus
  - volt. attenuation
  - with high voltage slow activity

What is important…is

- To recognize and assess the epileptic spasms
- To precize the symetrical or asymetrical type
- To detect associated focal seizures
- To analyze the interictal EEG

- All these data provide documented diagnosis and prognosis tools

Seizure types in infancy

- Epileptic spasms
- Myoclonic seizures
- Focal seizures
- Generalized tonic seizures

- Generalized tonic clonic seizures
- absences

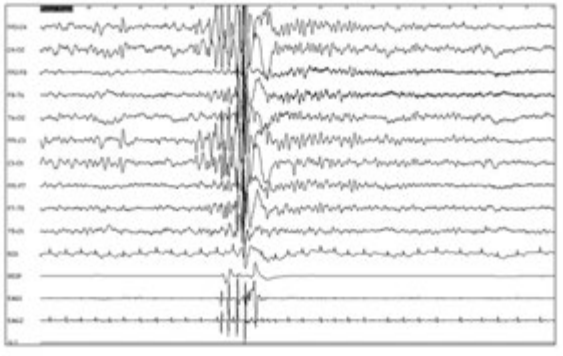
Myoclonic seizures

- Myoclonic seizures (MS) consist of involuntary, quick, arrhythmic movements distinctive of their abrupt, lightninglike character. Muscles most frequently involved are those of the neck, arm, or shoulder. Movements may result in extension or flexion. If the legs are involved, the person may be thrown to the ground.
- Myoclonic seizures can be experienced in a mild or vehement manner, symmetrically or asymmetrically, in the entire body or in regional or localized parts of the body.
- If jerks occur in rapid succession or in the form of a myoclonic status epilepticus, there may be a blurring of awareness.

Epileptic Versus Non epileptic Myoclonia

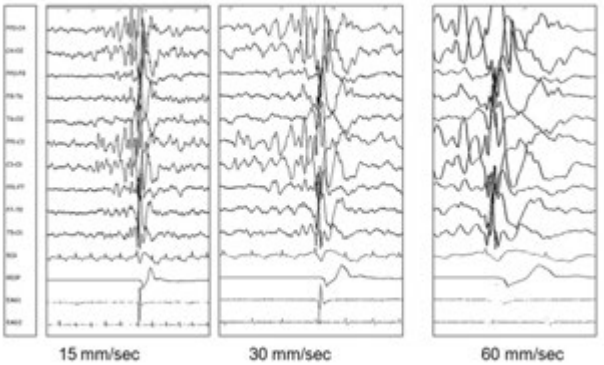
- Phenomenologically, epileptic myoclonia cannot be distinguished from brisk, nonepileptic movements associated with physiologic or pathologic conditions. The classification as epileptic manifestations requires knowledge of the clinical context or electroencephalographic (EEG) correlates.

Myoclonia

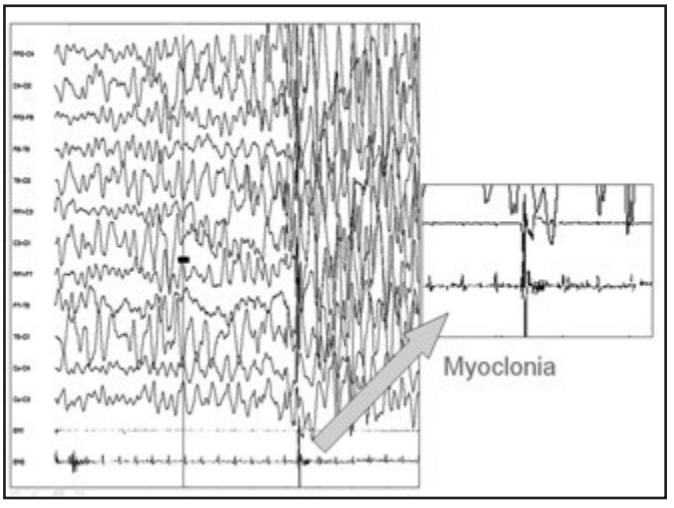


CHA…Yanis 4 ans NEM

Myoclonia recorded on left deltoide surface EMG with a synchronous SW: 3 different speeds



15 mm/sec 30 mm/sec 60 mm/sec



Myoclonic epilepsies in infancy

- Benign myoclonic epilepsy in infancy (reflex or not)
- Dravet syndrome
- Myoclonic status in non progressive encephalopathies: Angelman syndrome
- Menkes disease, mitochondriopathies, ceroid lipofushinosis

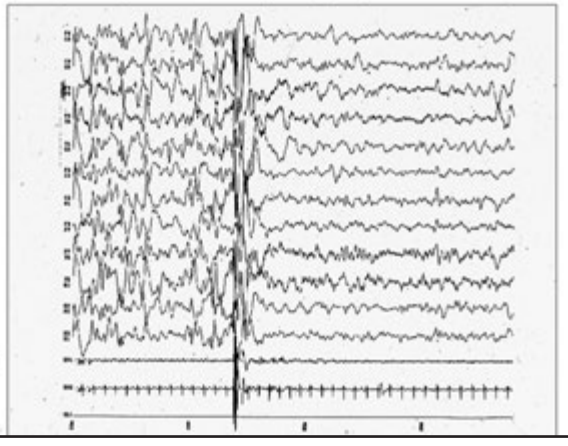
Benign myoclonic epilepsy of infancy

- Myoclonic seizures in this rare syndrome occur during the first or second years of life in normal children who often have a family history of seizures or epilepsy.
- Seizures are characterized by frequent, brief, mostly symmetrical myoclonias isolated or grouped in clusters and involving the axis of the body and the limbs, enhanced by drowsiness.
- The myoclonias represent the only seizure type except for occasional febrile convulsions and rare GTCSs later during adolescence.Generalized tonic seizures or absence seizures are never observed.
- Myoclonic seizures are easily controlled by appropriate medical treatment.

Benign myoclonic epilepsy of infancy

- On EEG, myoclonias are accompanied by a discharge of bilateral spike-waves or polyspike-waves that sometimes occur in rapid succession. The background activity is normal for the child's age, and drowsiness and the early stage of sleep may activate bilateral spike-waves.

Benign myoclonic epilepsy of infancy

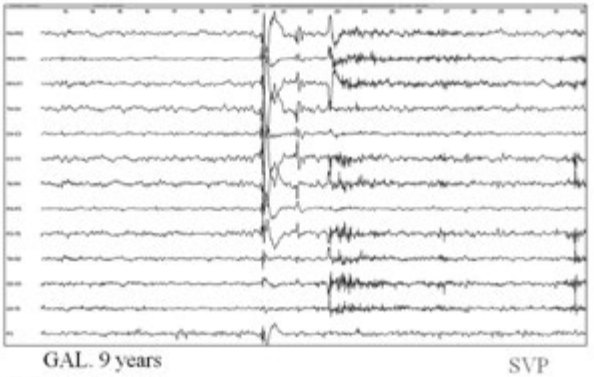


- Isolated or grouped axial-dominant bilateral myoclonias, which may lead to throwing of objects the child is holding and to falling, are typical of the MS of severe myoclonic epilepsy in infancy. These symptoms appear between the ages of 1 and 4 years, most commonly during the second part of the second year of life, and occur very frequently, especially on awakening or in the hours preceding a major seizure. They are associated with frequent, distally predominant erratic myoclonias that exist at rest but increase with movement.

Dravet syndrome

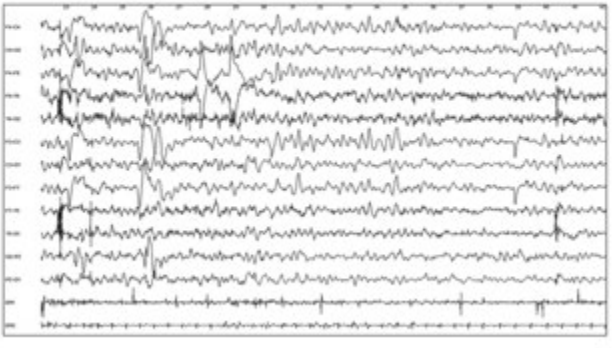
- Normal infant before onset of seizures
- Fébrile seizures or not, uni or bilateral < 1 year of age
- massive myoclonia during 2nd ans 3rd years of life
- normal EEG ---> 2 years (ILS >0)
- Myoclonic status epilepticus
- Progressive deterioration
- Resistant epilepsy

Massive Myoclonia



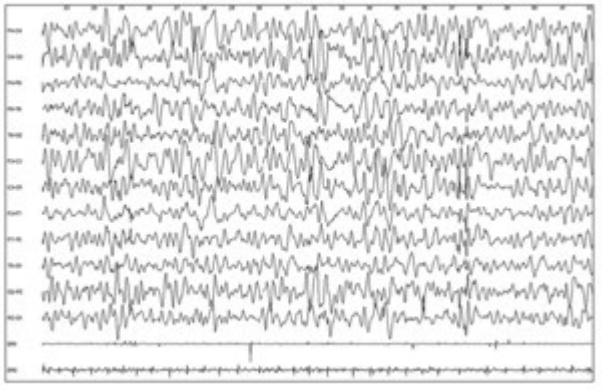
GAL. 9 years SVP

Dravet Syndrome. Myoclonic Status



VIG... 4 y.

Dravet Syndrome. Myoclonic Status

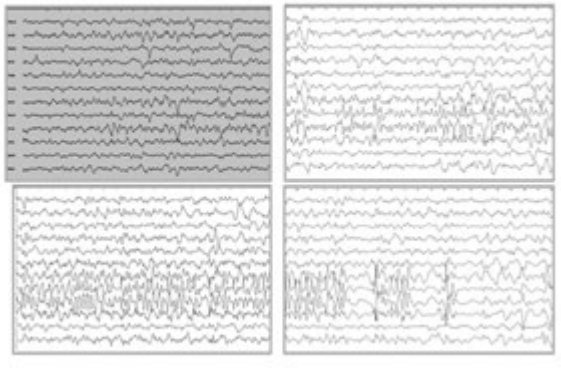


VIG… 4 y.

Focal seizures

- Firstly described associated with spasms
- Various and numerous in Partial Migrant Seizures in Infancy
- Long term EEG monitoring for potentially surgical patients

MPSI left temporal focal sz



Samuel 3 months SVP

Symptomatology of epileptic seizures in the first three years of life

- 76 infants, 296 seizures with vidéo
  - Epileptic spasms (24%)
  - Clonic seizures (20%)
  - tonic seizures (17%)
  - hypomotor seizures (20%)
  - Myoclonic, atonic, versive.

Hamer et al. 1999

Focal seizures in infancy: electroclinical semiology

- 32 patients, 68 seizures (1990-1995)
- Abnormal MRI: n= 21
- 32 SPECT and 3 PET in 17 patients
- Surgery for 10 patients
  - 4 hemispherotomies
  - 6 cortectomies FCD
- Retrospective analysis of seizure semiology

JP Rathgeb et al, 1998

First clinical sign and localisation

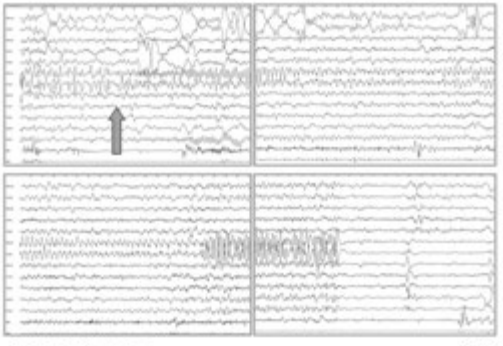
	frontal	rolandic	temporal	occipital	hémi
Oculo clonias	0	0	0	**3**	0
head +/- eyelids clonias	1	1	0	1	0
Head or eye Déviation	1	0	3	**16**	0
Unilatéral clonias	0	1	0	0	0
Body mov	1	2	0	0	0
Motor Arrest	6	1	**10**	7	1
uni ou bilatéral hypertonia	1	3/2	0	0	3/3

FCD in infancy

Lortie et al, 1998

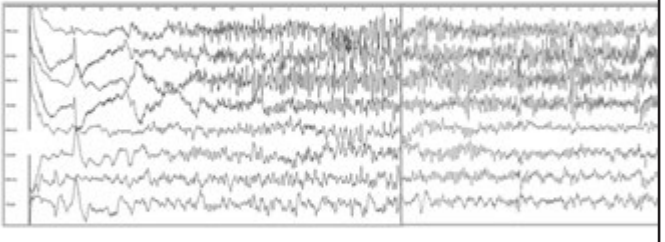
Frontal FCD	→	Focal seizures: 8 (poor symptoms or motor) Spasms : 1 case
Posterior FCD	→	Focal seizures: 9 (eyelids and eyes jerks)
Central FCD	→	Focal seizures motor: 4

Left central FCD



Nicolas 6 weeks SVP

Right frontal FCD



Cynthia 2 months SVP

In the childhood
Vera Terra (Brazil)

CIREP PEDIÁTRICO
COORDENADOR
AMÉRICO SAKAMOTO
EPILEPTOLOGIA
VERA CRISTINA TERRA
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CHEFIA ENFERMAGEM
MEIRE AKIKO NISIYAMA


Time-perspective in epilepsy syndromes. Changes in seizure semiology through age:

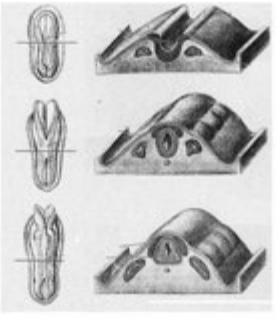
In Childhood

Vera Cristina Terra
EPILEPTOLOGIA

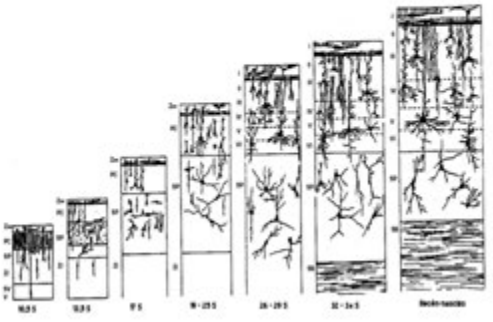
Hélio Rubens Machado
NEUROCIRURGIA PEDIATRICA

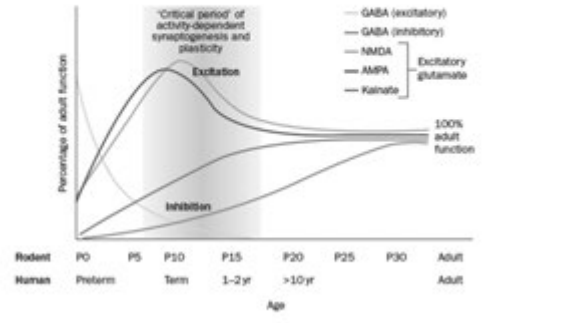
CIREP - CIRURGIA DA EPILEPSIA NA INFÂNCIA

EPILEPTOGÊNESE E EPILEPSIA



EPILEPTOGÊNESE E EPILEPSIA





EPILEPTOGÊNESE E EPILEPSIA

O cérebro imaturo exibe uma maior excitabilidade e menor inibição, favorecendo o aparecimento de padrões eletroclínicos específicos.

Na infância existe uma marcada redução do limiar para crises epilépticas.

EPILEPTOGÊNESE E EPILEPSIA

Existem diferenças nas propriedades moleculares, celulares e das redes neurais do SNC.

Aumento da freqüência de disparos das sinapses.

Aumento na densidade de espinhas sinápticas.

Aumento da densidade de receptores GLURs grupo I.

GABA com ação excitatória.

EPILEPTOGÊNESE E EPILEPSIA

Desenvolvimento de processos sinápticos.
Mielinização
Arborização dendrítica.
Morfologia das espinhas dendríticas
Desenvolvimento de sinapses
Neurotransmissores

↓

Mudanças na semiologia das crises com a idade

EPILEPTOGÊNESE E EPILEPSIA

Como a mesma etiologia pode causar sintomas clínicos diversos?

↓

Epileptogenicidade intrínseca das lesões
Ex: EMT, MDC

SEMIOLOGIA

- **Período neonatal:** ***alterações cardiovasculares, pedalar, crises hipomotoras.***
- **Até 6 meses: crises focais raras,** ***ocorrem ainda espasmos epilépticos, despertares***
- **Até 2 anos: crises tônicas simétricas como manifestação de crises focais.**
  Ação de estruturas subcorticais e do tronco cerebral?
- **Crises com componentes motores menos exuberantes.**

SEMIOLOGIA

3-6 anos

- Fenômenos tônicos, clônicos, mioclônicos, atônicos.
- Espasmos epilépticos.
- Crises hipermotoras.
- Automatismos oroalimentares e gestuais simples.
- Piscamento unilateral forçado.

SEMIOLOGIA

Após os 7 anos

- Automatismos mais complexos.
- Fenômenos tônicos menos frequentes.
- Postura distônica.
- Aumento da incidência de crises tônico-clônicas generalizadas.

SEMIOLOGIA

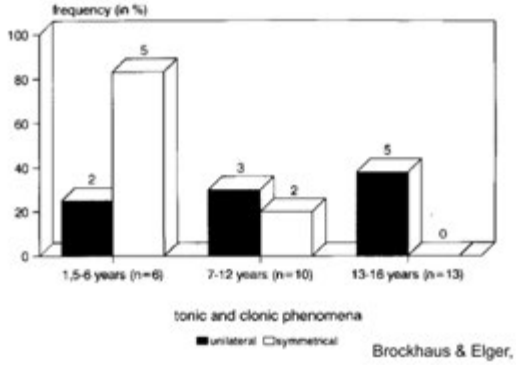
Maturação do sistema límbico e estruturas extratemporais

↓

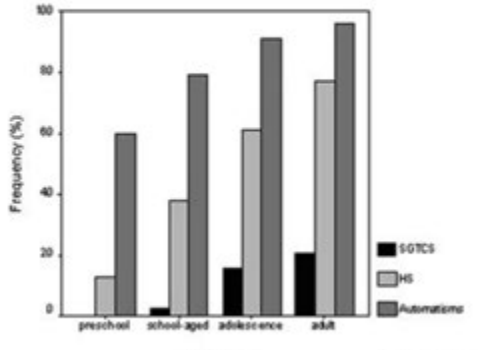
Crise semelhante a do adulto

SEMIOLOGIA

EPILEPSIA DO LOBO TEMPORAL



Brockhaus & Elger, 1995



Fogarasi et al, 2007

TABLE 2. *Unadjusted and HS-adjusted differences in age in relation to semiology axes in patients with temporal lobe epilepsy.*

Semiology axes	N	Age with (years, median, 25–75% range)	Age without (years, median, 25–75% range)	Unadjusted differences (SE)	p	HS adjusted differences (SE)	
Presence of aura	117 (75%)	13.4 (8.8–26.5)	12.5 (3.0–29.3)	0.9 (2.4)	0.69	−1.0 (2.1)	0.96
Emotional signs	39 (25%)	15.2 (8.1–31.0)	13.3 (7.4–21.7)	3.1 (2.3)	0.19	4.3 (2.1)	0.039
Autonomic signs	51 (33%)	13.1 (7.2–31.0)	13.5 (8.9–24.0)	0.6 (2.2)	0.78	0.4 (1.9)	0.84
Automatisms	130 (84%)	14.9 (10.5–30.0)	6.5 (2.4–11.0)	10.8 (2.6)	<0.001	7.5 (2.5)	0.003
SGTCS	18 (12%)	28.0 (13.5–33.0)	13.0 (7.1–26.0)	7.8 (3.1)	0.014	5.9 (2.8)	0.038
Number of different lateralizing signs*	—	—	—	3.6 (0.5)	<0.001	2.9 (0.5)	<0.001
Ratio of motor seizure component**	—	—	—	−2.7 (1.0)	0.007	−1.7 (0.9)	0.07

SGTCS, secondarily generalized tonic–clonic seizure; HS, hippocampal sclerosis, SE, standard error. *Difference in age was calculated for each increase in the number of lateralizing signs.
**Difference in age was calculated for each SD increase in the ratio of motor seizure component.

Fogarasi et al, 2007

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TABLE 3. *Clinical features of TLS in children*

Feature	Age (yr) 1.5–6	7–12	13–16
Simple automatisms	4 (8)	8 (14)	9 (16)
Complex automatisms	0 (0)	2 (2)	4 (4)
Motor phenomena	5 (12)	5 (13)	5 (16)
Versive movements	3 (5)	8 (20)	12 (28)
Hypermotoric activity	2 (4)	3 (4)	2 (3)
Dystonic postures	3 (3)	6 (15)	5 (12)
Secondarily generalized	0 (0)	1 (4)	5 (10)
Total	6 (15)	10 (31)	13 (37)

Brockhaus & Elger, 1995

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ELETRENCEFALOGRAMA

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CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

- Descargas nos quadrantes posteriores – primeiro ano de vida.
- Migração para padrão mais temporal anterior e frontal – início do segundo ano de vida.
- Padrão eletrodecremental – após os 6 meses.
- Hipsarritmia.

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CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

São sugestivos de Epilepsia Focal no primeiro ano de vida:

- Presença de crises ou descargas focais + padrão difuso.
- Alternância entre achados focais e difusos/generalizados.
- Padrões generalizados típicos

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CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Após os 6 anos

- Presença de ondas ogudas ou pontas localizadas.
- Na epilepsia do lobo temporal – registro de ondas agudas ou atividade teta com propagação para regiões extratemporais

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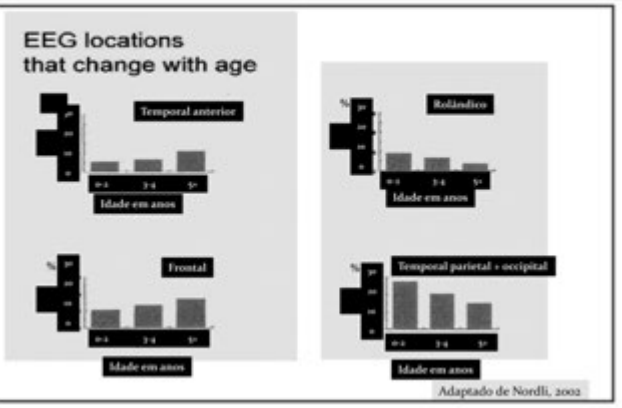
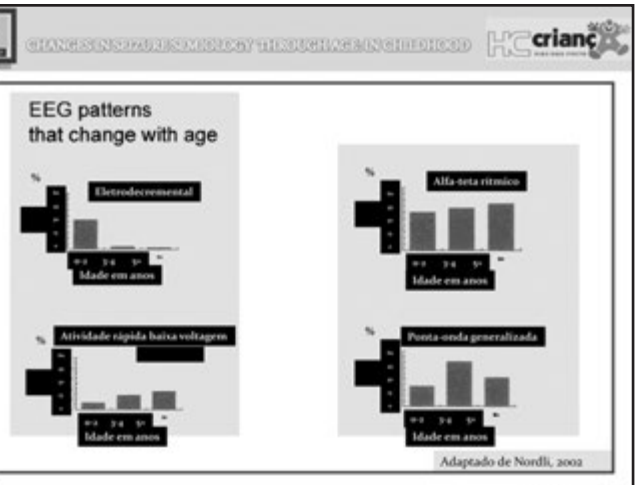




Epilepsia - *continuum*, com variabilidade de expressão entre as diferentes idades.

A maturidade e a integridade clínica do sistema nervoso influenciam fortemente as manifestações clínicas e eletrográficas dos eventos interictais e ictais.

Diferentes síndromes epilépticas em diferentes faixas etárias.

Período neonatal	Crises neonatais benignas familiares (3) Encefalopatia mioclônica precoce (3) Síndrome de Ohtahara (3)
Lactentes	Crises migratórias parciais do lactente (3) Síndrome de West (3) Epilesia mioclônica do lactente (3) Crises infantis benignas (3) Síndrome de Dravet (3) Encefalopatia mioclônica em desordens não progressivas (3)
Infância	Epilepsia occipital benigna da infância de início precoce (tipo Panayiotopoulos) (3) Epilepsia com crises mioclono-astáticas (2) Epilepsia benigna da infância com descargas centrotemporais (3) Epilepsia occipital da infância de início tardio (tipo Gastaut) (1) Epilepsia com ausências mioclônicas (2) Síndrome de Lennox-Gastaut (3) Encefalopatia epiléptica com descargas de espícula-onda contínuas durante o sono incluindo a síndrome de Landau-Kleffner (3) Epilepsia ausência da infância (3)

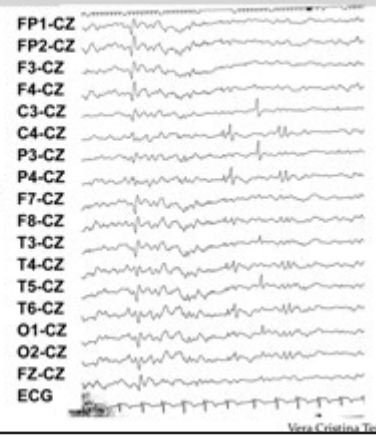
Engel, 2006

Relação com idade menos específica	Epilepsia do lobo frontal noturna autossômica dominante (3) Epilepsias do lobo temporal familiar (3) Epilepsia do lobo temporal mesial com esclerose hipocampal (2) Síndrome de Rasmussen (3) Crises gelásticas com hamartoma hipotalâmico (3)
Condições epilépticas especiais	Epilepsias focais sintomáticas não especificadas de outra forma Epilepsia apenas com crises tônico-clônicas generalizadas Epilepsias reflexas - Epilepsia occipital fotossensível (2) - Epilepsia primária da leitura (3) - Epilepsia da água quente em lactentes (3) Crises febris plus Epilepsia focal familiar com focos variáveis (3)

Engel, 2006

EPILEPSIAS IDIOPÁTICAS

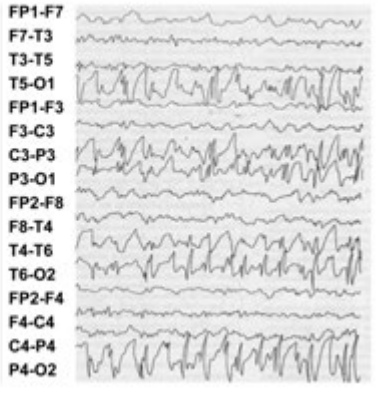
Epilepsia Benigna da Infância: pontas rolândicas



Epilepsia Benigna da Infância: pontas occipitais

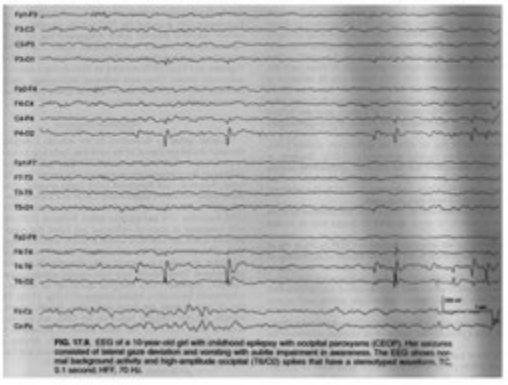
- *forma precoce (tipo Panauiotopoulos).*
- *forma tardia (tipo Gastaut).*

Epilepsia Benigna da Infância: pontas occipitais



CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Epilepsia Benigna da Infância: pontas occipitais



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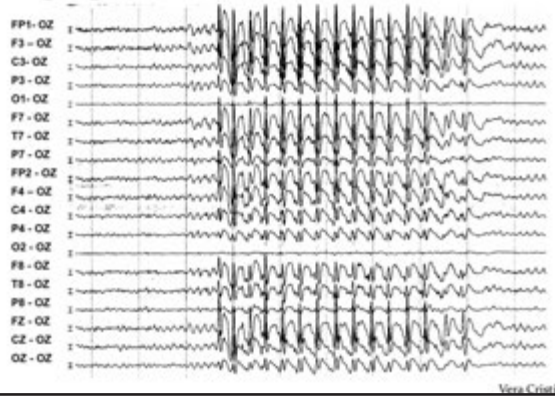
CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Epilepsia Generalizada – Ausência Infantil



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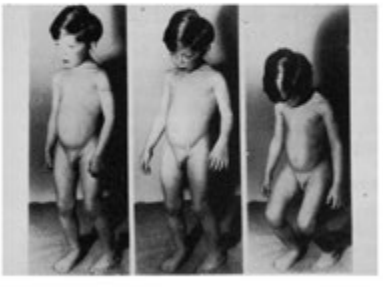
CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Síndrome de Doose ou Epilepsia Mioclonico-Astática



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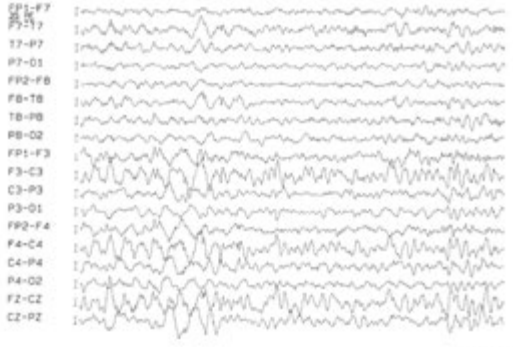
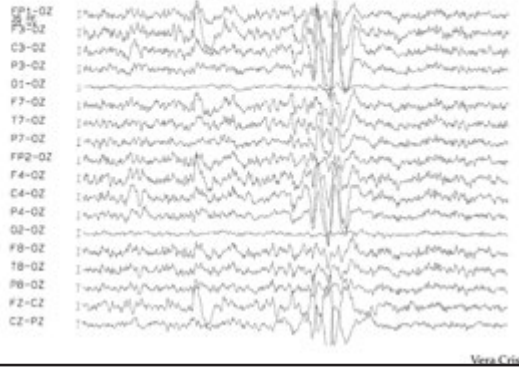
Síndrome de Doose ou Epilepsia Mioclonico-Astática

Tipo de queda	Astática	Tónica
Duração da queda	Reta, com direção às nádegas. Depende do centro de gravidade	Propulsiva
Confusão pós-ictal	Ausente	Depende da duração, pode haver confusão e automatismos
Manifestação na posição supina	Sursun vergens (versão ocular p/ cima)	Flexão do tronco e abdução dos membros superiores
EEG crítico	Complexos ponta-onda; Atenuação da atividade de base.	Ritmo recrutante
Síndrome relacionada	EMA	SLG

Síndrome de Doose ou Epilepsia Mioclonico-Astática



Síndrome de Doose ou Epilepsia Mioclonico-Astática



Epilepsias Provavelmente Sintomáticas e/ou Sintomáticas

EPILEPSIAS FOCAIS SINTOMÁTICAS

Lobo frontal

Lobo temporal

Lobo parietal

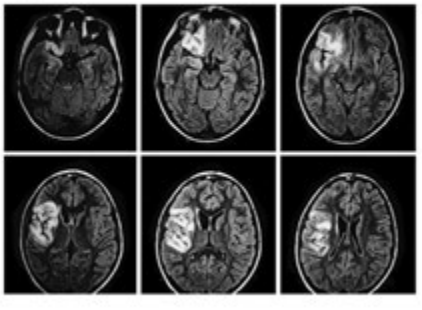
Lobo occipital

Epilepsia parcial contínua - Rasmussen

Epilepsias focais com formas específicas de precipitação

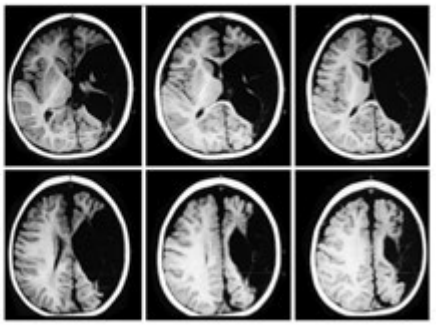
Epilepsias Hemisféricas

Encefalite de Rasmussen.



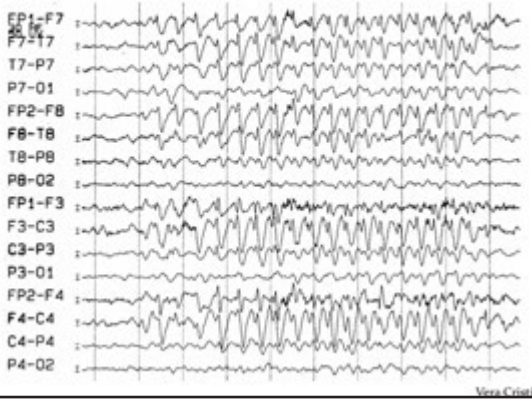
Epilepsias Hemisféricas

Síndrome HHE



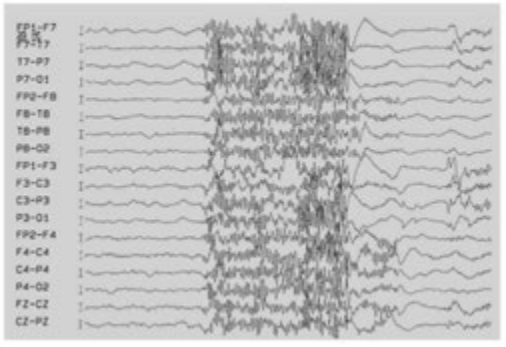
ENCEFALOPATIAS EPILÉPTICAS

Síndrome de Lennox-Gastaut



CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Síndrome de Lennox-Gastaut



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CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Síndrome de Landau-kleffner

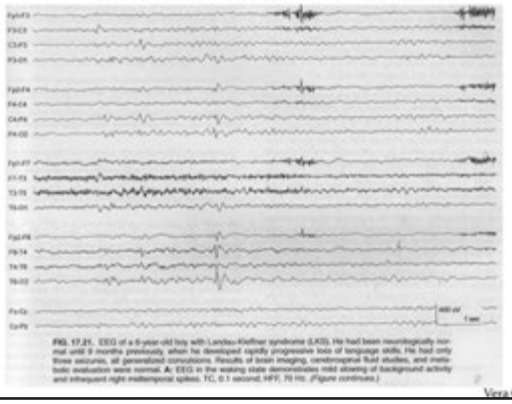

FIG. 17.21. EEG of a 6-year-old boy with Landau-Kleffner syndrome (LKS). He had been neurologically normal until 5 months previously, when he developed rapidly progressive loss of language skills. He had only three seizures, all generalized convulsions. Results of brain imaging, cerebrospinal fluid studies, and metabolic evaluation were normal. A: EEG in the waking state demonstrates mild slowing of background activity and infrequent right midtemporal spikes. TC, 0.1 second; HFF, 70 Hz. *(Figure continues.)*

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CHANGES IN SEIZURE SEMIOLOGY THROUGH AGE IN CHILDHOOD

Síndrome de Landau-kleffner

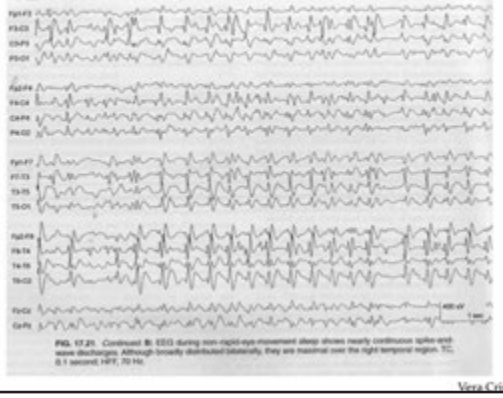

FIG. 17.21. Continued. B: EEG during non-rapid-eye-movement sleep shows nearly continuous spike-and-wave discharges. Although broadly distributed bilaterally, they are maximal over the right temporal region. TC, 0.1 second; HFF, 70 Hz.

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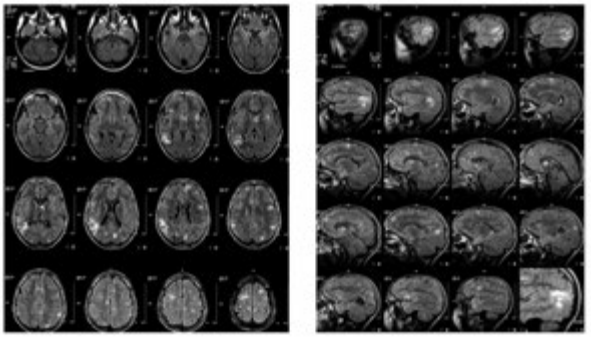
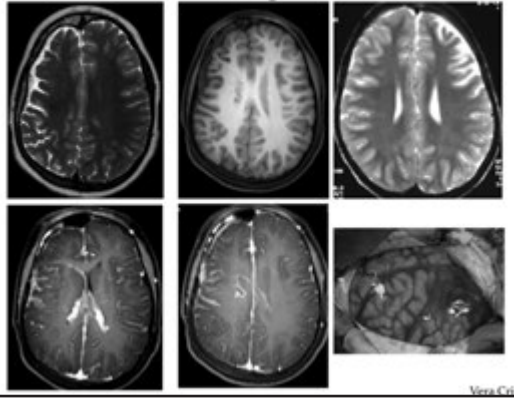
DOENÇAS ASSOCIADAS COM EPILEPSIA NA INFÂNCIA

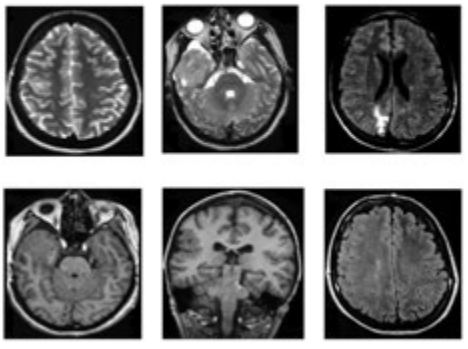
Complexo Esclerose Tuberosa



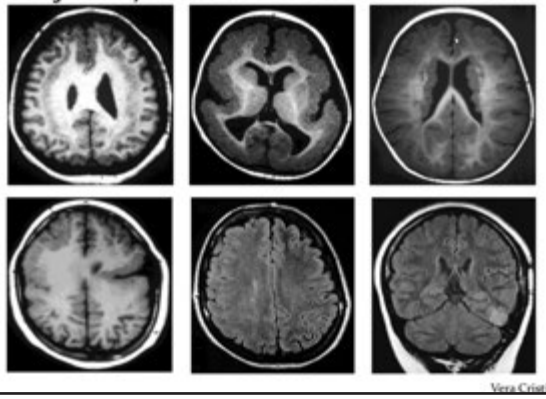
Síndrome de Sturge-Weber



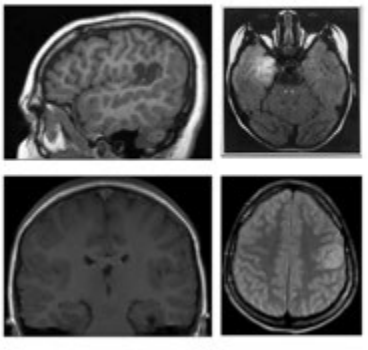
Malformações do desenvolvimento Cortical



Malformações do desenvolvimento Cortical



Tumores do sistema nervoso central



In the adolescence
Elza márcia yacubian (Brazil)

Epilepsia na adolescência

Elza Márcia Targas Yacubian
Unidade de Pesquisa e Tratamento das Epilepsias
Universidade Federal de São Paulo, São Paulo, Brasil

ADOLESCÊNCIA

- A adolescência é a transição entre a infância e a vida adulta, cujos limites nem sempre são bem definidos
- Início com a puberdade (do lat. *Pubescere*: cobrir-se de penugem) e terminada quando o crescimento e a maturidade física se completam
- Algumas epilepsias da infância estão em resolução
- Grande parte das epilepsias da vida adulta aqui se iniciam, sendo muitas vezes difícil o diagnóstico das síndromes epilépticas que se manifestam exclusivamente nesta fase

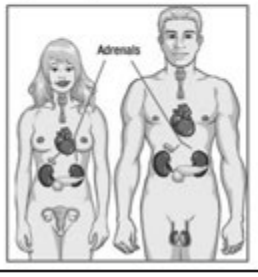
Prevalência

- 1,5 – 2% dos adolescentes; 19% das epilepsias de todas as idades

Gastaut, 1981; Ismoto et al., 1981; Oller-Daurella et al., 1982; Wheless & Kim, 2002

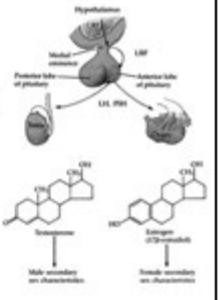
Desenvolvimento puberal
ADRENARCA OU PUBARCA

- Aparecimento de pêlos pubianos, axilares ou ambos, sem outros sinais de desenvolvimento de puberdade pelo início da produção de androgênios pelas supra-renais que ocorre antes da gonadarca



Desenvolvimento puberal
GONADARCA

- Maturação do eixo hipotálamo-hipófise-gônadas com início da maturação gonadal e produção hormonal pelas gônadas. Aumento de mamas, útero e ovários nas meninas; aumento da genitália, pênis e testículos nos meninos, devido ao aumento dos esteróides sexuais, estrogênios nas meninas e androgênios nos meninos



- **MENARCA:** primeira menstruação
- Meninas a puberdade tem início entre 8-13 anos de idade, 1-2 anos antes do que meninos

Epileptogênese na adolescência

- A maturação sexual tem início com a secreção de **esteróides excitatórios durante a adrenarca e a gonadarca** entre 8 e 10 anos de idade:
  - Sulfato de dehidroepiandrosterona
  - Sulfato de pregnenolona
  - Estrogênios

- Em indivíduos do sexo masculino acredita-se que diferentes níveis dos **metabólitos da testosterona** possam atuar no cérebro seja como anticonvulsivante (como o 3-α-androstanediol) ou pró-convulsivante (como o estradiol)

Epileptogênese na adolescência

- A secreção do **esteróide neuroinibitório progesterona** só começa quando os ciclos menstruais se tornam ovulatórios, um ou dois anos após a menarca
- Os **esteróides neuroexcitatórios** estão presentes 4 a 6 seis anos antes da progesterona e podem promover **sinaptogênese excitatória** e **desenvolvimento da epilepsia**

Influência da menarca no início da epilepsia

- 94 meninas e mulheres pós-menarca
- 9-55 anos de idade
- Idade da menarca
- Idade do início das crises

Início da epilepsia no período peri-menarca

Média do início das crises: 10.1 anos; predomínio 12-15 anos

Klein et al., 2003

Início da epilepsia no período peri-menarca

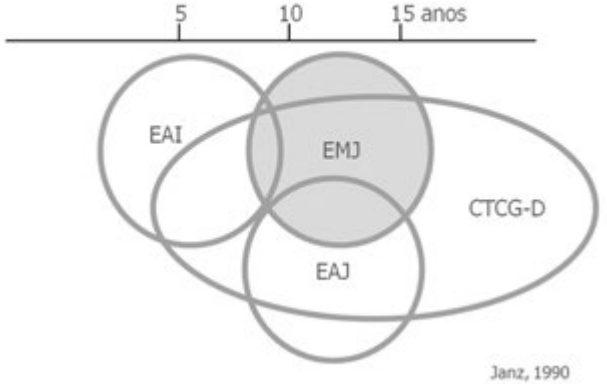
Klein et al., 2003

As síndromes epilépticas iniciadas na adolescência

Epilepsias generalizadas idiopáticas com fenótipo variável	Epilepsia mioclônica juvenil
	Epilepsia ausência juvenil
	Epilepsia com crises tônico-clônicas do despertar
Epilepsias fotossensíveis	
Epilepsia da leitura	
Epilepsia mesial temporal por esclerose hipocampal	
Epilepsias mioclônicas progressivas	

1. Epilepsias generalizadas idiopáticas

Superposição das síndromes de EGI da infância e adolescência

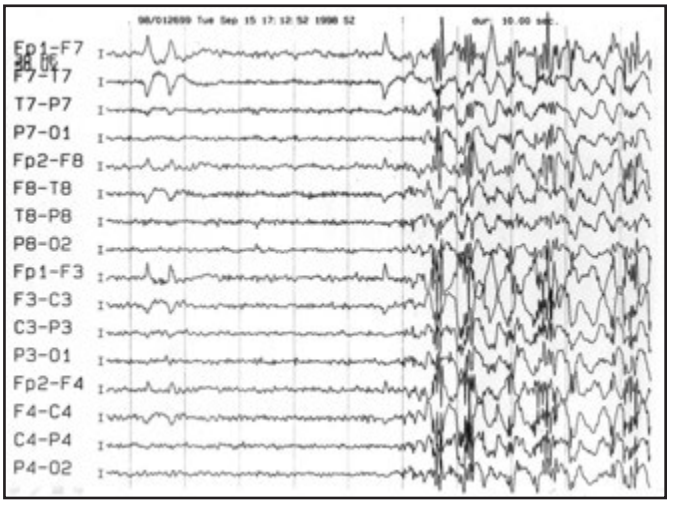


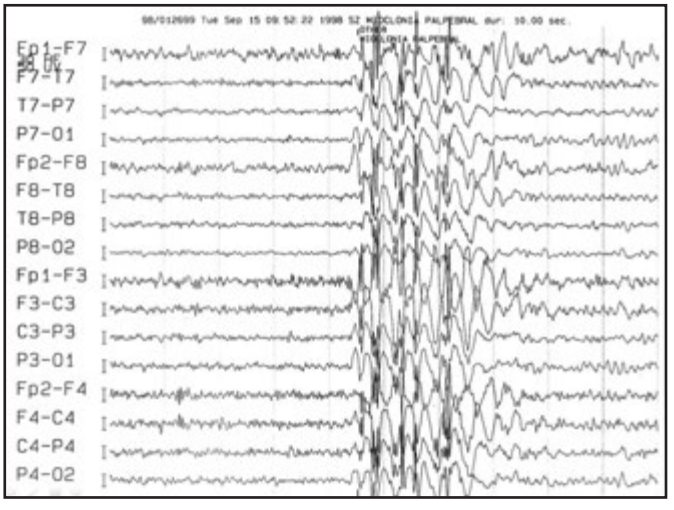
EPILEPSIA MIOCLÔNICA JUVENIL

- 10% de todas as apilepsias
- Início na puberdade; crises ocorrem principalmente pela manhã, ao despertar
- Mioclonias, presentes em todos os casos,
- Crises tônico-clônicas generalizadas (80% dos casos)
- Ausência breves e infreqüentes (30% dos casos)
- Fotossensibilidade (30% dos casos)

Janz & Christian, 1957
Wolf & Goosses, 1986
Genton et al, 2000
ILAE Commission on Classification and Terminology, 1989

Vídeo


Fp1-F7
F7-T7
T7-P7
P7-O1
Fp2-F8
F8-T8
T8-P8
P8-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2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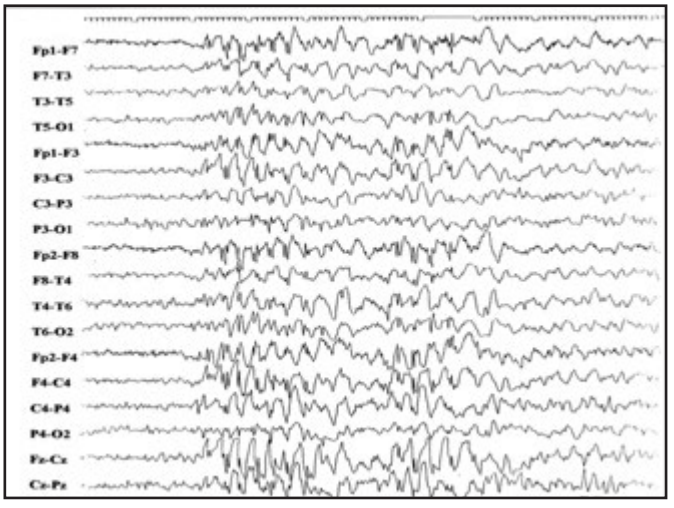
F8-T8
T8-P8
P8-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2

Vídeo


Fp1-F7
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T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz

Vídeo

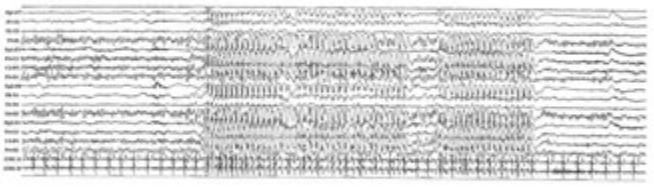
Vídeo

Epilepsia ausência juvenil

- Início 7-16 anos (pico 10-12)
- Ausências: comprometimento menos importante da consciência
- 9-10/dia - ausências espaniolépticas
- Duração mais longa (16,3±7,1s na epilepsia ausência juvenil, 12,4±2,1s na epilepsia ausência da infância e 6,6±4,2 na epilepsia mioclônica juvenil).
- Ausências constituem o tipo de crise predominante, embora a maioria dos pacientes apresente mioclonias e raras crises tônico-clônicas generalizadas
- Esta forma de epilepsia não apresenta remissão, embora as ausências melhorem com a idade quanto ao grau de comprometimento da consciência, duração e freqüência

Panayiotopoulos et al., 1989

Vídeo



AUSÊNCIA NA EPILEPSIA AUSÊNCIA JUVENIL

Epilepsia com crises tônico-clônicas ao despertar

- Crises tônico-clônicas generalizadas ao despertar
- Seis crises
- Para alguns esta denominação deve ser restrita à forma pura de crises tônico-clônicas generalizadas que ocorrem de 1 a 2 horas após o despertar,
- Privação de sono, fadiga e consumo excessivo de álcool
- O despertar independe do horário do dia, havendo ainda um segundo pico de incidência no período de relaxamento no final do dia
- Com esta definição, esta síndrome é extremamente rara
- Fotossensibilidade é comum (13% dos casos) e a resposta à terapia é satisfatória

Janz, 1994; ILAE Commission, 1989; Wolf & Goosses, 1986

Características gerais

- As crises ausências, quando isoladas, têm idade de início mais precoce do que as crises mioclônicas com ou sem crises de ausência;
- A privação de sono como fator precipitante é mais freqüente nas crises mioclônicas com ou sem crises de ausências do que nas crises de ausências isoladas;
- O uso excessivo de bebidas alcoólicas como fator precipitante é mais comum nos pacientes com crises mioclônicas não acompanhadas de ausências;

Reutens & Berkovic, 1995

Características gerais

- As epilepsias com crises de ausência isoladas têm uma freqüência máxima de aparecimento das crises no período vespertino em comparação com as ausências acompanhadas de mioclonias ou mioclonias isoladas, que apresentam predomínio matutino;
- As crises tônico-clônicas generalizadas são menos freqüentes na síndrome de Epilepsia Ausência Juvenil do que nas epilepsias acompanhadas de mioclonias;
- Os pacientes que apresentam os dois tipos de crises não convulsivas, ausências e mioclonias, têm maior número de crises tônico-clônicas generalizadas.

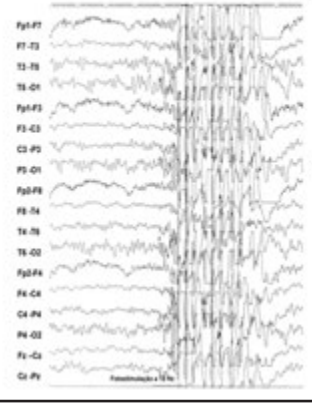
Reutens & Berkovic, 1995

2. Epilepsias fotossensíveis

Epilepsias fotossensíveis

- **Epilepsia fotossensível** é o nome da epilepsia na qual todas ou quase todas as crises são provocadas por flashes ou luzes intermitentes ou por algumas formas ou padrões visuais
- **Fotossensibilidade** é uma resposta anormal à luz ou a padrão visual que ocorre em 0.3-3% da população submetida ao EEG
- A prevalência estimada de crises induzidas por estímulos luminosos é de 1 por 10.000 (1 por 4.000 indivíduos entre 5 a 24 anos)
- Entre as pessoas com epilepsia, 2-14% têm crises precipitadas por luz ou padrão visual

Epilepsias fotossensíveis



- A fotossensibilidade tem máxima expressão ao redor da puberdade e declina com a idade, provavelmente após os 25 anos e está presente em várias síndromes epilépticas
- Estes pacientes, principalmente mulheres, apresentam resposta fotoparoxística no EEG, em geral com estímulos com intensidade de 1 joule, com freqüência de flashes entre 10-30 Hz

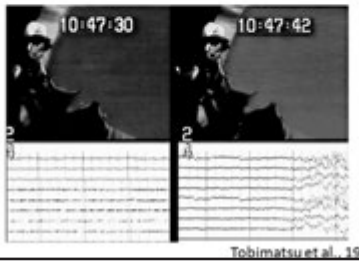
Epilepsia cromatossensitiva

- A importância da cor na provocação de crises foi noticiada em 16 de dezembro de 1997 quando da transmissão do desenho Pokémon no Japão, o qual provocou crises em 685 crianças
- Neste episódio, alterações rápidas a 12 Hz nas telas de cor vermelha e azul, foram identificadas como o fator provocador das crises

Tobimatsu et al., 1999; Parra et al., 2005

Pokemon
Epilepsia cromatossensitiva

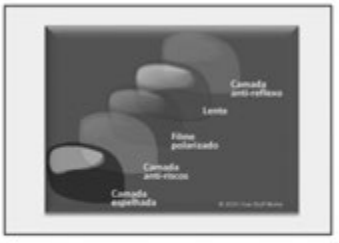
- O conteúdo epileptogênico de uma sequência de vídeo relacionada à cor foi filtrado sem alterar seu conteúdo espacial e luminescência



Tobimatsu et al., 1999; Parra et al., 2005

Tratamento

- **Medidas não farmacológicas**
- **Tratamento farmacológico**



- Lentes azuis Z1
- 610 pacientes com RFP grau 4
- Lentes Z1: desaparecimento da resposta fotoparoxística em 463 (75,9%) dos pacientes

Capovilla et al., 2006

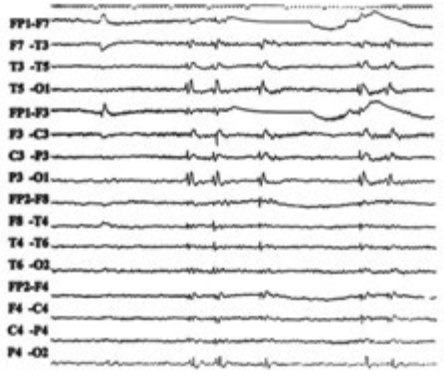
3. Epilepsia da leitura

Epilepsia da leitura

- Mioclonias envolvem a musculatura orofaringolaríngea e podem evoluir para crise tônico-clônica generalizada
- Idade de início entre 12-25 anos (média 17,7)
- Sexo: homens 1,8:mulheres 1
- Precipitadas pela leitura (100%), fala (27%), escrita (11%), leitura de formas (4-7%), leitura Braille ou partitura musical (raramente)
- Crises não provocadas: ausentes em 95%, muito raras em 5% dos pacientes

Wolf, 1992

Vídeo


FP1-F7
F7 -T3
T3 -T5
T5 -O1
FP1-F3
F3 -C3
C3 -P3
P3 -O1
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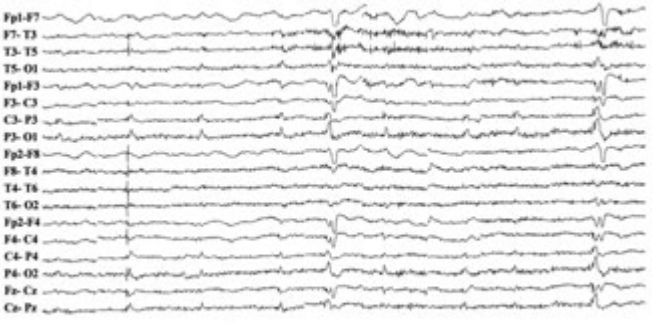
F8 -T4
T4 -T6
T6 -O2
FP2-F4
F4 -C4
C4 -P4
P4 -O2


Fp1-F7
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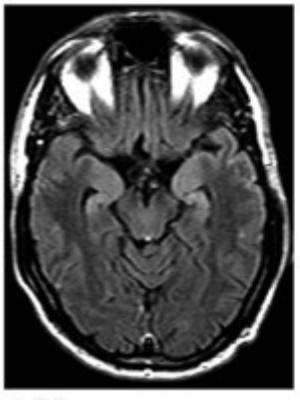
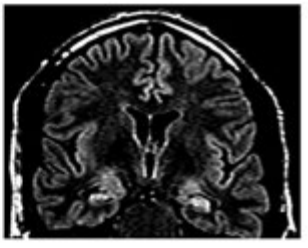
Fp2-F8
F8- T4
T4- T6
T6- O2
Fp2-F4
F4- C4
C4- P4
P4- O2
Fz- Cz
Cz- Pz

4. Esclerose mesial temporal na adolescência

Esclerose hipocampal clássica

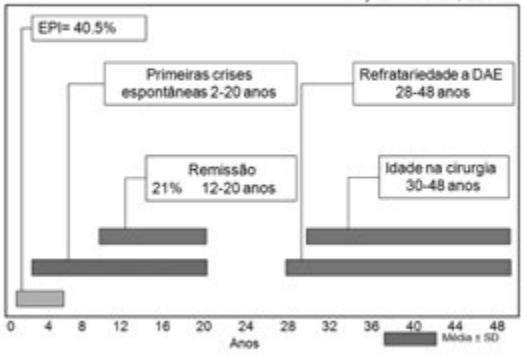




Atrofia hipocampal
Perda da estrutura interna
Hiposinal em T1
Hipersinal em T2

Curso da epilepsia relacionada à esclerose mesial temporal em 180 pacientes

Miyashira et al., 2004



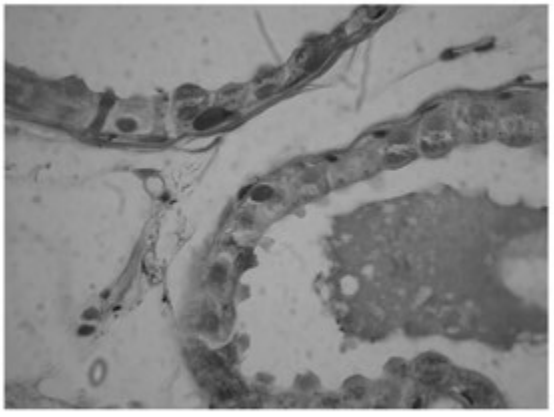
5. Epilepsias mioclônicas progressivas

Epilepsias mioclônicas progressivas

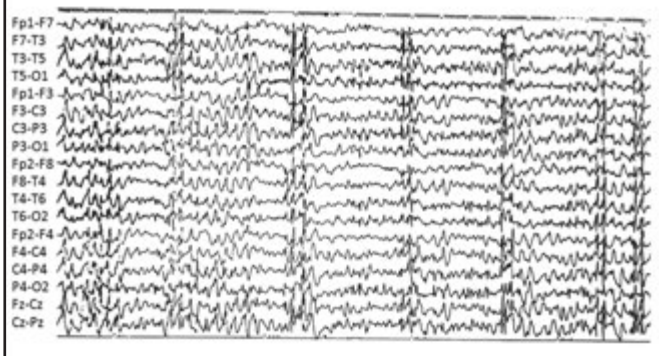
- 1% de todos os casos de epilepsia na infância e adolescência
- Mioclonias do tipo parciais ou segmentares, arrítmicas, assíncronas, assimétricas e maciças, chamadas de 'mioclonias do tipo Unverricht'
- Epilepsia com crises generalizadas tônico-clônicas, clônico-tônico-clônicas ou clônicas, as quais se associam a ausências e crises focais
- Deterioração mental culminando em demência e sintomas neurológicos entre os quais se destaca a ataxia cerebelar

Epilepsias mioclônicas progressivas

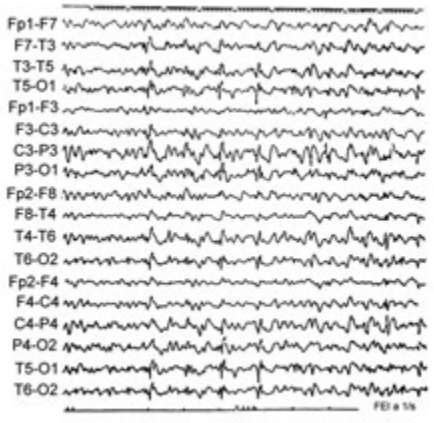
- São doenças genéticas e várias já tiveram seus genes identificados
  - Doença de Unverricht–Lundborg (mioclonia báltica)
  - Doença de Lafora
  - Mitocondriopatias entre as quais se destaca a síndrome MERRF-Myoclonic epilepsy with ragged-red fibers caracterizada por epilepsia, mioclonia intencional, fraqueza muscular, ataxia progressiva e surdez
  - Ceróides lipofuscinoses com duas formas juvenis, a doença de Batten–Spielmeyer–Vogt caracterizada por déficit visual, demência progressiva e manifestações extrapiramidais além de crises epilépticas e a doença de Kuf com epilepsia mioclônica progressiva ou demência com distúrbios motores, sem sintomas visuais



CORPOS DE LAFORA



DOENÇA DE LAFORA



DOENÇA DE LAFORA

6. Epilepsias parciais idiopáticas da adolescência. As crises focais benignas da adolescência

Pierre Loiseau
(1926-2004)

Crises focais benignas da adolescência

Epidemiologia	Um quarto das crises focais de adolescentes
Idade	11 a 18 anos
Exame neurológico	Normal
Tipo de crises	Crises focais simples com características somato-sensitivas, motoras focais clônicas ou tônicas, versivas, sem marcha jacksoniana. Generalização secundária em 50% dos casos. Raramente parciais complexas.
Frequência	O evento é uma CRISE ÚNICA em 75%, nos restantes 25%, um cluster de 2-4 crises ocorrem em 36-48 horas
Ritmo circadiano	Em vigília, menos frequentes em sono
EEG	Normal ou algumas ondas lentas centro-parieto-occipitais quando registrado após o evento crítico
Etiologia	Desconhecida. Raramente há história familiar de epilepsia
Pato fisiologia	Desconhecida. Crises que afetam o córtex sensório-motor
Outros exames	Deve-se realizar RM na busca de uma lesão focal em todos os casos
Diagnósticos diferenciais	Epilepsias focais sintomáticas Epilepsias benignas idiopáticas da infância de início tardio Epilepsia mioclônica juvenil com mioclonias 'focais' Migrânea com parestesias focais Crises pseudo-epilépticas
Tratamento	Deve-se evitar tratamento. O curso é benigno e as crises são isoladas

Loiseau P et al., 1972; Loiseau & Orgogozo, 1978; Loiseau & Louiset, 1992

O significado da epilepsia iniciada na adolescência- 212 adolescentes de 16 países

- Dois terços (65%) das crianças e adolescentes referiram impossibilidade de comparecer às aulas sete dias por ano, em média
- 36% referiram que escondiam a epilepsia de outros por medo de serem tratados de forma diferente e por acreditarem que outras pessoas não deveriam ter ciência de sua condição (47%)

Baker et al. (2008)

O significado da epilepsia iniciada na adolescência- 212 adolescentes de 16 países

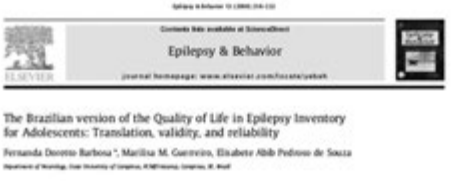
- A maioria (87%) tomava medicamentos antiepilépticos. Mais de um terço reportaram efeitos adversos:

  - alteração no peso (49%), cefaléia (46%), tontura (41%), e tremores (33%)

- Mais de um terço antecipavam que sua condição exerceria impacto negativo em suas vidas futuras e as áreas mais citadas foram comprometimento das oportunidades de emprego (73%), viagens (37%) e educação (36%)

Baker et al. (2008)

QOLIE-AD 48


Epilepsy & Behavior

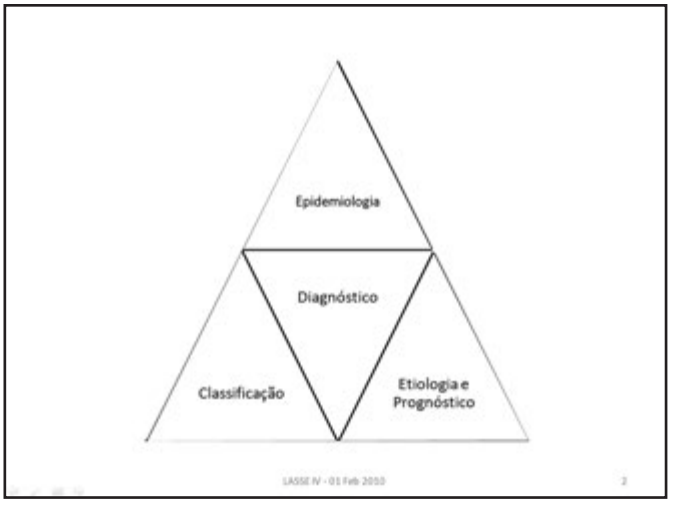
The Brazilian version of the Quality of Life in Epilepsy Inventory for Adolescents: Translation, validity, and reliability

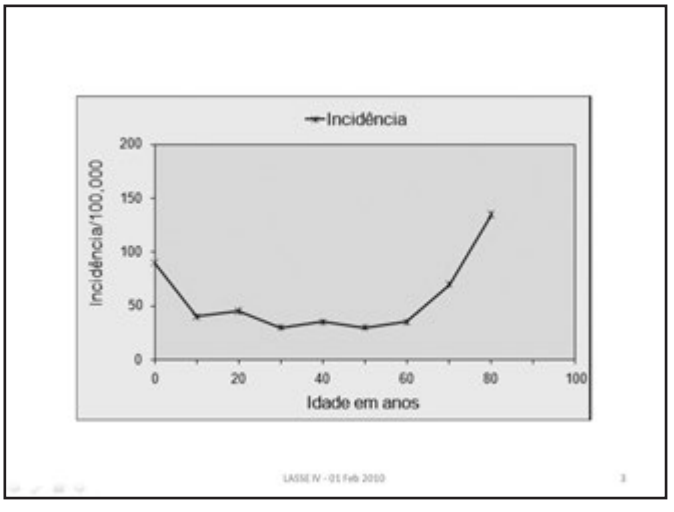

Joyce Cramer

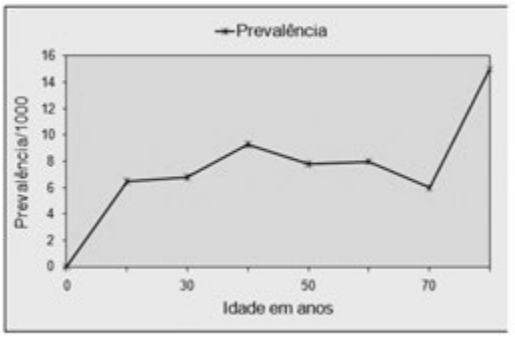
Development of the Quality of Life in Epilepsy Inventory for Adolescents: the QOLIE-AD-48. Cramer JA, Westbrook LE, Devinsky O, Perrine K, Glassman MB, Camfield C. Epilepsia 1999 Aug;40(8):1114-21.

Muito obrigada

In the adulthood
Veriano Alexandre Junior (Brazil)







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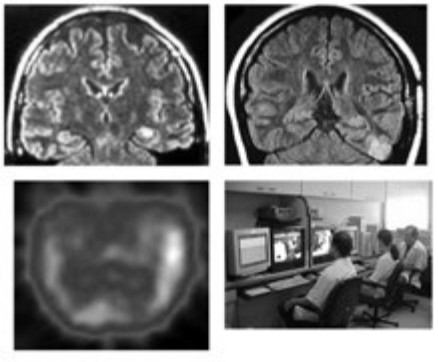
Etiologias



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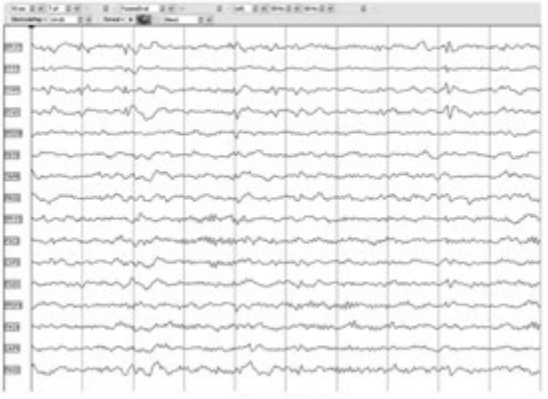
Atividade focal



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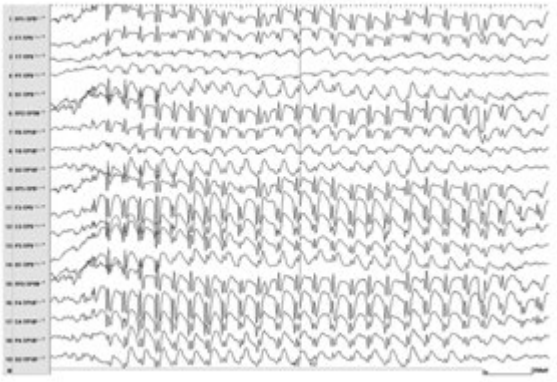
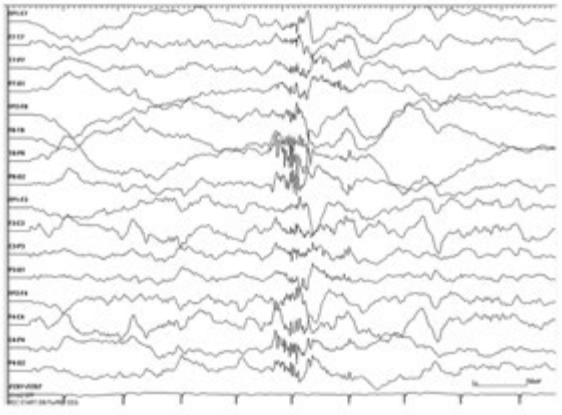
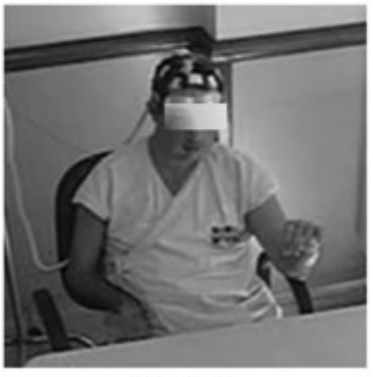
Atividade generalizada



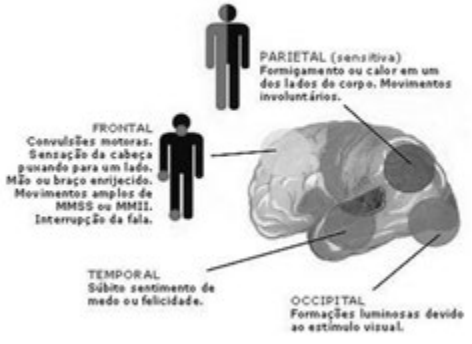


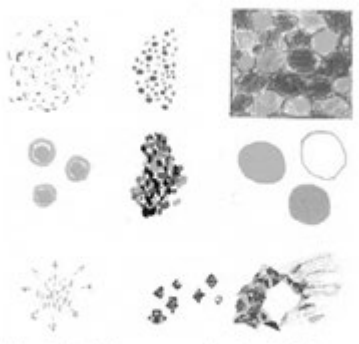
Exame físico



Semiologia

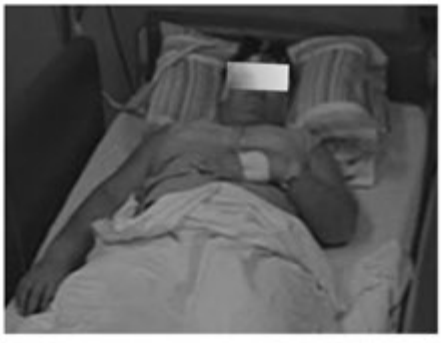
O homúnculo de Penfield



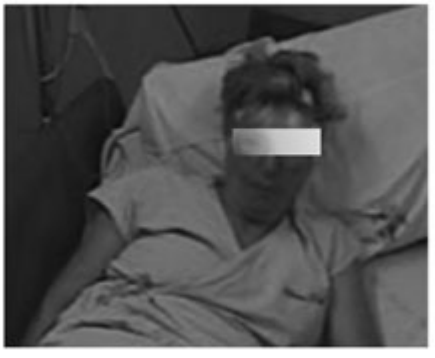


Alucinações visuais elementares como descritas e desenhadas por pacientes com crises de lobo occipital.
Extraído de Panayiotopoulos, J Neurol Neurosurg Psychiatry 1999.

Aura abdominal



Automatismos mastigatórios

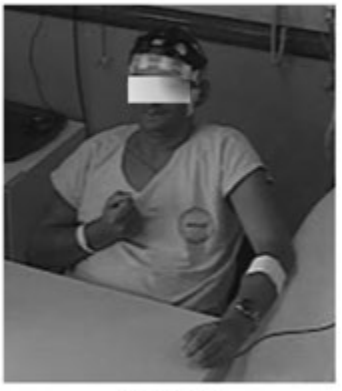


Auras

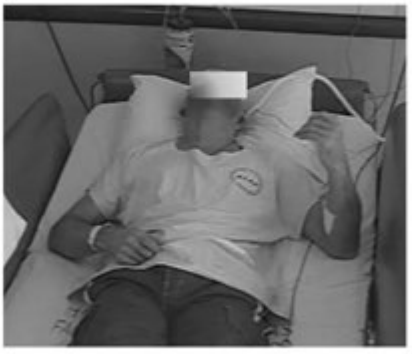
Sinais lateralizatórios

Sinais lateralizatórios	Hemisfério cerebral
Versão ocular e cefálica	Contralateral
Postura distônica da mão	Contralateral
Sinal do 4	Contralateral
Automatismos mantendo responsividade	Não dominante
Fala ictal	Não dominante
Afasia pós-ictal	Dominante
Vômito ictal	Não dominante
Cuspir durante a crise	Não dominante
Urgência urinária peri-ictal	Não dominante
Coçar nariz pós-ictal	Ipsilateral
Tosse pós-ictal	Não dominante
Clonias unilaterais	Contra-lateral
Hipertonia unilateral	Contra-lateral
Piscamento unilateral	Ipsilateral

Postura distônica



Crise tônica assimétrica



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Crise tônico-clônica generalizada

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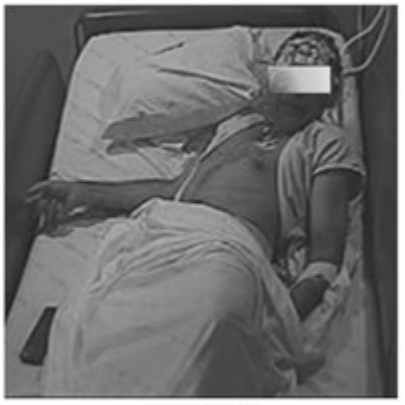
Crise hipermotora



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Diferenças regionais

COMMISSION REPORT 28 July 2009

Revised terminology and concepts for organization of the epilepsies: Report of the Commission on Classification and Terminology

Anne T. Berg, PhD, [1]
Samuel F. Berkovic, MD[2]
Martin J. Brodie, MD [3]
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Douglas Nordli Jr., MD[12]
Perrine Plouin, MD[13]
Ingrid E. Scheffer, MBBS, PhD, FRACP[2]

In the elderly
Carlos Guerreiro (Brazil)

Agenda: Epilepsia Geriátrica

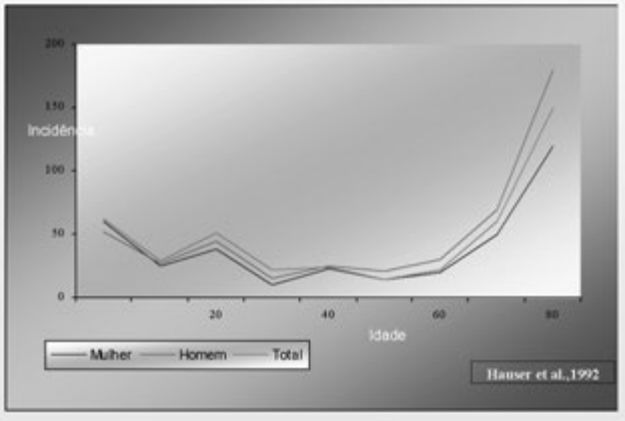
- Aspectos especiais e epidemiológicos
- Etiologia de crises sintomáticas agudas e das epilepsias
- Tipos de crises
- Diagnóstico diferencial
- Avaliação diagnóstica
- Princípios do tratamento medicamentoso

Epilepsia em Idosos e Jovens

	Idosos	*Jovens*
Incidência	Alta	Baixa
Freqüência Crises	Rara	Pode ser freqüente
Duração Pós-ictal	Geral/ prolongado	Breve
Risco de acidentes	Alto	Baixo
Resposta a única DAE	Boa	Variável

Epidemiologia

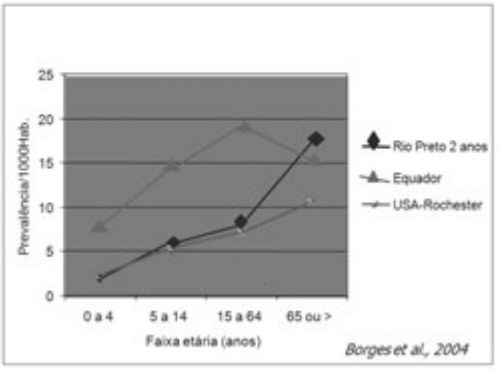
Incidência



Dados Epidemiológicos

- 70 anos: incidência de epilepsia é 2 X infância
- 80 anos: incidência de epilepsia é 3 X infância
- > 65 anos incidência anual: 134/100.000
- > 65 anos incidência DA: 123/100.000
- > 80 anos incidência: > 135/100.000
- ~ 10% idosos em casas de repouso usam DAE (UK)

Prevalência de Epilepsia Ativa: Equador, EUA e Brasil



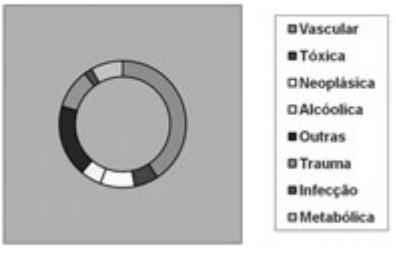
Etiologia

Crises Agudas Sintomáticas (Idosos)

(Lesão aguda ou distúrbio metabólico)

AVC	40-54 %
Condições Tóxico-metabólicas	15-30 %
Neoplasia	8-10 %
Trauma	4-10 %
Álcool	3-5 %
Infecção do SNC	2-3 %

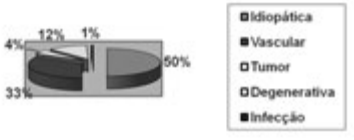
Causas de Crises Sintomáticas Agudas (Hauser, 1997



Etiologia de Crises Não Provocadas em Idosos

Idiopático	33-50 %
AVC	33-40 %
Demência	11-16 %
Neoplasia	4-6 %
Infecção do SNC	2-3 %
Trauma	1-3 %

Causas de Epilepsia em Idoso (Hauser, 1997)



Tipos de Crises em Pacientes > 60 anos

CPC	51,7 %
CPS	19,1 %
CTCG	21,3%
Mioclônicas	4,5 %
Não especificadas	3,4 %

* Pós-ictal: mais prolongado

Drogas Que Provocam Crises ou ↓ Limiar Epileptogênico

Psicotrópicos Antidepressivos Tricíclicos Inibidores da recaptação da serotonina Antipsicóticos Bupropiona	**Antibióticos** Penicilina Imipenem Gentamicina Cefalosporina
Narcóticos Meperidina Propoxifeno	**Simpatomiméticos** Efedrina Fenilpropanolamina
Agentes cardiovasculares Digoxina Metoprolol Verapamil	**Quimioterápicos** Metotrexate Clorambucil Cisplatina

Estado de Mal Epiléptico

- **Até 35 % crises sintomáticas agudas: EME**
- **EME mais prolongados**
- **Mortalidade: 50% > 80 anos**

Diagnóstico Diferencial

- **Alteração de consciência e quadros confusionais**
- **Movimentos involuntários transitórios**
- **Afasia**
- **Distúrbio da marcha**

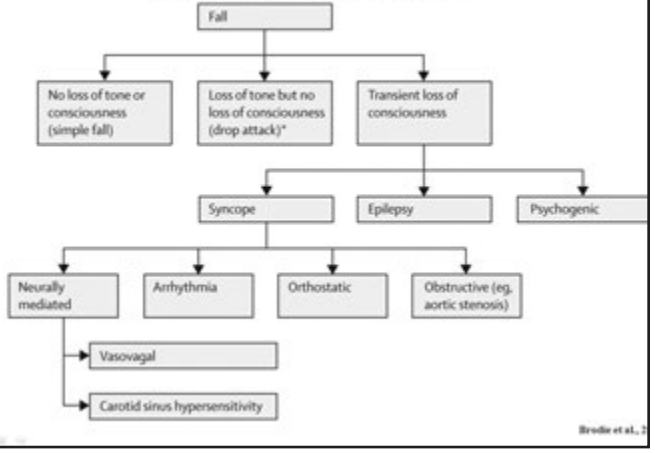
Diagnóstico Diferencial

- Síncope neurocardiogênica (ou vasovagal)
- Hipotensão ortostática
- EIT
- Afasia
- Amnésia global transitória
- Distúrbio comportamental do sono REM

Avaliação Diagnóstica

- História
- Eletrólitos, glicose, cálcio, magnésio, função renal e hepática
- EEG (558 pac>60a:26%AE; 300pac>65a:45% AI; 5%AE)
- Neuroimagem: hematoma subdural, AVCI, tu, infecção. Gadolíneo: tu, infecções

Avaliação de Queda em Idoso



Características Clínicas que podem Ajudar na Diferenciação entre Síncope e Epilepsia no Idoso

	Síncope mais Provável	Epilepsia mais Provável
Antes	Eventos ocorrem exclusivamente na posição ortostática Eventos ocorrem consistentemente em associação com micção, tosse, ou evacuação Pródomo é dominado por tontura, náusea e vômito, ou sudorese Eventos precipitados por estímulos emocionais (ex. medo, dor)	Aura(ex. cheiro) Eventos ocorrem em várias posições, posturas ou circunstâncias Eventos ocorrem exclusivamente durante o sono
Durante	Palidez facial Contrações mioclônicas Testemunha confiável descreve queda com imobilidade	Desvio da cabeça no início de mov lateralizados, ou mastigação ou estalar dos lábios Mov tônico-clônicos Eventos estereotipados
Após	Náusea e vômito	Cianose facial, mordedura de língua, ou cefaléia e mialgia sugerem crise generalizada Confusão ou amnésia durando mais que 1 h

Brodie et al., 2009

Comorbidades Comuns e suas Implicações no Idoso com Epilepsia

	Implicação	Ação
Demência	Aderência ao tratamento deve ser comprometida Freqüência de crises pode ser difícil de monitorar Educação do paciente pode ser impossível	Considerar screening rotineiro em idosos com epilepsia ou suspeita Acessar indicação para trat da demência Rever supervisão da tomada da medicação Prover treinamento apropriado do cuidador
AVC	Risco do 1.o ou de adicionais	Priorize risco de fatores vasculares
Osteoporose	Algumas DAEs > taxa de perda óssea Possível ↑risco de lesão óssea	Considerar proteção farmacológica do osso
Doença Renal Crônica	Eliminação alterada de algumas DAEs	Rever o uso da DAE
Diabetes Mellitus	Hipoglicemia pode ↓ limiar epileptogênico	Rever o controle glicêmico
Fragilidade	Prejuízo do exame físico geral	Avaliar mobilidade e a necessidade de alarme de segurança

Brodie et al., 2009

Quadro 1. Normas Gerais para o Tratamento Medicamentoso das Epilepsias

O tratamento é geralmente prolongado (meses a anos)

É recomendado o uso inicial de uma única droga antiepiléptica: monoterapia

A medicação, de modo geral, deve ser titulada (aumentada) lentamente até atingir a dose mínima eficaz ou surgirem eventos adversos; não está claramente definida a dose mínima (só há parâmetros aproximados); a dose máxima é aquela que o paciente tolera sem apresentar efeitos colaterais inaceitáveis

Nunca se deve retirar abruptamente uma droga antiepiléptica (DAE); com raras exceções, tais como nas reações idiossincrásicas (alérgicas)

Todos os fármacos antiepilépticos podem causar eventos adversos sistêmicos ou neurotóxicos; este fato justifica a monitoração clínica e laboratorial do paciente pelo médico prescritor da medicação a intervalos variáveis

Tratamento Medicamentoso: Princípios Gerais para Idosos

- **Absolutamente necessário saber toda a medicação em uso, dietas, remédios "naturais"**
- **Monoterapia**
- **Titulação lenta: dose mínima necessária**
- **Adesão (custo e facilidade posológica)**
- **E. Adversos (SNC, quedas, ↓Na, interação de drogas)**

Estudo Cooperativo dos Hospitais de Veteranos de Guerra

Estudo randomizado, controlado, multicêntrico, duplo-cego:
CBZ X LTG X GBP

- Crises parciais recém-diagnosticadas em pacientes com 60 ou >
- Avaliação principal (*primary outcome measure*): índice de retenção por 12m
- Doses alvos: GBP:1.500mg, LTG: 150mg, CBZ:600mg
- Pacientes com efeitos colaterais e controle inadequado de crises foram retirados do estudo. Média de idade (n= 593) = 72 anos

Rowan et al., Neurology, 2005

Estudo Cooperativo dos Hospitais de Veteranos de Guerra

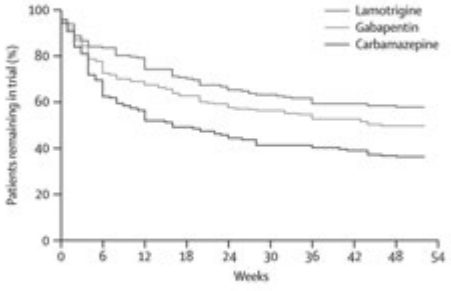
• Tipos de crises: 43% crises parciais complexas e 25 % tônico-clônicas somente.

• Etiologias mais comuns infarto cerebral (32%), desconhecida (24,7%), arterioesclerose cerebral (14,7%), e trauma craniano (6,8%).

• Condições clínicas: hipertensão arterial (65,7%), AVC (51,7%), doença cardíaca (47,8%), diabetes (28,2%), câncer ou antecedente de câncer (23,9%).

Rowan et al., Neurology, 2005

Porcentagem de Pacientes Remanescentes no Estudo de Veteranos (52 semanas)



Estudo Cooperativo dos Hospitais de Veteranos de Guerra

Estudo randomizado, controlado, multicêntrico, duplo-cego:
CBZ X LTG X GBP

- Abandonaram: LTG: 44,2%
  GBP: 51%
  CBZ: 64,5%
- Livres de crises: taxas semelhantes
  3m: 63,2%
  6m: 58,6%
  1ano: 53,3%

Rowan et al., Neurology, 2005

Efeitos Adversos

Efeitos sistêmicos

- ganho de peso (55,3%),
- problemas GI (29,5%)
- perda de peso (27,6%)
- hiponatremia (7,1%)
- impotência (7,0%)
- trombocitopenia (0,4%)
- neutropenia (0,4%)

Neurotoxicidade

- sedação (44,3%)
- distúrbio de marcha (28,4%)
- tontura (28,7%)
- declínio cognitivo (27,2%)
- alt. humor e afetividade (29,1%)

Estudo Cooperativo dos Hospitais de Veteranos de Guerra

Principal Conclusão

LTG e GBP melhores toleradas que a CBZ, porém não mais eficazes que a CBZ

Rowan et al., Neurology, 2005

DAEs: Farmacocinética em Idosos

DROGA	Dose Inicial (dose/dia ou mg/Kg/dia)	Ligação Proteínas (%)	Eliminação Metabolização	Comentários
Carbamazepina (CBZ)	100 mg (4-6)	75-85	Hepática CYP 3A4/5	Ligação protéica diminui com a idade. Indutor do metabolismo de muitas drogas (Diminui o nível de bloqueadores de cálcio (diltiazem, verapamil), de antidepressivos tricíclicos, de anticoagulantes orais e a efetividade da quimioterapia
Fenobarbital (PB)	50 mg (2)	50	Hepática/Renal	Indutor do metabolismo de muitas drogas
Fenitoína (DPH)	100 mg(3)	80-93	Hepática	Indutor do metabolismo de muitas drogas (Diminui o nível de bloqueadores de cálcio (diltiazem, verapamil), de antidepressivos tricíclicos, e a efetividade da quimioterapia
Lamotrigina (LTG)	25 mg/	55		Níveis são diminuídos por CBZ, PB, DPH e alguns hormônios

DAEs: Farmacocinética em Idosos

DROGA	Dose Inicial (dose/dia ou mg/Kg/dia)	Ligação Proteínas (%)	Eliminação Metabolização	Comentários
Levetiracetam	500mg	< 10	Renal	Sem interações de drogas
Gabapentina	300mg	< 10	Renal	Eliminação correlaciona-se com clearance de creatinina; sem interação de drogas
Oxcarbazepina	150 mg/	40		Causa hiponatremia
Topiramato	25 mg/	7-19%	Hepática, renal	Inibe CYP 2c19 e aumenta DPH e outras drogas. Induz CYP3A4
Valproato	250 mg (5-10)	87-95%	(glucoronização e betaoxidação)	Ligação protéica diminui no idoso. Inibe glucoronidação e pode aumentar o nível da LTG e outras drogas. Diminui função plaquetária

Modificado de Leppik I.& Birnbaum AK (1998).

Vantagens e Desvantagens de DAE

DAE	Vantagens	Desvantagens
Fenobarbital	Baixo custo	Muito sedativa, depressão
	Efetiva	Tolerância, crises na retirada
Fenitoína	Efetiva	Difícil de usar, ataxia
	Baixo custo	Efeitos col. cosméticos
Carbamazepina	Eficácia	Reação idiossincrásica
	Fácil de usar	Efeitos col. SNC
	Formulação liberação lenta	Interações DAE
Valproato	Amplo espectro	Ganho de peso, tremor
	Bem tolerado	Teratogenicidade, quedas
	Poucas r. idiosincrásicas	Interações DAE

Vantagens e Desvantagens de DAE

DAE	Vantagens	Desvantagens
Lamotrigina	Amplo espectro	Rash
	Relativa/não sedativa	Titulação lenta
	Poucos prob.longo prazo	Interações DAE
Vigabatrina	Fácil de usar	Retinopatia gabaérgica
	Sem r. idiossincrásicas	Efeitos psiquiátricos
	Poucas interações	Menos eficaz contra CTCG
Oxcarbazepina	Fácil de usar	Rash
	Melhor tolerada que CBZ	Interação anticoncepcional
	Sem interações com DAE	Hiponatremia
Topiramato	Eficácia	Alterações cognitivas
	Amplo espectro	Calculose renal
	Poucas interações	Titulação lenta
Gabapentina	Fácil de usar	Sedativo, ganho de peso
	Bom perfil tolerância	Três tomadas ao dia
	Ausência de interações	Eficácia modesta

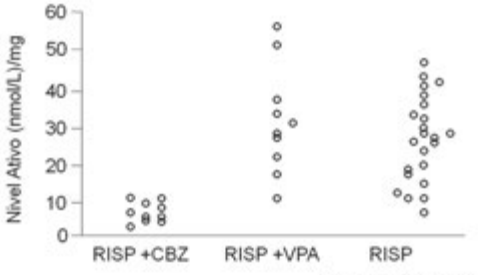
Como Prever Interações Metabólicas das DAEs?

- A maioria das vías metabólicas envolve as isoenzimas do citocromo P450 (CYP)
- Efeitos de outras drogas nestas isoenzimas (e efeito da droga em outras isoenzimas) são tambem conhecidos ou podem ser determinados *in vitro*

Prevendo Interações de Drogas
Exemplo da Carbamazepina

- CBZ é primaria/metabolizada pelo CYP3A4. Previsível: diminui o nível plasmático por drogas inductoras de CYP3A4, tais como PHT e PB
- Carbamazepina é indutora do CYP3A4. Previsível: diminui o nível de substratos do CYP3A4, tais como risperidona, antagonistas de cálcio e anticoncepcionais orais

Efeito da Carbamazepina e Valproato no Nível de Risperidona em Pacientes com Esquizofrenia



Spina et al, Ther Drug Monit 2000

Avaliação de Potencial Interação de Drogas em Pacientes com Epilepsia:

Impacto da Idade e Sexo

Table Demographic and clinical characteristics of patients with epilepsy

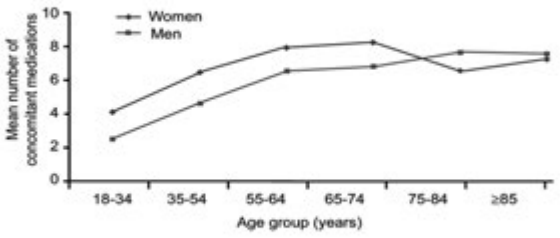
Characteristic	EIAED, n = 7,142	NEIAED, n = 4,046
Sex, no. (%) male	3,053 (42.8)	1,306 (32.1)
Age, mean ± SD, y	42.3 ± 14.0	39.5 ± 14.0
Seizure type, no. (%)		
Partial seizures	2,380 (33.3)	1,496 (36.8)
Generalized seizures	4,762 (66.7)	2,568 (63.2)
AED therapy, no. (%)		
Monotherapy	1,172 (16.4)	508 (12.5)
Adjunctive	5,970 (83.6)	3,556 (87.5)

EIAED = enzyme-inducing antiepileptic drug; NEIAED = non-enzyme-inducing antiepileptic drug; AED = antiepileptic drug.

Ostal et al. Neurology, 2008

- **45 milhões de pessoas**
- **11.206 pacientes com epilepsia**

Número Médio de Medicações Concomitantes, por Idade e Sexo



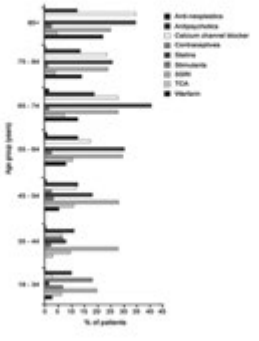
Gidal et al. Neurology, 2009

Uso de Medicações em Pacientes con Epilepsia e População em Geral (EUA)

- 18-44a: 23% masc e 39% fem — Grupo PCE
- 18-44a: 2% masc , 3% fem — População Geral
- 45-64a: 47% masc , 60% fem — Grupo PCE
- 45-64a: 10% masc, 15% fem — População Geral

Gidal et al. Neurology, 2009

Porcentagem de Pacientes com Medicações mais Utilizadas por Grupo Etário



Gidal et al. Neurology, 2009

Summary of Evidence and Recommendations
Partial onset seizures

Seizure type or epilepsy syndrome	Class I	Class II	Class III	Level of efficacy and effectiveness evidence (in alphabetical order)
POS: Adults	2	1	30	Level A: CBZ, PHT, (LEV) Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB
POS: Children	1	0	17	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA
POS: Elderly	1	1	2	Level A: GBP, LTG Level B: None Level C: CBZ

Questões de Qualidade de Vida em Idosos

- Autoestima pelas crises
- Preocupação com carta de motorista
- Perda da independência
- Superproteção familiar
- Peso da medicação
- Declínio do bem-estar
- Redução da autoconfiança

(Stephen & Brodie, 2000)

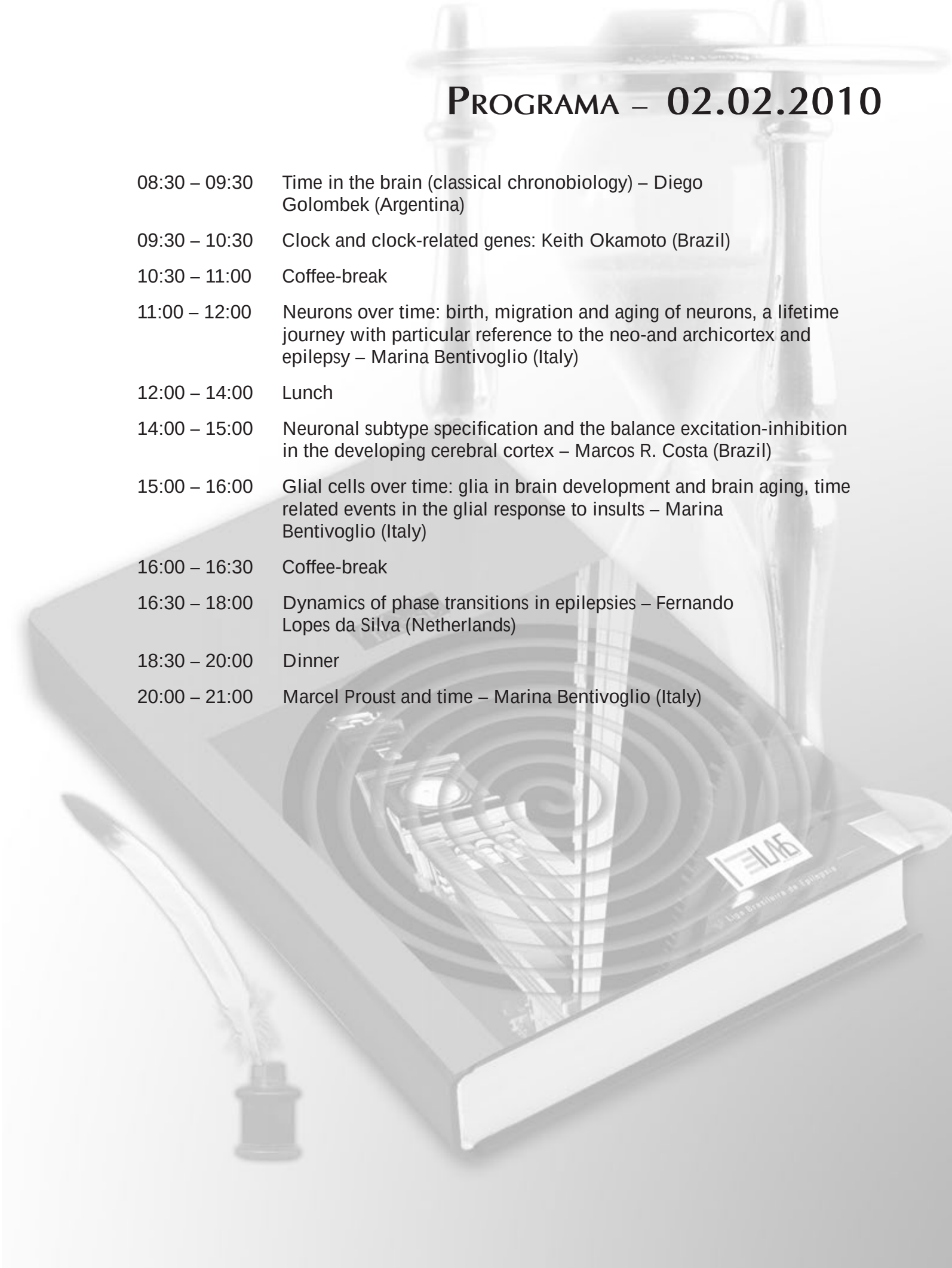
Pontos Essenciais na Epilepsia Geriátrica

- Epilepsia em idoso é muito freqüente
- Crises são #: - CTCG, + CPC
- Pós-ictal: + prolongado
- Escolher as DAE melhor toleradas
- Usar doses baixas de DAE
- Assegurar e monitorizar aderência


40
ANOS
F.C.M. UNICAMP

Programa – 02.02.2010

08:30 – 09:30	Time in the brain (classical chronobiology) – Diego Golombek (Argentina)
09:30 – 10:30	Clock and clock-related genes: Keith Okamoto (Brazil)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Neurons over time: birth, migration and aging of neurons, a lifetime journey with particular reference to the neo-and archicortex and epilepsy – Marina Bentivoglio (Italy)
12:00 – 14:00	Lunch
14:00 – 15:00	Neuronal subtype specification and the balance excitation-inhibition in the developing cerebral cortex – Marcos R. Costa (Brazil)
15:00 – 16:00	Glial cells over time: glia in brain development and brain aging, time related events in the glial response to insults – Marina Bentivoglio (Italy)
16:00 – 16:30	Coffee-break
16:30 – 18:00	Dynamics of phase transitions in epilepsies – Fernando Lopes da Silva (Netherlands)
18:30 – 20:00	Dinner
20:00 – 21:00	Marcel Proust and time – Marina Bentivoglio (Italy)



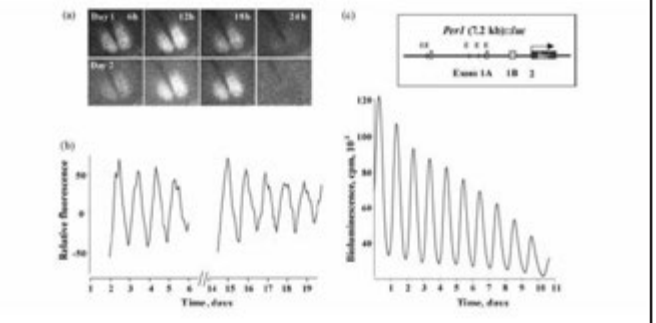
Clock and clock-related genes:
Keith Okamoto (Brazil)

LASSE IV: EPILEPSIA E TEMPO

CLOCK AND CLOCK-RELATED GENES

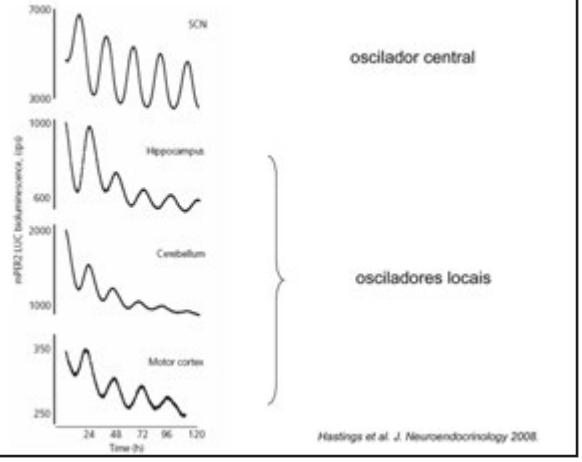
Oswaldo Keith Okamoto
Disciplina de Neurologia Experimental
Universidade Federal de São Paulo, Brasil

Detecção em tempo real da expressão de *Per* no núcleo supraquiasmático



Reddy et al. Mol. Res. 2005.

Regulação circadiana de expressão gênica no cérebro

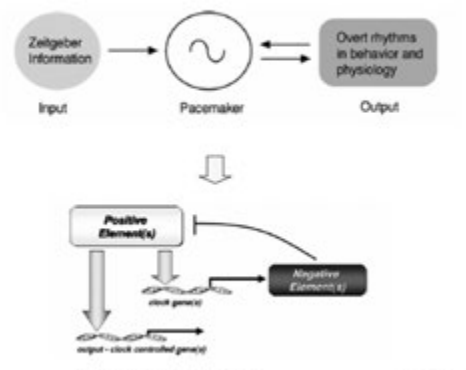


oscilador central

osciladores locais

Hastings et al. J. Neuroendocrinology 2008.

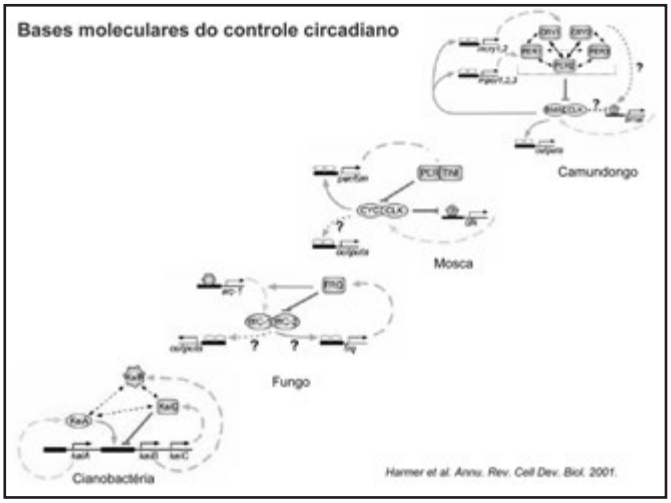
Mecanismo geral do sistema circadiano



'Auto-regulatory feedback loop'

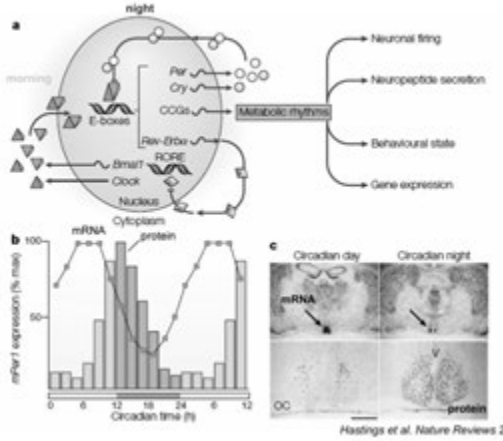
Albrecht, J. Physiol 2006.

Bases moleculares do controle circadiano

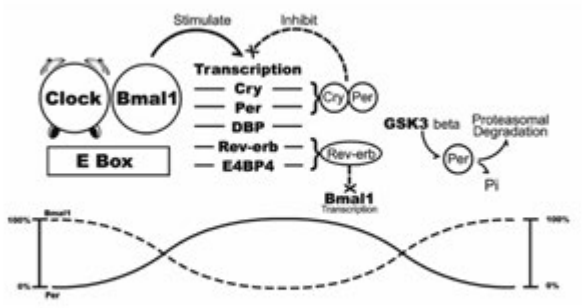


Harmer et al. Annu. Rev. Cell Dev. Biol. 2001.

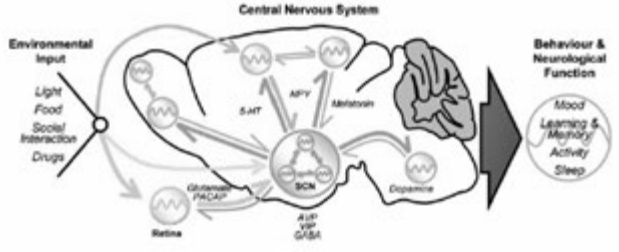
Natureza molecular do relógio circadiano em neurônios do Núcleo Supraquiasmático



Hastings et al. Nature Reviews 2003.

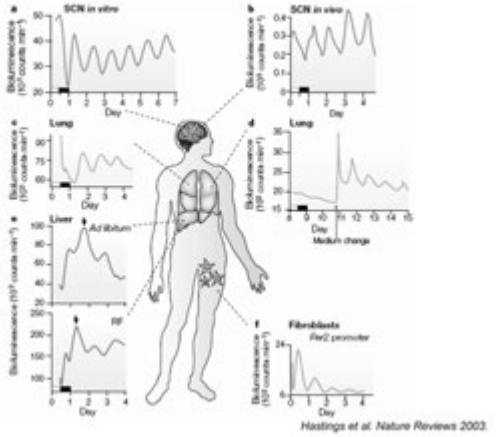


Gimble et al. J Cell Biochem. 2009



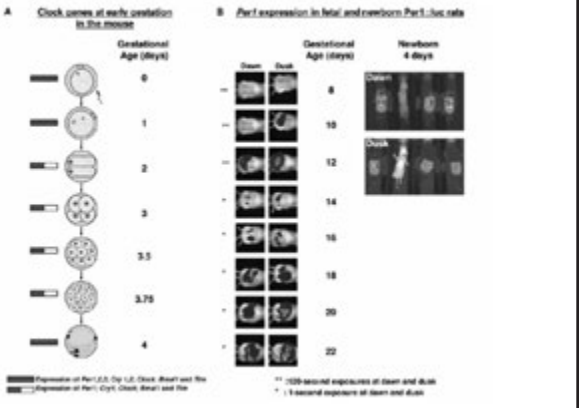
Bernard & Nolan, Plos Genetics 2006.

Relógio central e relógios periféricos



Hastings et al. Nature Reviews 2003.

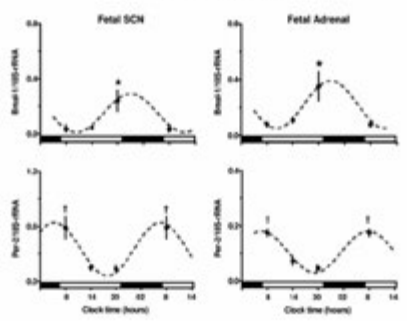
Expressão de genes centrais do relógio circadiano durante o desenvolvimento embrionário



Seron-Ferre et al. Birth Defects Research (Part C) 2007.

Expressão de genes centrais do relógio circadiano durante o desenvolvimento embrionário

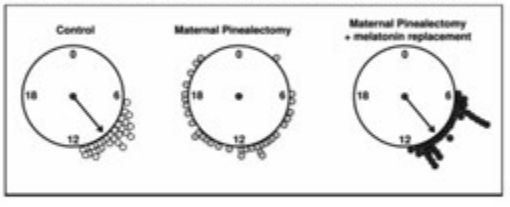
Primatas não-humanos



Seron-Ferre et al. Birth Defects Research (Part C) 2007.

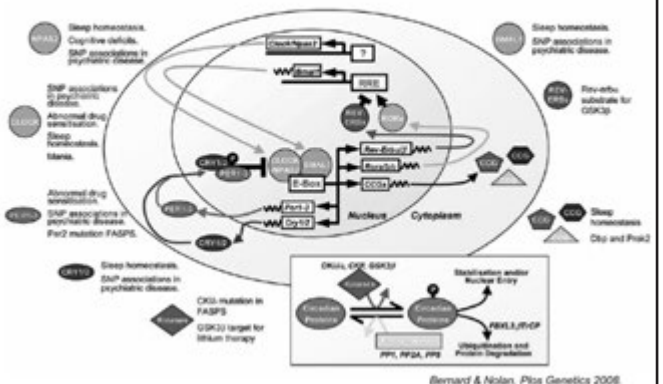
Sinais maternos regulam o relógio circadiano em neonatos

Maternal melatonin entrains the rhythm of drinking behavior in rat pups



Seron-Ferre et al. Birth Defects Research (Part C) 2007.

Alterações neurocomportamentais associadas ao desbalanço circadiano



Bernard & Nolan, Plos Genetics 2008.

Distribuição temporal da frequência de crises parciais complexas em pacientes com epilepsia

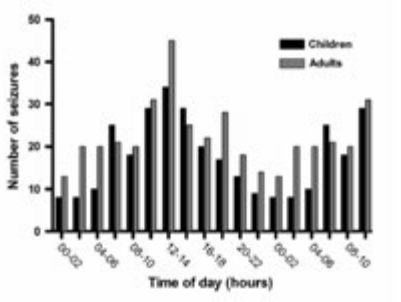
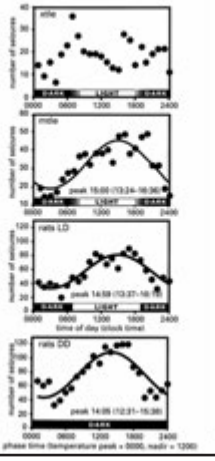


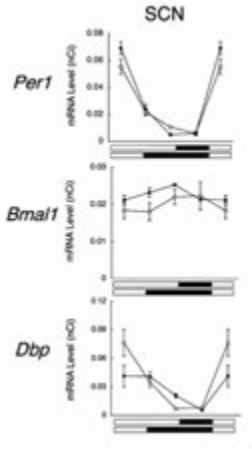
Figure 2. Bar histogram showing temporal distribution of complex partial seizures in children and adults (numbers of seizures are $n = 215$ and $n = 265$ respectively). Each bar represents numbers of seizures per 2 h. Data of 36 h is given in order to show the 24 h cosinor rhythmicity. Data adapted from. [19]

Quigg, Epilepsy Res. 2000.

Crises límbicas são influenciadas pelo relógio circadiano



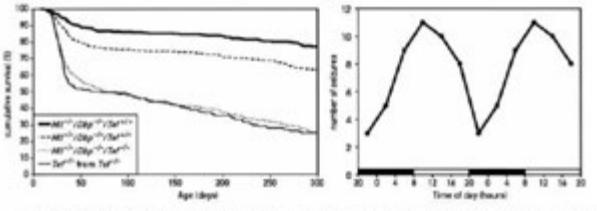
Hofstra & Weerd, Sleep Med Rev 2009.



DBP is a clock-controlled gene that presents a robust circadian rhythm in tissues with high amplitudes of clock gene expression, such as the suprachiasmatic nucleus (SCN).

Yasuo et al. European Journal of Neuroscience, 2008.

Deleção de genes PAR bZip provoca crises epilépticas



DBP (albumin D-site-binding protein), HLF (hepatic leukemia factor), and TEF (thyrotroph embryonic factor) are the members of the PAR bZip (proline and acidic amino acid-rich basic leucine zipper) transcription factor family.

Gachon et al.Genes Dev. 2004.

Practice points

1. The occurrence of seizures in certain human epilepsy syndromes seems to have 24-h rhythmicity, depending on the origin. This rhythmicity has also been shown in animals, a pattern continuing with free running circadian rhythm.
2. There seems to be a variation in chronotypes between certain epilepsy syndromes.
3. Reduced heart rate variability and changed hormone levels, which are under the influence of the biological clock, are observed in people with epilepsy.
4. Large gaps remain in the data on the interaction between circadian rhythms and (human) epilepsy.

Hofstra & Weerd, Sleep Med Rev 2009.

Dynamics of phase transitions in epilepsies
Fernando Lopes da Silva (Netherlands)

LASSE IV
Latin-American Summer School on Epilepsy
1 – 10 February 2010
São Paulo, Brazil

Dynamics of phase transitions in epilepsies

Fernando Lopes da Silva
University of Amsterdam, The Netherlands

Epilepsy as diseases of the dynamics of neuronal networks. Models and predictions

How does the transition from normal brain activity to "epileptic activity" take place?

Basic neurophysiology: two different cases.

Principles of interictal-ictal transitions and precursors of seizures

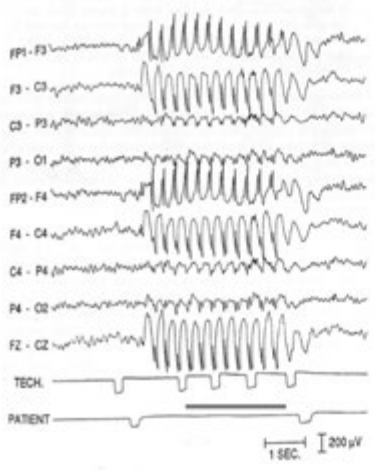
- Case 1:
- The occurrence of Spike-and-Wave discharges in the thalamo-cortical system, typical of absence seizures.

- Case 2:
- The occurrence of seizure activity in the hippocampus

Principles of interictal-ictal transitions and precursors of seizures

- Case 1:
- The occurrence of Spike-and-Wave discharges in the thalamo-cortical system, typical of absence seizures.

- Case 2:
- The occurrence of seizure activity in the hippocampal formation.



Spontaneous absence:

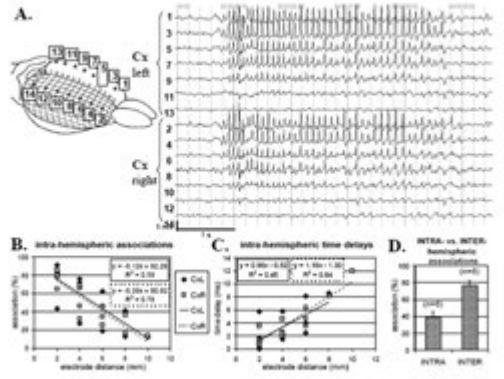
Patient is requested to press a button immediately after a technician did the same.

The WAG/Rij rat as model for absences seizures

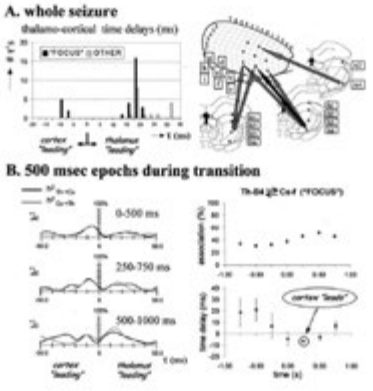
- genetic model.
- no neurological defects.
- absences are characterized by behavioral arrest and spike-and-wave discharges (SWDs) in the EEG.
- pharmacological responses is similar to that of patients with absences.

Typical SWDs start and end abruptly

Cortico-Cortical Associations: Bilaterally Symmetric Sites

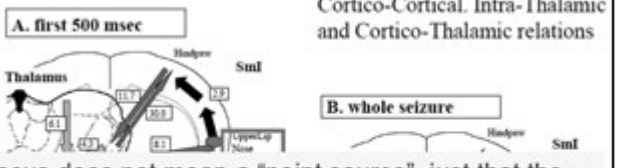


Meeren, Pijn, van Luijtelaar, Coenen and Lopes da Silva, J. Neurosci 2002,22:1480-95



Evolution of absence seizures: a summary

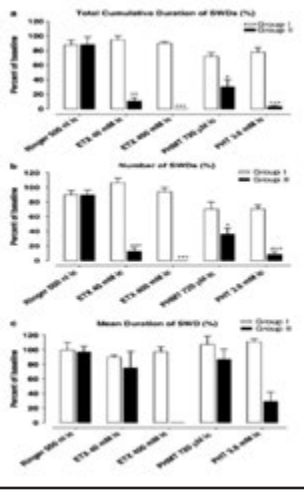
Cortico-Cortical. Intra-Thalamic and Cortico-Thalamic relations

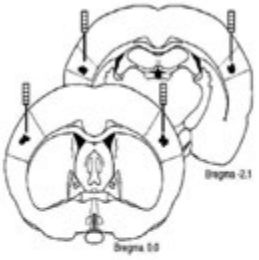


Focus does not mean a "point source", just that the local neuronal population has a low threshold for initiating seizures.

During the seizures it becomes just a part of the oscillating network.

The oscillations constitute an emergent property of the whole system.



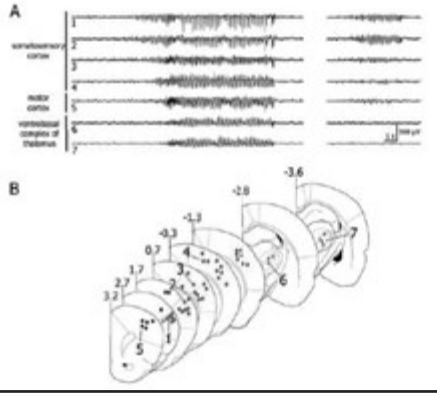


Effect of systemic and intracortical administration of phenytoin in two genetic models of absence epilepsy

Ayten A Gurbanova,[1] Rezzan Aker,[1] Kemal Berkman,[1] Filiz Yilmaz Onat,[1] Clementana M van Rijn,[2] and Gilles van Luijtelaar[2]*

Br J Pharmacol. 2006 August; 148(8): 1076–1082.

Principles of interictal-ictal transitions and precursors of seizures



SWDs are initiated in the facial somatosensory cortex in GAERS and propagate to other cortical areas and to the thalamus.

Polack, Guillemain, Hu, Deransart, Depaulis and Charpier,

J. of Neurosci June 2007

Principles of interictal-ictal transitions and precursors of seizures

The occurrence of SWD in the local ECoG coincides with rhythmic membrane depolarizations superimposed on a tonic hyperpolarization of this layer IV neuron (filled with neurobiotin) (GAER rat)

Polack, Guillemain, Hu, Deransart, Depaulis and Charpier, J. of Neurosci June 2007

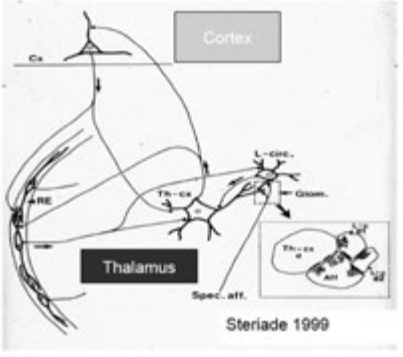
Principles of interictal-ictal transitions and precursors of seizures

In order to understand this behaviour of the neuronal networks we need a computational model

Computational model of the thalamo-cortical neuronal networks

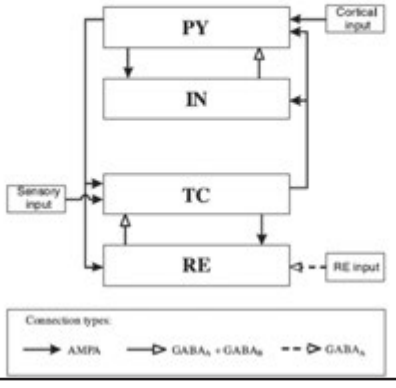
Suffczynski, Kalitzin, Lopes da Silva,Dynamics of non-convulsive epileptic phenomena modelled by a bistable neuronal network, *Neuroscience* 126 (2004) 467–484

Basic neuronal network responsible for 3 Hz spike-and-wave paroxystic activity: thalamo-cortical circuits

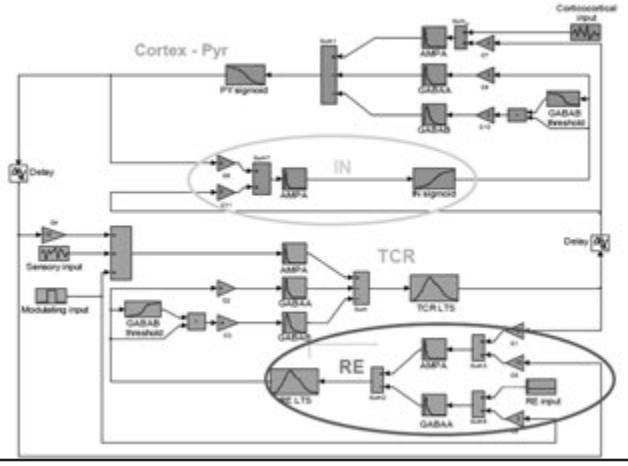


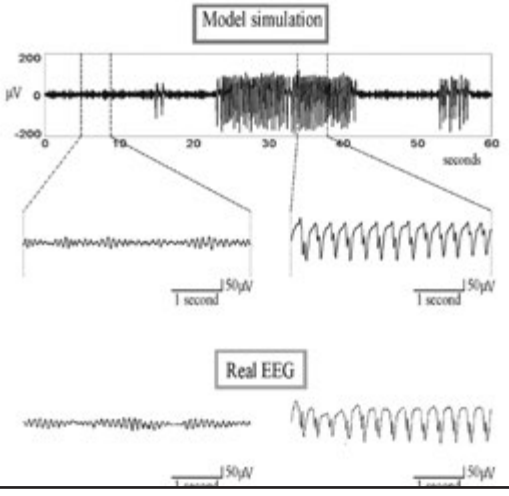
Steriade 1999

Epilepsy as diseases of the dynamics of neuronal networks. Models and predictions



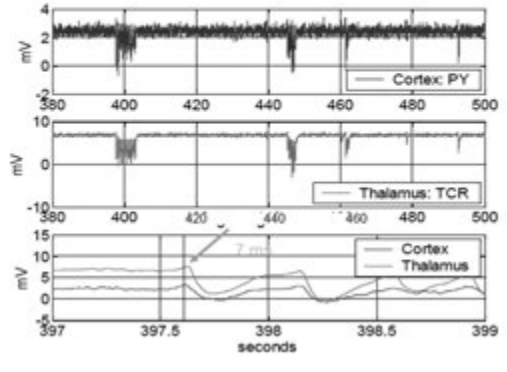
Lumped model of thalamo-cortical network



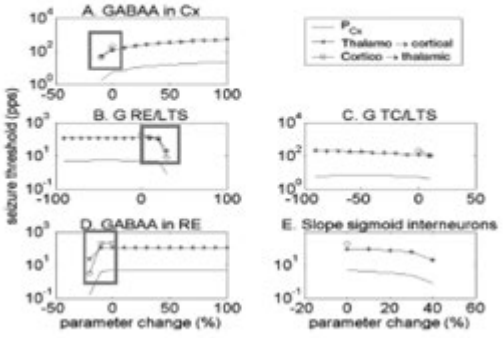


Example of a bifurcation between two states: "normal" & "seizure" (absence type), both in the model and in EEG real signals.

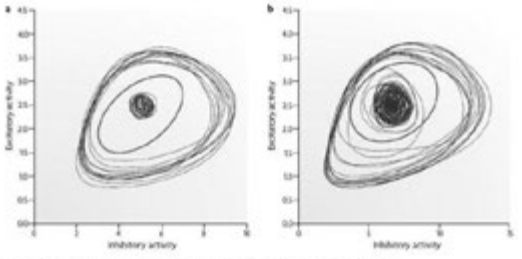
Model simulation of cortical and thalamic activity



Occurrence of transition to "epileptic seizure" mode: parameter sensitivity



Phase portraits of the system under non-epileptic and epileptic conditions



Sample trajectories (thin lines) from normal (left) and epileptic model (right) projected onto a 2-dimensional slice of state space. The axes are values of two state variables: cortical excitatory and inhibitory activity. The thick line is a separatrix separating 2 attractors (Lopes da Silva et al 2003).
Lytton, W.W. Computer modelling of epilepsy. Nature Reviews Neuroscience, 2008, 9:626-637.

Principles of interictal-ictal transitions and precursors of seizures

What are the predictions of the model of type 1 with respect to the dynamics of absence seizures?

- One prediction is that for this kind of seizures the transition occurs randomly;

Principles of interictal-ictal transitions and precursors of seizures

- This prediction was tested by calculating the distributions of durations and of intervals inter-paroxysms.

Distribution of Durations either of paroxysmal events or of inter-paroxysmal events

In common language:

Termination of a process is random in time with constant probability

simple calculation

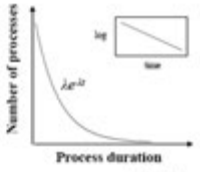
Prediction

Exponential distribution of process durations

In math language:

Probability of termination in unit time : p
Probability of survival of unit time : $1-p$

$P(t) = (1-p)^t p \dots (1-p)^n p$
$1-p = e^{\ln(1-p)} = 1-e^{\lambda}$
$P(t) = (1-e^{\lambda})e^{\lambda t}$
$e^{\lambda} \approx 1+\lambda$
$P(t) = \lambda e^{-\lambda t}$

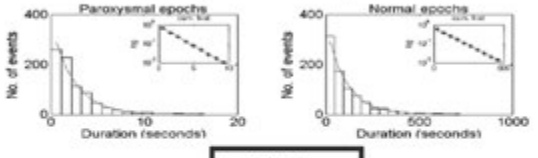


Medical Physics Department

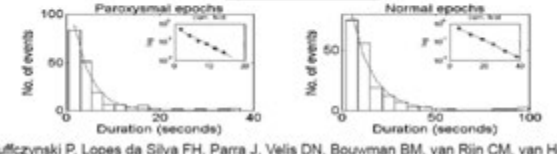
© SEIN, 2003

Distributions of epochs duration

Model simulation



Rat data



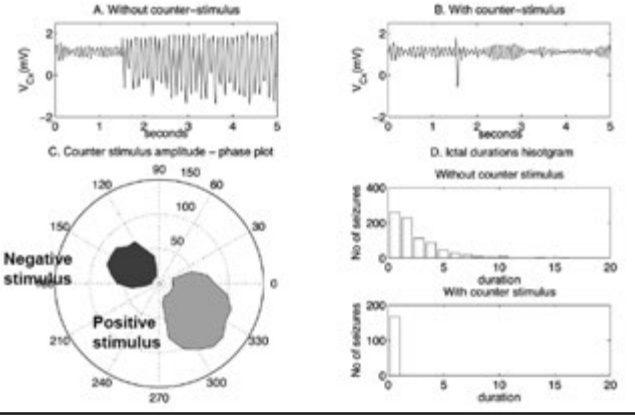
Sufficzynski P, Lopes da Silva FH, Parra J, Velis DN, Bouwman BM, van Rijn CM, van Hese P, Boon P, Khosravani H, Derchansky M, Carlen P, Kalitzin S. Dynamics of epileptic phenomena determined from statistics of ictal transitions. *IEEE Trans Biomed Eng.* 2006 Mar;53(3):524-32.

Neuronal models and the routes to epileptic seizures

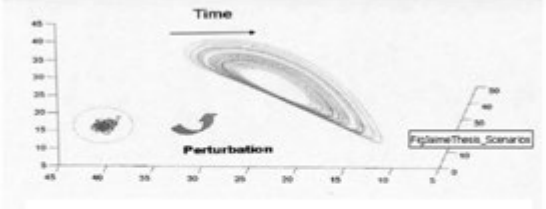
Another prediction is that it should be possible to control seizure occurrence, i.e. the transition from "normal" to "epileptic" state.

In a bi-stable system it is possible to abort a limit cycle by applying a perturbation ("counter stimulation") at the appropriate phase of the oscillation.

Counter-stimulation is capable of annihilating the transition to the paroxysmal oscillation



In Conclusion:



The absence types of epilepsy seizures follow a bifurcation dynamical scenario: they display jump transitions (Model type 1).

Principles of interictal-ictal transitions and precursors of seizures

- Case 1:
- The occurrence of Spike-and-Wave discharges in the thalamo-cortical system, typical of absence seizures.

- Case 2:
- The occurrence of seizure activity in the hippocampal formation.

Principles of interictal-ictal transitions and precursors of seizures

- Case 1:
- The occurrence of Spike-and-Wave discharges in the thalamo-cortical system, typical of absence seizures.

- Case 2:
- The occurrence of seizure activity in the hippocampal formation.

Principles of interictal-ictal transitions and precursors of seizures

An example from basic neurophysiology shows what the properties of a pre-ictal state may be.

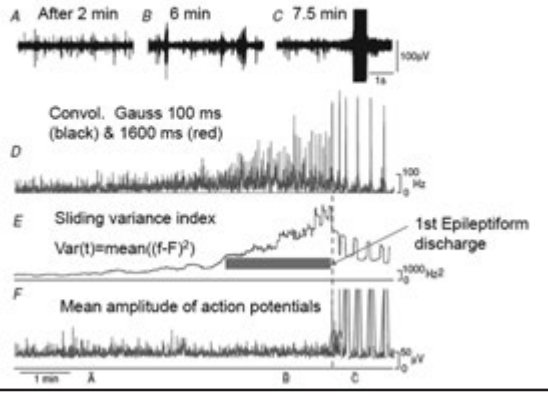
J Physiol 570.3 (2006) pp 583–594

Emergence of disinhibition-induced synchrony in the CA3 region of the guinea pig hippocampus *in vitro*

Ivan Cohen, Gilles Huberfeld and Richard Miles

Disinhibition-induced synchronization of CA3 population firing

(perfusion with 10 um bicucculine)

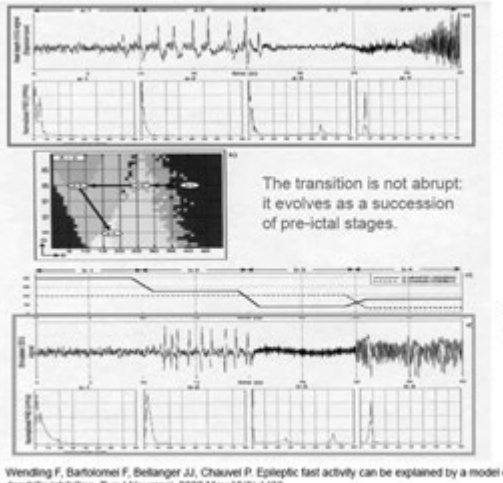


Principles of interictal-ictal transitions and precursors of seizures

Cohen et al (2006) experiments show the existence of what may be called a precursor state.

These results imply that in this case there exists a pre-ictal state with special properties.

The sliding variance index = mean $[(f - F)^2]$ starts to change several minutes before the first epileptiform spike is detected.



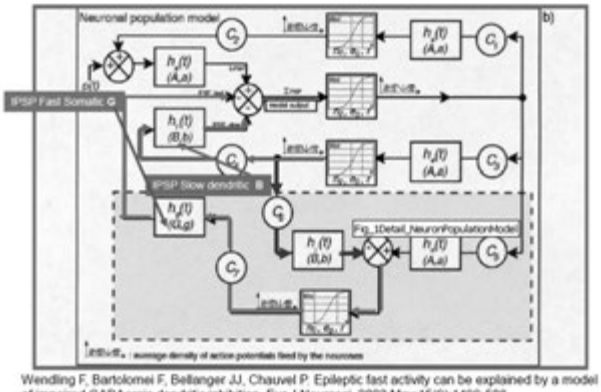
Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. Eur J Neurosci. 2002 May;15(9):1499.

Principles of interictal-ictal transitions and precursors of seizures

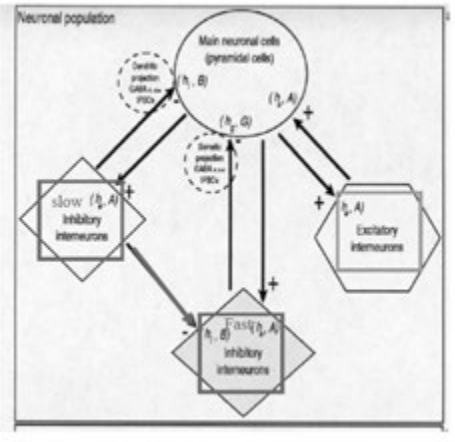
In order to understand this behaviour of the neuronal networks we need a computational model

Computational model of the neuronal networks of the Hippocampal system

Wendling's model of Hippocampal network

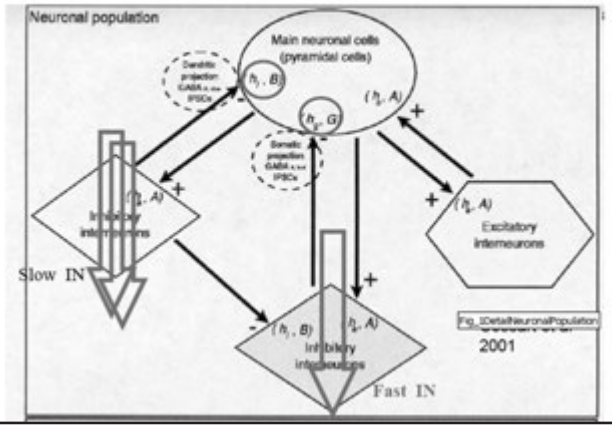


Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. Eur J Neurosci. 2002 May;15(9):1499-508.

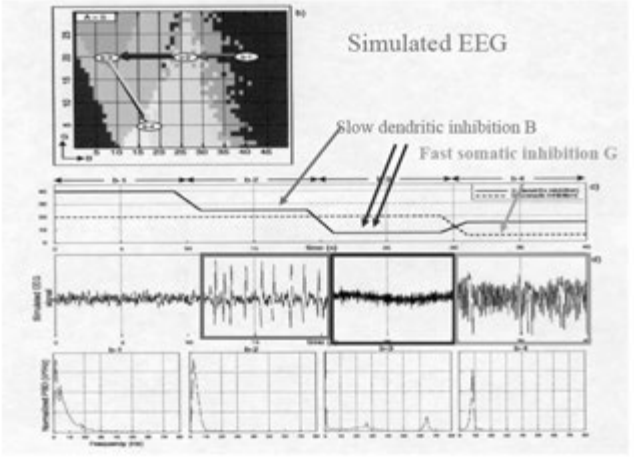


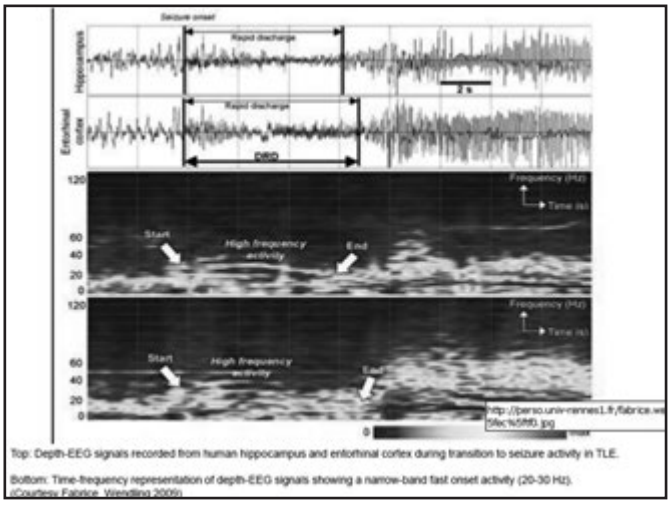
Detail of the model: interaction between different types of inhibitory interneurons and principal (pyramidal) cells (Bank et al Neuron 2000).

Hippocampal Neuronal Population Model



Simulated EEG

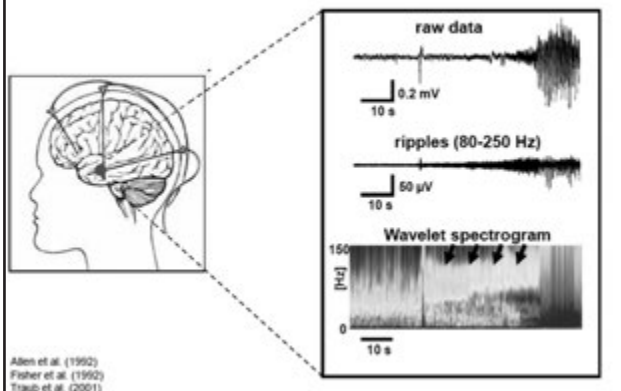




Top: Depth-EEG signals recorded from human hippocampus and entorhinal cortex during transition to seizure activity in TLE.

Bottom: Time-frequency representation of depth-EEG signals showing a narrow-band fast onset activity (20-30 Hz).
(Courtesy Fabrice Wendling 2009)

Fast Oscillations Preceding Seizures in Man



Allen et al. (1992)
Fisher et al. (1992)
Traub et al. (2001)
Worrel et al. (2004)
Ochi et al. (2007)

John Jefferys, Petr Marusic, Martin Tomasek

Principles of interictal-ictal transitions and precursors of seizures

- The main question in cases of the second type is how to detect the special properties of the pre-ictal state, or better the pro-ictal state.

Many analytical methods have been proposed: passive and active paradigms of EEG analysis.

Here I will consider those methods that use an active paradigm, i.e. using a probe or a stimulation protocol - in order to estimate changes of the excitability state of the neuronal networks that may be characteristic of this pre-ictal state.

Principles of interictal-ictal transitions and precursors of seizures

Passive or Active paradigms of seizure anticipation?

A computer model yields evidence for the necessity of using an active paradigm

Piotr Suffczynski, Stiliyan Kalitzin, Fernando Lopes da Silva, Jaime Parra, Demetrios Velis, Fabrice Wendling [Submitted for publication]

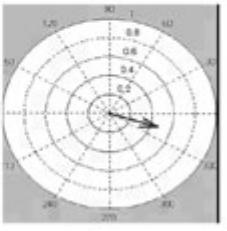
Active observation: stimulation with "carrier frequency" Phase clustering index (PCI)

Z_f^k

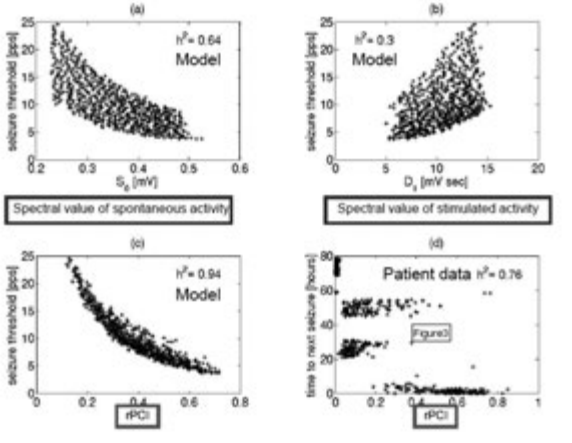
Repetitive stimulus

$$|< Z_f^k >_k| = \kappa_f \lhd |Z_f^k| \rhd_k \equiv \kappa_f A_f$$

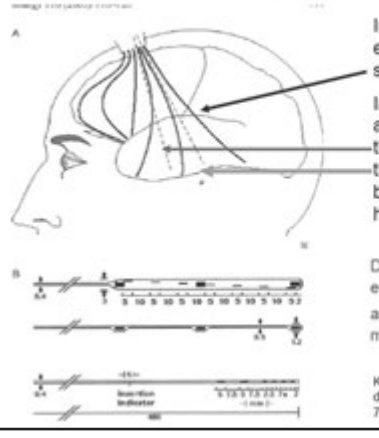
$$\kappa_f = \left| \frac{< Z_f^k >_k}{\lhd |Z_f^k| \rhd_k} \right|$$



S. Kalitzin, J. Parra, D. Velis, F. Lopes da Silva, Enhancement of phase clustering in the EEG/MEG gamma frequency band anticipates transition to paroxysmal epileptiform activity in epileptic patients with known visual sensitivity, IEEE-TBME, v.49, 11 p 1279-1286, 2002



Principles of interictal-ictal transitions and precursors of seizures



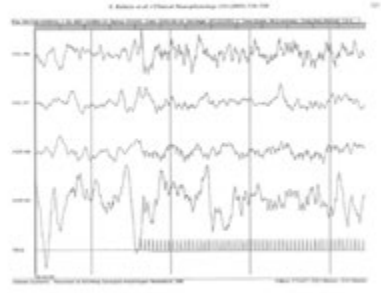
Implantation layout and electrode bundles: subdural reeds and

Intracerebral electrodes aimed at the head of the hippocampus and the midportion of the body of the hippocampus.

Direct intra-cerebral electrical stimulation using a carrier frequency modulation probe

Kalitzin, Velis, Suffczynski, Parra, Lopes da Silva, Clin. Neurophysiol. 2005, 116: 718 – 728.

Principles of interictal-ictal transitions and precursors of seizures

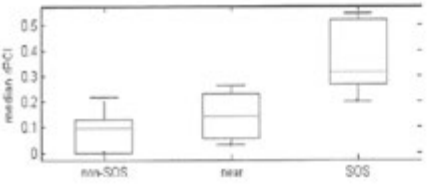


Bilateral electrical stimulation [20 Hz, 800 µA, duration 5 sec] stimulated electrodes are HCL K4 and HCL K5 on the left hippocampus, and HCR H4 and HCR H5 on the right.

The relative phase clustering index (rPCI) is computed for all signals and all stimulated epochs

Kalitzin, Velis, Sufficzynski, Parra, Lopes da Silva, Clin. Neurophysiol. 2005, 116: 718 – 728.

Principles of interictal-ictal transitions and precursors of seizures

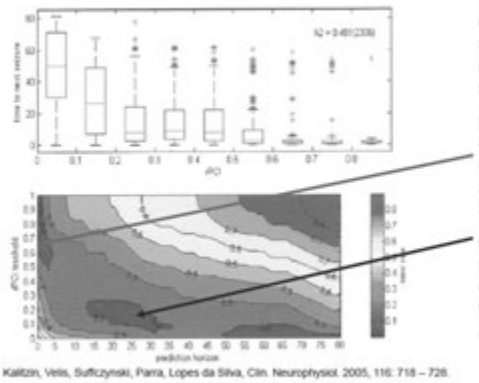


Statistics of the interictal rPCI values for 18 Traces of 6 patients; grouped according to whether the electrodes were at the Site of Seizure Onset (SOS) or near to it, or not (non-SOS).

Fig.3 Clin Neurophysiol 2005

Kalitzin, Velis, Sufficzynski, Parra, Lopes da Silva, Clin. Neurophysiol. 2005, 116: 718 – 728.

rPCI as function of time preceding a seizure



Values of rPCI en route to a seizure combined for all sites

rPCI > 0.6 – Seizure occurring <2h, accuracy >80%;

0.1>rPCI<0.3 – seizure expectancy within 15-30h, accuracy >80%.

Kalitzin, Velis, Sufficzynski, Parra, Lopes da Silva, Clin. Neurophysiol. 2005, 116: 718 – 728.

Sufficzynski P, Kalitzin S, da Silva FL, Parra J, Velis D, Wendling F. Active paradigms of seizure anticipation: computer model evidence for necessity of stimulation. Phys Rev E Stat Nonlin Soft Matter Phys. 2008 Nov;78(5 Pt 1):051917

Basic Mechanisms of Transition to Seizures

Basic mechanisms:

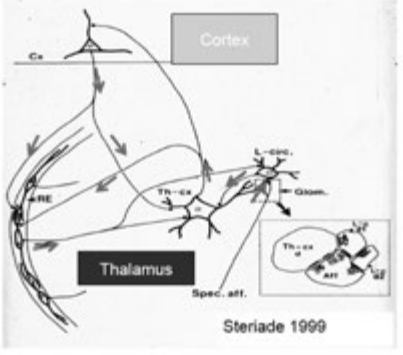
- ❑ **Re-entrant loops**
- ❑ **Reverberating circuits** / coupled oscillators
- **Run-down of inhibition**
- **Sustained excitation**
- **Extracellular chemical changes (K^+)**

Markers of the pre-ictal stage and of "driver network":

- ❑ **Increase of Relative Phase Clustering Index (rPCI) of high frequency components**
- ❑ **High frequency activity**:
- ripples, fast ripples
- Fast inhibition
- Field effects

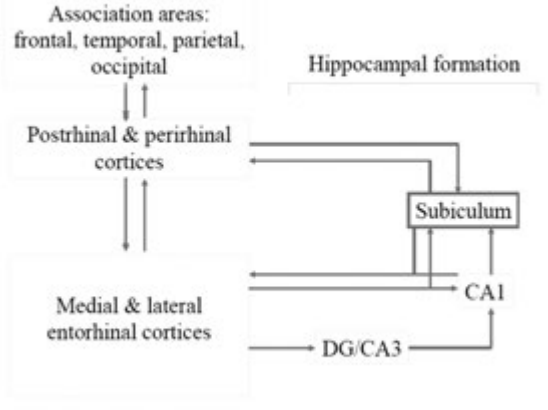
Modified from John Jefferys, 4th Int Symposium Seizure Prediction. Kansas City 2009

Basic neuronal network responsible for 3 Hz spike-and-wave paroxystic activity: thalamo-cortical circuits



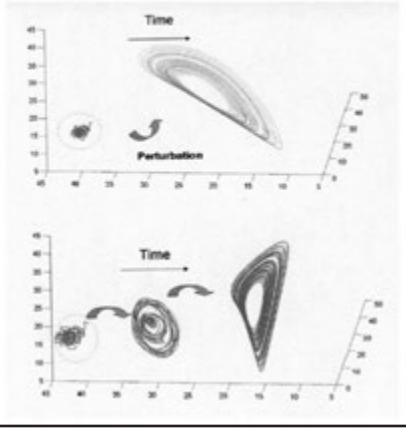
Steriade 1999

Re-entrant loops in the Temporal Lobe



Lopes da Silva et al 2000

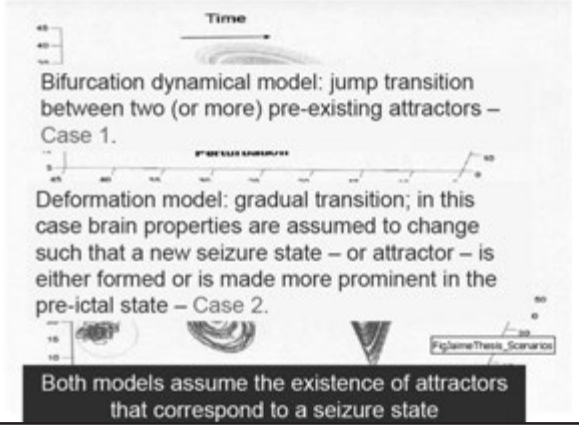
In Conclusion: there are 2 main classes of models that may explain the transition to epilepsy



Bifurcation dynamical model: jump transition – Case 1.

Deformation model: gradual transition – Case 2.

In Conclusion: there are 2 main classes of models that may explain the transition to epilepsy

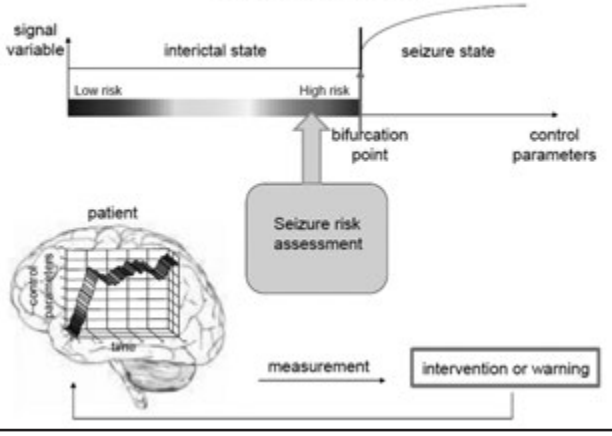


Bifurcation dynamical model: jump transition between two (or more) pre-existing attractors – Case 1.

Deformation model: gradual transition; in this case brain properties are assumed to change such that a new seizure state – or attractor – is either formed or is made more prominent in the pre-ictal state – Case 2.

Both models assume the existence of attractors that correspond to a seizure state

Seizure anticipation



Principles of interictal-ictal transitions and precursors of seizures
Questions *and* Answers

- Is it possible to anticipate the occurrence of epileptic seizures by means of (chronic) ICES in refractory epileptic syndromes? ✓
- Is it possible to prevent the occurrence of epileptic seizures by means of (chronic) ICES in refractory epileptic syndromes? ?

Principles of interictal-ictal transitions and precursors of seizures

Collaborators from the Institute of Epilepsy SEIN ("Meer en Bosch", Heemstede) and Center of NeuroSciences, University of Amsterdam):

Stiliyan Kalitzin,
Piotr Suffczynski
Jaime Parra.
Elan Ohayon
Fernando Lopes da Silva
Dimitri Velis.

Principles of interictal-ictal transitions and precursors of seizures

Details are described in

Kalitzin, Parra, Velis, and Lopes da Silva, (2002)
Enhancement of Phase Clustering in the EEG/MEG Gamma Frequency Band Anticipates Transitions to Paroxysmal Epileptiform Activity in Epileptic Patients With Known Visual Sensitivity.
IEEE Transactions on BioMedical Engineering. 49 (11), 1279-85.

Parra, Kalitzin, Iriarte, Blanes, Velis and Lopes da Silva, (2003)
Gamma-band phase clustering and photosensitivity: Is there an underlying mechanism common to photosensitive epilepsy and visual perception?
Brain. 126(Pt 5):1164-72.

Lopes da Silva FH, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN.
Dynamical diseases of brain systems: different routes to epileptic seizures.
IEEE Trans Biomed Eng. 2003 May;50(5):540-8.

Principles of interictal-ictal transitions and precursors of seizures

Kalitzin, Velis, Suffczynski, Parra, Lopes da Silva, (2005) Electrical brain-stimulation paradigm for estimating the seizure onset site and the time to ictal transition in temporal lobe epilepsy. *Clin Neurophysiol.* 116(3):718-28.

Suffczynski P, Lopes da Silva FH, Parra J, Velis DN, Bouwman BM, van Rijn CM, van Hese P, Boon P, Khosravani H, Derchansky M, Carlen P, Kalitzin S. Dynamics of epileptic phenomena determined from statistics of ictal transitions. *IEEE Trans Biomed Eng.* 2006 Mar;53(3):524-32.

Kalitzin SN, Parra J, Velis DN, Lopes da Silva FH Quantification of unidirectional nonlinear associations between multidimensional signals. *IEEE Trans Biomed Eng.* 2007 Mar;54(3):454-61.

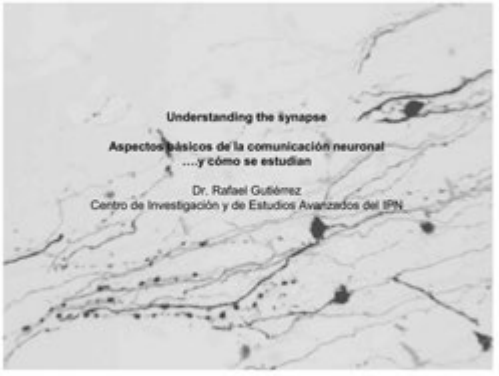
Bouwman BM, Suffczynski P, Lopes da Silva FH, Maris E, van Rijn CM. GABAergic mechanisms in absence epilepsy: a computational model of absence epilepsy simulating spike and wave discharges after vigabatrin in WAG/Rij rats. *Eur J Neurosci.* 2007 May;25(9):2783-90.

Suffczynski P, Kalitzin S, Lopes da Silva FH, Parra J, Velis D, Wendling F. Active paradigms of seizure anticipation: computer model evidence for necessity of stimulation. Phys Rev E Stat Nonlin Soft Matter Phys. 2008 Nov;78(5 Pt 1):051917

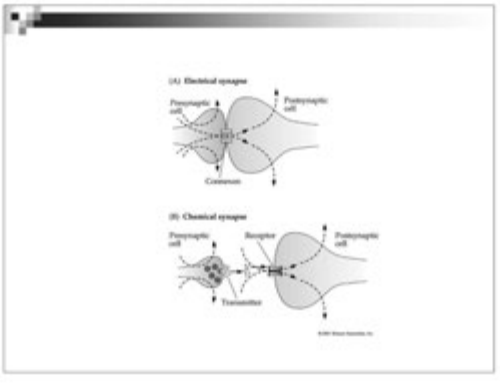
Programa – 03.02.2010

08:30 – 09:30	Understanding the synapse – Rafael Gutierrez (México)
09:30 – 10:30	Not a simple brake – the complex mechanisms of GABAenergic inhibition – Andreas Draguhn (Germany)
10:30 – 11:00	Coffee-break
11:00 – 12:00	The GABA and how dynamic chloride explains seizure generation – Y. Bem-Ari (France)
12:00 – 14:00	Lunch
14:00 – 15:00	It's time to seize: temporo-spatial relationship of epileptic discharge – Roberto Spreafico (Italy)
15:00 – 16:00	Processes mediating epileptogenesis revealed by micro-array analyses and the modulation of specific molecular targets – F. Lopes da Silva (Netherlands)
16:00 – 16:30	Coffee-break
16:30 – 17:30	High frequency activity in the human epileptic brain – J. Engel Jr. (USA)
17:30 – 18:30	Temporal aspects of very fast brain oscillations prior to seizures – Roger Traub (USA)
18:30 – 20:00	Dinner
20:00 – 21:00	The aberrant kainate synaptic currents and how they are crucial in TLE – Y. Bem-Ari (France)

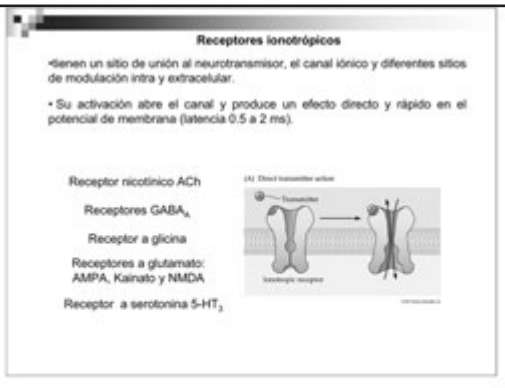
UNDERSTANDING THE SYNAPSE
RAFAEL GUTIERREZ (MÉXICO)



This presentation is an introduction to the following talks. The goal is to get an overview of the synapse.



There are two types of synapses: electrical and chemical, although we will learn that there can also be mixed synapses.



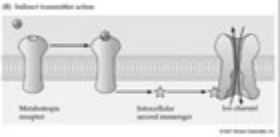
The released neurotransmitter acts on different receptors and, thus, the timing of its action depends on them.

Activation of ionotropic receptors directly promotes ion flux… whereas….

Receptores metabotrópicos

- La respuesta sináptica es más lenta comparada con la respuesta sináptica mediada por receptores ionotrópicos (latencia 20 a 300 ms).
- disparan la abertura del canal de forma indirecta.
- Pueden estar acoplados a proteínas G o a cinasa de tirosina

Receptor adrenérgico β y α1
Receptor muscarínico a ACh
Receptor $GABA_B$
Receptores metabotropicos a glutamato mGluR1-mGluR7
Receptor a serotonina $5\text{-}HT_{1,2,4}$
Receptores para neuropéptidos



The activation of metabotropic receptors implies the turning on of an intracellular cascade.

La transmisión química implica:

síntesis del neurotransmisor
transporte
preparación
la llegada de un potencial de acción a la terminal la liberación en paquetes o cuantos
(modulacion por CANALES DE K Y Ca!)

la difusión del neurotransmisor por el espacio sináptico que separa a la pre de la Postsinapsis

la acción del transmisor en los receptores de la membrana postsináptica

la inactivación del efecto del transmisor
la apertura de canales y, eventualmente, cambios en el potencial de membrana y de excitabilidad de la neurona postsináptica que "integra" la señal entrante
CONDUCCION

Tercer jugador: glia, quien modula neurotransmisores, iones, factores tróficos

Alteraciones :
incremento de la liberación de glutamato u otro neuro-transmisor excitador
consecuencia: excitotoxicidad

reducción de la liberación de GABA u otro neurotransmisor inhibidor;
consecuencia: hiperexcitabilidad

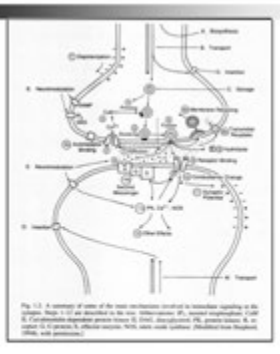
cambio del espacio extracelular "acercamiento": interacciones ETópticas "alejamiento": cambios en la concentración en la sinapsis

incremento / decremento de la recaptura

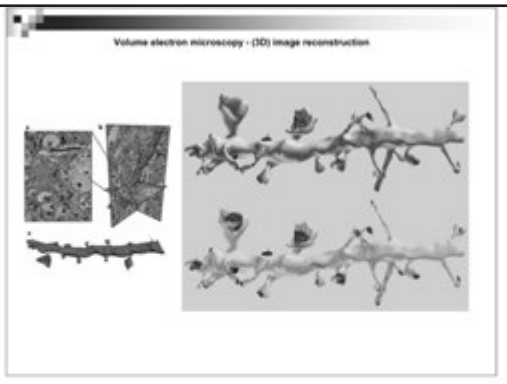
acción de enzimas catalíticas

concentración extracelular de iones
estado previo de la neurona
mutaciones de canales y receptores, expresión selectiva de diferentes conformaciones de los receptores

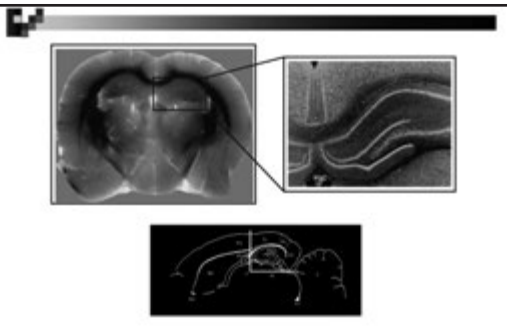
Neurotransmitter release implies several steps, from synthesis to release itself. Each step can be modified and, thus, can alter communication between neurons.



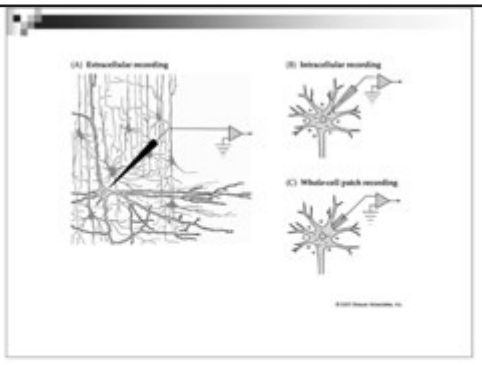
Schematic view of the processes involved in the signaling at the synapse.



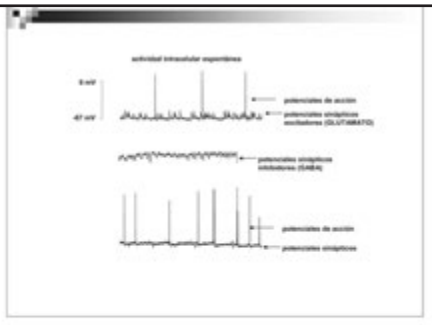
Further, transmission of the message does not only depend on the type of receptor activated but on where the receptor is. Integration of the signal depends on the anatomy.



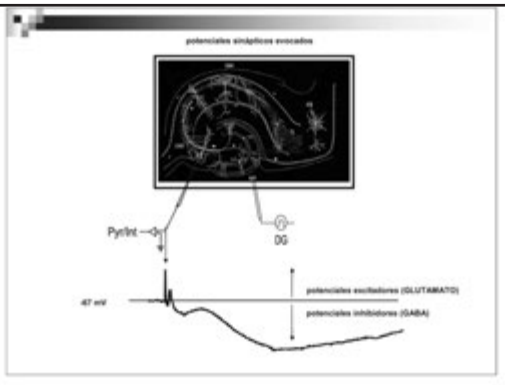
To study all this, one of the favorite models for electrophysiologists is the hippocampal slice.



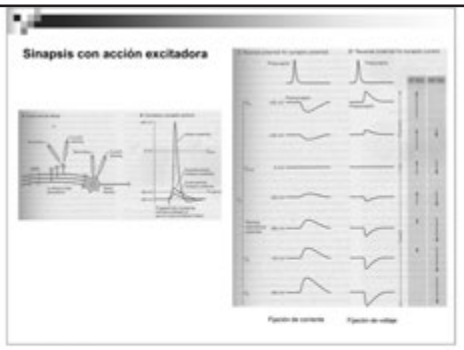
Electrophysiologists mainly record 3 types of signals: Extracellular, which reflects the field potentials (implying hundreds of cells); Intracellular, which implies the use of sharp electrodes inserted to the cell to record the difference of potential between the inside of the cell and the extracellular space; Whole-cell recordings, which opens a window at the membrane and forms a continuum between the electrode's solution and the intracellular space (gives high sensitivity).



Intracelular recordings show synaptic activity of a pyramidal cell. The membrane potential at rest has around -67 mV and, from that value, synaptic activity moves the potential toward depolarized or hperpolarized values. Excitatory post-synaptic potentials or EPSPs are upward deflections or depolarizations. When an EPSP reaches certain voltage, it can generate an action potential. This is called the "threshold" for action potential initiation. On the contrary, IPSPs are downward deflections, hyperpolarize the cell and, thus, moves the membrane potential far from threshold for initiation of action potentials. EPSPs are mainly produced by the activation of glutamate receptors, whereas IPSPs are produced by the activation of GABA receptors.



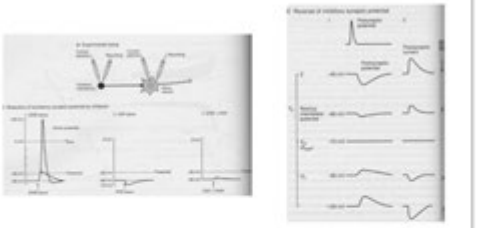
Activation of a group of cells (in the example granule cells of the dentate gyrus- DG) produces simultaneous release of glutamate from their axons and activate receptors in the recorded cell. Therefore, with an intracellular recording, one can detect the release of neurotransmitters. The example depicts a sequence of EPSP, fast IPSP and slow IPSP evoked in a pyramidal cell on stimulation of the DG.



The recording of evoked responses can be done in different ways. One can record the currents or the voltages (potentials) produced by the stimulus. In the former, the experimenter maintains the voltage of the membrane at a certain level and "sees" the current, whereas in the later, the experimenter can inject a current and detects the voltage changes.

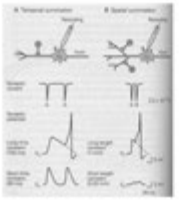
The example shows EPSPs or EPSCs and how their amplitude depend on the membrane potential.

Sinapsis con acción inhibidora



The example shows IPSPs or IPSCs and how their amplitude depend on the membrane potential. This behavior allows to know which ion type is the responsible for the movement of charge.

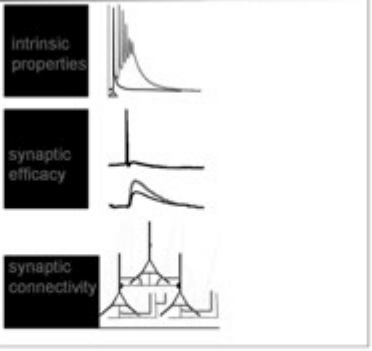
Mecanismos de integración



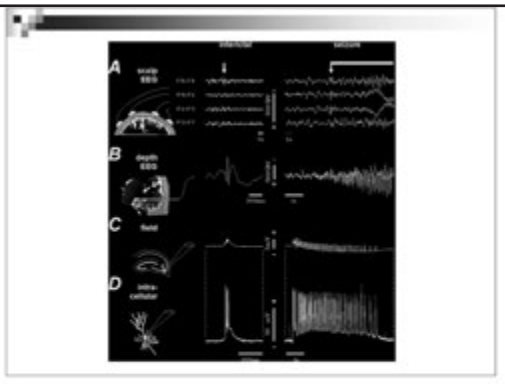
Sumación temporal: Dependiendo del momento en que una segunda respuesta es evocada, los cambios en la membrana pueden "superponerse" y sumarse.

Sumación espacial: Dos o más botones liberan neurotransmisor y activan diferentes "sitios" de la neurona. Éstos se suman

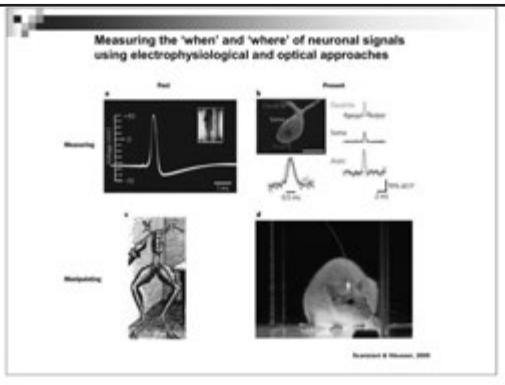
The hundreds or thousands of signals that a cell receives are integrated according to biophysical properties of the membrane in the vicinity of the receptors that are activated.



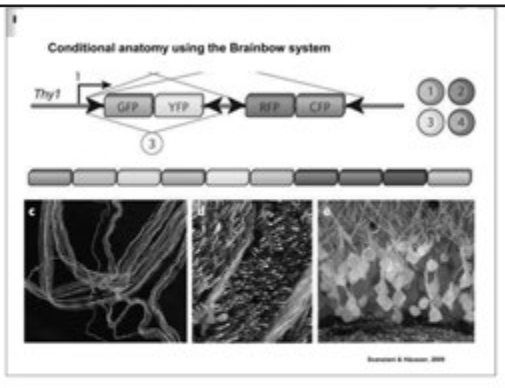
When studying the behavior of a cell, one has to consider its biophysical (intrinsic) properties, the strenght of the communication with other cells (synaptic efficacy) and how it interacts within a circuit.



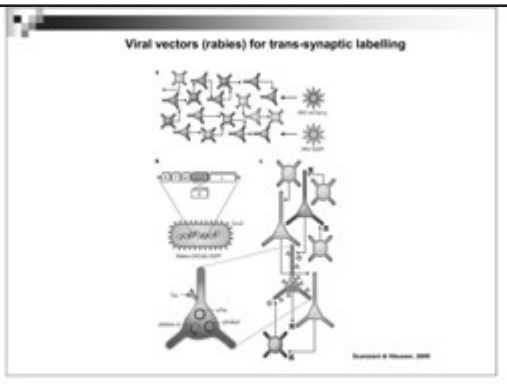
How an epileptiform event, detected on the skull, is reflected in field and intracellular recordings.



Evolution of the methodology to study neuronal communication. Electrophysiology addresses mainly the "when". New imaging technologies allow to study the "where"

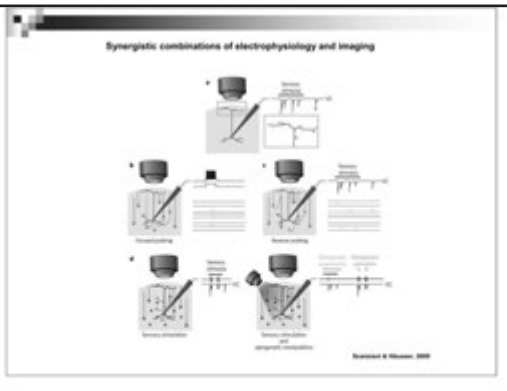


Brainbow mice can be used to identify neuronal subsets by conditional activation of fluorescent reporters

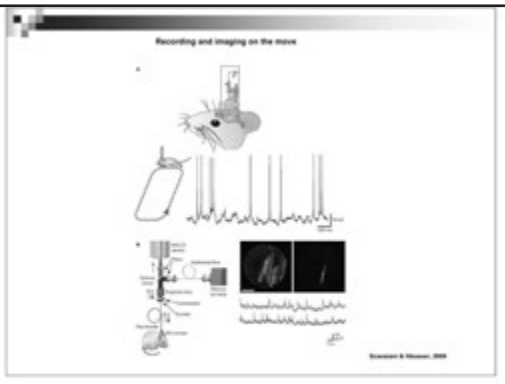


The use of viral vectors allow to infect targeted cells. The infection allows to label the cells for further study.

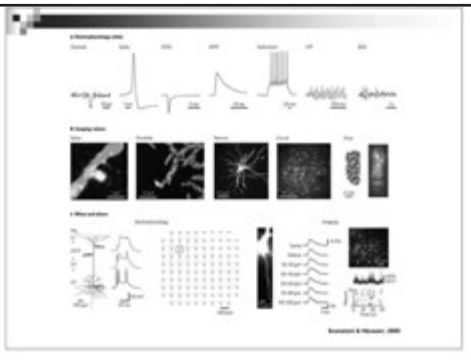
Imaging techniques take advantage of luminiscence of several compounds which can be coupled to ions, receptors, channels, etc.



Labeled cells, usually with fluorescence, can be actually seen and then selected under the microscope so that recordings can be directed.

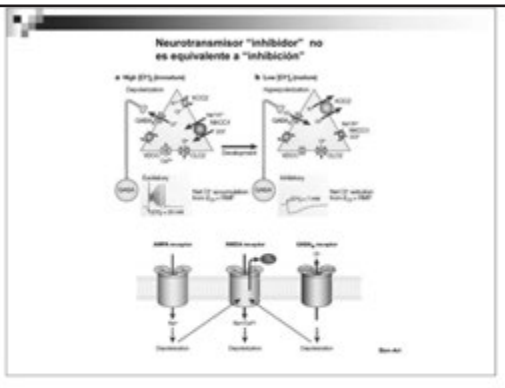


Electrophysiological recordings combined with imaging techniques can now be applied on behaving animals.



Electrophysiology addresses mainly the "when". New imaging technologies allow to study the "where".

However, refining electrophysiological techniques by the use of multiple electrode recordings in multiple sites (of a structure or circuit, and of a cell) as well as the combination of this with imaging techniques allow for the integration of the when and the where.



It's not that simple…….. Neurotransmitters are not inherently "inhibitory" or "excitatory". The type of receptor (in the case of metabotropic glutamate receptors) and the intracellular millieu (chloride regulation – GABAA receptors) define the action of the neurotransmitter.

TRANSMISION

Un neurotransmisor es una sustancia que al liberarse de una terminal nerviosa transmite un mensaje a las células vecinas o a la terminal de la que se libera para modificar su acción ulterior.

Según su modo de acción, se han considerado como neurotransmisores "clásicos" o de acción rápida, como neuromoduladores, o como factores tróficos.

CO-TRANSMISION

"Principio de Dale" : una neurona libera un solo neurotransmisor de todas sus terminales, y no otro, debido a que es una unidad metabólica.

Pero: en los 70s se comprobó que la coliberación era posible cuando se observó que el ATP se liberaba de terminales que liberaban noradrenalina. Posteriormente se comprobó que varios péptidos podían liberarse de terminales que liberaban neurotransmisores de "acción rápida".

Actualmente se sabe que hay varias combinaciones de neurotransmisores "clásicos" que son coliberados.

Another important and recently address phenomenon in neuronal communication is co-transmission, that is, the possiblity of a single cell releasing more than one neurotransmitter.

CO-TRANSMISION

Actualmente es claro que la coliberación es la regla, más que la excepción.

Usualmente se libera un neurotransmisor ("clásico") de acción rápida y un transmisor de alto peso molecular -un péptido (con acción moduladora), o un gas (óxido nítrico), o un metal (Zn^{++}), o ATP, o un factor trófico.

....sin embargo, (en 2001) solo existían dos ejemplos de coliberación de neurotransmisores de acción rápida:

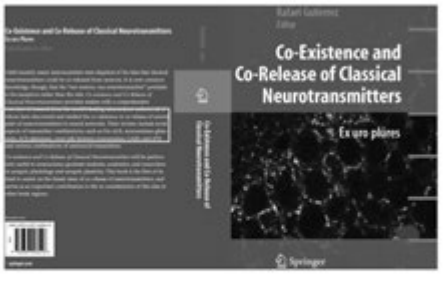
GABA y glicina en la médula espinal
(el transportador vesicular es común para ambos)

glutamato y GABA
en la sinapsis que forman las fibras musgosas con las células de la zona CA3 del hipocampo
(la descarboxilación del glutamato origina GABA.....)

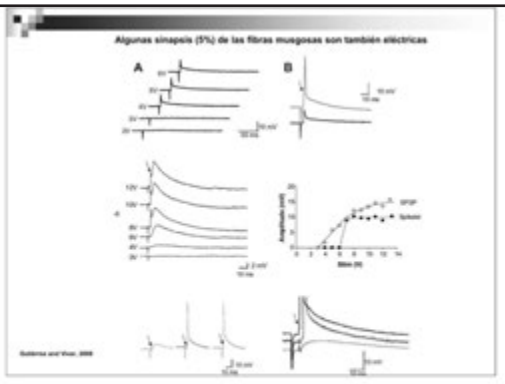
¡....y la unidad metabólica no se rompe!

More and more examples of this phenomenon appear.

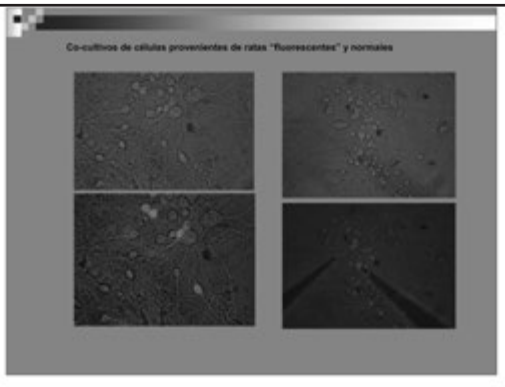
....a la fecha (2009) entre los ejemplos de coliberación de neurotransmisores de acción rápida están.....



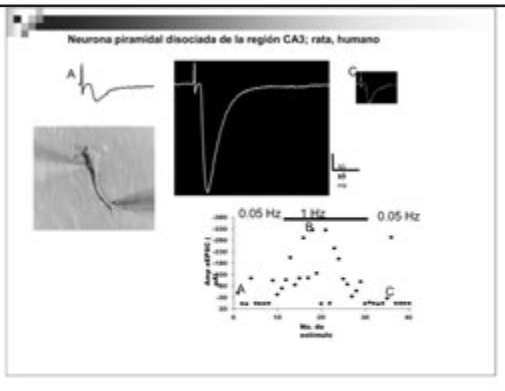
Now, we have several combinations or neurotransmitters that are packed and released together. We have gathered them in a book.



Another novelty: Evidence for mixed electrical-chemical synapses in some Mossy fibers contacting CA3 pyramidal cells.

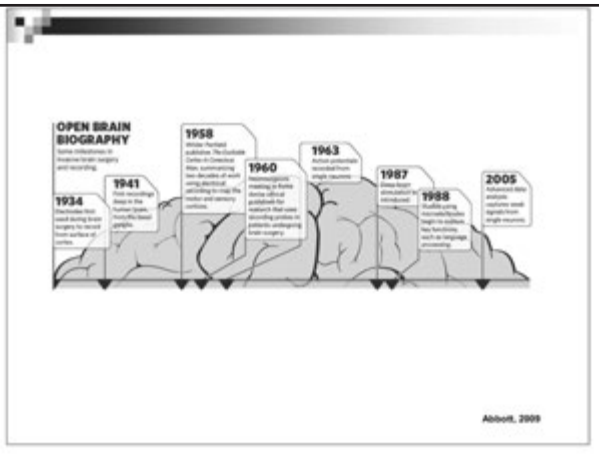


To be able to study synaptic physiology in greater detail, co-cultures of GFP-expressing granule cells with wild type pyramidal cells allows for immediate recognition of the cells and for complete control of recording conditions.



Another way to explore synaptic physiology is by directly stimulating synaptic boutons attached to dissociated cells, which can be recorded in whole-cell configuration.

.....but we need to explore the better model there is! … the human brain…. Let's team up with neurosurgeons!!



Neurological and Psychiatric Diseases are "diseases of neuronal communication"

- Stroke (pumps, transporters –pH-; ion homeostasis)
- Multiple Sclerosis (transmission of electrical signals)
- Amyotrophic Lateral Sclerosis (functional muscle denervation)
- Epilepsy (intrinsic properties; channelopaty; receptors' modifications or expression; circuit rearrangement)
- Alzheimer's (membranal and soluble b-amyloid)
- Parkinson's (DA transmission; cell death)
- Huntington's (GABAergic transmission; cell death)
- Channelopaties (excitability)
- Pain (channels; Cl- homeostasis)
- Depression (neurotransmitter output; receptors' alterations)
- Schizophrenia (neurodevelopment; histoarchitecture)

In the end, most of eurological and psychiatric disorders are "disorders" of neuronal communication

Not a simple brake – the complex mechanisms of GABAenergic inhibition

Andreas Draguhn (Germany)

IZN

Interdisziplinäres Zentrum für Neurowissenschaften der Ruprecht-Karls-Universität Heidelberg

Sao Paulo, Feb 3rd, 2009

LASSE IV

Not a simple break – the complex mechanisms of GABAergic inhibition

Andreas Draguhn

GABAergic inhibition

I Classical View: Reduction of Excitability

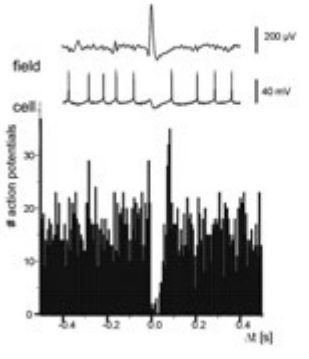
II Complications

III Inhibition within Networks:

- Excitation-Inhibition-Balance
- Signal-to-Noise-Ratio
- Spatial and Temporal Patterns

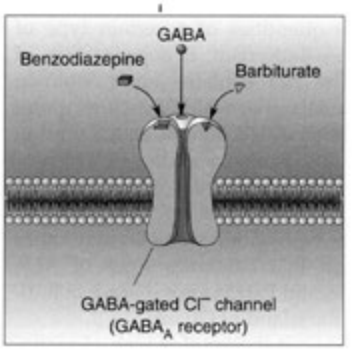
IV Perspectives

Inhibition is reduction of discharge probability

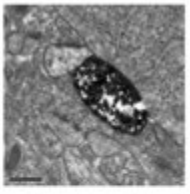


Maier et al., 2003

Inhibition is reduction of discharge probability

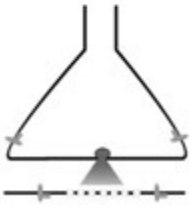


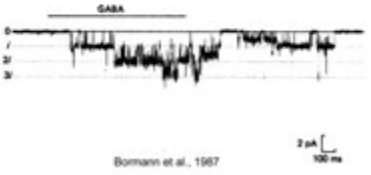
Maier et al., 2003



Gunnar Birke (HD) & Michael Frotscher (FB)

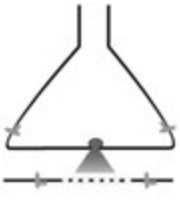
The GABAergic synapse – simple scheme

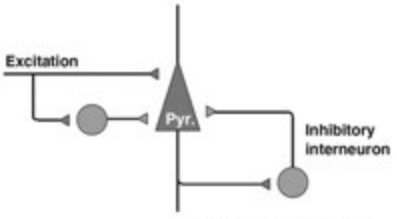




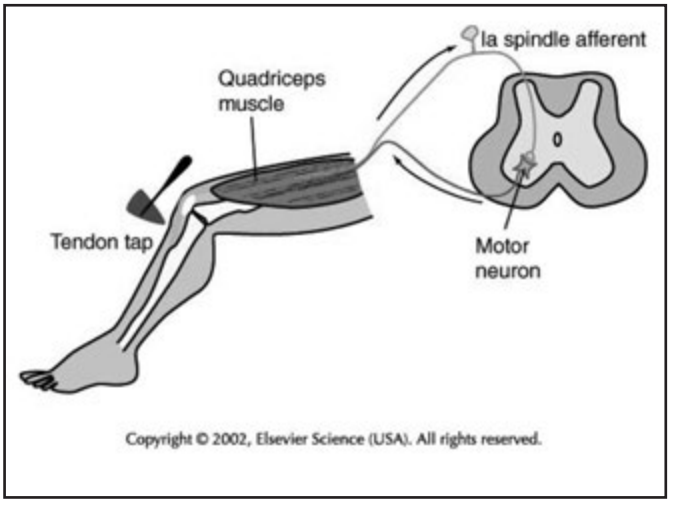
Bormann et al., 1987

GABAergic "circuits" – simple scheme





H. Möhler, J Neurochem 102, 2007



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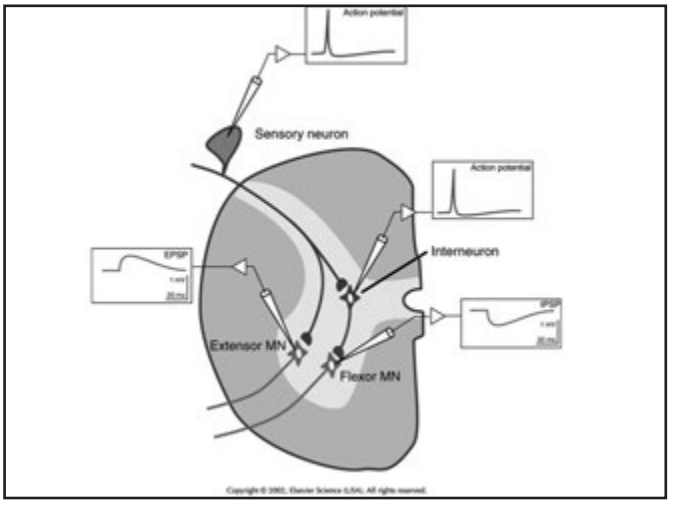


GABAergic inhibition

I Classical View: Reduction of Excitability

II Complications

III Inhibition within Networks:

- Excitation-Inhibition-Balance
- Signal-to-Noise-Ratio
- Spatial and Temporal Patterns

IV Perspectives

Complications I

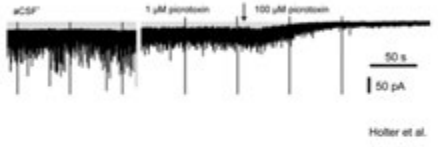
Molecular heterogeneity of $GABA_A$ receptors

Möhler, 2006

α	1-6
β	1-3
γ	1-3
δ	1
ε	1
θ	1
ρ	1-3

- 18 different subunit isoforms
- ~ 2 Mio receptor isoforms possible
- different properties:
  - agonist affinity
  - subcellular distribution
  - sub- vs. extrasynaptic
  - sensitivity to modulators
  - pharmacology

Example: extrasynaptic $GABA_A$ receptors and tonic inhibition

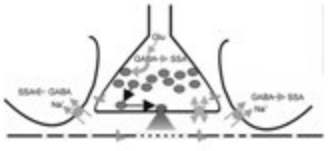


Holter et al.

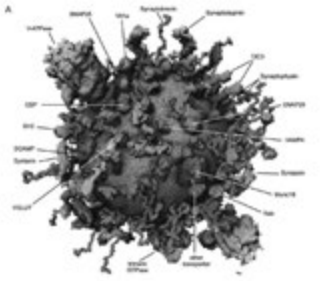
- different subunit composition ($\alpha 5$, $\alpha 6$, δ)
- high agonist affinity
- target of neurosteroids (?)
- in some cells ediating < 50% of charge transfer

Complications - II

Multiple molecular constituents of GABAergic synapses



- GABA metabolism and use-dependent changes in $[GABA]_{presynaptic}$
- Receptor turnover, traffic and scaffolding
- Pre- and postsynaptic modulation ($GABA_BR$, $GABA_AR$, CB1, PKA …)

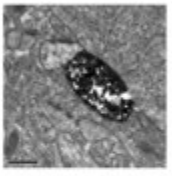


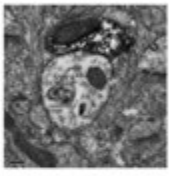
Molecular Anatomy of a Trafficking Organelle

Quantitative data needed!

Complications - III

Structure-function relationship





Gunnar Birke and Michael Frotscher

- Vesicle pools and vesicle dynamics
- Precise geometry of intra- and extracellular spaces
- Electrical synapses? *Mixed syapses?*

Complications - IV

Ion gradients: Chloride and HCO_3^-

Hyperpolarizing GABA (adult neurons)

E_{GABA} = –70 mV

Depolarizing GABA (immature neurons, epileptic tissue?)

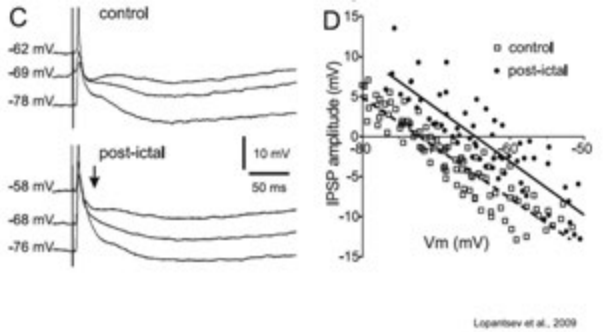
E_{GABA} = –40 mV

Cossart et al., TINS 2005

Net effect of inhibitory synapses:

- complex function of E_{GABA}, E_M, g_{SYN}
- set by (secondary) active transport – KCC2, NKCC1
- relative position of I- and E-synapses matters
- pH and E_{GABA} influenced by flux of HCO_3^-

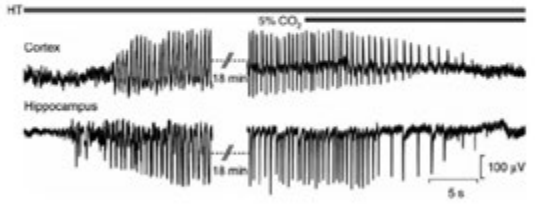
Seizures can shift chloride equilibrium



Lopantsev et al., 2009

Hyperventilation-induced alkaline pH-shift:

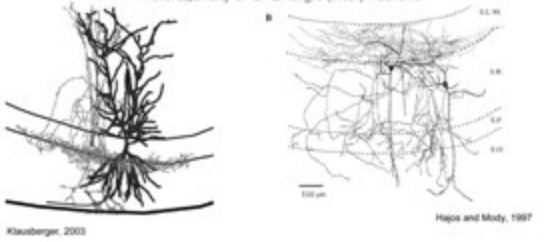
Increasing P_{CO2} as a therapeutic strategy in febrile seizures



Schuchmann et al., 2006, 2009

Complications - V

Heterogeneity of GABAergic (inter)-neurons

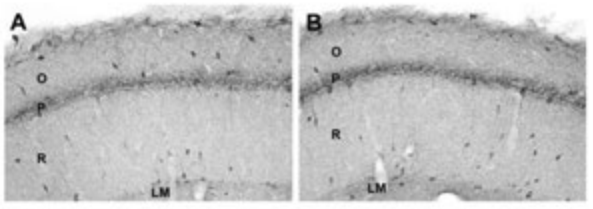


Klausberger, 2003

Hajos and Mody, 1997

- Multiples classes of IN
- Highly specific connectivity patterns
- State-dependent activation
- Different intrinsic and synaptic properties

Selective loss of interneuron subtypes in epilepsy



α-GAD67, Dinocourt et al., 2003

GABAergic inhibition

I Classical View: Reduction of Excitability

II Complications

III Inhibition within Networks:

- Excitation-Inhibition-Balance
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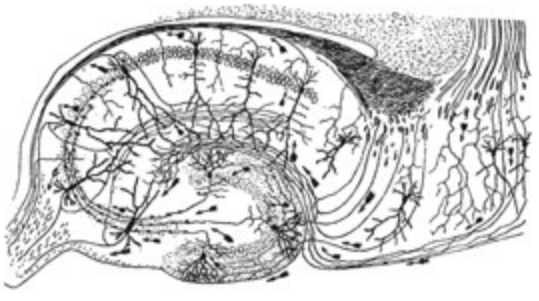
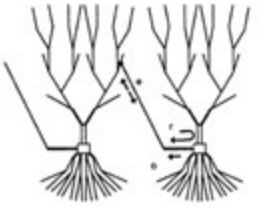
IV Perspectives

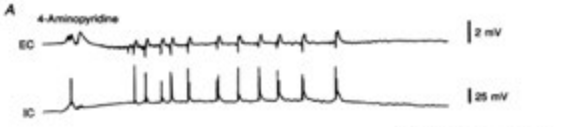
Excitation-Inhibition-Balance



Mod. from Ramón y Cajal

Recurrent excitatory coupling:
a mechanism for synchronous
(epileptic) discharges

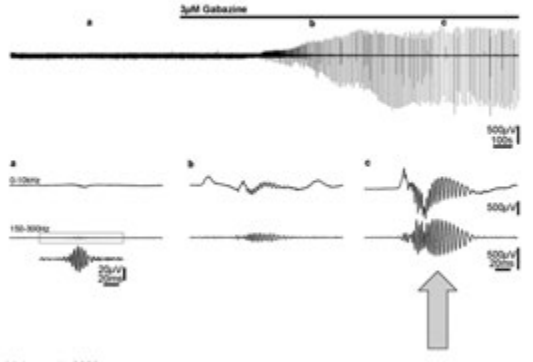




Traub, Colling & Jefferys, 1995

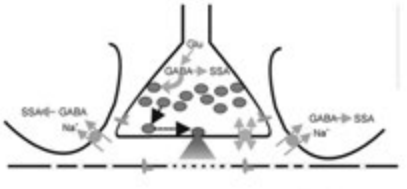
see also: Traub and Wong, 1982

Reduced GABAergic Inhibition → Epilepsy



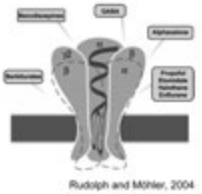
Maier et al., 2003

GABAergic drugs in epilepsy



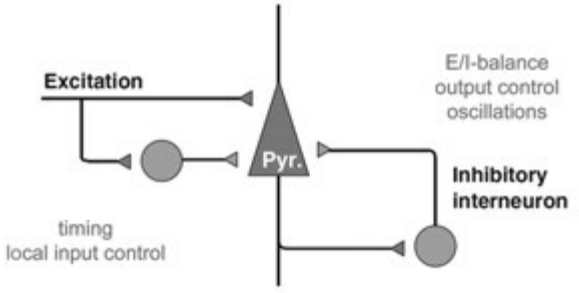
Pharmacological targets:

- $GABA_AR$
- GABA-uptake
- GABA-degradation



Rudolph and Möhler, 2004

"Circuitry" of E/I-Balance: Recurrent Inhibition



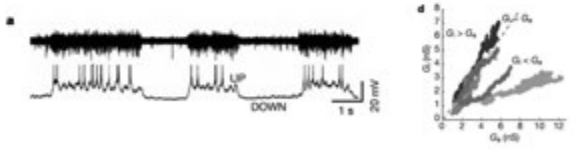
H. Möhler, J Neurochem 102, 2007

Turning on and off recurrent balanced cortical activity

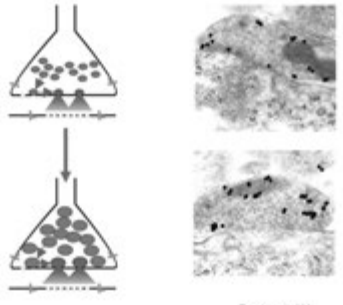
Yousheng Shu, Andrea Hasenstaub & David A. McCormick

Department of Neurobiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA

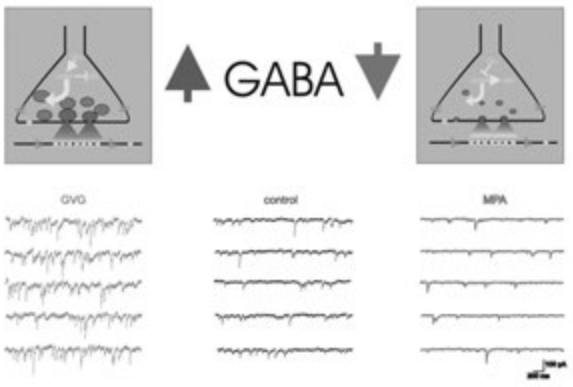
NATURE | VOL 423 | 15 MAY 2003 | www.nature.com/nature



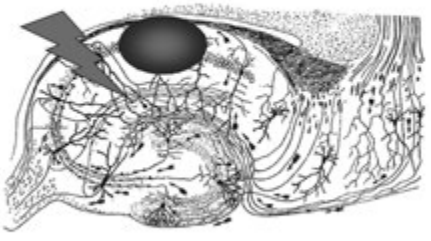
Presynaptic GABA content as a variable for homeostatic plasticity

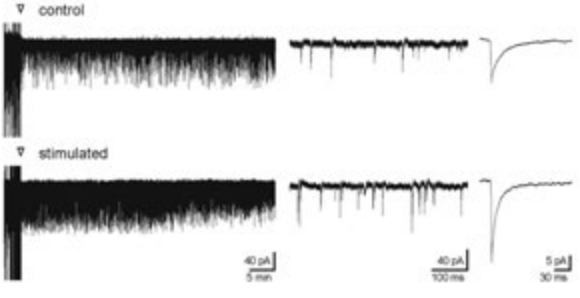


Engel et al., 2001



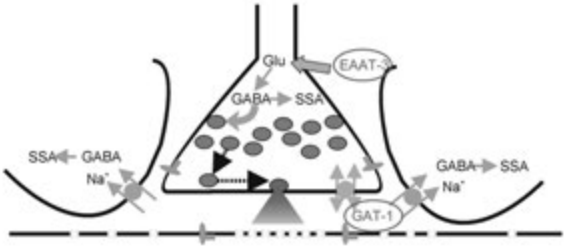
Acuteadaptation of $[GABA]_{pre}$ to changes in activity





Hartmann et al., 2008

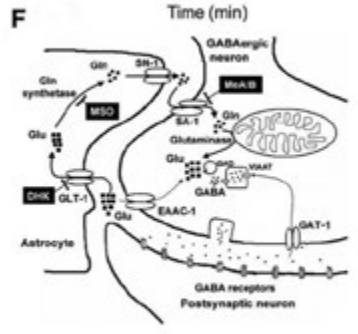
GABAergic terminals are fast sensors for release of GABA and glutamate



Hartmann et al., 2008

See also: Matthews and Diamond, 2003

A further source of GABA: glutamine



Liang et al., 2006

See also: Fricker et al., 2007

GABAergic inhibition

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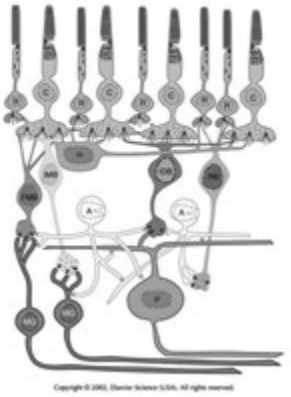
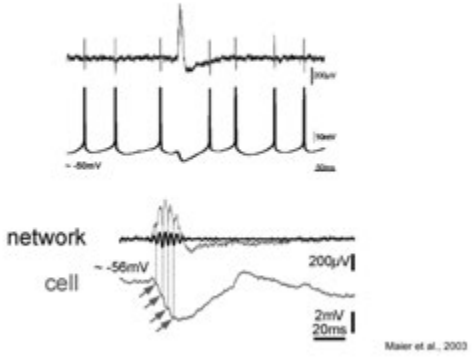
IV Perspectives

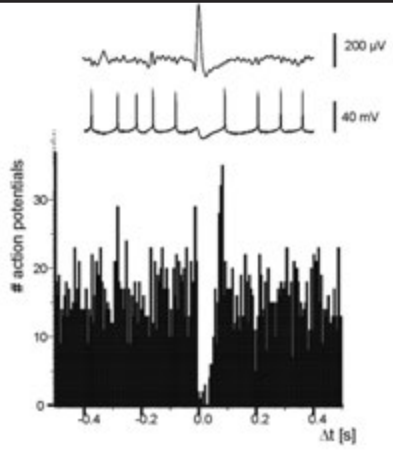
Signal-to-Noise I: lateral inhibition



Signal-to-Noise II:
background suppression in sparsely firing networks

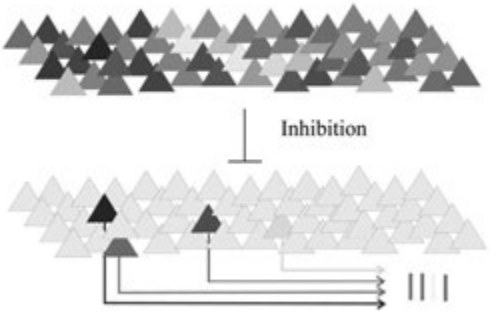


Maier et al., 2003



Maier et al., 2003

Background suppression in sparsely firing networks:
How do participating cells fire?



GABAergic inhibition

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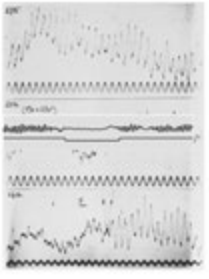
IV Perspectives

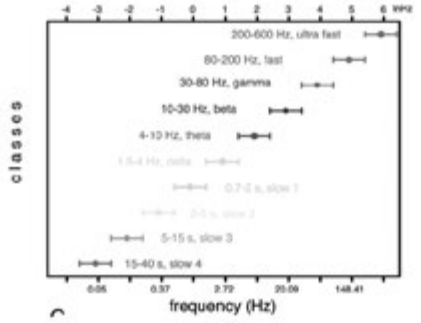
Neuronal correlates of cognitive processes can be measured…

Hans Berger
1873-1941



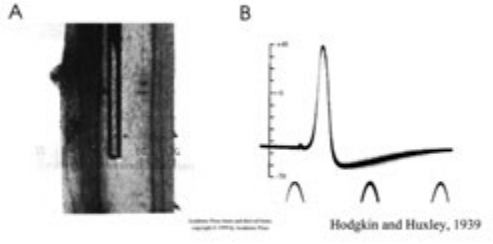
… and appear frequently as coherent rhythmic activity

Specific cognitive/behavioral states are associated with specific network oscillations



Buszaki et al., Thalamus and Related Systems

Why network oscillations?



Hodgkin and Huxley, 1939

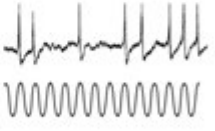
Action potentials • *are short (~ 1 ms)*

• *are uniform ("all-or-none")*

Possible "codes" based on spikes

Frequency codes

Temporal codes



→ Need for a temporal reference signal!

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Review TRENDS in Neurosciences Vol.30 No.7
ScienceDirect

INMED/TINS special issue

Role of GABAergic inhibition in hippocampal network oscillations

Edward O. Mann and Ole Paulsen

Department of Physiology, Anatomy and Genetics, Parks Road, Oxford, OX1 3PT, UK

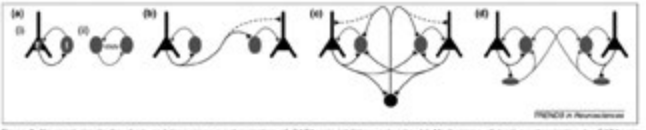
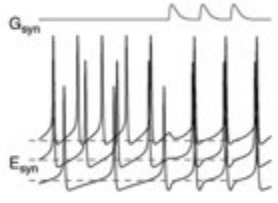
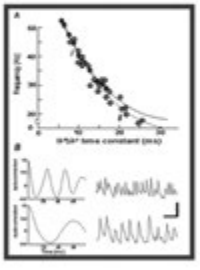


Figure 2. Neuronal circuits for short- and long-range synchronization of GABAergic inhibitory networks. (a) Mechanisms of local synchronization by GABAergic interneurons. Two main models have been proposed: (i) an excitatory–inhibitory (E–I) feedback loop, and (ii) an independent interneuronal network interconnected by inhibitory synapses and gap junctions (illustrated by a resistor symbol). (b) Propagation of fast oscillation. Downstream synchronization is mediated most effectively via excitatory connections onto GABAergic interneurons (solid line), rather than excitatory–excitatory connections (dashed line). (c) Long-range synchronization could be achieved by the phase resetting of local oscillators through mutual excitation and/or a common excitatory input. (d) Long-range synchronization by inhibition. The existence of GABAergic neurons that display long-range projections that selectively target other interneurons offers the additional possibility for long-range synchronization of fast local oscillators by mutual inhibition. Excitatory neurons are shown in black, inhibitory neurons in red.

GABAergic IPSPs: setting cycle time

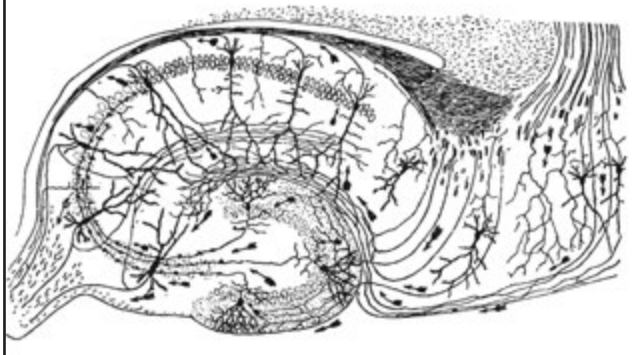




Mann and Paulsen, 2006, 2007

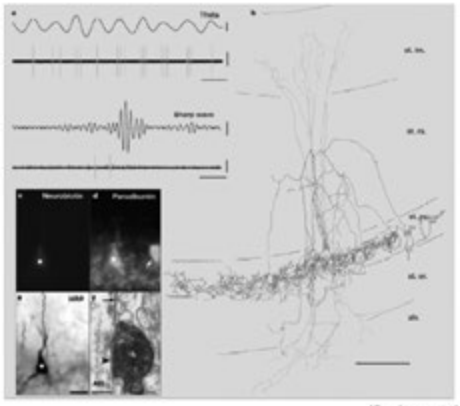
Miles A. Whittington / John G.R. Jefferys / Roger D. Traub

Different interneurons for different oscillation modes

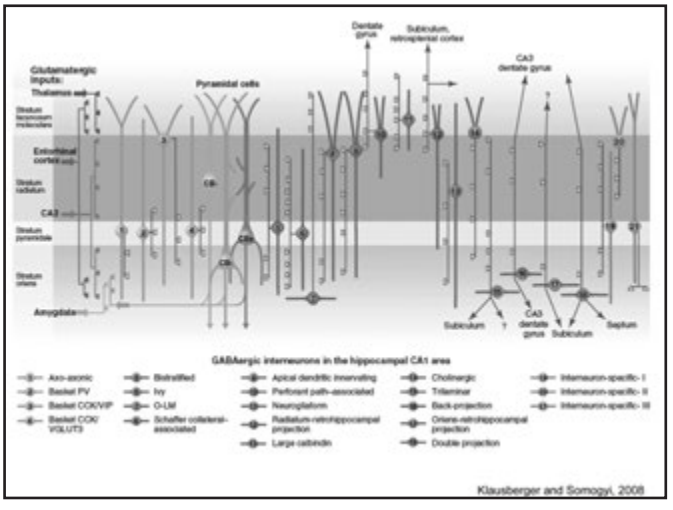


Mod. from Ramón y Cajal

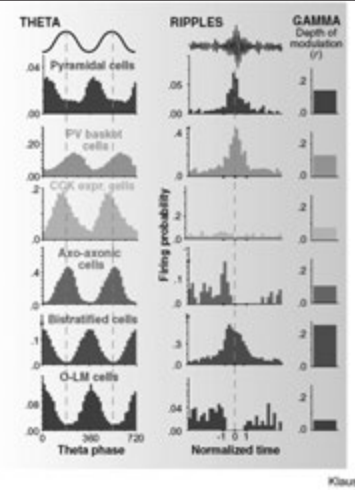
Heterogeneity of inhibitory neurons
➔ state-specific activation!



Klausberger et al. 2003

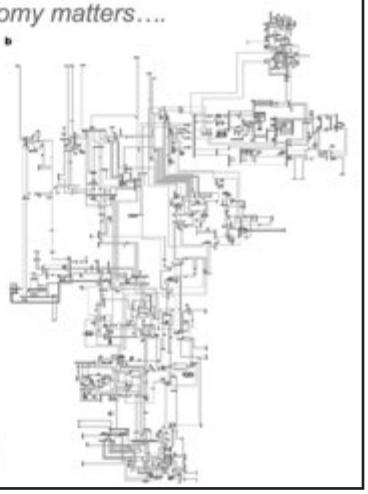


Klausberger and Somogyi, 2008



Klausberger and Somogyi, 2008

➔ *Neuroanatomy matters….*

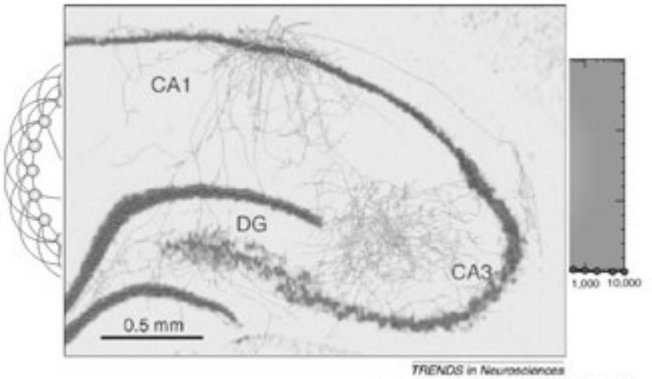


review articles

Exploring complex networks

NATURE | VOL 410 | 8 MARCH 2001 | www.nature.com

Neuroanatomy matters….



TRENDS in Neurosciences

Buzsáki et al., 2004 / Sik et al., 1995 / S.H. Strogatz, 2001

GABAergic inhibition

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Molecular and Neuronal Substrate for the Selective Attenuation of Anxiety

Karin Löw,[1*†] Florence Crestani,[1*] Ruth Keist,[1*]
Dietmar Benke,[1] Ina Brünig,[1] Jack A. Benson,[1]
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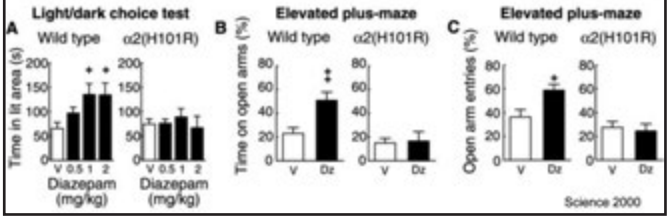

Science 2000

Molecular specificity of behavior- or disease-specific inhibitory systems

Table 1 $GABA_A$ receptor subtypes*

Subunits	Localization	Pharmacology
$\alpha_1\beta_2\gamma_2$	Major subtype (60%). Synaptic and extrasynaptic	Benzodiazepine-sensitive. Mediates sedative and anti-convulsant activity
$\alpha_2\beta_3\gamma_2$	Minor subtype (15-20%). Synaptic	Benzodiazepine-sensitive. Mediates anxiolytic activity
$\alpha_3\beta_3\gamma_2$	Minor subtype (10-15%)	Benzodiazepine-sensitive. Pharmacology yet unclear
$\alpha_5\beta_{1,2,3}\gamma_2$	<5% of receptors. Extrasynaptic (cerebral cortex, hippocampus, olf. bulb)	Benzodiazepine-sensitive. Mediates modulation of temporal and spatial memory
$\alpha_4\beta_x\delta$	<5% of receptors. Extrasynaptic	Insensitive to benzodiazepines. Sensitive to low concentration of ethanol
$\alpha_6\beta_x\gamma_2$	<5% of receptors. Extrasynaptic	Insensitive to benzodiazepines
$\alpha_6\beta_x\delta$	Small population. Extrasynaptic (only in cerebellum)	Insensitive to benzodiazepines. Sensitive to low concentration of ethanol
$\alpha_6\beta_{1,2,3}\gamma_2$	<5% of receptors. Synaptic (only in cerebellum)	Insensitive to benzodiazepines

Möhler, J. Neurochem. 102, 2007

TO DO:

- Quantitative understanding of molecular constituents
- Quantitative understanding of ultrastructure
- Understanding normal and pathological network states
- Understanding pathological plasticity of inhibition

- Specific tools for GABAergic sub-systems
- Protection of vulnerable interneuron populations
- Targeting mechanisms of homeostatic plasticity

Claus Bruehl
Andreas Draguhn
Dominique Engel
Kristin Hartmann

Gudrun Ahnert-Hilger
Nikolai Axmacher
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Michael Frotscher
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Roger D. Traub
Gabriel Wittum
Werner Zuschratter

Processes mediating epileptogenesis revealed by micro-array analyses and the modulation of specific molecular targets

F. Lopes da Silva (Netherlands)

LASSE IV São Paulo
February 2010

Processes mediating epileptogenesis revealed by micro-array analyses

and the modulation of specific molecular targets

Jan Gorter, Erwin van Vliet, Eleonora Aronica and Fernando Lopes da Silva

Swammerdam Institute for Life Sciences (SILS);
Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede;
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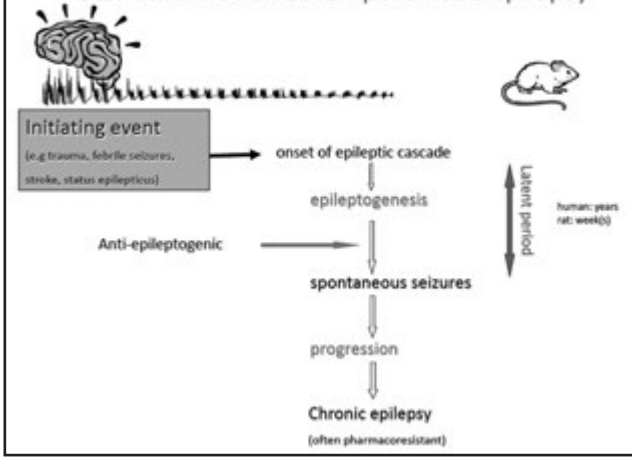
University of Amsterdam, Amsterdam, The Netherlands

Standard model of temporal lobe epilepsy

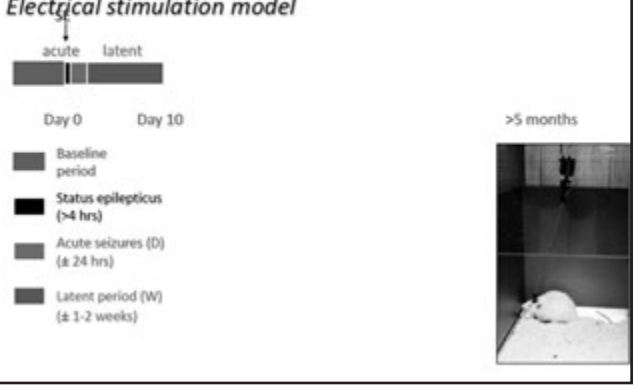


Status Epilepticus (SE) and later development of temporal lobe epilepsy

Electrical stimulation model

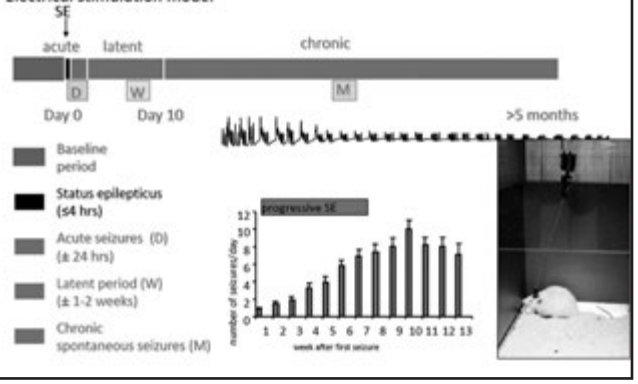
Status Epilepticus (SE) and later development of temporal lobe epilepsy

Electrical stimulation model



Status Epilepticus (SE) and later development of temporal lobe epilepsy

Electrical stimulation model



Microarray studies have suggested targets that could prevent the development of epilepsy

Micro-Array Department

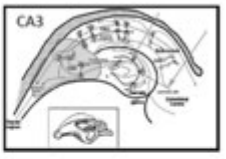
Neurobiology of Disease J Neurosci. 2006 Oct 25;26(43):11083-110.

Potential New Antiepileptogenic Targets Indicated by Microarray Analysis in a Rat Model for Temporal Lobe Epilepsy

Jan A. Gorter,[1,2] Erwin A. van Vliet,[1,2] Eleonora Aronica,[3] Timo Breit,[4] Han Rauwerda,[4] Fernando H. Lopes da Silva,[1] and Wytse J. Wadman[1]

Five groups and three brain regions

- Control (C)	(n=6)
- 1 day post SE (D)	(n=3) acute
- 1 week post-SE (W)	(n=6) latent
- >90 days (M)	(n=5) chronic (daily seizures)
- >90 days non-SE (nS)	(n=5) non-SE



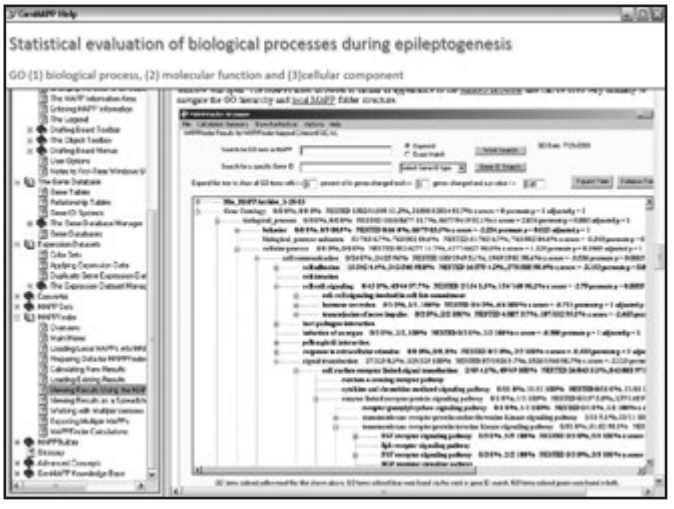
In this model, CA3 and TL both belong to the epileptogenic network while cerebellum does not

Micro-Array analyses

Here we compare findings obtained using micro-array analysis in the post-status epileptic rat and in patients with gangliogliomas (GG) who underwent surgery for intractable epilepsy.

In both rat and human gene expression analysis was performed using Affymetrix Gene Chip Systems, RAE230A and U133 plus 2.0 arrays, respectively.

In both cases GENMAPP and Gene Ontology were used to identify global biological trends in gene expression data.



Micro-Array analyses

Both studies revealed patterns of gene expression that presented a number of similar characteristics.

A common feature was that the immune and inflammatory responses were the most prominent processes up-regulated.

Further GABA receptor subunits involved in tonic inhibition were persistently down-regulated in rat and GABA receptor signalling was an under-expressed process in patients.

Several genes involved in the complement pathway displayed a high level of expression compared with controls.

Higher expression was also observed for genes involved in cell adhesion, extracellular matrix and proliferation processes.

Inflammation and immune response peak in the latent period (rat post-SE model study)

559 probes upregulated in both CA3 and EC (298 GO

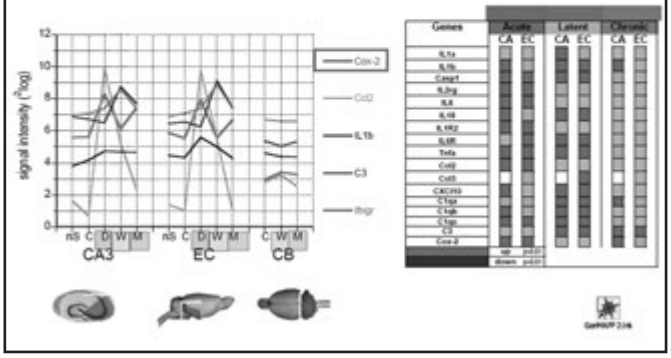
	Process	No. genes up	% changed	Z score
DM	Immune response	13	45	8.65
	Antigen processing, exogenous antigen via MHC class II	6	100	7.61
	Antigen presentation, exogenous antigen	5	100	6.94
	Response to wounding	4	67	4.82
	Inflammatory response	5	42	4.50
	Cell proliferation	4	33	4.25
M	Intracellular signaling cascade	18	20	3.74
	Proteolysis	19	19	3.43

Synaptic transmission is acutely downregulated (rat post-SE model study)

763 probes downregulated in both CA3 and EC (317 GO)

	Process	No. genes	% changed	Z score
	Synaptic transmission e.g. downregulation of various GABAR subunits	4	24	4.65
	Regulation of synaptic plasticity e.g. downregulation of CamKIIa	3	50	3.92
	CNS development	3	60	2.92
	Calcium ion homeostasis	3	75	2.90
W	Calcium ion transport	6	29	2.84
	Nervous system development	5	22	2.77
	Phospholipid biosynthesis	3	38	2.50
	Ion transport	15	18	2.20
	Cell adhesion	8	19	2.12

Inflammation and activation of the *immune response* play a role during early epileptogenesis



Micro-Array analyses

Biological process	# genes ; % up-regulated ; Z-score > 1.96 (p< 0. 05)	
Significantly up-regulated in brain of	Rat TLE model – **1 week after SE (CA3 & EC)**	Human Ganglioglioma
Immune response	13 ; 45% ; Z = 8.7	71; 59% ; Z = 15.6
Inflammatory response	5 ; 42% ; Z = 4.5	47 ; 60% ; Z = 9.7
Cell proliferation	4 ; 33% ; Z = 4.3	42 ; 31% ; Z = 4.2
Cell adhesion	7 ; 18% ; Z = 2.2	59 ; 30% ; Z = 4.4

Modifying epileptogenesis and seizure progression with inflammation and/of the BBB as target

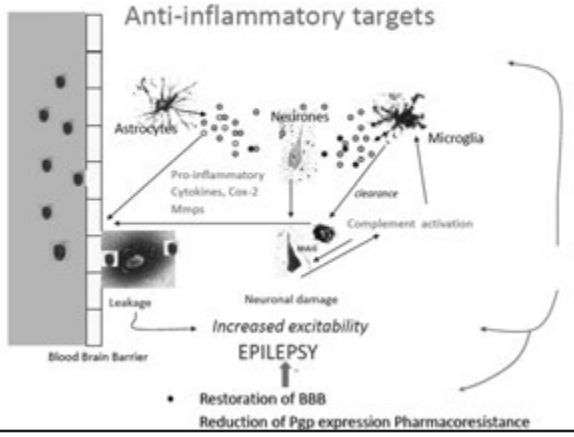
The microarray studies suggest various possible therapeutic strategies aimed at counteracting inflammation:

1) Cox-2 inhibition;
2) Complement inhibition;
3) Il1b / caspase 1inhibition;
4) Chemokine inhibition;
5) Cell adhesion molecule inhibition;
6) (Matrixmetallo)protease inhibition;

We pass in review a few of the experimental approaches that have been carried out recently to test the following targets:

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

Anti-inflammatory targets



- Restoration of BBB
  Reduction of Pgp expression Pharmacoresistance

Modifying epileptogenesis and seizure progression with inflammation and/of the BBB as target

We pass in review a few of the experimental approaches that have been carried out recently to test the following targets:

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

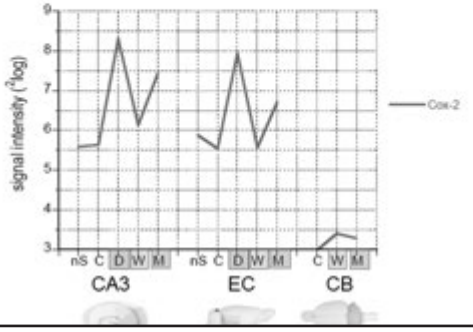
Exploring potential targets

(a) prostaglandin synthesis;
(b) protein synthesis;
(c) cell-adhesion regulation.

Prostaglandin synthesis: a potential target for anti-inflammatory treatment in epilepsy is cyclooxygenase-2 (cox-2), an enzyme that is responsible for the conversion of arachidonic acid (AA) into prostaglandins, (e.g. PGE2).

The fact that up-regulation of cox-2 is associated with seizures, led us to investigate the effects of a 7-day treatment with the Cox-2 inhibitor SC58236 immediately after SE.

Regulation of Ptgs2 (cox-2) is activity dependent



Does inhibition of Cox-2 lead to milder form of epilepsy

Experimental protocol:

1. Daily 1x oral administration of Cox-2 inhibitor (SC58236) during 7 days after SE; starting 4 hrs after SE
2. Using a dose that was previously shown to be effective in reducing ischemic neuronal damage (10mg/kg)
3. Monitor EEG during 35 days after SE.
4. PGE_2 immuno assay to test effectiveness of application at 1 day, 5hrs after last SC58236 administration

Inhibition of Cox-2 using SC58236

7 day SC58236 treatment after SE during the latent period:

- Does not delay epilepsy or lead to a milder form of epilepsy
- Does not lead to reduced microglia activation or neuroprotection.
- It effectively inhibits COX-2, as indicated by reduced PGE_2 production comparable to control levels (Holtman et al 2009).
- Consequently COX-2 inhibition was able to reduce the expression levels of P-glycoprotein despite recurrent seizure activity, and thus it helped to modify the Blood-Brain Barrier (BBB) in the epileptic rat brain (van Vliet et al 2009).

Holtman L, van Vliet EA, van Schaik R, Queiroz CM, Aronica E, Gorter JA. Effects of SC58236, a selective COX-2 inhibitor, on epileptogenesis and spontaneous seizures in a rat model for temporal lobe epilepsy. Epilepsy Res. 2009 Mar;84(1):56-66.

van Vliet EA, Zibell G, Pekcec A, Schlichtiger J, Edelbroek PM, Holtman L, Aronica E, Gorter JA, Potschka H.COX-2 inhibition controls P-glycoprotein expression and promotes brain delivery of phenytoin in chronic epileptic rats. Neuropharmacology. 2009 Sep 26

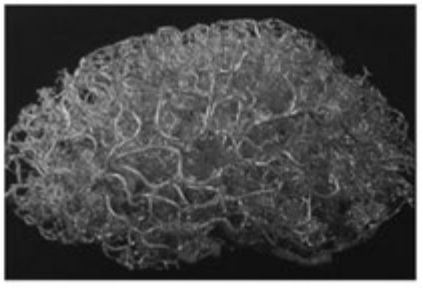
Cox-2: regulator of P-gp expression

arachidonic acid (AA) —cox-2→ Prostaglandins (PGE) → → *inflammation*

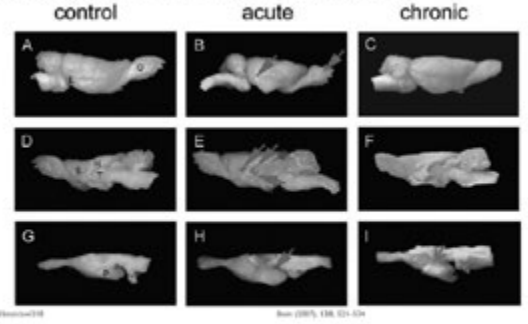
glutamate → NMDA receptors → cox-2 → PGE →
→ P-gp upregulation in the BBB

Bauer B, Hartz AM, Pekcec A, Toellner K, Miller DS, Potschka H Seizure-induced up-regulation of P-glycoprotein at the blood-brain barrier through glutamate and cyclooxygenase-2 signaling. Mol Pharmacol. 2008 May;73(5):1444-53

INTERMEZZO:
The role of BBB disruption in inflammation and in epileptogenesis



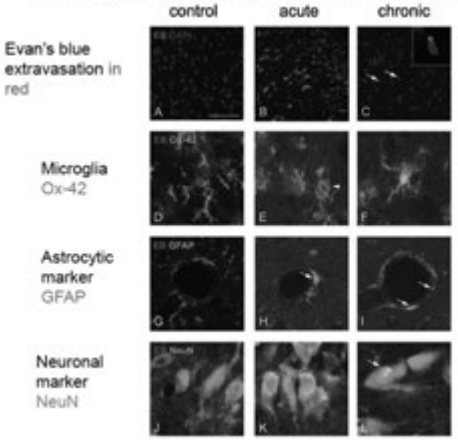
Leaking BBB: Source of inflammation?



Blood–brain barrier leakage may lead to progression of temporal lobe epilepsy

Evan's blue extravasation during epileptogenesis

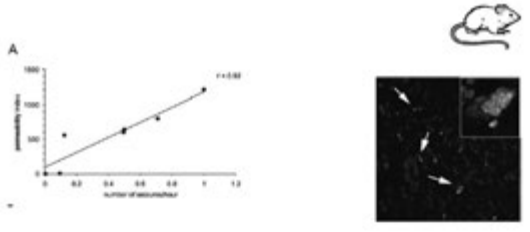
Albumin uptake in microglia, astrocyte endfeet and neurons



Does BBB leakage influence progression of seizure activity?

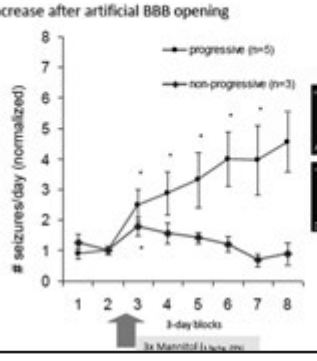
Chronic epileptic rats

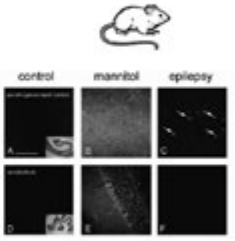
BBB leakage is proportional to severity of epilepsy



Modifying seizure progression in chronic epileptic rats with the BBB as target

Seizures increase after artificial BBB opening



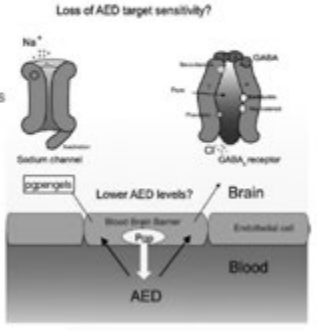


Fluorescein (green) as marker for BBB leakage – Parahippocampal cortex and Cerebellum

Mechanisms of pharmacoresistance

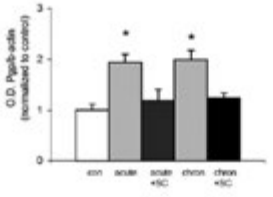
1) "Transport Hypothesis"
Poor penetration of drugs into the brain due to overexpression of drugtransporters (Pgp, and other MDR transporters)

2) "Target hypothesis"
Alterations of pharmacological targets



Inhibition of cox-2: P-gp

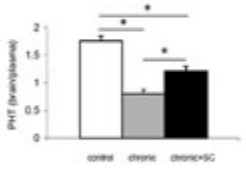
Can inhibition of cox-2 reduce P-gp expression?



Cox-2 inhibition effectively reduces P-gp

Inhibition of cox-2: drug delivery

Can inhibition of cox-2 enhance AED delivery into the brain?



Entrance of phenytoin in the brain of chronic epileptic rats is enhanced by cox-2 inhibition.

Exploring potential targets.

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

From these experimental findings we may conclude that although inibition of COX-2 does not counteract epileptogenesis it may have a beneficial effect on pharmacoresistance induced by up-regulation of Pgp.

Modifying epileptogenesis and seizure progression with inflammation and/of the BBB as target

We pass in review a few of the experimental approaches that have been carried out recently to test the following targets:

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

- To discuss this theme we introduce first micro-array findings obtained in another kind of epilepsy:
- tuberous sclerosis in human.

Gene Expression Analysis of Tuberous Sclerosis Complex Cortical Tubers Reveals Increased Expression of Adhesion and Inflammatory Factors

Karin Boer, Peter B. Crino, Jan A. Gorter, Mark Nellist, Floor E. Jansen, Wim G.M. Spliet,Peter C. van Rijen, Floyd R.A. Wittink, Timo M. Breit, Dirk Troost, Wytse J. Wadman,Eleonora Aronica.
Brain Pathology. Oct 2009, ISSN 1015-6305

Signaling Pathways	Number of genes	P value <
mTOR Signaling Pathway	8	0.0291
TNFR1 Signaling Pathway	9	0.0339
PDGF Signaling Pathway	8	0.0360
Classical Complement Pathway	5	0.0447
Complement Pathway	6	0.0476

(a) prostaglandin synthesis;
(b)
(c) cell-adhesion regulation

Target of Rapamycin

(a) prostaglandin synthesis;
(b) protein synthesis
(c) cell-adhesion regulation

Protein synthesis:
A promising strategy appears to be the interference with the mammalian target of Rapamycin (mTOR, a serine/threonine kinase or FRAP or RAFT1) signalling pathway that controls protein synthesis related to neuronal development and synaptic plasticity*.

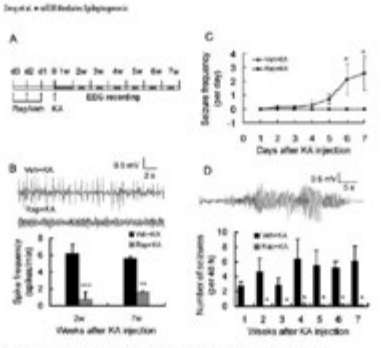
The mTOR inhibitor Rapamycin was shown (Zeng et al 2009) to prevent epilepsy in a mouse model of tuberous sclerosis complex, and in a rat model of temporal lobe epilepsy initiated by SE.

Interestingly Rapamycin was able to block the chronic phase of epilepsy and to reduce mossy fibre sprouting but not neurogenesis or neuronal death. These findings indicate that mTOR inhibitors have potential antiepileptogenic effects in this rat model.

* Tang et al PNAS 2002, 99 :467 – 472.

Target of Rapamycin

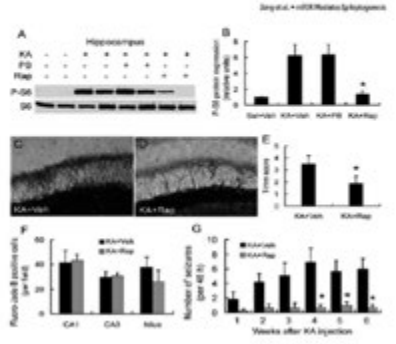
Effects of pre-treatment with Rapamycin



Zeng et al J. Neuroscience 2009, 29(21):6964-6969

Target of Rapamycin

Effects of post-treatment with Rapamycin



Exploring potential targets.

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

- From these experimental findings we may conclude that mTOR signaling pathway appears to play a significant role in post-SE kainate rat model.
- Thus this pathway may be a relevant target to counteract this form of epileptogenesis;
- mTOR inhibitors as Rapamycin have potential antiepileptogenic effect.

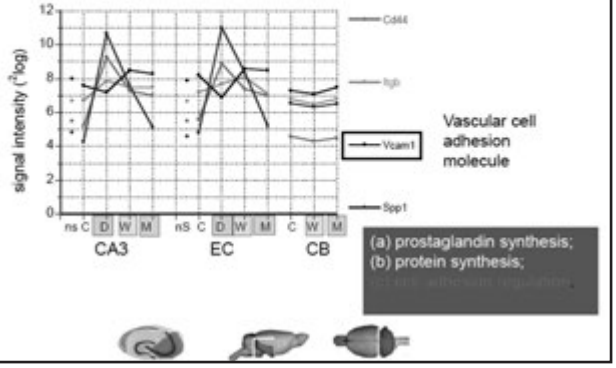
Modifying epileptogenesis and seizure progression with inflammation and/of the BBB as target

We pass in review a few of the experimental approaches that have been carried out recently to test the following targets:

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

Target: Cell adhesion molecules

Promotion of leukocyte infiltration and macrophage migratory activity



(a) prostaglandin synthesis;
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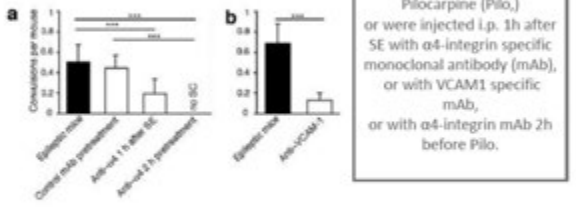
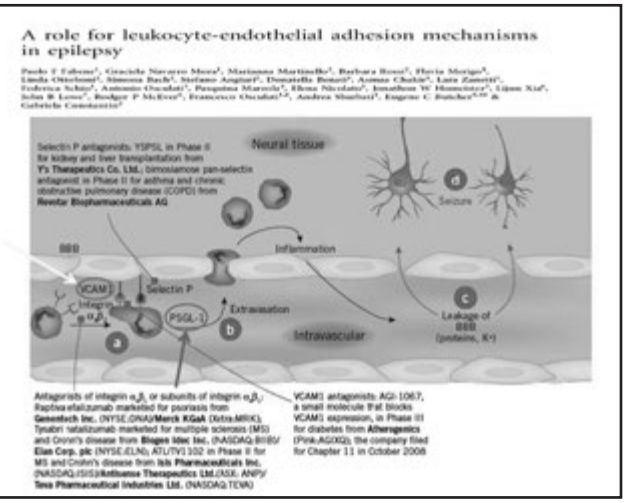
(c) cell-adhesion regulation

Target: Cell adhesion molecules



Epileptic mice received Pilocarpine (Pilo,) or were injected i.p. 1h after SE with α4-integrin specific monoclonal antibody (mAb), or with VCAM1 specific mAb, or with α4-integrin mAb 2h before Pilo.

Fabene et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nature Medicine 2008, 14: 1377 – 1383.


A role for leukocyte-endothelial adhesion mechanisms in epilepsy

Target: Cell adhesion regulation

Cell adhesion regulation:
Seizures enhance the expression of vascular cell adhesion molecules and enhanced leukocyte rolling and arrest in brain vessels mediated by the leukocyte mucin P-selectin glycoprotein ligand-1 (PSGL-1).

This finding led to explore the effect of inhibiting leukocyte-vascular interactions, either with blocking antibodies or by genetically interfering with PSGL-1 function in mice (Fabene et al 2008).

We may conclude that treatment with blocking antibodies against vascular cell adhesion molecules can prevented the development of epilepsy in this animal model.

Modifying epileptogenesis and seizure progression with inflammation and/or the BBB as target

We passed in review a few of the experimental approaches that have been carried out recently to test the following targets:

- (a) prostaglandin synthesis;
- (b) protein synthesis;
- (c) cell-adhesion regulation

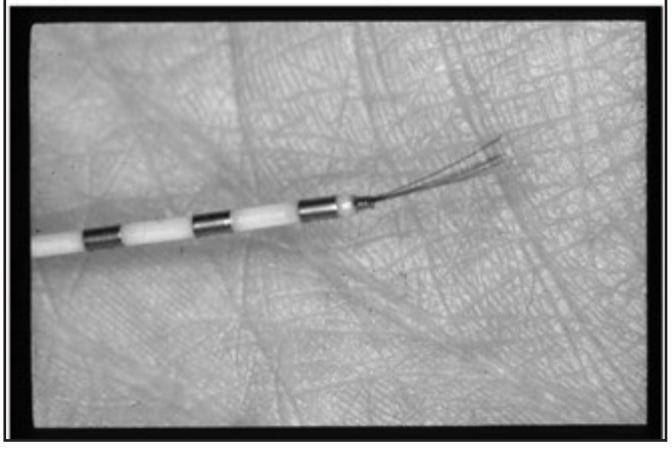
High frequency activity in the human epileptic brain

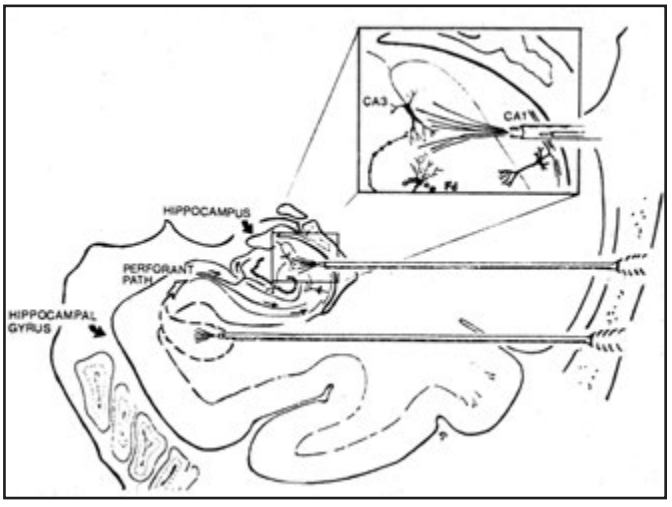
J. Engel Jr. (USA)

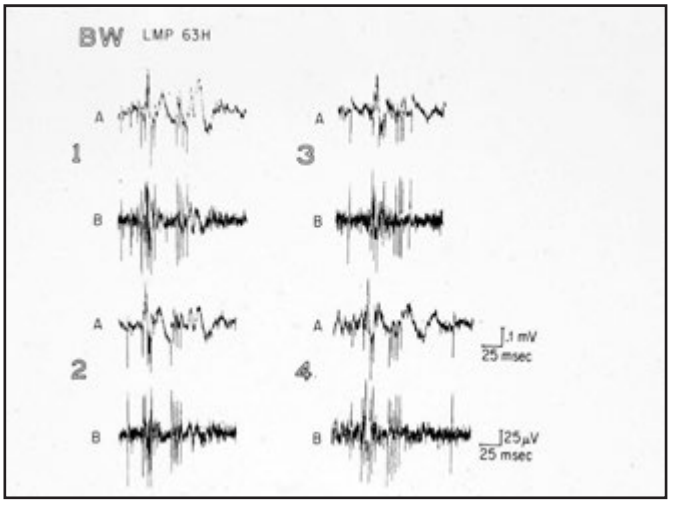
High frequency activity in the human epileptic brain

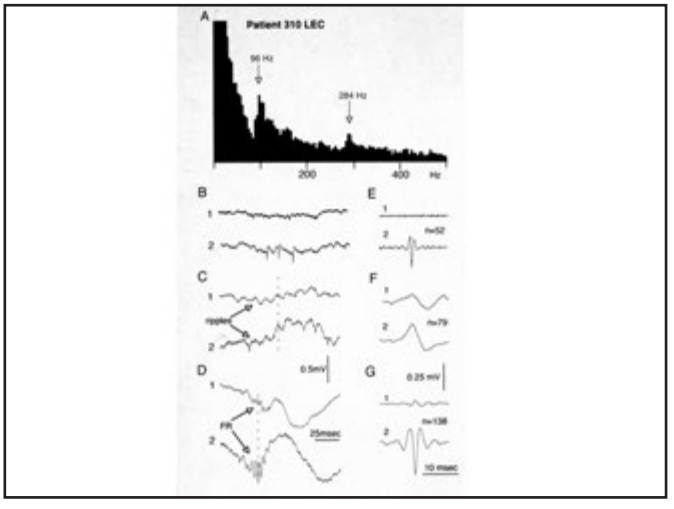
Jerome Engel Jr. (UCLA-USA)

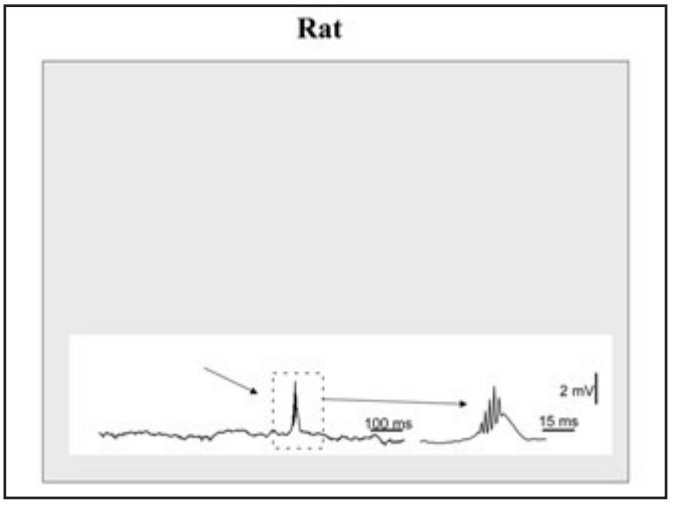
Depth electrode with 40 µ microelectrodes

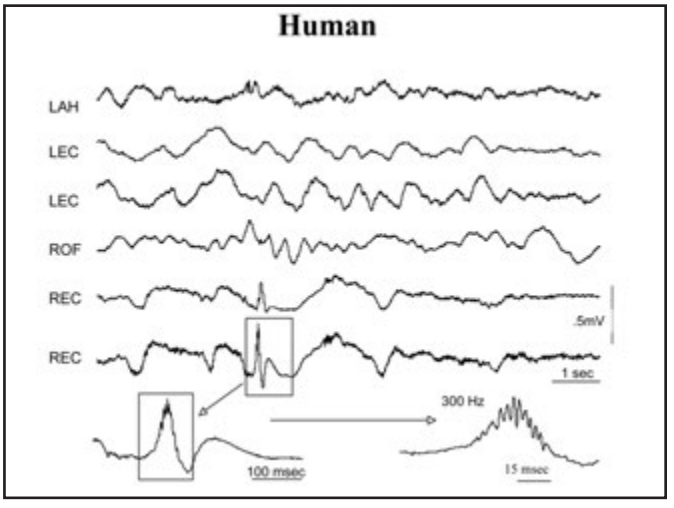


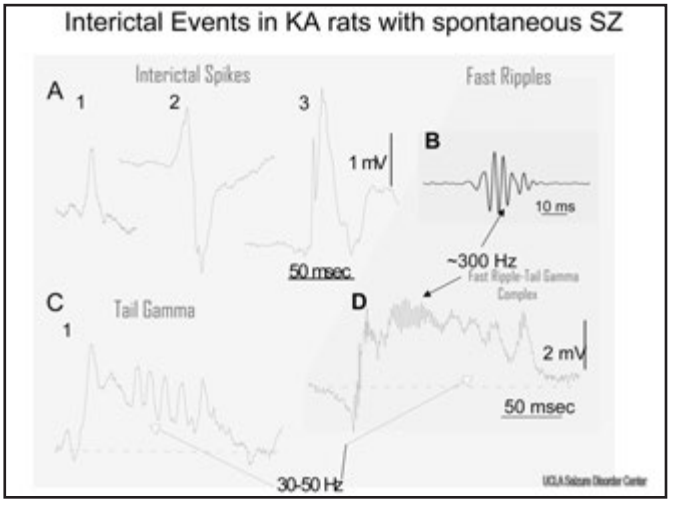


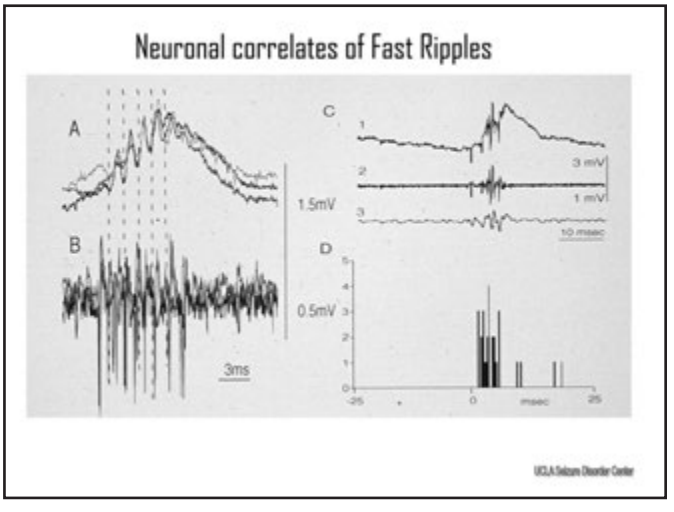

BW LMP 63H
A
B
1
2
3
4
.1 mV
25 msec
25 μV
25 msec

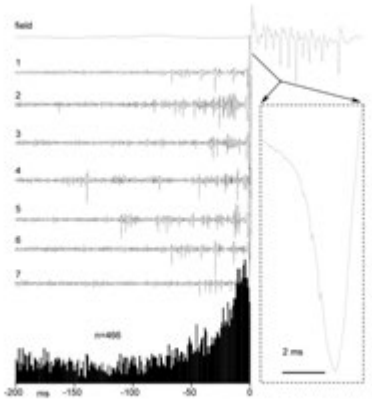

A
Patient 310 LEC
90 Hz
284 Hz
200
400
Hz
B
C
D
E
F
G
25msec
10 msec

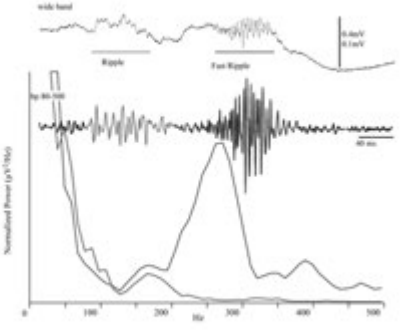

Rat
2 mV
100 ms
15 ms

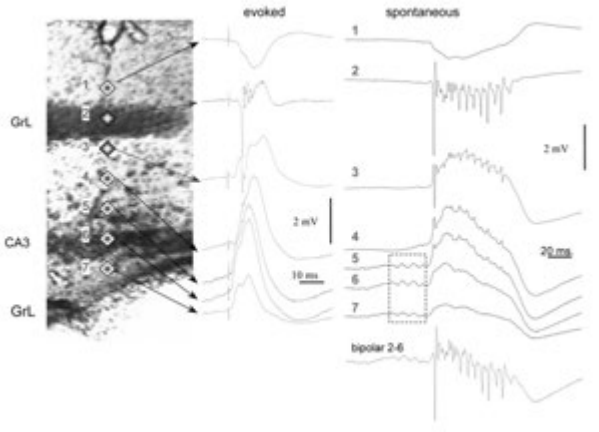

Human
LAH
LEC
LEC
ROF
REC
REC
.5mV
1 sec
300 Hz
100 msec
15 msec

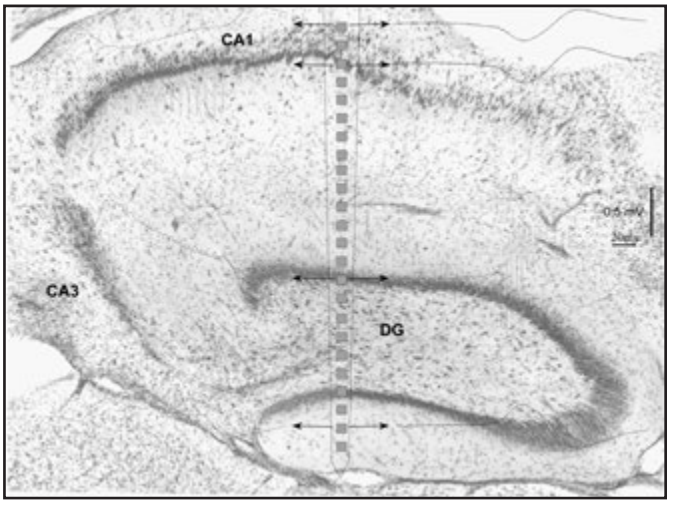

Interictal Events in KA rats with spontaneous SZ
Interictal Spikes
Fast Ripples
A
1
2
3
1 mV
B
10 ms
~300 Hz
Fast Ripple-Tail Gamma Complex
50 msec
C
Tail Gamma
D
1
2 mV
50 msec
30-50 Hz
UCLA Seizure Disorder Center

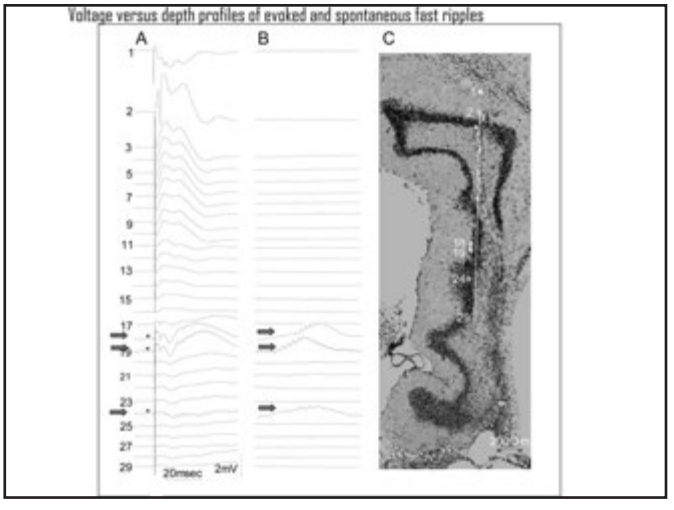

Neuronal correlates of Fast Ripples
A
B
1.5mV
3ms
C
1
2
3
3 mV
1 mV
10 msec
D
0.5mV
-25
0
msec
25
UCLA Seizure Disorder Center

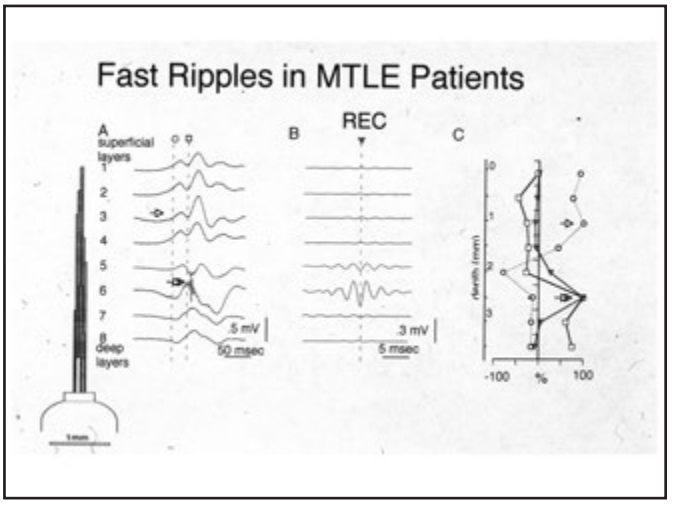

field
1
2
3
4
5
6
7
n=466
2 ms
-200
ms
-150
-100
-50
0


wide band
Ripple
Fast Ripple
40 ms
0
100
200
300
400
500


evoked
spontaneous
GrL
CA3
GrL
2 mV
10 ms
2 mV
20 ms
bipolar 2-6

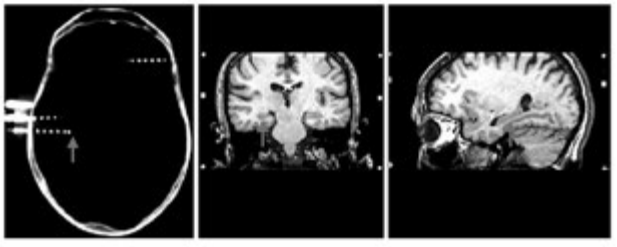

CA1
CA3
DG
0.5 mV
1msec


Voltage versus depth profiles of evoked and spontaneous fast ripples
A
B
C
1
2
3
5
7
9
11
13
15
17
19
21
23
25
27
29
20msec
2mV

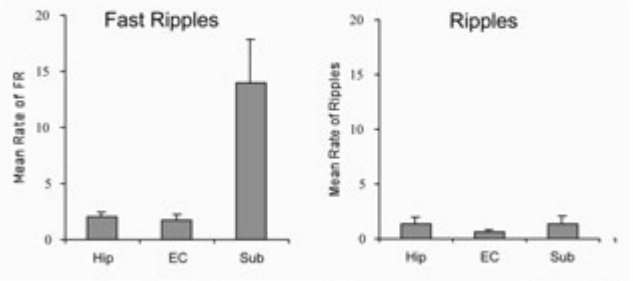

Fast Ripples in MTLE Patients
A
superficial layers
deep layers
1
2
3
4
5
6
7
8
.5 mV
50 msec
B
REC
3 mV
5 msec
C
depth (mm)
-100
%
100

Ripples	Fast Ripples
80-200 Hz	200-600 Hz
Not in DG	In DG
VSD unclear	VSD localized
Diffuse	PIN clusters
Summated IPSPs	Population spikes

Microelectrode Localization
CT to MRI registration

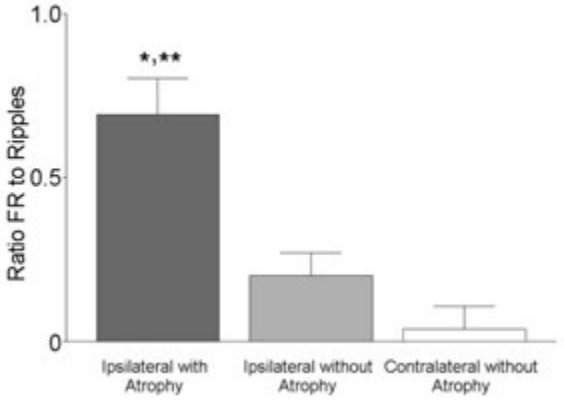


Rate of High Frequency Oscillations in Limbic Structures

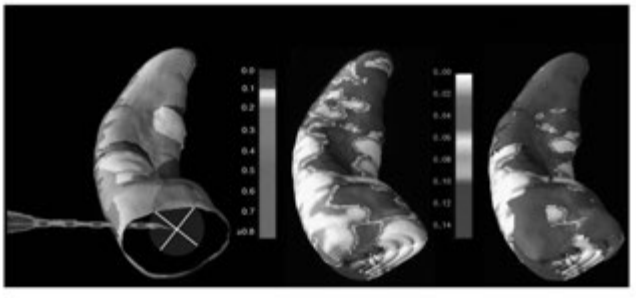


Hip n=27 sites; EC n=19; Sub n=4 * p=.001 Sub vs Hip, ** p=.001 Sub vs EC

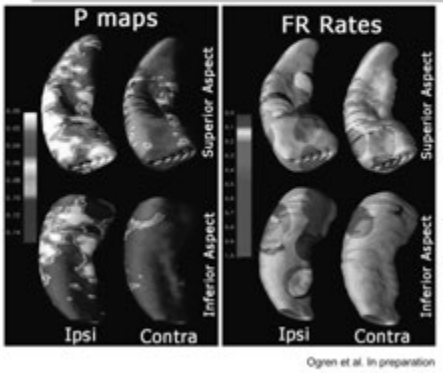
Influence of hippocampal atrophy upon Ratio of FR to Ripple rates (human)



Are Fast Ripple generating sites associated with local anatomical disturbances ?



Fast Ripple-generating sites strongly associated with local atrophy

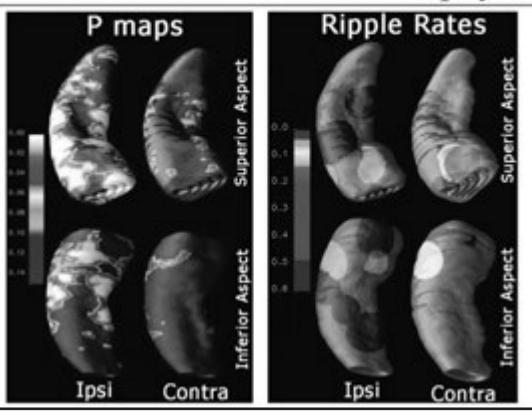


Significantly higher rates of Fast Ripple occurrences in local atrophic vs. non-atrophic areas.

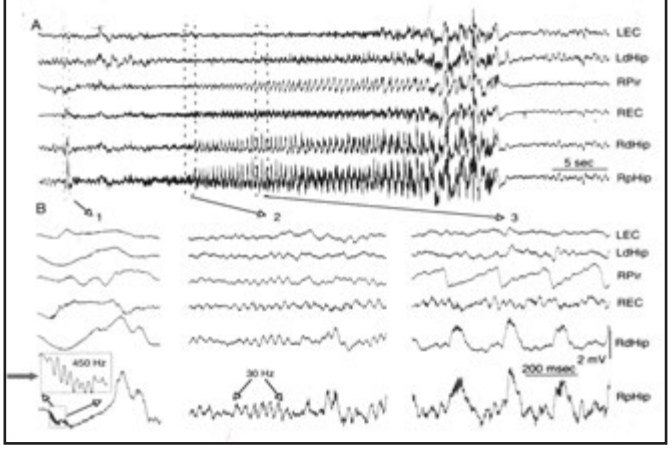
Higher rates of Fast Ripple discharge correlate with greater atrophy.

Ogren et al. In preparation

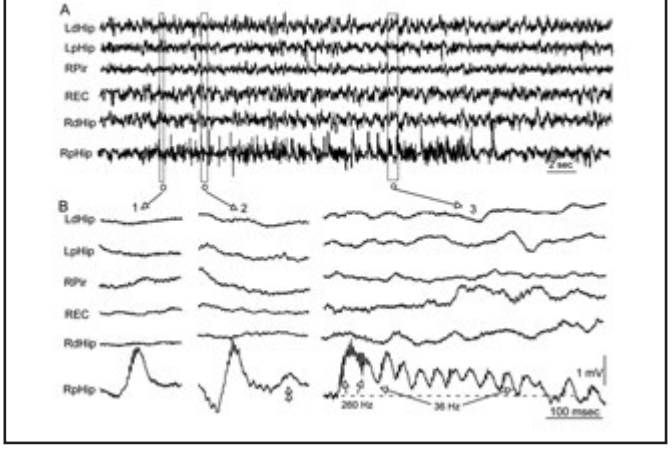
No significant association between Ripple occurrence and local atrophy



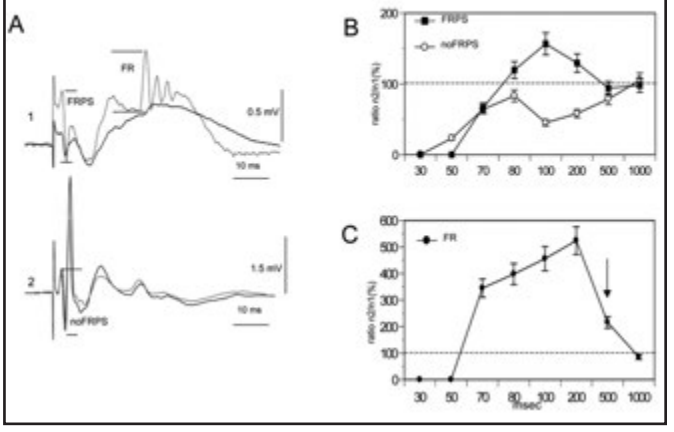
Fast Ripples at the Spontaneous Seizure Onset



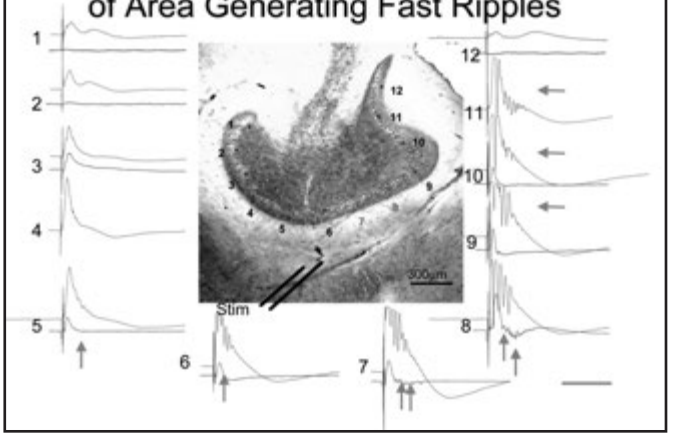
Fast Ripple and Tail Gamma Components of Seizure Discharge



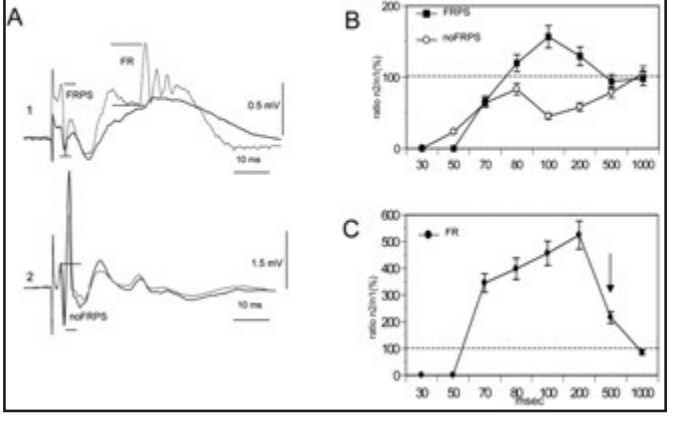
Strength of Paired Pulse Inhibition in Areas Generating FR and Areas Not Generating FR (rats)



Influence of Bicuculline on the Size of Area Generating Fast Ripples



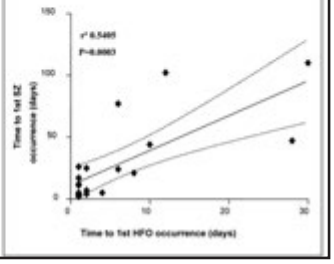
Strength of Paired Pulse Inhibition in Areas Generating FR and Areas Not Generating FR (rats)



Fast Ripples occur days to weeks after intrahippocampal kainate injection in rats that eventually develop spontaneous seizures months later, but not in rats that do not develop seizures.

Day of 1st FR appearance after status n=23	Day of 1st seizure appearance
NO FR (n=7)	NO SZ
1st two days (n=11)	11 ± 8.5 (Mean ± SD)
2nd week and later (n=5)	65 ± 39 (Mean ± SD)

The earlier FR occur, the earlier spontaneous seizures occur.



Frequency Considerations

- Early in development ripple frequency HFOs (80-200 Hz) occur in dentate where normal ripples never occur
- Therefore pathological HFOs (pHFOs) can be less than 200-600 Hz
- Some ripple frequency oscillations outside dentate may also be pHFOs
- Unable, as yet, to distinguish normal from pathological ripples

Biomarkers

Epileptogenesis:
- Predict seizures
- Identify progression

Epileptogenicity:
- Diagnose epilepsy
- Determine effectiveness of drugs
- Localize the epileptogenic region

Research:
- Screen potential antiepileptic compounds
- Streamline clinical trials

Clinical Studies

Others (Gotman, Worrell) have confirmed our work using clinical depth and subdural grid electrodes in patients

- pHFOs identify the epileptogenic region
- FR are better than ripple frequency HFOs
- Neocortical epileptogenic regions also identified
- pHFOs are better than interictal spikes
- pHFOs are better than seizure onset

Etiology as a risk factor for medically refractory epilepsy
Paris 1990-1997

- 26% generalized
- 76% localization-related
  - 66% temporal lobe epilepsy
  - 35% hippocampal atrophy on MRI

Seizure free for the past year

• Generalized	82%
• Stroke	54%
• Dysgenetic	24%
• Hippocampal atrophy	10%
• Dual pathology	3%

Semah F., Picot, M-C., Adam C., Broglin D., Arzimanoglou A., Bazin B., Cavalcanti D. and Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 51:1256-1262, 1998. of refractory epilepsy.

The Syndrome of Mesial Temporal Lobe Epilepsy
History

- Increased incidence of complicated febrile convulsions or other predisposing insults within first 5 years of life
- Increased incidence of a family history of epilepsy
- Onset in mid-to-late childhood
- Auras common and occur in isolation

The Syndrome of Mesial Temporal Lobe Epilepsy
History

- Secondarily generalized seizures occur infrequently.
- Seizures often remit for several years during adolescence or early adulthood.
- Seizures often become medically intractable.
- Interictal behavioral disturbances can occur (most commonly depression)

The Syndrome of Mesial Temporal Lobe Epilepsy
Clinical Seizure

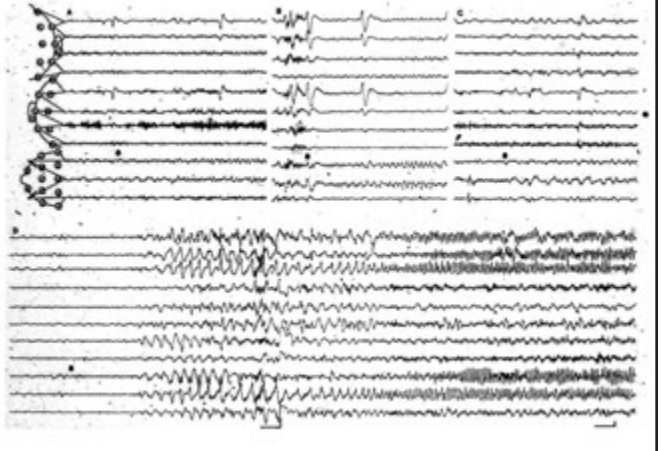
- Aura usually present; most common is epigastric rising, often other autonomic or psychic symptoms, with emotion (e.g., fear), can be olfactory or gustatory sensation (several seconds).

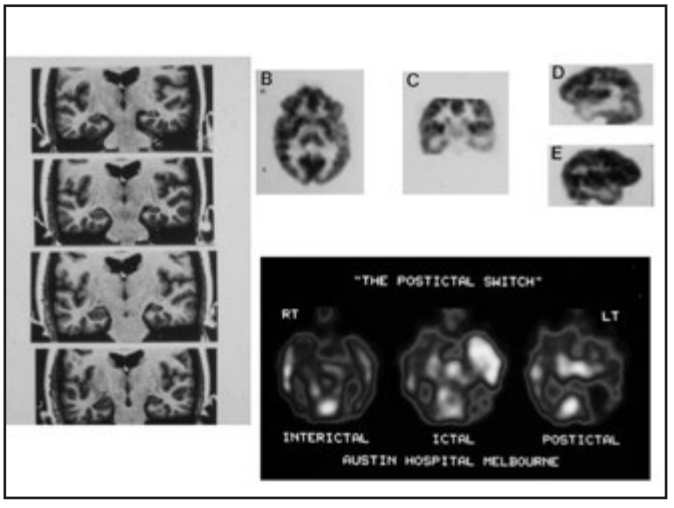
The Syndrome of Mesial Temporal Lobe Epilepsy
Clinical Seizure

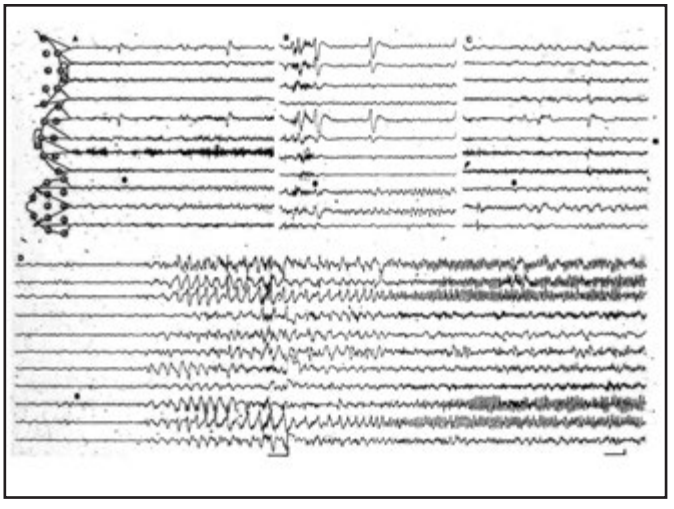
- Complex partial seizure often begins with arrest and stare, oroalimentary automatisms common. Posturing of one upper extremity may occur contralateral to the ictal discharge (1 to 2 minutes)
- Postictal phase usually includes disorientation, recent memory deficit, amnesia for the event, and dysphasia if seizures begin in the language-dominant hemisphere (several minutes).

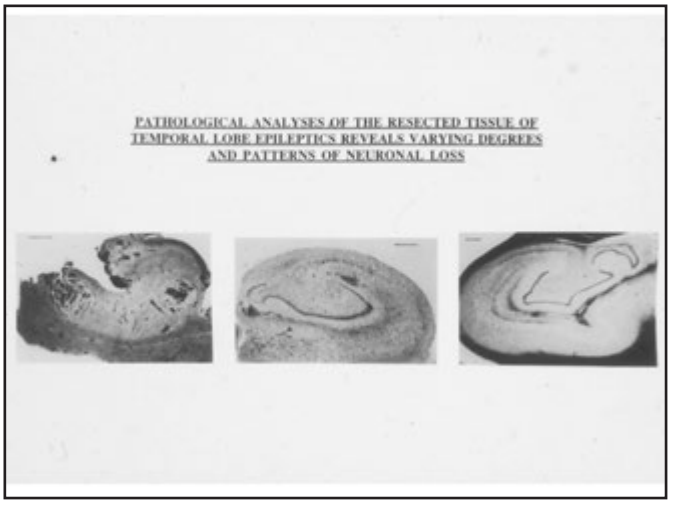
The Syndrome of Mesial Temporal Lobe Epilepsy
Neurologic Examination

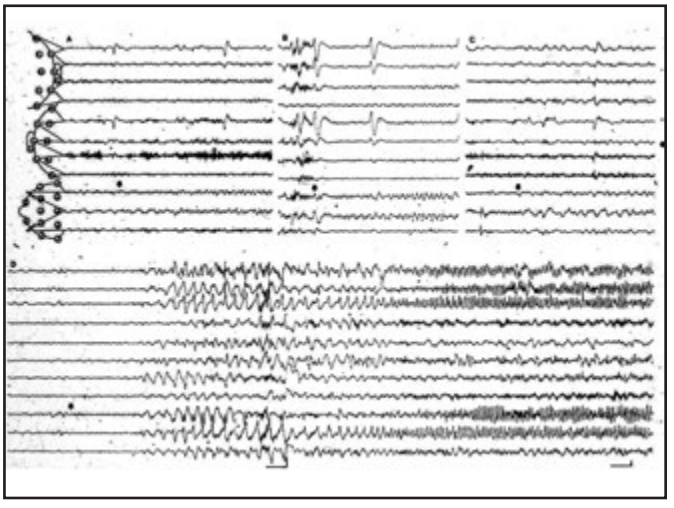
- Usually Normal
- May have recent memory deficit
- Focal motor or sensory deficits are very rare

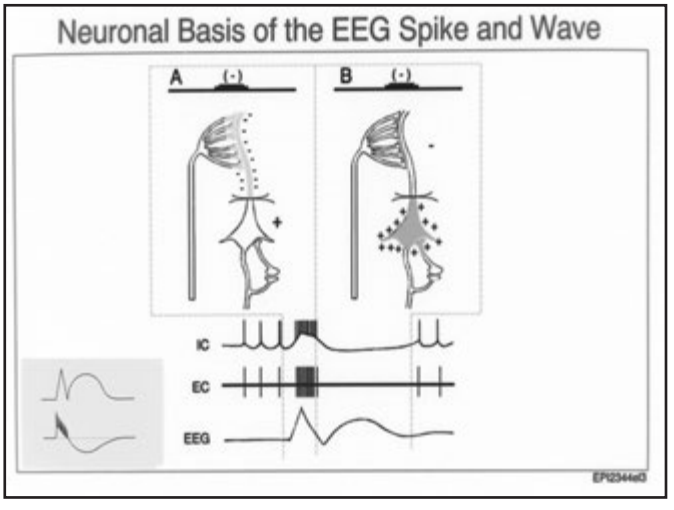


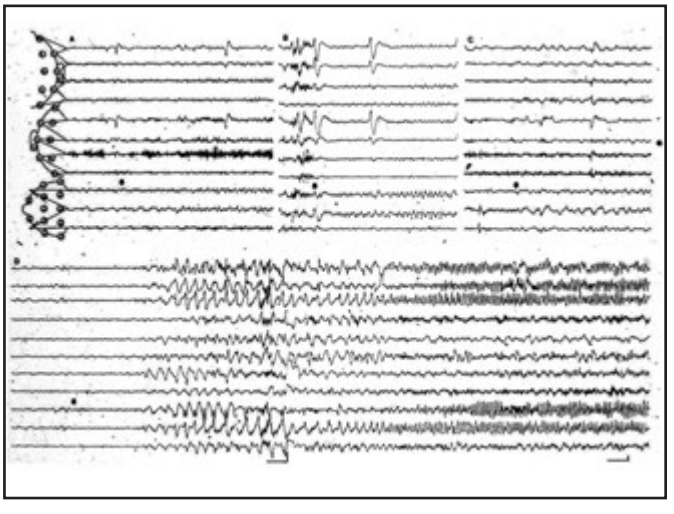

B
C
D
E
"THE POSTICTAL SWITCH"
RT
LT
INTERICTAL
ICTAL
POSTICTAL
AUSTIN HOSPITAL MELBOURNE

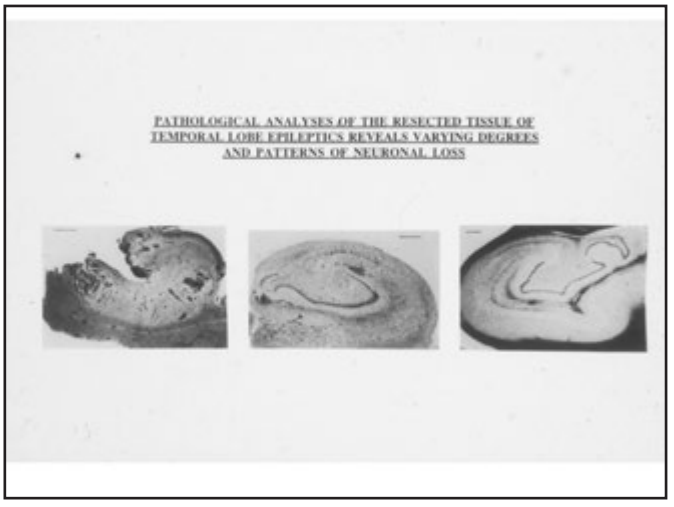


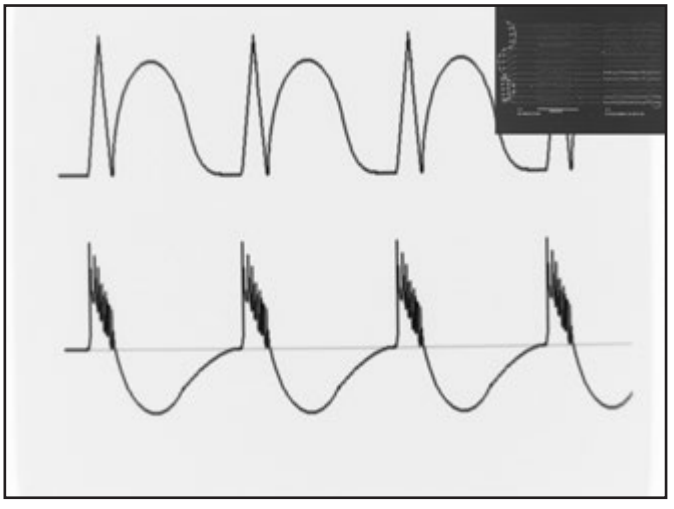

PATHOLOGICAL ANALYSES OF THE RESECTED TISSUE OF
TEMPORAL LOBE EPILEPTICS REVEALS VARYING DEGREES
AND PATTERNS OF NEURONAL LOSS

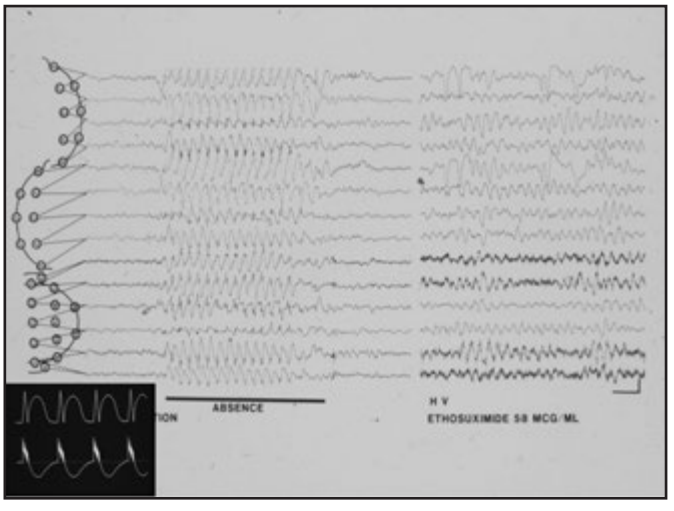


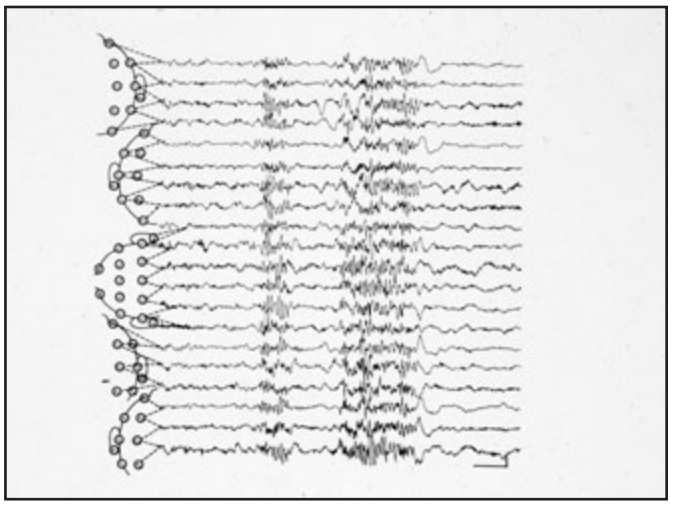

Neuronal Basis of the EEG Spike and Wave
A
(-)
B
(-)
+
-
IC
EC
EEG

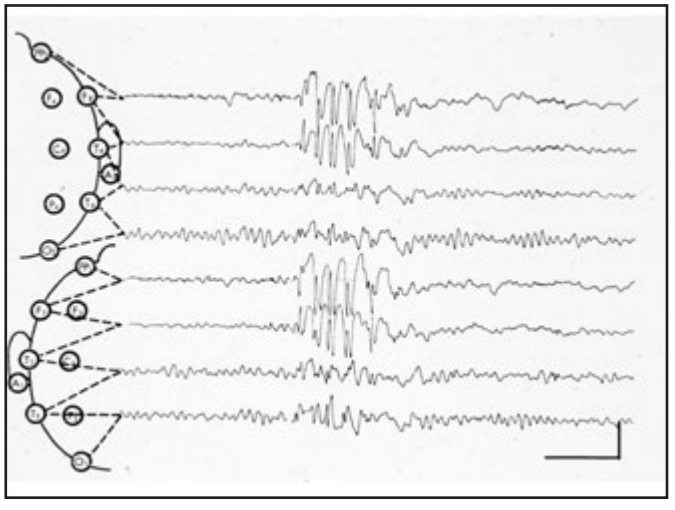


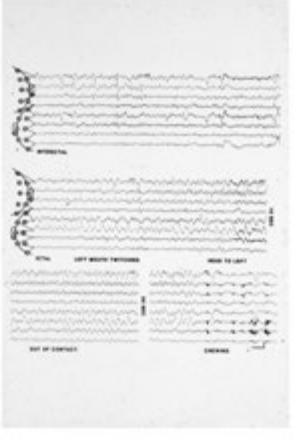

PATHOLOGICAL ANALYSES OF THE RESECTED TISSUE OF
TEMPORAL LOBE EPILEPTICS REVEALS VARYING DEGREES
AND PATTERNS OF NEURONAL LOSS

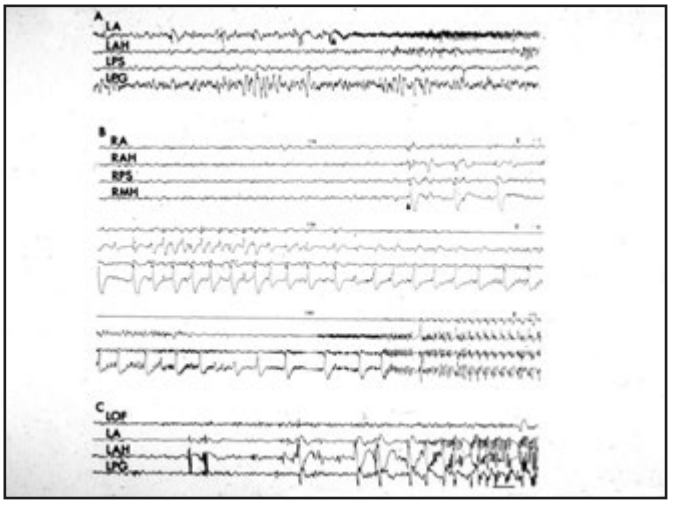


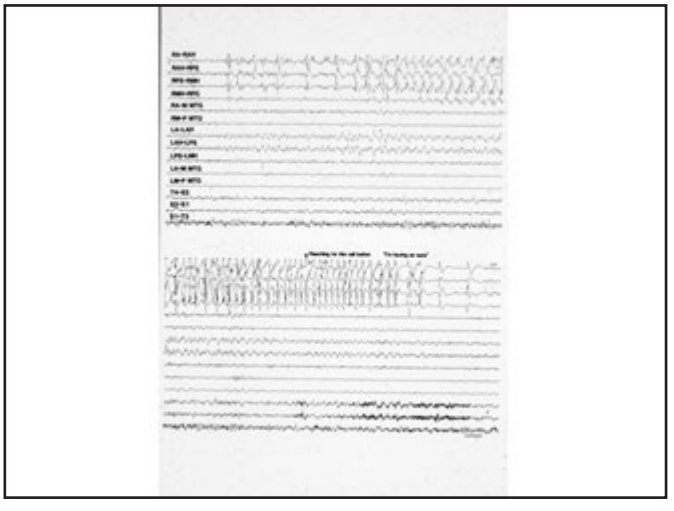

ABSENCE
H V
ETHOSUXIMIDE 50 MCG/ML

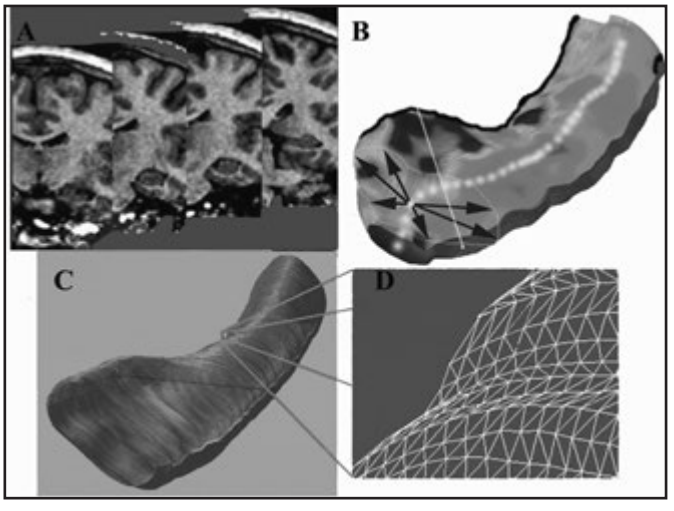




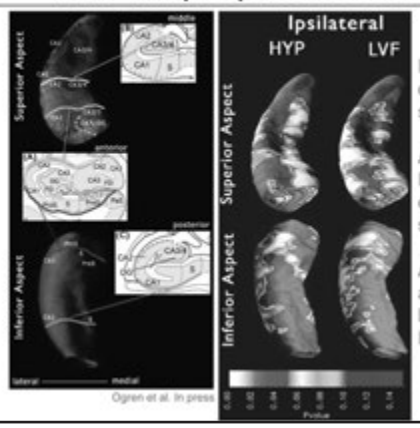



A
LA
LAH
LPS
LPG
B
RA
RAH
RPS
RMH
C
LOF
LA
LAH
LPG




A
B
C
D

HYP & LVF seizure onsets associated with unique patterns of damage



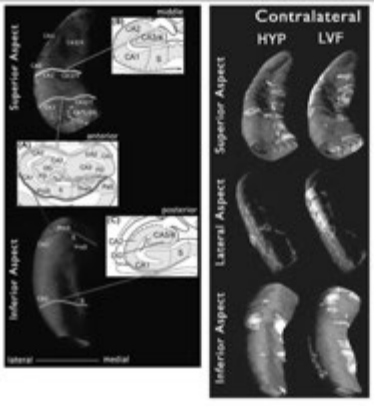
Ogren et al. In press

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.

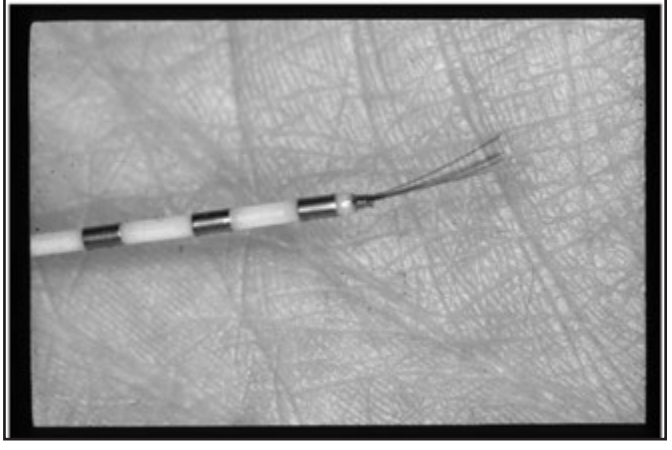
Contralateral damage in patients with LVF seizure onsets



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.

Depth electrode with 40 µ microelectrodes



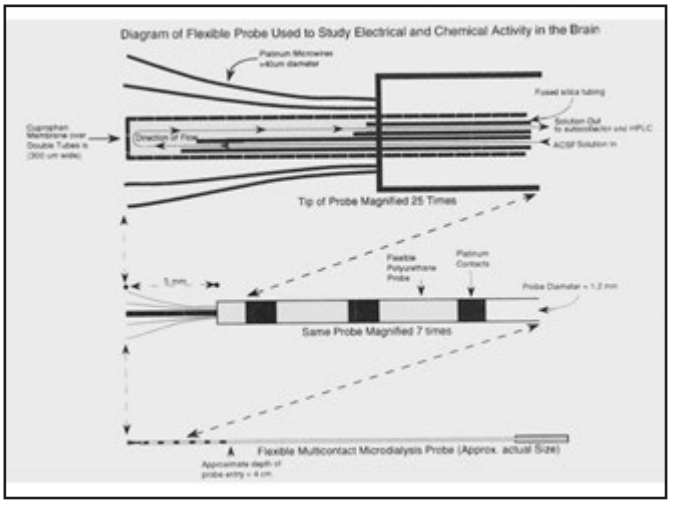
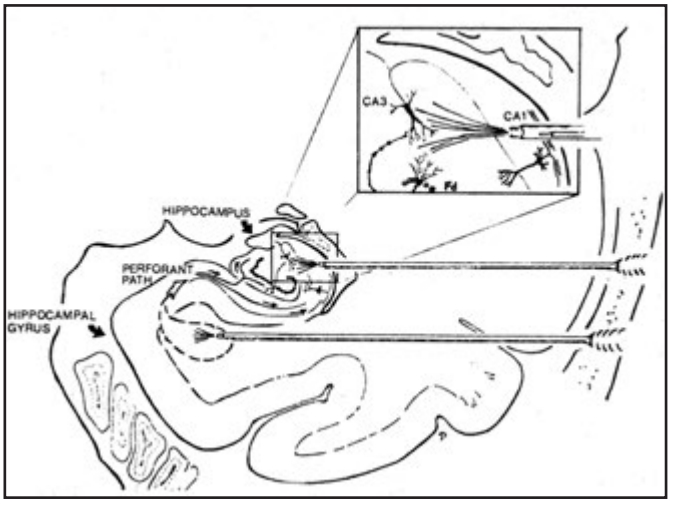
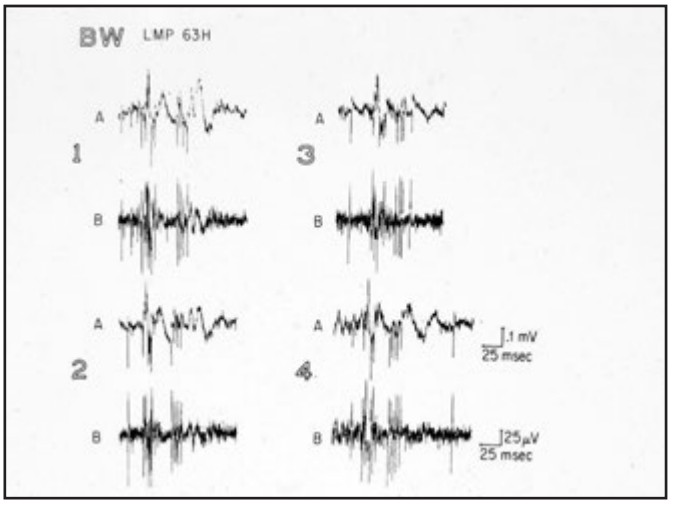
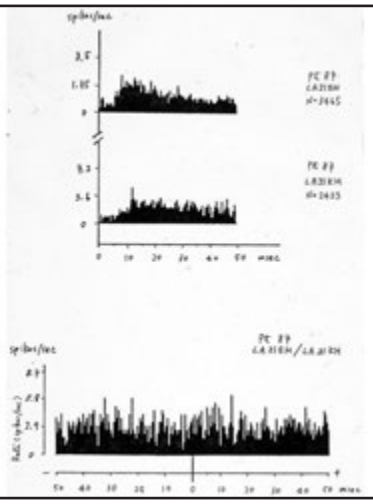
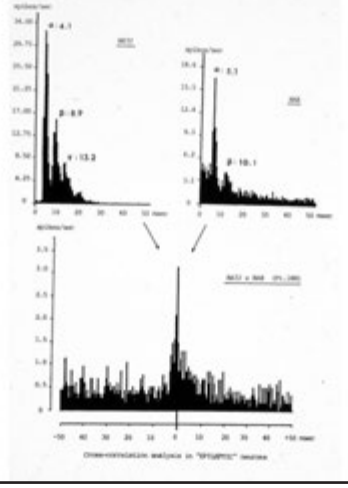


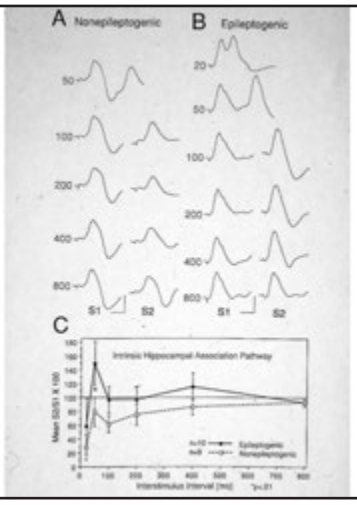
Diagram of Flexible Probe Used to Study Electrical and Chemical Activity in the Brain
Platinum Microwires
Fused silica tubing
Solution Out
to autosampler and HPLC
Direction of Flow
Tip of Probe Magnified 25 Times
Flexible
Polyurethane
Probe
Platinum
Contacts
Same Probe Magnified 7 times
Flexible Multicontact Microdialysis Probe (Approx. actual Size)

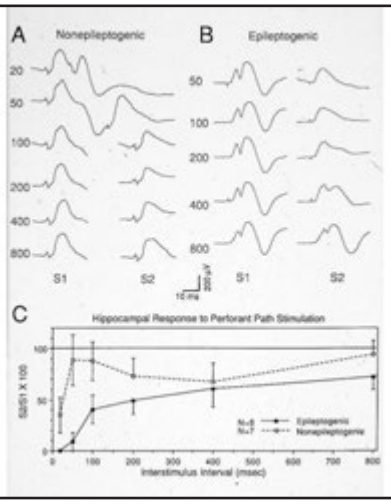

CA3
CA1
HIPPOCAMPUS
PERFORANT
PATH
HIPPOCAMPAL
GYRUS

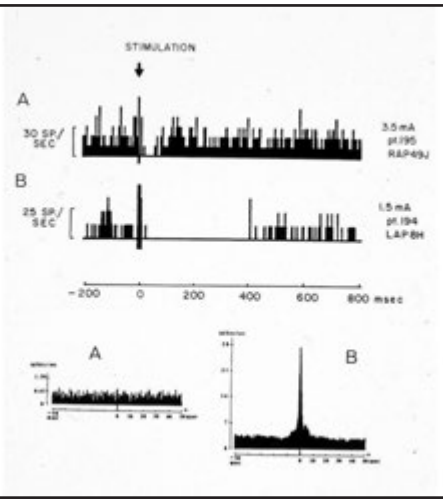

BW LMP 63H
A
B
1
2
3
4
.1 mV
25 msec
25 μV
25 msec

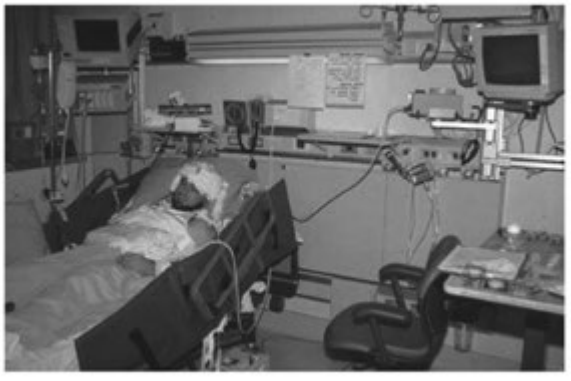


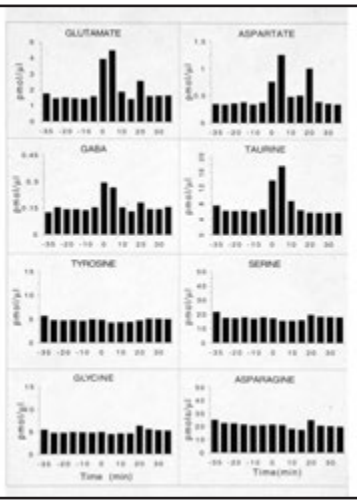


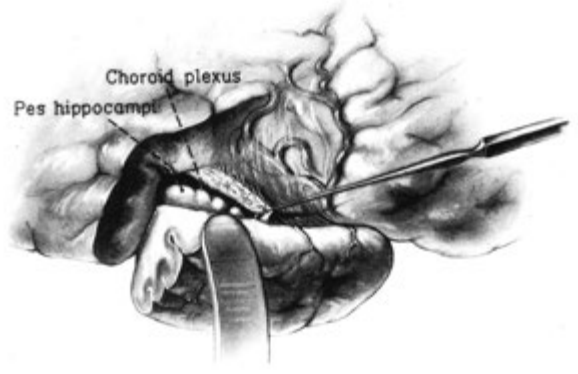

A Nonepileptogenic
B Epileptogenic
50
100
200
400
800
S1
S2
C
Intrinsic Hippocampal Association Pathway
Mean S2/S1 X 100
Epileptogenic
Nonepileptogenic
Interstimulus Interval (ms)

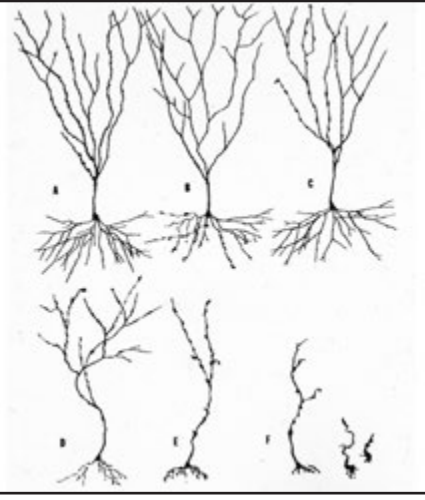

A
Nonepileptogenic
B
Epileptogenic
20
50
100
200
400
800
S1
S2
C
Hippocampal Response to Perforant Path Stimulation
S2/S1 X 100
Epileptogenic
Nonepileptogenic
Interstimulus Interval (msec)

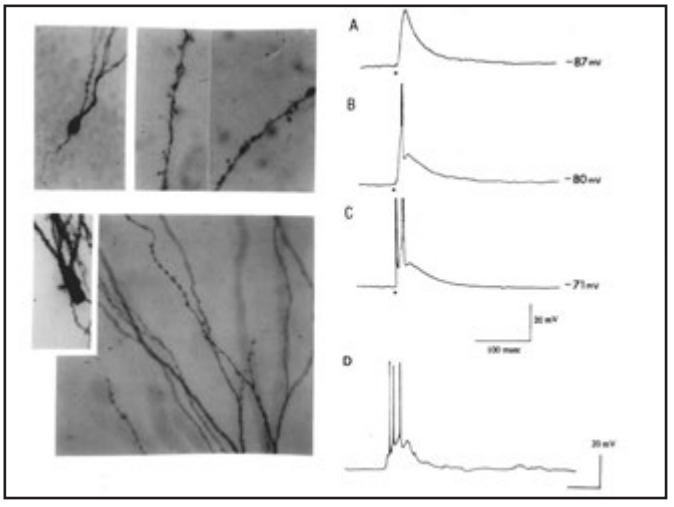

STIMULATION
A
30 SP/SEC
3.5 mA
pt.195
RAP49J
B
25 SP/SEC
1.5 mA
pt.194
LAP8H
-200
0
200
400
600
800 msec
A
B

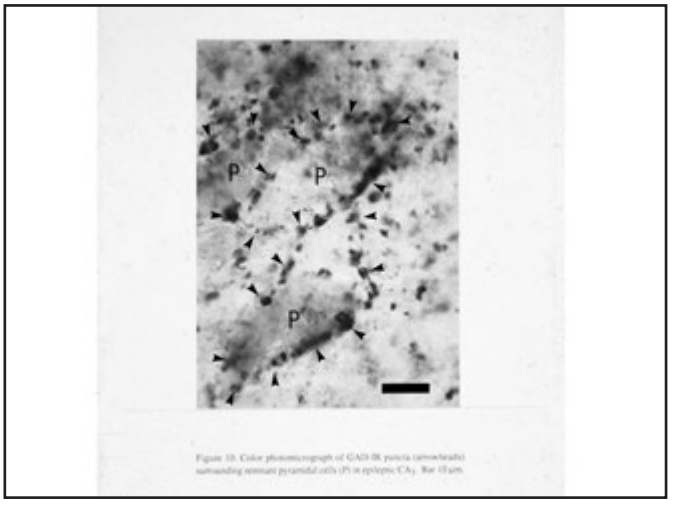


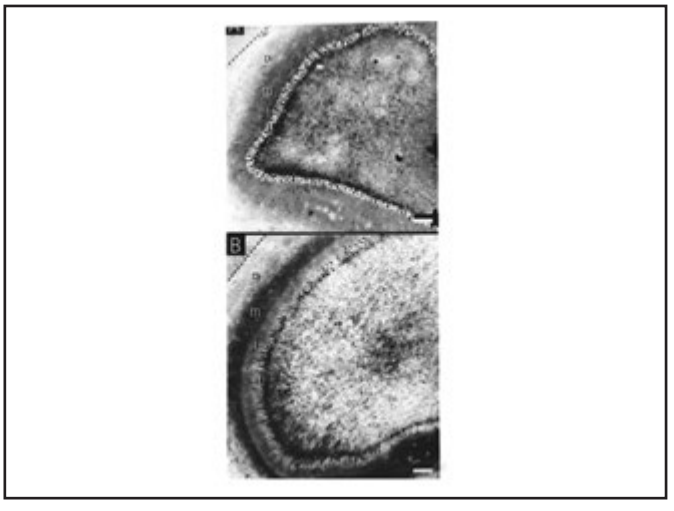

GLUTAMATE
ASPARTATE
GABA
TAURINE
TYROSINE
SERINE
GLYCINE
ASPARAGINE
Time (min)
Time(min)

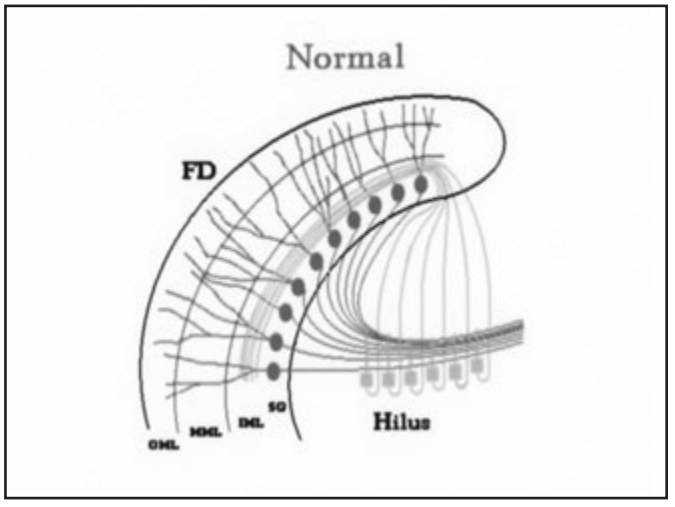

Choroid plexus
Pes hippocampi

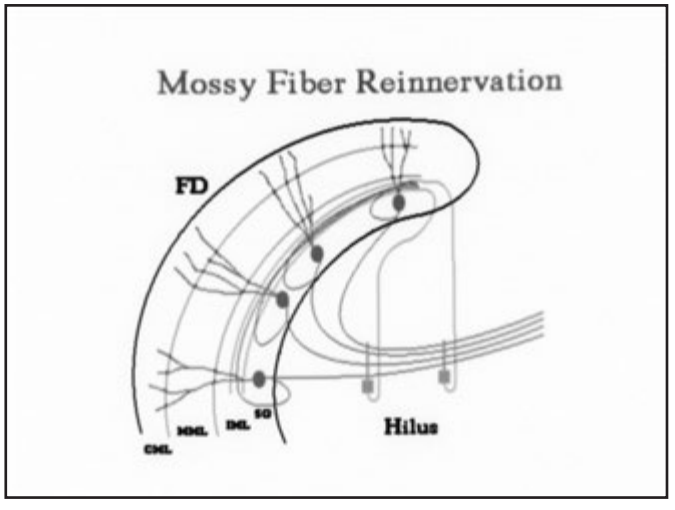


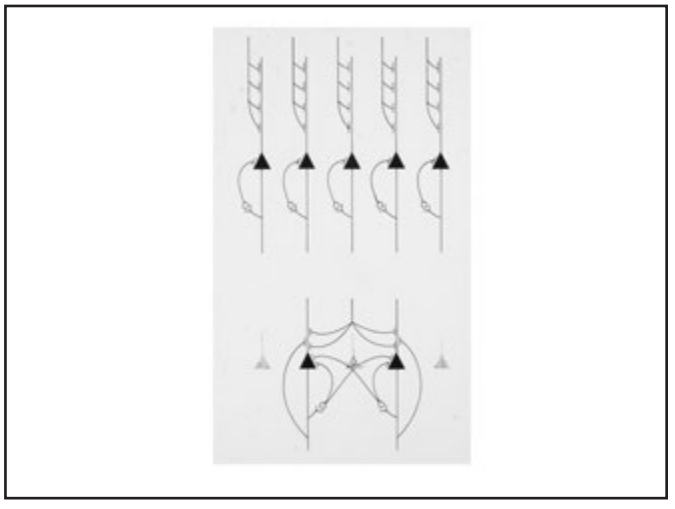

A
-87 mv
B
-80 mv
C
-71 mv
20 mV
100 msec
D
20 mV


P
P
P


B


Normal
FD
SG
Hilus
GML
MML
IML


Mossy Fiber Reinnervation
FD
SG
Hilus
GML
MML
IML



Aberrations in:

- Neuronal migration and differentiation
- Axonal sprouting and circuit reorganization
- Synaptic plasticity

Temporal aspects of very fast brain oscillations prior to seizures

Roger Traub (USA)

Very Fast Oscillations (> 80 Hz)
& Gap Junctions

Roger D. Traub
IBM T.J. Watson Research Center
Yorktown Heights, NY

&

Miles A. Whittington
Institute of Neuroscience
University of Newcastle School of Medicine

Some network oscillation mechanisms

- Correlated IPSPs (e.g. gamma)
- Pacemaker, with spread (the heart)
- Re-entry (Wolff-Parkinson-White)
- Coupled oscillators

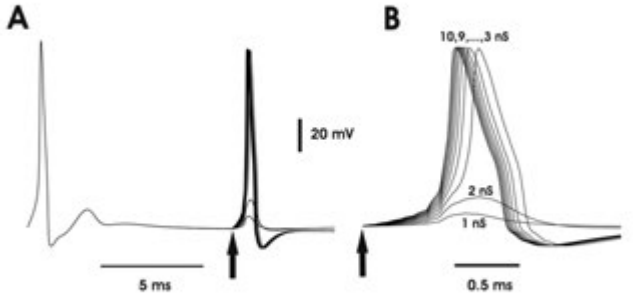
- Propagation through (locally) random network
- Propagation + intrinsic refractoriness

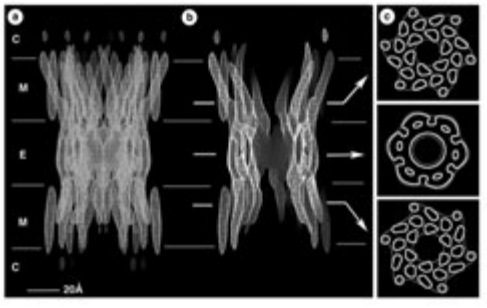
Interesting Physical Principle

Gap junctions "synchronize", e.g. spike times.

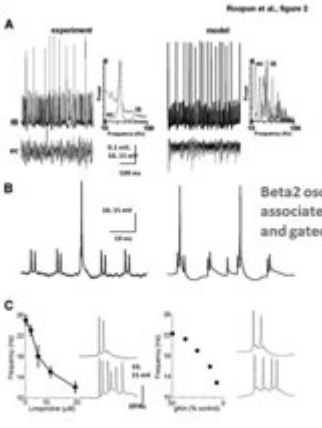
BUT propagation time from cell to cell across a gap junction takes finite time, say, 0.25 ms.

In a sparse network, these brief propagation times summate in such a way as to determine oscillation period.

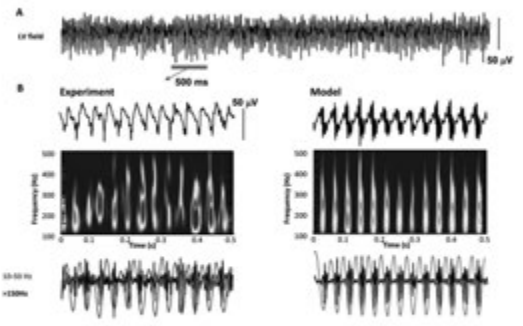




Gap junction structure: recombinant cardiac connexin (lacking COOH-terminal domain), expressed in BHK cells. Electron crystallography, ~7.5 Å resolution in membrane plane, 21 Å in vertical plane. V.M. Unger et al., 1999, Science.



Beta2 oscillation is associated with spikelets, and gated by M-current



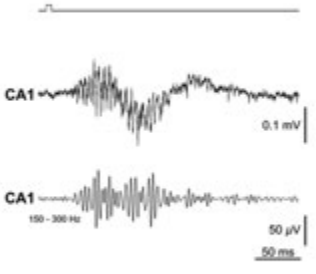
Nested "non-synaptic" oscillations: beta2 + VFO

Miles A. Whittington, unpublished data

VFO ("very fast oscillations") in low calcium

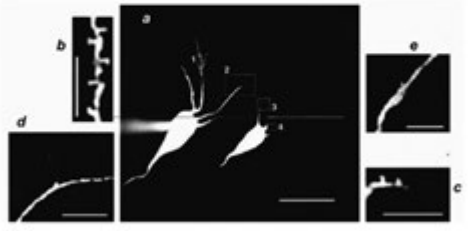
Andreas Draguhn et al., Nature, 1998

VFO with GABA-A receptors blocked



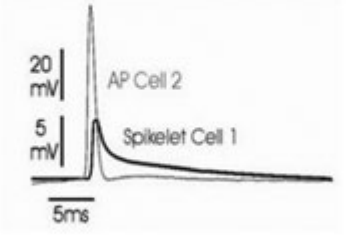
Nimmrich et al., J. Physiol. 2005

Dye-coupling between the axons of two CA1 pyramidal neurons



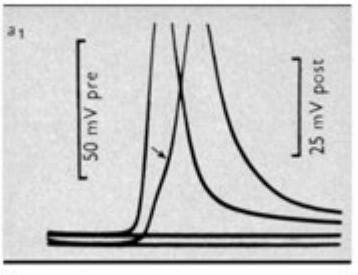
Dietmar Schmitz et al., Neuron, 2001

Action potential in one CA1 pyramidal cell causing short-latency spikelet in another one



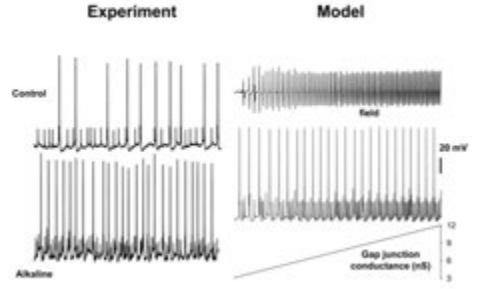
Mercer et al., 2006

Spike in one axon leading to short-latency spike in electrically coupled 2nd axon (crayfish nerve cord)



Furshpan & Potter, J. Physiol., 1959

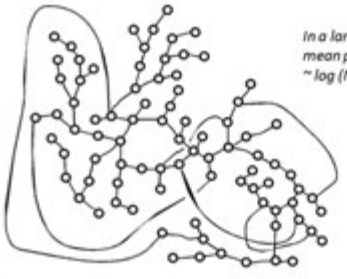
Spikelet frequency depends on pH, hence putatively on gap junction conductance



Miles A. Whittington & RDT, unpublished data

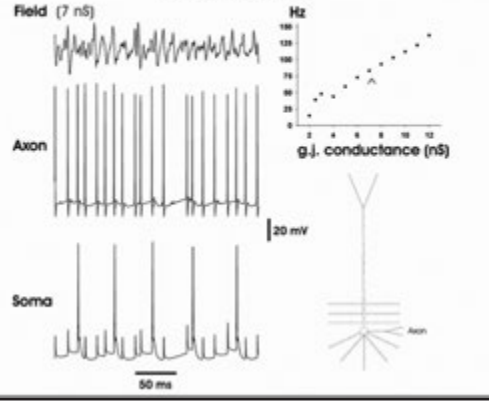
Why do network oscillations occur when gap junctions allow spikes to propagate from cell to cell? -

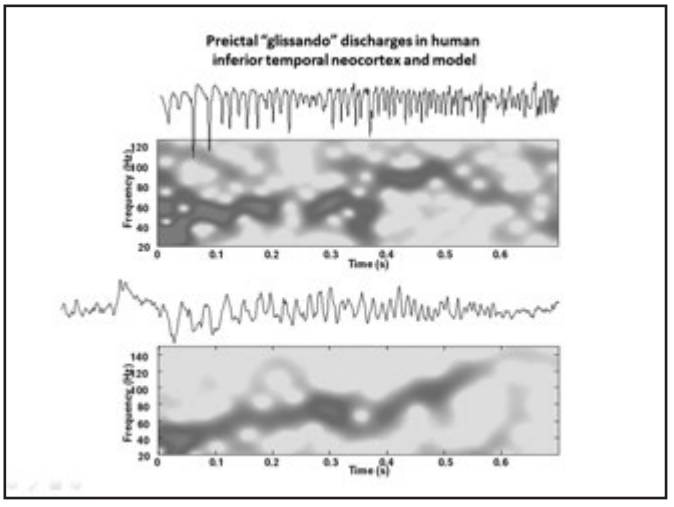
It can happen as a result of "percolation" in a large, sparsely connected network, with period INDEPENDENT of intrinsic and synaptic conductances (!!)

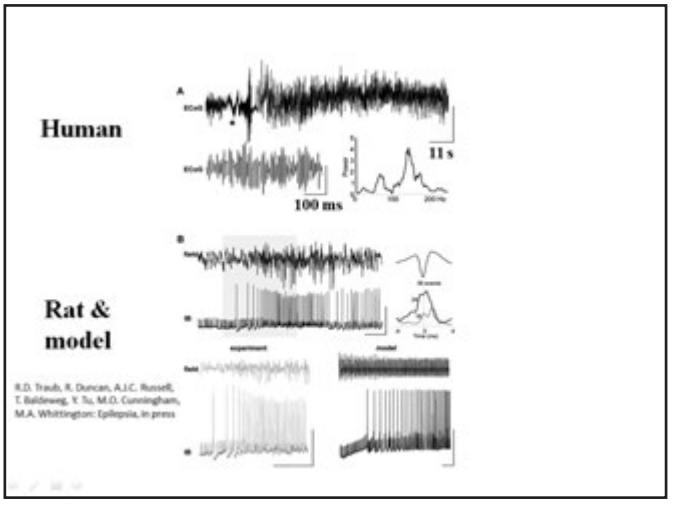


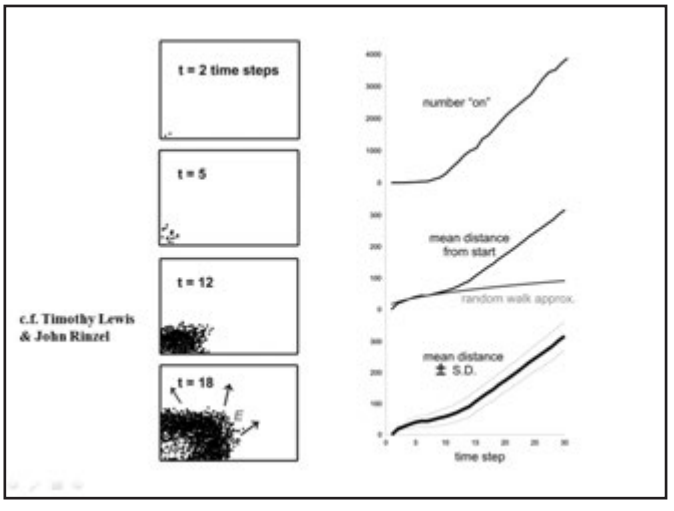
In a large random graph, mean path length ~ log (N) / log (< i >)

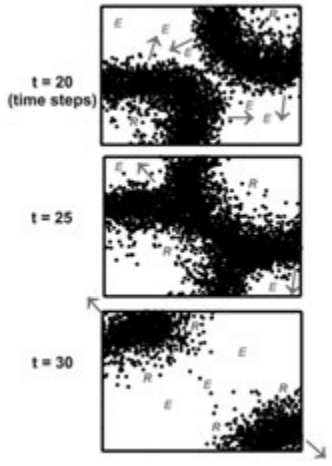
Simulated very fast oscillations in network of 15,000 tufted IB pyramidal cells, with g.j. between axons

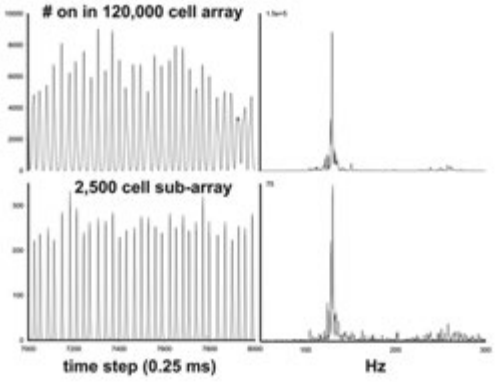


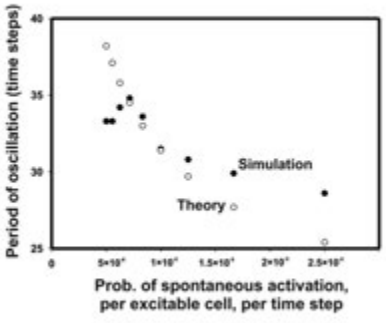

Preictal "glissando" discharges in human inferior temporal neocortex and model
Frequency (Hz)
Time (s)

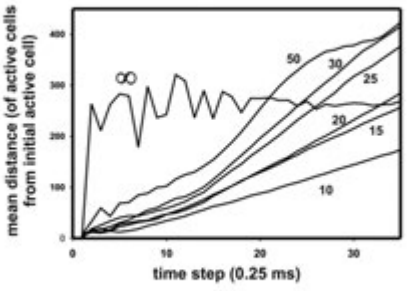

Human
11 s
100 ms
Rat & model
R.D. Traub, R. Duncan, A.J.C. Russell, T. Baldeweg, Y. Tu, M.O. Cunningham, M.A. Whittington: Epilepsia, in press

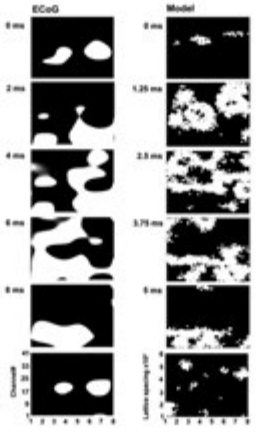

t = 2 time steps
t = 5
t = 12
t = 18
E
c.f. Timothy Lewis & John Rinzel
number "on"
mean distance from start
random walk approx.
mean distance ± S.D.
time step


t = 20
(time steps)
t = 25
t = 30
E
R


on in 120,000 cell array
2,500 cell sub-array
time step (0.25 ms)
Hz


Period of oscillation (time steps)
40
35
30
25
0
Simulation
Theory
Prob. of spontaneous activation,
per excitable cell, per time step



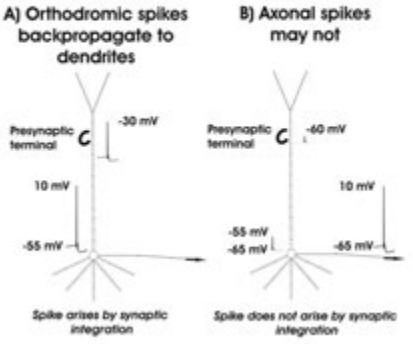


Some network oscillation mechanisms

- Correlated IPSPs (e.g. gamma)
- Pacemaker, with spread (the heart)
- Re-entry (Wolff-Parkinson-White)
- Coupled oscillators

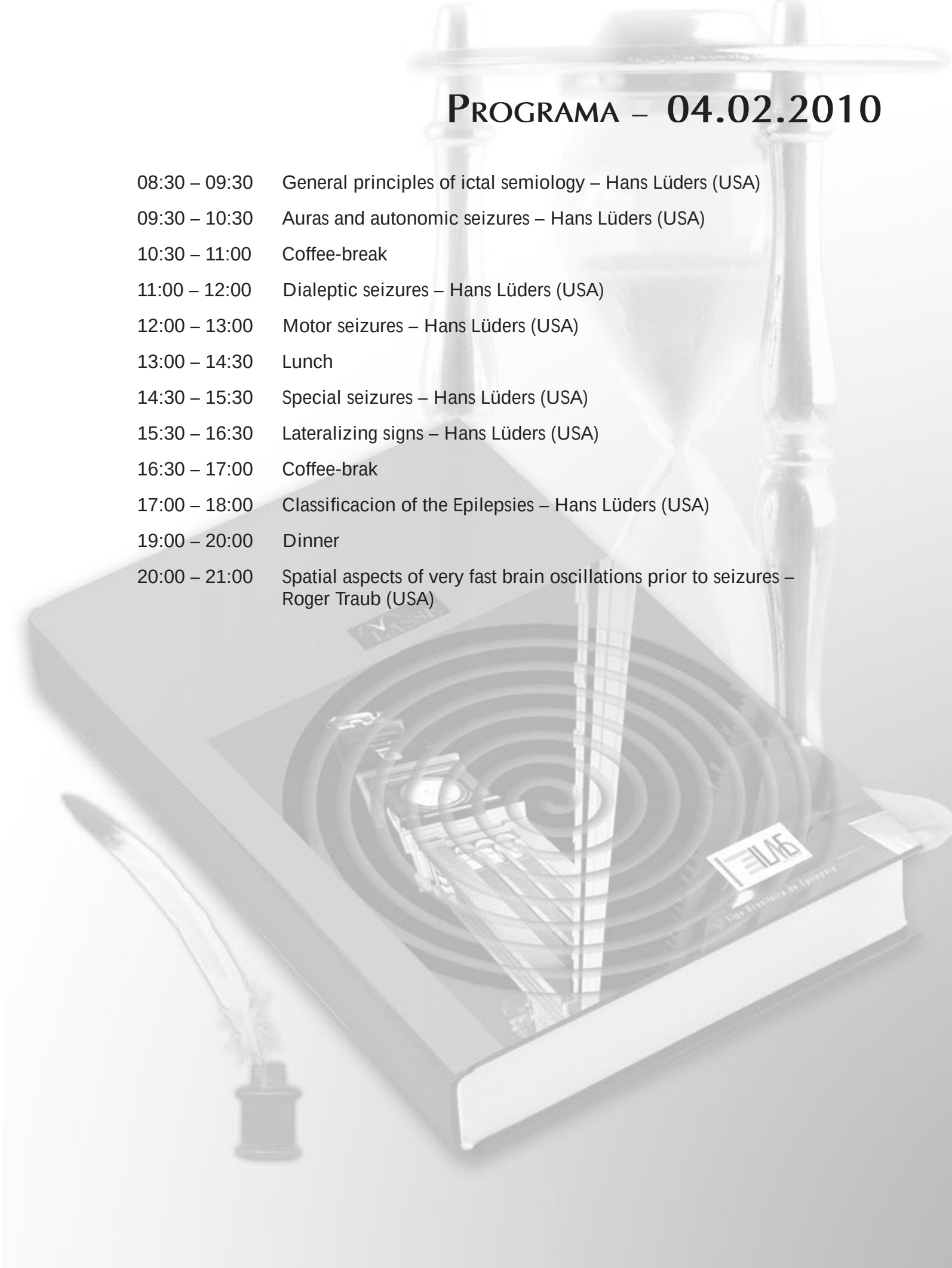
- Propagation through (locally) random network
- Propagation + intrinsic refractoriness

Functional significance of orthodromic vs. antidromic spike initiation



Programa – 04.02.2010

08:30 – 09:30	General principles of ictal semiology – Hans Lüders (USA)
09:30 – 10:30	Auras and autonomic seizures – Hans Lüders (USA)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Dialeptic seizures – Hans Lüders (USA)
12:00 – 13:00	Motor seizures – Hans Lüders (USA)
13:00 – 14:30	Lunch
14:30 – 15:30	Special seizures – Hans Lüders (USA)
15:30 – 16:30	Lateralizing signs – Hans Lüders (USA)
16:30 – 17:00	Coffee-brak
17:00 – 18:00	Classificacion of the Epilepsies – Hans Lüders (USA)
19:00 – 20:00	Dinner
20:00 – 21:00	Spatial aspects of very fast brain oscillations prior to seizures – Roger Traub (USA)



Electro-clinical manifestations of epilepsies over time
Hans Lüders (USA)

Four dimensions epilepsy classification

Hans O. Lüders
Epilepsy Center

Essential features of a classification system

- Define the nature of the disease (epilepsy)
- DIMENSION #1: define the location of the disease (location of the epileptogenic zone)
- DIMENSION #2: define the cause of the disease (etiology)
- DIMENSION #3: define the main symptomatology (ictal symptomatology, frequency and "triggering factors" of seizures or status epilepticus)
- DIMENSION #4: define related medical conditions

Define the Nature of the Disease

- Epilepsy
- Paroxysmal Disorders
  - Psychogenic Seizures
  - Syncope
  - Breath Holding Spells
  - Unspecified

Essential features of a classification system

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- DIMENSION #4: define related medical conditions

DIMENSION #1: Location of the epileptogenic zone

- Generalized
- Hemispheric
- Multifocal
- Multilobar
- Regional
  - Frontal lobe
  - Perirolandic
  - Parieto-occipital lobe
  - Temporal lobe

- For non-generalized epilepsies the following modifiers apply:
  - Left
  - Right
  - Left and Right

Test used to define the location and extend of the epileptogenic zone

- All the available clinical information and the results of all tests are used to define the epileptogenic zone (clinical history, neurological exam, interictal EEG(scalp and invasive), ictal EEG (scalp and invasive), MRI, genetic testing, PET, ictal SPECT, etc). Usually the precision with which we can define the location and extend of the epileptogenic zone will increase with more testing (example: invasive EEG/video). However, an estimate of the approximate location and extend of the epileptogenic zone can always be made (example: clinical history and neurological exam only)

How to code dimension #1: epileptogenic zone

- Pick one of the terms listed in the previous slide
  - Example: temporal lobe
- Pick left, right or left and right if it is not a generalized epilepsy
  - Example: left and right temporal lobe
- You can include in parenthesis a more precise location of the epileptogenic zone if available
  - Example: left temporal lobe (left temporal pole)

DIMENSION #1: Location of the epileptogenic zone

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  - Example: left and right temporal lobe
- You can include in parenthesis a more precise location of the epileptogenic zone if available
  - Example: left temporal lobe (left temporal pole)

How not to code dimension #1: epileptogenic zone

- Do not add additional information
  - Example: Left temporal lobe (by history)
  - Example: Left temporal lobe (by MRI)
- Do not add questions marks, etc
  - Example: Left (?) temporal lobe
  - Example: Left temporal lobe (??)
  - Example: Left temporal lobe (Left temporal pole?)
- This is a classification which we will use to define specific categories in the computer. Details of how we reached a certain conclusion regarding the epileptogenic zone should be included in the body of the report (example: by history, by MRI)
- The classification should be refined as we get more information. There is always a margin of error. The classification we decide on is the best estimate with the information available at the time we classify the epilepsy.

Essential features of a classification system

- Define the nature of the disease (epilepsy)
- DIMENSION #1: define the location of the disease (location of the epileptogenic zone)
- DIMENSION #2: define the cause of the disease (etiology)
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- DIMENSION #4: define related medical conditions

DIMENSION #2: Etiology

- The etiology is the essential characteristic which in many cases defines the prognosis of the epilepsy as also guides important management decisions (like need for follow up imaging)
- High resolution MRI is currently the most important test to define the etiology of the epilepsy. Genetic testing most probably will become in the near future an essential test to define the etiology of all epilepsies.

DIMENSION #2: Etiology

- Neoplasm
- Hippocampal sclerosis
- Head trauma
- Malfomation of cortical development
- Hemimegalencephaly
- Infarction
- Central nervous system infection
- Tuberous sclerosis
- Sturge Weber Syndrome
- Epidermal nevus syndrome
- Metabolic Disorder
- Genetic
- Other

How to code DIMENSION #2

- Pick one of the etiologies listed above
  - Example: Neoplasm
- You can specify in parenthesis a more precise diagnosis (free text)
  - Example: Neoplasm (left mesial temporal ganglioglioma)
- Define triggering factor(s) for seizures or epileptic status:
  - Examples:
    - Seizure triggering factor: intermittent light
    - Status triggering factor: anticonvulsant withdrawal
    - Triggering factor: none

How not to code dimension #2: etiology and triggering factors

- Do not add additional information
  - Example: neoplasm (left temporal ganglioglioma) (by MRI)
  - Example: neoplasm (left temporal ganglioglioma) (biopsy)
- Do not add questions marks, etc
  - Example: Neoplasm (?)
  - Example: Neoplasm (?) (Left temporal ganglioglioma??)
  - Example: Left temporal lobe (Left temporal pole?)
- This is a classification which we will use to define specific categories in the computer. Details of how we reached a certain conclusion regarding the epileptogenic zone should be included in the body of the report (example: by biopsy, by MRI)
- The classification should be refined as we get more information. There is always a margin of error. The classification we decide on is the best estimate with the information available at the time we classify the epilepsy.
  - Instead of neoplasm (left temporal ganglioglioma?) use neoplasm
  - In other words, use a less specific category if you are uncertain
  - Differential diagnosis can be discussed in the body of the report (not in the classification).

Essential features of a classification system

- Define the nature of the disease (epilepsy)
- DIMENSION #1: define the location of the disease (location of the epileptogenic zone)
- DIMENSION #2: define the cause of the disease (etiology)
- DIMENSION #3: define the main symptomatology (ictal symptomatology, frequency and "triggering factors" of seizures or status epilepticus)
- DIMENSION #4: define related medical conditions

Semiology of epileptic seizures

- Symptoms occurring during epileptic seizures can affect the following spheres:
  - Sensory sphere ⇒ Aura
  - Autonomic sphere ⇒ Autonomic seizure
  - Cognition sphere ⇒ Dyscognitive seizure
  - Motor sphere ⇒ Motor seizure

Aura

- Epileptic auras are defined as sensations which the patient reports and are the consequence of epileptic activation of a limited cortical region. They are usually of short duration (seconds) and occur at the beginning of the seizures.

Auras

- Somatosensory aura
- Auditory aura
- Olfactory aura
- Abdominal aura
- Visual aura
- Gustatory aura
- Autonomic aura
- Psychic aura

Semiology of epileptic seizures

- Symptoms occurring during epileptic seizures can affect the following spheres:
  - Sensory sphere ⇒ Aura
  - Autonomic sphere ⇒ Autonomic seizure
  - Cognition sphere ⇒ Dyscognitive seizure
  - Motor sphere ⇒ Motor seizure

Sensorial and cognition sphere (auras and dyscognitive seizures)

- Sensory: "relating to sensation or perception of a stimulus" (aura)
- Cognition: "the mental activity by which an individual is aware of and knows about his or her environment , including such processes as perceiving, remembering, reasoning, judging, and problem solving."

Autonomic Seizures

- Autonomic seizures are seizures in which the main symptomatology is autonomic
  - Example: taquicardia, unilateral body sweating, salivation, etc

Dyscognitive Seizures

- Discognitive seizures are characterized by relative unresponsiveness and amnesia for the seizure. Some motor manifestations may be observed but the alterations of cognition are always the predominant symptom.

Dyscognitive Seizures

- Dyscognitive seizures are subdivided into 2 groups:
  - Dialeptic seizures
    - Dyscognitive seizure with significant decrease of motiliy
  - Delirious seizures
    - Dyscognitive seizure with significant increase of motility

Dialeptic Seizures

- Dialeptic comes from the Greek verb *dialeipin* which means *to stop, to interrrupt or to seize. Dialeipin* is a synonym of *epileipin* which is the Greeek root of epilepsy.

Motor Seizures

- Simple Motor Seizures
  - Myoclonic seizures
  - Tonic seizures
  - Epileptic spasms
  - Clonic seizures
  - Tonic-clonic seizures
  - Versive seizures
- Complex Motor Seizures
  - Hypermotor seizures
  - Automotor seizures
  - Gelastic seizures

Myoclonic Seizures

- Myoclonic seizures consist of muscle contractions of brief duration (less than 200 msec). Myoclonic seizures are either non-rhythmical or affect different muscle groups each time (multiregional myoclonic seizures)

Tonic Seizures

- Tonic seizures consist of sustained muscle contractions usually lasting more than 5 to 10 seconds

Epileptic Spasm

- Epileptic spasms consist of a more or less sustained contraction of axial muscles leading to flexion of the trunk and abduction and elevation of both arms in a "salaam" position.The initial movement tends to be relatively fast, like a myoclonic contraction. However, usually the patient remains in the salaam position for a few seconds before relaxation occurs. These spasms tend to occur in clusters.

Clonic Seizures

- Clonic seizures consist of myoclonic jerks that recur at regular intervals of less than 1 to 2 seconds

Tonic-clonic seizures

- These seizures consist of an initial tonic phase during which the patient has the legs and arms in extension with the arms adducted and crossed in front of the body. Occasionally also tonic flexion at the elbows may be observed. This tonic phase lasts only 5-10 seconds and is followed by a slight tremor produced by rapid, small flexions of the arms at the elbow. The flexions of the arms increases progressively in amplitude as the rate diminishes (clonic phase). This is followed by postictal coma that lasts for many minutes with a slow, but steady recovery. It is used only for generalized tonic-clonic seizures. It is always associated by loss of consciousness (coma).

Versive Seizure

- Versive seizures consist of sustained, unnatural turning of the head and eyes to one side. Usually the head and eyes also move slightly upward.

Motor Seizures

- Simple Motor Seizures
  - Myoclonic seizures
  - Tonic seizures
  - Epileptic spasms
  - Clonic seizures
  - Tonic-clonic seizures
  - Versive seizures
- Complex Motor Seizures
  - Hypermotor seizures
  - Automotor seizures
  - Gelastic seizures

Hypermotor seizures

- Complex motor seizures in which the automatisms affect primarily the proximal body segments. This results in large movements which, when executed rapidly, appear "violent".

Automotor Seizures

- Complex motor seizures in which the predominant movements consist of distal automatisms of the hands or month and tongue. Consciousness is usually compromised but may be preserved in seizures arising form the non-dominant temporal lobe.

Gelastic Seizures

- Seizures in which the main symptomatology consists of laughter.These seizures are most frequently seen in patients with hypothalamic hamartomas.

Semiology of epileptic seizures

- Symptoms occurring during epileptic seizures can affect the following spheres:
  - Sensory sphere ⟹ Aura
  - Autonomic sphere ⟹ Autonomic seizure
  - Cognition sphere ⟹ Dyscognitive seizure
  - Motor sphere ⟹ Motor seizure

Special Seizures

- Astatic Seizures
- Atonic Seizures
- Akinetic Seizures
- Negative Myoclonic Seizures
- Aphasic Seizures
- Hypomotor Seizures

Hypomotor Seizures

- Hypomotor seizures are characterized by immobility or a marked decrease in motility in newborns, infants, or in severely mentally retarded patients in whom the cause of immobility (alterations of consciousness, inability to move, distraction by an aura, etc) can not be determined.

Semiological Seizure Classification

- Each seizure type is considered as a seizure component of an epileptic seizure. A seizure may consist of up to four seizure components. Example: clonic seizure, dialeptic seizure, visual aura, etc
- Each seizure component is modified by a somatotopic attribute. Example: left hand clonic seizure, right visual aura, etc

Somatotopic modifiers

- Seizures that accept a somatotopic modifier:
  - Auras:
    - Somatosensory aura, Auditory aura, Visual aura, autonomic aura
  - Some Autonomic seizures
  - All simple motor seizures
  - Special seizures:
    - Akinetic seizures, Negative myoclonic seizures, atonic seizures
- Seizures that do not accept a somatotopic modifier:
  - Auras:
    - Olfactory aura, gustatory aura, abdominal aura, psychic aura
  - All dyscognitive seizures
  - All complex motor seizures
  - Special seizures:
    - Astatic seizures, aphasic seizures, hypomotor seizures

Semiological Seizure Classification

- The order in which each component occurs is specified by linking the seizure components by arrows:
  - Example: Left visual aura → left hand clonic seizure → generalized tonic-clonic seizure
- The three types of semiological components (semiological seizure type, somatotopic attribute, order) included in the seizure classification are independent and can occur in any constellation

Seizure Frequency

• Daily	≥ 1 per day
• Persistent	≥ 1 per 6 months
• Rare or no seizures	< 1 per 6 months
• Undefined	New onset seizures or unclear frequency

Each category can be followed by the precise seizure frequency in parenthesis. Example:

Seizure frequency: persistent (3-4/month)

DIMENSION #2: Triggering factors

- Epileptic seizures and status epilepticus may be triggered by external "factors". Examples:
  - Intermittent bright light (photosensitive seizures)
  - Darkness
  - Reading aloud or swallowing
  - A specific music
  - etc

How to code dimension #3: seizure semiology

- Identify the main seizure components (maximum four components)
- Order the seizure components in "chronological order"
- Add a somatotopic modifier for seizure components that accept somatotopic modifiers
- Indicate the first seizure component for which the patient is amnestic and was unresponsive with (LOC)
  - Example: abdominal aura → automotor seizure (LOC)
- Identify lateralizing signs
  - Example: right hand dystonia, left nose wiping, etc
- Identify seizure triggering factors:
  - Example: intermittent light, darkness, music, etc
- Specify seizure frequency

How not to code dimension #3

- Do not classify poorly defined seizure components. Only classify clearly identifiable seizure components
- Do not exceed 4 seizure components when describing a seizure sequence. If more than 4 seizure components can de identified drop "redundant" components. Example:
  - Abdominal aura → dialeptic seizure → automotor seizure → left face clonic seizure (LOC) → left versive seizure → generalized tonic-clonic seizure

How not to code dimension #3

- In the final classification do not list all observed seizure sequences. "Idealize" a seizure sequence. Example:
  - Observed seizure sequences:
    - Abdominal aura
    - Abdominal aura → automotor seizure
    - Automotor seizure → left face clonic seizure (LOC) → generalized tonic-clonic seizure
    - Generalized tonic-clonic seizure
  - "idealized" seizure sequence)
    - Abdominal aura → automotor seizure → left face clonic seizure (LOC) → generalized tonic-clonic seizure

How not to code dimension #3

- Do not list all the somatotopic modifiers in a clonic or tonic "Jacksonian" seizure sequence
  - Example: Left mouth clonic seizure →left face clonic seizure → left arm clonic seizure → left hand clonic seizure → left foot clonic seizure
- Only list the first seizure component of the "Jacksonian" sequence:
  - Example: Left mouth clonic seizure

How not to code dimension #3

- **Remember:**
  MORE IS NOT BETTER

Classification of seizures in newborns, infants and children

- Apply the same semiological classification outlined above
- The following seizures do not occur or can not be documented in very young children
  - Auras, dyscognitive seizures, automotor seizures, generalized tonic-clonic seizures
- The following seizures are diagnosed almost only in children of less then 3 years of age:
  - Epileptic spasms
  - Hypomotor seizures

Classification of Epileptic status

- Apply the same semiological classification of seizures.
- The status classification assumes that during status the epileptic condition can produce the same symptoms observed during epileptic seizures
  - Example: right hand clonic status, dialeptic status, generalized tonic-clonic status

Classification of Epileptic status

- The evolution of status is also expressed by linking individual seizure status components by arrows. However, during status epilepticus the following evolutions may be observed:
  - A single seizure component may repeat over and over again.
    - Example: left visual aura status (implies that the patient experiences continuous left visual hallucinations for > 10 minutes
  - A sequence of seizure components may repeat over and over again
    - Example: left visual aura → automotor seizure (LOC)
  - A status episode is started by a "usual" seizure but then one of the usual seizure components repeats over and over again
    - Example: Left vidual aura → automotor seizure(LOC) → generalized tonic-clonic status

Classification of Epileptic status

- There are a few status components that appear only as status epilepticus
  - Delirious status
- Status may have specific triggering factors:
  - Withdrawal of antiepileptics
  - Alcohol ingestion
  - Sleep depriovation

Classification of Epileptic status: example

- Dimension #1: Epileptogenic zone:
  - Left temporal lobe (left mesial temporal)
- Dimension #2: Etiology:
  - Neoplasm (ganglioglioma)
- Dimension #3:
  - Seizures:
    - Semiology: Abdominal aura → Automotor seizure(LOC)
    - Lateralizing sign: Left nose wiping
    - Frequency: Persistent (2-3/month)
    - Triggering factor: alcohol
  - Status:
    - Semiology: Abdominal aura → Automotor seizure(LOC) → right face clonic seizure → generalized tonic-clonic seizure
    - Triggering factor: Withdrawal of antiepileptics
- Dimension #4: Related Medical Conditions:
  - Moderate depression

Dimension #4: Related Medical Conditions

- List all other major medical conditions:
  - Mental retardation
  - Memory or other major cognitive deficits
  - Significant neurological deficits
  - Significant psychiatric disease
  - Drug addictions
  - Skin abnormalities or othe major medical diseases
  - Previous surgeries
  - etc

Epilepsy and EEG/video classification

- An EEG/video evaluation should be summarized by providing 2 types of classification:
  - Four dimension Epilepsy Classification
  - EEG/video classification

Epilepsy and EEG/video classification

- Four Dimensions Epilepsy Classification: final four dimensions epilepsy classification that integrates all the information obtained before the current EEG/video evaluation and the information obtained in the current EEG/video evaluation
- EEG/video classification: EEG/video classification that summarizes the interictal EEG, the ictal EEG, and the seizure semiology recorded during the current EEG/video evaluation

Epilepsy and EEG/video classification: Example

- **Four dimensions epilepsy classification before the current EEG/video evaluation:**
  - Dimension #1: Epileptogenic zone:
    - **Temporal lobe**
  - Dimension #2: Etiology:
    - **Unknown**
  - Dimension #3: Seizures:
    - Semiology: **Gustatory aura → Dialeptic seizure → generalized tonic-clonic seizure**
    - Frequency: **Persistent (2-3/month)**
    - Triggering factor: **alcohol**
  - Dimension #4: Related Medical Conditions:
    - **Moderate depression**

Epilepsy and EEG/video classification: Example

- **EEG/video classification of current EMU evaluation**
- **EEG/video (non-invasive)**
  - **Abnormal III**
    - Interictal: **right inferior frontal sharp** waves
    - Ictal:
      - EEG seizure pattern: **right frontal**
      - Semiology: **gustatory aura → automotor seizure → left face clonic seizure**
        - » Lateralizng signs: **right nose wiping**

Epilepsy and EEG/video classification: Example

- **Four dimensions epilepsy classification after the current EEG/video evaluation:**
  - Dimension #1: Epileptogenic zone:
    - **Right frontal lobe**
  - Dimension #2: Etiology:
    - **Unknown**
  - Dimension #3: Seizures:
    - Semiology: **Gustatory aura → Automotor seizure (LOC) →**
    - **Left face clonic seizure → generalized tonic-clonic seizure**
    - Lateralizing sign: **Right nose wiping**
    - Frequency: **Persistent (2-3/month)**
    - Triggering factor: **alcohol**
  - Dimension #4: Related Medical Conditions:
    - **Moderate depression**

Example of Classification

- Epileptogenic Zone: **Left temporal lobe (Mesial Temporal Lobe)**
- Etiology: **Mesial temporal sclerosis**
- Seizures: **Abdominal aura → Automotor seizure (LOC)**
  - Frequency: **Persistent (1 seizure/month)**
- Related Medical Conditions: **Severe verbal memory problems**

Example of epilepsy classification

- Epileptogenic zone: **Generalized**
- Etiology: **Unknown**
- Seizures: **Generalized tonic-clonic seizures**
  - Frequency: **rare (1 seizure/3 years)**
  - Triggering factors: **alcohol**
- Related Medical Conditions: **None**

Example of epilepsy classification

- Epileptogenic Zone: **Generalized**
- Etiology: **Malformation of Cortical Development**
- Seizures: **Generalized tonic seizures**
  Hypomotor seizures
  - Frequency: **Daily (20 seizures/day)**
- Related Medical Conditions: **Severe Developmental Delay**

Example of Classification

- Epileptogenic Zone: **Generalized (Juvenile Myoclonic Epilepsy)**
- Etiology: **Genetic**
- Seizures: **Generalized Myoclonic Seizure → Generalized Tonic-Clinic Seizure**
  - Frequency: **Persistent (1 seizure/week)**
  - Triggering factors: **alcohol, sleep deprivation**
- Related Medical Conditions: **None**

SPATIAL ASPECTS OF VERY FAST BRAIN OSCILLATIONS PIOR TO SEIZURES
ROGER TRAUB (USA)

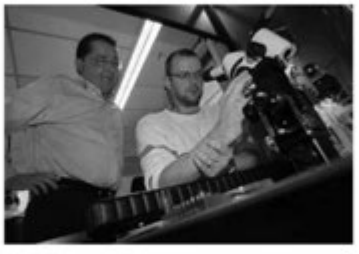
VFO (very fast oscillations, > 70 – 80 Hz):

- What are the cellular mechanisms?

-Where does the frequency come from?

Roger D. Traub, M.D.

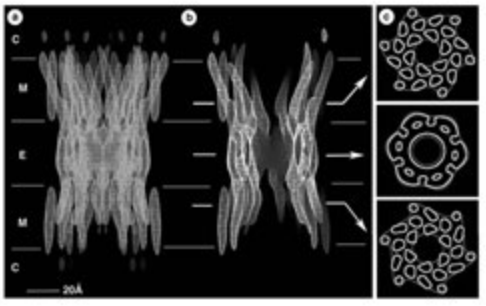
(with help from Miles Whittington, Andreas Draguhn, and many others)



Eberhard Buhl & Miles A. Whittington, Leeds, 2002

Rodolfo Llinas,
Mircea Steriade

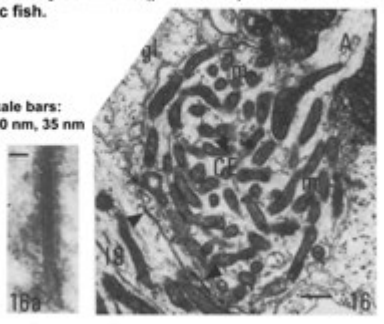
1996, Quebec.
Ph.D. defense of
Diego Contreras



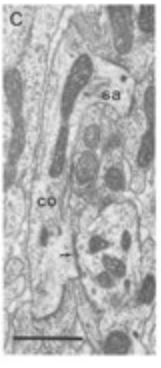
Gap junction structure: recombinant cardiac connexin (lacking COOH-terminal domain), expressed in BHK cells. Electron crystallography, ~7.5 Å resolution in membrane plane, 21 Å in vertical plane. V.M. Unger et al., 1999, Science.

2 gap junctions on the axon initial segment of a neuron in the medullary command (pacemaker) nucleus of a weakly electric fish.

Scale bars:
500 nm, 35 nm



Elekes & Szabo (1985) Experimental Brain Research

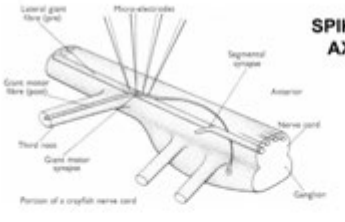


Two obliquely cut axon initial segments of dentate granule cells with a junction between them (arrow) – possibly a reticular gap junction (Dr. John E. Rash).

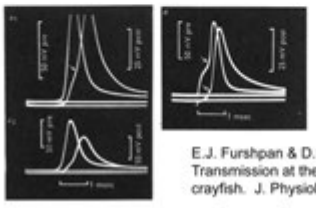
But one can't be positive from this image.

From: Toshio Kosaka (1983)
Axon initial segments of the granule cell in the rat dentate gyrus: synaptic contacts on bundles of axon initial segments.
Brain Res. 274: 129-134.

Scale bar 1 micron

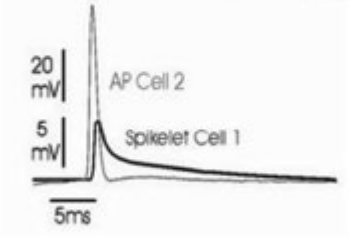


SPIKES CROSSING, AXON-TO-AXON

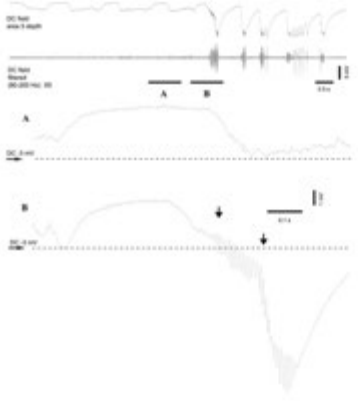


E.J. Furshpan & D.D. Potter (1959)
Transmission at the giant motor synapses of the crayfish. J. Physiol. 145: 289-325.

Action potential in one CA1 pyramidal cell causing short-latency spikelet in another one

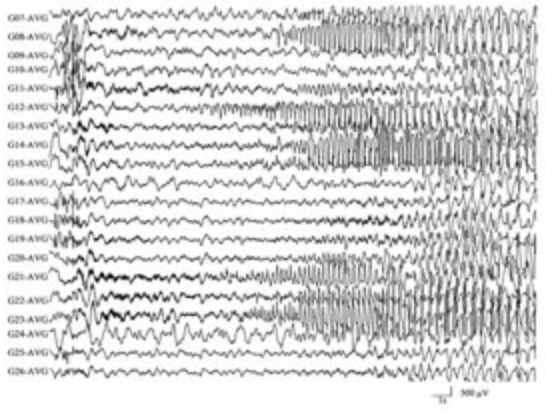


Mercer et al., 2006



Very fast oscillation, ~100 Hz, prior to initial EEG spike of seizure. Cat in vivo, ketamine/ xylazine, neocortex.

Grenier, Timofeev & Steriade, 2003, J. Neurophysiol.



Very fast oscillations preceding electrographic sz: subdural grid

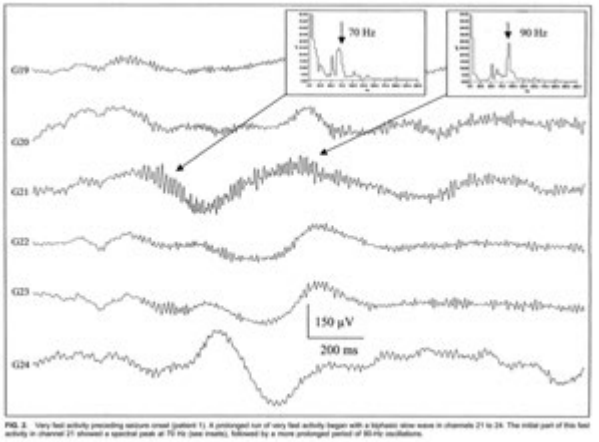
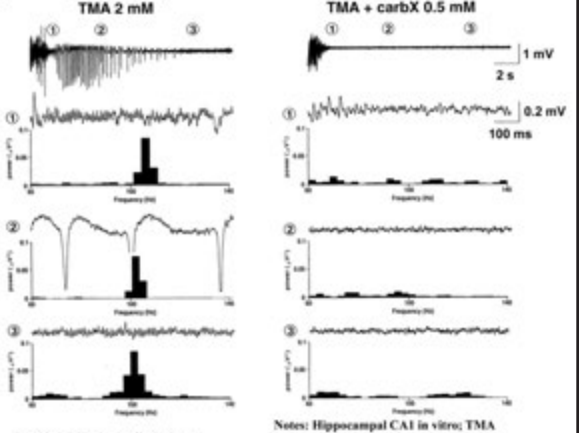


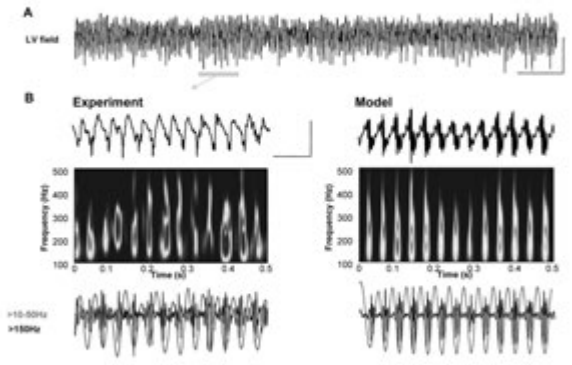
FIG. 2. Very fast activity preceding seizure onset (patient 1). A prolonged run of very fast activity began with a biphasic slow wave in channels 21 to 24. The initial part of this fast activity in channel 21 showed a spectral peak at 70 Hz (see insets), followed by a more prolonged period of 80-Hz oscillations.

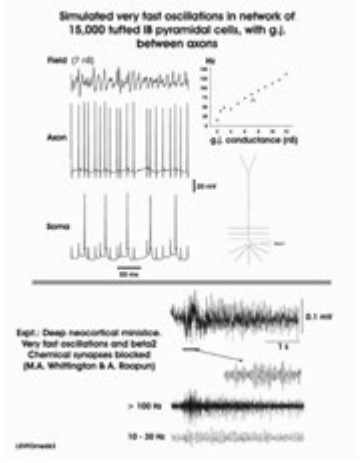
VFO preceding electrographic sz in slice

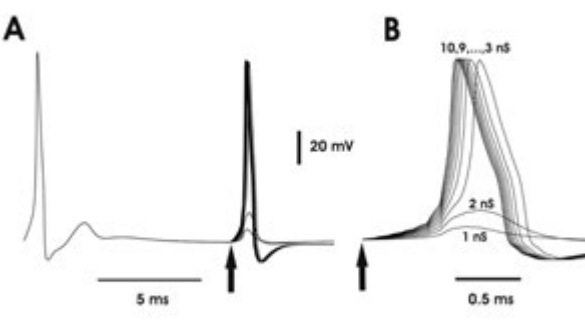


Traub *et al. Epilepsia.* 42: 153-170, 2001.

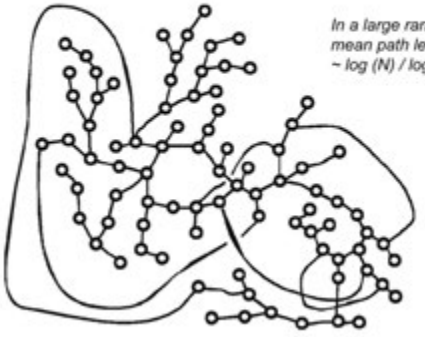
Notes: Hippocampal CA1 in vitro; TMA alkalinizes tissue & opens gap junctions.


A
LV field
B
Experiment
Model
Frequency (Hz)
Time (s)
>10-50Hz
>150Hz

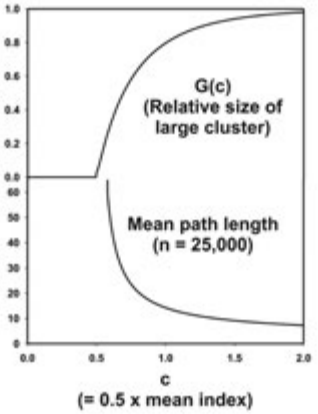

Simulated very fast oscillations in network of 15,000 tufted IB pyramidal cells, with g.j. between axons
Field
Axon
Soma
g.j. conductance (nS)
Expt.: Deep neocortical minislice. Very fast oscillations and beta2. Chemical synapses blocked (M.A. Whittington & A. Roopun)
> 100 Hz
10 - 30 Hz


A
B
20 mV
5 ms
10,9,...,3 nS
2 nS
1 nS
0.5 ms

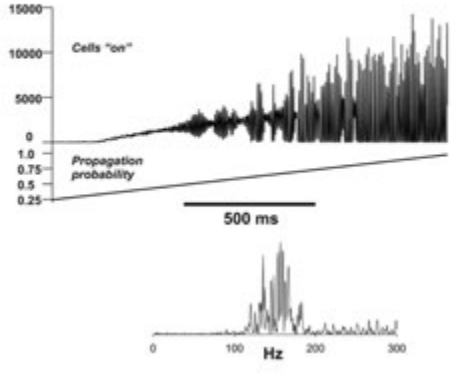
Example of the large cluster in a random graph: 150 nodes, average 1.6 branches leaving each node (Small cluster and isolated nodes not shown)

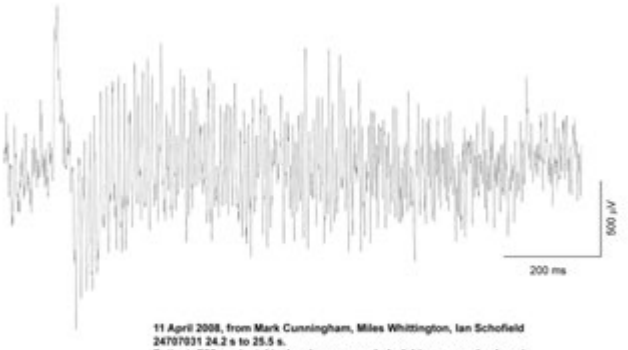


In a large random graph, mean path length ~ log (N) / log (< i >)



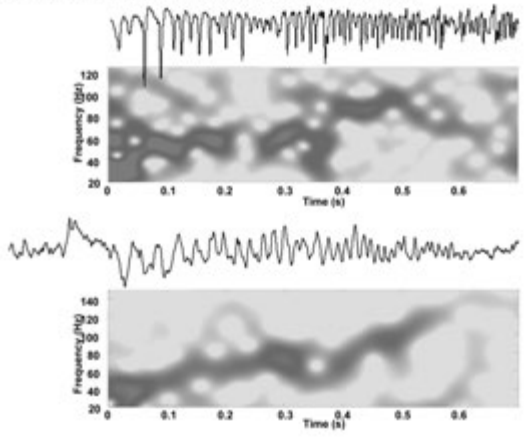
Cellular Automaton model: 120,000 "cells", dt = 0.25 ms

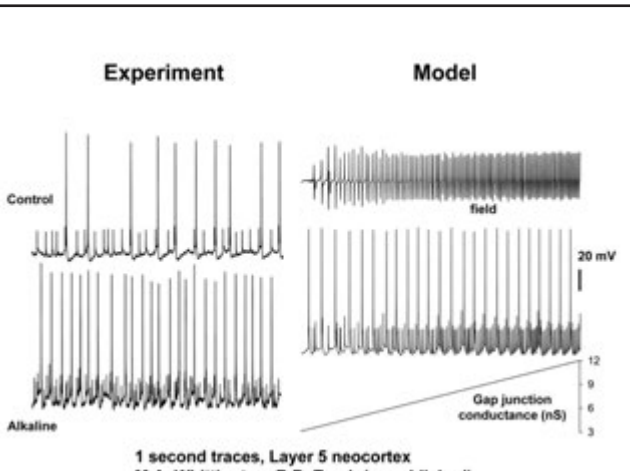




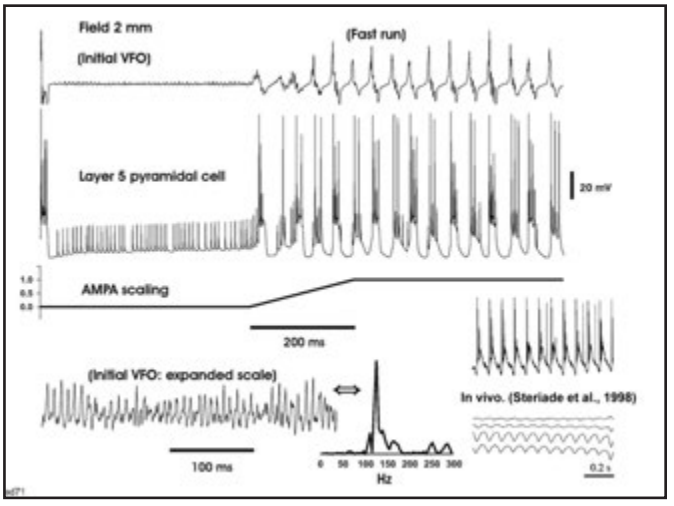
11 April 2008, from Mark Cunningham, Miles Whittington, Ian Schofield
24707031 24.2 s to 25.5 s.
Patient: F25, perinatal ischemia, porencephaly, L hippocampal sclerosis,
Partial complex seizures with olfactory/gustatory unpleasant aura.
L partial mesial temporal lobectomy, recording L inferior mesial temporal neocortex.
Compare LSVFOmed79 and subsequent.
Recording above in vitro, spontaneous, no drugs added.

Preictal glissando discharges in human IT cortex and model

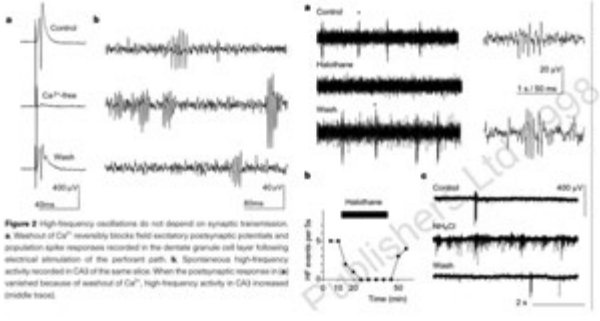




1 second traces, Layer 5 neocortex
M.A. Whittington, R.D. Traub (unpublished)

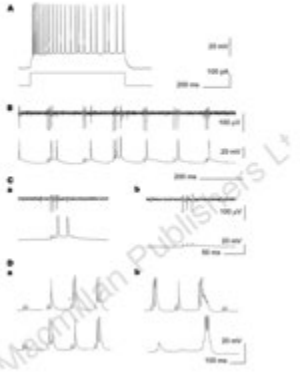


In vitro ripples are enhanced in calcium-free media, hence do not require synaptic transmission; they are suppressed by the gap junction blocker halothane. Draguhn et al. 1998, Nature



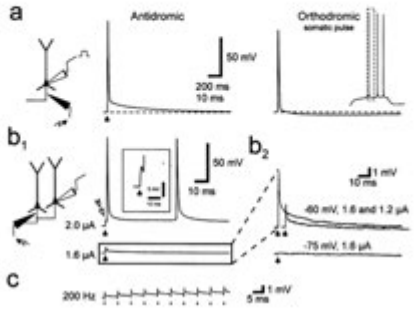
Publisher's Ltd 1998

During in vitro ripples, intracellular spikelets correspond to extracellular population spikes, hence presumably correspond to coupling potentials; Draguhn et al. 1998, Nature.

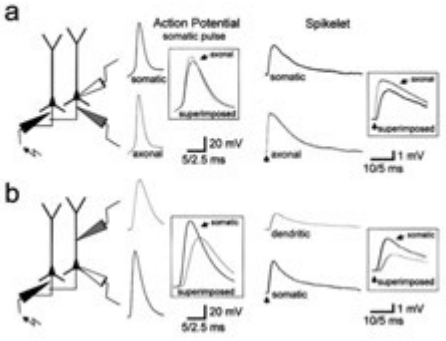


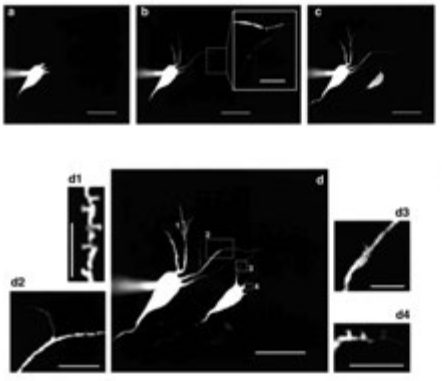
Mcmillan Publisher's L

Stimulation in s. oriens, away from the recorded cell, elicits spikelets. Spikelets follow >200 Hz stimuli 1:1, without failures. Zero calcium medium. Schmitz et al., 2001, Neuron.

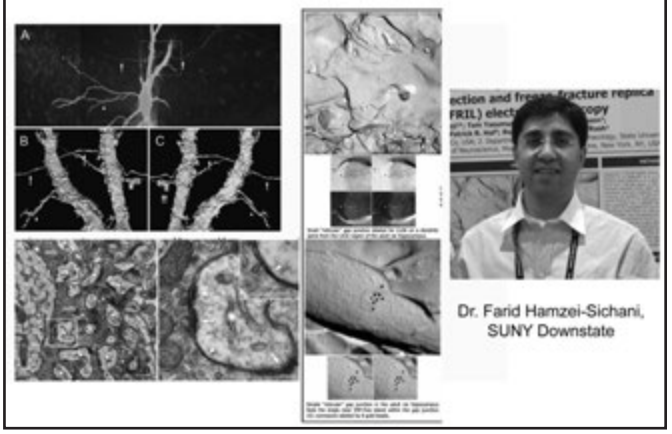


Spikelets appear 1st in the axon, next in the soma, finally in the apical dendrite. Schmitz et al. 2001, Neuron

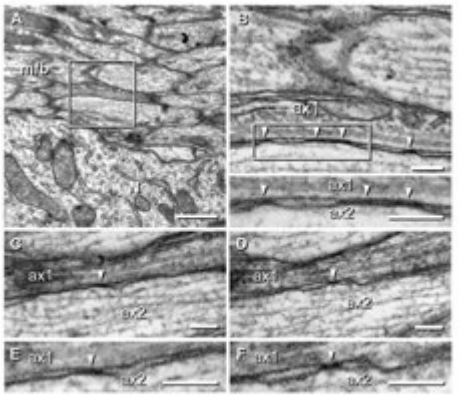




CA1 pyramidal cells are dye-coupled through their axons by light microscopic criteria. Schmitz et al. 2001, Neuron.

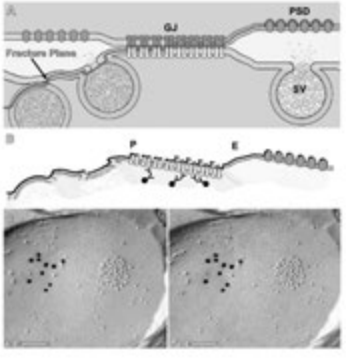


Dr. Farid Hamzei-Sichani, SUNY Downstate



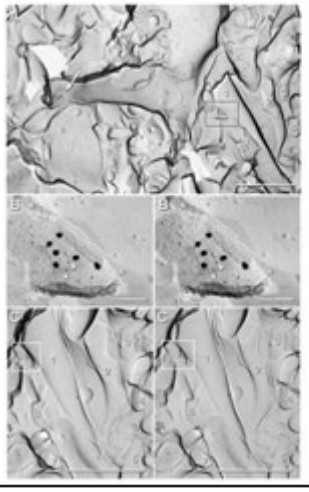
Transmission EM showing putative gap junctions between hippocampal mossy fiber axons: F. Hamzei-Sichani et al. (2007) PNAS

Principles of freeze-fracture replica immunogold labeling



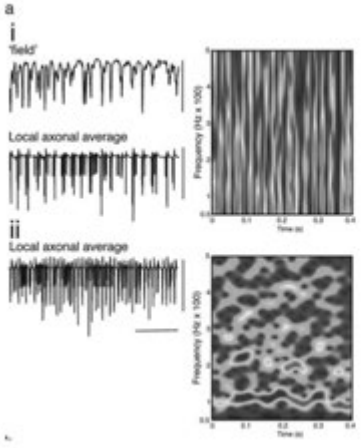
Scale bars 100 nm

James Nagy, F. Edward Dudek, John E. Rash, 2004, Brain Res. Reviews



Ultrastructural image of gap junction on a hippocampal mossy fiber axon, using freeze-fracture immunogold labeling for connexin36.

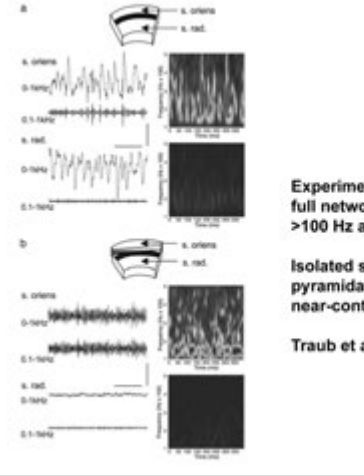
From the laboratory of John Rash, in F. Hamzei-Sichani et al. (2007) PNAS



Model: full network generates brief bursts of >100 Hz activity, every 30 ms (i.e. gamma period)

Isolated axonal plexus generates continuous 100 Hz.

Traub et al. 2003, PNAS.



Experiment (isolated CA1): full network generates bursts of >100 Hz activity at gamma frequency.

Isolated stratum oriens (containing pyramidal axonal plexus) generates near-continuous ~150 Hz activity.

Traub et al. 2003, PNAS

Thanks to:

- IBM, NIH/NINDS
- Andreas Draguhn, Hannah Monyer, Gabriel Wittum, *Alexander von Humboldt Stiftung*
- Miles A. Whittington, *Newcastle*
- Nancy Kopell, Mark Kramer, *Boston*
- Farid Hamzei-Sichani, *Downstate*
- Anita Roopun, *Newcastle*
- Steven J. Middleton, *Newcastle, RIKEN*
- Thomas Knöpfel, *RIKEN*
- John E. Rash, *Colorado State University*
- Rafael Gutiérrez, *Centro de Investigación y Estudios Avanzados del IPN, Mexico City*
- Andrea Bibbig, *Downstate*
- Mark Cunningham, *Newcastle*

Very Fast Oscillations (> 80 Hz): Spatial Aspects

Roger D. Traub
IBM T.J. Watson Research Center
Yorktown Heights, NY

&

Miles A. Whittington
Institute of Neuroscience
University of Newcastle School of Medicine

Some network oscillation mechanisms

- Correlated IPSPs (e.g. gamma)
- Pacemaker, with spread (the heart)
- Re-entry (Wolff-Parkinson-White)
- Coupled oscillators

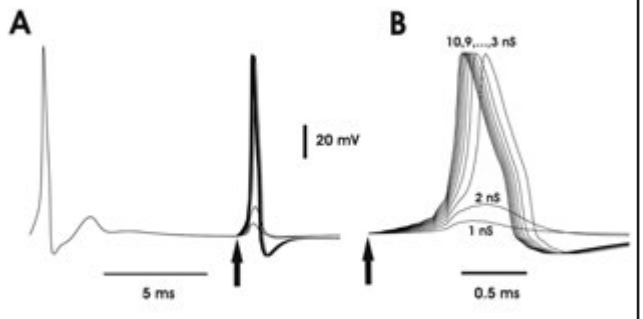
- Propagation through (locally) random network
- Propagation + intrinsic refractoriness

Interesting Physical Principle

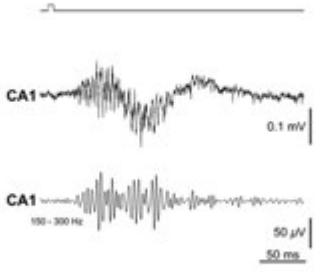
Gap junctions "synchronize", e.g. spike times.

BUT propagation time from cell to cell across a gap junction takes finite time, say, 0.25 ms.

In a sparse network, these brief propagation times summate in such a way as to determine oscillation period.



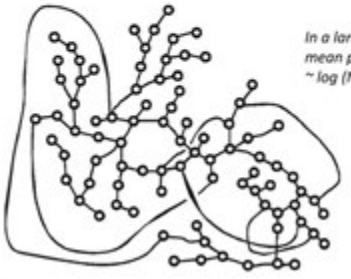
VFO with GABA-A receptors blocked



Nimmrich et al., J. Physiol. 2005

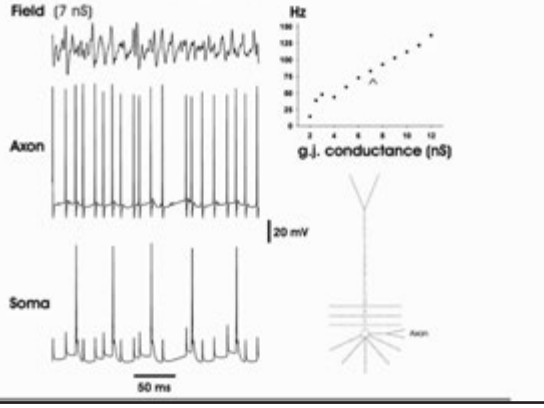
Why do network oscillations occur when gap junctions allow spikes to propagate from cell to cell? -

It can happen as a result of "percolation" in a large, sparsely connected network, with period INDEPENDENT of intrinsic and synaptic conductances (!!)



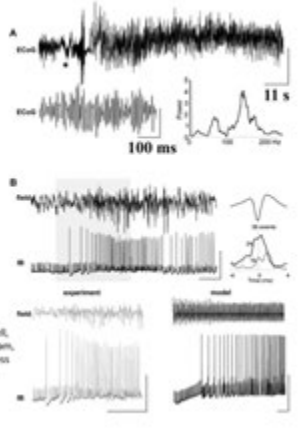
In a large random graph, mean path length ~ log (N) / log (< i >)

Simulated very fast oscillations in network of 15,000 tufted IB pyramidal cells, with g.j. between axons

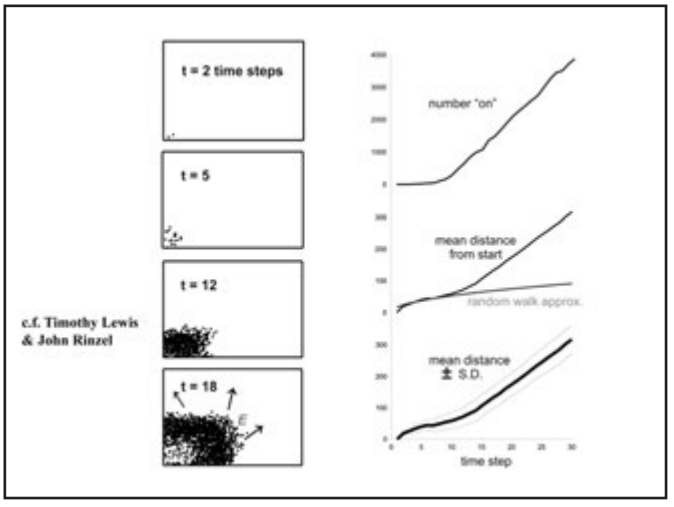


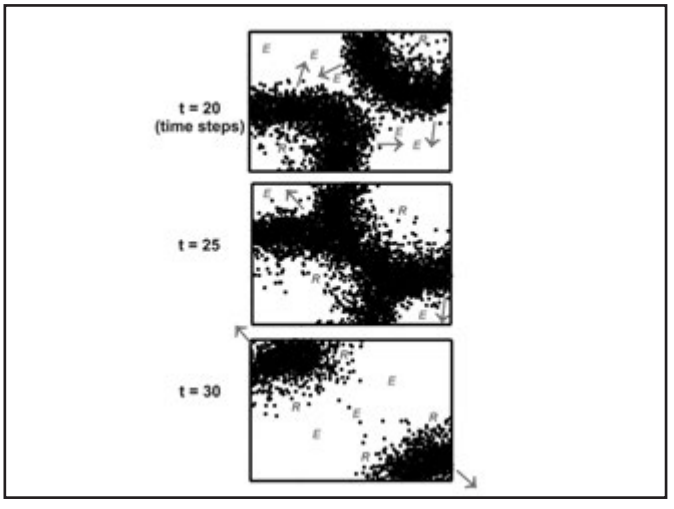
Human

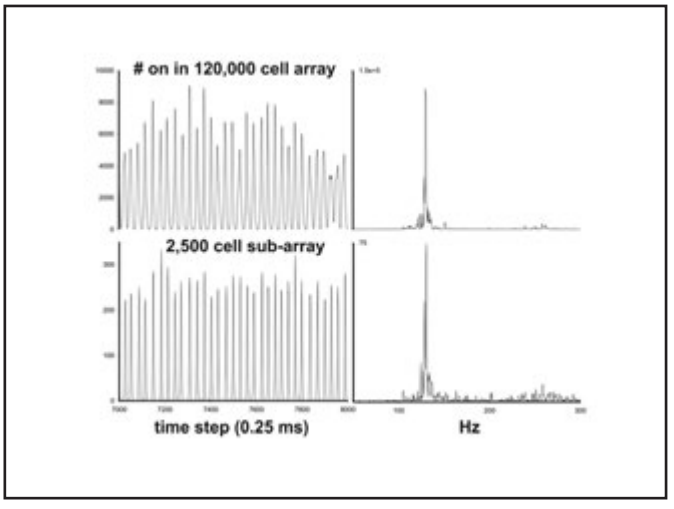
Rat & model

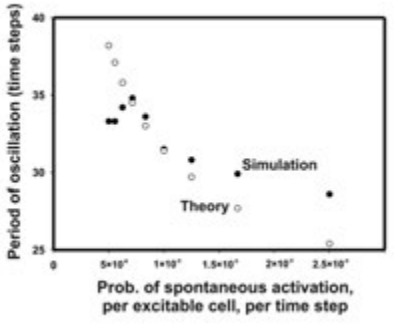


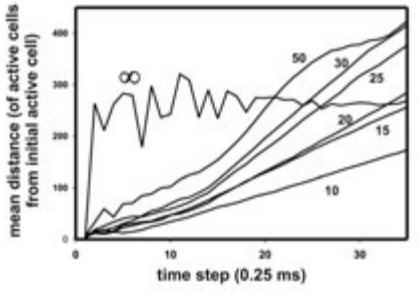
R.D. Traub, R. Duncan, A.J.C. Russell, T. Baldeweg, Y. Tu, M.O. Cunningham, M.A. Whittington: Epilepsia, in press

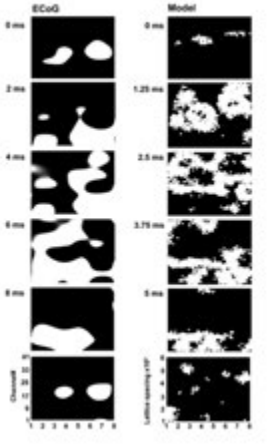

t = 2 time steps
t = 5
t = 12
t = 18
E
c.f. Timothy Lewis
& John Rinzel
number "on"
mean distance
from start
random walk approx.
mean distance
± S.D.
time step


t = 20
(time steps)
t = 25
t = 30
E
R


on in 120,000 cell array
2,500 cell sub-array
time step (0.25 ms)
Hz


Period of oscillation (time steps)
40
35
30
25
0
Simulation
Theory
Prob. of spontaneous activation,
per excitable cell, per time step


mean distance (of active cells
from initial active cell)
400
300
200
100
0
∞
50
30
25
20
15
10
0
10
20
30
time step (0.25 ms)

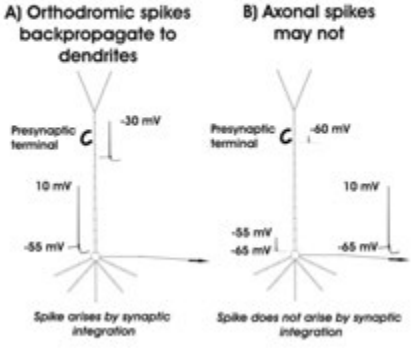

ECoG
Model
0 ms
2 ms
4 ms
6 ms
8 ms
0 ms
1.25 ms
2.5 ms
3.75 ms
5 ms

Some network oscillation mechanisms

- Correlated IPSPs (e.g. gamma)
- Pacemaker, with spread (the heart)
- Re-entry (Wolff-Parkinson-White)
- Coupled oscillators

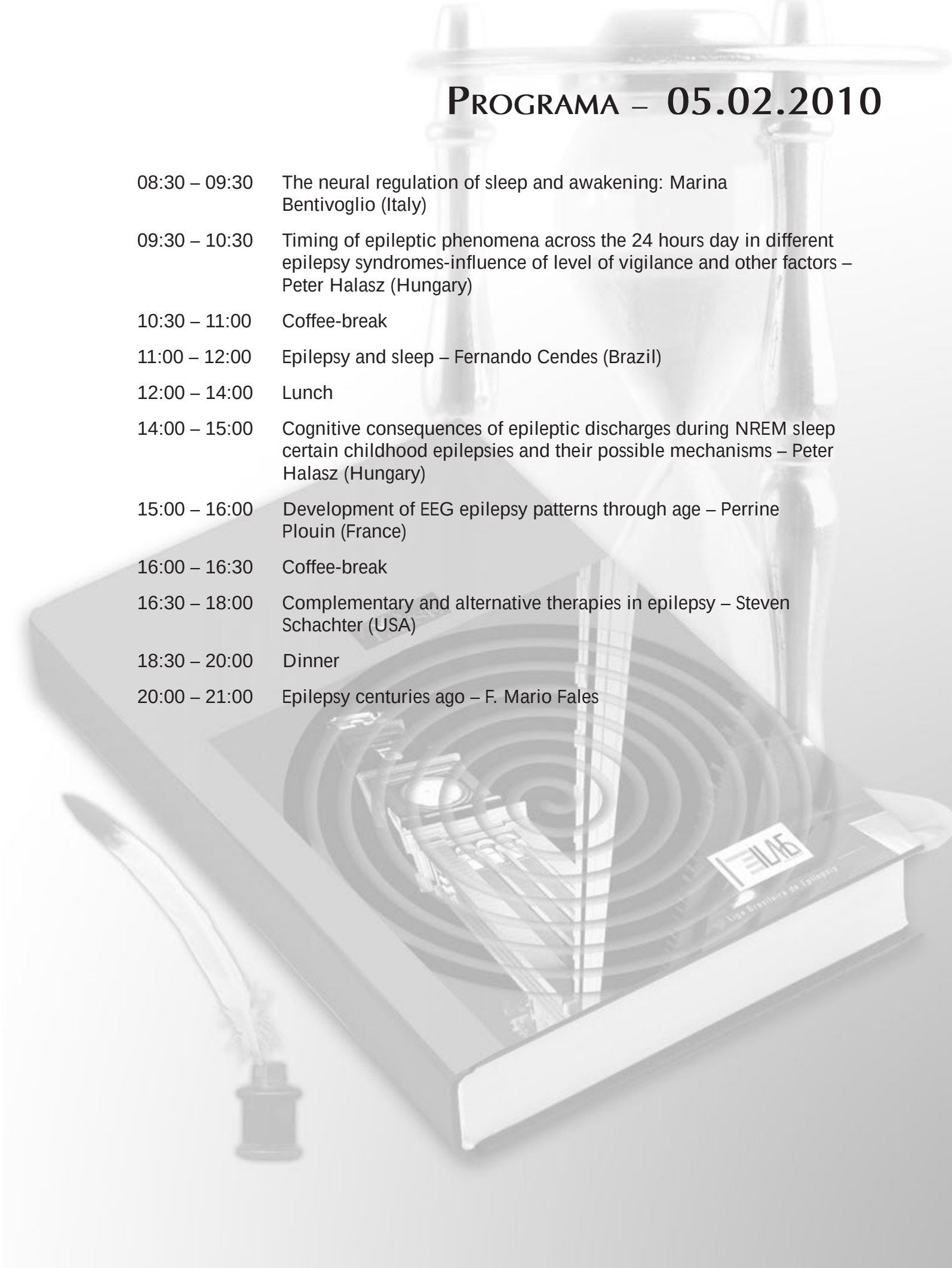
- Propagation through (locally) random network
- Propagation + intrinsic refractoriness

Functional significance of orthodromic vs. antidromic spike initiation



Programa – 05.02.2010

08:30 – 09:30	The neural regulation of sleep and awakening: Marina Bentivoglio (Italy)
09:30 – 10:30	Timing of epileptic phenomena across the 24 hours day in different epilepsy syndromes-influence of level of vigilance and other factors – Peter Halasz (Hungary)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Epilepsy and sleep – Fernando Cendes (Brazil)
12:00 – 14:00	Lunch
14:00 – 15:00	Cognitive consequences of epileptic discharges during NREM sleep certain childhood epilepsies and their possible mechanisms – Peter Halasz (Hungary)
15:00 – 16:00	Development of EEG epilepsy patterns through age – Perrine Plouin (France)
16:00 – 16:30	Coffee-break
16:30 – 18:00	Complementary and alternative therapies in epilepsy – Steven Schachter (USA)
18:30 – 20:00	Dinner
20:00 – 21:00	Epilepsy centuries ago – F. Mario Fales



Timing of epileptic phenomena across the 24 hours day in different epilepsy syndromes-influence of level of vigilance and other factors

Peter Halasz (Hungary)

Pázmány Péter Catholic University,
Faculty of Information Technology, Budapest

Timing of epileptic phenomena across the 24 hours day Influence of vigilance level, endogenous and evoked oscillations

P Halász

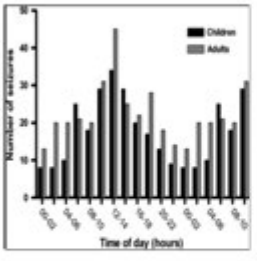
Lasse IV: Epilepsy and Time, Sao Paulo, Brazil

Factors of timing epileptic discharge and seizure propensity

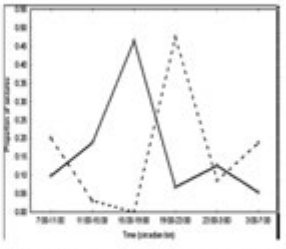
- Influence of Circadian rhytm (Quigg 2000, Pavlova 2004, Hostra 2009)
- Sleep/wake cycle
- Within sleep:
  - Two types of sleep: REM/NREM
  - Sleep stages
  - Oscillations (delta and sigma/ spindling/)
  - Phasic events (gating by CAP)
  - Infraslow delta oscillation up-and down-states

Influence of Circadian rhytm

(Quigg et al 2000, Pavlova et al 2004, Hostra et al 2009)



Bar histogram showing temporal distribution of complex partial seizures in children and adults (numbers of seizures are $n = 215$ and $n = 265$ respectively). Each bar represents numbers of seizures per 2 h. Data of 36 h is given in order to show the 24 h cosinor rhythmicity. Data adapted from: Hostra and Weerd 200



Proportion of seizures during each 4-hour interval (bin) in patients with TLE and XTLE. The circadian bins are presented on the *x* axis, and the proportion of seizures, on the *y* axis. The time trend is presented as a solid line for TLE and a punctuate line for XTLE. As seen, there is a peak in the proportion of seizures between 15:00 and 19:00 in the TLE patients and between 19:00 and 23:00 in the XTLE patients. (Pavlova et al 2004)

Influence of sleep/wake cycle

Seizures:

- Sleep epilepsies : FLE , MTLE –GTC
- Awakening epilepsies : IGE (diff. Forms), West sy/ IS
- Awake epilepsies: MTLE partial seizures

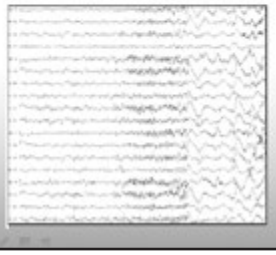
Strongly NREM sleep related epileptic EEG patterns

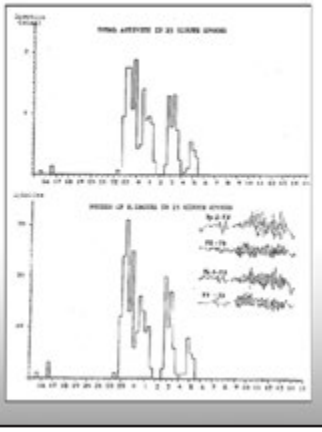
- Electrical Status Epilepticus in Sleep (ESES) - exclusively during sleep
- Generalized Paroxysmal Fast Activity (GPFA) with polygraphic subtle ictal signs – almost allways during sleep
- Generalized spike-wave bursts in the awakening GTC form – almost exclusively during sleep in the awakening period
- Focal sharps/spikes in Frontal Lobe Epilepsies – frequently only during sleep
- Bilateral independent spiking in temporal lobe epilepsy – compared with wakefulness more frequently during sleep
- Centro-temporal uni-or bilateral spiking in Rolandic epilepsy – compared to wakefulness more freqently in sleep

Distribution of GPFA during a 24 h. sleep-wake cycle

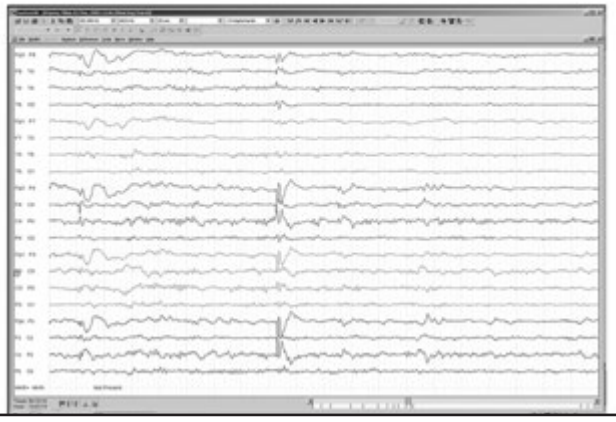
Up: Duration of GPFA events (min)

Bellow: number of GPFA events

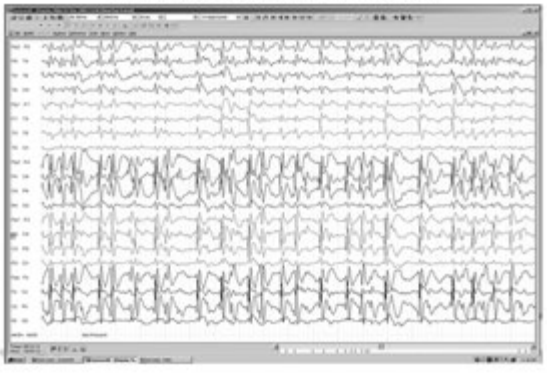




„Benign" focal childhood epilepsy with variation in localisation



The same patient in NREM sleep



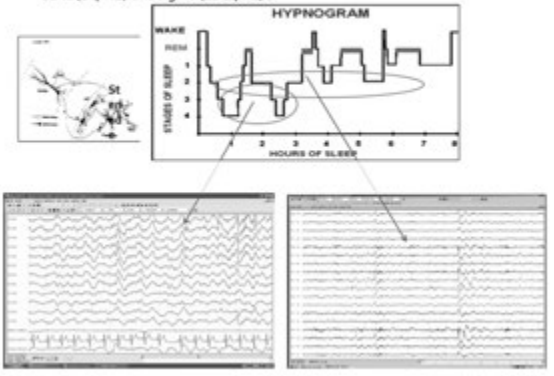
Factors of activation within sleep:

Two types of sleep: REM/NREM

New viewpoints:

- **Correlations with different sleep EEG synchronisation mechanisms (like oscillations in delta and sigma /sleep spindle/ range) and underlying physiological brain systems, and not only with classical R-K sleep stages – continuous influence**
- **Correlations with the arousal dynamic - phasic influence**

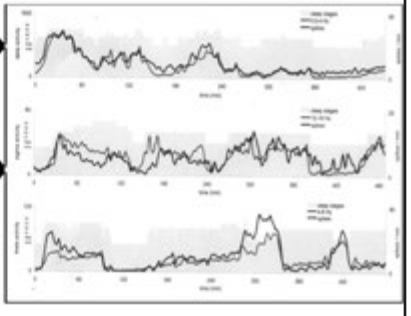
NREM sleep EEG is composed mainly by two kind of oscillation :thalamo-cortical delta (1-4 HZ) and sigma (12-14 Hz) s



Activation of epileptiform discharges connected with sleep oscillations

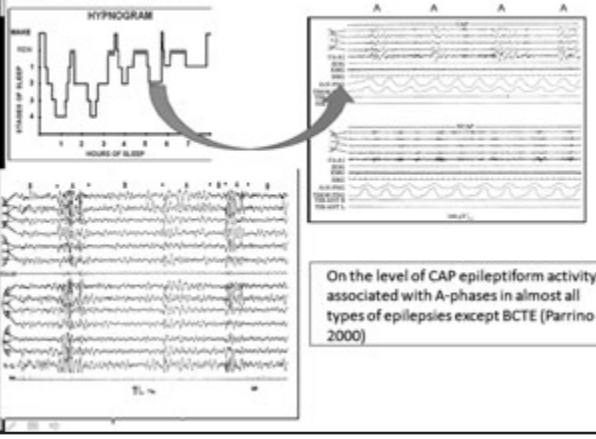
Correlation with delta oscillation:
MTLE (Mallow et al 1998)
Several adult epilepsies :
errillo et al 2000)F

Correlation with spindles
BCTE : (Nobili et al 1999, Kelleway 2000, Beelke et al 2000)
Several childhood epilepsies (Ferillo et al 2000)



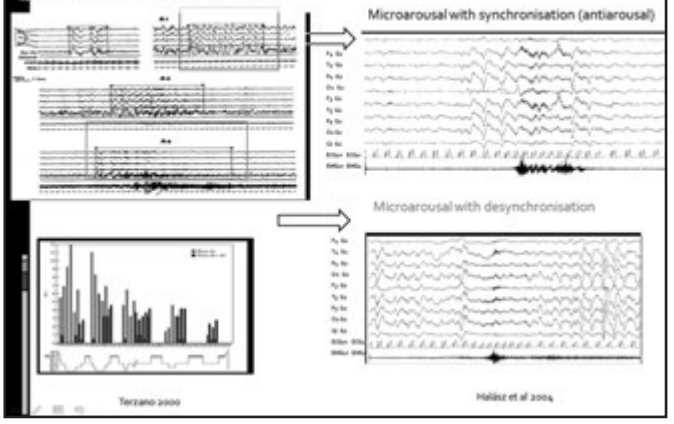
Ferrillo et al 2000

Cyclic Alternating Pattern (CAP) is one of the most global oscillation pattern in NREM sleep (Terzano and Parrino 1985)



On the level of CAP epileptiform activity is associated with A-phases in almost all types of epilepsies except BCTE (Parrino 2000)

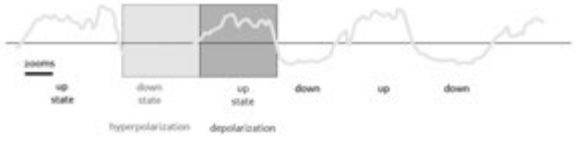
Subtypes of CAP phase A:
A1: composed entirely by K-complexes and deltas
A2: with moderate
A3: with definitive EEG desyncronisation



NREM slow oscillation

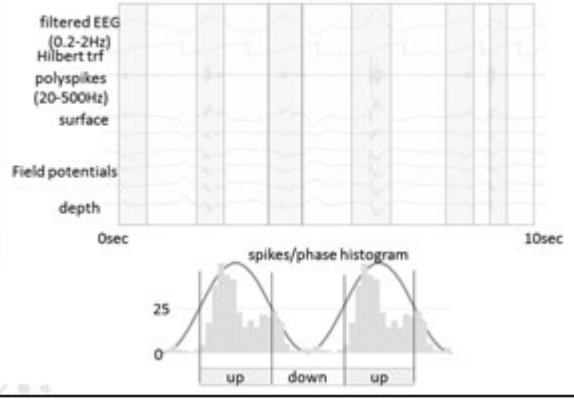
Alternation of hyper- and de-polarized phases

- **depolarized phase:** high synaptic and neuronal activity
- **hyperpolarized phase:** interrupted synaptic and neuronal activity



Relationship of slow oscillation and spiking in NREM sleep

Frontal lobe epilepsy, intracortical recording with multicontact microelectrode
Ulbert et al 2006



Sleep activation of epileptiform activity

Macro

Hypnogram level – NREM sleep
CAP level – phase A – phase A1 (antiarousal)
Sleep EEG oscillation level – delta and (less) sigma oscillation
Infraslow (beyond 0.5 Hz) oscillation – up - and down - states

Micro

Antiarousals by cortical slow and infraslow oscillation provide a cyclic regulation of cortical excitability creating gates for epileptiform activity

Circadian influence on seizure and EEG discharge propensity in different kind of epilepsies

- Idiopathic generalized **epilepsies show peak of seizure and EEG discharges propensity in awakening periods (during sleep/awakening macro-and micro-shifts)**
- Localisation related **epilepsies show peak of seizure and EEG discharge propensity during slow wave sleep**

Distribution of EEG discharges in different kind of epilepsies according to type of sleep

- Slow wave sleep **promotes** generalization,
- REM sleep **promotes** localisation **of EEG discharges**
- EEG discharges **of** generalized **epilepsies are expressed in** slow wave sleep, **EEG discharges of**
- Localisation related epilepsies **are expressed** mostly in slow wave **and** rarely in REM sleep

Timing of epiletiform discharges and seizures in different major epilepsies

Idiopathic generalized epilepsies (IGE)

Vigilance level dependency of absence type 3 Hz SWD (wakefulness)

Spontaneous paroxysms are promoted by transitory decreases of vigilance level (Lennox 1969, Passouant 1972, Stevens 1971)

- after awakening
- after lunch
- in evening sleepiness
- during boring tasks or situations
- experimental depression of RAS functions (Gloor and Testa 1974)
- after sleep deprivation

Spontaneous paroxysms are inhibited by sudden increase of vigilance (Li 1952, Jung 1957, Rajna et al 1989)

- arousals (calling by name)
- experimental stimulation of RAS (Guerrero-Figueroa et al 1963, Pollen 1963)

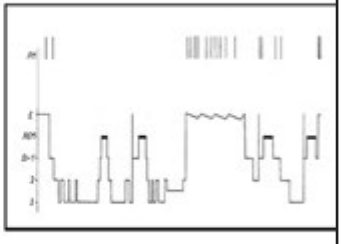
Vigilance level dependency of absence type 3 Hz SWD (sleep)

- Spontaneous paroxysms are promoted by transitional fields of sleep-wakefulness

in humans:
(Niedermeyer 1967-72-96, Passouant 1975, Halász et al 1974-81-91, Horita et al 1991)

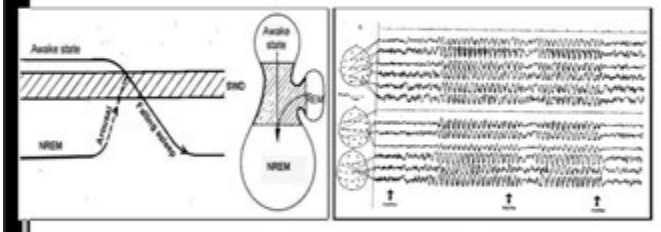
in animal studies:
(Shouse 1987, Lannes et al 1988, Coenen et al 1991, Drinkenburg et al 1991)

- ✧ in falling asleep
- ✧ around momentary awakenings in sleep
- ✧ In shift periods between NREM and REM .
- ✧ before and after awakening.



- Spontaneous paroxysms are inhibited by deep NREM and full REM sleep

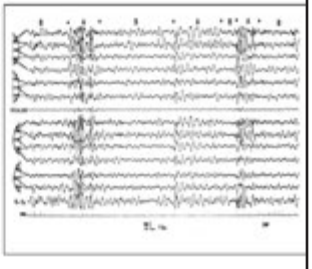
Critical vigilance level promoting occurence of SWD



Association of generalized spike-wave pattern in IGE with sleep instability in NREM measured by the CAP phenomenon

Sleep EEG analysis of 10 IGE patients (Terzano et al 1989):

- Significant prevalence of SWD during CAP as compared to NCAP
- 93 % of all the SWD pattern occured in CAP were found in phase A

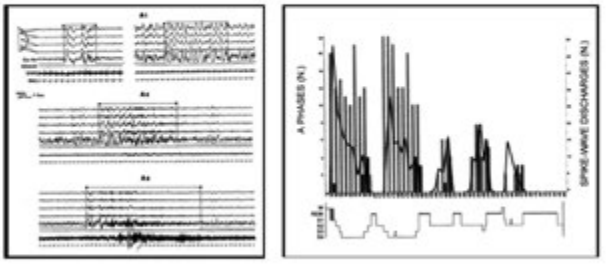


Sleep EEG analysis of 10 JME patients (Gigli et al 1992):

- spiking rate was significantly higher in CAP A phase compared to NCAP and showed strong inhibition in CAP B phases

Correlation of SWD with the A1- phase of CAP

(Terzano et al 2000, Parrino et al 2000)



Two extreme examples for sleep activation

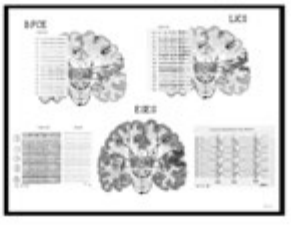
1) Sleep activation of epileptiform discharges = BCT-LKS-ESES spektrum and IGE

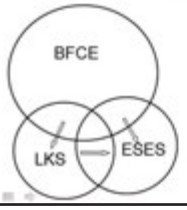
2) Sleep activation of seizures = FLE

What is the difference?

Involvement of the cortico-thalamic system?
Underlined by the activation of two sytems with contrasting functional role

Activation of epileptiform discharges and their impact in perisylvian epilepsy spectrum





- **SWD (amount, generalisation)**
- **sleep activation**
- **cognitive impairment**

BFCE
LKS/PLGS
ESES

Focal

Diffuse, bilateral

NFLE - seizures from the mediobasal part of FL - not related with the thalamocortical system

➢Short dystonic-dyskinetic seizures with agitation arousal and autonomic symptoms, involving both sides of the body, clustering in NREM (max st2), almost daily The interictal and ictal EEG is very poor

➢**Several forms were reported, including with autosom dominant inheritance (ADNFLE) having mutation in the neuronal nicotinic acethylcholine receptor alpha4 subunit.**

Overlapping FLE syndromes

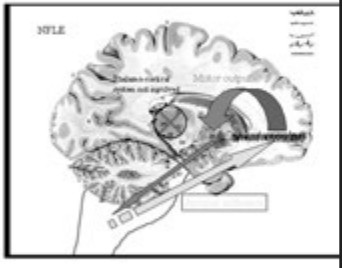
Author/syndrome	Age at onset	Seizure type	EEG ictal	EEG interictal	MRI	Genetics	Sleep relations	Pharmacological response
Lugaresi, Cirignotta (1981), Lugaresi et al (1986) - Hypnogenic/nocturnal paroxysmal dystonia	Young adulthood	Dystonic - choreic	Movement artifacts	No abnormality	No abnormality	Reported families	Rare awake events	Good CBZ response
Pared, Lavie (1986) - nocturnal epilepsy with paroxysmal awakenings	?	Violent nonconvulsive body movements	Arousals	Epileptiform discharges	?	No hint	In deep per definitionem	3/14 received antiepileptics with good results
Vigevano, Pocos (1993) - Hypnic tonic postural seizures in children	Childhood	Tonic postural	Rhythmic thets	Variable in 50% epileptiform discharges	No abnormality	In 10/8 positive family history	Rare awake REM events	Good CBZ response
Scheffer et al (1995), Oldani et al (1996) - ADNFLE	From childhood to adulthood	Wide spectrum from dystonic choreic to tonic posturing	Epileptic pattern in only 33.3% or less	Epileptiform discharges in 16-41%	No abnormality	Autosom dominant heredity with 69% penetrancy	Rare awake events	Good CBZ response

NFLE - seizures from the mediobasal part of FL - not related with the thalamocortical system

- **Association with synchronization type (CAP A1) arousals are obvious (Terzano et al 1997)**

NFLE - relations of brain systems and sleep

- There are no signs of thalamocortical system involvement (no SWD emanation), and no signs of cognitive impairment
- There is a direct association of the clinical (motor) epileptic events with synchronisation type NREM sleep arousal events
- The role of the mutation in an Ach receptor, probably connected with arousal functions, is still not known
- Basal ganglia involvement indicated by the motor seizure symptoms
- Symptoms reflect fear, panic, agitation, with important autonomic activation



IGE and FLE represent two different system (network) involvement with contrasting functions

- IGE involves the thalamo-cortical circuit representing trophotrop –endophylactic (Hess 1949) function

  Absences: transitory epileptic activation of thalamo-cortical NREM sleep mechanism

- FLE involves (probably) the cortical-basal ganglia ergotropic-dynamogenic function (representing ancient emergency mechanisms originally liberated when attacked from sleep?)

  Frontal hypermotor seizures: motor and autonomic representation of emergency state

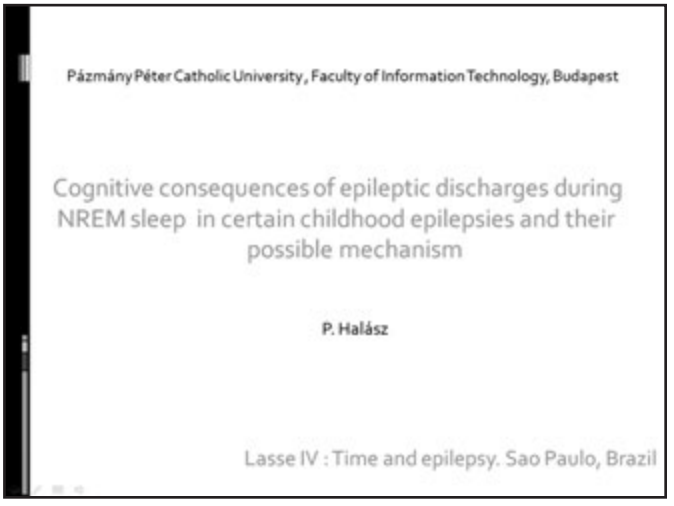
Another kind of sleep activation: activation of discharges without the seizures=MTLE

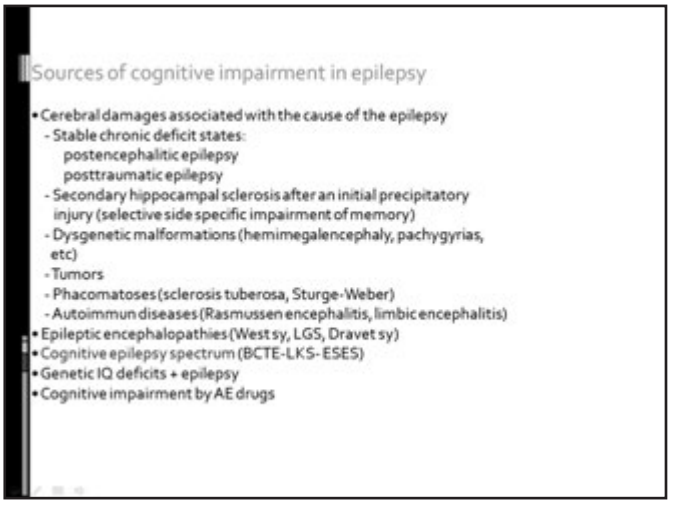
Epilepsies with involvement of the temporo-medial structures - sleep relations

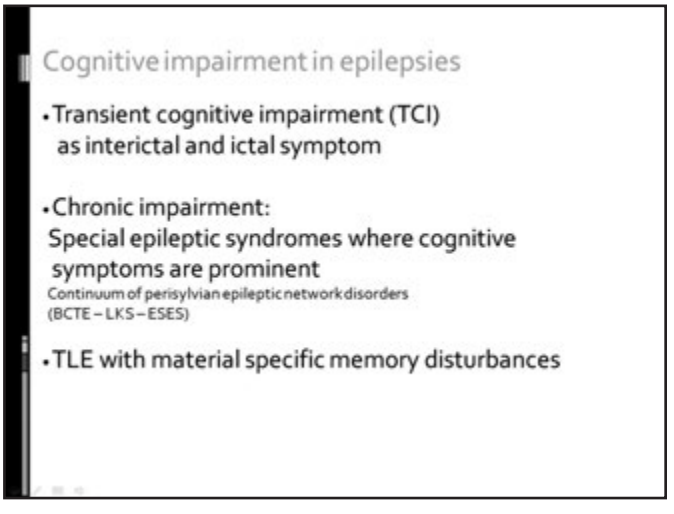
- **Partial seizures occur in wake ate**
- **Important activation of IEDs in ep slow wave -connected with lta oscillation**
- **A part of patients show localised D activation in REM sleep (Why d who unknown).**

Cognitive consequences of epileptic discharges during NREM sleep certain childhood epilepsies and their possible mechanisms

Peter Halasz (Hungary)







Transitory cognitive impairment during and after seizures

Partial functional impairments
- memory impairment in TLE complex partial (cp) seizures
- pure amnestic seizures
- speech disturbances in and after cp seizures

Impairment of consciousness
- in generalised tonic-clonic seizures
- in absences
- in cp seizures

The five big neuro-cognitive network:

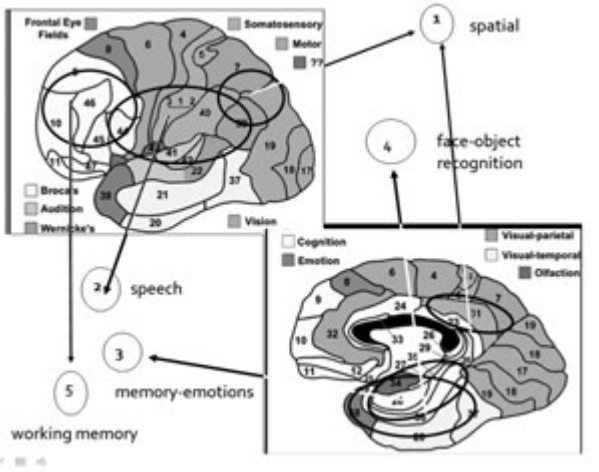
1) Right hemisphere dominant spatial consciousness with the involvement of the right posterior parietal cortex and cingulum

2) Left hemisphere dominant speech network with the involvement of the perisylvian speech areas

3) Network of memory and emotional functions with the involvement of the hippocampus and amygdala

4) Face and object recognition network with the medial temporal and temporopolar cortex

5) Working memory – executive functions network with the involvement of the prefrontal and probaly with the posterior parietal cortex



Sources of cognitive disturbances in childhood

➢Early beginning epileptic encephalopathies

„Deterioration of cognitive and/or sensory functions due to frequent seizures and/or interictal paroxysmal activity" (Dulac, 2001)

The pruning process became reprogramed by frequent discharges and seizures („firing together-wiring together")

Ohtahara syndrome, early myoclonic encephalopathy,
West syndrome,
Dravet syndrome,
Lennox-Gastaut syndrome (Ohtahara – West – LGS continuum),
Rolandic epilepsy-Landau-Kleffner- ESES syndrome continuum,
migrating parcialepilepsy (Copolla),
metabolic disturbances- epileptogenic chromosoma disorders,
Extended cortical dysplasias,
Hemimegalencephalia,
sclerosis tuberosa,
Rassmussen syndrome

➢ Negative cognitive effect of interictal and ictal epileptic activity

- A neuronal plasticity serves as model in the development of epilepsy
- Epileptic disorders develop especially in structures and networks playing role in cognitive functions (hippocampus, thalamo-cortical system) and interfere with them

The ability to learn (plasticity) includes the possiblity of the epileptic type functional changes

➢An other mechanism through which cognitive impairment might be related to certain childhood epilepsies is

impairment of cognitive sleep function by epileptic discharges

To understand this relationship we should discuss what is supposed to be the cognitiv sleep functions

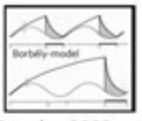
Data support that NREM sleep serves to recuperate cortical (frontal dominant) cognitive functions

- Slow wave (delta) sleep has left frontal dominance *(Werth et al 1990, Achermann et al 2001*), which increase after sleep deprivation *(Cajochen et al 1999)* and is under use dependent *(Kattler et al 1994)* homeostatic regulation (*Borbély et al 1990*)

  Deprivation of it impairs, supplementation improves cognitive functions

The homestatic behaviour of sleep delta activity points to a use dependent frontal recuperative process during NREM sleep

- Diseases which decrease cognitive level show simultaneously decrease in frontal delta power and the rebound capacity of frontal delta after sleep deprivation.



(Alzheimer disease, alcoholism ((*Colrain and Crowley 2002*, obstructive sleep apnea *(Ilioudi et al 2004, Grunstein et al 2004)* , depression, and frontal atrophic processes, and insomnia having deprivatory influence on sleep also associated with decrease in cognitive abilities (*Haimov et al 2004, Rayman és mtsai 2004)*

- With the development of cognitive abilities in childhood the delta activity of sleep increase, while with cognitive decline it decreases in senium
- NREM Sleep improves memory consolidation and the parameters of sleep delta and sigma (spindling) activity show relationship with consolidation of explicite memory (*Schabus et al, 2004, Clemens et al 2005, 2006, Bodizs et al 2008)*

NREM delta sleep serves to recuperate frontal cognitive functions - if this process is interrupted by epileptic discharges able to interfere with them, cognitive impairment is a possible consequence

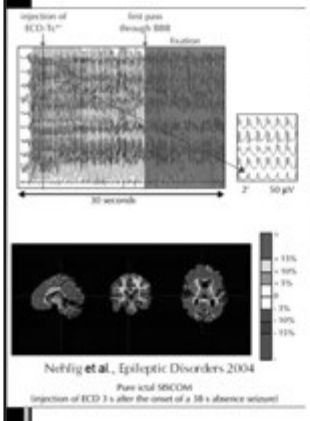
Sleep activation explores the „dark side" of of epilepsy – the cognitive impairment

„Penelope syndrome": instead of elaboration of them sleep ruins down cognitive functions (what was weaved during the day has been dissolved during the night)

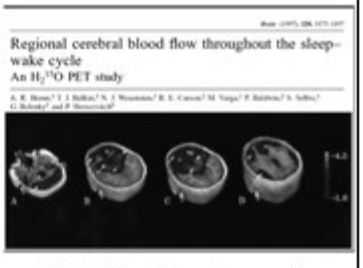
May play role in:
Rolandic epilepsy – LKS – ESES and LGS sy
West sy

Mechanism of cognitive impairment:

a) spike-wave activity „wave" components represent disfacilitation (neuronal desactivation) with bold negativ fMR signs, interrupting cognitive functions over wide cortical fields
b) Spike-wave activity interferes with spindling associated memory functions (spike-waves represents pathologically distorted spindling)



Nehlig et al., Epileptic Disorders 2004

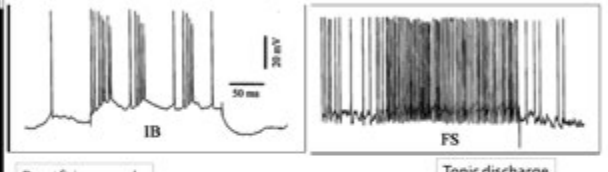


Regional cerebral blood flow throughout the sleep–wake cycle
An $H_2{}^{15}O$ PET study

NREM alvásban és absence-ban egyaránt csökkent vérátáramlás (TCD, SPECT, fMR, PET)

Thalamo-cortikális diszkonnekció = kortikális (frontális) hipofunkció

Two different working modes of the thalamo-cortical system



Burstfiring - mode

Tonic discharge

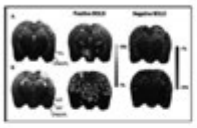
NREM sleep
Absence

Decreased Blood flow and disactivation (disfacilitation) of the cortex
(TCD, SPECT, fMR)

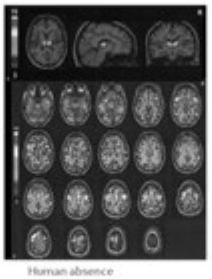
Wakefulness

Seizure free state

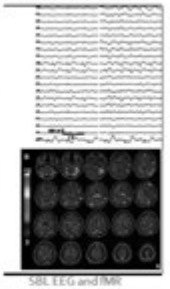
Wave component of spike-wave pattern represents cortical disfacilitaion proved by electrophysiological (Steriade, 2003) and fMR (Aghakhani et al 2004, 2005) studies



Rat GHB absence model
Tre nney et al 2003



Human absence
Aghakhani et al 2004



SBL EEG and fMR
Aghakhani et al 2005

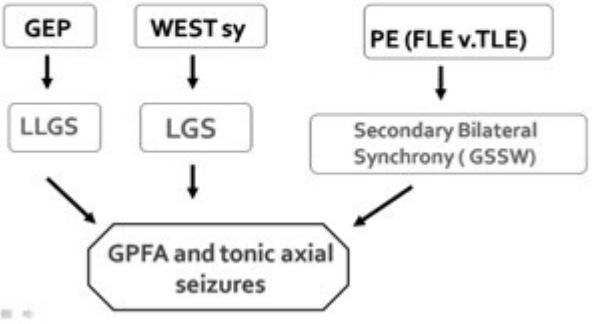
The rythmic recurrent disfacilitation interfers with cognitive functions, requiring cortical fast oscillations. Due to recurrent disfacilitation continuous depolarisation of the pyranidal cell's membranes is not possible which works against the overt seizures and in the same time interfers with cognition in childhood epileptic encephalopathies.

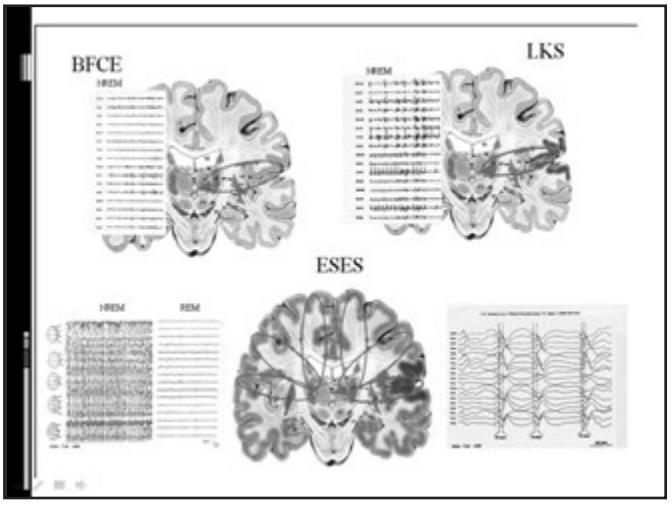
Model: ESES=Penelope syndrome (Tassinari 2009)

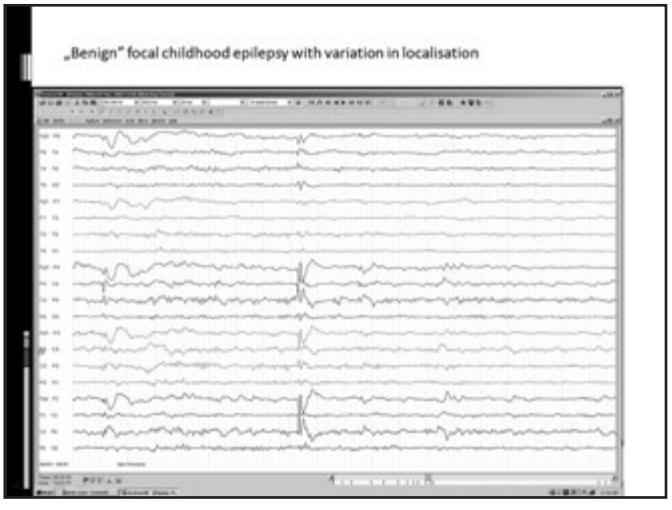
"Lennoxisation"

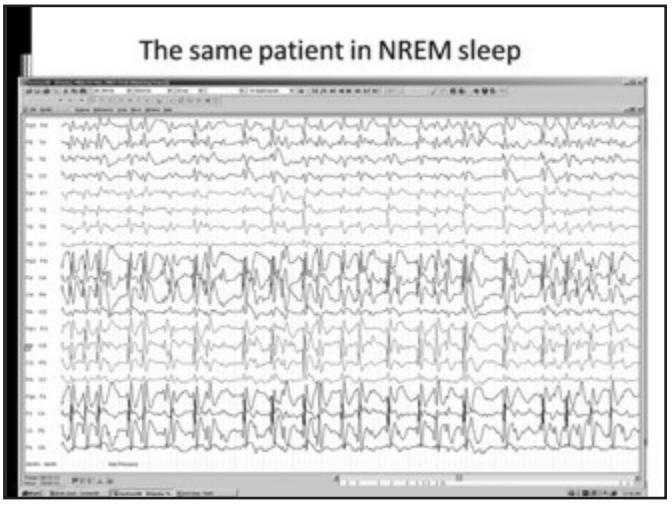
- GPFA (Generalized Paroxysmal Fast Activity) is a „common final pathway" in evolution of different epilepsies
- Three routes of development:
  - West sy. → Lennox-Gastaut sy. (Ohtahara 1988)
  - Generalized epilepsies → Late Lennox Gastaut sy. (Lipinski 1977,Bauer et al. 1983, Stenzel and Panteli 1983,Roger et al. 1987)
  - Partial Epilepsies (mainly FLE) → Secondary Bilateral Synchrony (SBL)
- Lennoxisation is characterized by GPFA + mental deterioration + tonic axial seizures + therapy resistancy (Magnudda et al., 1989, Agnglia et al. 1990, Halász 1991)

Common final pathway of malignisation




BFCE
LKS
ESES
NREM
REM

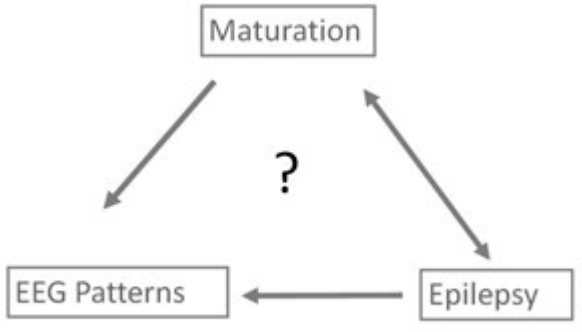

„Benign" focal childhood epilepsy with variation in localisation


The same patient in NREM sleep

Development of EEG epilepsy patterns through age
Perrine Plouin (France)

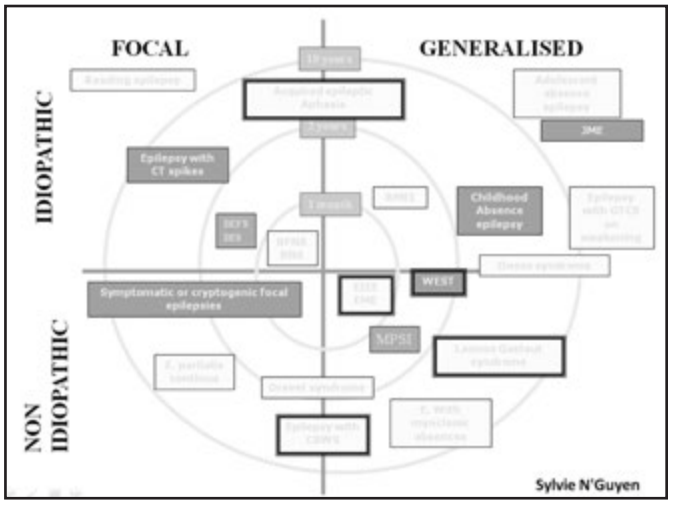
Development of EEG epilepsy patterns through age

Perrine Plouin
Hôpital Necker Enfants Malades,Paris, France



Classification
better think and better treat

Semiology
EEG Seizure
EEG Syndrome
No: idiopathic
Yes: symptomatic
Etiology EEG
No but : cryptogenic
Prognosis
Treatment



Evolution of EEG patterns

- Epileptic encephalopathies
- Benign focal epilepsies
- Symptomatic focal epilepsies

Evolution of EEG patterns

- Epileptic encephalopathies
  - EIEE, EME
  - West syndrome
  - Lennox Gastaut Syndrome
- Benign focal epilepsies
- Symptomatic focal epilepsies

Benign focal epilepsies

– BFNS and BINS in neonates

– BIS and BFS in infancy

– BECTS and BEOS in childhood

.

Benign Familial Neonatal Seizures

- Rett & Teubel (1964) reported the first BFNS family, with 8 cases over 3 generations.
- On the third day of life the male proband developed an initial tonic phase with cyanosis followed by clonic movements of the whole body including the face and eye muscles, and he had 15-20 seizure events on the following day.
- A brother born 16 months later had a similar experience.
- Several normal interictal EEGs were reported for these two boys and single EEGs for three other affected relatives.
- The authors noted the familial history, the normality of the interictal EEG and the favorable outcome.

Benign Familial Neonatal Seizures

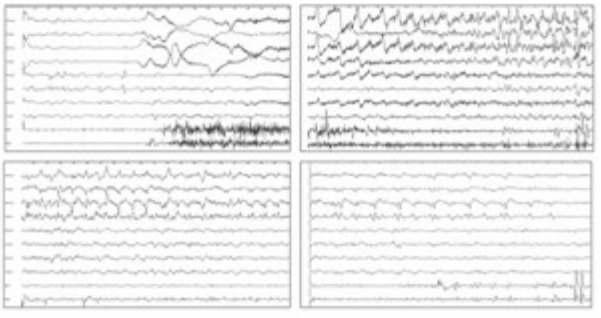
- Incidence estimated as 14.4 /100.000 live births (Ronen et al, 1993)
- 44 reported families, 355 cases
- Onset on D2 and D3 (80% of cases)
- Normal neurological examination
- Normal interictal EEG
- Normal biological work up
- Positive familial history
- Treatment selection?

Benign Familial Neonatal Seizures

- All seizures start with a tonic component, uni or bilateral, but assymetrical, changing side from one seizure to the next in a given baby
- Autonomic, oculofacial features and/or clonic movements follow
- Duration is around one minute
- Ronen et al, 1993, Hirsch et al, 1993, Bye 1994, Plouin and Anderson, 2002

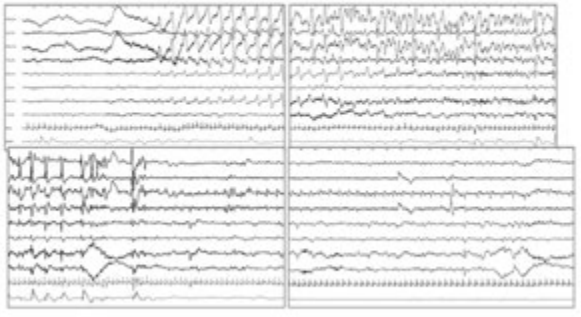
No myoclonic sz, no epileptic spasm, no GTCSz

BFNC Seizure



ELG…D8 SVP

Benign Familial Neonatal Seizures



DEL…Maxime 4 days NEM

Benign Familial Neonatal Seizures

Interictal EEG is described as normal, subnormal, with mild abnormal patterns, rarely as "théta pointu alternant", but never with patterns associated with a severe outcome.

No generalized SW bursts, no Suppression Burst pattern

Benign familial neonatal-infantile seizures

Sodium-channel defects in benign familial neonatal-infantile seizures
Heron et al Lancet, 2002

Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy
Berkovic et al, Ann Neurol 2004

13 individuals in 2 families
Mean seizure onset: 1.9 months
Mean offset: 3.8 months
Normal interictal EEG: 6/9 cases
One seizure recorded: focal onset

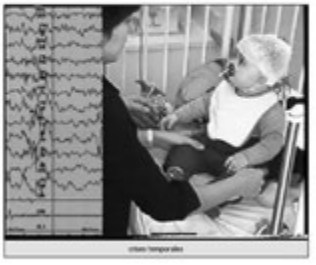
Benign focal epilepsies

- BFNS and BINS in neonates
- **BIS and BFS in infancy**
- BECTS and BEOS in childhood

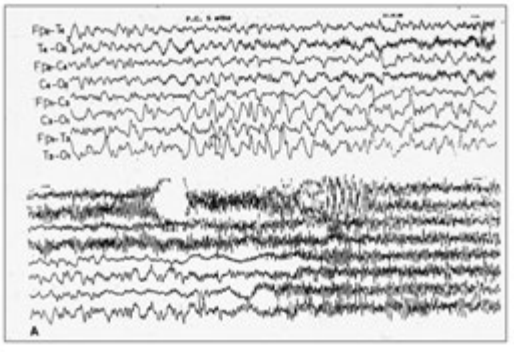
.

Benign familial infantile seizures*
Benign infantile seizures*

- Normal interictal EEG (including sleep) with normal patterns according to age
- Ictal EEG: focal seizures, mostly temporal or occipital



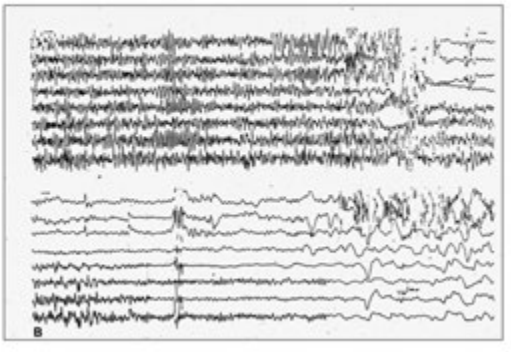
Benign familial infantile seizures1.1



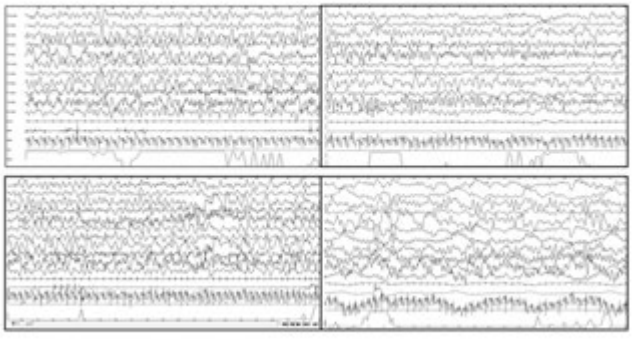
Vigevano

Benign familial infantile seizures1.2

Vigevano et al 1992

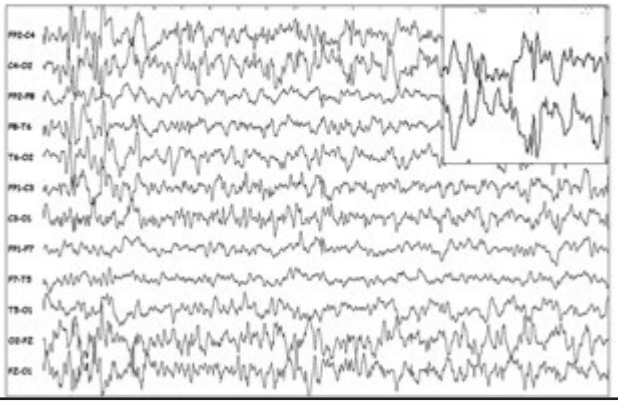


Benign infantile seizures



Mohamed 9 mois

Benign focal epilepsy of infancy with rolandic spikes during slow sleep

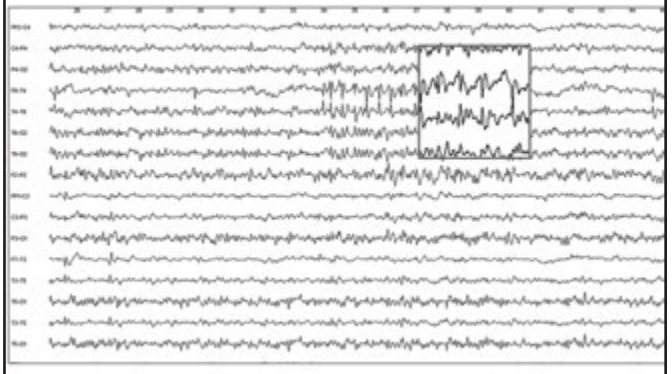


Benign focal epilepsies

- BFNS and BINS in neonates
- BIS and BFS in infancy
- **BECTS and BEOS in childhood**

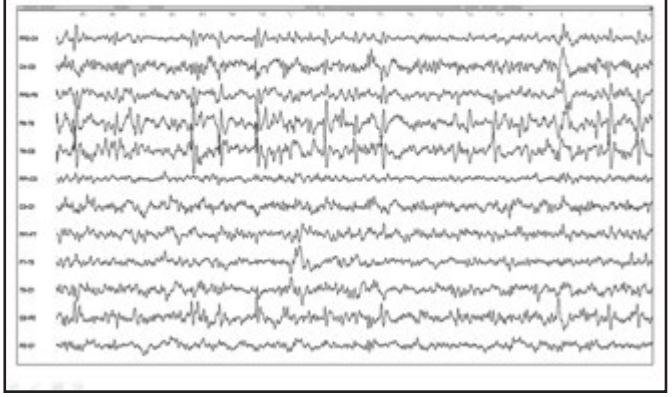
.

ECTS

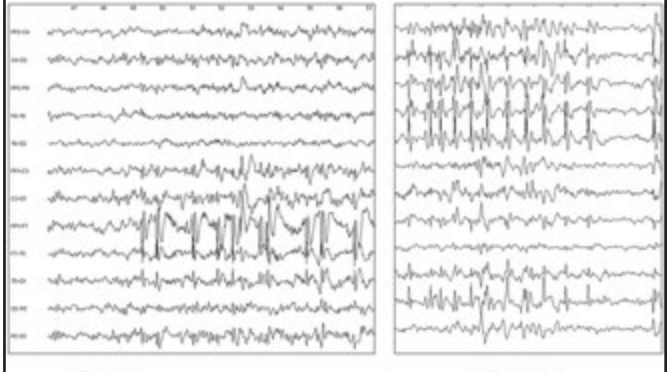


Pus.. 10 years SVP

ECTS

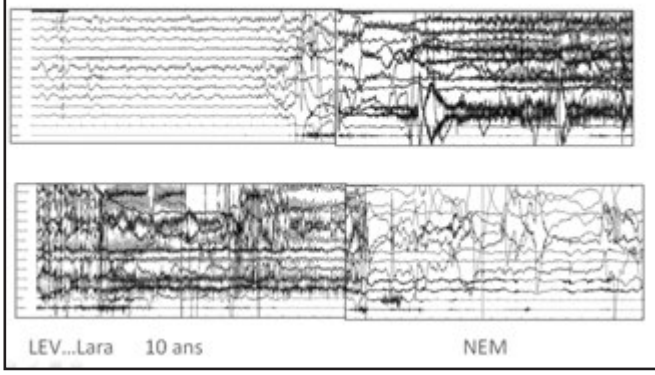


EPCT

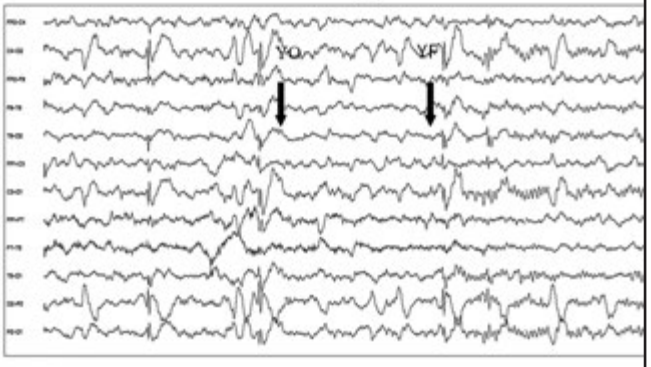


7 years 10 years

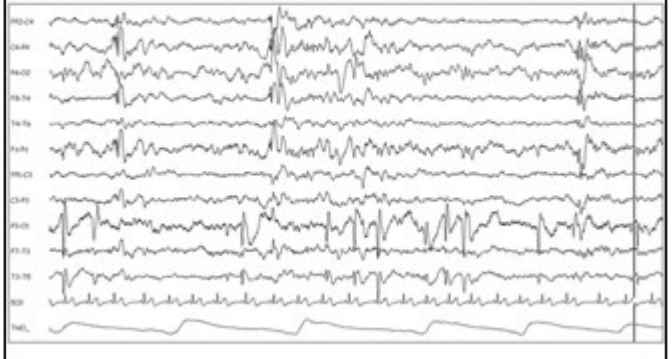
BECTS seizure at 7h12



Benign occipital epilepsy Gastaut type



Panayiotopoulos syndrome



Evolution of EEG patterns

- Epileptic encephalopathies
  - EIEE, EME
  - West syndrome
  - Lennox Gastaut Syndrome
- Benign focal epilepsies
- Symptomatic focal epilepsies

Neonatal epilepsy and FCD (Ville et al)

- Epilepsy :
  - 7: focal seizures associated with spasms
  - 5: focal seizures only
  - 1: no precise data
- Early EEG data in 6 children

  All tracings are asymmetrical, with an interictal lateralized focus of slow waves and spikes

FCD and neonatal epilepsy

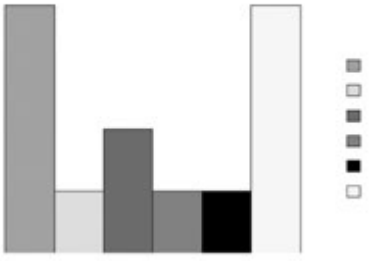
8: early diagnosis before age of one year

4: diagnosis > 18 months

- 3 no diagnosis on first MRI
- 1 no early MRI
- 1: no result of first MRI

Localization of these FCD

n=13



Evolution

Surgery :

- 2 hemispherotomies without seizures
- 4 focal surgery (14 months, 4, 5, 7 years): no one is seizure free

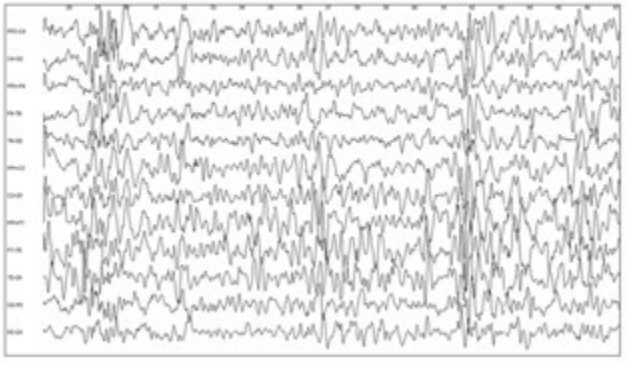
No surgery:

- 2 without seizure
- 2 in presurgical evaluation
- 2 lost before surgery
- 1 with multiple foci

ROY Benjamin

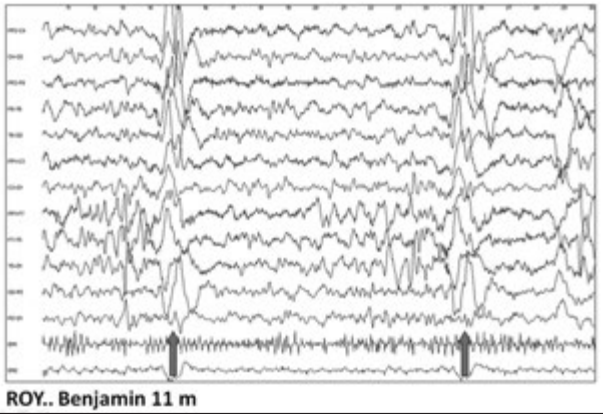
- No familial or personnal history
- 1st seizure at 3 months : head deviation to the left, stop moving, redness of the face: no treatment
- 6 months : increase of seizure frequency Diagnosis: GOR : adéquate treatment
- No change concerning seizures…
- 11 months : video EEG
  - Diurnal and nocturnal focal seizures
  - Epileptic Spasms
- Right Hemiparesis
- RMI : lefy centro-temporal cortical dysplasia

Left Central CD Interictal



ROY.. Benjamin 11 m

Left Central CD Spasms



ROY.. Benjamin 11 m

Chloé born19/09/1999

- Normal birth
- 2 months: focal seizures
  - Head and eyes deviation to the right
  - Clonia of the left hemibody, +/- Left upper limb
  - EEG: nl background activity, right fronto-temporal focus of S and SW
  - VPA, CLB: no change
- CTscan: normal

Chloé

- No efficacy of VPA
- Transitory improvement of Sz frequency with CBZ
- At one year (09/2000):

New type of seizures: eyelids jerks, head and eyes deviation to the right, clonic jerks of right upper limb and head drops in clusters.

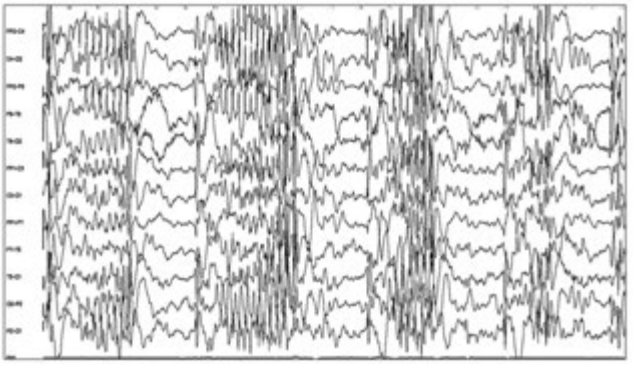
EEG: right focus of S and SW + generalized bursts of S and SW.

MRI: normal (1 year)

SVP: left heminegligence; mild retardation; no regression

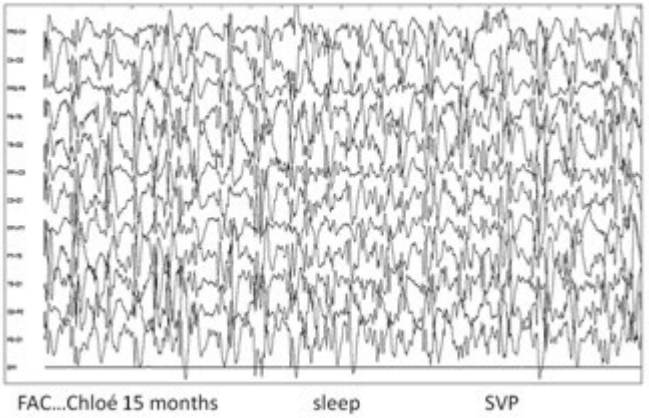
First video EEG

Chloé



FAC...Chloé 15 months eyelids jerks +++ SVP

Chloé



FAC...Chloé 15 months sleep SVP

Chloé

- No efficacy of corticosteroids
- EPT is given in association with VPA and CLB
- Then ketogenic diet....

Chloé

- New MRI which confirms the diagnosis of right centro-parietal focal cortical dysplasia
- Left hemineglígence
- Surgery to be performed

Complementary and alternative therapies in epilepsy
Steven Schachter (USA)

Botanicals and Herbs:
A Time-Honored Approach to Treating Epilepsy

Steven C. Schachter, M.D.
Harvard Medical School

5 February, 2010

BETH ISRAEL DEACONESS MEDICAL CENTER
A member of CARE GROUP

Schachter 2010

Why Botanicals?

- Botanicals have a rich history as a source of compounds for therapeutic use
- Substantial number of prescription drugs contain natural product derivatives
- Latest example – Razadyne (Ortho-McNeil)
  - Galantamine (*Galanthus nivalis*; Common snowdrop)
  - Possibly the herb "moly" in Homer's Odyssey

Schachter 2010

Why Botanicals?

- A large number of Asian, African and South American herbs have been historically used singly and in combinations to treat seizures
- A number of herbal medicines have been shown to have mechanisms of action that are relevant to epilepsy
- Systematic study of botanicals as sources for new epilepsy therapies appears promising

Schachter 2010

East Asian Literature: Herbs for Epilepsy

- Search strategy
  - A literature search was carried out using PubMed, Embase, PsychInfo, AltHealth (from inception to March 2005), the Chinese Medicine Database, the Korean Medical Database, and the Korean Drug Research Information Center. Bibliographies of initially identified articles were also checked.
  - All clinical studies, including case reports, that reported the results of treating epilepsy with herbal formulas were included.

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East Asian Literature: Herbs for Epilepsy

- 71 studies in the East Asian medical literature report clinical effects of herbs for epilepsy, including:
  - 3 randomized controlled trials
  - 5 non-randomized controlled trials
  - 6 case control studies
  - 57 observational studies, including case reports
- Over 135 different herbs were used singly or in combination formulas

Park and Schachter, in preparation

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East Asian Literature: Herbs for Epilepsy

- The ten most frequently used herbs were *Pinella ternate* (Ban Xia), *Arisaemi japonicum* (Tian Nan Xing), *Acorus calamus* (Shi Chang Pu), *Gastrodia elata* (Tian Ma), *Buthus martensii* (Quan Xie), *Poria cocos* (Fu Ling), *Bombyx bartryticatus* (Jiang Qiang), *Citrus reticulate* (Chen Pi), *Uncaria rhynchophylla* (Gou Teng), *Glycyrrhiza glaba* (Gan Cao) and *Salivae miltiorrhizae* (Dan Shen).

Park and Schachter, in preparation

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Why Botanicals?

- The FDA has a guidance for INDS and NDAs for "botanical drug products" such as extracts

  http://www.fda.gov/cder/guidance/4592fnl.pdf
- On 11/9/06, the FDA approved an extract of green tea for topical treatment of genital warts caused by human papilloma virus (brand name – Veregen Ointment).

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(+) syringaresinol O-β-D-glucoside, 1-hydroxypinoresinol-4''-O-β-D-glucopyranoside, 1-hydroxypinoresinol-4', 4''-di-O-β-Dglucopyranoside, 1-hydroxypinoresinol-4'-O-β-D-glucopyranoside, 3''-methyleriodictyol, 3''-methyleriodictyol-7-O-β-D-glucoside, 3, 4-dihydroxybenzaldehyde glucoside, 3-O-galloylprocyanidin, 3-O-galloylprocyanidin, 3-O-galloylprocyanidin, 4, 4'-dihydroxydibenzyl ether, 4, 4'-dihydroxydiphenyl methane, 4-ethoxymethylphenol, 4-ethoxymethylphenol-4'-hydroxybenzyl ether, 4-guanidino-1-butanol, 4-guanidinobutyric acid, 5, 2''-dihydroxy-6, 7, 8-trimethoxyflavone, 5, 8-dihydroxy-6, 7-dimethoxyflavone, 7-isoformosanine, 7-methoxy-baicalein, 7-methoxynorwogonin, agglutinins, apugoside, akuammigine, akuammigine, akuammigine, arabinose, arginine, aspartic acid, aucubigenin-1-betaisomaltoside, aucubin, aucuboside, avicularin, baicalein, baicalein-7-O-beta-D-glucopyranoside, baicalin, β-acetylamyranol, β-amyradiol, β-amyrandiol, β-amyranol, β-amyrin, β-amyrin acetate, β-amyrin palmitate, β-sitosterol, β-sitosterol, betulic acid, betulinic acid, betulin, bis (4-hydroxybenzyl) ether, butan-2, 3-diol-3-O-monoglucoside, caffeic acid, calcium oxalate, campesterol, catechol, chlorogenic acid, chrysin, chrysin-6-C-α-L-arabinoside-8-C-β-D-glucoside, chrysin-6-C-β-D-glucoside-8-C-α-L-arabinoside, citric acid, citric acid symmetrical monomethyl ester, citrusin B, D, corymantheine, corynoxeine, corynoxine B, coryxine, cycloolivil, cystine, daucosterol, dehydrodiconiferyl alcohol-4, gamma'-di-O-β-D-glucopyranoside, dehydrodiconiferylalcohol-4, γ'-di-O-β-D-glucopyranoside, dihydrobaicalin, dihydrocorynantheine, dihydrocorynantheine, dihydrodehydrodiconiferyl alcohol, dihydrooroxylin A, dihydroxydehydrodiconferyl alcohol, ecdysterone, eleutheroside E, encommiol, epicatechin, epipinoresinol, eriodictyol, erythro-dihydroxydehydrodiconferyl alcohol, erythroguaiacyl glycerol, erythro-guaiacyl-glycerol-β-coniferyl aldehyde ether, eucommin A, eucommiol, eucommioside I, fatty oils, ferulic acid, flavoyadorinin A (alboside), flavoyadorinin B, galactitol, galactose, galacturonic acid, galeopsin, gastrodin, gastrodioside, i.e. bis-(4-hydroxybenzyl) ether-mono-β-D-glucopyranoside, geissochizine methyl ether, genipin, geniposide, geniposidic acid, glucuronic acid, glutamic acid, glycine, guaiacyl glycerol-β-coniferyl aldehyde ether, guaiacylglycerol, guttapercha, gyiringin, harpagide acetate, hedyotol C-4'', 4''-di-O-β-D-glucopyranoside, hirsutseine, histidine, homoflavoyadorinin B, inokosterone, isocorynoxeine, isoleusibirin, isoleucine, isopteropodic acid, isopteropodine, isorhamnetin-3-O-β-D-glucoside, isorhamnetin-3-O-glucoside, isorhamnetin-7-O-β-D-glucopyranoside, isorhamnetin-7-O-β-D-glucoside, isorhynchophylline N-oxide, isorhynchophylline, kaempferol, L-arginine, leonardine, leonurine, leucine, liriodendrin, lupeol, lysine, medioresinol, medioresinol-4'-O-β-D-glucopyranoside, mesoinositol, methionine, methyl chlorogenate, myristic acid, nonacosane, oleanolic acid, oleanolic acid-α-L-rhamnopyranosyl-β-D-galactopyranoside, olivil, olivil 4''-O-β-D-glucopyranoside, olivil 4'-O-β-D-glucopyranoside, olivil-4', 4''-di-O-β-D-glucopyranoside, palmitic acid, phenylalanine, pinoresinol, pinoresinol-di-β-D-glucoside, proline, protocatechuic acid, querbrachitol, quercetin, quercitol, quercitrin, reploside, rhamnazin, rhamnazin-3-O-β-D-glucoside, rhamnose, rhynchophylline, rubrosterone, scutellarin, serine, skullcapflavone I, skullcapflavone II, stachydrine, succinic acid, syringaresinol, syringaresinol-O-β-D-glucopyranoside, syringenin-O-β-D-apio-furanosyl(1→2)-β-D-glucopyranoside, syringin, syringylglycerol-β-syringaresinol ether 4'', 4''-di-O-β-D-glucopyranoside, tartaric acid, threo-dihydroxydehydrodiconiferyl alcohol, threo-guaiacyl glycerol, threo-guaiacyl-glycerol-β-coniferyl aldehyde ether, threonine, triacontanol, tryptophan, tyrosine, ulmoprenol, ulmoside, ursolic acid, valine, vanillic acid, vanillin, vanillyl alcohol, viscotoxin A2, viscotoxin A3, viscotoxin B, viscumneoside, vitamin A, vitamin C, vitamin E, wogonin, wogonoside

Why Botanicals?

- May be a viable regulatory pathway to commercialize extracts for epilepsy, especially in parts of the world where patients cannot afford AEDs or who are culturally inclined to take natural products rather than "Western" medicines

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Harvard Epilepsy Botanical Program

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Harvard Epilepsy Botanical Program

- Global team
  - Herbal experts
  - Natural product chemists
  - Neuroscientists with expertise in testing natural products
  - Animal experimentalists

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Global Collaborators

- Collaborations with herbal experts at:
  - Chinese University of Hong Kong
  - Keio University (Tokyo)
  - Kyung Hee University (South Korea)
  - Tzu Chi University (Taiwan)
  - University of Chile
  - University Hospital of Dakar (Senegal)

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The Process. Step 1: Identify

- Methods for selecting botanicals (use in epilepsy, relevant mechanism of action)
  - Review of TCM textbooks
  - Opinion of herbal medicine experts
  - Original literature (eg, Chinese, Japanese)
  - English literature

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The Process. Step 2: Acquisition

- Acquisition of herbal medicine extracts (water based, methanol based, etc)
  - Herbal experts in the field
- Authentication
  - Analytic laboratories
  - Methods range from visual inspection to DNA fingerprinting

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Harvard Epilepsy Botanical Program

- Goals
  - Find herbal medicine extracts with promising activity in animal epilepsy models (ASP of the NINDS) and in vitro assays relevant to epilepsy
  - Isolate compounds from these extracts and then retest them in the same models and assays

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Harvard Epilepsy Botanical Program

- Goals
  - Conduct the necessary pre-clinical studies and then proceed to early stage clinical studies
  - Partner to develop and commercialize the compounds and extracts as FDA-approved products for epilepsy

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Results to date

- 40 herbal extracts and pure compounds derived from herbal extracts have been tested in animal epilepsy models through the ASP
  - 70% showed anticonvulsant activity in a variety of models, several with wide therapeutic windows and several that inhibit glutamate-mediated neuronal death
  - Lead compound is Huperzine A, which is ready for clinical testing; other compounds undergoing further pre-clinical testing

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Results to date: example

- An herbal extract was found by ASP to be effective and non-toxic in vitro
- 4 pure compounds (> 300 mg each) were isolated from ~ 5 kg of this herbal extract
  - 1 compound is active in mouse ScMET model given i.p. at a non-toxic dose (ASP), and is active in the formalin pain model (ASP)
  - All 4 compounds inhibit NMDA-mediated neuronal death (Sucher lab, HMS)

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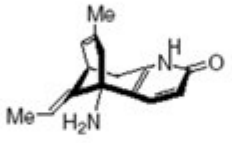
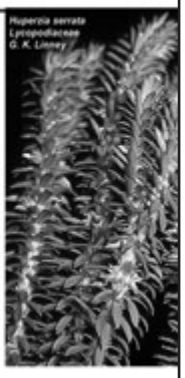
Huperzine A

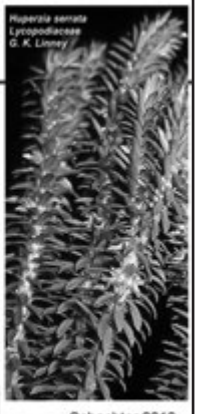




Origin of Huperzine

- *Huperzine serrata* (Chinese Club Moss), also known as Qian Ceng Ta "thousand-laid pagodas"
- Whole herb traditionally used for fever, swelling, inflammation and schizophrenia

Liu, Can J Chem 1986



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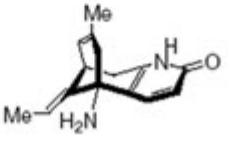
Chemistry

- (-)-Huperzine A first isolated from *Huperzia serrata* in 1986; average content of Huperzine A by weight is 0.011%
- Sesquiterpene Lycopodium alkaloid
- [5*R*-(5a,9b,11*E*)]-5-amino-11-ethlidene-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta [*b*] pyridin-2(1*H*)-one.
- $C_{15}H_{18}N_2O$
- MW 242.32 g/mol



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Mechanisms of Action: NMDA

- Non-competitive antagonist of NMDA receptor
- Likely acts at or near the PCP and MK-801 ligand sites
- No evidence of histopathological changes in experimental animals or psychotomimetic side effects in humans

Gordon, J Appl Toxicol 2001; Zhang, Neurosci Lett 2000; Zhang, Neurosci 2001

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Mechanisms of Action: ACh

- Specific, reversible inhibitor of acetylcholinesterase
- Comparable potency to
  - Physostigmine
  - Galantamine
  - Donepezil
  - Tacrine
- Basis for its use in Alzheimer's disease and myasthenia gravis

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Animal Studies: Epilepsy (ASP: ADD 357133)

- Active against:
  - rat MES (i.p. and oral)
  - rat ScMET (i.p. and oral)
  - mouse MES (i.p.)
  - mouse ScMET (i.p.)

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6-Hz Mouse Model

- ED_{50} values (i.p.)
  - 0.28 mg/kg for 22 mA
  - 0.34 mg/kg for 32 mA
  - 0.78 mg/kg for 44 mA
- All below TD_{50} of 0.83 mg/kg i.p.

Presented at 2006 AES meeting. ASP: ADD 357133

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AEDs and the 6-Hz Model

Data courtesy of Steve White

AED	ED_{50} (mg/kg, i.p.) 22 mA	32 mA	44 mA
Phenytoin	9.4	>60	>60
Lamotrigine	4.4	>60	>60
Ethosuximide	86.9	167	>600
Levetiracetam	4.6	19.4	1089
Valproic acid	41.5	126	310
Huperzine	0.28 (0.16 – 0.48)	0.34 (0.28 – 0.40)	0.78 (0.56–1.01)

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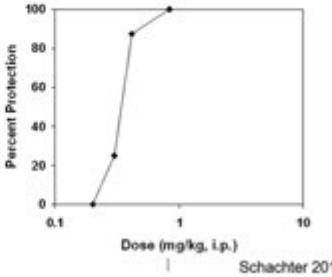
6-Hz Mouse Model (32 mA)

Huperzine A displays dose-dependent protection against 6-Hz seizures for 32 mA.
ED50 (95% confidence interval) 0.34 (0.28 – 0.40) mg/kg, i.p.



ASP: ADD 357133

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Animal Studies: Pain (ASP: ADD 357133)

- Mouse formalin model of pain
  - 1 mg/kg i.p.: complete elimination of paw licking at all time points (0 – 40 minutes) in all huperzine-treated mice (n=8)
  - 0.5 mg/kg i.p.: complete elimination of paw licking in all animals except first time point in several animals, no behavioral toxicity
- Sciatic ligation model - effective without toxicity

Presented at 2006 AES meeting. ASP: ADD 357133

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Initially Planned Huperzine Clinical Study in Epilepsy

- Phase IIA proof-of-principle study; Investigator IND
  - Safety, tolerability and early stage pharmacokinetics
  - Doses up to 200 µg QID (0.8 mg/day) as add-on, open-label therapy in patients with medically-refractory partial seizures with or without other seizure types (same dose as NIH AD study)
  - Provide preliminary data on efficacy and its effects on mood and memory function

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Every Culture Has An Herbal Medicine Tradition

- Brazilian herbs anecdotally said to be beneficial for epilepsy include
  - Passionflower (Maracujá)
    - Chrysin (5,7-di-OH-flavone), an ingredient in Passiflora coerulea L.,is a competitive ligand for benzodiazepine receptors. ICV administration to mice blocks PTZ-induced tonic-clonic seizures (Medina et al, 1990, Biochem Pharmacol).
  - Tayuya root
    - Has anti-inflammatory effects in the laboratory

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Thank you!

For further information and
collaboration inquiries, contact:
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Join the AES Botanical Special Interest Group

Acknowledgments

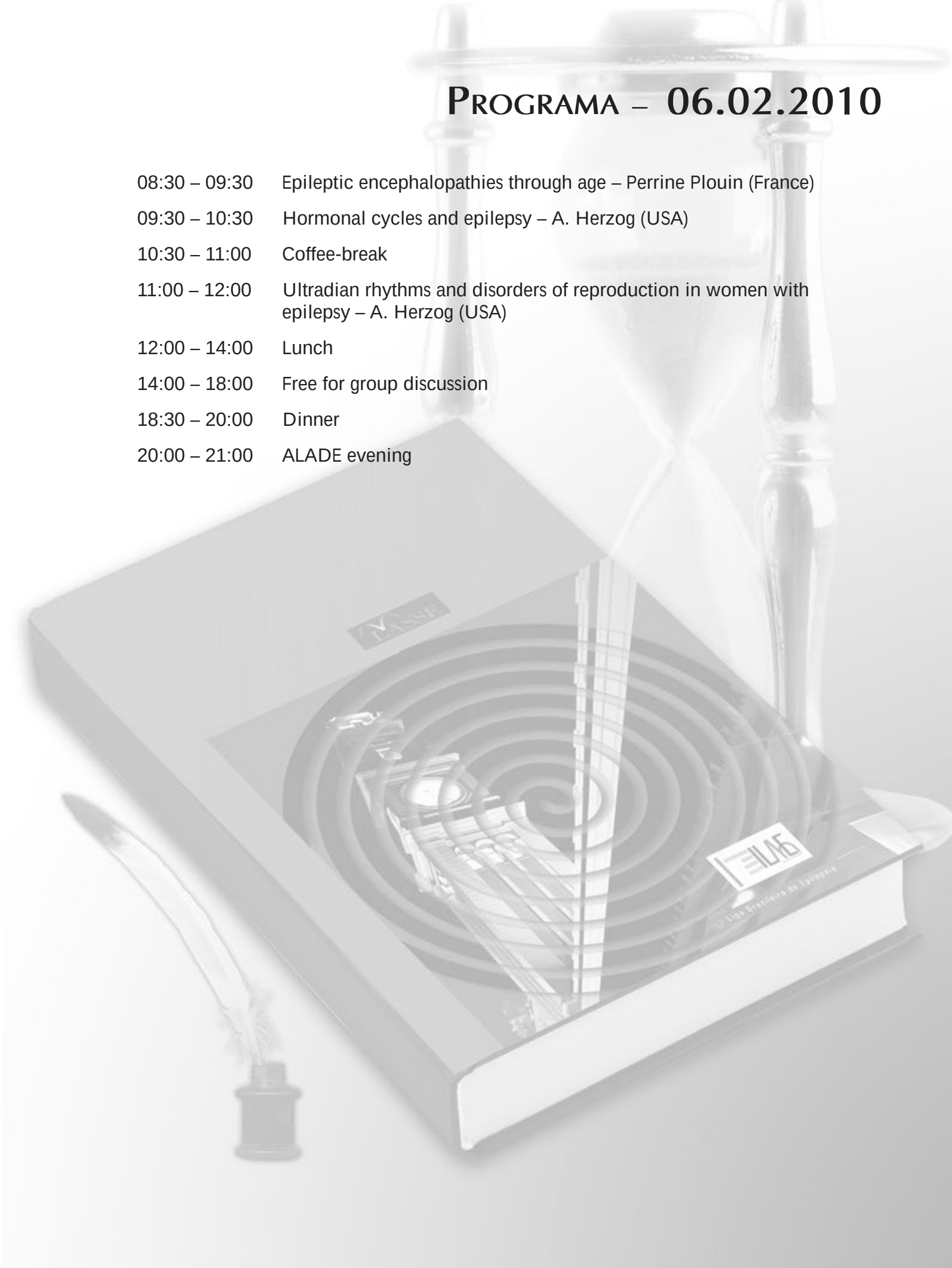
NINDS Anticonvulsant Screening Program
- Steve White, Lauren Murphree, Jim Stables

Harvard Epilepsy Botanical Program
- Epilepsy Therapy Project
- Epilepsy Research Foundation
- American Epilepsy Society
- Nikolaus Sucher, N. Baek, Jongbae Park

Mother Nature

Programa – 06.02.2010

08:30 – 09:30	Epileptic encephalopathies through age – Perrine Plouin (France)
09:30 – 10:30	Hormonal cycles and epilepsy – A. Herzog (USA)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Ultradian rhythms and disorders of reproduction in women with epilepsy – A. Herzog (USA)
12:00 – 14:00	Lunch
14:00 – 18:00	Free for group discussion
18:30 – 20:00	Dinner
20:00 – 21:00	ALADE evening



Epileptic encephalopathies through age
Perrine Plouin (France)

Epileptic Encephalopathies

Perrine Plouin
Hopital Necker Enfants Malades
Paris France

. Epileptic encephalopathy.

- The concept of epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology (e.g. cortical malformation) alone, and that these can worsen over time.
- Inherent in this concept is the idea that by suppressing or preventing the epileptic activity, one may improve the cognitive and behavioral outlook of the disorder. In the developing brain, this concept has lead to the hope that rapid effective intervention should and can be used before the abnormal epileptic activity interferes irrevocably with normal processes of brain development.

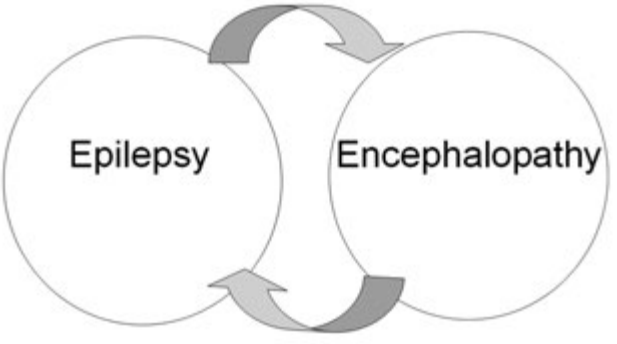
Epileptic encephalopathy

- The term "epileptic encephalopathy" can be used to characterize syndromes as well as be applied to individuals. As a *domain for clustering and describing syndromes*, **an epileptic encephalopathy is an electro-clinical syndrome associated with a very high probability that the individual will develop encephalopathic features that present or worsen after the onset of epilepsy.**
- The best known and most common of these are West, Lennox-Gastaut, Dravet, Landau-Kleffner-CSWS, and Doose syndromes.

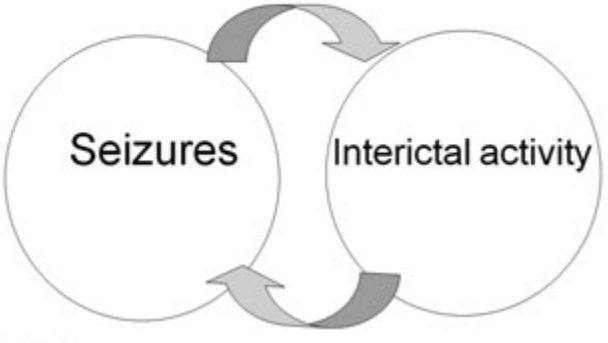
Epileptic encephalopathy

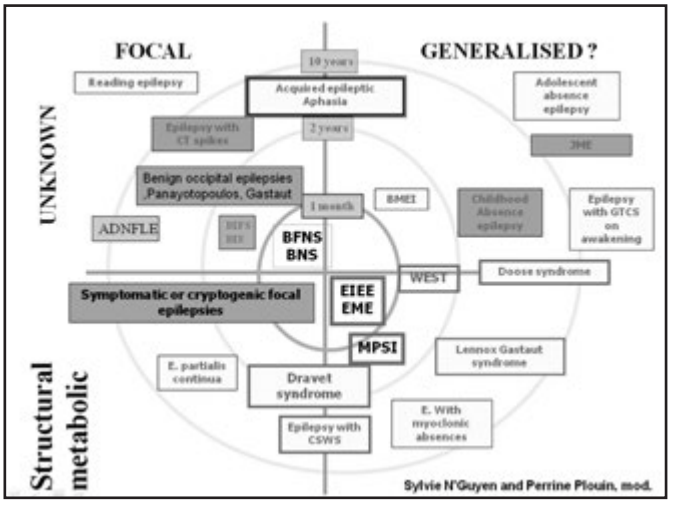
- "Epileptic encephalopathy" should be viewed as a concept and a description of what is observed clinically with the recognition that, we are rapidly approaching a clearer understanding of the effects of seizures on brain function and their potential for lasting deleterious impact in the developing brain.
- At the same time, however, we must recognize that the source of an apparent encephalopathy is usually unknown. It may be the product of the underlying cause, the result of epileptic activity, or a combination of both.

. Epileptic encephalopathy.



. Epileptic encephalopathy.





Epileptic encephalopathies

- EME, Ohtahara syndrome
- MPSI
- West syndrome
- Dravet syndrome
- Lennox Gastaut syndrome
- Epilepsies with CSWSS

. Epileptic encephalopathy.

- According to age, EEG interictal patterns are different from neonates to childhood
  - Neonates: Suppression burst tracing
  - Infancy: Hypsarhythmia
  - Childhood: Slow SW and tonic seizures, CSWS
- Although seizures may have or not the same electro-clinical presentation

Epileptic Encephalopathies in Neonates

- Ohtahara syndrome: EIEE
- Early Myoclonic Encephalopathy
- Migrating partial seizures in Infancy
- Incidence ???

Early Infantile Encephalopathy with Epilepsy: EIEE Ohtahara et al 1976

- Epileptic Spasms, , tonic spasms, focal seizures
- Onset from D1, up to 2 or 3 months
- Abnormal neurological examination
- Suppression-Bursts EEG pattern
- Abnormal findings on Neuro radiology
- No familial history

Suppression-Burst pattern

- Suppression-burst pattern was first described in animals, then in post anoxic adult patients;
- In neonates with Anoxo ischemic encephalopathy this pattern may be present but in a transitory way, evolving to a more normal EEG or to a flat EEG.
- In France we use "tracé paroxystique" in these cases and SB only for epilepsy syndromes
- In the US burst suppression is used to reflect the EEG of severe hypoxia and trace paroxystique for te epileptic syndrome

(Glossary of neonatal EEG, Neurophysiol. Clin,2000)

EIEE: etiology

Malformations, are often found:

- Porencephaly,
- Aicardi syndrome
- cerebral dysgenesis
- olivary-dentate dysplasia
- hemimegalencephaly
- linear sebaceous nevus
- Leigh's encephalopathy
- subacute diffuse encephalopathy
- A few cryptogenic cases have also been reported

EIEE: outcome

- 1982-2004: more than 100 reported cases
- Among 61 cases in 7 series:
  - 23 deaths < age of one year (38%)
  - Severe sequellae among others: severe epilepsy (spasms), hypsarhythmia and mental retardation
- Four children underwent surgery: 2 FCD and 2 hemimegalencephaly with a dramatic improvement on sz

Early Myoclonic Encephalopathy

Aicardi and Goutieres 1978

- Massive myoclonic sz, erratic myoclonia, focal seizures
- Onset before D28
- Abnormal neurological exam
- Suppression Burst EEG pattern
- Normal work up
- Possible familial history
- Treatment selection?

EME

SB may be "extreme" with very short paroxysmal bursts and very longperiods of suppression.

EME

- In EME, the most striking feature is the frequency of familial cases: 4 of 12 families in the series of Aicardi and 2 of 8 families in the series of Dalla Bernardina et al.. This fact suggests that an inborn error of metabolism is most likely.
- Nonketotic hyperglycinemia , propionic aciduria and d-glycine acidemia have been reported, but there are many cases with unknown causes.
- It is considered that neither clinical nor neuroimaging findings disclose obvious brain damage before the onset of EME.

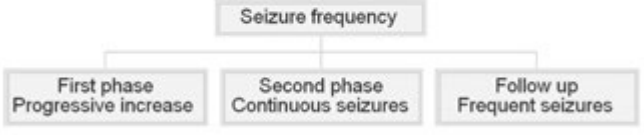
EME: outcome

- 50% of death before the age of 2 years was already reported in the first publication, with no normal outcome in the other 50%
- Since 1990 20 cases have been reported, half of them died before the age of one year

Migrating Partial Seizures in Infancy

- seizure onset in the first year of life
- mean age at first seizure: 3.3 months
- continuous multifocal seizures involving both hemispheres
- no etiology
- normal brain imaging at onset
- intractability to conventional AED

Migrating Partial Seizures in Infancy



MPSI: ictal clinical manifestations

- lateral deviation of the head and eyes
- lateral eye jerks, fixed sight, eyelids jerks
- hypertonia and/or clonic jerks of one or more limbs
- chewing movements, apnea, flushing
- secondary generalization
- Seizures usually last for 1-4 minutes, sometimes longer

Ictal characteristics

- Good clinical/EEG correlation according to topography of the discharge
- Very complex combination of simultaneous partial seizures
- Without video/EEG, seizures are often overlooked
- Seizures can affect a single hemisphere for several months

Interictal EEG

- Slow background
- Often asymmetrical
- Rare multifocal spikes
- Rare spindles in sleep

Interictal neurological condition

- Somnolent and drooling
- Unable to drink or swallow
- Ocular tracking fluctuent depending on seizures
- Hypoptonia turning to athetotic movements
- Progressive microcephaly

Long-term course

- Effects of :
  - Bromides ?
  - Stiripentol ?
- For some patients, seizures tend to become less severe by the second or third year
- Death at the end of infancy or the end of the first decade

Etiology

One case with Ito syndrome. In most instances :

- Neuroradiology negative
- Electroretinography negative
- EMG and conduction velocity negative
- Biochemistry negative
- Skin biopsy negative
- Neuropathology : only post-ictal abnormalities

West Syndrome

- West syndrome :
  - infantile spasms
  - Hypsarrhythmia
  - Lack of development or regression
  - infantile spasms with a spike focus
  - partial epilepsy +/- hypsarrhythmia

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Hypsarrhythmia

- random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location... The abnormality is almost continuous, and in most cases it shows as clearly in the waking as in the sleeping record.
- It is referred as hypsarrhythmia (Gibbs and Gibbs, 1952)

Hypsarrhythmia

- if associated with epileptic spasms and eventually focal seizures
- and with a psycho motor regression
  - –West Syndrome or Infantile Spasms

Hypsarrhythmia atypical or modified

- Gastaut et al. 1970
  - – fragmented awake
  - – excessive slowing
  - – rapid activity
  - – asymmetrical
  - – with a focus
- Hrachovy et al. 1984
  - – with increased interhemispheric synchronization
  - – asymmetrical
  - – a consistent focus
  - – volt. attenuation
  - – with high voltage slow activity

Hypsarrhythmia variations

- functional origin
  - states of wakefulness and sleep
  - age
- structural origin
  - metabolic diseases
  - brain malformation
  - clastic forms
  - cryptogenic and idiopathic cases

West syndrome

- Deleterious effect of phenobarbital and cabamazepine (if necessary, EEG follow-up +++)
- Early identification of situations at risk (tuberous sclerosis, focal cortical dysplasia, uni- or multifocale, or diffuse lesions)
- Prophylaxis in various etiologies (tuberous sclerosis) ?

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Dravet Syndrome

- Onset < one year in all cases
- Febrile convulsive seizure either generalized or unilateral
- Recurrence of seizures with or without fever
- Diurnal then nocturnal convulsive seizures
- Worsening of neurological state

- After 18 months generalized myoclonias
- Risk of myoclonic status epilepticus

Dravet Syndrome

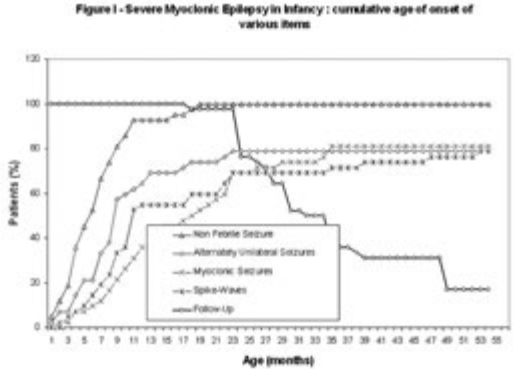
EEG

- normal at onset then slowing of background activity
- Generalized spike and waves or polyspikes synchronous to myoclonic jerks
- Bursts of rhythmic spike and waves with atypical absences

Evolution

- Valproate de sodium-Clobazam-stiripentol
- topiramate

Dravet Syndrome



SME : Neuropsychological Data

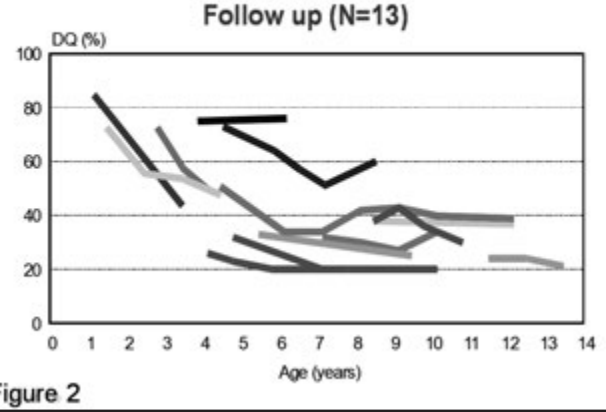
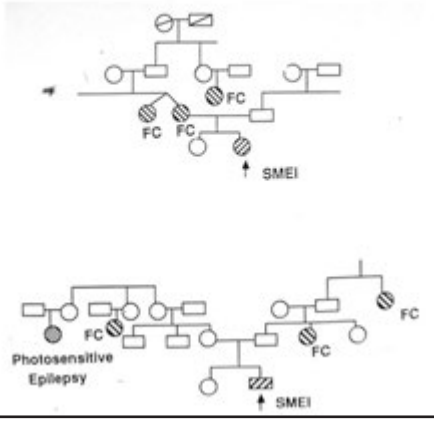


Figure 2

Dravet syndrome familial history



Mutation of SCN1A gene in Dravet syndrome

Sensibility? major gene of SD (70% of patients)
Spécificity? Mutation SCN1A in GEFS+ ...
Diagnosis? One « plus » to clinical presentation at onset of the disease

Genetic advice? (cas transmis, mosaïque)
Prognosis Non correlated to severity
Negative Patients?

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Negative patients?

Lennox-Gastaut Syndrome (I)

- On,set: 1 to 8 years
- Main seizure types: tonic, atypical absences, chutes
- More rare seizures: focal, myoclonic, generalized tonic clonic
- EEG : generalized slow spike and waves +/6 a focus of spikes
- Frequent episodes of status epilepticus

Syndrome de Lennox-Gastaut (II)

Pharmacoresistance

- Variable aetiology :
  - Malformative , including double cortex
  - Post natal brain lesion lesion
  - Unknown
- May be preceded by west syndrome or focal epilepsy

ESES CSWS POCS

- ESES: Electrical Status Epilepticus during Slow Sleep. Patry, Tassinari 1971
- 6 children with more than 85% of TST with continuous SW in nonREM Sleep, this activit disappearing in REM sleep
- Mental retardation, major cognitive troubles
- Seizures of different types, focal or generalized, excluding tonic seizures
- Remission: spontaneous, or following the « treatment » of the EEG abnormalities
- Persistance of cognitive dysfunction

Continuous Spike and Waves during Slow Sleep

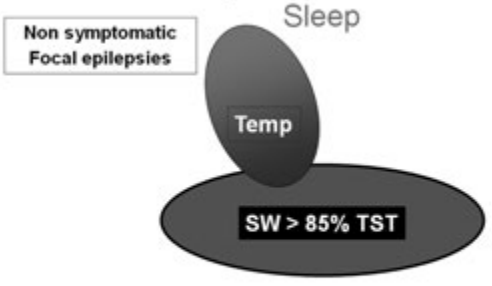
CSWSS

- In fact in the definition of ESES SW were « sub continuous » (>85%) but not continuous
- Spike and Waves does not mean Spikes and this is not clear where the border is between these two situations
- Non REM sleep is always concerned , REM sleep may also be involved as well as wakeness (in french: POCV)
- The amount of SW is not constant through the different cycles during night

CSWSS

- The main problem is that SW are rarely truly generalized, they can be unilateal, and even focal

Continuous Spike and Waves during Slow Sleep



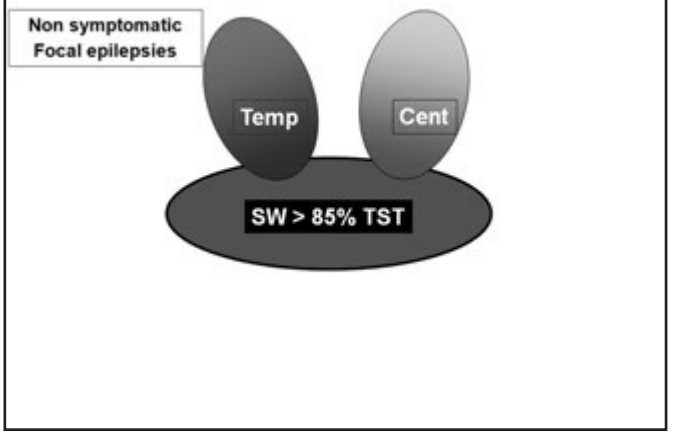
Landau Kleffner Syndrome , 1957

- Acquired Aphasia Epilepsy : 248 reported cases
- Progressive Aphasia between 5 et 7 years
- Hyperkinesy and disturbances of the personnality
- Seizures in 70 à 80 % of cases (1 only seizure in 30% of cases)
- Temporal Spikes and Spike and waves (50% des cas) in wakeness
- Sleep Activation +++
- Treatment: Benzo, corticotherapy, sub pial transsection

Landau Kleffner Syndrome

- Sleep activation leading to CSWSS, has often been reported, and even an increase of SW during REM sleep
- In these cases regression of cognitive performance and behaviour is major and sequellaae are more important

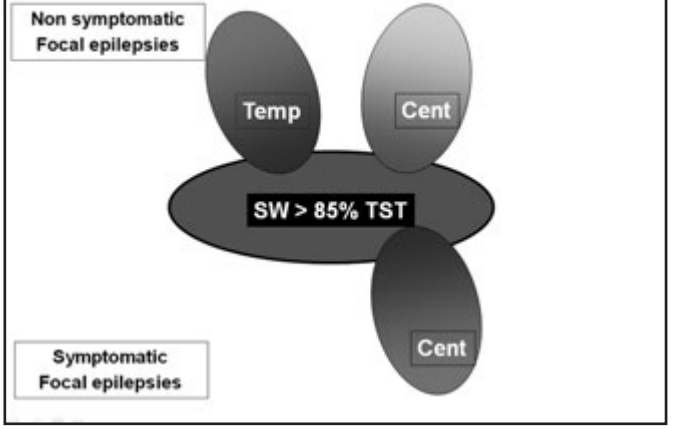
Continuous Spike and Waves during Slow Sleep

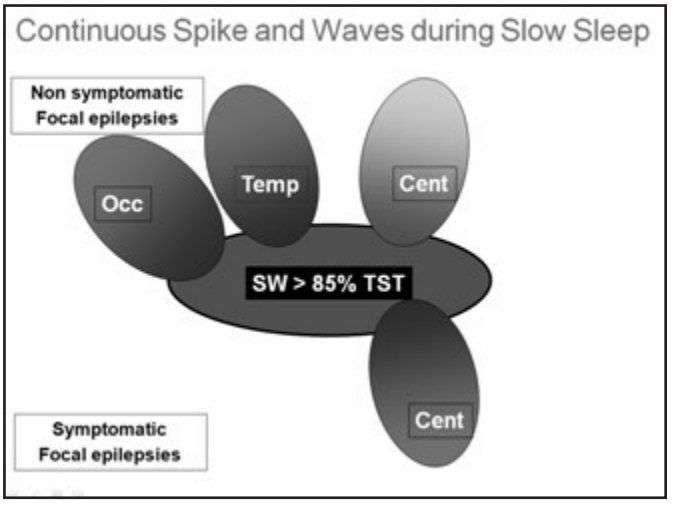


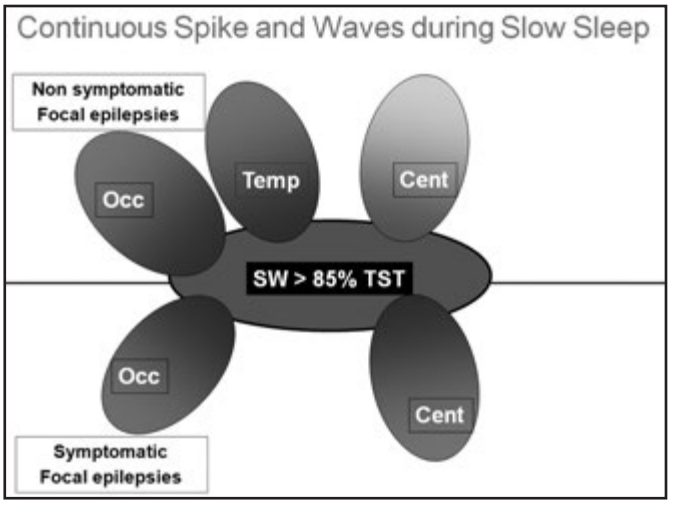
CSWSS and central focus

- Atypical benign partial Epilepsy (ABPE)
  - Motor seizures
  - Atonic fits, atypical absences
  - Focal centro temporal spikes +/- CSWSS
  - Epilepsy and mental outcome are favourable

Continuous Spike and Waves during Slow Sleep




Continuous Spike and Waves during Slow Sleep
Non symptomatic Focal epilepsies
Occ
Temp
Cent
SW > 85% TST
Cent
Symptomatic Focal epilepsies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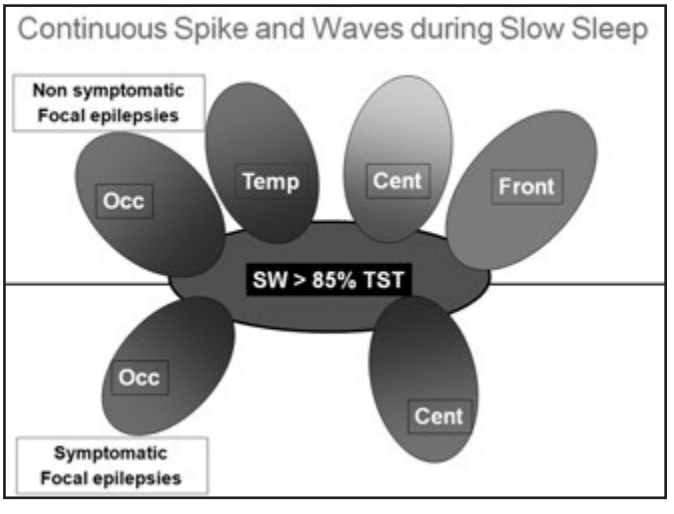
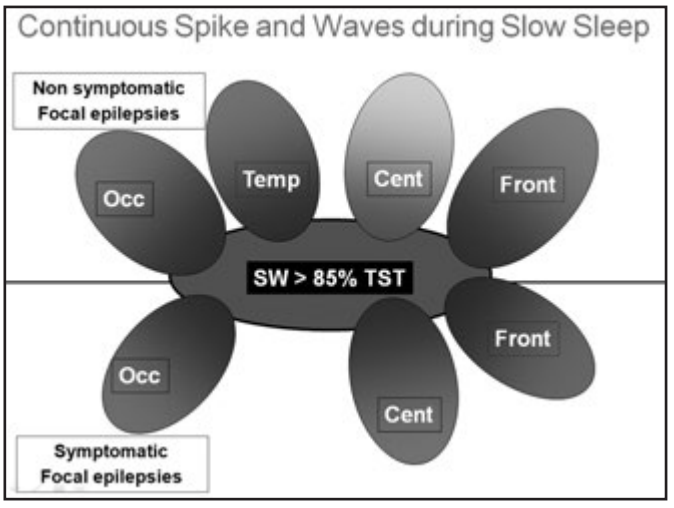
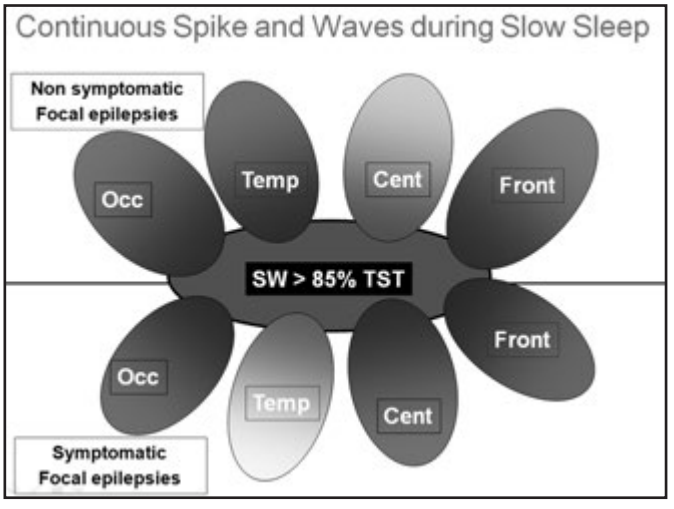

Continuous Spike and Waves during Slow Sleep
Non symptomatic Focal epilepsies
Occ
Temp
Cent
Front
SW > 85% TST
Occ
Cent
Symptomatic Focal epilepsies





CSWSS and neuropsychological troubles

- Strict association in time between CSWSS and neuropsychological degradation
- Clear parallelism between duration of CSWSS and final neuropsychological outcome
- Strict association between the neuropsychological pattern and the focus localization

CSWSS for ever???

- Continuous is uncorrect
- Spike an waves pattern is not always the case
- 85% : should we perform a precise counting of the SW?
- Does it make any difference in the treatment selection?

Hormonal cycles and epilepsy
A. Herzog (USA)

Hormonal Cycles and Catamenial Epilepsy

Andrew G. Herzog M.D., M.Sc.
Harvard Neuroendocrine Unit
Beth Israel Deaconess Medical Center
Boston, Massachusetts, USA

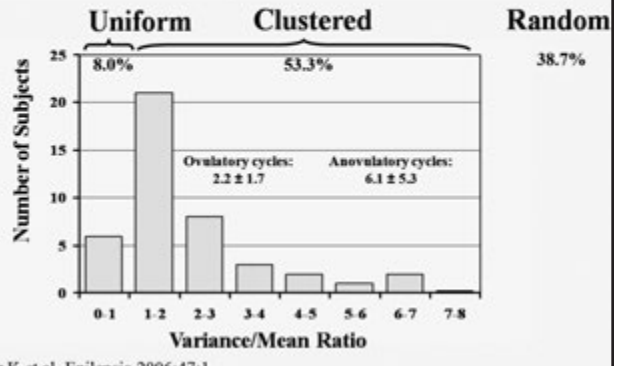
Catamenial Epilepsy

- What is it?
- What causes it?
- What proportion of women have it?
- How do you treat it?

Background

- Seizures do not occur randomly in the majority of men and women with epilepsy (Tauboll 1991)
- Seizures cluster (Almqvist 1955; Tauboll 1991; Fowler 2006)
- Seizure clusters show temporal periodicity in 29% of men and 35% of women with epilepsy (Almqvist 1955)
- Periodicity in women may conform to the menstrual cycle (catamenial epilepsy) (Gowers 1884; Laidlaw 1956; Herzog 1997; Herzog 2004)

Distribution of Seizures Among 75 Women with Epilepsy



Fowler K et al. Epilepsia 2006;47:1.

Seizure Chart

Dec - '86	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Cycle Day	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Seizures					**H**		**H**		**H**							**H,C**

Dec - '86	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1
Cycle Day	20	21	22	23	24	25	26	27	28	29	30	31	32	1	2	3
Seizures												**H**	**C**	**H**	**C**	**H,C**

H – hearing

T – twitching

C – loss of consciousness

Distribution of Seizures During the Menstrual Cycle

- **100 women with localization-related epilepsy**
- **Each participated for three cycles**
- **Complete data collected for 292 of 300 cycles**
- **Pair-wise multiple comparisons of menstrual cycle days for**
  - **1) average daily seizure frequency (ADSF)**
  - **2) seizure occurrence**

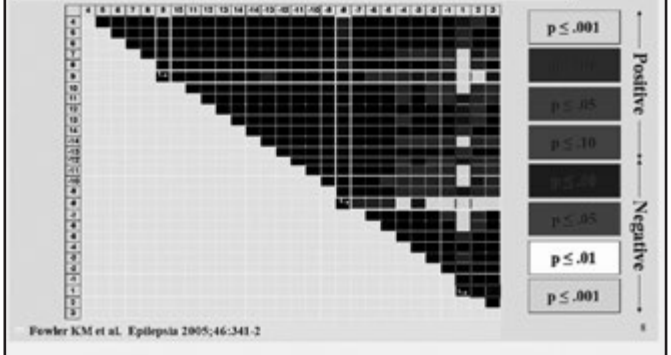
Fowler KM et al. Epilepsia 2005;46:341-2

Distribution of Seizures During the Menstrual Cycle For 292 Cycles in 100 Women

	Average Daily Seizure Frequency	Proportion of Cycles with Seizure Occurrence
Day 1	.68	.33
Day -8	.30	.17

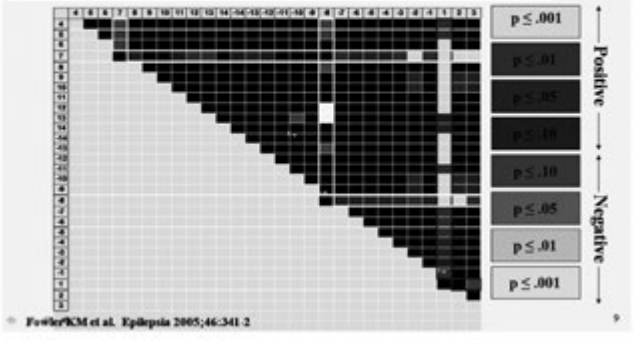
Fowler KM et al. Epilepsia 2005;46:341-2

Pair-wise comparisons of seizure numbers (ADSF) on the various days of the cycle for 292 cycles



Fowler KM et al. Epilepsia 2005;46:341-2

Pair-wise comparisons of days with seizures during the menstrual cycle for 292 cycles



Fowler KM et al. Epilepsia 2005;46:341-2

Basis of Catamenial Epilepsy

- Reproductive steroids have neuroactive properties
- Neuroactive steroid serum levels vary during the menstrual cycle
- There are hormonally sensitive brain substrates

Basis of Catamenial Epilepsy

- *Reproductive steroids have neuroactive properties*
- Neuroactive steroid concentrations in the serum vary during the menstrual cycle
- There are hormonally sensitive brain substrates

Neuroactive Steroids & Neurosteroids

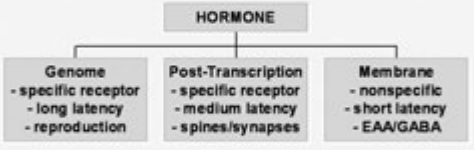
- Neuroactive Steroids:
  - steroids capable of modifying neural activity
- Neurosteroids:
  - steroids synthesized in the brain (Baulieu 1981)
  - formed from precursors mostly by glia
  - bind & modulate membrane receptors that regulate ion channels as well as intracellular receptors that regulate gene expression

Neuroactive Properties of Reproductive Steroids

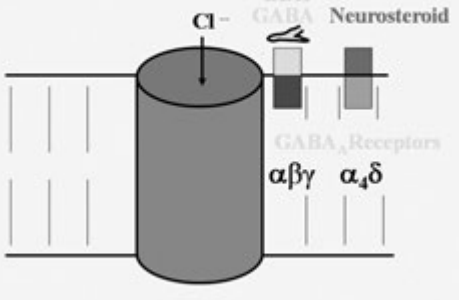
Scientific Evidence

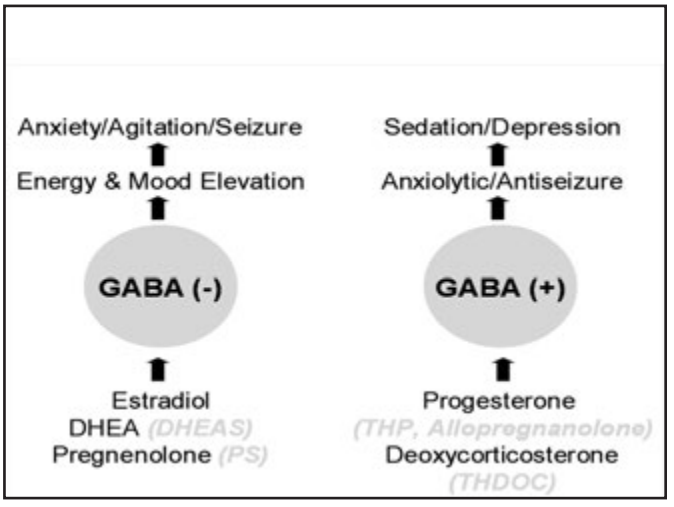
- Molecular biological
- Neuronal
- Animal experimental
- Clinical

Mechanisms of Hormone Action



Mechanisms of Neurosteroid Action





Reproductive Steroid Effects on Epilepsy

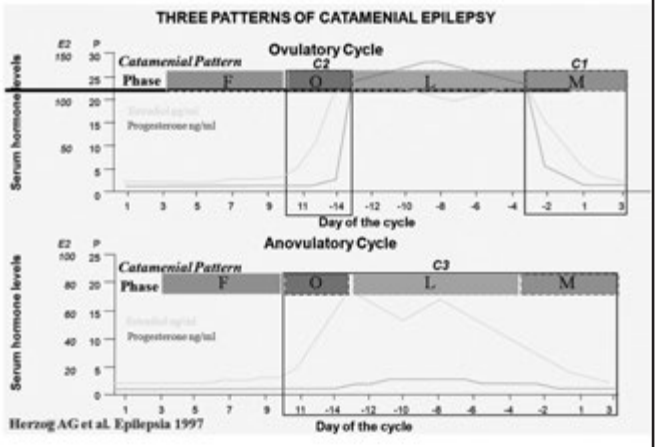
- **Estrogen:**
  - ⇩ GABA
  - ⇧ Glutamate
  - ⇧ metabolism
  - ⇧ cell firing
  - ⇧ kindling
  - ⇧ seizures
- **Progesterone:**
  - ⇧ GABA
  - ⇩ Glutamate
  - ⇩ metabolism
  - ⇩ cell firing
  - ⇩ kindling
  - ⇩ seizures

Clinical

- Physiological
  - catamenial seizure exacerbation (Laidlaw 1956; Herzog 1997)
  - seizure frequency correlates with E_2/P (Backstrom 1976)
- Pathological
  - anovulatory cycles are associated with more seizures (Backstrom 1976; Mattson 1981; Herzog 1997; Herzog 2006)
- Pharmacological
  - estrogen facilitates seizures (Logothetis 1959)
  - progesterone retards seizures (Backstrom 1984, Herzog 1995)

Basis of Catamenial Epilepsy

- Reproductive steroids have neuroactive properties
- *Neuroactive steroid serum concentrations vary during the menstrual cycle*
- **There are hormonally sensitive brain substrates**



Three Patterns of Catamenial Epilepsy

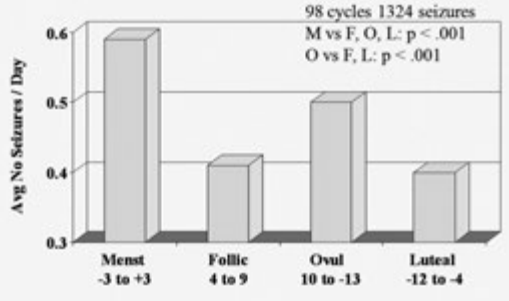
Neuroactive Steroid Based Hypothesis

- **Menstrual (Day -3 to 3)**
- **Midcycle (Day 10 to -13)**
- **Luteal (ILP) (Day 10 to 3)**

Method

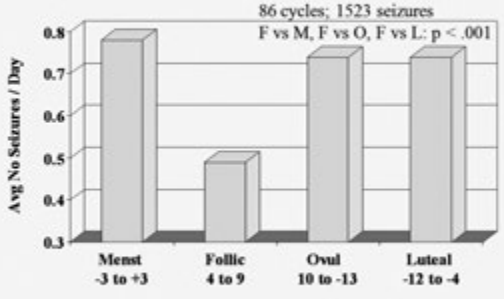
- 184 women aged 18-45
- with localization-related epilepsy
- 23-35 day cycle intervals
- seizure and menstrual chart for 1 cycle
- day 22 serum progesterone (N ≥ 5 ng/ml)
- comparison of average daily seizure frequency among phases of cycle separately for normal and ILP cycles (Newman-Keuls)

Ovulatory Cycles



Herzog AG, Klein P, Ransil BJ. Epilepsia 1997; 38:1082-88

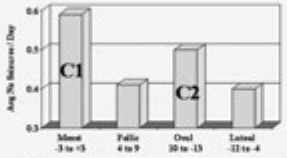
Anovulatory Cycles



Herzog AG, Klein P, Ransil BJ. Epilepsia 1997; 38:1082-88.

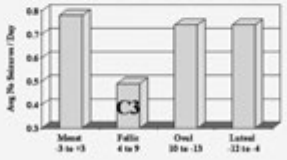
Three Patterns of Catamenial Epilepsy

C1 & 2



98 cycles 1324 seizures
M vs F, O, L: p < .001
O vs F, L: p < .001

C3



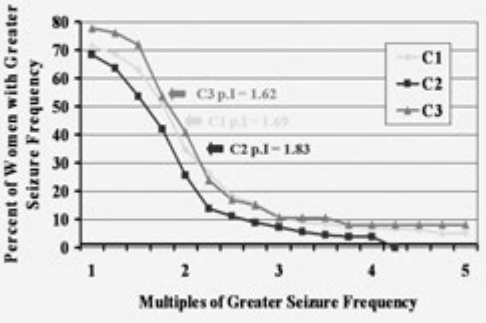
86 cycles; 1523 seizures
F vs M, F vs O, F vs L: p < .001

Herzog AG, Klein P, Ransil BJ. Epilepsia 1997; 38:1082-88

Frequency of Catamenial Epilepsy

- Tauboll - 78%
- Laidlaw - 72%
- Rosciszewska - 67%
- Ansell and Clarke - 63%
- Duncan et al. - 12.5%
- Dickerson - 10%
- Almqvist - non-menstrual periodicity
- Bandler - no periodicity

Frequency of Catamenial Epilepsy



Herzog AG, Klein P, Ransil BJ. Epilepsia 1997; 38:1082-88

Catamenial Categorization Formulas

Day 22 Progesterone level ≥ 5 ng/ml

C1 - Avg daily sz freq ratio: (–3 to +3)/[(-12 to –4) + (+4 to +9)] ≥ 1.69

C2 - Avg daily sz freq days: (+10 to -13)/[(-12 to –4) + (+4 to +9)] ≥ 1.83

Day 22 Progesterone level < 5 ng/ml

C3 - Avg daily sz freq days: (+10 to +3)/(+4 to +9) ≥ 1.62

Occurrence of Catamenial Epilepsy

Proportion Of Women	C1	C2	C3
>	71.4%	68.4%	77.9%
Point of Inflection	35.7%	28.5%	41.4%
3x	11.2%	7.1%	10.5%

Basis of Catamenial Epilepsy

- Reproductive steroids have neuroactive properties
- Neuroactive steroid concentrations in the serum vary during the menstrual cycle
- *There are hormonally sensitive brain substrates*

Frequency of Catamenial Epilepsy by Laterality and Focality

Catamenial Epilepsy	Left (43.5%)	Right (28.9%)
Temporal (37.1%)	45.2%	28.6%
Non-Temporal (32.0%)	33.0%	30.1%

CE was more frequent with L than R sided epilepsy overall ($\chi 2 = 3.878$, $p=.0489$) and especially greater with LT than RT localization ($\chi 2 = 4.239$, $p=.0395$).

Levels of Catameniality by Laterality and Catamenial Pattern

	Left Temporal	Right Temporal
C1: perimenstrual	2.5 [1.0,3.75]	1.25 [0.76,2.50]
C2: pre-ovulatory	1.67 [1.05,3.75]	1.13 [0.75,1.88]
C3: entire luteal	1.82 [0.66,5.00]	1.66 [0.76,5.0]

The levels of catameniality (median [quartiles]), were greater with LT than RT for the C1 (Mann Whitney U test: $p=.010$) and C2 ($p=.004$), but not C3 ($p = .949$) patterns.

Progestogen Therapy

- 1973 - Zimmerman; depoMPA: no seizures
- 1983 - Dana Haeri; norethistrone: no effect
- 1983 - Herzog; MPA: no effect
- 1984 - Mattson; depoMPA: -39% sz freq
- 1986 - Herzog; prog supp's: -68% sz freq
- 1995 - Herzog; prog loz: -55% sz freq

Suppressive Progestin Therapy

Treatment	DepoMPA IM (1973)	MPA Oral/Depo (1984)
Regimen	150 mg X 3	10 mg b-qid/ 120-150 mg q 6-12 wk
N	1	14 11developed amenorrhea
No. improved	1 (100%)	7 (50%)
Seizure frequency	-100%	-39%*

* p < .05; **: p < .01

Cyclic Progestogen Therapy

Treatment	Norethistrone Oral (1983)	MPA Oral (1983)	Progesterone Suppositories (1986)	Progesterone Lozenges (1995)
Regimen	high/low placebo 21 d X 4 mos	5-10 mg qd days 15-28 3 mos	200 mg bid days 15-28 3 mos	100-200 mg tid days 15-28 3 mos
N	9	24	8	25
No. improved	No effect	10 (42%)	(6) 75%	18 (72%)
Seizure frequency	No effect	-10%	-68%*	-54%** CPS -58%* SGMS

* p < .05; **: p < .01

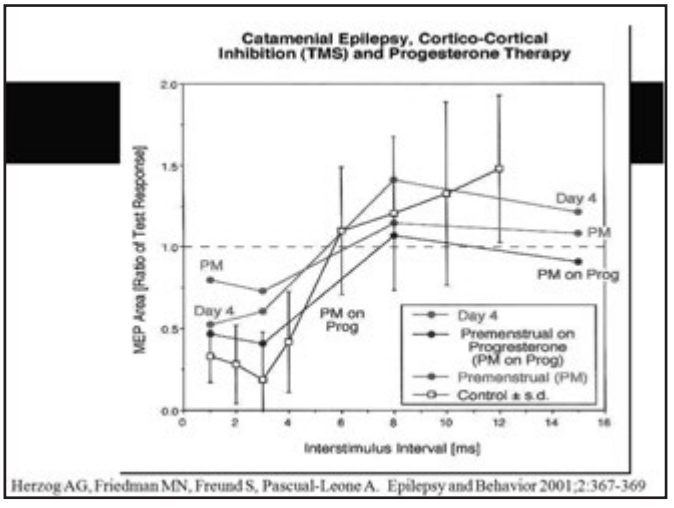
Herzog AG. Neurol 1986; 36:1607-10; Herzog AG. Neurol 1995; 45:1660-62

Cyclic Progestogen Therapy

Treatment	MPA Oral (1983)	Progesterone Lozenges (1995)	Progesterone Lozenges (3-year follow-up)
Regimen	5-10 mg qd days 15-28	100-200 mg tid days 15-28	100-200 mg tid days 15-28
N	24	25	15 of original 25
Assessment	@ 3 months	@ 3 months	@ 3 years
No. improved	10 (42%)	18 (72%)	15 (100%; 60% overall)
Seizure frequency	-10%	-54%** CPS -58%* SGMS	-62%** CPS -74%** SGMS

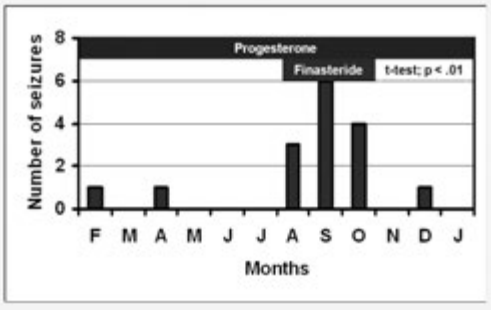
* p < .05; **: p < .01

Herzog AG. Neurol 1995; 45:1660-62; Herzog AG (3-year follow-up) Neurol 1999; 52:1917-18



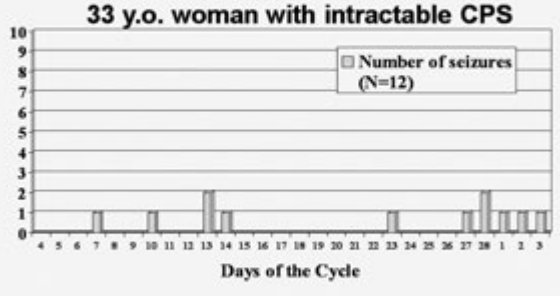
Herzog AG, Friedman MN, Freund S, Pascual-Leone A. Epilepsy and Behavior 2001;2:367-369

Reductase Inhibitor Effect on Progesterone Therapy

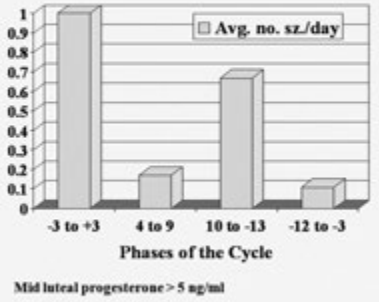


Herzog AG, Frye CA. Ann Neurol 2003;53:390-1

Management of Catamenial Epilepsy

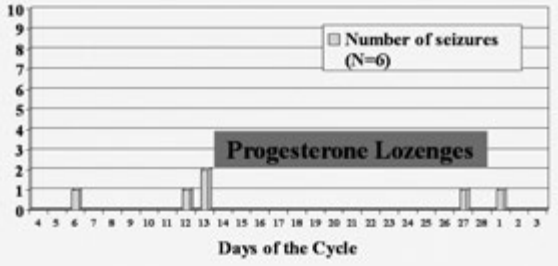


Average Number of Daily Seizures in the Various Phases of the Cycle

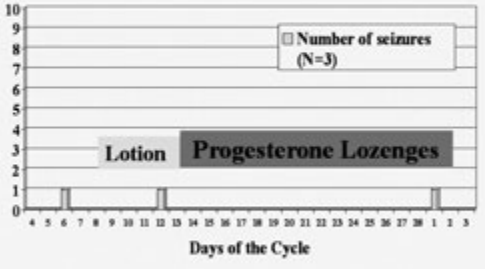


Mid luteal progesterone > 5 ng/ml

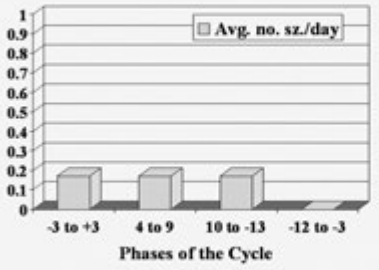
Seizure Chart



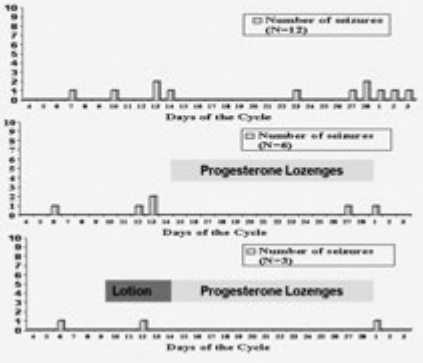
Seizure Chart



Average Number of Daily Seizures in the Various Phases of the Cycle



Progesterone Therapy: 33 y.o. Woman With Intractable CPS



Other Hormonal Therapies

- 1989 - Herzog - clomiphene: 10 of 12 improved; 87% decrease in seizures
- 1992 - Bauer - GnRH analogue: 8 of 10 improved; 3 seizure-free
- 1990's – CoCensys/Marinus - ganaxolone

Catamenial Epilepsy: Definition, Cause, Prevalence & Management

1. Seizure frequency varies during the menstrual cycle
2. There are 3 patterns of catamenial seizure exacerbation:
   a) C1 – perimenstrual (Day -3 to +3)
   b) C2 – preovulatory (Day 10 to Day –13)
   c) C3 – entire luteal phase, mostly in anovulatory cycles (Day 10 to 3)
3. Approximately, one-third of women have a two-fold or greater increase in average daily seizure frequency conforming to one of these patterns
4. The neuroactive properties of reproductive steroids and the cyclic variation of their serum levels as well as the specific brain substrate may be important pathophysiological factors
5. Hormones, especially natural progesterone and its reduced metabolites, may have a role in therapy

Ultradian rhythms and disorders of reproduction in women with epilepsy

A. Herzog (USA)

Ultradian Hormonal Rhythms and Disorders of Reproduction in Women with Epilepsy

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Harvard Neuroendocrine Unit
Beth Israel Deaconess Medical Center
Boston, Massachusetts, USA

Disorders of Reproduction in Women with Epilepsy

- Definition
- Characteristics
- Frequency
- Significance
- Mechanisms (etiology & pathophysiology)
  - Epilepsy as primary cause
  - AEDs as primary cause

Definition

- Reproductive failure involves failure of one or more of the following:
  - Ovulation
  - Fertilization
  - Gestation
- Neuroendocrine regulation of ovulation:
  - » Ultradian pattern of GnRH secretion
  - » Lunar pattern of preovulatory GnRH surge
  - » Modulation by limbic and brainstem neural as well as hormonal inputs
- Anovulatory cycles are substantially and significantly more common among women with epilepsy

Characteristics of Anovulatory Cycles

- **Clinical:**
  - *Menstrual disorders, hirsutism, galactorrhea*
- **Endocrine:**
  - *Pituitary: abnormal gonadotropins, hyperprolactinemia*
  - *Thyroid: low thyroid level*
  - *Gonadal: elevated testosterone and/or other androgen level; low mid-luteal progesterone level < 5 ng/ml*
- **Structural:**
  - *Ovarian enlargement with cysts*

Frequency

- **Menstrual disorders**
  - **TLE = 1/3 vs Ctrl = 1/8**
- **Anovulatory/inadequate luteal phase cycles**
  - **TLE = 14-39% vs Ctrl = 8-11%**

Frequency

- **Reproductive disorders are substantially and significantly more common in women with epilepsy than in the general population**
- **Reported frequencies, however, vary widely depending, in part, on variable definitions**
- **What should be the basis for the definition of normal reproductive function?**

Menstrual Disorders

- Amenorrhea (no menses for 6 months)
- Oligomenorrhea (>35 day cycle interval)
- Polymenorrhea (<21 day cycle interval)
- Irregular cycles (> 5 days variability)
- Menometrorrhagia (heavy menses and intermenstrual bleeding)

Basis For Definition

- Statistical base e.g. range = mean ± 2 SD for cycle intervals in the general population
- Biological base e.g. significant drop in ovulatory rates outside of a certain range of cycle intervals
- Transferability between populations: if 90% of cycles are ovulatory in the general population regardless of cycle intervals, what cycle intervals are associated with ovulation in women with epilepsy?

Cycle Intervals and Mid Luteal Phase Progesterone Levels

Cycle Intervals	%	Ovulation (Prog > 5 ng/ml)	Anovulation (Prog < 5 ng/ml)
<21	2	0 (0%)	2 (100%)
21-25	11	5 (45%)	6 (55%)
26-32	68	50 (74%)	18 (26%)
33-35	10	5 (50%)	5 (50%)
>35	9	1 (11%)	8 (89%)
Total	100	61 (61%)	39 (39%)

Herzog AG, Friedman MN. Neurology 2002;57:2133-2135.

Cycle Intervals and Mid Luteal Progesterone Levels in Women with Epilepsy

Cycle Intervals	%	Ovulation	Anovulation
A: 26-32	68	50 (74%)	18 (26%)
B: 21-25, 33-35	21	10 (48%)	11 (52%)
C: <21, >35	11	1 (9%)	10 (91%)

A vs B: p = .05; A vs C: p = .0001; B vs C: p = .07

Herzog AG, Friedman MN. Neurology 2002;57:2133-2135.

Significance of Reproductive Disorders

Reproductive Failure (Infertility)

- **69-85% of expected offspring** *(Dansky LV et al. Epilepsia 1980;21:261–271. Webber MP et al. Epilepsia 1986;27:746–752)*
- **1/3 as many as unaffected siblings** *(Schupf N, Ottman R. Epilepsia 1994;35:750–756)*

Significance of Reproductive Disorders

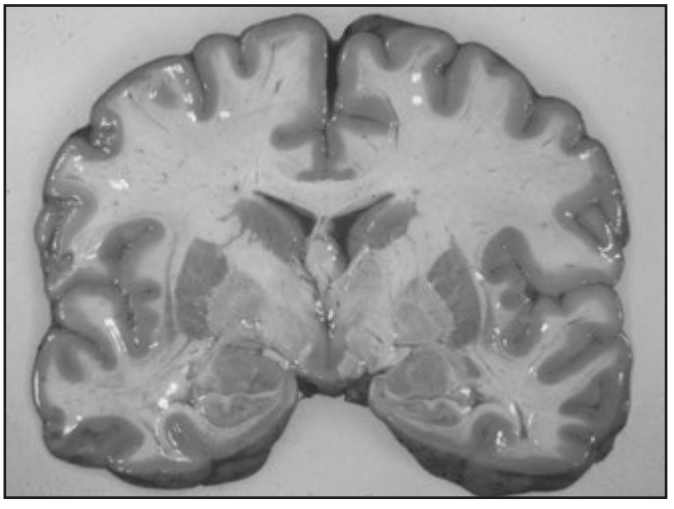
- **Migraine** (*Herzog AG, Schachter SC. Epilepsia. 2001:42:311-315.)*
  - **80% with RDs vs 30% in controls**
- **Emotional Disorders** *(Herzog AG. Psychosomatics 1999; 40:95-116. Heck ET, Cobb WE. Arch Clin Neuropsychol 1991;6:192-193)*
  - **75% of women with PCOS vs 30% in general population**
- **Female cancers** *(Jafari K et al. Obstet Gynecol 1978;51:97-101)*
  - **breast, uterus, ovary**
- **(For PCOS) Cardiovascular Disease & Diabetes** *(Guzik DS et al. Am J Obstet Gynecol 1996;174:1224-32. Wild RA et al. Fertil Steril 1990;54:255.)*

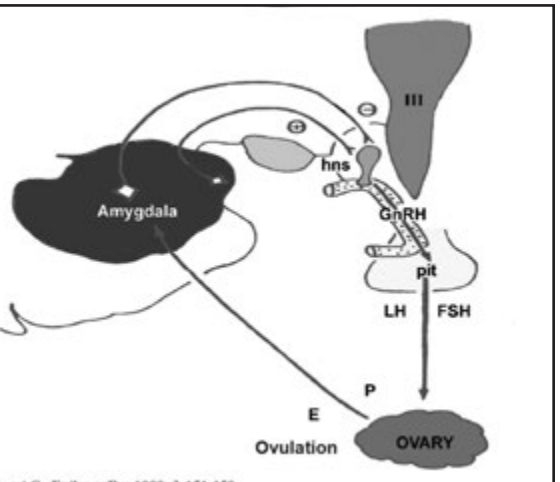
Neurological Significance for Epilepsy

- **Anovulatory cycles are associated with greater seizure frequency** *(Backstrom 1976; Mattson 1981)*
  - **Population study: In 184 women, each of whom participated for one cycle, there were 31.0% more seizures, on average, in 86 anovulatory cycles than in 98 ovulatory cycles** *(Herzog AG et al. Epilepsia 1997;38:1082-8)*
  - **Individual Study: During three months of observation, 30 of 100 women who had been identified to have both ovulatory & anovulatory cycle, had 28% more seizures during their anovulatory cycles than during their ovulatory cycles** *(Herzog AG et al. Neurol 2006;66:342)*

Etiology & Pathophysiology

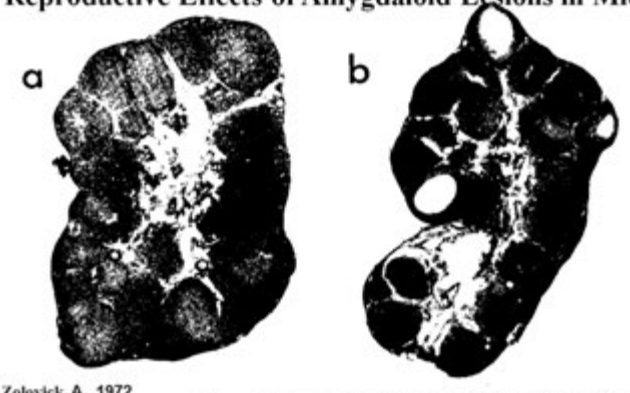
- **Primary neurological dysregulation resulting from epilepsy**
- **AED effects**
- **Both**
- **Other contributory factors: e.g. stress & depression via hypothalamo-pituitary-adrenal mechanisms**





Herzog AG. Epilepsy Res 1989; 3:151-159.

Reproductive Effects of Amygdaloid Lesions in Mice

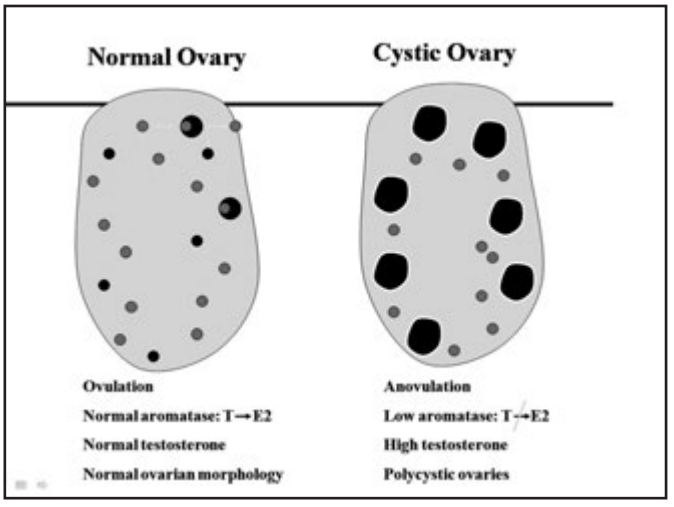


Zolovick, A. 1972
Fig. 1. Ovarian sections taken (a) two weeks and (b) three weeks after placement of bilateral lesions in the basolateral amygdaloid nuclei of adult deermice.

Reproductive Effects of Amygdala-Kindled Seizures in Female Rats

- Persistent estrus (anovulatory cycles)
- Hyperandrogenism
- Polycystic ovaries

Edwards H. et al. Epilepsia 1999;40:1370-7



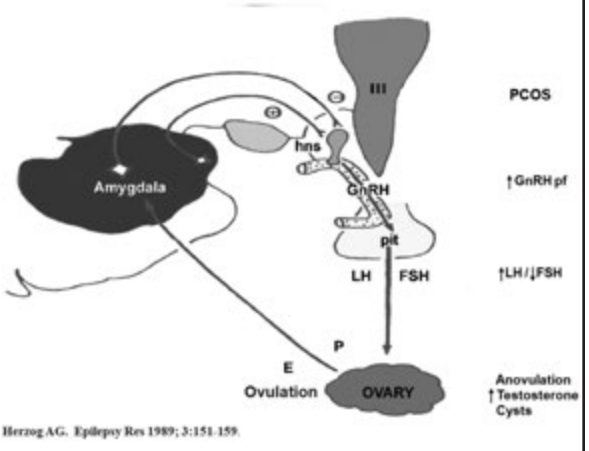
Reproductive Endocrine Disorders in 50 Women with TLE

- ***Overall:*** **38% vs 8% (p < .001)**
- ***PCOS:*** **20% vs 5% (p < .05)**
- ***Hypothalamic Amenorrhea:*** **12% vs 1.5% (p < .05)**
- ***Hyperprolactinemia:*** **4% vs <1% (p = NS)**
- ***Premature Menopause:*** **4% vs <1% (p = NS)**

Herzog AG et al. Arch Neurol 1986; 43:341-346.

PCOS: Epileptic vs AED Causes

- **2 ½ times more common among untreated than treated women with TLE** *(Herzog et al. 1986)*
- **Significantly more common with unilateral LTLE than RTLE** *(Herzog et al. 1993)*
- **PCO (86.7% vs 16.7%) and hyperandrogenism (50.3 ± 18.2 vs 42.2 ± 20.9) are significantly more common in untreated than in controls** *(Hamed et al. Acta Scand Neurol 2007)*
- **PCO and hyperandrogenism are significantly more common with VPA** *(Isojarvi JI 1993;)* **& with OXC** *(Lofgren, E. et al. Epilepsia 2006;47:1441-6)* **than with CBZ**



Herzog AG. Epilepsy Res 1989; 3:151-159.

Epilepsy Effects on Hormonal Secretion

1. What are the effects of paroxysmal temporolimbic EEG discharges on pulsatile gonadotropin secretion?
2. Are there lateralized asymmetries in these effects?
3. Are these effects affected by AED use?

Epilepsy Effects on Hormonal Secretion

Subjects

- 48 women (36 with CPS/SGMS of unilateral temporolimbic origin and 12 normal controls) between 18-40 years of age
- Antiepileptic Drugs:

CBZ - 10	Other - 7
DPH - 8	None - 9
VPA - 2	

Supported by NIH RO1 NS33189

Subjects

Demographics of Controls and Women with Epilepsy

	Ctrl	LTLE M	LTLE NM	RTLE M	RTLE NM
N	12	15	5	12	4
Age (years)	29.6 ± 6.1	30.9 ± 5.8	28.8 ± 7.5	32.9 ± 5.4	29.8 ± 7.2
Ep Duration (years)	-	8.2 ± 6.4	5.4 ± 4.8	7.7 ± 5.4	6.2 ± 4.1
Sz Freq (per month)	-	7.2 ± 4.8	5.2 ± 4.5	6.8 ± 5.4	4.6 ± 4.4
Proportion with SGMS	-	8 (53%)	2 (40%)	7 (58%)	2 (50%)

Methods

- Documentation of epilepsy characteristics, antiepileptic drug use and reproductive function
- Investigation: early-mid follicular phase (Day 3-7)
- Baseline reproductive endocrine & thyroid profile (FSH, LH, PRL, Testosterone, DHEAS, TFT's)
- q 10 min serum samples for LH & PRL measurement from 8 AM to 4 PM during concomitant, continuous EEG recording in order to assess hypothalamopituitary function

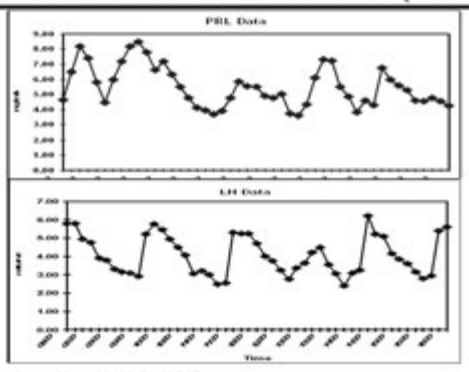
Hormonal Analysis

LH and PRL pulses were defined by peak values that were both 20% and three coefficients of variation higher than preceding nadirs. Pulses were verified by the Cluster Analysis software program for pulse detection.

EEG Analysis

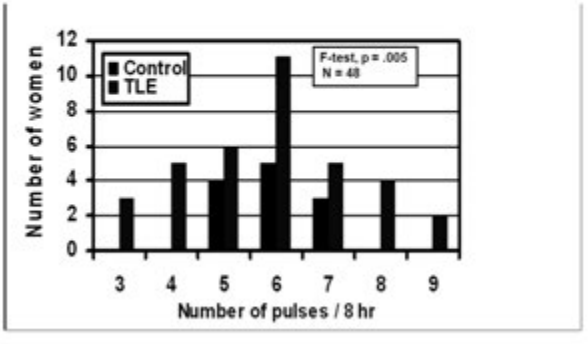
- Occurrence, time, laterality and number of paroxysmal events:
  1) epileptiform discharges
  2) bursts/runs of slowing

Pulsatile Secretion of PRL & LH (Control)



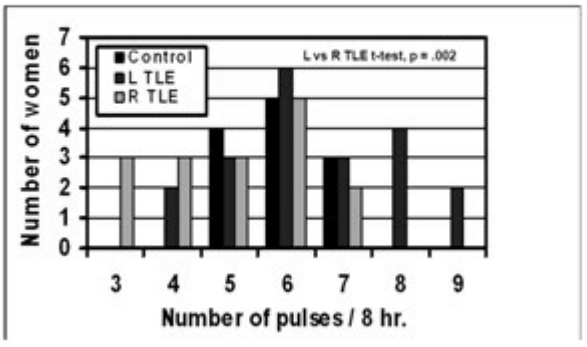
Herzog AG et al. Ann Neurol 2003;54:625-37.

LHPF: Women with TLE vs Controls



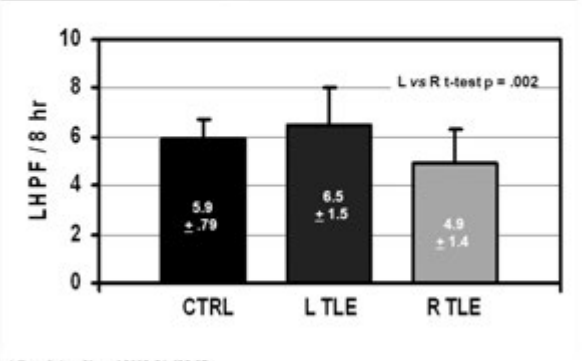
Herzog AG et al. Ann Neurol 2003;54:625-37.

LHPF: L and R TLE vs Controls



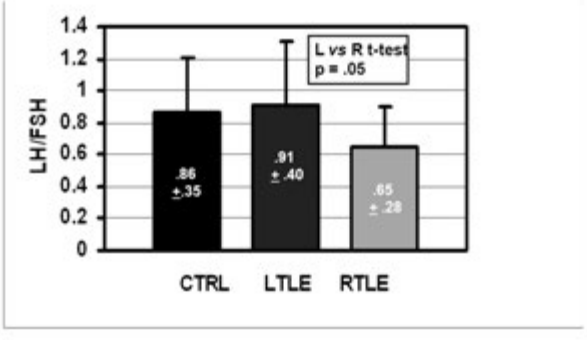
Herzog AG et al. Ann Neurol 2003;54:625-37.

LHPF Summary



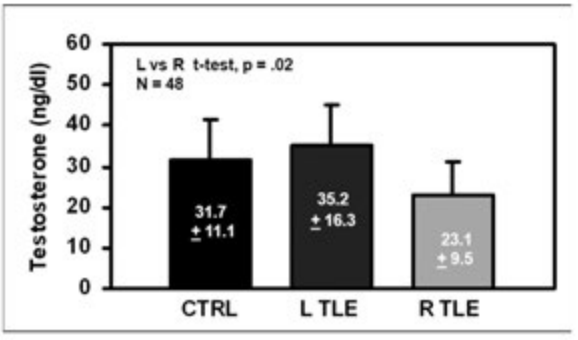
Herzog AG et al. Ann Neurol 2003;54:625-37.

LH/FSH Ratios and TLE Laterality



Herzog AG et al. Ann Neurol 2003;54:625-37.

Testosterone: L and R TLE vs Control



Herzog AG et al. Ann Neurol 2003;54:625-37.

Reproductive Endocrine Disorders and EEG Laterality in Women with TLE

	L TLE (N = 20)	R TLE (N = 16)
PCOS	7	1
HA	0	2
Normal	13	13

$\chi 2$: $p < .05$

Herzog AG et al. Ann Neurol 2003;54:625-37.

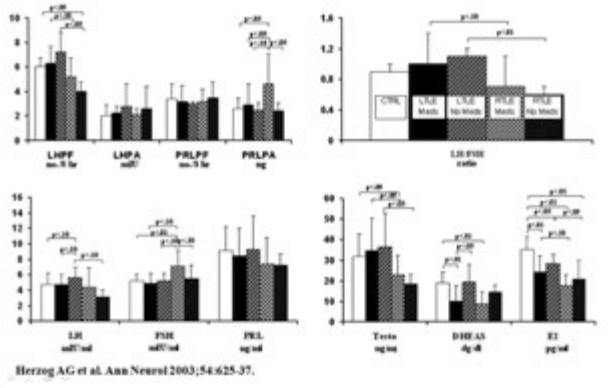
Reproductive Endocrine Disorders in Women with TLE

- PCOS
  1) occurrence in 8 of 36 (22.2%)
  2) more common with L TLE (7/20 = 35%) than R TLE (1/16 = 6.25%)
  3) more common among untreated (3/9 = 33.3%) than treated (5/27 = 18.5%) women with TLE

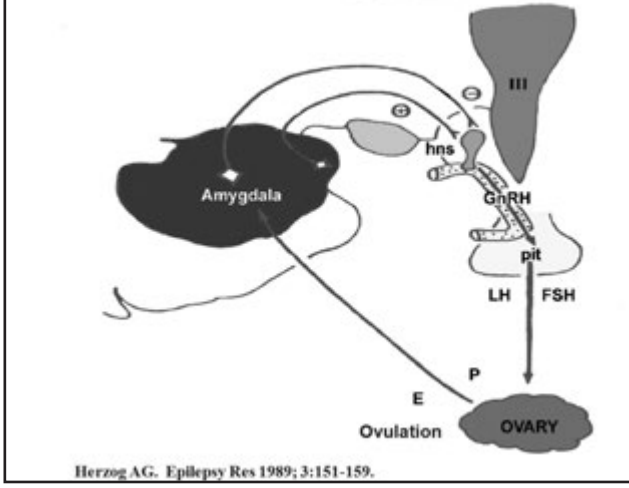
Herzog AG et al. Ann Neurol 2003;54:625-37.

Relationships Among EEG Discharges, Hormonal Changes and Menstrual Disorders

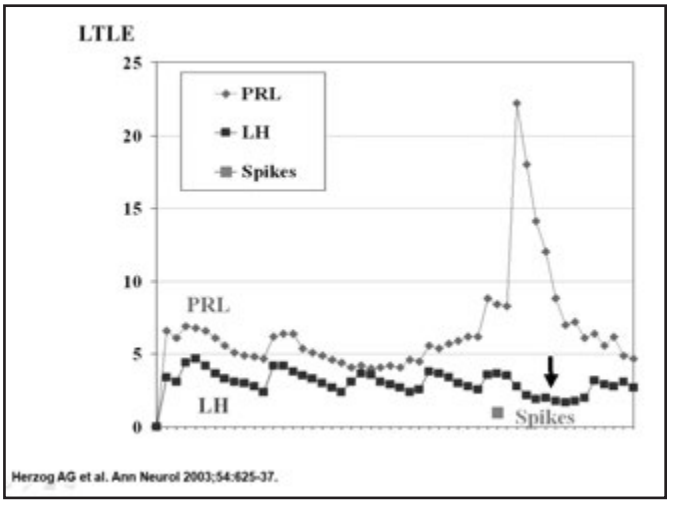
- Menstrual disorders were more common among women with TLE who had
  1) abnormal LHPF
     (8/14 = 57.1% vs 4/22 = 18.2%; p = .04)
     and
  2) interictal epileptiform discharges
     (9/18 = 50% vs 3/18 = 16.7%; p = .08).



Herzog AG et al. Ann Neurol 2003;54:625-37.



Herzog AG. Epilepsy Res 1989; 3:151-159.


LTLE
25
20
15
10
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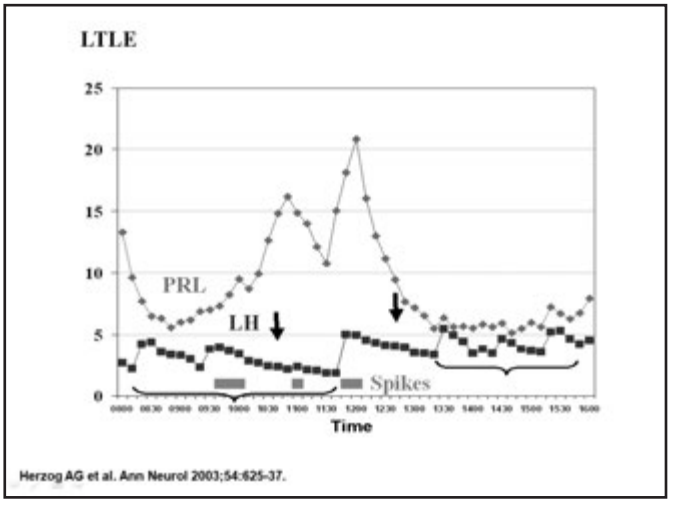
0
PRL
LH
Spikes
PRL
LH
Spikes
Herzog AG et al. Ann Neurol 2003;54:625-37.


LTLE
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PRL
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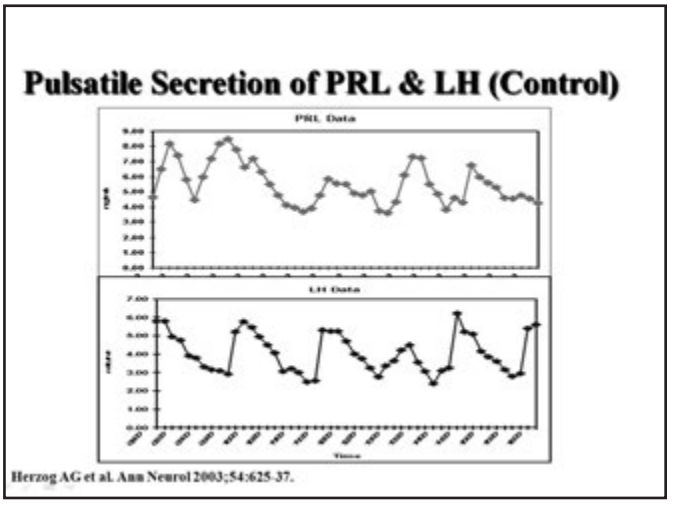
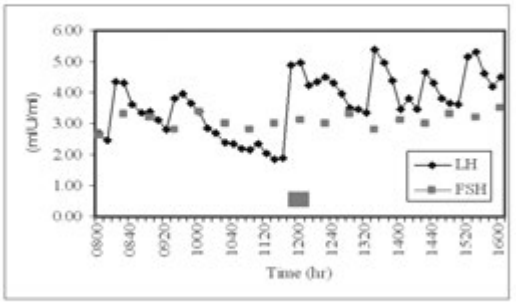
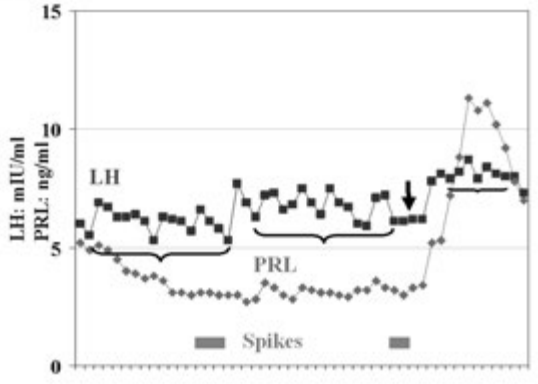
Spikes
Time
Herzog AG et al. Ann Neurol 2003;54:625-37.


Pulsatile Secretion of PRL & LH (Control)
PRL Data
LH Data
Herzog AG et al. Ann Neurol 2003;54:625-37.

LH/FSH Ratios in Women with TLE

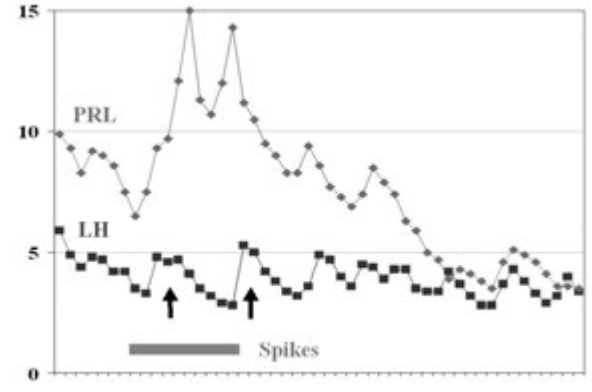


LTLE



Herzog AG et al. Ann Neurol 2003;54:625-37.

RTLE



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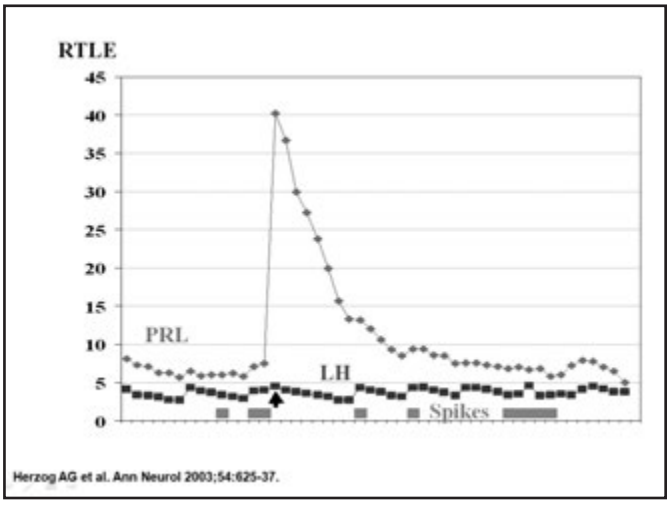
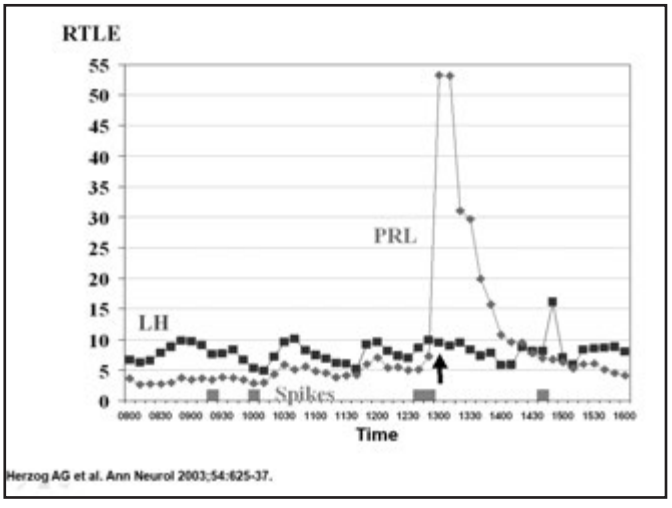


Herzog AG et al. Ann Neurol 2003;54:625-37.



Herzog AG et al. Ann Neurol 2003;54:625-37.

Acute PRL and LH changes following interictal epileptiform discharges

	L TLE (N = 10)	RTLE (N = 8)	χ^2-test: p value
Abnormal PRL elevation (peak/nadir > 2.5)	8 (80%)	7 (75%)	NS
Abnormal PRL elevation (peak value > 15.6 ng/ml)	2 (20%)	6 (75%)	.06
Loss of LH pulsatility (no peak for > 104.3 min)	8 (80%)	2 (25%)	.06
Abnormal ↑ (>27%) in mean baseline LH	8 (80%)	2 (25%)	.06

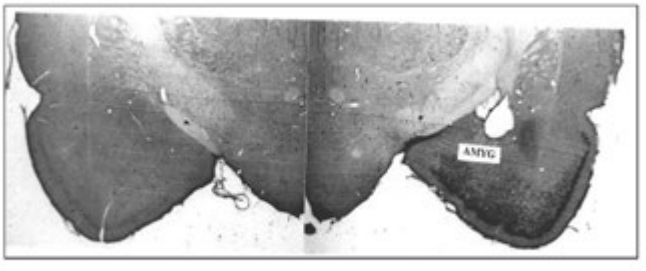
Epilepsy Effects on Hormonal Secretion and Reproductive Function in Women

- Epileptiform discharges can result in both acute and chronic changes in hormonal secretion at the hypothalamic, pituitary and gonadal levels
- The specific nature of hormonal changes may relate to the laterality and focality of the epileptiform discharges
- L and R TLE may promote the development and over-representation of different reproductive endocrine disorders: LTLE – PCOS (10-20% vs 5%), RTLE – Hypothalamic Amenorrhea (12% vs 1.5%)
- Menstrual dysfunction varies with the extent of endocrine deviation from the norm and the presence of interictal discharges

Basis for Lateralized Asymmetry in Reproductive Neuroendocrine Function

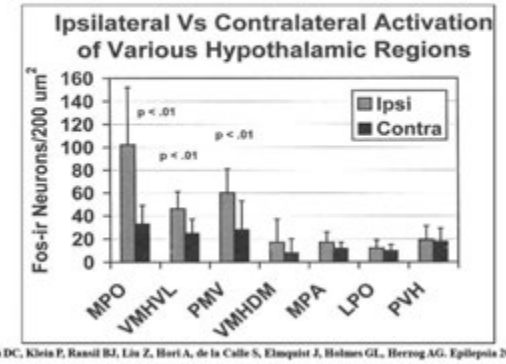
- Amygdaloid seizures have predominantly ipsilateral effects of on the hypothalamic regulation of reproductive function
- There are lateralized asymmetries in hypothalamic hormonal content and reproductive function

Lateralized Temporolimbic Activation of the Hypothalamus

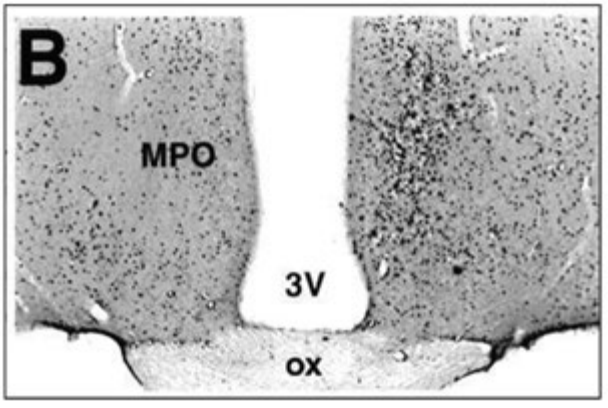


Silveira DC, Klein P, Ransil BJ, Liu Z, Hori A, de la Calle S, Elmquist J, Holmes GL, Herzog AG. Epilepsia 2000;41:34-41.

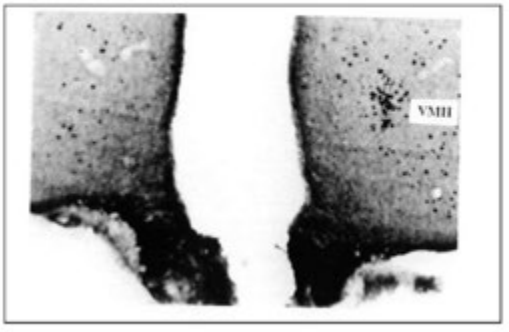
Ipsilateral vs Contralateral Activation of Various Hypothalamic Regions

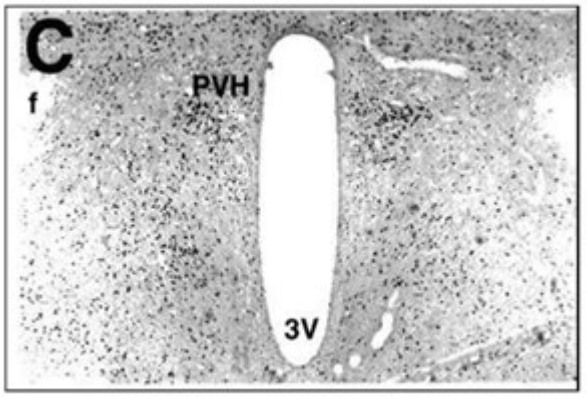


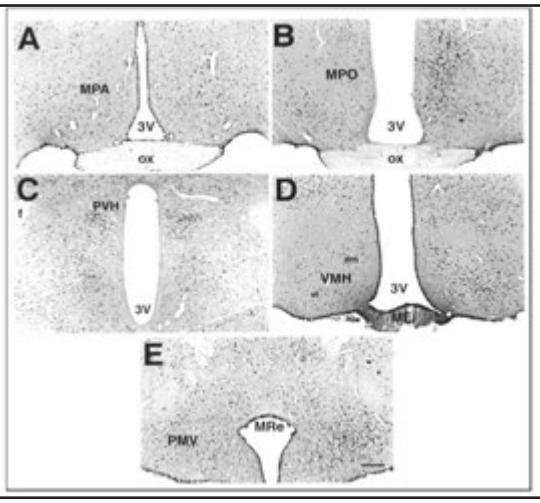
Silveira DC, Klein P, Ransil BJ, Liu Z, Hori A, de la Calle S, Elmquist J, Holmes GL, Herzog AG. Epilepsia 2000;41:34-41.



Lateralized Temporolimbic Activation of the Hypothalamus





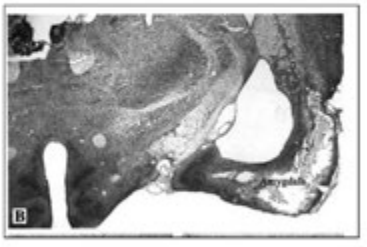


Lateralized Asymmetries in the Reproductive Neuroendocrine System

In female rodents

- ***GnRH content:*** 50-100% greater in R than L ventromedial hypothalamus (VMH) (Gerendai)
- ***Fos immunoreactivity in GnRH cells:*** R-L assymetry following E2 activation of GnRH release (Iglesia)
- ***Reproductive function:*** anovulatory cycles – more with R than L amygdalectomy (Sanches & Domingues)
- ***Endocrine function:*** unilateral ovx - ipsilateral decrease in VMH GnRH; bilateral ovx - R sided increase in VMH GnRH (Gerendai)
- ***Sexual behavior:*** E2 in L VMH – defeminization; E2 in R VMH – masculinization (Nordeen & Yahr)

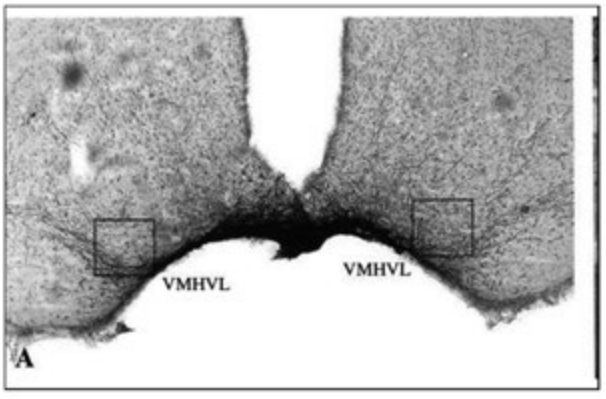
Effects of Seizures on GnRH Fibers

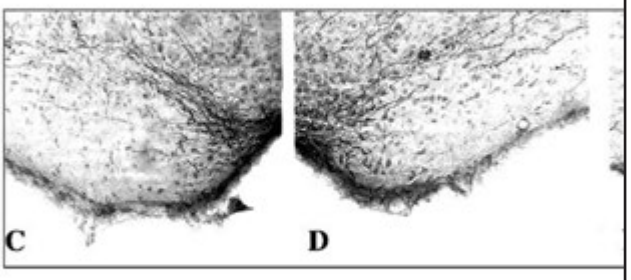


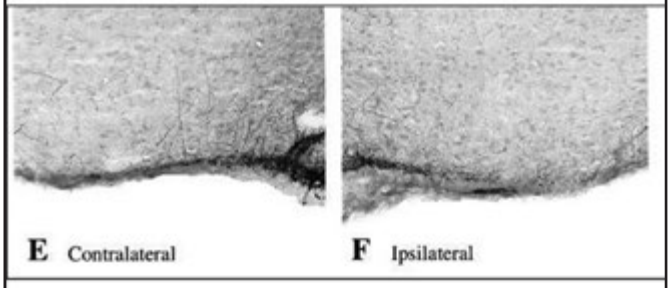
Friedman MN, Geula C, Holmes GL, Herzog AG. GnRH-immunoreactive fiber changes with unilateral amygdala-kindled seizures. Epilepsy Research 2002;52:73-77.

Lateralized Asymmetry in GnRH Fiber Staining After Unilateral Temporolimbic Seizures

				p-values		
	KA (N = 10)	S (N = 7)	C (N = 5)	KA v C	S v C	KA v Sal
VMH	28 (6-60)	79 (18-225)	73 (47-144)	0.06	NS	0.08
VMHi	*17 (3-52)*	*81 (9-216)*	*72 (47-167)*	*0.05*	*NS*	*0.05*
VMHc	*39 (6-73)*	*77 (18-234)*	*73 (54-89)*	*NS*	*NS*	*NS*
VMHi/c	*0.6 (0.23-1.2)*	*1.13 (0.92-1.2)*	*0.99 (0.73-1.3)*	-	-	*0.01*







AED Effects on Reproductive Hormone Levels

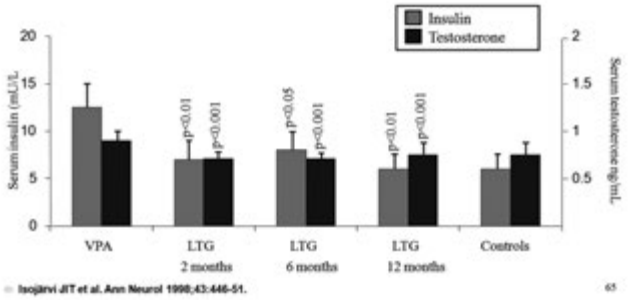
AEDs	SHBG	BAT	A	DHEAS	E2
Inducing *(PB,DPH,CBZ)*	↑	↓	↓	↓	↓
Inhibiting *(VPA)*	N	↑	↑	↑	N
Neutral *(LTG,GBP)*	N	N	N	N	N

1. Levesque LA et al. *J Clin Endocrinol Metab* 1986;63:243-5. 2. Isojärvi JI et al. *Epilepsia* 1988;29:781-786. 3. Isojärvi JI et al. *N Engl J Med* 1993;329:1383-1388. 4. Murialdo G et al. *Clin Neuropharm* 1998;56:31-6. 5. Morrell MJ et al. *CNS Spectrums* 2001;6:771-785. 6. Morrell MJ et al. *Epilepsy Res* 2003;54:189-99. 7. Herzog AG et al. *Ann Neurol* 2003; 54:625-37.

AED Effects on Reproductive Function

AEDs	Menstrual Disorders	Anov Cycles	Ovarian Cysts	Pathophysiology
Inducing *(PB,DPH,CBZ)*	12-43%	11-32%	13-28%	↓E2; ↑SHBG
Inhibiting *(VPA)*	18-59%	12-38%	10-60%	↑Androgens
Neutral *(LTG,GBP)*	-	-	-	-
Control	12-14%	10-11%	4-18%	

VPA-LTG Conversion Study
Serum Insulin and Testosterone Levels



Isojärvi JIT et al. Ann Neurol 1998;43:446-51.

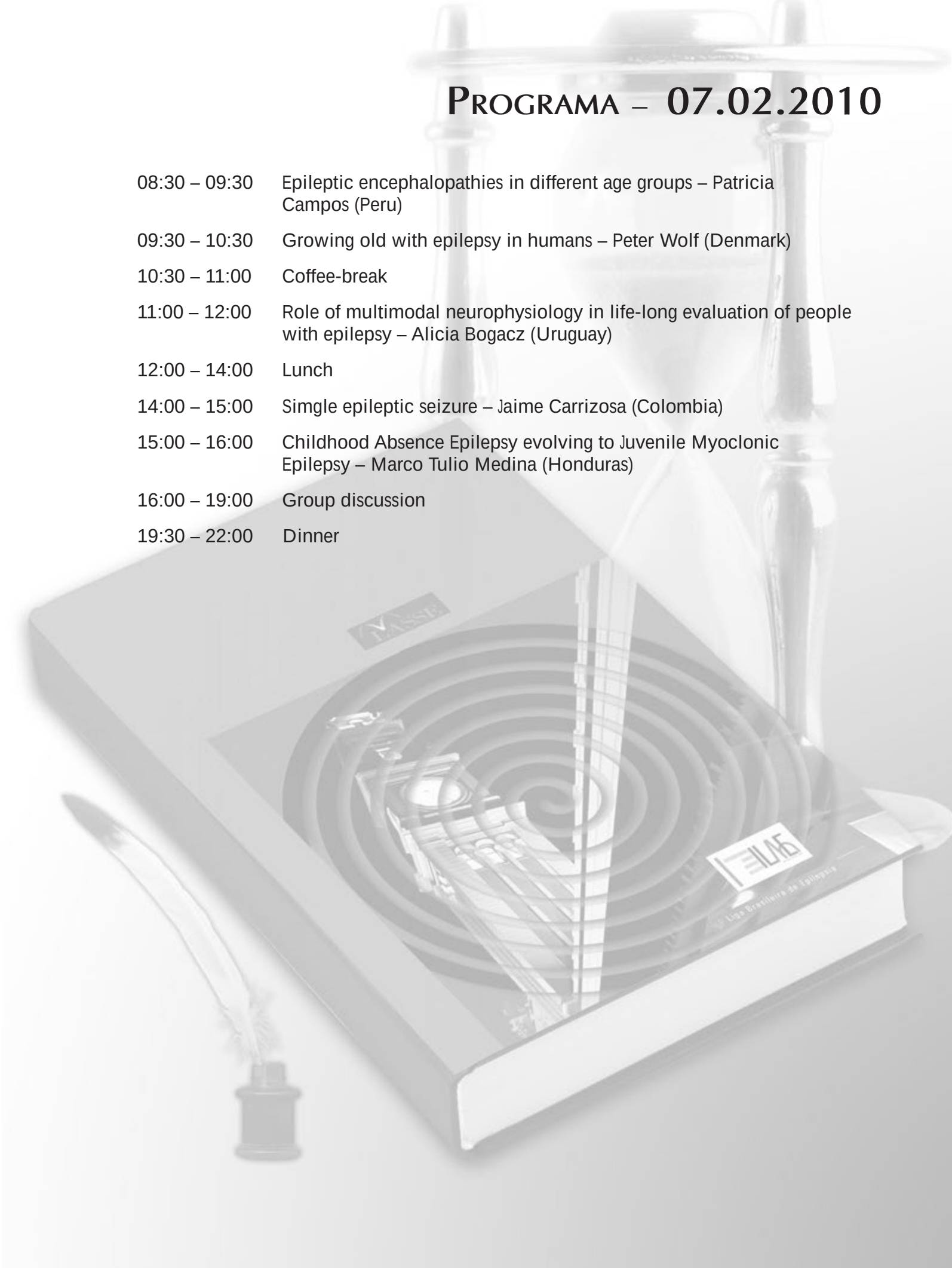
65

CONCLUSIONS

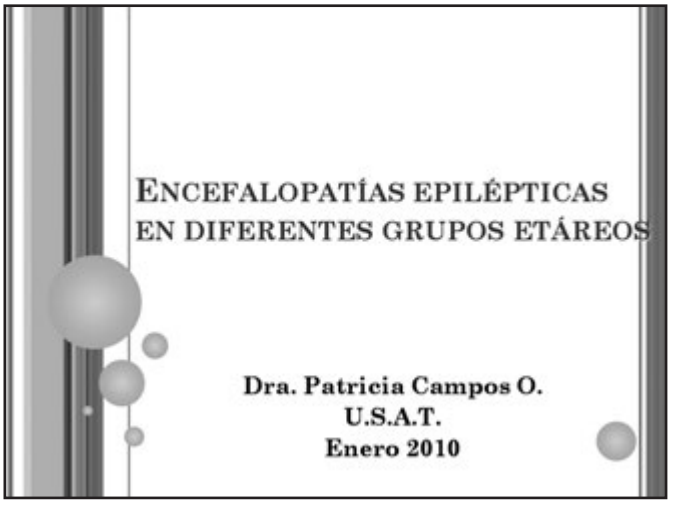
- Reproductive disorders are unusually common among women with epilepsy
- Disruption of ultradian and lunar patterns of GnRH secretion by epilepsy may be a factor
- Lateralized asymmetries in the temporolimbic modulation of the hypothalamo-pituitary-gonadal axis may promote the development of different reproductive disorders with L and R epileptic foci
- AEDs are another factor
- Enzyme inducing and inhibiting AEDs differ in their effects on reproductive hormones and function

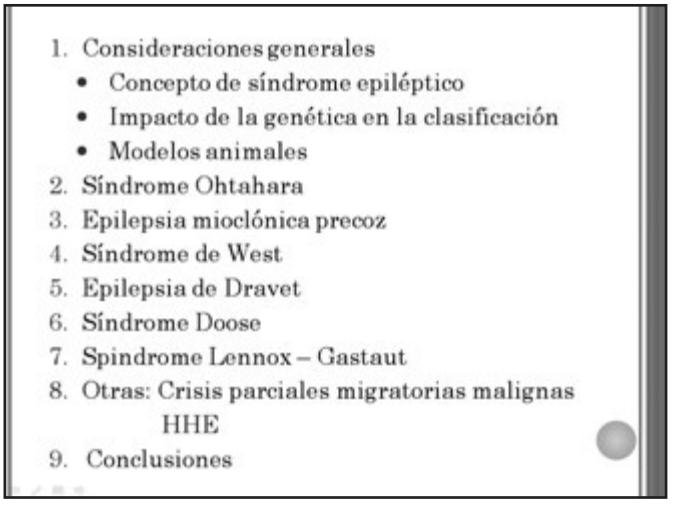
Programa – 07.02.2010

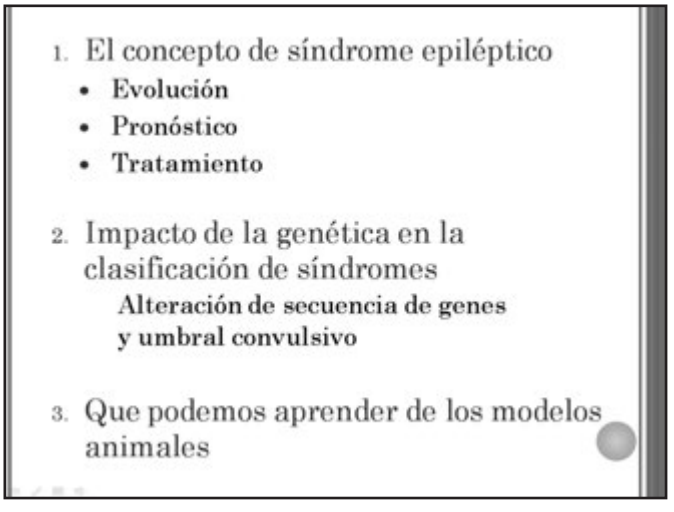
08:30 – 09:30	Epileptic encephalopathies in different age groups – Patricia Campos (Peru)
09:30 – 10:30	Growing old with epilepsy in humans – Peter Wolf (Denmark)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Role of multimodal neurophysiology in life-long evaluation of people with epilepsy – Alicia Bogacz (Uruguay)
12:00 – 14:00	Lunch
14:00 – 15:00	Simgle epileptic seizure – Jaime Carrizosa (Colombia)
15:00 – 16:00	Childhood Absence Epilepsy evolving to Juvenile Myoclonic Epilepsy – Marco Tulio Medina (Honduras)
16:00 – 19:00	Group discussion
19:30 – 22:00	Dinner



EPILEPTIC ENCEPHALOPATHIES IN DIFFERENT AGE GROUPS
PATRICIA CAMPOS (PERU)





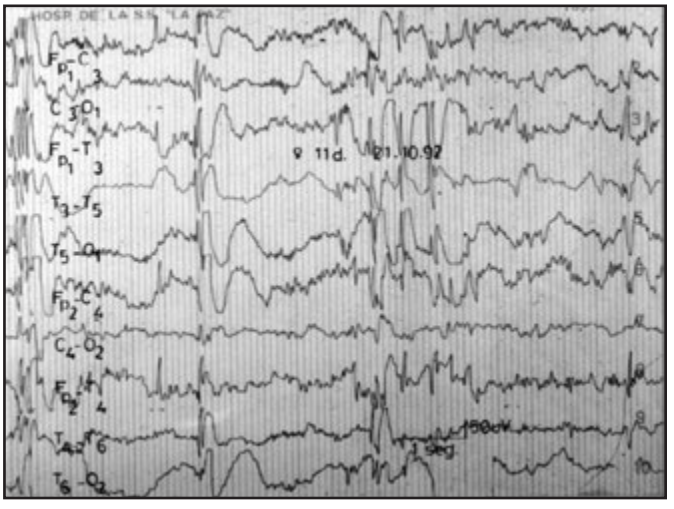


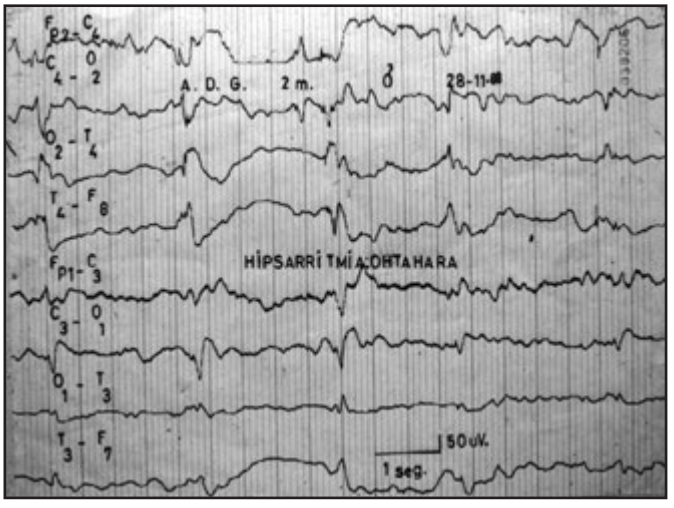
Síndrome de Ohtahara
(Lombroso 1990, Aicardi 1986, Kelley 1996)

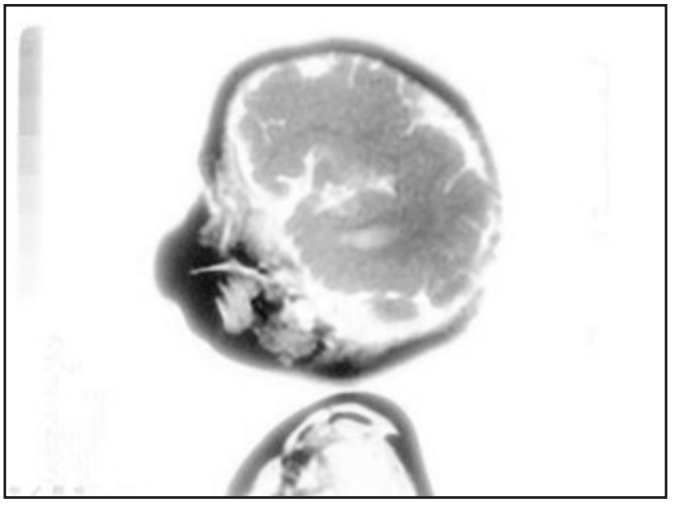
Inicialmente descrito en 1976	
Edad:	**20 días – 3 meses**
Clínica:	**Espasmos tónicos**
	Retardo psicomotor severo
	Crisis intratables
EEG:	**Burst – supresión en vigilia y sueño**
Etiología:	**Múltiple**
Pronóstico:	**Pobre**
Evolución:	**A síndrome de West y SLG**

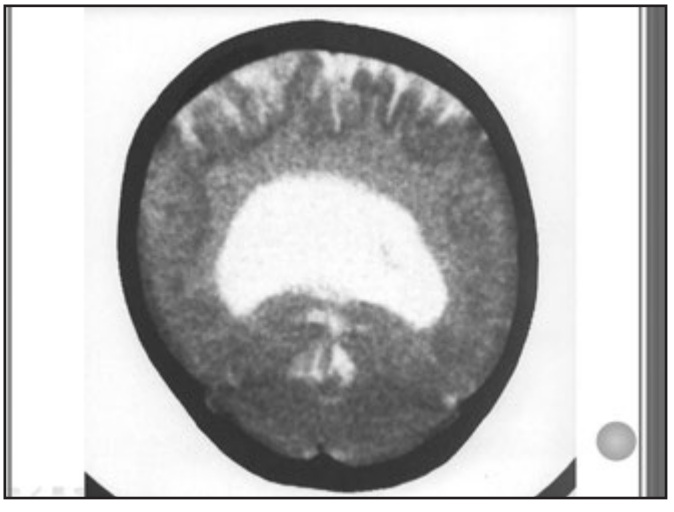
Síndrome de Ohtahara
(*Yamatogi Y, Ohtahara S., Brain Dev. 2002*)

- 16 pacientes
- Entre 1 día a 3 meses
- 7 Ohtahara-SW-SLG: murieron
- 9 con foco EEG: 1 murió y los otros sin crisis pero con RM severo




A. D. G. 2 m.
28-11-
HİPSARRİTMİA:OHTAHARA
50 uV.
1 seg.



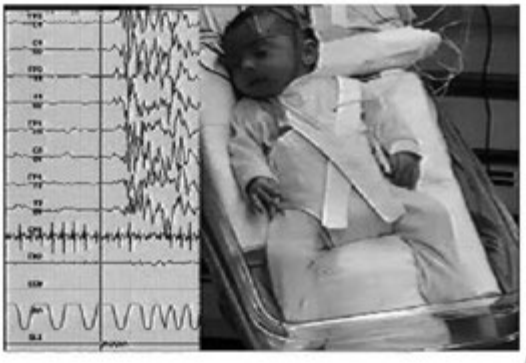


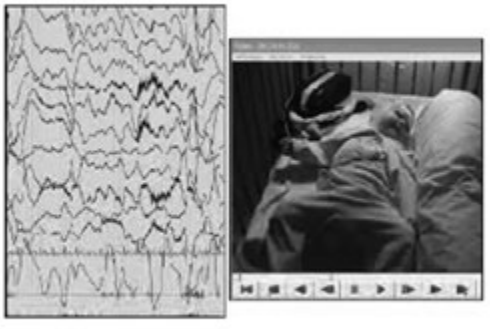
Síndrome de West

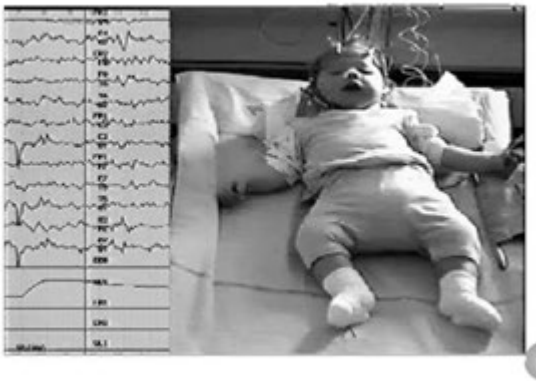
Edad:	3 – 6 meses
Clínica:	Espasmos infantiles en flexión y extensión
	Retardo psicomotor
EEG:	Hipsarritmia
Pronóstico:	Pobre
Etiologías:	Diversas

Respuesta al ACTH: Buena en 50%

Evolución: A síndrome de Lennox - Gastaut







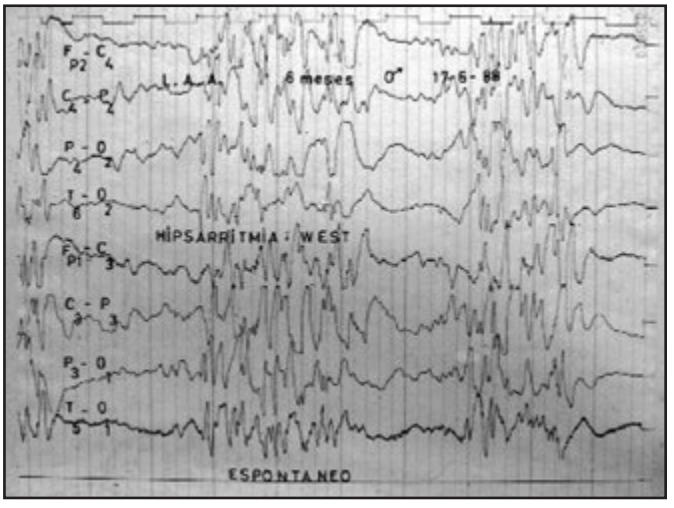
SINDROME DE WEST

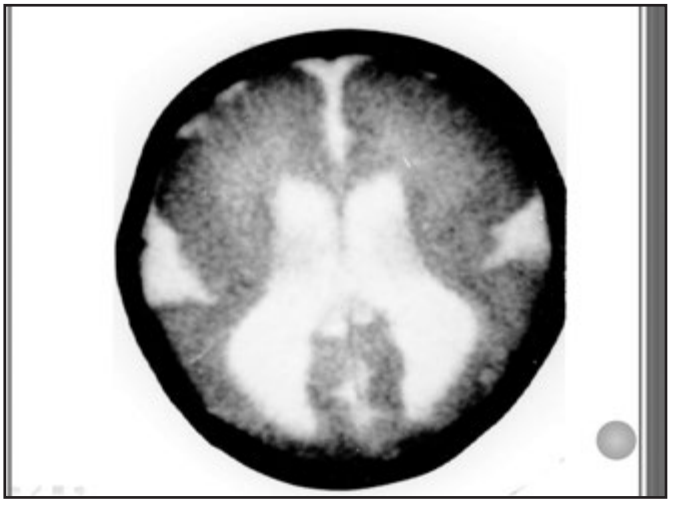
- Remisión espontánea:
  - 6- 15% en máximo 6 meses
  - 28% al año
- 50 – 60% epilepsia hasta 99% en 5 años
- 75% anormalidad EEG focal

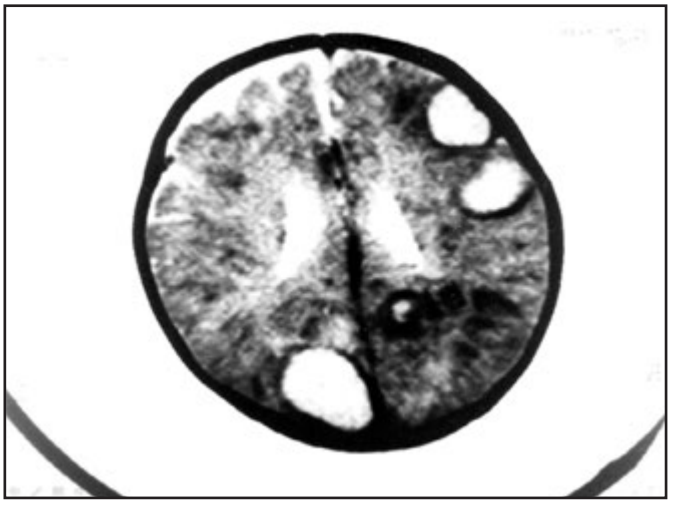
FACTORES GENÉTICOS EN SW

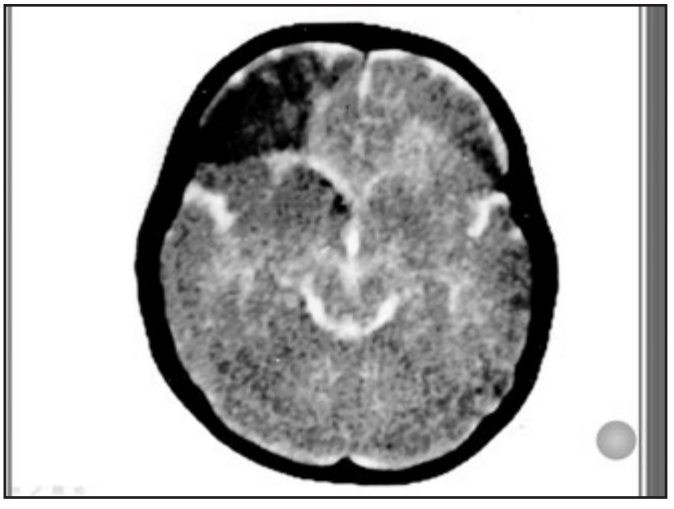
- 7 – 17% historia familiar de epilepsia
- 40% de incidencia familiar

(Matsumoto, 1981)


L. A. A.
6 meses
♂
17-6-88
HIPSARRITMIA : WEST
ESPONTANEO

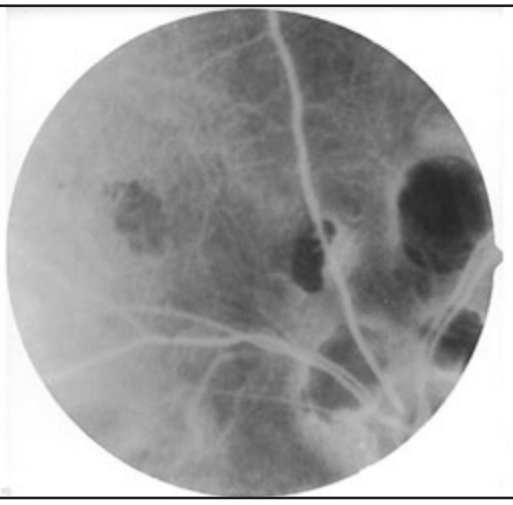






Síndrome de Aicardi

- Descrito en 1969
- Pacientes sexo femenino
- Espasmos infantiles
- Agenesia de cuerpo calloso
- Retardo mental
- Corioretinopatía específica
- Anomalías vertebrales
- EEG Característico



Tratamiento SW

1. Tx específico en función de etiología
   ACTH en SW criptogénico / VGB en SW sintomático

2. Dosis y duración de Tx

ESPASMOS INFANTILES
DIAGNÓSTICO DIFERENCIAL

- Mioclonus benigno de la primera infancia
- Epilepsia Mioclónica benigna
- Epilepsia Mioclónico – Astática
- Encefalopatía Mioclónica Precoz
- Reflejo de Moro
- Cólico abdominal
- Mioclonías del sueño
- Reacción de sobresalto

FACTORES QUE INFLUENCIAN LA EVOLUCIÓN DE SE A SLG

- *(Su Jeong You et al. Epilepsia 2009)*
  - 98 pacientes
  - Seguimiento 3 años
  - Sintomática 62 Cripto 36
  - 48/98
- No hay relación con edad de inicio del SW o etiología
- El riesgo de desarrollar SLG es significativamente menor si hubo uso de esteroides o dieta cetogénica

SLG DE INICIO TARDÍO Y CRISIS PREDOMINANTEMENTE REFLEJAS EN PACIENTES CON TRISOMÍA XXI

(FEILOZZO 2009)

- 13 niños (8 | - 5J)
- x inicio 9.1 años
- x seguimiento 23 años
- 62% luego de los 8 años
- No SW previo
- 69% crisis reflejas resistentes
- Maduración tardía del lóbulo frontal ó inicio temprano de cambios degenerativos en la misma zona cortical

REVISIÓN CRÍTICA DE UN MODELO ANIMAL EMERGENTE

C.E. STAFSTROM (EPILEP CURRENTS, 2009)

- Modelo animal idealmente válido
  - La ocurrencia de EI en respuesta a varias etiologías
  - Una ventana específica de desarrollo
  - Un tiempo de aparición en relación a ciclo vigilia – sueño
  - La presencia de "salvas"
  - Intentar comprender la fisiopatología a través del modelo animal
  - CRH y el rol del stress en el cerebro en desarrollo
  - Modelo NMDA: EI criptogénicas
  - Modelo síndrome Down: ratón Ts 65 Dn

EPILEPSIA MIOCLÓNICA PRECOZ

- *Aicardi 1978*
- *Dalla Bernardina 1983*
  (encefalopatía mioclónica neonatal)
- 3 primeros meses
- EEG: **burst-suppression predominantemente en el sueño**
- Varios otros tipos de crisis
- Alta incidencia de casos familiares
- Frecuentemente sin lesión demostrable
- Alta mortalidad
- Asociación con hiperglicinemia no cetósica

SÍNDROME DE DOOSE: EPILEPSIA MIOCLÓNICO-ASTÁTICA

(PM CENTROENCEFÁLICO MIOCLÓNICO-ASTÁTICO, *DOOSE 1970*)

- 1-5 años (x 3-4 años)
- Niños normales
- Predominancia en varones
- EEG: 2-3Hz bilateral y sincrónico
- Raramente es orgánica
- Fuerte sospecha de causa genética
- Pronóstico variable
  - *Lagenstein (1980)* 58 pacientes
    77% siguen normales en seguimiento a 7 años

Pronóstico malo: Persistencia de ritmo theta
TCG en el primer año
SE no convulsivos y tónicos

SÍNDROME DE DRAVET

- **Epilepsia mioclónica severa**
- **Antecedente CF atípica**
- **Epilepsia polimórfica**
- **Claes (2001) nueva mutación en canal Na+ (gen SCN1A)**
- **Regresión del desarrollo**
- **Alta morbi - mortalidad**

Síndrome de Dravet

- Se describen tres estadíos evolutivos bien definidos, descritos por *Lamberri et al*, como fase febril, fase catastrófica y fase de secuelas.
- ***Fase Febril:*** Crisis entre 3 y 8 meses, clónicas generalizadas o unilaterales, de duración variable, precipitadas por fiebre con recurrencia temprana, EEG y DPM normal. Luego crisis afebriles.

Síndrome de Dravet

- ***Fase Catastrófica de Estado:*** A partir de los 2 años, aparecen crisis afebriles, mioclónicas, estados convulsivos y crisis polimorfas, resistentes a tratamiento, con EEG paroxístico.
- ***Fase de Secuelas o de Deterioro Neuropsicológico:*** Constituye el estadio final con un deterioro neurológico y cognitivo grave. Se inicia entre 6 y 12 años, coincidiendo con la disminución o desaparición de crisis sobretodo las mioclonías.

Síndrome de Dravet

Pac.	Sexo	Complic. natales	Antecedentes perinatales	Antecedentes familiares	Inmunización previa a inicio de crisis	Desarrollo psicomotor
1	Fem.	No	Ninguno	No	DPT 1ª dosis	Deterioro leve Hipotonía global Retraso del lenguaje
2	Fem.	No	Ninguno	No	DPT 2ª dosis	Deterioro leve
3	Fem.	No	Ninguno	No	DPT 3ª dosis	No deterioro
4	Fem.	No	Ninguno	Si	DPT 3ª dosis	Deterioro leve
5	Masc.	No	Ninguno	no	No	Deterioro severo

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Síndrome de Dravet

Pac	Edad	1ª crisis				Intervalo a 2ª crisis	Inicio de mioclonías	Estado epiléptico		
		Edad	Post vacunal	Tipo	Asociado a fiebre			Edad	Tipo	Asociado a fiebre
1	6a	3m	Si	TCG	Si	5m	No	3m	TCG	Si
2	2a 6 m	5m	Si	Parcial	Si	1m	No	1a 5m	TCG	No
3	3a	4m	Si	TCG	Si	1m	No	–	–	–
4	6a 5m	6m	Si	Parcial	Si	5m	No	–	–	–
5	8a 10m	8m	no	Parcial	Si	1m	3 años	1a 6m	No datos	Si

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HALLAZGOS EN RMN EN EPILEPSIA DE DRAVET Y CORRELATO GENOTIPO-FENOTIPO

(P. Striano et al, Epilepsia 2007)

- 58 pacientes: 60% mutación SCN1A
  22.4% RMN anormal
- Las que no tenían la mutación tenían RMN anormal.

TRATAMIENTO

- Valproato de sodio
- Topiramato
- Stiripentol
- Zonizamida
- Dieta cetogénica
- **No:** DPH
  PB
  CBZ
  LMT

Síndrome de Lennox Gastaut

Edad: **A partir de 2 años**

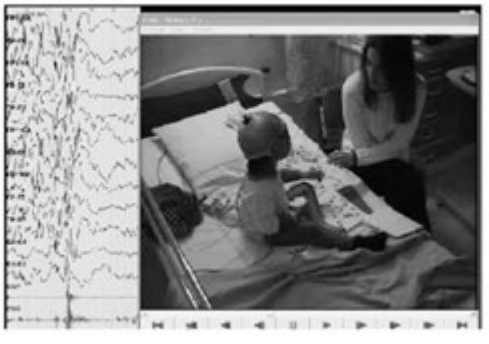
Clínica: **Crisis mixtas (ausencias atípicas, tónicas y atónicas más frecuentemente)**
Retardo Mental y/o demencia asociados

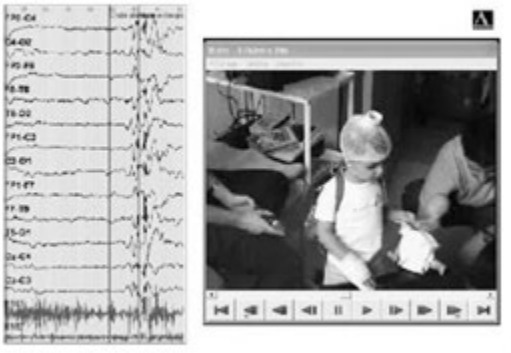
EEG: **Punta-onda menor que 2.5 Hz**

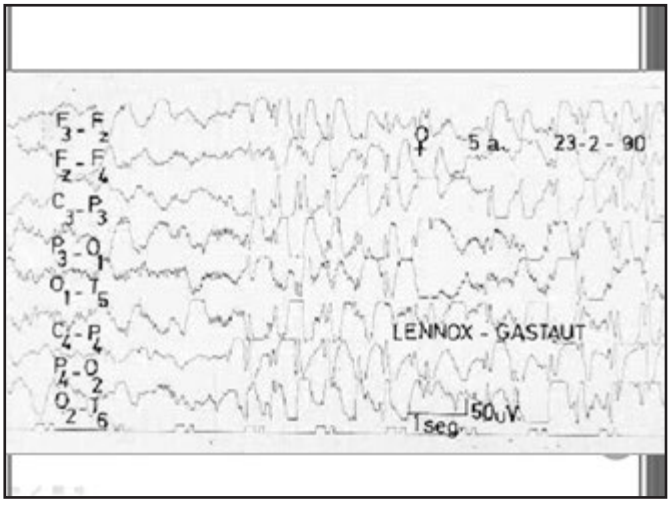
Etiologías: **Diversas**

Respuesta aL ACTH: **Pobre**
Resistencia a terapia anticonvulsivante convencional

Pronóstico: **Pobre**

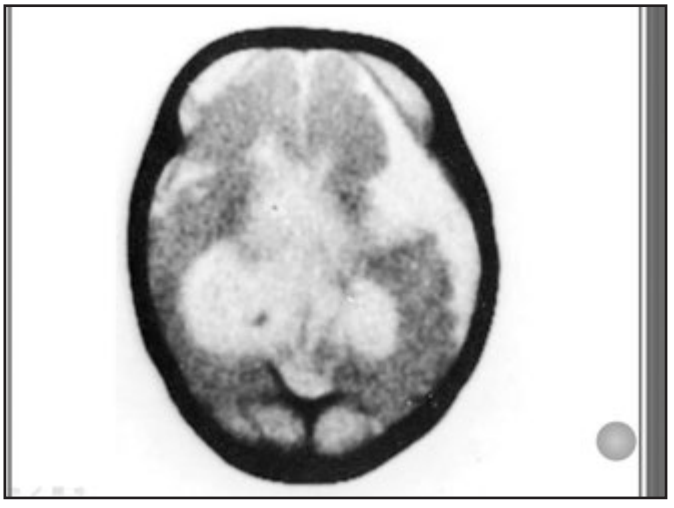


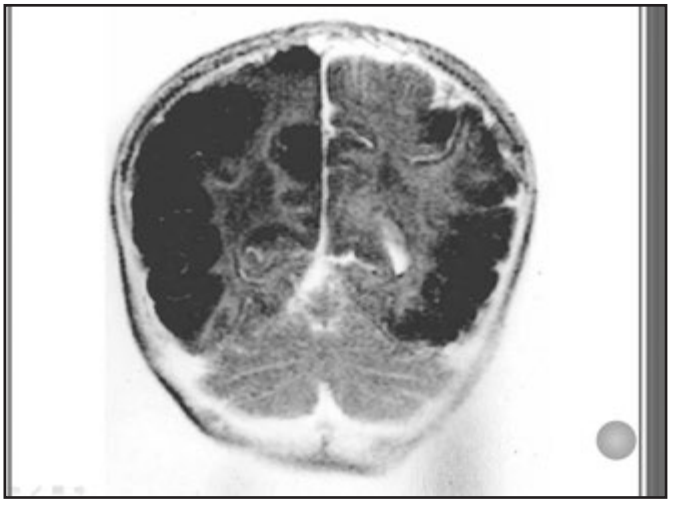


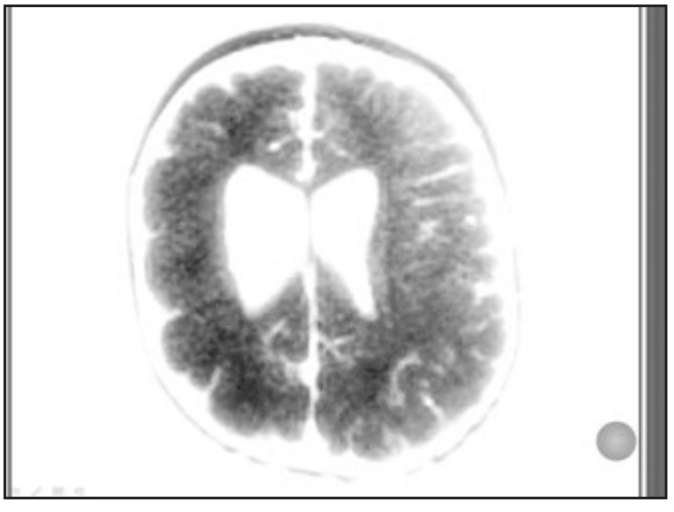


NEUROIMÁGENES EN SLG

- Atrofia cortical difusa: 75%
- PET no anomalías consistentes pero si disminución difusa del metabolismo cortical en aprox.50% *(Chugani H, 1987)*







- El síndrome crisis gelásticas-hamartoma hipotalámico: encefalopatía severa y potencialmente reversible.

S. Striano et al, Epilepsia 2009

Casuística H.C.H. (1983-2005)

128 pacientes
3 OHT
53 SW
72 SLG

Edad de Inicio	OHT	SW	SLG
< 6 meses	3	37	48
< 2 años	0	16	21
> 2 años	1+	0	3

Etiología	OHT	SW	SLG
Sintomática	3	36	59
Criptogénica	0	11	13
Idiopática	0	6	1
Desconocida	0	0	1

CONCLUSIONES

- La clasificación de síndrome epilépticos actualmente electro clínica debe y esta siendo revisada a la luz de los hallazgos genéticos
- El cerebro en desarrollo tiene respuestas diferentes frente a SE y a diferentes ventanas de ocurrencia de crisis
- Existen factores de riesgo diferentes para grupos de pacientes que pasan de uno a otro tipo de encefalopatías epilépticas (EE)
- La mayor parte de estas EE son refractarias a tratamiento médico y tienen mal pronóstico
- Otras formas de tratamiento no médico están siendo usadas.
- Los modelos animales nos sirven actualmente para comprender la fisiopatología de la ocurrencia de crisis, características de las EE.

Muchas Gracias

Growing old with epilepsy in humans
Peter Wolf (Denmark)

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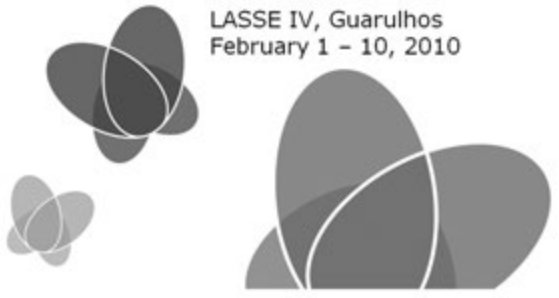
Growing old with epilepsy in humans
Peter Wolf (Denmark)



LASSE IV, Guarulhos
February 1 – 10, 2010

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"Growing old with": long-term course of epilepsies starting earlier and continuing into late adulthood

- Three possible developments:
  1. Improvement
     - remission (conditional or unconditional)
     - no disabling seizures
  2. Continuation
     - with or without change in presentation
  3. Deterioration
     - (or remanifestation)

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Age-relation and remission

- Many epilepsy syndromes are "age-related"
- Refers commonly to age of onset
- May also refer to age of remission (e.g. in benign childhood epilepsies)
- In these syndromes remission usually is "unconditional" (no more drugs required)
- It seems to be due to some qualitative mechanism
- Otherwise remission has been little investigated
- It is often "conditional" (i.e. dependent on drug intake)
- Growing old with epilepsy may mean to grow old without seizures but with life-long intake of drugs - example?

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Seizure propensity and seizure threshold

- Whereas "seizure propensity" sums up all the factors which facilitate the generation of seizures,
- "seizure threshold" sums up all intrinsic factors which counteract generation of seizures. These factors are less well known.
- A seizure would occur when the seizure propensity rises above the seizure threshold,
- in other words: when the sum of facilitating factors is higher than the sum of protective factors:
- Epilepsy needs to be seen as a dynamic condition.
- That is what the patient is growing old with

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The therapeutic threshold

- Whereas seizure propensity and seizure threshold are to some extent theoretical concepts that can help us to understand the dynamics of ictogenesis but cannot be measured,
- the therapeutic threshold can be calculated.
- It is the level of antiepileptic drug (AED) action which needs to be surpassed to prevent seizures at the time when the interaction of facilitating and protective factors is most unfavourable for the patient, i.e. when the risk of a seizure is highest.

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Seizure propensity, thresholds and remission

- A high therapeutic threshold reflects a high seizure propensity or a low seizure threshold or both
- Remission could be due to a decrease of sz propensity or an increase of sz threshold
- In either case it would be reflected by a decrease in the therapeutic threshold
- This we have attempted to study with longitudinal antiepileptic drug monitoring in seizure free patients undergoing reduction and discontinuation of AEDs

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Different types of remission in human epilepsies

- Wolf P, Pastuchova T, Mataringa M. *Decline in seizure propensity in seizure-free patients as reflected in the evolution of the therapeutic antiepileptic drug threshold.* Epilepsy & Behavior 8 (2006) 384-390

117 pat seizure free on monotherapy in slow AED withdrawal.	**Extent of reduction**	**Relapses (51= 43.6%)** ***(No relapse: 66, of which 30 off drugs)***
(after 2 – 5 years without seizures)	<50% 50 (42.7%) ≥ 50% 32 (27.4%) off drugs 35 (29.9%)	1st red. 5 (4.3%) <50% 28 (23.9%) ≥ 50% 13 (11.1%) off drugs 5 (4.3%)

The mechanisms of remission are diverse and may be both qualitative or quantitative. The no-relapse group may include patients with intrinsic spontaneous remission

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Those who relapse have to grow old *with* epilepsy?

- If the fall of SP were always either qualitative, or quantitative but limited, the patient would either become seizure free without drugs or require continuous treatment above a new TT.
- If the fall of SP is quantitative and gradual, it would be possible, in these cases, to take AED taper up again after a relapse – respecting a new seizure free interval.

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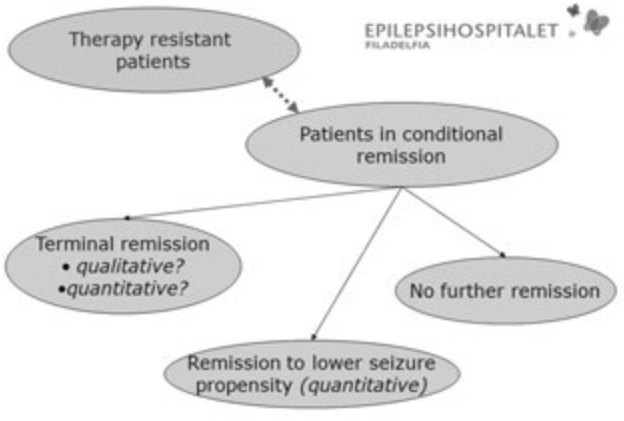

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Course after 2nd reduction

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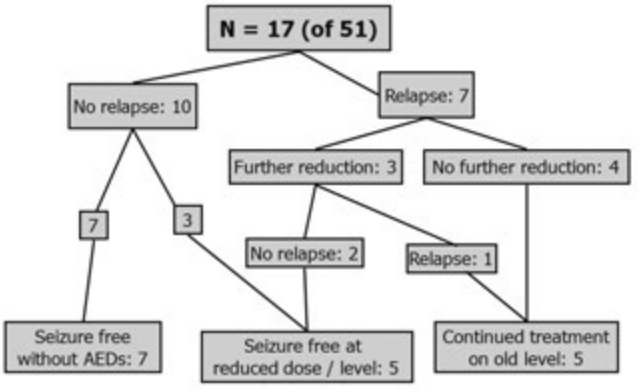

Conclusion

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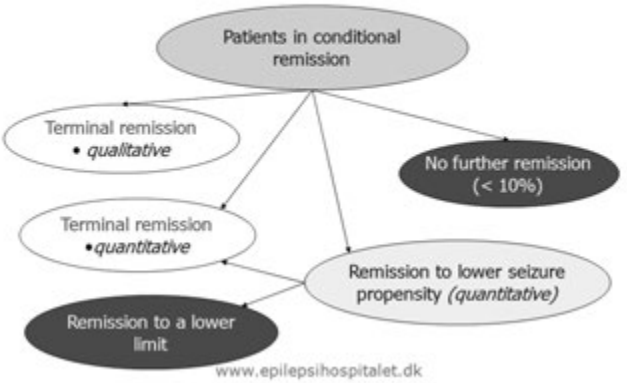

A 22 year development of seizure propensity

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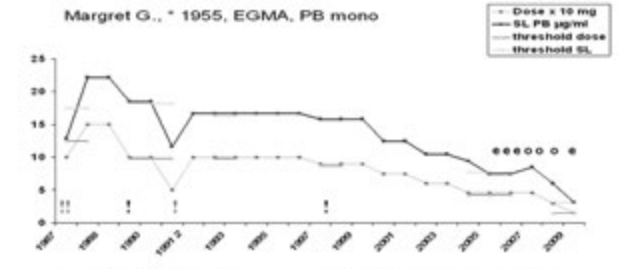

! = unprovoked seizures ! = seizures with non-compliance

e = runs of generalized spike – waves for 40 sec, subclinical o = normal EEG

ITT (1987) 125 mg (17.5), TT$_0$ (1991) 100 (16.3), last TT (2009) 15 mg (3.1)

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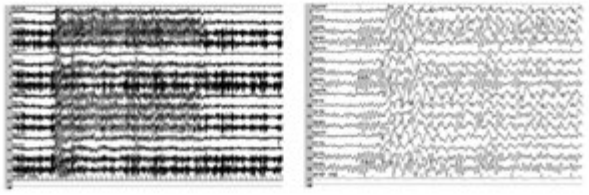

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Conclusions about remission

- Some epilepsy syndromes have an intrinsic mechanism of termination
- Not all these sydromes have yet been identified
- In patients with conditional remission (i.e. seizure free with AED treatment) usually a descrease of seizure propensity occurs which is reflected in a decrease of the therapeutic AED threshold
- The decrease may be limited:
  - sz propensity stays above seizure threshold
  - life-long treatment required
  - (like in drug-resistant patients)

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Conclusions about remission (cont.)

- Processes of quantitative remission may also end up with unconditional remission: sz propensity falls below individual seizure threshold
- *Seizure propensity* and its counterpart *seizure threshold* are theoretical concepts and could be summary effects of many contributing factors
- Quantitative mechanisms of remission require time and are not necessarily linear

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Some specific developments

- PRE + JME
  - The two syndromes often share a reflex epileptic trait, i.e. orofacial reflex myocloni (ORM)
  - Some patients develop the full picture of both syndromes which then each take its typical time course (Radhakrishnan et al. *Brain 1995; 118: 75-89;* Wolf P, Mayer Th, Reker M. *Seizure 1998; 7: 271-279*)
  - Best-known example of two different epilepsy syndromes in one patient. Probably due to shared gene for ORM

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An unusual development

- Female pat *1960. Febrile convulsions (hereditary)
- GTCS on awakening since age 11, sporadic absences starting at about the same age: JAE.
- First seen age 25 with a record of 38 GTCS; absences?
- 24 hr EEG: 27 groups of generalised 3 hz SW, lasting 5 to 24 sec, apparently subclinical
- Student of philosophy; paints, plays piano, sports, ballet
- Declared non-complier (takes less than prescribed, regularly)
- Occasional hospital admission after seizure.
- Twice near-drowning with seizure in pool
- From age 25 to 31 another 38 GTCS

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Pat with JAE (cont.)

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- At age 32 change in attitude. Wants seriously to get rid of epilepsy. VPA mono, SC 117 µg/ml
- Avoidance of precipitating factors: sz continue
- Wants to try only self-control without drugs, under supervision
- Cautious slow withdrawal of VPA: in 15 mths without drugs 13 GTCS, in preceding 12 mths with VPA: 16
- No absences; EEG: no spikes and waves!
- The JAE has remitted

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Pat with two epilepsies (cont)

- Resistant to LTG (postictal level of 5.9 µg/ml)
- GTCS start now with tonic contraction of left arm
- EEG: some slow activity on the right
- Treated with DPH: seizure free since 10 years, initial therapeutic threshold at 13.5 µg/ml
- Patient is now, at age 49, in slow reduction (with one relapse 5 years ago). Therapeutic effect now at 6 µg/ml
- Apart from the peculiar epileptological situation with an IGE followed by cryptogenic focal epilepsy: the patient is an excellent example of the ontological and emotional challenges of epilepsy

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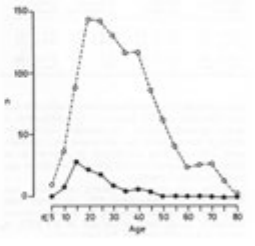
Other specific developments: photosensitivity

- Age distribution of patients in Berlin seizure clinic
  - ----- ***non-photosensitive***
  - —— ***photosensitive***
- Delayed diagnosis of JME, delayed treatment of jerks and prognosis



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More specific developments

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Absence status in elderly persons

- Age 55+
- Vast majority females
- Often precipitated by Benzodiazepine withdrawal
- Untreated at the time, often ill-remembered history of mild IGE in adolescence (few GTCS, sporadic absences), very rare interval seizures: prototype of re-manifestation

- Thomas P et al. *'De novo' absence status of late onset: Report of 11 cases.* Neurology 1992; 42:104-110
- Bauer G et al. *Absence status in the elderly as a late complication of idiopathic generalized epilepsies.* Epileptic Disorders 2007; 9: 39-42
- Fernandez-Torre JL, Rebollo M. *Typical absence status epilepticus as late presentation of idiopathic generalised epilepsy in an elderly patient.* Seizure 2009; 18:82-83

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Role of menopause?

- Is the de novo absence status related to menopause? (unlikely because of delay)
- Many patients with non-remitted epilepsy hope that their seizures will decrease in menopause.
- This appears to be a logical development in catamenial epilepsy
- Anecdotal reports
- The matter has been very little investigated and the possible effects are obviously not striking.
- Røste LS et al. Does menopause affect the epilepsy?. Seizure 2008;17:172-175

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Patients who are not seizure free

- Employment
- Driver's licence
- Mobility
- QOL
- Seizure-related complications

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Examples: complications

- Physical
  - trauma
  - status epilepticus
  - side effects of treatment
  - SUDEP
- Psychical
  - depression and suicide
  - control perceptions, self-estimation
  - learnt helplessness
- Social

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Complications : delayed side-effects

- PB: frozen shoulder, M. Dupuytren and other reactions of the connecting tissue
- VPA: chronic encephalopathy
- CBZ / OXC: water retention (hyponatremia)

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About side effects

- Our principal therapeutic aim is complete seizure control without inacceptable side effects
- What makes a side effect acceptable?
  - That it is slight
  - That it provides freedom of seizures
  - That it is hopefully temporary

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Epilepsy as a social condition

- Driver's licence
- Independent living
- Epilepsy and employment
- Insurance

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Employment

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- To get employment and earn one's own living is an important source of satisfaction and independence
- One of the important aspects of comprehensive care for epilepsy therefore is to help the patients overcome possible obstacles to employment
- Full seizure control makes increases the chances to get employment
- To have a job helps to structure the day which can improve the therapeutic success
- However, in patients who get old with (uncontrolled) seizures stress at the workplace may have a negative effect.
- Such patients may experience an improvement of epilepsy when they retire

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Examples of a fulfilled life with epilepsy

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Edward Lear 1812-1888

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Fyodor M. Dostoyevsky (1821-1881)

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Declined medical treatment (bromides) for fear that it would affect his creativity

Major works with epileptic characters

The Insulted and the Injured (1861)
Idiot (1868/69)
Devils (1871/72)
Brothers Karamazov (1879/80)

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Joaquím Maria Machado de Assis 1839 - 1908

- Dominant figure of Brasilian literature
- Founder and President of Brasilian Academy of Letters
- Humble extraction, half-mulatto
- Life-long epilepsy, probably right TLE
- Tried to hide diagnosis which, however, was widely known and did not affect the great respect he enjoyed

Akira Kurosawa (1910-1998)

- Mentions in his autobiography seizures diagnosed as epileptic, probably complex partial
- No concern
- Not affected by them

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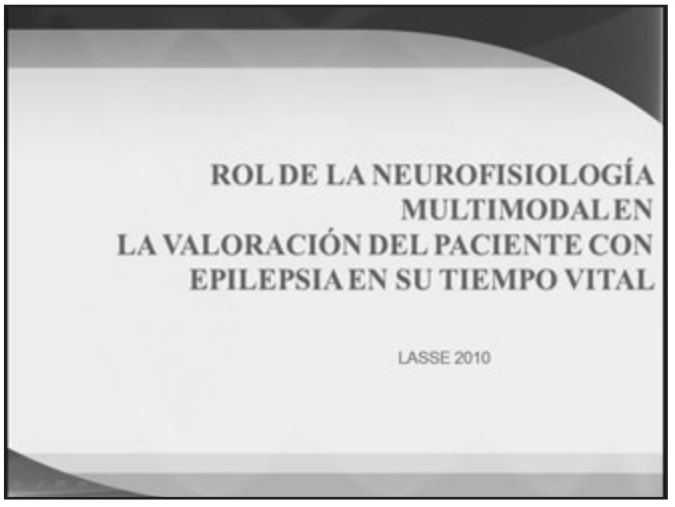
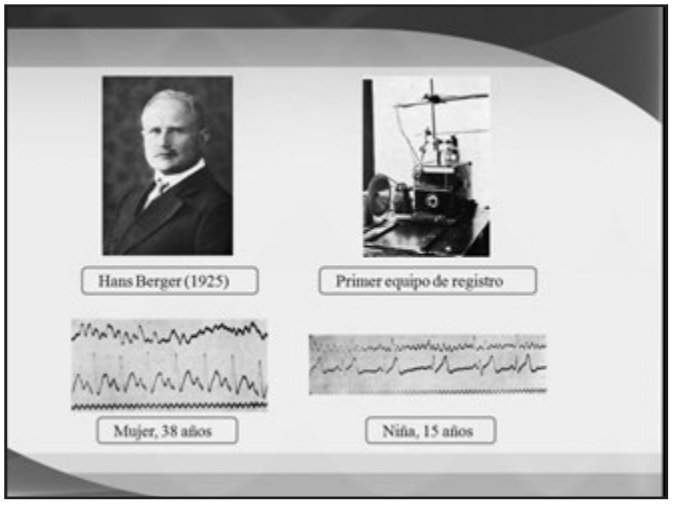
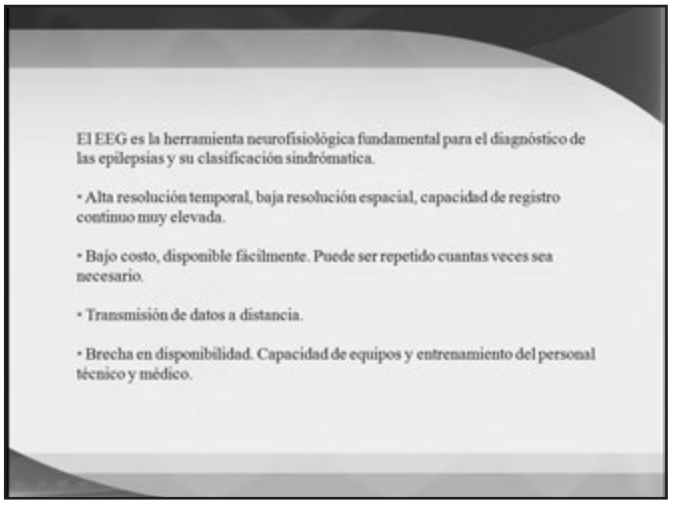
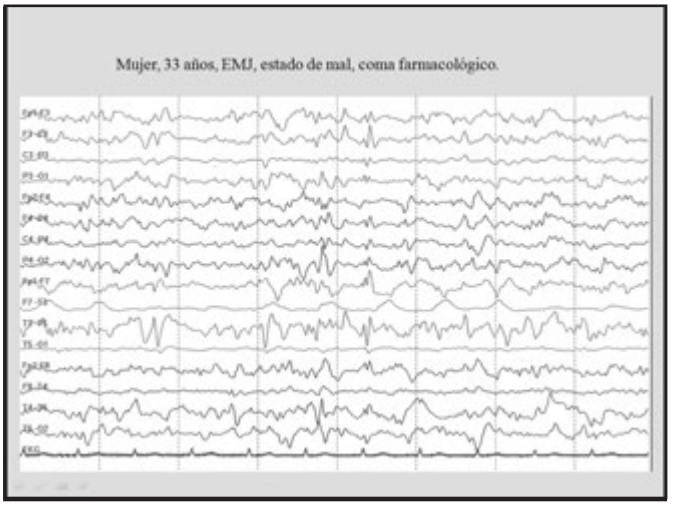
Role of multimodal neurophysiology in life-long evaluation of people with epilepsy

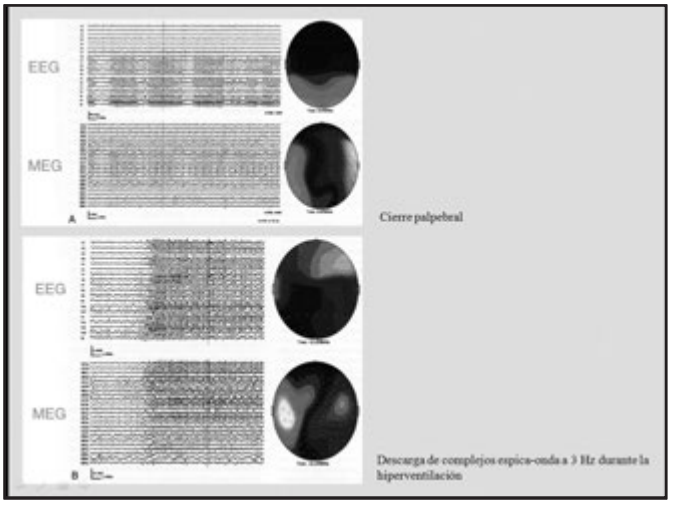
Alicia Bogacz (Uruguay)

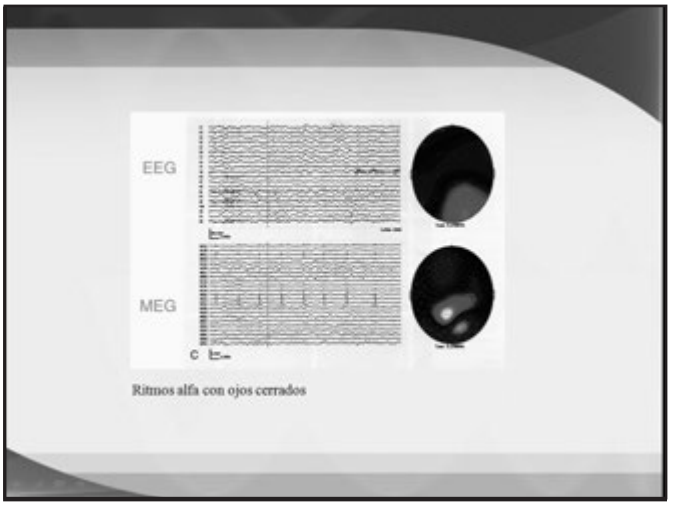







Mujer, 33 años, EMJ, estado de mal, coma farmacológico.


EEG
MEG
A
Cierre palpebral
EEG
MEG
B
Descarga de complejos espica-onda a 3 Hz durante la hiperventilación


EEG
MEG
C
Ritmos alfa con ojos cerrados

POTENCIALES EVOCADOS

Se extraen del EEG, que es una mezcla de actividad espontánea e inducida por estímulos internos y externos, por su relación temporal con el estímulo.

Edgar Douglas Adrian

POTENCIALES EVOCADOS

FACTORES QUE DETERMINAN EL REGISTRO:

- Tipo de estímulo:

- Visuales fóticos o de formas (Pattern) a diferentes frecuencias, intensidades, colores, tamaños y condiciones de iluminación.
- Auditivos clicks o tonos, a diferentes intensidades y frecuencias.
- Somestésicos muy variados, lo más frecuente son pulsos eléctricos.

POTENCIALES EVOCADOS

- Parámetros de registro:

- Lugar de registro en relación con posiciones del sistema 10-20 para EEG. Determina que se registren potenciales de campo cercano o alejado.
- Tiempo de análisis (Precoces y tardíos)
- Banda pasante (intervalo de frecuencias analizadas)
- Número de muestras que deben ser promediadas

POTENCIALES EVOCADOS

Los Potenciales Evocados en todas sus modalidades visuales (PEV), auditivos (PEA), somatosensitivos (PESS) y motores (PEM) abren otras posibilidades dado que:

- Son métodos no invasivos

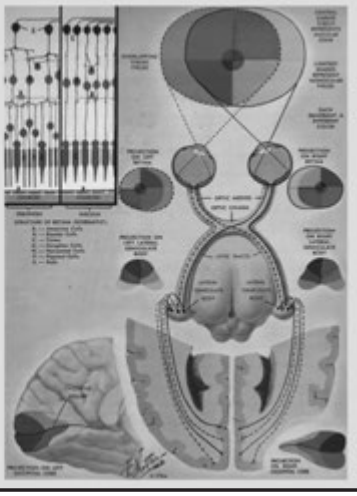
- Permiten estudiar en vivo:

- El desarrollo normal o patológico de las diferentes vías.
- La respuesta al tratamiento y sus efectos secundarios.
- Mapas funcionales de la corteza frente a diferentes tipos de estímulos.
- Estado funcional de la corteza y su nivel de excitabilidad.
- Caracterización fenotípica.

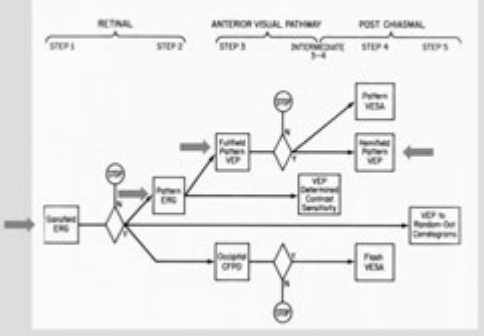
VÍA VISUAL

ERG

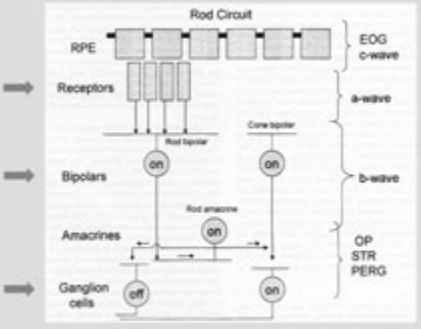
PEV



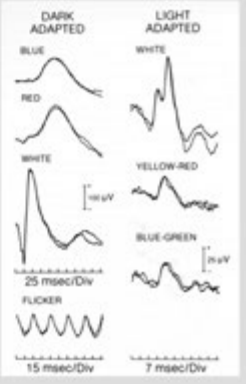
ALGORITMO DE ANÁLISIS DE LA VÍA VISUAL



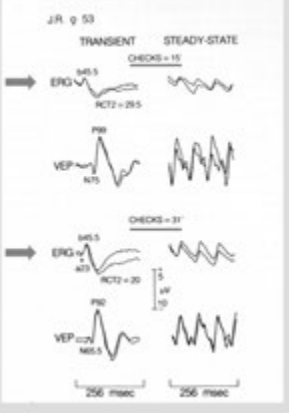
RELACIÓN DE LAS CÉLULAS DE LA RETINA CON EL ERG



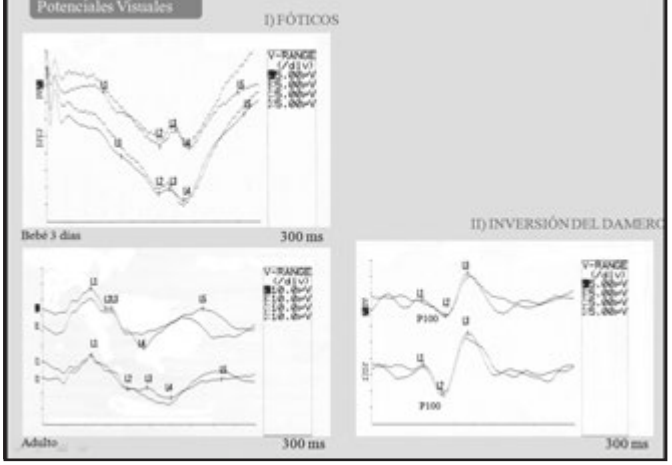
ERG por Flash



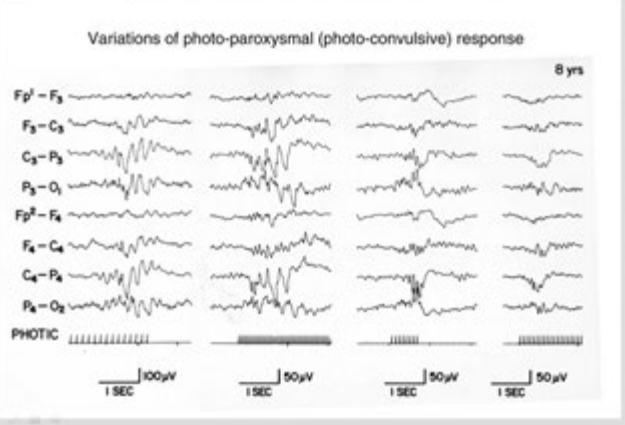
ERG por Pattern



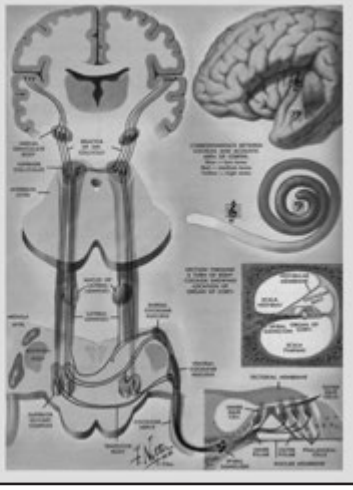
Potenciales Visuales



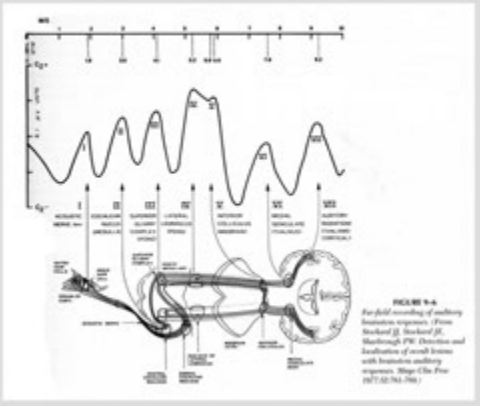
ELI con Flash



VÍA AUDITIVA



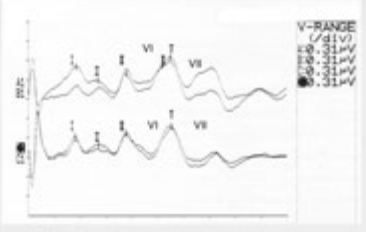
Relación de los PEA de TC y sus probables generadores



PEA por clicks a 80 dB

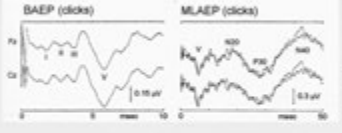
O. izquierdo

O. derecho



- Tiempo de análisis 10 mseg.
- Banda pasante 150 Hz a 3000 Hz.
- 4 muestras promediación de 2000 estímulos

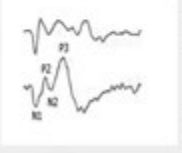
Potenciales evocados auditivos



PEA de Latencia Media
Tálamo y áreas auditivas no primarias.

Estímulo monótono (background)

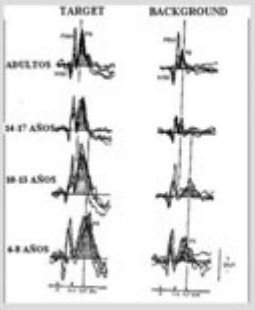
Estímulo aleatorio (target)



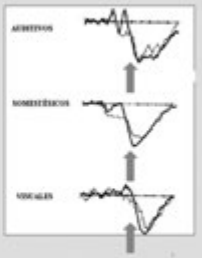
PEA de larga latencia o
Potenciales evocados cognitivos

Corteza Auditiva y Frontal
de asociación.

Potenciales evocados de larga latencia

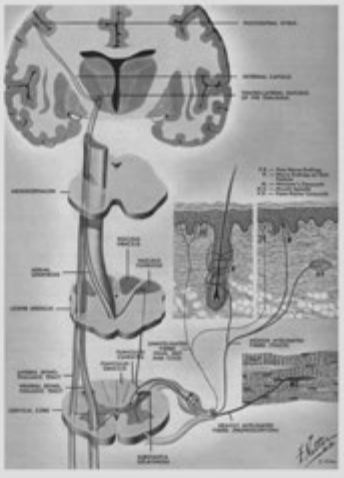


Evolución de los PEC con la edad

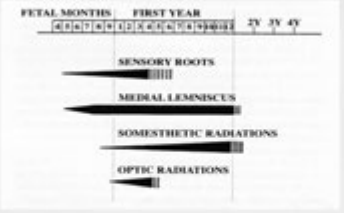


PEC con diferentes modalidades de estimulación

VÍA SOMATOSENSITIVA

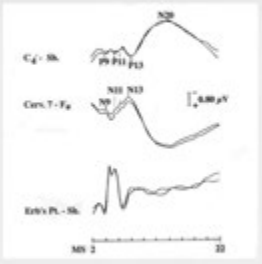


Desarrollo de la Mielogenesis de la vía somatosensitiva

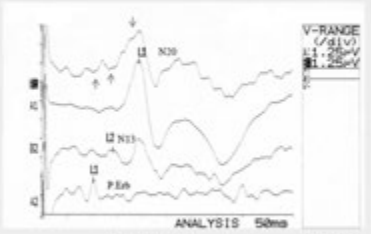


El tálamo es critico en la transmisión cerebral de señales periféricas.
Se puede anticipar que el desarrollo de los PES corticales va a estar relacionado con la maduración talámica y su mielinización.
Diferencias en su mielinización determinan variabilidad en los registros de superficie.
Con menos de 31 semanas de gestación no se ven los PESS.

Potenciales evocados somatosensitivos

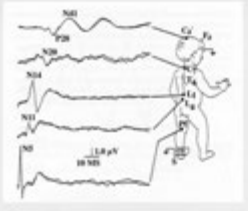


Estimulación del nervio mediano en niño de 2 años

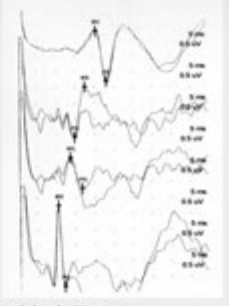


Estimulación del nervio mediano en adulto de 22 años

Potenciales evocados somatosensitivos



Niño 1 año
Estimulación del nervio Tibial posterior



Adulto de 20 años

ESTUDIOS EN EPILEPSIAS

Cortical auditory dysfunction in benign rolandic epilepsy

Dana F. Boutman, William H. Trescher, Cynthia Smith, Joshua Ewen, Jenna Los, Heather M.Wied, Barry Gordon, Eric H. Kossoff, Qian Guo, and Eileen P. Vining

Epilepsia, 49(6):1018–1026, 2008

- 14 niños con ERB, 7 controles
- PEA provocados con estímulos de tonos y lenguaje
- Audición periférica y subcortical normal
- Los niños con ERB tuvieron alteraciones en el reconocimiento del lenguaje
- Probable disfunción de la corteza auditiva no primaria
- Riesgos en el desempeño académico

Pattern-Reversal VEP and Cortical SEP Latency Prolongations in Epilepsy

Esa Mervaala, Tapani Keranen, Marja Pentila, Juhani V Partanen, and Paavo Riekkinen

Epilepsia, 28(5):441-445, 1985 Raven Press, New York International League Against Epilepsy

- Se estudiaron 20 pacientes con EGI fotosensibles, 11 pacientes con CPC no fotosensibles y 34 controles normales con PEV por inversión del damero y PESS por estimulación del nervio Mediano
- Los pacientes con EGI presentaron latencias elevadas en el PEV (P2 y N3), y en los PESS (P22) $p<0.001$
- Los pacientes con CPC presentaron latencias elevadas en el PEV (N3) $p<0.005$
- Se concluye que factores funcionales y estructurales pueden causar enlentecimiento en la conducción central de los impulsos

Pattern-reversal Visual Evoked Potentials in Patients with Newly Diagnosed Epilepsy

Bülent O. Gen,ç, Emine Genç, Figen Güney, and Nurhan Ilhan

Epilepsia, 46(8):1219–1223, 2005 Blackwell Publishing, Inc 2005 International League Against Epilepsy

- Se estudiaron 55 pacientes no fotosensibles (no FS), 34 de ellos con CPC; 24 pacientes fotosensibles (FS) y 42 controles normales
- Se estudió el PEV por inversición del dámero, evaluando la latencia del N1, P1 y la amplitud N1-P1
- Los pacientes no FS presentaron un aumento significativo de la latencia P1 en relación a los controles y pacientes FS, $p<0.001$
- Los pacientes FS presentaron una reducción significativa de la latencia N1 y un aumento de la amplitud N1-P1, $p=0.002$
- Estas diferencias se relacionaron con la presencia o no de fotosensibilidad y no con el tipo de crisis
- Se plantean alteraciones en uno o más neurotransmisores y daños morfológicos sutiles como microdisgenesis

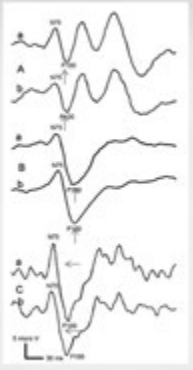


FIG. 1. Examples of P-VEPs from (A) a normal control, (B) a patient with nonphotosensitive epilepsy, and (C) a patient with photosensitive epilepsy. The two curves represent the right (a) and left eye (b) of the same patient.

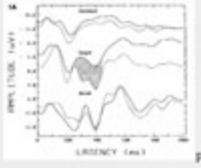
Pattern-reversal Visual Evoked Potentials in Patients with Newly Diagnosed Epilepsy

Pre- and Postoperative Auditory Event-Related Potentials in Temporal Lobe Epilepsy

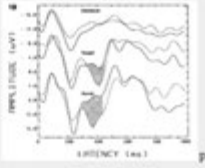
Esa Mervaala, Unto Nousiainen, Jukka Kinnunen, Matti Vapalahti, and Paavo Riekkinen

Epilepsia, 33(6): 1029-1035, 1992 Raven Press, Ltd., New York International League Against Epilepsy

- Se estudiaron 11 pacientes con ET refractaria en el pre y postoperatorio.
- Se realizaron PEC con estimulación auditiva y registro en electrodos esfenoidales.
- Se observó una asimetria de amplitudes en el P300 y aumentos de las latencias bilateralmente.
- La disfunción de los PEC lateralizó en 9 pacientes, con confirmación de EEG, ECG, neuroradiologia y neurosicologia.



preoperatorio



postoperatorio

Somatosensory Evoked Potentials in Juvenile Myoclonic Epilepsy

J. Salas-Puig, A. Tuñon, M. Díaz, and C. H. Lahoz

Epilepsia, 33(3):527-530, 1992 Raven Press, Ltd., New York International League Against Epilepsy

- Se estudiaron 35 pacientes con EMJ, 26 con EGI y 24 controles normales con PESS
- Se observó:
- en los pacientes con EGI un aumento en las latencias N19 y P25 significativo, $p<0.002$
- en los pacientes con EMJ un aumento en la amplitud del P25 y N 35 significativo, $p<0.001$
- en 14% de los pacientes con EMJ los PESS fueron gigantes (3 DS del grupo control)
- no hubo diferencias electroclínicas entre los pacientes con EMJ con PESS gigantes y sin PESS gigantes

.Giant somatosensory evoked magnetic field in patients with myoclonus epilepsy.
Uesaka Y, Ugawa Y, Yumoto M, Sakuta M, Kanazawa I.
Electroencephalogr Clin Neurophysiol. 1993 Nov;87(5):300-5

- We investigated somatosensory evoked magnetic fields (SEFs) and somatosensory evoked potentials (SEPs) in patients with myoclonus epilepsy.
- The median nerve was stimulated at the wrist, and responses were recorded over the contralateral hemisphere.
- The source of the enlarged cortical component of the giant SEF was localized on the post-central sensory cortex.
- The P1 component of the giant cortical response was composed mainly of a tangentially oriented dipole at area 3b.

Visual Evoked Potentials, Brainstem Auditory Evoked Potentials, and Quantitative EEG in Baltic Progressive Myoclonus Epilepsy
Eija Mervaala, Tapani Kerranen, Ari Paakkonen, Juhani V. Partanen, and Paavo Riekkinen
Epilepsia, 28(5):441-445, 1985 Raven Press, New York International League Against Epilepsy

- Se estudiaron 16 pacientes con epilepsia mioclónica progresiva Baltica con PEV por inversión del damero, PEA de TC y EEG cuantitativo
- Se observaron: -aumentos en las latencias de el PEV, con amplitudes normales
  -prolongación del tiempo de conducción central en el PEA
  -disminución de la actividad beta y alfa y aumento de la actividad theta y delta en el EEGq
- Se concluye que existe una alteración multimodal de las proyecciones sensoriales a las áreas sensoriales corticales en la EMP Báltica
- Los resultados evidencian que más allá de un transtorno desmielinizante, los defectos en la transmisión sináptica pueden producir alteraciones en los PE
- Los cambios en el cerebro epiléptico no están confinados a las neuronas epilépticas hiperexitables, sino que serían fenómenos electrofisiológicos más extensos

Differences in Evoked Potential Findings between DRPLA Patients and Patients with Cortical Reflex Myoclonus
Kiyoto Kasai, Teiichi Onuma, Masaaki Kato, Takeji Kato, Jun Takeya, Masanori Sekimoto, Keiichiro Watanabe, Narihiro Minami, Yu-ichi Goto, and Yoshio Minabe
Epilepsia, vol.41. Supple.9.200

- Se estudiaron:-10 pacientes con atrofia dentorubrotalámica (DRPLA), con confirmación genética basada en la expansión de la repetición del triplete CAG (62-75) en el cromosoma 12p.
  - 3 pacientes con epilepsia mioclónica progresiva tipo Unverrich-Lundborg (EMP) con confirmación genética de la expansión de la repetición para el gen de la cistatina B.
- Se estudiaron los PESS por estimulación del nervio Mediano y los PEA de TC.
- Los pacientes con DRPLA mostraron una reducción en la amplitud de los PESS y ausencia de ondas III y V en los PEA.
- Los pacientes con EMP mostraron aumento en la amplitud de los PESS y presencia de todas las ondas en los PEA .
- Existe una clara diferencia entre ambas entidades con predominio de las alteraciones subcorticales en la DRPLA y hiperexcitabilidad cortical en la EMP.

Epilepsy in Schizencephaly : Abnormal Cortical Organization Studied by Somatosensory Evoked Potentials

David G. Vossler, Robert J. Wilkus, Webster H. Pilcher, and Jacqueline R. Farwell

Epilepsia, 33(3):487494, 1992 Raven Press, Ltd., New York International League Against Epilepsy

- El estudio de los PESS de superficie y sobre la corteza se utilizan en la evaluación prequirúrgica para identificar áreas sensitivas y motoras.
- Se estudio un niño con una esquizencefalia parietal derecha y crisis parciales simples frecuentes, con PESS en el preoperatorio,.
- Se obtuvó un N18 normal bilateralmente, ausencia de N20 y P27 a derecha, normales a izquierda.
- Estos hallazgos sugieren: -El N18 se genera a nivel o por debajo del tálamo.
  -El N20 y el P27 se generan en la corteza parietal o en la sustancia blanca subcortical.
  -El registro cortical de PESS puede fallar en la localización del surco central, cuando existen anormalidades congénitas del lóbulo Parietal

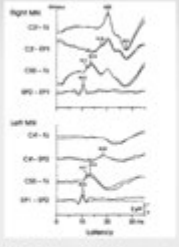


FIG. 2. Scalp-recorded short-latency somatosensory evoked potentials (SSEPs) to right and left median nerve (MN) stimulation (two averages of 1,000 trials).

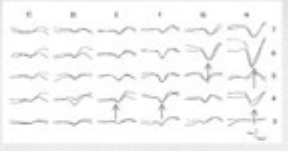


FIG. 3. Short-latency somatosensory evoked potential recorded from a sub dural grid of electrodes over the right centro-parietal-temporal area (C3 reference, two averages of 100 trials). Electrodes are identified by lettered vertical columns and numbered horizontal rows. A positive wave at 22 ms and a negative wave at ~30 ms appeared most prominently at the elec- 1-4 4 tradenagrid columnsEand Fandat electrodes 5G and 4G. Anterior to these (at 5G-H, 6G-H, and 4H), a larger amplitude positive potential at 27 ms was recorded

ESTUDIOS DE EFECTOS DE DAE

The Effect of Sodium Valproate on Sleep, Reaction Times, and Visual Evoked Potential in Normal Subjects

G. E A. Harding, C. A. Alford, and T. E. Powell Epilepsia, 26(6):597-601, 1985 Raven Press, New York International League Against Epilepsy

- Se estudiaron en 10 voluntarios normales los efectos del Ácido Valproico en el Tiempo de reacción simple, los PEV y el EEG durante el sueño.
- Se analizaron con dosis bajas (500mg), dosi altas (1000mg), placebo y luego de la deprivación.
- No se encontraron alteraciones del Tiempo de reacción, los PEV ni el EEG durante el sueño

No Effect of Long-Term Vigabatrin Treatment on Central Nervous System Conduction in Patients with Refractory Epilepsy: Results of a Multicenter Study of Somatosensory and Visual Evoked Potentials

F. Mauguière, P. Chauvel, J. Dewailly, N. Dousse, and the PMS Study Multicenter Group

Epilepsia, 26(6):597-601, 1985 Raven Press, New York International League Against Epilepsy

- En estudios en perros el uso de Vigabactrina (VGT) se asoció a edema intramielínico y retardo en la conducción central estudiada con PESS y PEV.
- 201 pacientes con epilepsia parcial refractaria, tratados con VGT por períodos prolongados ,con dosis promedio de 2 a 3g/día.
- Se estudiaron los PESS por estimulación del nervio Mediano, y los PEV por inversión del damero, al inicio y cada 6 meses por 2 años.
- 109 pacientes completaron el estudio, 92 abandonaron la medicación ,37 de los cuales continuaron siendo estudiados.
- No sé observaron cambios consistentes en el grupo total de pacientes tratados.
- El número de anormalidades fue similar en el grupo tratado que en los que discontinuaron la VGT.
- Se concluyó que no hay evidencia de cambios en los PESS y PEV atribuibles a una conducción neuronal anormal en el CNS durante el tratamiento prolongado con VGT

Effects of Long-Term Vigabatrin on Somatosensory- Evoked Potentials in Epileptic Patients

C. Liegeois-Chauvel, P. Marquis, D. Gisselbrecht, R. Pantieri, D. Beaumont, and P. Chauvel

Epilepsia 30(Suppl. 3):S23-S25. 1989 Raven Press, Ltd. New York 1989 International League Against Epilepsy

- La VGT es una DAE efectiva y un inhibidor específico e irreversible de la GABA-transaminasa.
- En estudios en animales produce efectos tóxicos variados según la especie.
- Se estudiaron 54 pacientes tratados en politerapía con VGT a dosis de 1a 4g/día en períodos de 1 a 25 meses y 7 controles voluntarios.
- Se analizaron los PESS por estimulación del nervio Mediano, al inicio y a los3, 6, 12 y 24 meses.
- No sé encontraron alteraciones a nivel la la conducción nerviosa central en el CNS.
- La medicación sería segura en humanos

Electro-Oculography, Electroretinography, Visual Evoked Potentials, and Multifocal Electroretinography in Patients with Vigabatrin-Attributed Visual Field Constriction

G. F. A. Harding, J. M. Wild, K. A. Robertson, M. C. Lawden, T. A. Betts, C. Barber, and P. M. F. Barnes
Epilepsia, 41(11): 1420-1431 , 2000 Lippincott Williams & Wilkins, Inc., Baltimore International League Against Epilepsy

- Se estudiaron 8 pacientes con alteraciones del campo visual (CV) atribuidas a el uso de VGT, 6 de ellos no recibían más VGT.
- Se analizó el campo visual central y periférico, ERG por flash y pattern, ERG multifocal y los PEV por flash y pattern.
- 8 mostraron constricción concentrica del CV
- 7 retardo de los potenciales oscilatorios en los PEV, 5 retardo de las ondas b en la respuesta flicker del ERG.
- En el ERG multifocal las alteraciones se relacionaron con la alteración del CV y confirmaron que el déficit ocurre a nivel de la retina.
- Se concluyó que una marcada constricción del CV se asocia al uso de VGT y esta alteración así como las alteraciones electrofisiológicas persisten luego de suspendida la terapia con VGT

Effects of Carbamazepine on Auditory Brainstem Response, Middle-Latency Response, and Slow Cortical Potential in Epileptic Patients

G. Japaridze, D. Kvernadze, T. Geladze, and Z. Kevanishvili
Epilepsia, 34(6): 1105-1109, 1993 Raven Press, Ltd., New York International League Against Epilepsy

- Se estudiaron 21 pacientes con epilepsia, tratados con CBZ en monoterapia, antes y durante el tratamiento.
- Se realizaron PEA de corta latencia (ABRs) y latencia media (MLR) y latencia prolongada (SCPs), valorando las latencias, los intervalos interpico y las amplitudes.
- Se observó un incremento significativo de las latencias en todas las modalidades de PEA ($p<0.005$ a $p<0.001$)
- Se sugiere que la CBZ produce alteraciones en las vías específicas (lemniscales) y no específicas (extralemniscales) de la vía auditiva central.

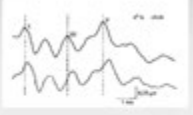


FIG. 1. Auditory brainstem responses registered in an epileptic patient before (top) and during treatment (bottom) with carbamazepine.

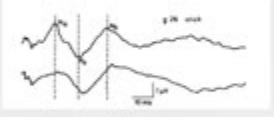


FIG. 2. Middle-latency responses registered in an epileptic patient before (top) and during (bottom) treatment with carbamazepine.

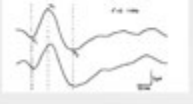


FIG. 3. Slow cortical potentials registered in an epileptic patient before (top) and during (bottom) treatment with carbamazepine.

Effects of Carbamazepine on Auditory Brainstem Response, Middle Latency Response, and Slow Cortical Potential in Epileptic Patients

Carbamazepine Does Not Affect Short-Latency Somatosensory Evoked Potentials: A Longitudinal Study in Newly Diagnosed Epilepsy

L. Carenini, E. Bottacchi, M. Camerlingo, G. D'Alessandro, and A. Mamoli

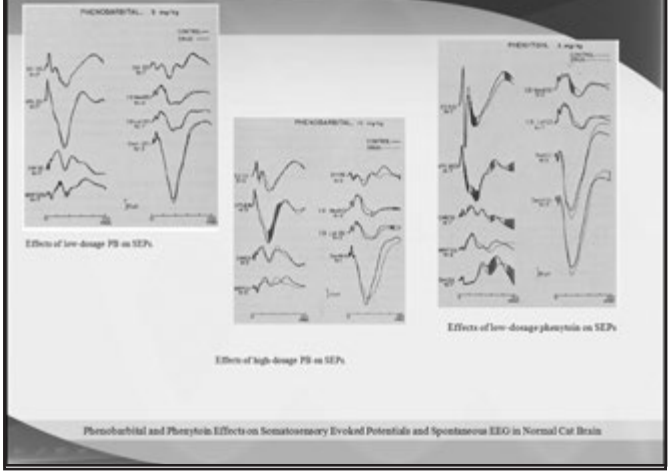
Epilepsia, 29(2): 143-148. 1988 Raven Press, Ltd., New York International League Against Epilepsy

- Se estudiaron 12 pacientes con diagnóstico reciente de epilepsia y tratamiento con CBZ en monoterapia y 12 controles normales.
- Se realizaron PESS por estimulación del nervio Mediano.
- Se valoró las latencias a nivel espinal (N13) y a nivel parietal (P14, N20, P25) y las latencias interpico (N13-N20), (P14-N20).
- No sé observaron anormalidades.
- No hubo diferencias significativas entre los pacientes y los controles normales, así como antes del tratamiento y después de un año del mismo.

Phenobarbital and Phenytoin Effects on Somatosensory Evoked Potentials and Spontaneous EEG in Normal Cat Brain

Bonnie J. Kaplan Epilepsia, 18(3), 1977. Raven Press, New York

- Se estudiaron gatos implantados crónicamente, con administración oral crónica de fenobarbital (FB) y fenitoína (DFH).
- Se analizó el efecto de dos dosis: FB a 3mg/Kg y 15mg/Kg y DFH a 5mg/KG y 8mg/Kg en los PESS y en el análisis espectral del EEG.
- El FB a dosis bajas soló alteró los registros en la formación reticulada mesencefálica; a dosis altas provocó una atenuación generalizada de las respuestas.
- La DFH en ambas dosis provocó: 1) Un aumento de los PESS, especialmente en el hipocampo dorsal.
  2) Cambios en la vía dentado-talámica.
  3) Los cambios en el EEG no ocurren en los picos de frecuencia, como fue reportado en humanos.
- Se concluye que los cambios en los PESS y el EEG son minimos a dosis no tóxicas de FB y DFH



Effects of low-dosage PB on SEPs

Effects of high-dosage PB on SEPs

Effects of low-dosage phenytoin on SEPs

Phenobarbital and Phenytoin Effects on Somatosensory Evoked Potentials and Spontaneous EEG in Normal Cat Brain

Estimulación magnética

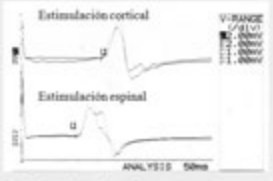
Silvanus P. Thompson estimulando su cerebro (1910)

Primer estimulador magnético de uso Clínico. Baker y col. (1985)

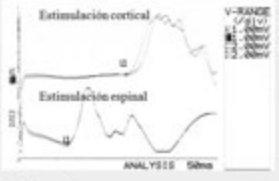
Estimulación magnética

- La estimulación magnética de la corteza motora induce la estimulación transináptica de la neuronas corticoespinales, por la generación de un potencial de acción excitatorio o inhibitorio de las interneuronas corticales
- Esto se traduce en una serie de potenciales (I wave) que inducen una contracción en músculos contralaterales a la estimulación
- La estimulación espinal logra la estimulación de las raíces motoras
- El registro en el músculo estudiado de los potenciales inducidos por ambas estimulaciones y su diferencia de latencias permite el cálculo de un tiempo de conducción motora central (TCMC)
- Se obtienen respuestas desde las 33 semanas de edad concepcional, y alcanzan los valores del adulto alrededor de los 11 años

Estimulación magnética



Primer interóseo dorsal



Tibial anterior

Estimulación magnética

SEGURIDAD EN SU USO:

- Desde su introducción en 1985 se estudiaron miles de pacientes y controles con EMT de pulso único y EMT repetitiva

- Se realizaron estudios en animales y humanos para valorar las características de la técnica y sus efectos

- La corriente inducida en el cerebro es comparable a la usada en la estimulación de los nervios periféricos y de magnitudes de orden cuatro veces menores que las usadas en terapia electroconvulsiva

- No se detectaron efectos significativos en frecuencia cardiaca, presión arterial, EEG, y funciones cognitivas

- La presencia de objetos metálicos intracraneanos es una contraindicación relativa

- La EMT repetitiva tiene mayor probabilidad de producir crisis, dependiendo de la intensidad y frecuencia del estímulo

- Guías de seguridad para el uso de EMT de pulso único y repetitiva. (Pascual-Leone, 1993; Chen,1997; Wassermann, 1998)

Estimulación magnética

USOS EN EPILEPSIA:

- Estudio de la excitabilidad cortical

- Valoración de la acción de DAE

- Localización de área motora y lateralización del lenguaje

- Inducción de crisis

- Tratamiento en epilepsia

Estudio de la excitabilidad cortical

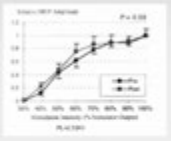
ESTUDIOS CON ESTÍMULOS AISLADOS:

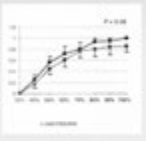
- Umbral de la respuesta motora: intensidad de estimulación mínima para producir una contracción en el músculo estudiado en 50% de 10 estimulaciones

- Amplitud del potencial motor: la medida más usada del efecto excitatorio de la EMT

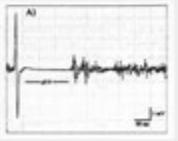
- Período de silencio cortical: período de silencio en el EMG, luego de un estímulo cortical, en un músculo que se estaba contrayendo y que continúa haciéndolo luego del mismo

Análisis de la amplitud del potencial motor

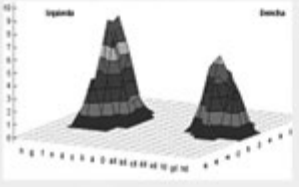


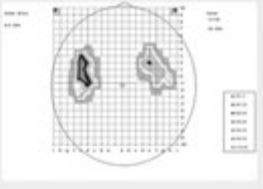


Periodo de silencio cortical



Mapa de área y volumen de corteza motora





Estudio de la excitabilidad cortical

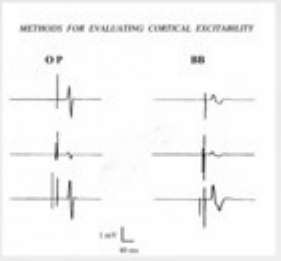
ESTÍMULOS PAREADOS:

- Inhibición y facilitación cortical: se analizan curvas de recuperación con estímulos pareados en períodos de interestímulo breves (1 a 16 mseg) y prologados (25 a 400 mseg) para estudiar la inhibición y facilitación intracortical

- Inhibición transcallosa: se analiza el efecto del estímulo en la corteza ipsilateral a un músculo, seguido de un estímulo contralateral

- Extensión de la excitabilidad intracerebral: se analiza el aumento de la amplitud del potencial motor y la extensión de la respuesta cortical a otros músculos próximos con estímulos de diferente intensidad, frecuencia y duración. En general se produce con estímulos de más de 10 Hz

Análisis de estímulos pareados



Oponente del pulgar

Bíceps braquial

Table 17–1 TRANSCRANIAL MAGNETIC STIMULATION OF MOTOR EXCITABILITY IN EPILEPSY

Epilepsy/ Number of Patients	Medication	RMT	MEP	cMEP	CSP	SICI	ICF	IN	LICI	LICF	Reference
IGE/11	Untreated	↓									Ruetens, Berkovic y col, 1992
IGE/34	VPA	↑[1]									
IGE/20	Untreated	↓									Ruetens, Berkovic y col, 193
IGE/36	VPA	↑[1]									
IGE/8	Untreated	↑									Gianelli, Cantello, 1994
IGE/12	VPA/PB	↑									
IGE/14	?		↓[2]								
JME/7	VPA	↑[1]				↓					Caramia, Gigli y col, 1996
IGE/7	Untreated	⟷							↓	↑[3]	Brodtmann, Macdonell y col, 1999
IGEv/10	VPA/PB	⟷[4]									Aguglia, Gambardella y col,2000
IGE/13	VPA/PB	⟷									
JME/15	VPA/PB/ Untreated	⟷[5]	⟷		⟷	↓	⟷		⟷		Manganotti, Zanette y col, 2001
IGE/21	Untreated	⟷[4]			↑						Macdonell, King y col, 2001
PME/3	VPA/CLZ	↑[1]		↑							Reutens, Puce y col, 1993
IGE/8	VPA	↑		⟷							
PME/3	VPA	↑[1]	⟷	↑							Cantello, Gianelli y col, 1997
PME/12	VPA/CLZ	⟷			⟷				↓	↑[7]	Valzania, Strafella y col, 199
PME/4	VPA/PHT/CBZ/ CLZ/Untreated	↑[1]	⟷	↑		↓					Manganotti, Bongiovanni y col,2000

Table 17–1 CONTINUED

Epilepsy/ Number of Patients	Medication	RMT	MEP	cMEP	CSP	SICI	ICF	IN	LICI	LICF	Reference
ADCME/8	Various AEDs	↓			↓						Guerrini, Bonanni y col, 2001
Generalized CM/8	CLZ, others	⟷				↓	⟷	↓			Brown, Ridding y col, 1996
Focal CM/10	CLZ, others	↑			↑	⟷	⟷				
CME/5	?						↓[8]				Hanajima, Ugawa y col, 2001
BECT/8	VPA	↑[1]									Nezu, Kimura y col, 1997
BECT/5	Untreated	⟷									
BECT/7	Untreated			↑							Manganotti, Zanette y col, 2000
First-ever GS/18	Untreated	↑[9]	⟷[9]		⟷[9]	⟷[9]	↓[9]				Delvaux, Alagona y col,2001
TLE/53	CBZ/others	↑[1]	⟷								Hufnagel, Elger y col, 1990
FE(TLE)/7	Untreated	⟷[10]			⟷[10]	↓	↓[11]				Werhahn, Lieber y col, 2000
FE/6	Untreated	⟷[10]			⟷[10]	↓	↓				
FE (motor cortex)/8	CBZ/others	↓[1,10]			↓[10]						Cincotta, Borgheresi y col, 1998
CFE/10	CBZ/others	↓[1,10]			⟷						
FE (motor cortex)/5	PB	⟷[10]			↓[10]						Cincotta, Borgheresi y col, 1997
	CBZ/PHT	⟷[10]			⟷[10]						
CFE/1											
FE (SMA)[12]/1	CBZ				↓[12]						Classen, Witte y col, 1995
FE (motor cortex)/1	?	↑[12]			↓[12]	↓[12]	↓[12]				Inghilleri, Mattia y col, 1998
FE (motor cortex)/7	CBZ/PHT/VPA					↓[13]	↑[13]				Fong, Werhahn y col, 1993
FE (motor cortex)/1	?	⟷	↑[13,14]		↓[13]	↓[13,14]	⟷				Shimizu, Maehara y col, 2001
EPC/1	PHT					↓[13]	⟷[13]				Hennerdorf, Ziemann y col, 1998
CFE/16	VPA/CBZ/others	↓[1,10]	⟷[10]		↓[10]						Cincinelli, Mattia y col, 2000
CFE/18	VPA/CBZ/others				⟷[10]	↓[10,15]	↓[10,15]				Cantello, Civardi y col, 2000

Idiopathic Generalized Epilepsy: Magnetic Stimulation of Motor Cortex Time-Locked and Unlocked to 3-Hz Spike-and- Wave Discharges

Maria Gianelli, Roberto Cantello, Carlo Civardi, Paola Naldi, Diego Bettucci, M. Pia Schiavella. and Roberto Mutani

Epilepsia, 35(1):53-60, 1994 Raven Press, Ltd., New York International League Against Epilepsy

- 20 pacientes con EGI y descargas de complejos espica-onda lenta a 3/seg en el EEG.
- 10 controles pareados por edad y sexo.
- Se estudio el umbral de la respuesta motora, en ambos hemisférios.
- El umbral estuvo significativamente aumentado en pacientes tratados con DAE ($p<0.01$) y en no tratados ($p<0.03$)
- En 4 pacientes se estudio el efecto de la EMT con relación a las descargas:
La amplitud del potencial motor estuvo significativamente reducida cuando se estimulo simultaneamente con la onda lenta($p<0.001$) e incambiado o reducido con la espica.
- La excitabilidad cortical estaría reducida en pacientes con EGI y descargas de complejos de espica-onda lenta a 3/seg en el EEG.

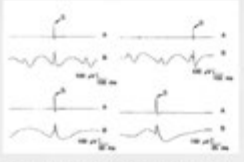


FIG. 3. Two typical examples of motor cortical stimuli (S) time-locked to a spike of the spike-and-wave complex (B), not followed by any motor evoked potentials (A). Bottom panels: Same signals (A and B) after off-line electronic expansion of the time base.

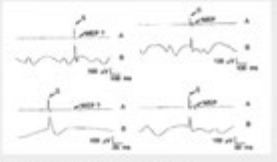


FIG. 4. Motor cortical stimuli (S) time-locked to the ascending (a) and descending (b) phase of a slow wave in the spikewave complex (B) and followed by very small motor evoked potentials (A). Bottom panels: Same signals after off-line electronic expansion of the time base

Early and Late Intracortical Inhibition in Juvenile Myoclonic Epilepsy

Paolo Manganotti, Luigi Giuseppe Bongiovanni, Gianpietro Zanette, and Antonio Fiaschi

Epilepsia, 41(8): 1128-1 138, 2000 Lippincott Williams & Wilkins, Inc., Baltimore International League Against Epilepsy

- 15 pacientes con EMJ y 12 controles se estudiaron con EMT con pulsos aislados y pareados para estudiar la inhibición motora cortical
- Se utilizaron intervalos interestimulo entre 1mseg a 400 mseg
- La inhibición del PEM estuvo significativamente descendida para intervalos de 1 a 4 mseg ($p<0.001$)
- No hubo diferencias significativas a intervalos mayores, 100 a 150 mseg
- Esto se observo en ambos hemisferios,en pacientes tratados con DAE y no tratados
- No hubo diferencias en la facilitación intracortical, umbral motor, amplitud del PEM y el período de silencio cortical
- Conclusión: Existe una alteración de los circuitos inhibitorios interneuronales en la EMJ

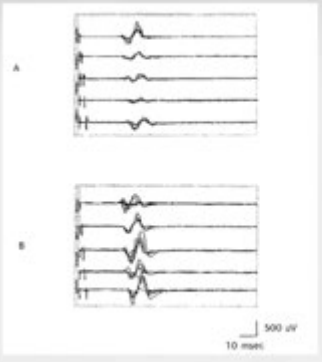


FIG. 1. Recordings from a control subject (A) and a JME patient (B) representing the ICI at short ISIS (1 to 4 milliseconds) of the MEP from the right TE. The first tracings at the top of each panel represent the baseline conditions, and the tracings below represent the different ISIs (see the signal artifact). The conditioned MEP is markedly inhibited at ISIs from 1 to 4 milliseconds in the control subject by a previous subthreshold conditioning stimulus. At the same ISI, the MEP inhibition is absent in the JME patient. The data are the superimposition of seven tracings.

Early and Late Intracortical Inhibition in Juvenile Myoclonic Epilepsy

Motor Responses to Afferent Stimulation in Juvenile Myoclonic Epilepsy

Paolo Manganotti, Stefano Tamburin, Luigi Giuseppe Bongiovanni, Giampietro Zanette, and Antonio Fiaschi

Epilepsia, 45(1):77–80, 2004 Blackwell Publishing, Inc. 2004 International League Against Epilepsy

- Se estudiaron 9 pacientes y 20 controles con PESS por estimulación de los aferentes cutáneos y el efecto de la misma en la respuesta inhibitoria y facilitadora intracraneal a la EMT con estímulos pareados
- La inhibición intracortical fue anormal en los pacientes, mientras que los PESS y la respuesta a la EMT pareada condicionada a la estimulación de los aferentes cutáneos no se alteraron en los pacientes con EMJ
- Conclusión: Un procesamiento anormal de las aferencias cutáneas no parece contribuir a las mioclonías en la EMJ

Efectos de DAE

TABLE 1
INFLUENCE OF DIFFERENT DRUGS ON TMS MEASURES OF CORTICAL EXCITABILITY

Drug	Mode of action	MT	MEP ampl.	CSP	ICI	ICE
Carbamazepine	Na^+	↑	→	↑	→	→
Phenytoin	Na^+	↑	→	→	→	→
Lamotrigine	Na^+	↑	?	→	→	→
Valproate	GABA-A/Na	↑	?	→	→	→
Lorazepam	GABA-A	→	?	↑	↑	↓
Diazepam	GABA-A	→	→	↓	→	↓
Ethanol	GABA-A	→	→	↑	↑	↓
Baclofen	GABA-B	→	?	→	↑	↓
Losigamon	Na/Ca	↑	?	→	→	→
Gabapentin	Anti-Glu?	→	?	↑	↑	↓
Riluzole	Anti-Glu	→	?	→	→	↓

Efectos de DAE

Table 17–2 ACUTE EFFECTS OF ANTIEPILEPTIC DRUGS ON MOTOR EXCITABILITY IN HEALTHY SUBJECTS

Drug	Mode of Action	Dose/Application	Time (hrs)	RMT	MEP	CSP	SICI	ICF	LICI	Trains Facilitation	Reference
CBZ	Na^+	600 mg/PO	**2, 5, 24, 48, 96**	↑		↑	↔	↔			Ziemann, Lönnecker y col, 1996
		600 mg/PO	6	↔	↔	(↑)	↔	(↓)			Schulze-Bonhage, Knoll y col, 1996
		600 mg/PO	**2, 5, 24**	↑						↔	Ziemann, Tergau y col, 1998
PHT	Na^+	18 mg/kg/IV	**1.5**, > 15 d	↑	↔	↔					Wennbuddkis, Carroyer y col, 1994
		18 mg/kg/PO	**9–12**	↑?	↔	↔	↔	↔			Chen, Samii y col, 1997
LTG	Na^+	300 mg/PO	**2, 5,** 24	↑		↔	↔	↔			Chen, Samii y col, 1997
		300 mg/PO	**2, 5,** 24	↑						↔	Chen, Samii y col, 1997
		200 mg/PO	2.5	↑	↓		↔	↔			Bonnorgoli,Bellaglia y col, 2001
VPA	Na^+/$GABA_B$	1,200 mg/PO	4, 8, 24, 48	↔		↔	↔	↔			Ziemann, Lönnecker y col,1996
LZP	$GABA_A$	2.5 mg/PO	**2, 5,** 24	↔		↑	↑	↓			Ziemann, Lönnecker y col, 1996
		2.5 mg/PO	**2, 5,** 24	↔	(↓)					↓	Ziemann, Lönnecker y col, 1996
		2.5 mg/PO	2.5	↔			↑			↔	Di Lazzaro, Oliviero y col, 2000
		0.038 mg/kg/PO	2.5	↔	↓		↔	↔			Di Lazzaro, Oliviero y col, 2000
DZP	$GABA_A$	0.17 mg/kg/IV	**5, 30,** 60 min	↔	↔	↓	↔	(↓)			Inghilleri, Berardelli y col, 1998
		3.75 mg/PO	20, 30, 45, 60 min	↔		↔					Palmieri, Iani y col, 1999
PB	$GABA_A$	200 mg/PO	**2, 6, 24,** 48	↔	↔					↓	Palmieri, Iani y col, 1999
TP	$GABA_A$	2 mg/kg/IV	5, **120,** 30 min	↔	(↓)	↔					Palmieri, Iani y col, 1999
VGB	GABA	2,000 mg/PO	6, **24,** 48, 96	↔		↔	↔	↓			Palmieri, Iani y col, 1999
		50 mg/kg/PO	24, > 30 d	↔	↔	↔					Wennbuddkis, Carroyer y col,1997
		2,000 mg/PO	**6,** 24, 48	↔	↔					↓	Wennbuddkis, Carroyer y col,1997
TGB	GABA	5–15 mg/PO	90–120 min	↔	↔	↑?	↓?	↑?	↑		Werhahn, Kunesch y col, 1999
BCF	$GABA_B$	30 mg/PO	**2, 5,** 24	↔		↔	↑	↓			Werhahn, Kunesch y col, 1999
		0.6 mg/kg/PO	15, 30, 60 min	↔	↔	↔					Werhahn, Kunesch y col, 1999
		50 mg/PO	2, 5, 24	↔	↔					↔	Werhahn, Kunesch y col, 1999
TPM	Na^+/$GABA_A$/ Anti-GLU	50/200 mg/PO	2	↔		↔	↑?	↓			Reis, Tergau y col, 2001
LSG	↑ Na^+/Ca^{2+}	1,000 mg/PO	**2,** 5, 24	↑		↔	↔	↔			Reis, Tergau y col, 2001
GBP	↑ GABA/anti-GLU	1,200 mg/PO	**2, 5,** 24	↔		↑	↑	↓			Reis, Tergau y col, 2001
		1,200 mg/PO	3, 6, 24	↔	↔					↔	Reis, Tergau y col, 2001
		800 mg/PO	**3,** 24	↔		(↑)	↑	↓			Rizzo, Quartarone y col, 2001
PTC	↑	4,000 mg/PO	1, 3, **6,** 24							↓	Wischer, Paulus y col ,2001
LTC	↑	3,000 mg/PO	**3, 9**	↔	↓	↔	↔	↔			Sohn, Kaelin-Lang y col, 2001

Cortical Excitability in Patients After Loading Doses of Lamotrigine: A Study with Magnetic Brain Stimulation

P. Manganotti, L. G. Bongiovanni, G. Zanette, M. Turazzini, and A. Fiaschi

Epilepsia, 40(3):318-321, 1999 Lippincott Williams & Wilkins, Inc., Philadelphia International League Against Epilepsy

- Se evaluaron los cambios de la excitabilidad motora cortical en 6 pacientes con crisis parciales complejas
- Antes del inicio del tratamiento con Lamotrigina (LMT) en monoterapia y en dosis crecientes desde 25 mg/día hasta alcanzar 200mg/día
- Se utilizó EMT con pulsos aislados
- El umbral de la respuesta motora aumentó luego de 2 semanas de tratamiento y continuó aumentando en paralelo con el aumento de las dosis de LMT
- La amplitud del PEM, el periodo de silencio cortical, el tiempo de conducción motora central no se modificaron con intensidades de estimulación bajas y altas
- Conclusión: dosis crecientes de LMT en monoterapia incrementa progresivamente el umbral motor en períodos cortos

Estimulación magnética

- Localización de área motora: el uso de EMT junto con RMN, en el preoperatorio de pacientes con disgenesias corticales que involucran el giro precentral, puede ser una herramienta no invasiva en el estudio de los mismos

- Localización de áreas del lenguaje: la EMT repetitiva puede generar déficit transitorios que permitan la localización del área del lenguaje y otras funciones corticales. Es cuestionable su utilización dado los efectos secundarios que puede producir

- Inducción de crisis: con la EMT con pulsos aislados existen escasos reportes de inducción de crisis en pacientes con epilepsia.
Con la EMT repetitiva deben ser respetados los protocolos de seguridad sugeridos. La posibilidad de inducir crisis está relacionada a la intensidad, frecuencia (mayor a 10 Hz) y duración del estímulo,así como la suceptibilidad individual del paciente

Tratamiento de la epilepsia

- La EMT con estímulos a 1Hz reduce la excitabilidad cortical (Chen 2000)

- La posibilidad de modular la excitabilidad cortical puede jugar un rol en el tratamiento potencial de enfermedades neurológicas y psiquiátricas

- Existen reportes de reducción de crisis durante la EMT y por períodos breves luego de finalizada:

  - EMT en trenes largos (15 minutos) en la corteza motora a baja frecuencia (0.9-1.0 Hz) reducen la excitabilidad de la corteza motora que persiste por períodos de más de 15 minutos , en ambos hemisferios. El mecánismo no es claro, pero podría ser similar a la depresión de duración prolongada (long term depression) (Chen,1997; Wassermann ,1998)
  - La estimulación a 1Hz por 15 minutos en la amígdala alterada por kindling en la rata, bloquea las postdescargas y las crisis (Weiss, 1995)
  - Un paciente con displasia cortical y crisis refractarias, redujo en 70% las crisis durante la EMT y durante el mes siguiente. (Menkes, 2000)

- No hay estudios doble ciego, con controles y placebo en grandes poblaciones

Simgle epileptic seizure
Jaime Carrizosa (Colombia)

CRISIS ÚNICA EPILÉPTICA

Jaime Carrizosa Moog
Neurólogo Infantil
Universidad de Antioquia - Medellín
Colombia

LASSE IV

DEFINICIONES

Epilepsia es un trastorno cerebral caracterizado por una predisposición a generar crisis y que produce consecuencias neurocognitivas y psicosociales.

Una crisis epiléptica es un episodio transitorio de signos y síntomas debidos a una descarga anormal hipersincrónica de las neuronas.

DEFINICIONES

Crisis aguda sintomática: crisis que ocurre en espacio temporal cercano a una lesión sistémica cercana como por ejemplo intoxicación, trauma, desequilibrio hidroelectrolítico etc.

-Tiene una clara relación temporal con el insulto

-No tiene una clara tendencia a recurrir

-No suelen desarrollar epilepsia

DEFINICIONES

Crisis única no provocada:

- No tiene un factor desencadenante
- Puede predisponer a recurrencia
- En mayores de 1 mes
- Todas las crisis que ocurren en 24 horas son una sola crisis
- 10 a 12% de las crisis únicas no provocadas son un estado epiléptico

EPIDEMIOLOGÍA

Table 1. Incidence (per 100,000 population per year) of seizures by type

Author (year)	Area (country)	Population	N. cases	Incidence				Design
				All	Acute symptomatic	Unprovoked	Single	
Loiseau et al. (1990)	Gironde (France)	1,128,164	804	71.3	29.0	42.3	18.3	Prospective
Hauser et al. (1993)	Rochester (U.S.A.)	2,003,357[a]	1,572	100.0	39.0	61.0	NA	Retrospective
Annegers et al. (1995)								
Forsgren et al. (1996)	Umea (Sweden)	101,583	218	76.0	20.0	56.0	NA	Prospective, adults
Jallon et al. (1997)	Geneva (Switzerland)	384,657	273	70.8	25.2	45.6	NA	Prospective
MacDonald et al. (2000)	London (U.K.)	100,230	NA	NA	NA	57.0	11.0	Prospective
Olafsson et al. (2005)	(Iceland)	882,151	501	NA	NA	56.8	23.5	Prospective

[a]Person-years (50-year period).
NA, not available.

Epilepsia, 49(Suppl. 1):8–12, 2008
doi: 10.1111/j.1528-1167.2008.01443.x

EPIDEMIOLOGÍA

Incidencia crisis única no provocada (Olaffson):

130,2 / 100 000 en menores de 12 meses

110,5 / 100 000 en mayores de 65 años

24,4 en hombres y 22,5 en mujeres

Table 2. Mortality of seizures in population-based studies by type

Author (year)	Area (country)	Person-years	N. cases	SMR (95% CI) All	Acute symptomatic	Unprovoked	Single	Design
Hauser et al. (1980)	Rochester (USA)	8,203	618	2.3 (1.9–2.6)	NA	2.3 (1.9–2.6)	2.3 (1.5–3.3)	Retrospective
Olafsson et al. (1998)	Iceland	6,308	224	1.6 (1.2–2.2)	NA	1.6 (1.2–2.2)	1.2 (0.1–4.0)	Retrospective
Loiseau et al. (1999)	Gironde (France)	864	864	9.3 (7.9–10.9)	10.3 (8.3–12.7)	4.1 (2.5–6.2)	NA	Prospective
Lindsten et al. (2000)	Vasterbotten (Sweden)	850	107	2.5 (1.2–3.2)	NA	2.5 (1.2–3.2)	NA	Prospective, adults
Beghi et al. (2005)*	(Italy)	3,098	333	2.8 (1.6–4.6)	NA	2.8 (1.6–4.6)	NA	Prospective, adults
Hesdorffer and D'Amelio (2005)	Rochester (USA)	35.7	438	149.1 (119.0–184.7)		NA	NA	Retrospective

NA, not available; SMR, standardized mortality ratio; 95% CI, 95% confidence interval.
*Randomized pragmatic trial.

"AL MENOS UN 10% DE LA POBLACIÓN MUNDIAL VA A TENER UNA CRISIS EPILÉPTICA DURANTE SU VIDA"

Berg&Shinnar, 1991

PROBLEMAS CLÍNICOS DIARIOS

- ¿Cuál es el diagnóstico diferencial?
- ¿Qué valor diagnóstico y pronóstico tienen el EEG y las imágenes?
- ¿Qué importancia tienen los exámenes de laboratorio?
- ¿Cuál es la probabilidad de recurrencia?
- ¿Se debe iniciar tratamiento?
- ¿Qué implicaciones tiene en la vida diaria: trabajo, estudio, conducción etc.?

FACTORES DE RIESGO DE RECURRENCIA

1. Edad menor de 12 años o mayor de 60 años
2. Antecedente familiar de epilepsia
3. Antecedente personal de convulsión febril
4. Etiología sintomática
5. Examen físico anormal
6. EEG anormal
7. Crisis durante el sueño (52% vs 30%)

IMÁGENES

Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society 2007

"Brain imaging with CT or MRI should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B)."

Practice parameter: Evaluating a first nonfebrile seizure in children Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society

- If a neuroimaging study is obtained, MRI is the preferred modality.

- Emergent neuroimaging should be performed in a child of any age who exhibits a postictal focal deficit (Todd's paresis) not quickly resolving, or who has not returned to baseline within several hours after the seizure.

• Nonurgent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic examination, a seizure of partial (focal) onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children under 1 year of age.

¿POR QUÉ LA DIFERENCIA ENTRE NIÑOS Y ADULTOS?

ESTUDIO Y AÑO	ANORMALIDADES EN IMÁGENES
Das; 2000	17%
Edmonstone; 1995	47%
Forsgren; 1996	4%
Hopkins; 1988	1%
Hui; 2001	11%
Schoenenberger; 1994	29%
Van Donselaar; 1992	3%

EXAMENES DE LABORATORIO

• Los examenes de laboratorio solo deben ser realizados teniendo en cuenta la condición individual del paciente, que incluye situaciones históricas o circunstanciales como vómito, diarrea, deshidratación o demora en recuperar la conciencia.

• El tamizaje toxicológico debe ser considerado si existe el antecedente de exposición a tóxicos o de abuso de sustancias.

EEG y Recurrencia

- Existen 12 estudios en adultos: Clase I: 1 y Clase II: 11
- Población total: 1799, 98% con EEG
- Anormalidades totales en EEG: 51%
- Anormalidades específicas como espiga onda lenta generalizadas o espigas focales: 29%
- Las anormalidades específicas están relacionadas con el riesgo de recurrencia.

Neurology 2007

HALLAZGOS EEG Y RIESGO DE RECAIDA EN EPILEPSIA NO SINTOMÁTICA – SHINNAR, 1993

HALLAZGOS EN EEG	RECAÍDA A 24 MESES
NORMAL	25%
ALTERACIONES NO EPILEPTIFORMES	34%
ALTERACIONES EPILEPTIFORMES	54%

RECOMENDACIÓN DE LA SAE Y DE LA AAN

A TODA PERSONA CON UNA CRISIS ÚNICA NO PROVOCADA SE LE DEBE REALIZAR UN EEG PORQUE AYUDA EN LA CLASIFICACIÓN DE LA CRISIS Y PORQUE TIENE UN VALOR PREDICTOR DE RECURRENCIA.

¿ES PERTINENTE ESA RECOMENDACIÓN?

- Con frecuencia, solo basados en la historia clínica se puede hacer una clasificación de la crisis o del síndrome ¿Validez del EEG?
- Si el consenso general es el de no tratar las crisis únicas no provocadas, entonces ¿para qué tomar un EEG?
- ¿Tiene sentido práctico invertir dinero en EEGs cuando no se va intervenir terapéuticamente o cuando se va solo a anunciar un posible riesgo de recurrencia?

PROPUESTA

- Realizar estudios propios, que consideren las particularidades latinoamericanas
- Diseñar guías o recomendaciones propias
- Analizar cada caso de manera individual

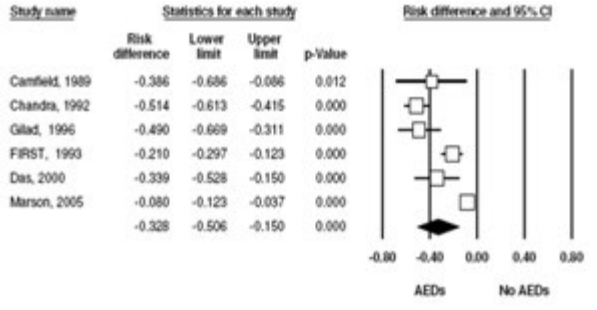
¿TRATAR O NO TRATAR?

ESTUDIO	EDADES	RECAIDAS % 1 AÑO
STOINK; 1998	NIÑOS	46
MARTINOVIC; 1997	NIÑOS	65
SHINNAR; 1996	NIÑOS	29
BOULLOCHE; 1989	NIÑOS	29
CAMFIELD; 1985	NIÑOS	40
ANNEGERS; 1986	NIÑOS-ADULTOS	36
HART; 1990	NIÑOS ADULTOS	37
HAUSER; 1990	NIÑOS ADULTOS	14

ESTUDIOS ALEATORIZADOS SOBRE EL TRATAMIENTO EN CRISIS ÚNICA

ESTUDIO Y AÑO	RECURRENCIA CON TRATAMIENTO	RECURRENCIA SIN TRATAMIENTO
CAMFIELD; 1989	14,3%	52,9%
CHANDRA; 1992	4,3%	55,7%
GILAD; 1996	22%	71%
FIRST; 1993	18%	39%
DAS; 2000	11,1%	45%
MARSON;2005	18%	26%

METANALISIS



EFECTO DEL TRATAMIENTO EN LA EVOLUCIÓN DE EPILEPSIA

- Estudio FIRST: es necesario tratar 4 personas con crisis única para lograr la remisión de una persona con epilepsia.
- Estudio MESS: es necesario tratar 14 personas con crisis única para lograr la remisión de una persona con epilepsia.
- El tratamiento de la crisis única no interfiere en el desarrollo normal de la epilepsia.

RIESGOS VITALES DEL TRATAMIENTO

EFECTO ADVERSO	MEDICACIÓN	RIESGO
SINDROME DE STEVEN JOHNSON o NECRÓLISIS EPIDÉRMICA TÓXICA	CBZ, PHT, LTG	1-10/ 10 000
SÍNDROME DE HIPERSENSIBILIDAD A ANTICONVULSIVANTES	PHT, CBZ, PB	1/ 1 000 – 10 000
ANEMIA APLÁSTICA	CBZ	1/ 200 000
AGRANULOCITOSIS	CBZ	1/ 70 000
MUERTE	CBZ	1/ 450 0000
ANEMIA APLÁSTICA	FELBAMATO	1/ 2000 – 37 000
HEPATOTOXICIDAD	VPA	1/ 500 – 37 000
ARRITMIAS	CBZ, PHT	?

Table 1. Proportion of patients reporting adverse events in the two arms of the MESS study, in which patients with single or rare seizures were randomized to immediate or deferred treatment with antiepileptic drugs[a]

	Patients randomized to immediate treatment (n = 722[a])	Patients randomized to deferred treatment (n = 721[b])
No adverse events reported	60.6%	69.2%
At least one adverse event reported	39.4%	30.8%
Depression, anxiety	5.8%	4.5%
Dizziness, unsteadiness	5.4%	4.6%
Gastrointestinal symptoms	6.0%	3.5%
Tiredness, drowsiness	6.0%	3.3%
Headache	5.4%	1.9%
Injury	4.1%	3.2%
Rash or acne	4.5%	2.0%
Surgery	3.1%	3.0%
Chest pain, myocardial infarction	3.1%	3.0%
Impaired memory or concentration	2.8%	2.2%
Weight gain, increased appetite	2.0%	2.7%
Behavioral problems	2.9%	1.7%
Tremor	2.5%	0.9%

INTERACCIÓN CON ANTICONCEPTIVOS (ACO)

FAE QUE REDUCEN ACO	CBZ, PHT,PB,PRM,OXC,TPM,LTG, FLB
ACO QUE REDUCEN FAE	VPA, LTG
NO PRODUCEN CAMBIOS	VPA,GBP, LTG,PGB, TG, ZS

RIESGO DEL TRATAMIENTO

1. TRATAMIENTO NO EFECTIVO
2. RIESGO VITAL
3. APARICIÓN DE EFECTOS SECUNDARIOS 15%
4. TOXICIDAD CRÓNICA
5. TERATOGENICIDAD
6. ROTULACIÓN DE ENFERMO Y ESTIGMA

BENEFICIOS DEL TRATAMIENTO

1. ¿POSIBILIDAD DE EVITAR LESIONES POR LAS CRISIS?
2. ¿POSIBILIDAD DE EVITAR UN ESTADO EPILÉPTICO?
3. REDUCCIÓN DE CRISIS EN LOS SIGUIENTES 24 MESES
4. SEGURIDAD EN EL AMBIENTE LABORAL Y SOCIAL

IMPACTO EMOCIONAL

- Personas con epilepsia refieren ansiedad ante una nueva crisis en un 30%
- Las mismas personas refieren molestia por cambios en el estilo de vida en un 25%
- Muchas personas refieren molestia por tener que tomar FAE
- Al recibir el diagnóstico de epilepsia sintieron rabia, tristeza y temor

IMPACTO EMOCIONAL CON CRISIS ÚNICA

Al comparar la calidad de vida de las personas con crisis única con personas con epilepsia controlada y con personas con hipertensión, no se encontraron diferencias.

Sin embargo al año de la crisis única la mitad de los pacientes estaban medicados, y un 17% tenía temor frente a una nueva crisis y un 38% refería que esa única crisis había provocado un impacto moderado a extremo en su calidad de vida. (Dworetzky; 2000)

IMPACTO PSICOSOCIAL

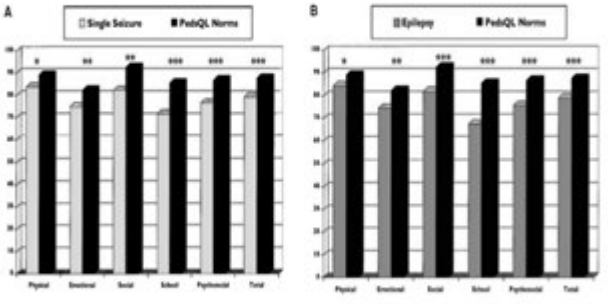
- **Restricciones en la vida diaria:** trasnocho, consumo de alcohol, conducir, deporte,cocinar
- **Empleo:** chofer, cirujano, militar, piloto etc.
- **Aseguradoras y prestamos bancarios:** limitan su ingreso o su aporte
- **Relaciones interpersonales:** madres con bebés, amigos, jefes, empleados, estigma o sensación de limitaciones
- **No tener dinero** para la medicación y las consultas o exámenes

Even a single seizure negatively impacts pediatric health-related quality of life

*Avani C. Modi, *Andrea S. King, †Sally R. Monahan, *Julie E. Koumoutsos, †Diego A. Morita, and †Tracy A. Glauser

*Division of Behavioral Medicine and Clinical Psychology, Center for the Promotion of Adherence and Self Management, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.; and †Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.

CALIDAD DE VIDA EN CRISIS ÚNICA Y EPILEPSIA EN NIÑOS



RECOMENDACIÓN

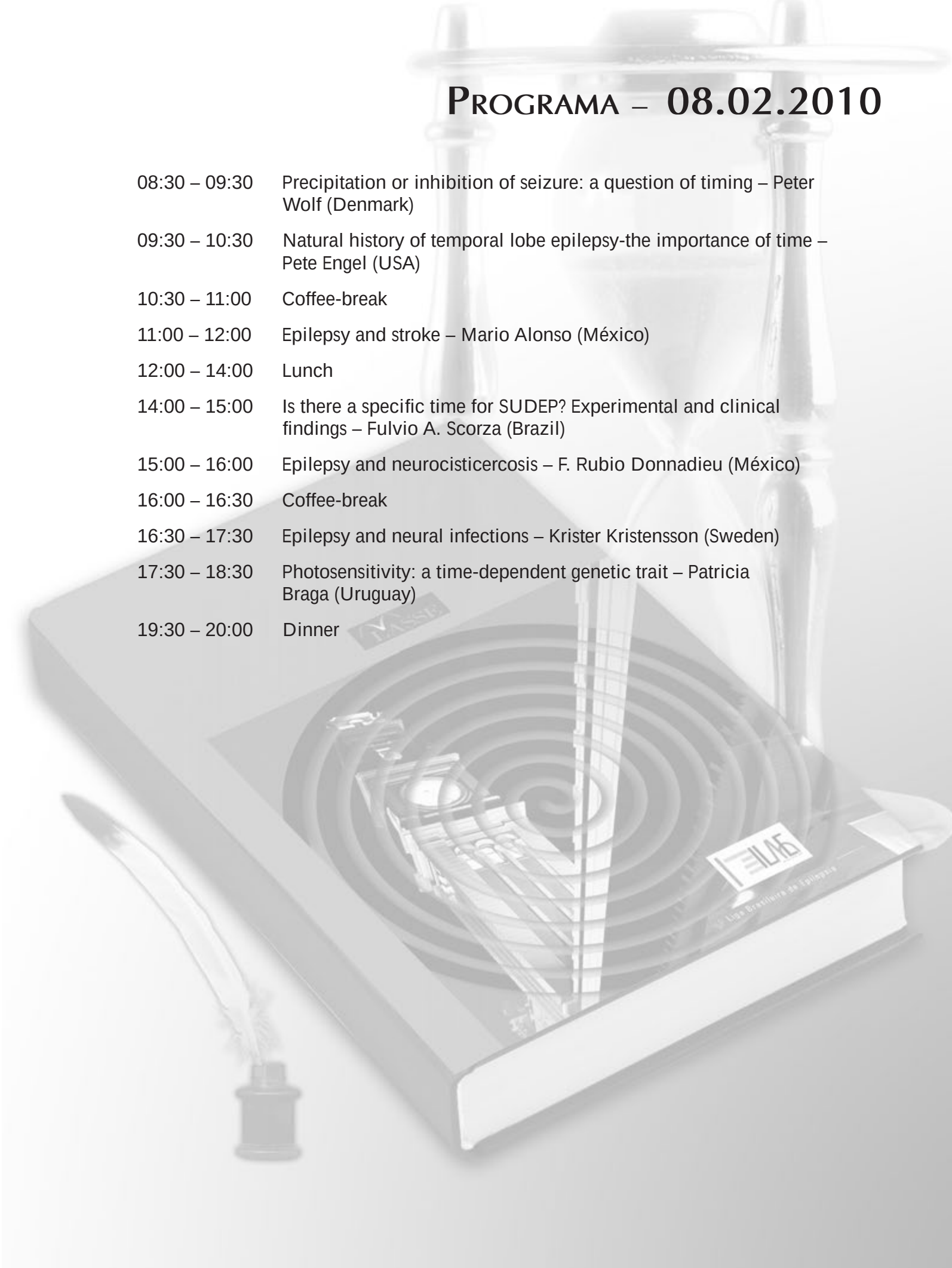
La decisión de iniciar tratamiento en una persona con crisis única debe ser consultada de manera individual, tomando en cuenta los riesgos y beneficios del tratamiento.

Existe una fuerte orientación a no tratar la primera crisis epiléptica en niños y adultos, por el bajo riesgo de recurrencia (30%) y la posibilidad de efectos secundarios con los FAE (15%).

GRACIAS

Programa – 08.02.2010

08:30 – 09:30	Precipitation or inhibition of seizure: a question of timing – Peter Wolf (Denmark)
09:30 – 10:30	Natural history of temporal lobe epilepsy-the importance of time – Pete Engel (USA)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Epilepsy and stroke – Mario Alonso (México)
12:00 – 14:00	Lunch
14:00 – 15:00	Is there a specific time for SUDEP? Experimental and clinical findings – Fulvio A. Scorza (Brazil)
15:00 – 16:00	Epilepsy and neurocisticercosis – F. Rubio Donnadieu (México)
16:00 – 16:30	Coffee-break
16:30 – 17:30	Epilepsy and neural infections – Krister Kristensson (Sweden)
17:30 – 18:30	Photosensitivity: a time-dependent genetic trait – Patricia Braga (Uruguay)
19:30 – 20:00	Dinner



Precipitation or inhibition of seizure: a question of timing
Peter Wolf (Denmark)

EPILEPSIHOSPITALET
FILADELFIA

Precipitation or inhibition of seizures:
a question of timing
Peter Wolf (Denmark)

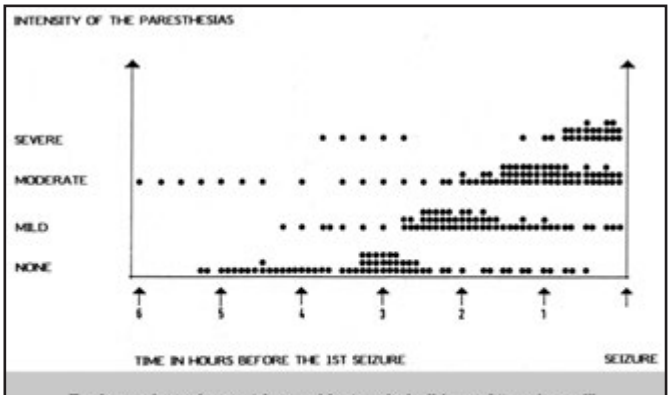
LASSE IV, Guarulhos
February 1 – 10, 2010

EPILEPSIHOSPITALET
FILADELFIA

Focal epilepsy: Patient with cryptogenic PLE and seizures precipitated by touch (video)

- Seizure types: tonic versive; secondary GTC
- Several versive sz per day, all provoked
- Preceded by increasing paresthesias in trigger zone (left cheek, neck and shoulder: epilepsia partialis continua, EPC)
- All sorts of touch, including by himself, trigger seizures
- No element of surprise (as in startle epilepsy)
- When paresthesias are slight or absent no seizure is triggered

www.epilepsihospitalet.dk



Tonic versive seizures triggered by touch: build-up of "prodromal" paresthesias before the 1. seizure of the day.

(Source: Wolf P, Dockweiler U: Deconditioning therapy in a patient with versive seizures precipitated by touch. In: A. Beaumanoir, H. Gastaut, R. Naquet (Eds): Reflex Seizures and Reflex Epilepsies. Ed. Médicine et Hygiène, Genève 1989, 447 – 451)

EPILEPSIHOSPITALET
FILADELFIA

Significance and treatment

- EPC = ictogenesis "on the edge": constant very limited epileptic avtivity without spread
- Treatment: frequent application of sensory stimuli *before* the paresthesias reached critical intensity
- Result: the paresthesias stayed on low level
- > 90% reduction of induced focal seizures
- Exemplary: identical stimuli trigger or inhibit or prevent, dependent of timing / activation of the ictogenic system
- GTCS in sleep were not influenced

In our retrospective case collection of non-Rasmussen, non-stroke Epc, exogenous precipitation was reported in 21/60 cases, and exogenous inhibition in 11/60

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Seizure precipitation by specific stimuli = reflex epilepsy

- Reflex epileptic mechanisms have over the last years received increasing interest because they enable us to non-invasively study ictogenic mechanisms in human epilepsies
- Their relations to various epilepsy syndromes have become better established
- Most common in idiopathic generalised epilepsies
- Frequently genetically determined
- Imaging studies have been performed

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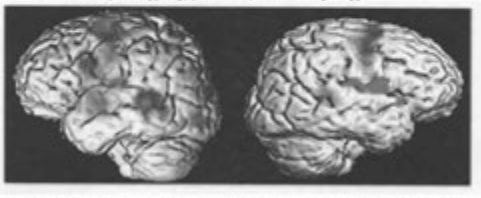
Primary Reading Epilepsy: the findings

FULL-LENGTH ORIGINAL RESEARCH

Imaging seizure activity: A combined EEG/EMG-fMRI study in reading epilepsy

*Afraim Salek-Haddadi, †Thomas Mayer, *Khalid Hamandi, *Mark Symms, ‡Oliver Josephs, *Dominique Fluegel, ‖Friedrich Woermann, *Mark P. Richardson, ‖Uta Noppeney, ¶Peter Wolf, and *Matthias J. Koepp



Reading-induced szs **Language activations** **Motor mapping mouth/jaw**

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"Reflex szs occur in RE when a critical mass of neurons are activated through a provoking stimulus within cortico-reticular and cortico-cortical circuitry subserving normal funtions." (Salek-Haddadi et al. Epilepsia 2009; 50:256-264)

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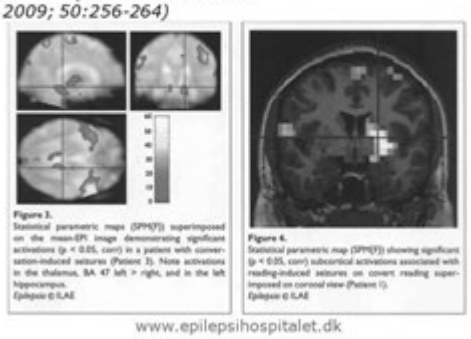

Figure 3.
Statistical parametric maps (SPM{T}) superimposed on the mean-EPI image demonstrating significant activations ($p < 0.05$, corr) in a patient with conversation-induced seizures (Patient 3). Note activations in the thalamus, BA 47 left > right, and in the left hippocampus.
Epilepsia © ILAE

Figure 4.
Statistical parametric map (SPM{T}) showing significant ($p < 0.05$, corr) subcortical activations associated with reading-induced seizures on covert reading superimposed on coronal view (Patient 1).
Epilepsia © ILAE

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Reflex epilepsies indicate ictogenic mechanisms

(Bickford and colleagues 1953, 1969)

Three possible pathways of convulsive effects of ILS:

1. Transcortical
2. Cortical-thalamic (eye → striate cortex → diffuse thalamic system → motor cortex)
3. Subcortical (eye → lateral geniculate body → thalamus → motor cortex

Very little discussed

Tools for study of these only recently available

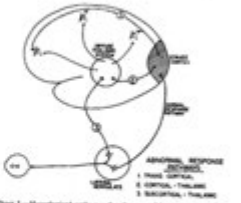

Chart 1.—Hypothetical pathways for the convulsive response to light.

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Thalamus, FS + absence: fMRI

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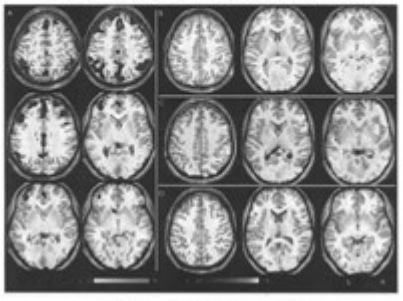
BRIEF COMMUNICATION

Mapping brain activity on the verge of a photically induced generalized tonic–clonic seizure



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Reflex epilepsy with simple triggers

- Idiopathic (Generalized) Epilepsies
  - Photosensitivity and television-induced seizures
  - Eye closure sensitivity
  - Fixation-off sensitivity
  - Pattern sensitivity
- Focal Epilepsies
  - Precipitation by somatosensory stimuli, e.g. touch
  - Precipitation by proprioceptive stimuli (movements, startle)
  - Other (olfactory, gustatory, audiogenic, vestibular)

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Reflex epilepsy with complex triggers

Oro-facial reflex myocloni (ORM)
Praxis-induced seizures
Seizures precipitated by eating
Other complex sensorimotor triggers
- (Hot water epilepsy?)
- Seizures precipitated by tooth-brushing

Complex auditory stimuli
- Musicogenic seizures
- Other (musical pitch, voices of radio speakers)

Complex visual stimuli (own hand, safety pin etc.)
Emotional precipitation, psychogenic epileptic seizures

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Inhibition of seizures?

- Seizure arrest is a traditional treatment going back to the time of Galen: ligature around the convulsing limb proximal to the convulsing part
- Jackson JH. Case of convulsive attacks arrested by stopping the aura. Lancet 1868; i:618, etc.

» Gowers WR. Epilepsy and other chronic convulsive diseases. Wood, London 1881: aspect of timing

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Inhibition and timing

- Efron R. The effect of olfactory stimulus in arresting uncinate fits. Brain 1956; 79: 267-281
- sGTC with complex aura of 30+ min, stereotyped evolution

Depersonalisation, distortion of time perception, altered sense of smell → "halfway point": increase + premonition of smell → olfactory hallucination → auditive hallucination → tonic version of eyes and head perceived as forced movement → sec GTCS

⋯→ no effect ⋯→ abortion, rotatory seizure ⟶ sz "lysis"

Ictal EEG demonstrated left TL seizure onset and confirmed suppression of discharges by olfactory stimulus
The stimulus had to be strong and unpleasant
"It was unnecessary to wait for the moment just before the particular sensory aura occurred to introduce the stimulus." But timing is important: "There is a time beyond which the stimulus is no longer effective"

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Sensory inhibition (cont)

Review of olfactory inhibition incl aromatherapy:

- Jaseja H. Scientific basis behind traditional practice of application of "shoe-smell" in controlling epileptic seizures in the eastern countries. Clin Neurol a Neurosurg 2008; 110:535-538: role of widespread desynchronisation?

Wolf P. Aura interruption: how does it become curative? . In Wolf P (ed) Epileptic seizures and syndromes, with some of their theoretical implications. J. Libbey, London 1994, 667 - 673

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Inhibition: mechanisms?

- ***Yanagisawa T et al. Movement induces suppression of interictal spikes in sensorimotor neocortical epilepsy. Epilepsy Research 2009; 87:12-17***
- 2 pat with perirolandic FCD in intensive monitoring with subdural plates: changes in spike count with voluntary movements.
- Role of desynchronisation especially in the theta band in the perirolandic region
- Timing not mentioned but stimulation was tested in phase of high spike frequency

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Conclusions

1. Seizure triggers in reflex epilepsies well-described, their relevance for the understanding og human ictogenesis is getting understood. Role of timing little investigated
2. Exogenous inhibition of seizures ("arrest", "lysis") time-honoured therapeutic approach, few publications, investigated modalities: somatosensory, olfactory, proprioceptive motor. Role of stimulus timing well demonstrated
3. What about precipitation and inhibition in same patients?

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Patient with tonic versive seizures precipitated by touch

- Presence of EPC (constant very limited epileptic avtivity without spread) precondition for reflex response
- Treatment: frequent application of sensory stimuli *before* the paresthesias reached critical intensity
- Result: the paresthesias stayed on low level
- > 90% reduction of induced focal seizures
- Exemplary: identical stimuli trigger or inhibit or prevent, dependent of timing / activation of the ictogenic system

In our retrospective case collection of non-Rasmussen, non-stroke EPC, exogenous precipitation was reported in 21/60 cases, and exogenous inhibition in 11/60

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Inhibition in reflex epilepsy?

EPILEPSIHOSPITALET FILADELFIA

- Guaranha MSB et al: Provocative and inhibitory effects of a video-EEG neuropsychological protocol in JME. Epilepsia 2009

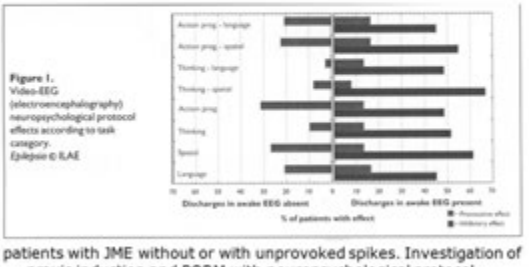

Figure 1.
Video-EEG (electroencephalography) neuropsychological protocol effects according to task category.
Epilepsia © ILAE

76 patients with JME without or with unprovoked spikes. Investigation of praxis induction and PORM with neuropsychological protocol

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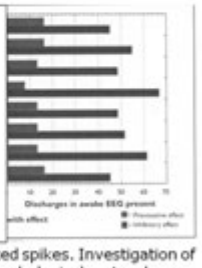
Inhibition in reflex epilepsy?

EPILEPSIHOSPITALET FILADELFIA

- Guaranha MSB et al: Provocative and inhibitory effects of a video-EEG neuropsychological protocol in JME. Epilepsia 2009

Patients with unprovoked spikes (n = 31)	
Only provocation	3 (10%)
Only inhibition	17 (55%)
Provocation and inhibition	11 (35%)

Inhibition by non-specific arousal?



76 patients with JME without or with unprovoked spikes. Investigation of praxis induction and PORM with neuropsychological protocol

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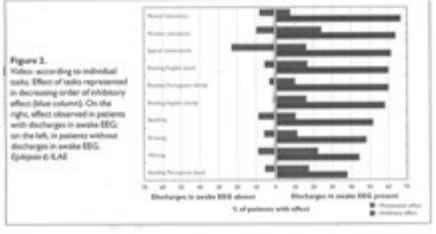
Individual tasks



Findings consistent with at least partially specific inhibitory action

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Summary and conclusion

- In many epilepsies, ictogenesis seems to be due to interactions in (still insufficiently investigated) neuronal networks or subsystems
- To some extent, these interactions seem to be modifiable by exogenous, specific and non-specific sensory and cognitive stimuli
- Although they seem to be different in focal epilepsies and system epilepsies, the fundamental principles seem to be similar

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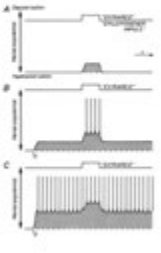
Seizure arrest: principle of action

- Does not prevent primary ictogenesis, but spread of seizures of local onset
- Treatment of focal, not of generalised seizures
- Principle: Blockade of relevant populations of neurons by maximal and sustained depolarisation which makes them non-recruitable.



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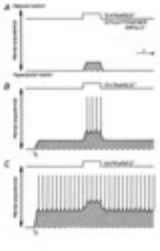
Significance of right timing

- Described by Gowers
- Analysed in more detail by Efron
- One and the same stimulus in one and the same patient can trigger, stop or prevent a seizure
- It depends on when the stimulus is given



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Epilepsy and stroke
Mario Alonso (México)

Epilepsy and Stroke

Mario A: Alonso Vanegas

LASSE

Tamemes
Código Mendoza
"¿Crees que soy tu tameme, ghey?"

Churchill, Roosevelt, and Stalin at a conference in Yalta after World War II.

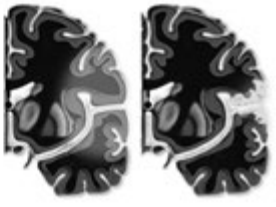
Stroke

- Es el término utilizado para el déficit neurológico focal o difuso que dura más de 24 horas y es causado por una lesión focal o difusa del tejido cerebral de origen vascular

World Health Organization

Causa y sitios más comúnes de hemorragia

Hemorragias intracerebrales
Hipertensión
Anormalidades de la coagulación
Prescripción de antiguagulantes (coumadin)
Anormalidades de la cuenta plaquetaria (trombocitopenia)
Sangrado como en la hemofilia
Prescripción de fármacos trombolíticos
Malformaciones vasculares
Amiloide en los vasos sanguíneos cerebrales
Trauma
Sangrado en tumores e infartos cerebrales
Hemorragias subaracnoideas
Aneurismas arteriales
Malformaciones vasculares cercanas a la superficie
Bleeding tendencies
Trauma craneal
Hemorragias subdurales
Trauma
Bleeding tendencies
Hemorragias epidurales
Trauma



Strokes can be divided into two very broad groups: hemorrhage and ischemia.

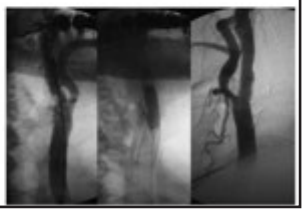
Statements

- The most important aspect of stroke is its effect on the individual who develops a stroke.
- Stroke is the third leading cause of death in most countries around the world.
- The history of the world has undoubtedly been greatly affected by stroke.
- Stroke is a term that is used to describe brain injury caused by an abnormality of the blood supply to a part of the brain.
- Strokes can be divided into two very broad groups: hemorrhage and ischemia.
- A decrease of blood supply to the brain is called *ischemia*.
- The importance of differentiating the types of ischemia is obvious.
- Degenerative changes in the arteries that supply blood to vital organs develop to some extent in all of us if we live long enough.
- Hypertension is the single most important risk for brain ischemia and brain hemorrhage.
- A number of different heart conditions and diseases can lead to brain embolism.
- Myocardial infarcts, commonly known as "heart attacks," are another common source of brain embolism.
- The ability of the blood to clot is a very important defense mechanism.
- There are risk factors and behaviors that predispose individuals to develop a stroke.
- Hypertension is more common in diabeticsthan in individuals who have normal blood sugar.
- High blood cholesterol levels are an important risk factor for coronary artery disease.
- Strokes cause psychologic and physiologic changes in self-image.

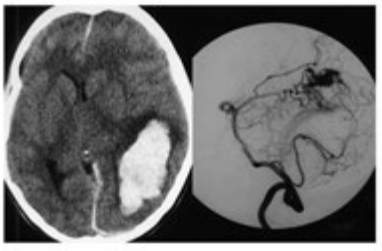
Listen. Listen to your patient. He is giving you the diagnosis."
Dr. Rene Laennec

Isquémico

- Oclusión vascular
  - Enfermedad arterial
  - Embolismo cardiáco
  - Enfermedad hematológica



Hemorrágico



- Ruptura vascular
  - Enfermedad arterial
  - Enfermedad hematológica

Factores de riesgo

- Modificables
  - Hipertensión arterial, Fibrilación auricular, Cardiopatía isquémica, Enfermedad carotídea, Diabetes Mellitus, Dislipidemia
  - Factores de riesgo conductuales
    - Tabaquismo, consumo de alcohol, actividad física, dieta, obesidad
- No modificables
  - Edad
  - Sexo
  - Grupo étnico
  - Herencia

Chong JY, Continuum 2005

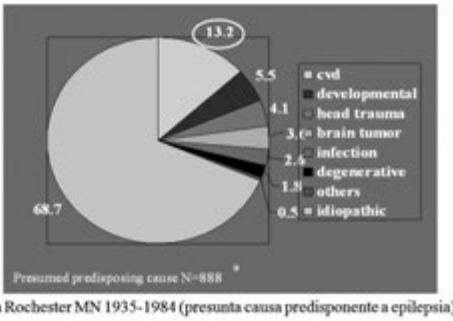
Epilepsia

- Epilepsia, como una afección crónica de etiología diversa, caracterizada por crisis recurrentes, debidas a una descarga excesiva de las neuronas cerebrales (crisis epilépticas) asociadas a manifestaciones clínicas y paraclínicas.

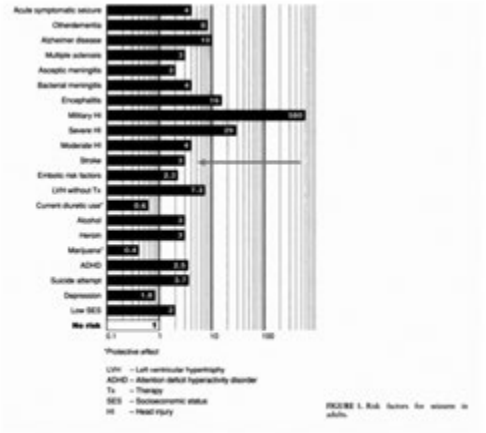
World Health Organization, 1973

Asociación entre epilepsia y stroke o ictus

- Bien documentada, numerosos estudios poblacionales y de cohorte clínico hospitalaria



Estudio de incidencia Rochester MN 1935-1984 (presunta causa predisponente a epilepsia)



Epilepsy: A ***Comprehensive Textbook*** 978-0-7817-5777-5. Editors Jerome ***Engel*** Jr and Timothy A. Pedley MD

Otras evidencias epidemiológicas

• El estudio de Rotterdam concluyó que la historia de stroke estaba asociada con un riesgo significativo de desarrollar epilepsia (OR 3.3; 95% CI 1.3—8.5), así como con el desarrollo de epilepsia tardía (OR 3.1; 95% CI 0.9—10.6)

TABLE 2. *Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between each putative risk factor and epilepsy, adjusted for age and gender*

Epilepsy (univariate)	Lifetime epilepsy (n = 45)		Late-onset (n = 39)	
	OR	95% CI	OR	95% CI
Vascular determinants				
Stroke	3.3	1.3–8.5	3.1	0.9–10.6
Total cholesterol (mmol/l)	1.1	0.6–2.0	1.3	0.6–2.8
Left ventricular hypertrophy	1.5	0.5–4.4	2.6	0.6–7.6
Myocardial infarction	1.4	0.5–3.9	1.7	0.6–4.9
Peripheral arterial disease	1.6	0.8–3.0	1.3	0.7–3.6
Any vascular determinant*	1.8	1.0–3.2	2.0	0.9–4.2
Other factors				
Head trauma	2.7	1.6–4.7	1.8	0.8–4.0
Meningitis	4.6	1.1–18.7	3.6	0.8–15.1

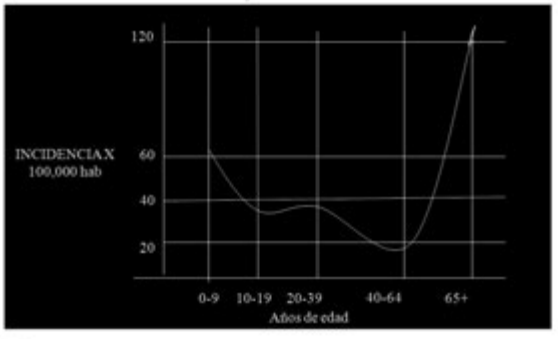
* Defined as total cholesterol >6.5 mmol/l or previous myocardial infarction or peripheral arterial disease or left ventricular hypertrophy.
OR, odds ratio; CI, confidence interval.

•En este estudio se encontró un relación entre epilepsia y factores de riesgo vascular tales como colesterol total e hipertrofia ventricular.

Li, X., et al. 1997. Vascular determinants of epilepsy: Rotterdam study. Epilepsia 38 (11), 1216—1220.

Incidencia

- Epilepsia en + 65 años: 134/100,000
- Alzheimer: 123/100,000



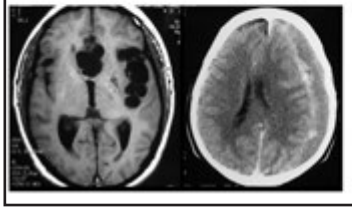
Causa de Crisis

20 a 60 años

- Tumor
- NCC
- Trauma
- EVC
- Infección

Más de 60 años

- EVC 33%
- Tumor, metastático 4%
- Trauma 1%
- T. metabólicos
- Infecciones 0.6%
- NCC
- Idiopatica 49%
- Alzheimer 11.7%



Stroke es la causa más común de crisis de reciente diagnóstico en los adultos mayores, correspondiendo a 35% de la epilepsia sintomática de reciente diagnóstico en los mayores de 65 años. (Asconape and Penry, 1991; Ramsay et al., 2004).

Table 1 Frequency of onset seizures and development of post stroke seizures by type of first stroke

Type of first stroke	No (%; 95% CI) of patients with onset seizures	Number (%) of patients with onset seizures who developed post stroke seizures
Cerebral infarction (n=545)	10 (2; 0.9 to 3.4)	4 (40)
Primary intracerebral haemorrhage (n=66)	2 (3; 0.4 to 10.5)	1 (50)
Subarachnoid haemorrhage (n=33)	2 (6; 0.7 to 20.2)	0
Unknown (n=31)	0 (0; 0 to 11.2)	0
Total (n=675)	14 (2; 1.1 to 3.5)	5 (36)

Table 2 Number (% of cohort; 95% confidence interval) of patients with single and recurrent seizures after first stroke (four patients who had seizures within a few hours of death as part of a terminal illness, or seizures that started before the stroke, were excluded)

Classification of first stroke	Single post stroke seizures	Recurrent post stroke seizures	Total
Cerebral infarction (n=545)	17 (3)	18 (3)	35 (6; 4 to 9)
Total anterior circulation infarction (n=92)	5 (5)	10 (11)	15 (16)
Partial anterior circulation infarction (n=185)	5 (3)	3 (2)	8 (4)
Lacunar infarction (n=137)	3 (2)	2 (1)	5 (3)
Posterior circulation infarction (n=129)	4 (3)	3 (2)	7 (5)
Primary intracerebral haemorrhage (n=66)	3 (5)	4 (6)	7 (11; 3 to 18)
Subarachnoid haemorrhage (n=33)	3 (9)	3 (9)	6 (18; 5 to 31)
Unknown (n=31)	0	0	0
Total (n=675)	23 (3)	25 (4)	48 (7; 6 to 9)

675 pacientes con stroke seguidos por un mínimo de 2 años.
19 de los 675 pacientes (3%) tenían historia de una o más crisis previas al evento.

Burn, J., et al. 1997. Epileptic seizures after a first-ever stroke: the Oxfordshire Community Stroke Project. BMJ 315, 1582—1587.

Table 3 Cumulative actuarial risks (95% confidence intervals) of experiencing a seizure after stroke by type of first stroke (19 patients with a history of prestroke seizures were excluded)

Time after stroke	Cerebral infarction	Primary intracerebral haemorrhage	Subarachnoid haemorrhage	Total
1 year	[illegible]	[illegible]	[illegible]	[illegible]
2 years	[illegible]	[illegible]	[illegible]	[illegible]
3 years	[illegible]	[illegible]	[illegible]	[illegible]
4 years	[illegible]	[illegible]	[illegible]	[illegible]
5 years	[illegible]	[illegible]	[illegible]	[illegible]

El riesgo actuarial a 5 años para desarrollar crisis (excluyendo los 19 pacientes con historia de crisis previa y 3 pacientes cuya crisis ocurrió poco antes de la muerte no relacionada) fue de 11.5% (95% intervalo de confianza 4.8% a 18.2%).

Los sobrevivientes que independientes a 1 mes del evento tuvieron un riesgo mínimo de crisis.

Burn, J., et al. 1997. Epileptic seizures after a first-ever stroke: the Oxfordshire Community Stroke Project. BMJ 315, 1582—1587.

En el Seizures After Stroke Study (SASS) un estudio prospectivo, multicéntrico con participación de hospitales universitarios de Canadá, Australia, Israel, e Italia

Se presentaron crisis
en 168 (8.9%) de 1897 pacientes con stroke
en 28 [10.6%] de 265 con stroke hemorrágico y
en 140 [8.6%] de 1632 con stroke isquémico).

Bladin c, et al. Seizures After Stroke: A Prospective Multicenter Study. Arch Neurol. 2000;57:1617-1622.

Estudio de cohorte poblacional en Suiza (409 pacientes con edad promedio de 72 años seguidos por 3.5-7 años)

Incluyó	Riesgo acumulativo de epilepsia
TIA (13%)	3%(±2) a 1 año
Hemorragia intracerebral (11%)	5%(±4) a 5 años
Infartos (76%)	

Viitanen M, Erikson S, Asplund K. Risk of recurrent stroke, myocardial infarction and epilepsy during long term follow up after stroke. *Eur Neurol* 1988;28:227-31

Se han atribuido crisis a TIA en 3.7% de pacientes (Kilpatrick et al., 1990), sin embargo es muy probable que algunos casos correspondan a 'limb shaking TIA's' por isquemia en zonas marginales más que crisis verdaderas (Tatemichi et al., 1990).

Seguramente las variantes en estas cifras corresponden a irregularidades en el diseño: tamaño, tipo y edad de la población, tipo de crisis, tiempo de seguimiento, facilidades de imagenología….

Otras asociaciones evidentes: Epilepsia ←——→ Infarto

• Un estudio poblacional encontró un riesgo relativo de 2.89 para un stroke subsecuente en pacientes con crisis tardias comparados con los controles (Paul et al., 2004), y el riesgo de desarrollar un stroke subsecuente en pacientes con crisis tardias se compara con:

el riesgo relativo de 1.4 asociado con colesterol de baja HDL
(Wannamethee et al., 2000)

el doble del riesgo asociado con fumar
(Shinton and Beevers, 1989; McCarron et al., 2001),

dos a tres veces el riesgo asociado con vida sedentaria.

•Un estudio de TC controlado de 132 pacientes mostró que 21% de los pacientes con epilepsia "criptogénica" arriba de 60 años de edad, tenian evidencia en la TC de infarto previo, generalmente sin evidencia clinica excepto por la epilepsia y esta tasa de infarto silencioso fue mucho mayor que en los controles.

•Similarmente, 23 de 118 pacientes con crisis post-trombóticas tuvieron evidencias de 'infartos silenciosos' (Sung and Chu, 1990).

Frecuencia de crisis postictus

Table 1 The frequency of seizures after stroke—prospective and retrospective studies.

S. no.	Author	Type of study	Name of study	Type of stroke	Pts recruited (n)	Frequency (overall)	Early seizures %	Late seizure %	0 %	Epilepsy
1	Kilpatrick et al. (1990)	P		B	1000		<2 weeks 4.4%		6.5% cortical location 7% 3.7%	
2	Kotila and Waltimo, 1992	R		B	200	14%			14%	
3.	Lancman et al. (1993)	P		B	219	10.4%	55% of total	45%	7.1%	
4	Giroud et al. (1994)	P		B	1640	5.5%	<15 days 5.5%			
5	So et al. (1996)	P		IS	535	4.7	<1 week 6%	1.0% during the first year to 7.4% by 5 years		3.3%
6	Arbix et al. (1997)	P		B	1220	<48h 2.4%	2.4%	–	2.4%	
7	Reith et al. (1997)	P	The Copenhagen stroke study	B	1197	<2 weeks 4.2%, <2y0 2.4%	4.2%			
8	Burn et al. (1997)	P	OCSP	B	675		<2y0 2%	5.7% at 1 year and 11.5% at 5 years		
9	Bladin et al. (2000)	P	SASS	B	1897	8.9%	<2 weeks 4.8	<2 weeks 3.8	8.6	2.5%
10	Labovitz et al. (2001)	P	nOmaSS	B	904	4.1%	4.1% <1 week			–
11	Cheung et al. (2003)	R		B	1000	3.4%	<1 month 1.6%	1 year 1.8%	3.4%	
12	Lamy et al. (2003)	P	Part of PFO-ASA study	IS	581	2.4%	2.4% <1 week	2% (1 year) 5% (2 year)	–	2.2% 2 year
13	Lossius et al. (2005)	P	Akershus Stroke study	IS	464		<1 week 5.7%	1 year 2.5% 7–8 year 1.1%		1.1%

Type of study: P—prospective, R—retrospective. Type of stroke: IS—ischaemic study, H—haemorrhage, B—both.

Numerosos estudios hospitalarios de la incidencia de epilepsia post-stroke encontrando una frecuencia de 2.4—14%

Crisis postictus

- Las crisis postictus se clasifican según el criterio temporal en tempranas o tardías. La Liga Internacional contra la Epilepsia define como crisis tempranas las ocurridas dentro de los primeros 7-14 días después del ictus, aunque en algunos estudios se han utilizado otras clasificaciones.

Crisis tardías vrs tempranas

- La incidencia de crisis tempranas se ha reportado entre 2.4% y 25%.
- El riesgo de crisis tardías se ha encontrado entre 3.0 y 8%.
- Las crisis tempranas (especialmente las ocurridas en las primeras 24 horas del evento) aumentan el riesgo de epilepsia subsecuente, desarrollándose epilepsia en aproximadamente un tercio, si ocurre una crisis tardía, el riesgo de epilepsia (recurrencia de crisis) es mayor.
- En el estudio de casos del RU se encontró una indiencia de crisis de 5.7% en las primeras 24 hrs en 230 pacientes . (Shinton et al. 1988).El Dx se hizo clínico, neuroimagen solo en 20%
- Un estudio con seguimiento de 26 meses mostró que 32% de pacientes con crisis tempranas tuvieron crisis tardías. (Kilpatrick et al., 1992).
- Estudio poblacional con 535 pacientes consecutivos mostró que los pacientes con crisis post isquémicas tempranas tenían una frecuencia 8 veces mayor de desarrollar crisis post isquémicas tardías (95% CI, 2.8—21.7) y 16 veces mayor de desarrollar epilepsia (95% CI, 5.5—49.2) comparado con pacientes sin crisis tempranas. (So et al., 1996)

- En el estudio de Oxfordshire, 35% de los pacientes que presentaron crisis eventualmente desarrollaron epilepsia. (Burn, J., et al. 1997).
- En un estudio de cohorte hospitalaria en Taiwan, 35 % de los pacientes que presentaron crisis tempranas y 90% de los pacientes que presentaron crisis tradías desarrollaron epilepsia. (Sung and Chu,1990).
- En el SASS las crisis con recurrencia tardía desde la primera crisis (>2 weeks) fueron un factor independiente de riesgo para el desarrollo de epilepsia después de stroke isquémico (HR, 12.37;95% CI, 4.74—32.32; $p < .001$) (Bladin et al., 2000).

Crisis tempranas

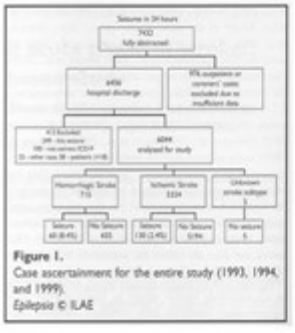


Figure 1.
Case ascertainment for the entire study (199), 1994, and 1999).
Epilepsia © ILAE

Table 2. Incidence of seizures in patients with ischemic and hemorrhagic strokes within the first 24 h of symptom onset ($p < 0.0001$)

Type of stroke	Seizure ($n = 190$) N	Seizure ($n = 190$) %	No seizure ($n = 5854$) N	No seizure ($n = 5854$) %	Rate of seizures
Infarct	120	63.2%	4069	69.5%	2.9%
TIA	10	5.3%	1125	19.2%	0.9%
ICH/IVH	43	22.6%	503	8.6%	7.9%
SAH	17	9.0%	152	2.6%	10.1%
Unknown	0	0.0%	5	0.1%	0.0%

Szaflarski JP, et al Incidence of seizures in the acute phase of stroke: a population-based study. Epilepsia. 2008, 49(6):974-81.

Crisis como primera manifestación

- Las crisis pueden ser la sintomatología inicial
- En un estudio francés de 90 pacientes con epilepsia después de stroke, la crisis fue el signo inicial en 80 (89%) (Giroud et al., 1994).
- De las crisis tempranas, éstas se desarrollaron en las primeras 24 horas del stroke en:
  - 40% and 78% de los casos (Giroud et al., 1994).
  - 40% (Bladin et al., 2000),
  - 46% (Labovitz et al., 2001),
  - 66% (Reith et al., 1997),
  - 71% (Lamyet al., 2003).

Epilepsia postictus en pacientes jóvenes

Estudio prospectivo de 581 pacientes con stroke isquémico entre las edades de 18 y 55 años,

- incidencia de crisis tempranas: 2.4% (71% en las primeras 24 h)
- incidencia de crisis tardias: 5.5% (hasta 3 años de seguimiento)
- los pacientes con crisis tempranas presentaron recurrencia de crisis con una frecuencia 5 veces mayor y la tasa de recurrencia en crisis tardías fue de 55%.
- los factores de riesgo para las crisis recurrentes tardías fueron:
  - crisis tempranas post stroke isquémico,
  - strokes de gran área y
  - signos corticales

(Lamy et al., 2003).

Dos estudios hospitalarios

- 6.6% de 287 pacientes con stroke isquémico entre 15 y 45 años desarrollaron crisis, con mayor frecuencia en el primer año.

Leys, D., et al . 2002. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. Neurology 59, 26—33.

- 10.5% de 232 adultos con stroke en las edades de 15—49 desarrollaron crisis

Naess, et al. 2004. Long-term outcome of cerebral infarction in young adults. Acta Neurol. Scand. 110, 107—112.

Stroke mimics in children

Diagnosis	No. of Patients
Benign	11
Migraine	3
Psychogenic	3
Musculoskeletal abnormalities	3
Delirium	1
Periodic hypertensive episodes	1
Not benign	19
Neonatal seizure	3
RPLS	3
Metabolic stroke	2
Epilepsy (new diagnosis)	1
Postictal paralysis	1
ADEM	1
Tumor	1
Cerebellitis	1
Drug toxicity	1
Idiopathic intracranial hypertension	1
Subdural empyema	1
AVM	1
Moyamoya	1
Intracranial abscess	1

Estado epiléptico (SE) postictus

Estudio	SE en pacientes con crisis postictus
(Labovitz et al., 2001).	27%
(Gupta et al., 1988),	8%
(Velioglu et al., 2001),	9%
(Lo et al., 1994),	10%
(Rumbach et al., 2000).	19%

- Puede ser el síntoma inicial de un EVC agudo.
- Un estudio sobre la causas de SE en adultos atribuyó el 24.8% a stroke. (Nazire et al., 2003).
- El estado epiléptico no convulsivo (NCSE) presenta problema diagnóstico, los estudios revelan que su incidencia es de 0% (Labovitz et al.,2001) o menos frecuente (32%) que el SE convulsivo (68%) (Rumbach et al., 2000). Otro estudio señaló que el NCSE fue el tipo predominante en los pacientes con crisis tempranas (85%) y tan frecuente como el SE convulsivo en crisis tardías (50%) (Nazire et al., 2003).

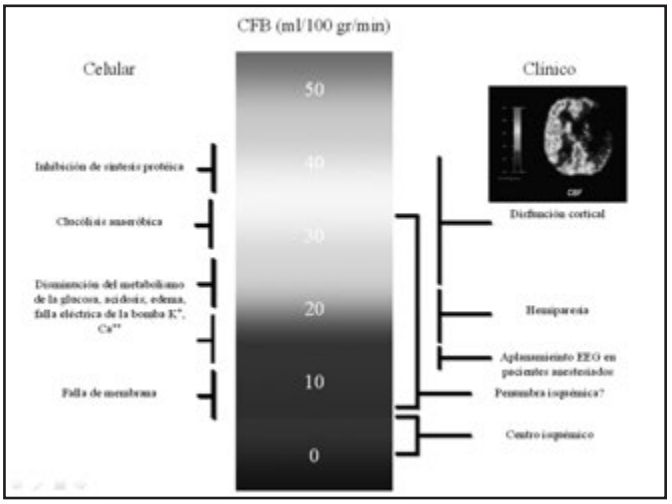
Otras asociaciones del SE

- Un estudio asoció al SE después de stroke con mayor discapacidad funcional y en el análisis multivariado encontró que la discapacidad funcional era el único factor predictivo de SE en stroke. (Veli˙oglu et al., 2001)
- En el análisis univariado encontró que el SE de presentación temprana /en los primeros 7 días del stroke se asoció con mayor riesgo de SE subsecuentes y una tasa de mortalidad más alta que el SE tardío. (Veli˙oglu et al., 2001).
- Hallazgos similares en un estudio en el que la severidad del stroke se asoció con mortalidad elevada en pacientes con SE de presentación temprana (<2 semanas) (Rumbach et al., 2000; Nazire et al., 2003), pero no fue un factor predisponente al desarrollo de epilepsia.

Fisiología de las crisis postictus

- Probablemente existan, como en la epilepsia post-traumática, procesos fisiopatológicos (epilepsia como una reacción patológica del tejido cerebral ante un insulto) diferentes subyacentes a las crisis tempranas y tardías.

Crisis tempranas	Crisis tardías
Predominancia de anormalidades bioquímicas agudas a nivel celular	Cicatrices glióticas
Alteraciones homeostáticas o sistémicas como desbalances electrolíticos y ácido-base	Muerte celular y apoptosis selectiva
La génesis se incrementa por la hiperglicemia durante la isquemia	Cambios en las propiedades de membrana o en los receptores (p.e. pérdida de receptores GABAérgicos)
↓	Desaferentación y "sprouting" colateral (tanto en el sitio de la isquemia como en áreas remotas)
Consideradas como crisis agudas sintomáticas (más que epilepsia)	



Otras consideraciones en la epileptogénesis

- Se ha propuesto que la zona de penumbra de una infarto contenga tejido irritable propicio como foco de actividad epiléptica (Heiss et al., 1992). Se ha demostrado que esta área exhibe
  - aumento en la liberación de glutamato excitotóxico,
  - alteraciones en la distribución iónica, (flujos de 8-18 ml/100 gr/min son el umbral para la falla de bomba iónica)
  - alteraciones en los fosfolípidos de la membrana con liberación de ácidos grasos (Reith et al., 1997).
- La isquemia aguda se ha asociado con aumento en la concentración extracelular de glutamato (Lohmann et al., 1995;Buchkremer-Ratzmann et al., 1998) y reducción en la función GABAérgica así como alteraciones funcionales y estructurales de la interneuronas GABAergicas.
- Se encontró hiperexcitabilidad neocortical pronunciada en las neuronas somatosensoriales en ratas 10 a 17 meses después de isquemia transitoria del cerebro anterior. (Smith MI, et al. Models for studying long term recovery following forebrain ischemia in the rat. 2. A 2 vessel occlusion model. *Acta Neurol Scand.* 1984; 69: 385–401)
- Kessler et al ha sugerido que la estimulación magnética transcraneal puede utilizarse para medir la función inhibitoria, y puede ser de gran ayuda para determinar el riesgo de crisis en los pacientes post stroke. (Kessler et al., 2002).
- Algunos estudios han sugerido que el stroke embólico conlleva mayor riesgo de crisis, 16% de 126 pacientes con evento embólico de 1640 pacientes con stroke y TIAS (tasa comparable a la del ictus hemorrágico pero mayor a la reportada en eventos isquémicos).

Impacto de las crisis en los resultados de un evento

- Las crisis pueden exacerbar el daño secundario al inducir excitotoxicidad de glutamato y/o aumentar el desbalance entre demanda y suplemento bajo las condiciones isquémicas, conllevando a anormalidades del gradiente iónico, daño mitocondrial y eventualmente daño irreversible.
- Los estudios experimentales muestran que la actividad "epiléptica" en condiciones isquémicas aumenta significativamente el tamaño del infarto y puede impedir la recuperación funcional.,
- Las crisis aceleran el metabolismo glicémico varias veces resultando en un aumento en los niveles de lactato que a su vez pueden incrementar la severidad de la zona de infarto..

Factores de riesgo para crisis postictus

Table 2 Risk factors for post-stroke seizures.

S. no.	Author	Risk factors	Variables analyzed	Follow up	Type of approach in study	P Predictor of epilepsy
1	Kilpatrick et al. (1990)	Cortical involvement	ES	7 months	Hospital based study	
2	Kotila and Waltimo, 1992	Female	B, E	40 months	Cohort	
3	Lancman et al. (1992)	Hemorrhagic stroke, cortical lesions, and lesions involving more than one lobe.	B	11.5 months	Hospital based study	
4	Giraud et al. (1994)	male gender, headache, loss of consciousness, hemianopia plus sensory deficit	ES	15 days	Hospital based study	
5	So et al. (1996)	Embolic for early seizures (uni-variate), anterior hemisphere location (uni/multi-variate)	B	5.5 ± 7.1 years	Population-based study	Early seizures, recurrent seizures
6	Arboix et al. (1997)	Cortical involvement, acute confusional state	ES	48 h	Hospital based study	
7	Reith et al. (1997)	Stroke severity	ES	2 weeks	Community based study	
8	Burn et al. (1997)	Severe stroke, total anterior circulation infarct.	B	2–6.5 years	Cohort	
9	Bladin et al. (2000)	Cortical location, stroke severity	B	9 months	multicenter, cohort	Late-onset of first seizures
10	Labovitz et al. (2001)	Cortical location	ES	1 month	Population-based cohort	
11	Cheung et al. (2003)	male, cortical location	B	1 year	Hospital based cohort	
12.	Lamy et al. (2003)	Stroke disability, cortical involvement		40 months	multicenter	Cortical signs, large infarct, early seizures.
13	Lossius et al. (2005)	Stroke severity; scandinavian stroke scale < 30	E	7–8 years	Hospital based study	Stroke severity

Variable: ES, early seizures; LS, late seizures; B, both; E, Epilepsy.

Localización

- En casi todos los estudios la localización cortical presenta un riesgo mayor para las crisis, mientras que las crisis son raras en infartos de la fosa posterior o sustancia blanca profunda.
- El daño cortical
  - fue un factor de riesgo independiente del tamaño del infarto cortical (Bladin et al., 2000; Cheung et al., 2003)
  - se asoció con tamaño mayor del infarto en imagenología (Kilpatrick et al., 1990)
  - se asoció a mayor riesgo de crisis pero no mostró significancia estadística en la asociación entre crisis tardías o tempranas comparadas con el tipo de infarto, localización o sitio de lesión (Lancman et al., 1993).
  - fue un factor de riesgo para crisis tempranas en adultos jóvenes (Lamy et al., 2003).
- El riesgo de crisis tempranas estuvo aumentado 8 veces en pacientes mayores con infarto cardioembólico de los giros temporal medial y posterior central, en tanto que el riesgo de crisis tardías se aumentó 5 veces en lesiones del los giros supramarginales y temporal superior.
- Sin embargo, el daño al lóbulo occipital causa crisis frecuentemente (Gupta et al., 1988; Giroud et al., 1994).

Otros factores de riesgo

- En el estudio de Szaflarski et al con una cohorte de 6044 casos los factores de riesgo independientes para el desarrollo de crisis fueron stroke hemorrágico, edad menor y escala de Rankin pre-stroke. La raza/etnicidad y la localización no fueron factores de riesgo.

  Szaflarski JP, et al Incidence of seizures in the acute phase of stroke: a population-based study. Epilepsia. 2008, 49(6):974-81.
- Los factores de riesgo vasculares
  - Hipertensión
  - Aumento del colesterol sérico
  - Hipertrofia ventricular izquierda

  se han asociado con el desarrollo de crisis o epilepsia, aun en ausencia de ictus evidente. (Li et al., 1997;Ng et al., 1993; Hesdorffer et al., 1996).

Severidad y tamaño de la lesión

- Algunos estudios han demostrado que la severidad del stroke es predictiva de crisis (Lossius et al., 2002, 2005) independiente del tamaño de la lesión isquémica en la TC (Reith et al.,1997; Bladin et al., 2000), probablemente porque la penumbra isquémica, no visualizada en la TC, es epileptogénica. (Reith et al., 1997)
- Pocos estudios han asociado el riesgo de crisis al tamaño del infarto. Los infartos mayores y los que involucran más de un lóbulo se asocian con mayor riesgo de crisis. (Gupta et al., 1988; Davalos et al., 1992; Lancman et al.,1993; Burn et al., 1997; Bladin et al., 2000; Lamy et al., 2003).

Embolismo

- El embolismo cardiaco o ateromatoso puede conllevar un riesgo particular de crisis (Meyer et al., 1971; Lambrakis and Lancman,1998) por la posibilidad de una reperfusión rápida después de la fragmentación y migración distal del émbolo (Macfarlane et al., 1991) o la extravasación de glóbulos rojos. (Fisher and Adams, 1951).
- En un estudio con 1640 pacientes con isquemia cerebral, las crisis tempranas fueron más frecuentes en el embolismo cardiaca que en los hematomas supratentoriales (Giroud et al., 1994). aunque otros estudios no apoyan estos hallazgos. (Kilpatrick et al., 1990; Bladin et al., 2000).

Transformación hemorrágica

- En varios estudios se ha asociado la transformación hemorrágica de una lesión isquémica con el riesgo de crisis.
- El análisis univariado de pacientes con stoke mostró que las crisis fueron más frecuentes en los infartos hemorrágicos $p < 0.005$ (Bladin et al., 2000).
- Un estudio de crisis epilépticas de presentación concomitante con el stroke encontró que las crisis fueron mas frecuentes en infartos hemorrágicos (19.2%) que en hemorragias (15.6%) e infartos isquémicos (6.2%) en lesiones superficiales. (Davalos et al., 1992).
- En un estudio prospectivo de pacientes con stroke isquémico encontró en el análisis multivariado que la transformación hemorrágica era un factor independiente para el desarrollo de crisis en primer stroke (OR 6.58; 95% CI: 1.4—1.61; $p = 0.001$) y con un resultado adverso (OR 8.45;95% CI: 1.72—41.20; $p = 0.008$) (Alberti et al., 2008). Presuntamente esto pudiera deberse a la epileptogenicidad de productos sanguíneos (hierro?) o el aumento en del tamaño del infarto.

Tipos de crisis

Table 3 A summary of the studies reporting seizure type in the acute phase after stroke.

Duration	SPS	SPS-S.G	CPS	GTCS
<2 weeks (Sung and Chu, 1990)	24%	32%	18%	4%
<2 weeks (Bladin et al., 2000)	53%	53%	--	--
2 weeks (Lo et al., 1994)	66%	--	--	24%
Early and late-onset (Cheung et al., 2003)	17.6%	17.6%	5.9%	58.9%
14 days (Reith et al., 1997)	68%	68%	--	22%
2 weeks (Kilpatrick et al., 1990)	21/44	5/44	--	18/44
15 days (Giroud et al., 1994)	61%	28%	--	11% +
48h (Davalos et al., 1992)	37.5%	27.5%	--	35%
<2 weeks (Gupta et al., 1988)	32%	18%	8%	42%

SPS—simple partial seizures, SPS-S.G—SPS to secondary generalization, CPS—complex partial seizures, GTCS—generalized tonic clonic seizures.

Valor del EEG

- No se ha identificado valor pronóstico para el EEG en el stoke instaurado
- Sin embargo es esencial en el contexto agudo, especialmente en el diagnóstico de NCSE:
  - en un estudio de 57 pacientes consecutivos con EEG continuo admitidos a la TI con isquemia cerebral, 26% tuvieron crisis no convulsivas identificadas por el EEG en el periodo do de monitoreo. (Jordan, 1995).
- Tanto en las situaciones agudas como crónicas debe considerarse el NCSE en pacientes con cambios inexplicables en conciencia o comportamiento.
- Las descargas epileptiformes lateralizantes (PLEDS) son anormalidades comunes en la fase aguda de la isquemia cerebral severa. (Lesser et al., 1985), especialmente comunes en infartos corticales (Giroud et al., 1994).
- Aun se discute si estas anormalidades son reflejo de tejido dañado o realmente fenómenos epilépticos..
- Un estudio enfocado a los factores contribuyentes a la aparición de PLEDS en el infarto agudo concluyó que las alteraciones metabólicas principalmente hiperglicemia y fiebre se presentaban con mayor frecuencia en los pacientes con PLEDS ($p < 0.05$) (Neufeld et al., 1997).

Morbilidad

- La epilepsia en los pacientes con stroke puede deteriorar aun más la calidad de vida, resultando en dependencia, aumento de discapacidad física o sicológica y restricciones sociales ——» difícil discernir los efectos biológicos directos en el tejido isquémico de los efectos sico-sociales adversos.
- En un estudio se encontró que los pacientes con infarto cortical pero no subcortical y crisis obtenían peores resultados en las escalas neurológicas durante la estancia hospitalaria y escala de Rankin en el seguimiento a largo plazo. (Bladin et al., 2000).
- Sin embargo, otros estudios muestran hallazgos contradictorios en los que el resultado funcional de los pacientes con crisis no difiere significativamente del de los pacientes sin crisis. (Kilpatrick et al., 1990; Davalos et al., 1992). De hecho en los pacientes sobrevivientes al stroke las crisis epilépticas predijeron un mejor resultado.

Se propuso que el mejor resultado podia deberse a la mayor zona de penumbra isquémica en los pacientes con stroke y crisis. Aunque la mayor penumbra se asocia con un resultado más favorable existe un aumento en el riesgo de crisis en el tejido metabólicamente comprometido pero que retiene su irritabilidad eléctrica. (Reith et al., 1997).

Mortalidad

- Varios estudios han mostrado un incremento en la mortalidad en pacientes con stroke y crisis. En un estudio la mortalidad intrahospitalaria del stroke en pacientes con crisis fue de 37.9% comparada con 14.4 % en pacientes sin crisis. ($p < .0005$) (Arboix et al., 1997).
- En el estudio multicéntrico prospectivo (Bladin et al., 2000). la mortalidad a 30 días y a un año en pacientes con crisis fue significativamente mayor.
- Otro estudio en un cohorte de 904 pacientes mostró que las crisis tempranas eran un predictor independiente significativo en la mortalidad a 30 días, sin embargo en el análisis multivariado, en el que se tomó en cuenta la escala de stroke de NIH (NIHSS) la asociación dejó de ser significativa. (Labovitz et al., 2001).

Mortalidad

Table 1. Demographic and clinical characteristics of all patients included in the study

	Seizure (n = 190)		No seizure (n = 5854)		
Variable	N	%	N	%	p-value
Age (years)[a]	68.0	(15.0)	71.7	(13.2)	0.001
Gender (male)	77	40.5%	2536	43.7%	0.39
Race (black)	33	17.34%	999	17.1%	0.91
Hypertension	119	62.6%	3872	66.1%	0.31
Heart disease	72	37.9%	2374	40.6%	0.46
Prior stroke	51	26.8%	1443	24.6%	0.49
LVH	26	13.7%	642	11.0%	0.24
Prestroke Rankin[b]	0	(0–3)	0	(0–3)	0.57
NIHSS[b,c]	12	(5–22)	6	(3–11)	<0.0001
GCS[b,d]	13	(7–15)	15	(14–15)	<0.0001
Hemorrhagic stroke	60	31.6%	655	11.2%	<0.001
30-day Mortality	61	32.1%	776	13.3%	<0.0001

Data are presented as n (%).
[a]mean (standard deviation) or
[b]median (interquartile range).
[c]NIHSS n's are 143 & 5249.
[d]GCS are 154 & 4808.

Table 4. Association of seizure with mortality, showing covariates

Variable	OR	95%CI	p-value
Seizure	2.63	1.85, 3.74	<0.0001
Hemorrhage	6.58	5.35, 8.09	<0.0001
Age (10 years)	1.40	1.30, 1.51	<0.0001
Gender (male)	1.00	0.84, 1.18	0.98
Race (black)	0.83	0.66, 1.05	0.12
Prior stroke	0.93	0.77, 1.12	0.46
Heart disease	1.55	1.31, 1.83	<0.0001
Prestroke Rankin (1 or more)	2.13	1.78, 2.54	<0.0001

Szaflarski JP, Rackley AY, Kleindorfer DO, Khoury J, Woo D, Miller R, Alwell K, Broderick JP, Kissela BM. Incidence of seizures in the acute phase of stroke: a population-based study. Epilepsia. 2008 Jun;49(6):974-81

Mortalidad

- La tasa de mortalidad aguda es mayor en presencia de SE.
- Dos estudios de SE en pacientes con stroke revelaron índices de mortalidad cercanos al 48% (Rumbach et al., 2000; Veli¨oglu et al., 2001).
- La instauración temprana de SR después del stroke se asoció con mortalidad más elevada que la registrada en aparición tardía de SE (Veli¨oglu et al., 2001).
- Un estudio multicéntrico de 346 pacientes con SE convulsivo reportó una mortalidad de 11% en pacientes sin historia previa de epilepsia. (Scholtes et al., 1994).
- El aumento en la mortalidad puede deberse tanto a la severidad del stroke subyacente como al efecto sinergístico del daño causado por el SE y la isquemia cerebral (Waterhouse et al.,1998)

Tratamiento

•Dependerá del contexto clínico del infarto.

Tratamiento

Una crisis aislada breve en la fase temprana puede no requerir tratamiento especifico

El SE requiere terapia intravenosa urgente

Las crisis tardías recurrentes requieren tratamiento con FAEs de acuerdo a lineamientos convencionales. Es practica común tratar las crisis tempranas con cursos cortos de FAEs (3-6 meses) aunque no se han estudiado correctamente las ventajas y desventajas de esta práctica. U
riesgo para el desarrollo de epilepsia mo
terapia AE prolongada a diferencia de la
Los pacientes con riesgo alto que desarr
del stroke deben ser tratados. Dado el fr
ocurrencia tradia se ha utilizado como pr
monoterapia. (Gabapentina, lamotrigina

Jacques L De Reuck is Director of the Ghent Stroke Centre and former Chairman of the Neurological Department of Ghent University Hospital and the Ghent Position Emission Tomography (PET) Centre. He is also President of the European Federation of Neurological Societies (EFNS). His main interest in stroke started with neuroanatomy and neuropathology research and continued with physiological studies using human PET. He is the author of more than 500 publications in national and international journals and books. Professor De Reuck trained in neurology and neuropathology at the Ghent University Hospital and at the Massachusetts General Hospital, Boston.

E: dereuck.jl@gmail.com

Tratamiento

- Las presencia de crisis influye en el abordaje de la terapia anti-stroke. Las crisis son una contraindicación al uso de t-PA (rt-PA Stroke Study Group, 1995). La anticoagulación prolongada conlleva un riesgo adcional rn pacientes con crisis con caídas, y esta relativamente contraindicada en estos casos.
- La presencia de otras condiciones co-mórbidas y otros fármacos también complican la terapia AE, y la interacción farmacológica es particularmente preocupante en pacientes añosos con politerapia farmacológica.
- Las lateraciones renales y hepáticas pueden resultar en procesos farmacoquinéticos inesperados.
- Los FAEs pueden interferir con la recuperación:
  la fenitoína sola o en combinación con GABA mostró en un estudio retardar la recuperación de la función motora tras daño (Brailowsky et al., 1986; Dikmen et al., 1991)
  el fenobarbital y las benzodiacepinas pueden también retardar la recuperación (Schallert et al., 1986; Hernandez and Russell, 1992).

FAEs específicos

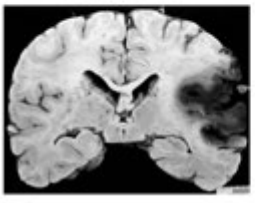
- En un estudio se aleatorizaron los pacientes con crisis postictus 1:1 a tratamiento con LTG o CBZ y seguimiento de 12 meses, encontrando que más pacientes estuvieron libres de crisis en el grupo de LTG (72%) versus CBZ (44%), sin significancia estadística (P = 0.06). El número de pacientes que se retiraron del estudio por efectos adversos del medicamento fue menor en el grupo de LTG (3%) comparado con CBZ (31%; P = 0.02). (Gilad R, et al. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol. 2007;30(4):189-95.)
- En un estudio prospectivo de 60 pacientes mayores (edad 69.76 ± 6.41) con cuando menos 2 crisis postictus tardías (promedio de crisis pre 3.61 ± 3.02/mes) se evaluó el uso de LEV en monoterapia:
  - A dosis diarias de 1000–2000 mg, 82.4% de olos pacientes estuvieron libres de crisis y 7 pacientes (20.6%) tuvieron efectos secundarios. En un pacientes se suspendió el LEV por somnolencia excesiva. Dos pacientes requirieron cambio de FAE por recurrencia de crisis a dosis de 3000 mg/día. (Kuthu G, et al. Levetiracetam monotherapy for late poststroke seizures in the elderly. Epilepsy & Behavior 13 (3), 542-544, 2008)

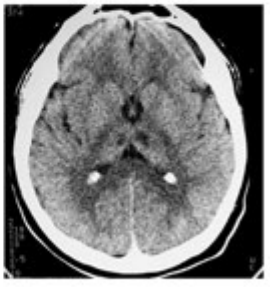
Tratamiento

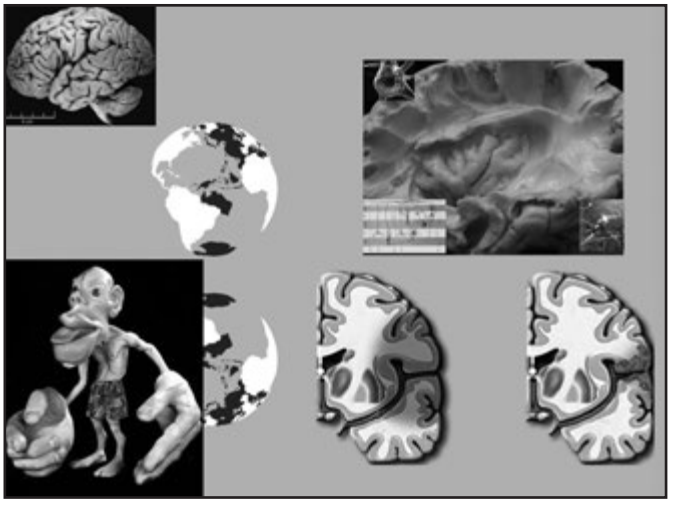
- Controversia particular en cuanto al tratamiento AE en casos de "estado epiléptico sutil" (~status epiléptico mioclónico en coma) en la fase aguda de anoxia severa. Algunos consideran que los movimientos anormales son fenómenos no-epilépticos indicativos de daño neuronal y por tanto no inician FAEs, otros administran dosis altas de antiepilépticos IV (generalmente barbitúricos) al considerarlo una forma de SE.
- El mioclonus de Lance Adam puede ser una secuela de la isquemia cerebral y generalmente se trata con valproato, piracetam o levetiracetam.

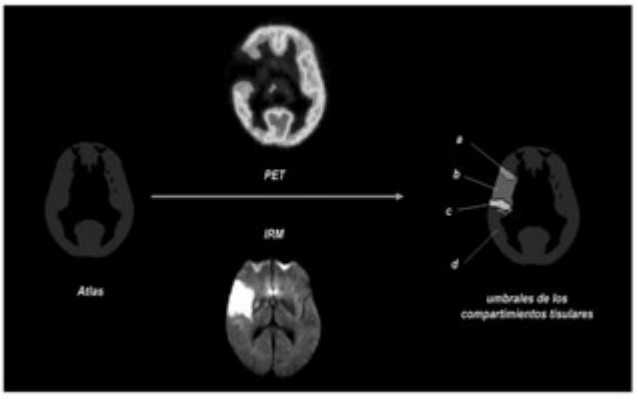
EVC

- 14% de los pacientes con EVC de pequeño vaso se asocian a crisis epilépticas

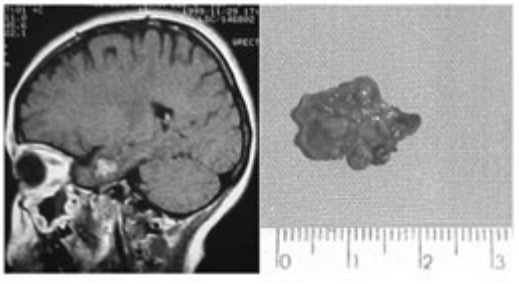








- El tratamiento fundamentalmente ha sido dirigido a restablecer en el menor tiempo posible el flujo sanguíneo cerebral o bien detener el sangrado (trombolisis, Factor VIIr)
- Los resultados han sido diversos dado que la ventana de intervención es mejor dentro de las 3 primeras horas
- Las intervenciones no están exentas de riesgo



Dime y lo olvido, enséñame y lo recuerdo, involúcrame y lo aprendo.

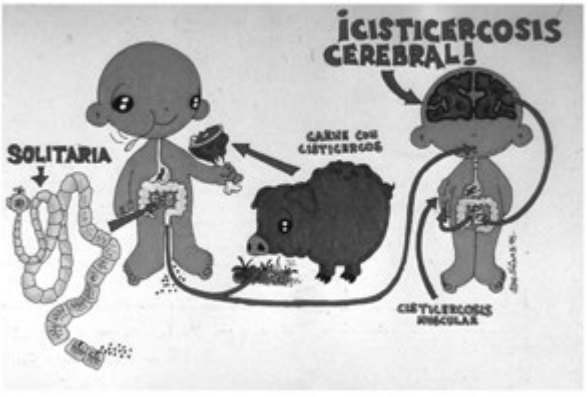
Benjamin Franklin (1706-1790)

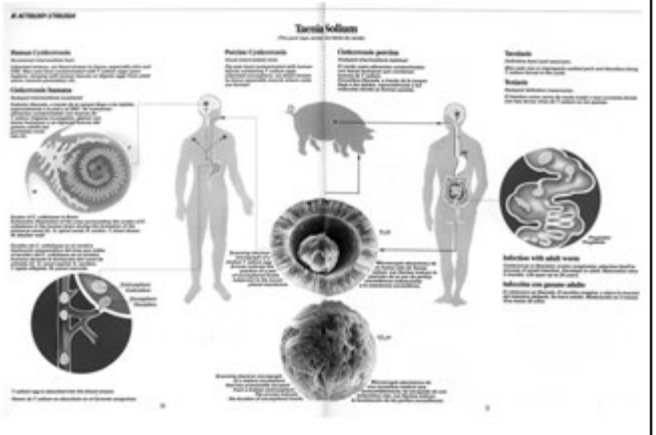
Epilepsy and neurocisticercosis
F. Rubio Donnadieu (México)

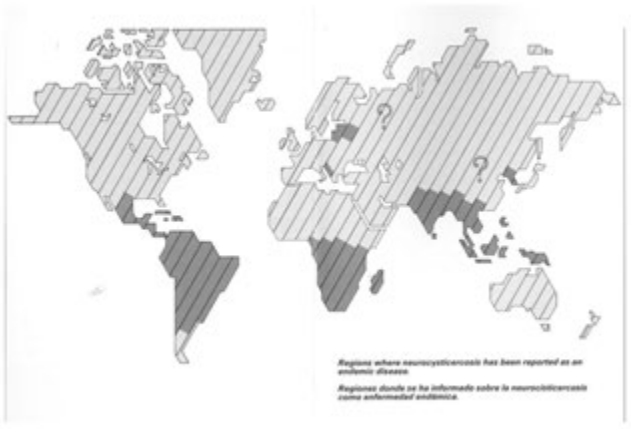
IV ESCOLA LATINO-AMERICANA DE VERÃO
DE EPILEPSIA
LASSE IV
Feb. 9, 2010.

Epilepsy and Time
Neurocisticercosis and Epilepsy
Late onset Epilepsy

F. Rubio-Donnadieu
Programa Prioritario de Epilepsia
Instituto Nacional de Neurología y Neurocirugía
México, D.F.







Regions where neurocysticercosis has been reported as an endemic disease.

Regiones donde se ha informado sobre la neurocisticercosis como enfermedad endémica.

Seroepidemiology of Human Cysticercosis in Mexico
Geoeconomic map of the Mexican Republic indicating the regional frequency of cysticercus antibodies. Area 5 has the highest percentage, followed by areas close to the Pacific Ocean.
A representative sample of the Mexican population was examined for antibodies against cysticerci extract from pigs. The area with almost 1% frequency represents the major pig breeding region in the country.

Seroepidemiología de la cisticercosis humana en México
Mapa geoeconómico de la república de México que indica la frecuencia regional de anticuerpos de cisticercos. El área 5 es la de mayor porcentaje, seguida por las áreas vecinas.
Una muestra representativa de la población mexicana fue examinada para anticuerpos contra el extracto de cisticercos del cerdo. El área con casi 1% de ocurrencia presenta la región con la mayor crianza de cerdos en el país.

Cysticercosis in Los Angeles County

Frank O. Richards, Jr, MD; Peter M. Schantz, VMD, PhD; Ernesto Ruiz-Tiben, PhD; Frank J. Sorvillo, MPH

• Four hundred ninety-seven patients were identified as having been treated for cysticercosis at four hospitals in Los Angeles during the 11-year period 1972 through 1982. Eleven deaths were recorded. Over 80% of these patients were Hispanics in productive age groups, the majority were Mexican by nationality. Hospitalizations were generally short, and maintenance for recurrence of symptoms or complications of therapy occurred in only 14% of patients. Cysticercosis was diagnosed in 12 US citizens who had no history of travel to countries considered traditionally endemic for *Taenia solium* taeniasis/cysticercosis. A dramatic rise in numbers of cases was observed after 1977, appearing to plateau at approximately 60 cases per year in 1981. The increase in cases beginning in 1977 coincided with the introduction of the computed tomographic scan.
(JAMA 1985;254:3411-3415)

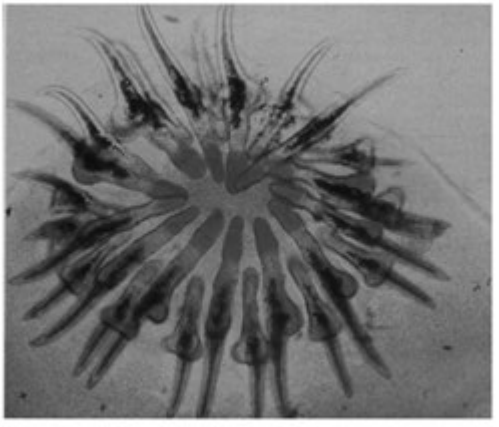
HUMAN cysticercosis is a potentially fatal condition caused by the larval tissue stage of the pork tapeworm, *Taenia solium*. Cysticerci may lodge in a variety of tissues, including muscle, brain, heart, bone, eye, and skin.[1] Cysticercosis of the brain can present clinically as epilepsy, hydrocephalus, cerebral atrophy, meningitis, encephalitis, abnormal behavior, focal deficits, and/or increased intracranial pressure.[2]

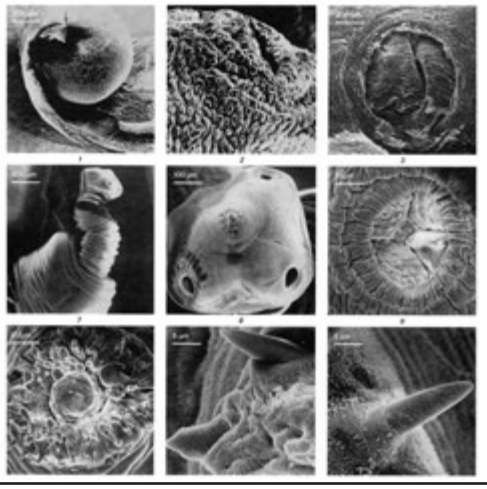
See also p 3428.

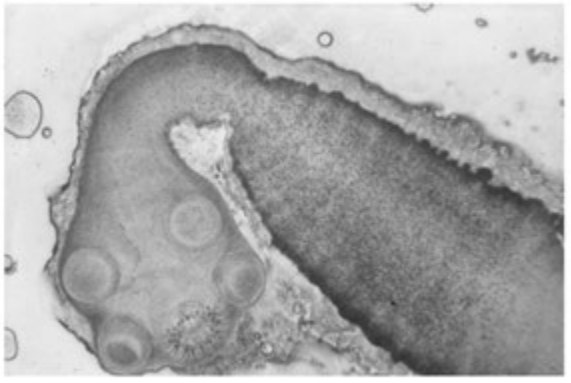
Ingestion of cysticerci in inadequately cooked pork results in intestinal taeniasis, but does not lead directly to acquisition of cysticercosis.[3] Human cysticercosis is contracted from fecal-oral contact, by ingestion of *T solium* eggs that are passed in the feces of the human tapeworm carrier. An individual with a mature *T solium* tapeworm releases an average of 60,000 eggs daily in his stool.[4] The vast majority of these eggs are contained within the encircled gravid proglottid. However, individual eggs remaining in the lumen of the intestine or around the perianal area are infectious, and direct personal contact with a tapeworm carrier may result in cysticercosis. Autoinfection may occur when the individual with taeniasis inadvertently infects himself through ingestion of his own tapeworm eggs. Cysticercosis can also result from less direct contact with the tapeworm carrier, through consumption of food and water contaminated with human feces.[5]

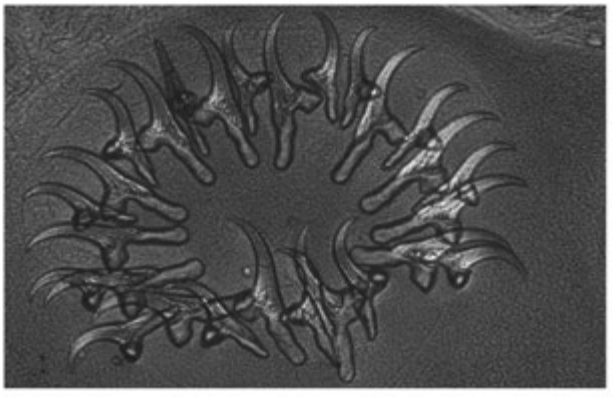
Extra-adipose cysticercosis is a common exotic disease and ranks as a major health problem in many developing countries of Central and South America, Asia, and Africa.[6] The clinical consequences of the infection have been perhaps least studied in Mexico that elsewhere. Published reports from Mexico indicate that cerebral cysticercosis is the cause of 9% of neurologic admissions, 11% to 30% of patients undergoing craniotomy for brain tumor, and 0.8% to 5.0% of all autopsies performed in the country.[7] However, because of technical difficulties in diagnosing both *T solium* taeniasis and result cysticercosis, few epidemiologic studies have been performed in Mexico or any other country where the disease is endemic. No data on the incidence and prevalence of either taeniasis or cysticercosis are available. The importance of the various proposed modes of transmission, the geographical differences, and the risk factors for infections have not been characterized.

Cysticercosis has recently become more visible as a health problem in the United States. Four published studies from southern California have reported a combined total of 190 patients with this condition.[8] Substrains for cysticercosis serodiagnosis in the reference diagnostic service of the Division of Parasitic Diseases at the Centers for Disease Control (CDC), Atlanta, have risen from 1,400 in 1978 to 1,954 in 1982, a 40% increase. Sixty-two percent of these specimens were from the states that border Mexico (New Mexico, Arizona, California, and Texas), and almost









TIPOS DE LESION PRODUCIDA POR NEUROCISTICERCOSIS

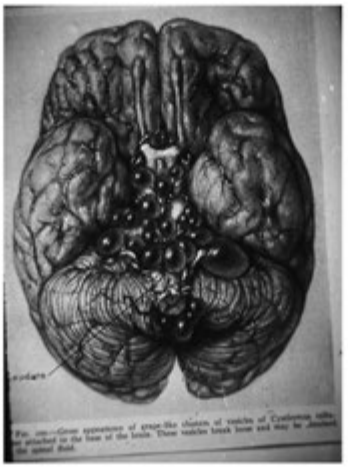
1. Reacción inflamatoria parenquimatosa
2. Aracnoiditis y panquimeningitis
3. Hidrocefalia secundaria a aracnoiditis basal
4. Hidrocefalia por bloqueo intraventricular de LCR
5. Vasculitis

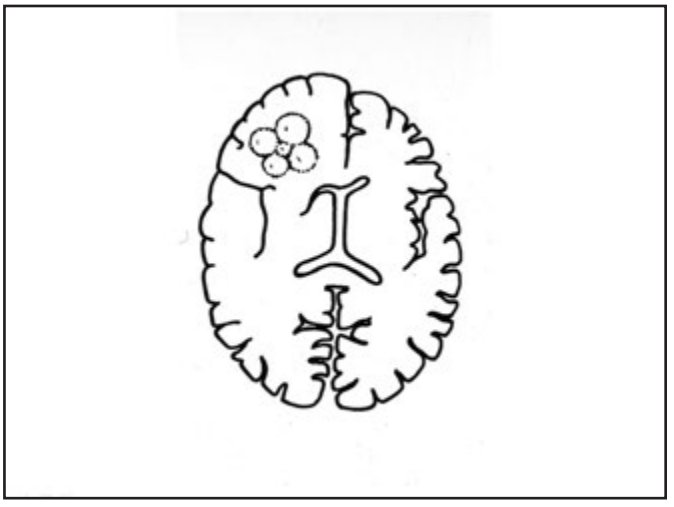
ETAPAS BIOLOGICAS DE CISTICERCOS EN EL SNC

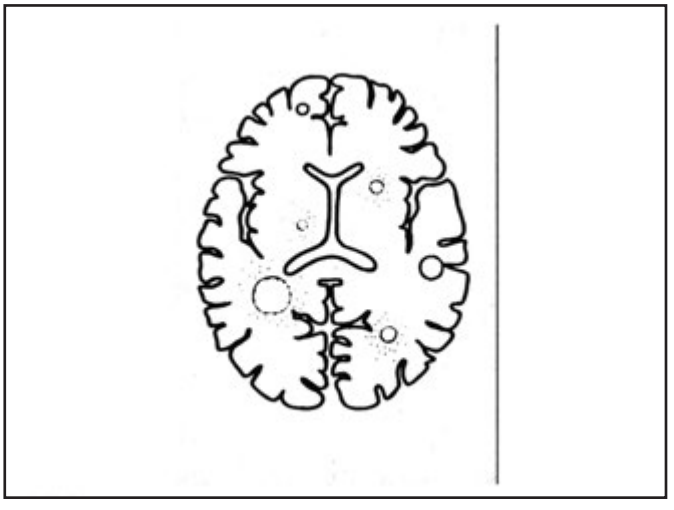
1. Cisticercos parenquimatosos microscópicos (forma miliar)
2. Cisticercos macroscópicos de 1-5 cms. (1 ó varios)
3. Cisticercos racemosos (efecto de masa ocupativa)
4. Cisticercos en etapa degenerativa (con necrosis y engrosamiento de membrana)
5. Granulomas calcificados (secuela)

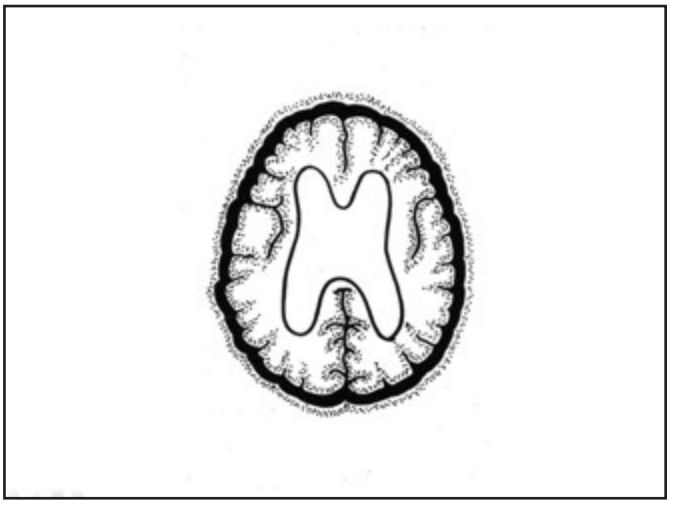
LOCALIZACION TOPOGRAFICA DE NEUROCISTICERCOSIS

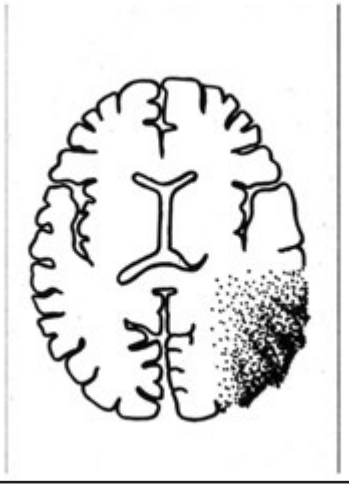
1. Cortical subaracnoidea
2. Subaracnoidea basal
3. Intraparenquimatosa
4. Intraventricular
5. Mixta
6. Espinal

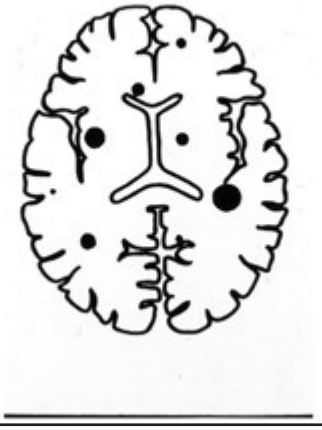










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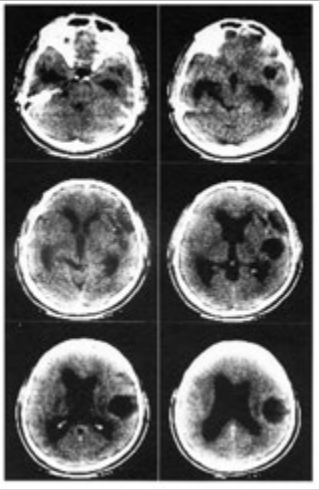

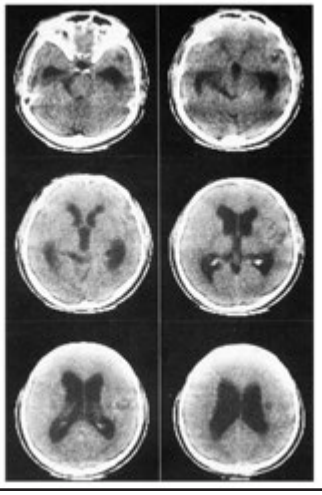

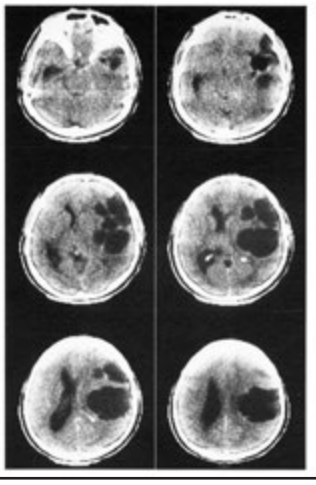

Neurocysticercosis: A New Classification Based on Active and Inactive Forms

A Study of 753 Cases

Julio Sotelo, MD; Vicente Guerrero, MD; Felipe Rubio, MD

CISTICERCOSIS

Signos y síntomas	% 753 Casos
Epilepsia	52.4
Cefalea	43.4
Papiledema	28.0
Vómito	27.2
Signos Piramidales	21.5
Marcha Atáxica	10.0
Disminución agudeza visual	10.0
Atrofia óptica	6.5
Brotes Psicóticos	4.7
Diplopia	4.5
Vértigo	4.1
Dismetría o temblor de acción	3.9
Afección nervios craneales VII al XII	3.4
Trastornos conductuales	2.7
Hipoestesia	1.8
Compresión médula espinal	1.4
Signos de irritación meningea	1.3
Síndrome radicular	1.0
Síndrome de Parinaud	1.0

NOTA: El 26.2 % (198 casos) tuvieron examen neurológico normal.

CISTICERCOSIS

I Formas activas	% 753 Casos
a. Aracnoiditis	43.2
b. Hidrocefalia por inflamación meningea	25.7
c. Quistes parenquimatosos	13.2
d. Infarto cerebral por vasculitis	2.3
e. Efecto de masa por quiste (s)	1.0
f. Quistes intraventriculares	0.7

II Formas inactivas	% 753 Casos
a. Calcificaciones parenquimatosas	57.6
b. Hidrocefalia secundaria a fibrosis subaracnoidea	3.8

NOTA: Aproximadamente el 50% de los casos tienen formas mixtas de Neurocisticercosis

TABLA V

Síntomas y signos	Criptocosis 26 casos		Tuberculosis 16 casos		Neurocisticercosis 753 casos	
	No.	%	No.	%	No.	%
Cefalea	19	(73)	9	(56)	313	(43.4)
Fiebre	13	(50)	11	(69)	NI	(0)
Epilepsia	NI	(0)	NI	(0)	381	(52.4)
Rigidez de nuca	8	(31)	12	(75	10	(1.3)
Papiledema	4	(15)	2	(13)	75	(10)
Ataxia	2	(8)	2	(13)	75	(10)
Cambios Mentales	12	(46)	14	(87)	120	(16)
Vómito	10	(38)	7	(44)	203	(27)

NI: No Informado

Instituto Nacional de Neurología y Neurocirugía

CISTICERCOSIS

ELISA

- ACTIVA
  - 133 SUEROS
  - 126 L.C.R.
- INACTIVA
  - 61 SUEROS
  - 32 L.C.R.
- CONTROLES
  - 556 SUEROS
  - 449 L.C.R.

Instituto Nacional de Neurología y Neurocirugía

CISTICERCOSIS

ELISA

352 Casos

Grupos Anatomo-Clínicos

- ACTIVA
  - I ARACNOIDITIS CRÓNICA
  - II QUISTES PARENQUIMATOSOS
  - III QUISTES INTRAVENTRICULARES
  - IV ARACNOIDITIS CRÓNICA + QUISTES PARENQ.
- INACTIVA
  - V GRANULOMAS PARENQUIMATOSOS
  - VI FIBROSIS SUBARACNOIDEA CON HIDROCEFALIA
- CONTROLES
  - 556 SUEROS (A.V.C., "DEGENERATIVAS", TUMORES).
  - 449 L.C.R.

Instituto Nacional de Neurología y Neurocirugía

CISTICERCOSIS

ELISA

ACTIVA — 50% Sensibilidad + en Cisticercosis; 70% Especificidad – en controles — Suero

ACTIVA — 87% Sensibilidad + en Cisticercosis; 95% Especificidad – en controles — L.C.R.

NEUROCISTICERCOSIS Y EPILEPSIA

NIÑOS ——— 81% con CTC

ADULTOS: 100 casos — LOE > 25 a — 70% con Crisis Parciales

CYSTICERCOSIS IN CHILDREN
Clinical Manifestations

	No. Cases	%
Symptomatic	74	83.2
Asymptomatic	15	16.8
	89	100
Symptoms	60	81
Seizures	41	55
Intracranial hypertension	20	27
Visual symptoms	18	24
Cranial nerves	17	22
Cerebellar	9	12
Psychotic reaction		

CYSTICERCOSIS AND EPILEPSY IN CHILDREN (89)
Type of Seizures in 60 Cases

GENERALIZED T-C	**78 %**
SIMPLE PARTIAL	**35 %**
COMPLEZ PARTIAL	**6.6 %**
ABSENCE	**1.6 %**

Reprinted from the Archives of Internal Medicine
February 1990, Volume 150
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Neurocysticercosis as the Main Cause of Late-Onset Epilepsy in Mexico

Marco T. Medina, MD; Enrique Rosas, MD; Francisco Rubio-Donnadieu, MD; Julio Sotelo, MD

Table 1. CT FINDINGS IN 50 PATIENTS WITH LOSE SECONDARY TO NEUROCYSTICERCOSIS

	No. of Patients
Active Forms of NCC	
Parenchymal cyst	23
Subarachonid cyst	2
Brain infarction secondary to vasculitis	1
Inactive Forms of NCC	
Parenchymal calcifications	41

* 15 patients had two or more forms of NCC

EPILEPSY IN ADULTS
533 Cases

192 c Definite DX.

	Cases	%
Cysticercosis	70	36
Atrophy	42	22
Infarct (acute)	32	17
Tumor	21	11
Hematoma	8	4.1
A.V. Malformation	3	1.5
Miscellaneous	16	8.3
	192	100

Epilepsia, 50(8):2019–2026, 2009
doi: 10.1111/j.1528-1167.2009.02044.x

FULL-LENGTH ORIGINAL RESEARCH

Temporal distribution of clinical seizures over the 24-h day: A retrospective observational study in a tertiary epilepsy clinic

*Wytske A. Hofstra, *Bertine E. Grootemarsink, *Rianneke Dieker, †Job van der Palen, and *Al W. de Weerd

*Department of Clinical Neurophysiology and Sleep Centre SEIN Zwolle, The Netherlands; and †Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands

Views & Reviews

CME

Calcific neurocysticercosis and epileptogenesis

T.E. Nash, MD; O.H. Del Brutto, MD; J.A. Butman, MD, PhD; T. Corvin, MD; A. Delgado-Escueta, MD; R.M. Duron, MD; C.A.W. Evans, MD, PhD; R.H. Gilman, MD; A.E. Gonzalez, DVM, PhD; J.A. Loeb, MD, PhD; M.T. Medina, MD; S. Pietsch-Escueta, MPH; E.J. Pretell, MD; O.M. Takayanagui, MD, PhD; W. Theodore, MD; V.C.W. Tsang, PhD; and H.H. Garcia, MD, PhD

Sex-Related Severity of Inflammation in Parenchymal Brain Cysticercosis

Oscar H. Del Brutto, MD; Esperanza García, PhD; Oscar Talámas, MD; Julio Sotelo, MD

Cysticercosis in Los Angeles County

Frank O. Richards, Jr, MD; Peter M. Schantz, VMD, PhD; Ernesto Ruiz-Tiben, PhD; Frank J. Sorvillo, MPH

Magnitud de la Epilepsia en México y Latinoamérica

Año	Resultado	Referencia
1983	Escolares Tlalpan Prevalencia 16.3/1,000	Neuroepidemiology 2: 16-23, 1983
1991	23,000 Escolares, México Prevalencia 10.9/1,000	Epilepsia Vol 3 2 Suppl 1 1991 pag. 111
1992	Naolinco, Ver Prevalencia 11/1,000	Archivos INNN, 1993, Vol 8, No 3
1993-94	Comalcalco, Tab. Prevalencia 20/1,000	Comunicación personal
2002	Copala, Gro. Prevalencia 15.6/1000	En prensa

Epilepsy and neural infections
Krister Kristensson (Sweden)

Pathogens and the Brain: Neuroinvasion, Immunopathogenesis and Epileptic Seizures

Krister Kristensson

Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Microbes and Epilepsy

1. Spread of pathogens to the brain
2. Immune control of pathogens in brain
3. Pathogens that cause epilepsy
4. Can seizures or epilepsy be caused by pathogens?

1. Spread of pathogens to the brain

a. Hematogenous route

– across the blood-brain barrier

b. Along peripheral nerves

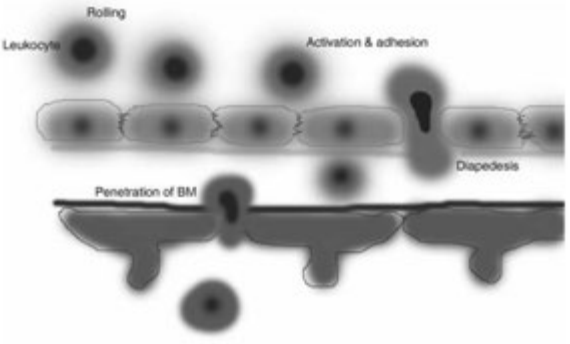
– the olfactory route to the "limbic system"

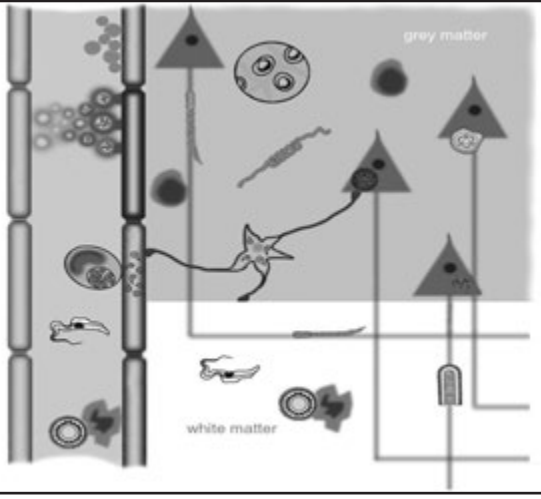
a. Hematogenous route

***Plasmodium, Taenia solium* larvae, toxoplasma, trypanosoma, HIV, measles**

The so-called blood-brain barrier (BBB) protects the brain from diffusion of macromolecules in the blood to the brain parenchyma.

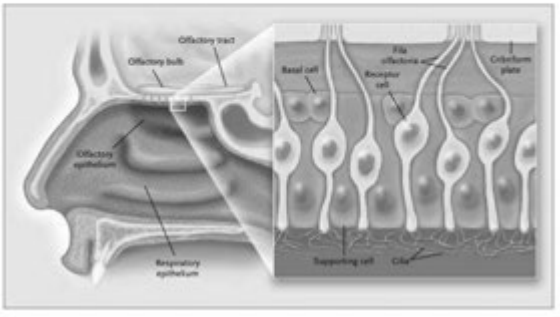
Multi-step leukocyte trafficking across the BBB

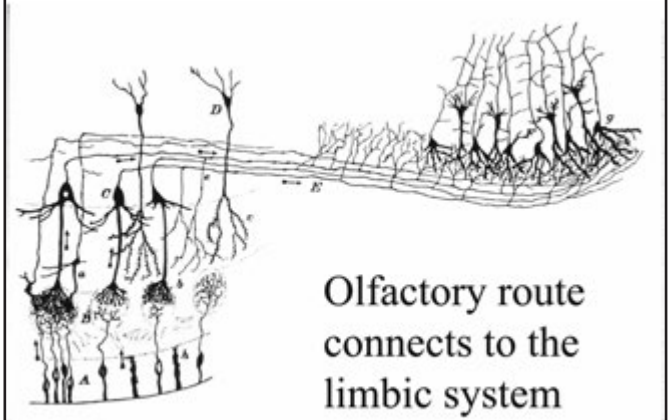




b. Neural route

Neurons in the olfactory mucosa are the only ones in direct contact with the ambient environment





Olfactory route connects to the limbic system

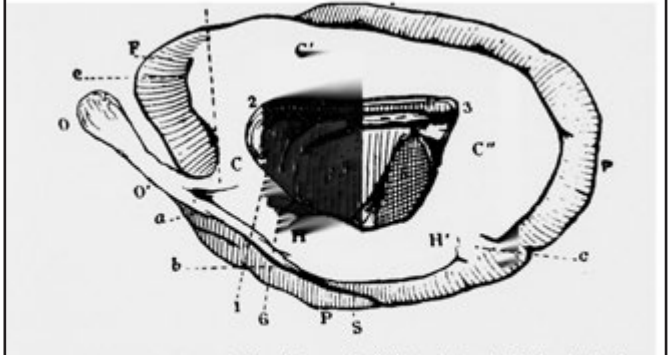
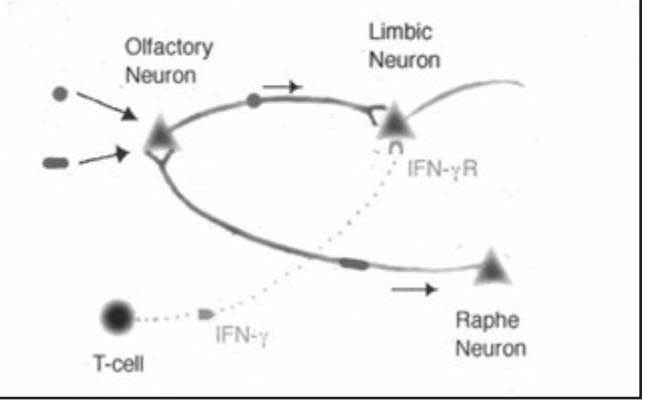


Fig. 1. *Schéma de la face infero-interne de l'hémisphère droit de la loutre*

A measles strain can attack limbic neurons to cause seizures



2. Immune control of pathogens in the brain

INNATE IMMUNITY

Carries memmory of the species

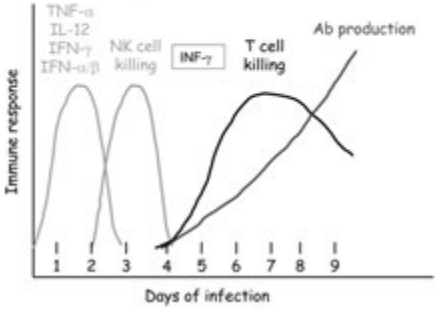
Toll-like receptors

ADAPTIVE IMMUNITY

Carries memory of the individual

B and T cells

CYTOKINES - highly inducible, secreted proteins mediating intercellular communication in the immune system



Pro –inflammatory cytokines

Tumor necrosis factor (TNF) – α

Interleukin (IL) -1, -4, -12

IL-12 Th1 cytotoxic response

IL -4 Th2 humoral response

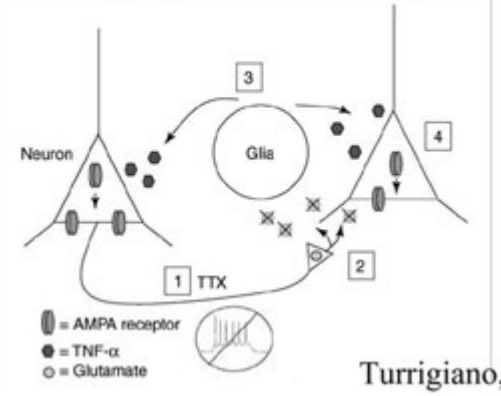
Interferon (IFN) - γ

Anti –inflammatory cytokines

Interleukin (IL) – 10, - 1receptor antagonist

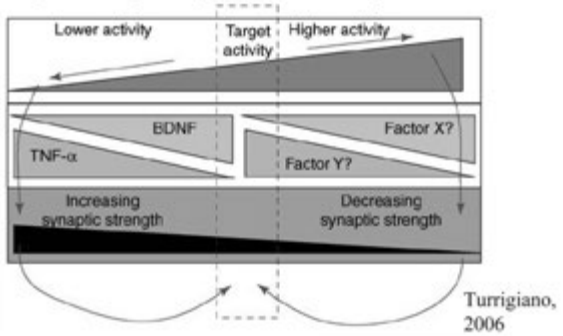
TNF-α and IFN-γ can disturb the balance between inhibitory and excitatory synaptic activities

If glutamate release is diminished, glia produce TNF-α that up-regulate AMPA receptors



Turrigiano, 2006

TNF-α up-regulates AMPA and down-regulate GABA receptors. i.e. up-scaling of synaptic activity

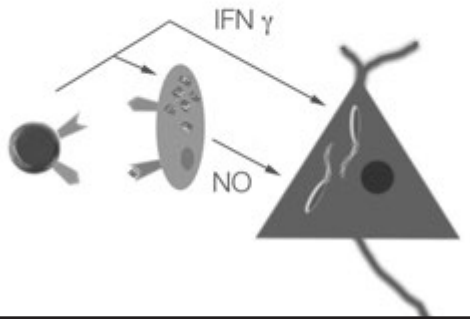


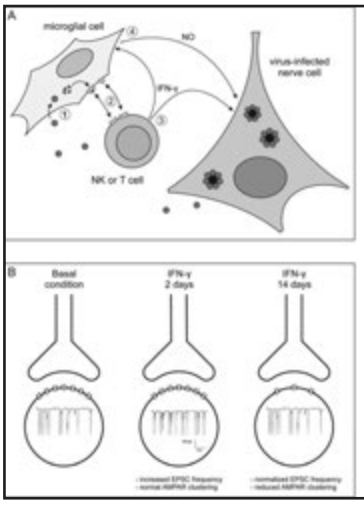
Turrigiano, 2006

Synaptic scaling

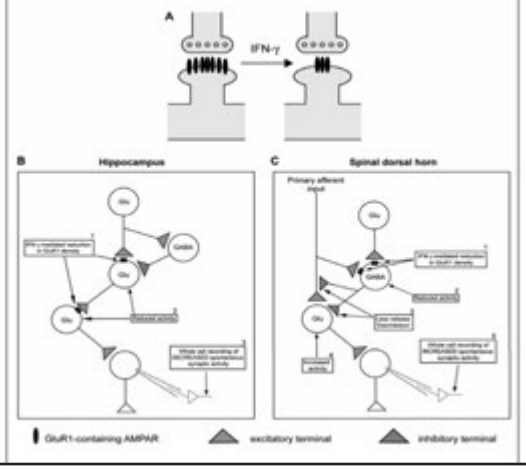
- May balance exitation and inhibition after changes in synaptic strength, while keeping the changes in memory
- Sleep – downscaling
- May prevent pathological states such as epilepsy

Immune control of pathogens in a neuron that survive by IFN-γ
-but does it function normally?

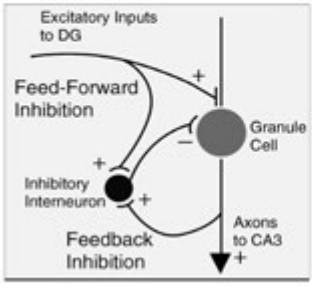




- Synaptic activity increases **2 days** after exposure to IFN-γ. After **2 weeks**, the excitatory postsynaptic currents (EPSC) have returned to normal paralleled by a reduced AMPAR clustering. Following longer exposure **(> 4 weeks)** synaptic activity will decrease.



TNF-α and IFN-γ affects synaptic scaling. Net-effect depends on concentrations, time scales and network constructions.



May modify sensitivity to seizures, but can they be a cause?????

Babb TL, Brown WJ. Pathological Findings in Epilepsy. In: Engel J. Jr. Ed. Surgical Treatment of the Epilepsies. New York: Raven Press 1987: 511-540.

3. Pathogens that cause epilepsy

- Taenia solium
- Plasmodium
- HIV
  - –Opportunistic infections
    - Toxoplasma
    - Tbc

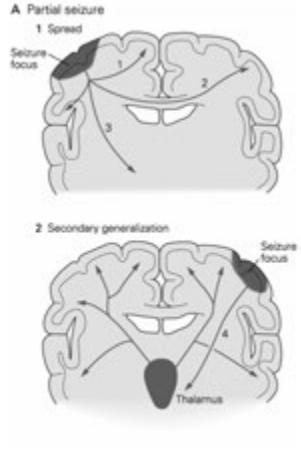
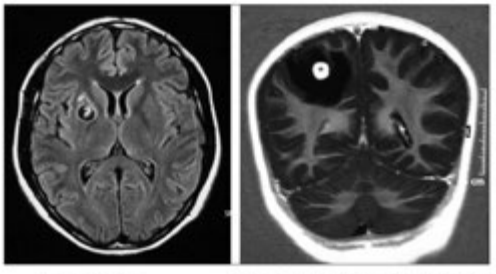


Fig 46.13 Kandel

Neurocysticercosis

Around 30% of all seizures in South and Central America *Garcia et al. 2005*



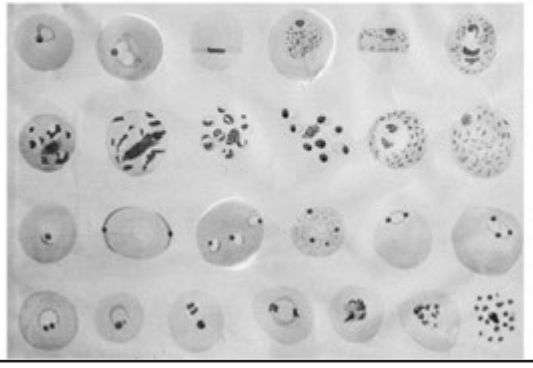
FLAIR MRI with inversion recovery

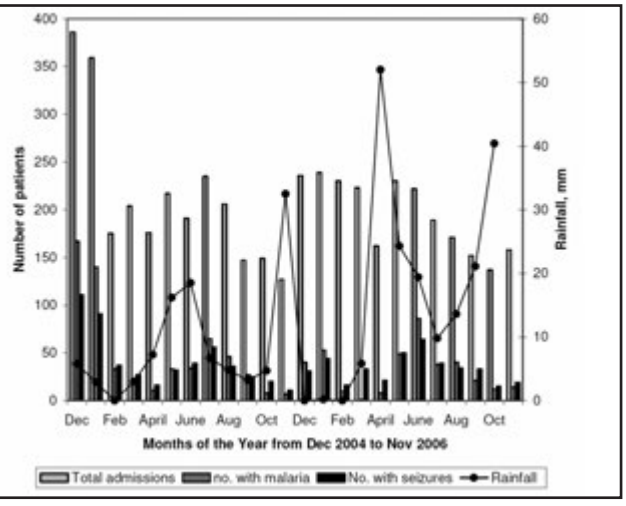
Cerebral malaria

- Causes death of 1.5-2.7 million persons every year
- *Plasmodium falciparum, vivax, ovale and malariae* are infectious to Man
- Parasitemia;
- Coma for 30 minutes or more
- Adhesion of erythrocytes to endothelial cells, secretion of "tumor necrosis factor"-α, phospholipids and malaria toxins

P. falciparum in erythrocytes

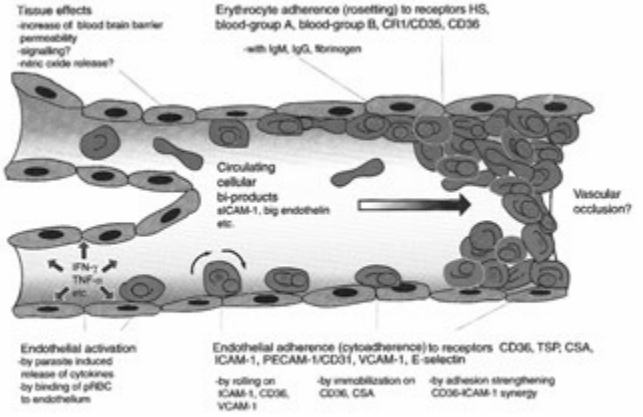
(from Camillo Golgi)





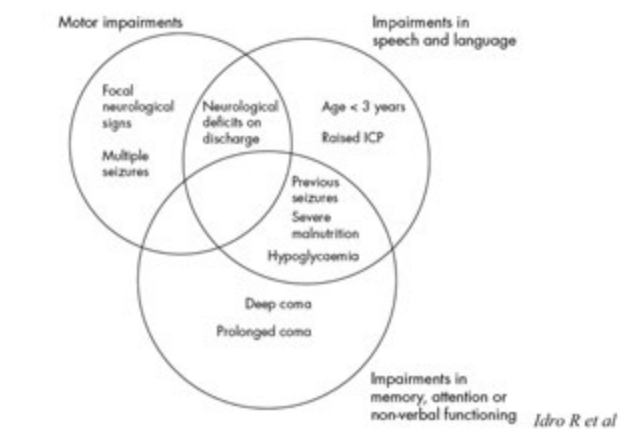
All children aged 0-13 years with or without seizures admitted to Kilifi District hospital over 2 years *Idro R:BMC Pediatrics* 2008

- 18.3% (900/4921) had seizures and 80% of these associated with infections
- Associated with faliciparum malaria in 58% of children 6 months and older



Complications of cerebral malaria

- Learning disabilities and behavior disturbances
- Auditory problems, cortical blindness
- Epilepsy



Idro R et al 2006

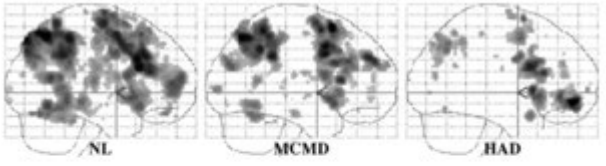
Figure 2 Risk factors associated with persisting motor, speech and language, and other cognitive impairments.

Seizures in 2-20% of HIV-seropositive individuals

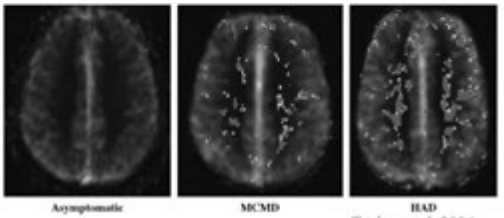
Problems:

- Drug-disease interactions
- Drug-drug interaction
- Effects on viral replication – valproic acid

Functional magnetic resonance imaging (fMRI)

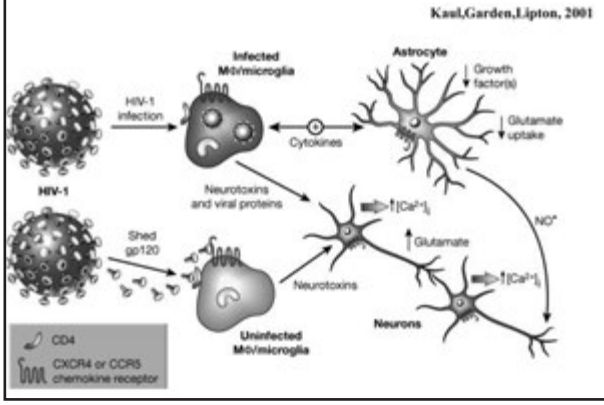


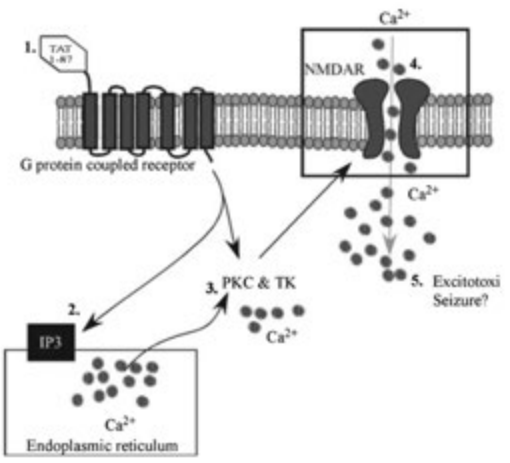
Perfusion MRI

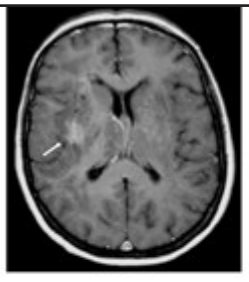


Tucker et al 2004

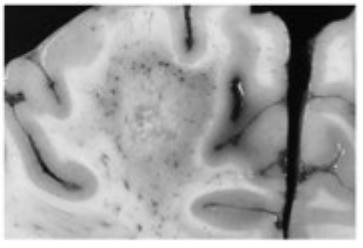
HIV







Opportunistic infections



Toxoplasmic encephalitis

4. Can seizures or epilepsy be caused by pathogens?

- Mesial temperal lobe epilepsy (MTLE)
- Febrile seizures
- Rasmussen's encephalitis

Fotheringham J et al., 2007

Table 2. HHV-6 DNA Detection in Temporal Lobe Resections from NIH/CNMC epilepsy cohort (n=38)

Patients	Pathology	HHV-6 Positive	HHV-6 Negative
MTLE ($n = 24$)	MTS, gliosis	15*	9
Non-MTLE ($n = 14$)	Hemimegalencephaly, dysplasia, cavernous hemangioma	0	14

Human herpesvirus-6 (HHV-6), isolated 1988, causes exanthem subitum and can establish latency in the central nervous system.

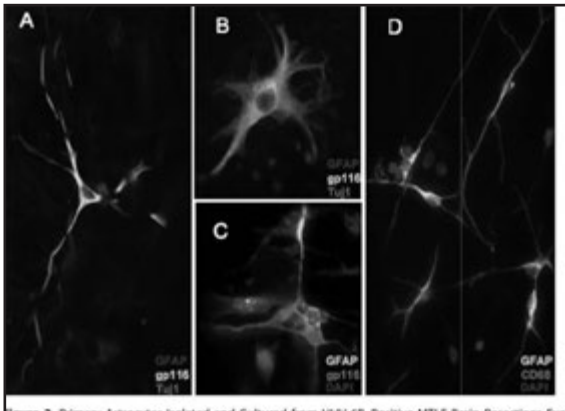


Figure 2. Primary Astrocytes Isolated and Cultured from HHV-6B–Positive MTLE Brain Resections Express Viral Antigen

Febrile seizures

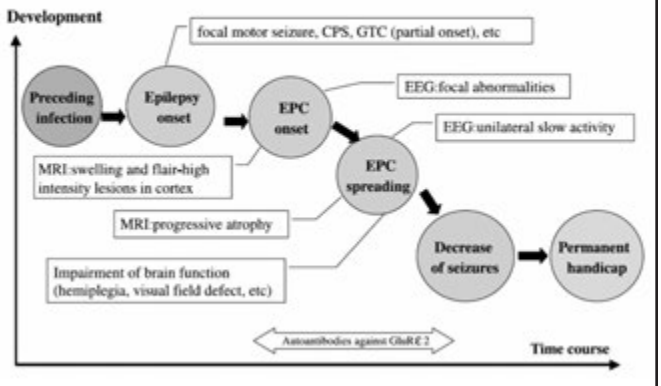
Reviews:

Van Zeil et al. 2002; Millichap and Millichap, 2006

16.5% HHV-6 patients had seizures and virus DNA found in the CSF in 14.5% of them, but inconclusive

Influenza A virus frequent cause of febrile seizures in Japan and China – not in Europe and USA

Rasmussen's encephalitis



- **Olfactory route to the limbic system**
- **TNF-α and IFN-γ, and synaptic scaling modulate level of excitatory activity in networks**
- **Neurocysticercosis, cerebral malaria and HIV**
- **Search for viruses in mesial temporal lobe epilepsy, febrile seizures and Rasmussen´s encephalitis**

Our presently known infectious agents have been isolated on cells or in animal tissues.

Novel genomic techniques can discover unknown viruses – a black box

Watch and see

Photosensitivity: a time-dependent genetic trait
Patricia Braga (Uruguay)

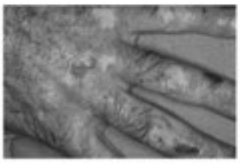
Fotosensibilidad en Epilepsia:

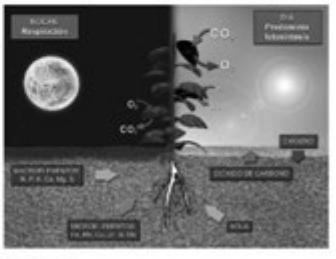
Un rasgo genético
Tiempo-dependiente

P.Braga - LASSE IV - 2010

¿Qué es Fotosensibilidad?

- Capacidad de sufrir modificaciones inducidas por la exposición a la luz





P.Braga - LASSE IV - 2010

¿Qué es Fotosensibilidad en Epilepsia?

- aumento en la **excitabilidad neuronal**, desencadenado por un **estímulo luminoso** o algunas características del mismo, y que excede la excitación fisiológica de la vía visual en su magnitud (extensión o intensidad) o en su efecto clínico
- En un enfoque más restrictivo, FS en epilepsia se puede considerar como un factor precipitante, que precede inmediatamente a la crisis, con una relación temporal estrecha entre el estímulo visual y la aparición del fenómeno ictal
  - relación de tipo causa-efecto
  - asociación temporal entre ambos como núcleo del diagnóstico

P.Braga - LASSE IV - 2010

"Causa": Estímulo visual

- el estímulo luminoso no es un evento único de características estáticas, homogéneas, sino que es un fenómeno que incluye numerosas variables
- un individuo puede ser "fotosensible" a determinadas características del estímulo y no a otras
- sensibilidad del examen estandarizado de la fotosensibilidad

"Causa": Estímulo visual (2)

- **Simple** (destello): intensidad, color-longitud de onda-, duración, distancia de la fuente
- **Más complejos**: patrones de repetición regulares o irregulares, frecuencia temporal, frecuencia espacial; homogéneos o heterogéneos en sus distintas cualidades simples y en diferentes combinaciones
- Conceptos vinculados a la percepción visual como el **contexto** visuo-espacial, la uni o plurimodalidad del estímulo, la atención, el reconocimiento o la novedad del mismo, entre otros.
- Las características reconocidas como más potentes desencadenantes de FS son la **frecuencia temporal** y la **luminancia**.

Frecuencia Temporal del Estímulo visual

- La FS puede ser expresada como el rango de frecuencias que induce una RFP (PPR) (Kasteleijn-Nolst Trenite´ 1989; Harding and Jeavons, 1994), siendo los límites habituales del rango entre 10 y 30 Hz (Leijten et al., 1998).
- La mayoría de los pacientes son sensibles a 16 flashes/s; 49% son sensibles a 50Hz en tanto que sólo 15% lo son a 60 Hz.
- Sólo aprox. 3% de la población FS con algún trastorno degenerativo, es sensible a la ELI a 1–3 flashes/s (Zifkin and Kasteleijn-Nolst Trenite´, 2000).
- Un patrón en movimiento continuo en una sola dirección es raramente precipitante de RFP.
- Sin embargo, si el patrón se mueve cambiando la dirección del movimiento en forma repetida y alternante, con similar velocidad, la susceptibilidad puede ser tan alta como para el flicker. (Stephani et al, 2004). En estos casos, la FS evocada también es frecuencia dependiente, asociando conceptos de periodicidad espacial y temporal en la característica evocadora del estímulo.

Estímulo visual complejo: video

- Un número significativo de pacientes (esp. con crisis por video-juegos) son sensibles a patrones, pero no a la ELI (Harding, 1998).
- Factores dependientes del hardware (frecuencia scan) o del software (color, contraste, luminancia, patrones geométricos) (Wilkins et al., 2004).
- Habitualmente FS es máxima a frecuencias de 20 Hz, con un rango entre 8-50 Hz. (Stephani et al., 2004).
- Varios estudios han mostrado mayor seguridad con frecuencias de scan de 100Hz en la pantalla de TV en comparación con frecuencias más bajas (Fylan and Harding, 1997; Badimand- Hubert et al., 1998; Ricci et al., 1998; Wilkins et al., 2004).
- El potencial del estímulo cromático combinado en varios patrones geométricos, particularmente la luz roja, ha demostrado ser eficaz para desencadenar RFP (Binnie et al., 1984; Takahashi et al., 1995; Wilkins et al., 2004).
- Pokemon – secuencia con pantallas flash alternativamente en rojo y azul, cambiando a 12.5/seg por aprox. 4seg

Acto perceptual

- Visión mono o binocular
- Ojos abiertos /cerrados
- Eye closure sensitivity
- Fixation-off sensitivity
- Distinta prevalencia en diferentes síndromes epilépticos
- EC, ECLS y FOS - pueden disociarse de FS
- Mecanismo?

Efecto: respuesta fotosensible

•**CLÍNICA:**
- Crisis foto-inducida: provocada por estímulo visual (luz intermitente, patrones de líneas, damero, otros).

•**PARACLÍNICA:**
- Neurofisiológica - EEG-MEG
- Patrones de perfusión - SPECT
- Patrones de metabolismo – PET-fMRI

•**RESPUESTA FOTOPAROXÍSTICA (RFP-PPR)** – Respuesta EEG anormal a la luz o patrones, consistente en puntas, punta-onda u ondas lentas intermitentes.

•**FOTOSENSIBILIDAD:** respuesta anormal del EEG a luz o patrones de estimulación, consistente en una RFP.

•**Crisis vs EEG** - pueden verse crisis inducidas por estimulación visual (flash-pattern), sin demostrarse FS en el EEG (inadecuada estimulación durante el EEG, medicación, variación al azar.

Efecto Clínico: CRISIS

- Más frec. CTCG, mioclonias bilaterales y concientes
- Menos frec. ausencias y crisis parciales (simples visuales, o parciales complejas)
- Mioclonias palpebrales (con o sin ausencias)
- Versión tónica óculo-cefálica
- CTCG habitualmente desencadenadas por exposición prolongada, siguiendo una ausencia, mioclonias, o de inicio.
- Crisis parciales, s/t del lób. occipital : secuencia de síntomas visuales y vegetativos, a/v con cefalea. A veces con síntomas vegetativos o aura epigástrica sin fenómenos visuales. (Guerrini et al., 1998; Hennessy and Binnie, 2000)
- Equivalentes ictales: trastornos de conciencia y sensación de placer han sido descritos en asociación a RFP.

Efecto EEG

- Varias respuestas EEG a la ELI, con diferente significado clínico.

- **Waltz (1992)-**
  I: Puntas Occipitales
  II: Puntas Regionales Parieto-Occipitales y Ondas Lentas Bifásicas
  III: Puntas Parieto-Occipitales y Ondas Lentas Bifásicas que propagan a Regiones Frontales
  IV: Puntas o Polipuntas y Ondas Generalizadas

- **Jeavons and Harding (1975):**
  1. Respuesta visible sólo en regiones frontales FOTOMIOCLÓNICA
  2. Respuesta visible sólo en regiones posteriores – ARRASTRE FÓTICO, PEV, PUNTAS OCCIPITALES
  3. Respuesta bilateral y difusa, anterior-posterior -FOTOCONVULSIVA (EOL 3 Hz, EOL 4-7 Hz, PP, PPOL, ondas lentas difusas de gran amplitud)

Efecto EEG: RFP

- La relación entre los diferentes tipos de respuesta a la ELI y el riesgo de crisis inducidas por el estímulo visual no está claro.
- Actualmente, sólo las descargas paroxísticas generalizadas (puntas, polipuntas, complejos EOL) son aceptadas como respuestas de valor patológico (Ziykin and Kasteleijn-Nolst Trenite´, 2000).
- La expresión de una RFP en el EEG es influida por
  - **edad –** penetrancia máxima entre 5-20 años
  - **sexo –** más frecuente en sexo femenino
  - **Estado de vigilia –** aumenta con fatiga post deprivación de sueño
  - **Síndrome epiléptico –** no sólo la prevalencia, sino la frecuencia de RFP en algunas EGI es mayor que en otros contextos clínicos.
  - **factores desconocidos –** variación en repetidas evaluaciones de un mismo paciente con intervalos variables
  - **agregación familiar** (Doose and Baier, 1987; De Graaf, 1992; Doose and Waltz, 1993; Harding and Jeavons, 1994; Famiulusi et al., 1998; de Graf et al., 1998; Stephani et al., 2004), por lo que se plantea una base genética, y es considerada un ENDOFENOTIPO

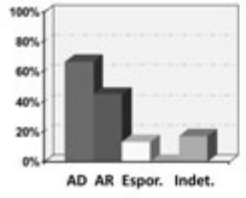
RFP como Endofenotipo

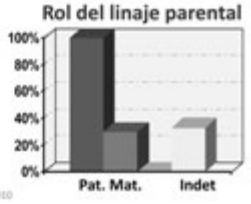
- **Base genética:**
  - gemelos monocigóticos - casi un 100% de concordancia
  - modo de herencia AD con penetrancia reducida, asociada a la edad.
- **Independiente de la Epilepsia:**
  - Pacientes con epilepsia FS y con familiares con FS sin epilepsia, en que FS se segrega en patrón AD.
  - En familias con EGI, RFP puede ser heredada a través de la línea parental que no posee epilepsia
- **Asociado al Síndrome Epiléptico:**
  - Se han identificado loci en los Cr 2, 6, 7 y 16, en correlación con el fenotipo de crisis predominante en los miembros de la familia afectada
  - Se ha propuesto un modo de herencia complejo y poligénico
- U. Stephani et al, 2004:
  - PPR idiopática - expresión de una vía anormal de PPR que puede predisponer también a crisis en pacientes ya predispuestos a epilepsia (EGI)
  - PPR sintomática - como resultado de una vía PPR normal en sí misma pero disfuncional a causa de un proceso neurodegenerativo específico (en raras patol AD como lipofucsinosis ceroide, Unverricht-Lundborg disease, etc.).

Fotosensibilidad como Subfenotipo de EGI:

	EMJ (n=42)	EA (n=8)
Sexo F:M	23:19	7:1
FS	10 (24%)	2 (25%)
AP CF	5 (12%)	2 (25%)
AF CF	14 (33%)	4 (50%)
AF Epilepsia	23(55%)	5 (62%)
AF EGI 1er gr	6 (14%)	1 (12%)

	Variable asociada	N=50 p
FS (EMJ)	AF Epilepsia	0.028
	AF CF/EGI pr gr	0.04



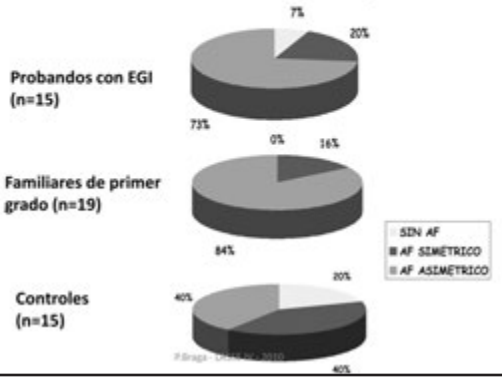


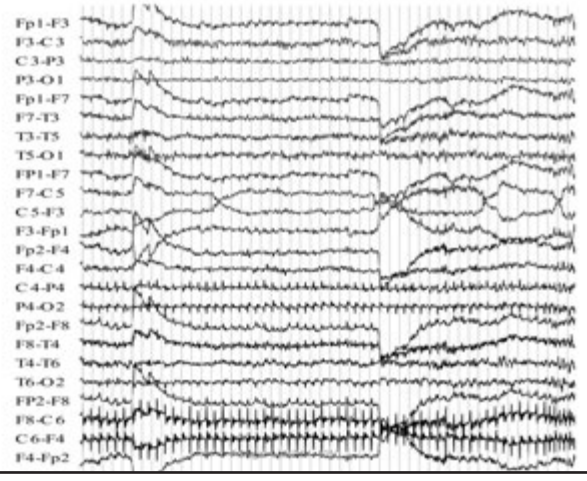
Endofenotipificación neurofisiológica

- **Muestra:**
  - n = 15
  - Edad- x =22.3±4.9 años
  - Sexo- F:M = 12:3
  - Síndrome epiléptico- **12 EMJ/ 2 EAJ / 1 EAI**
  - Historia familiar de epilepsia- 53%
  - Todos recibían DAE
- **Video-EEG**
  - No se registró sufrimiento cerebral
  - En un paciente actividad focal en FEI (F izq)
  - 1 registro ictal: ausencia típica en HVP
  - **Fotosensibilidad:** 5 (33%)
  - **Arrastre Fótico**: 14 (93%)

Endofenotipificación neurofisiológica

Arrastre Fótico Asimétrico (AFA):





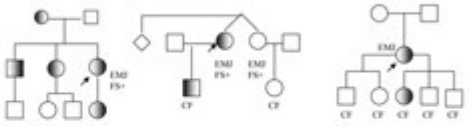
Endofenotipificación neurofisiológica

Arrastre Fótico y Fotosensibilidad

PROBANDO	SEXO	EDAD	SINDEPI	AFA	FS	VERSIVAS	EEGFOCAL	REMISION	RESPVPA
B.C.	F	20	EA	SI	SI	NO	NO	NO	EXCELENTE
M.P.	F	24	EA	SI	NO	NO	NO	NO	POBRE
W.R.	M	17	EA	SI	NO	NO	SI	NO	POBRE
M.A.	F	22	EMJ	SI	SI	NO	NO	NO	POBRE
V.G.	F	24	EMJ	SI	SI	NO	SI	NO	
C.M.	F	19	EMJ	SI	SI	NO	SI	SI	EXCELENTE
M.P.	F	27	EMJ	SI	SI	NO	NO	NO	POBRE
J.F.	M	18	EMJ	SI	NO	NO	NO	NO	EXCELENTE
L.P.	F	27	EMJ	SI	NO	NO	NO	NO	POBRE
N.G.	F	18	EMJ	SI	NO	SI	NO	SI	EXCELENTE
V.S.	F	19	EMJ	SI	NO	NO	SI	NO	POBRE
L.L.	F	15	EMJ	NO	NO	NO	NO	SI	EXCELENTE
A.M.	F	24	EMJ	NO	NO	SI	NO	NO	EXCELENTE
G.R	M	27	EMJ	NO	NO	NO	NO	NO	EXCELENTE
L.D.L.	F	33	EMJ	NO	NO	NO	NO	NO	POBRE

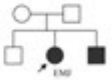
Modos de herencia:

Endofenotipo: Arrastre Fótico –



- LOS HIJOS DE PROBANDOS CON AFA PRESENTARON AFA CON PREDOMINIO IPSILATERAL
- TODOS LOS PROBANDOS CON AFA TENÍAN AL MENOS UN PROGENITOR CON AFA

FAMILIAR CON AFS



PROBANDO CON AFS

Modos de herencia:

Endofenotipo: Arrastre Fótico –

- AFA en todas las generaciones e igual distribución por sexo: ¿Herencia AD?
- AFA no se asoció con modo de herencia de EGI ni CF.
- AFA no se asoció con línea parental de historia familiar de epilepsia.
- Elevada prevalencia de AFA en familiares sin historia de epilepsia: Segregación independiente de la epilepsia, con contribución parcial al fenotipo completo.

FS y Cronobiología

- Se ha observado una variación en la prevalencia de FS en función de la edad, tanto para el endofenotipo EEG como para la expresión clínica.
- **Aparición de crisis fotosensibles:** 12-15 años. Pubertad.
- **Aparición de RPF en EEG:** máxima penetrancia 5 – 15 años
  - 7.6% de niños normales (Doose y Waltz)
  - 8% entre 1-15 años y 1% entre 16-21 años (Eeg-Olofsson and Petersen)
  - FS en pacientes con primer EEG registrado entre 10 y 25 años. Edad de inicio media 14.4 años (Wolf, Goosses 1986)
- **Remisión de FS:**
  - 2/3 de ptes FS –persiste media 14 años luego del diagnóstico inicial
  - >50% desaparece en seguimientos más prolongados (Harding y Jeavons)
- FS no evoluciona necesariamente en forma paralela con la evolución de la epilepsia.

FS y Sexo

- El sexo puede influir sobre el endofenotipo RFP:
  - Prevalencia hasta 2.5 veces mayor de PPR en niñas (Harding and Ioavone, 1994)
  - La incidencia de crisis epilépticas es mayor en familiares de sexo femenino de portadores del rasgo RFP (Doose et al., 1969).
  - En nuestra serie, los pacientes con AF de epilepsia por línea paterna tenían mayor prevalencia de FS.
- Se postulan mecanismos hormonales, que podrían también explicar la expresión dependiente de la edad.
- Hipótesis alternativas:
  - Podría estar relacionado con la carga genética doble de Cr X por mecanismos genéticos o epigenéticos
  - Rol protector directo o indirecto del cromosoma Y
  - Rol de impronta genómica

Ciclos ultradianos

AMBIENTE Y EXPRESIÓN- VARIACIONES CÍCLICAS

- FS estable en intervalos de días in un individuo dado, si se controla la variación circadiana (Binnie, 1986)
- **Variación estacional**
  - RFP menos común en pacientes evaluados en verano vs invierno (Danesi)
  - Quirk et al no encontraron variación estacional de FS
- Variación por **regiones climáticas**
  - no se encontraron factores climáticos relevantes para la evocación de RFP
- Otras variantes cíclicas en ritmos ultradianos han sido menos estudiadas en relación con FS:
  - **Ciclos hormonales** – epilepsias catameniales
- Por otra parte, la función circadiana de despertar puede modificarse por factores ultradianos, como la menstruación o el estrés, mediados por diferentes influencias hormonales.

Ritmos circadianos

- Centrado en la relación con el ciclo sueño-vigilia
- Otros factores : liberación cíclica de hormonas endógenas -melatonina o corticoides.
- Esta relación se considera más evidente para las crisis mayores
- En nuestra serie de 43 pacientes con EMJ, el agrupamiento de las crisis en la mañana, próximo al despertar, fue un hallazgo casi constante.
  - **Mioclonias: 42/43 al despertar** – 1/43 en vigilia
  - **CTCG (n=39) - 25 (64%) al despertar** - 11 (28%) en vigilia - 1 en relajación vespertina, 1 hípnicas y 1 al azar
  - **Ausencias (n=15): 9 (60%) al despertar**, 1 en relajación vespertina y 5 en vigilia
- **Crisis versivas o rotatorias (n=6): 4/6 al despertar** – 2 en vigilia.
- Excitabilidad motora cortical en EMJ con TMS: no diferencias entre la mañana y el atardecer en pacientes bajo DAEs. Plantean rol de estructuras subcorticales (no evaluables por TMS) (Pfutze M., 2007)

EGI y ciclo sueño-vigilia

- ✓ **¿Cómo puede entenderse que las crisis de las EGI ocurran habitualmente luego de despertar del sueño?**

1. **Precipitación de crisis por falta de sueño –**
2. **Calidad de la estructura del sueño que precede a las crisis** –planteo de distintos perfiles de sueño (Patry, 1931). El sueño de pacientes con epilepsia del despertar es claramente más inestable y más fácilmente influenciado por circunstancias externas que el de pacientes con crisis hípnicas.
3. **El despertar en sí mismo-** transición del sueño al estado de vigilia. Las crisis aparecen cuando el proceso es acelerado, y se evitan cuando el proceso es enlentecido o repetido. Los pacientes refieren que antes de la crisis, no estaban completamente despiertos, o habían sido instados por otros a apurarse, para finalmente estar prontos y vestidos (despertar incompleto o prodromos?)

Janz D. Epilepsy with grand mal on awakening and sleep-waking cycle. Clinical Neurophysiology 2000;111(Suppl 2):S109-S110.

Patrones cíclicos neuronales y ciclo sueño-vigilia

Rol del tálamo –

- Generador de actividad oscilatoria rítmica y patrones de sueño
  - Las neuronas talámicas pueden operar en dos modos:
  - Modo de relevo - asociado con el procesamiento de input sensorial en condición de vigilia activa , como relevo hacia el córtex.
  - Modo oscilatorio- generación de descargas rítmicas durante el sueño. Filtra el input externo sensorial para favorecer las interacciones endógenas, en bucle cerrado, con la corteza, durante el sueño.

  - Un estudio en el modelo felino de epilepsia generalizada con penicilina, demostró que luego de la inyección sistémica de penicilina, los husos de sueño desaparecieron para dar lugar a complejos espica onda lenta (Kostopoulos et al., 1981a,b).
  - Otro estudio en slices de tejido talámico sugiere que el circuito tálamo-reticular-talámico aislado es responsable de la generación de husos, y también es capaz de generar oscilaciones rítmicas en el rango de frecuencia de las EGI 3Hz.
- Relevo clave de la vía visual aferente - disparador

Cyclic alternating pattern and epilepsy during sleep: how a physiological rhythm modulates a pathological event. L Parrino et al. ,2000.

- CAP son patrones repetitivos transitorios en el sueño NREM, con una fase A (complejos K, despertar) alternada con intervalos de fase B (actividad de fondo propia de la etapa de sueño).
- Los pacientes con epilepsia mostraron mayor tasa de CAP que controles (52.7 versus 34.6%; P , 0:003).
- En EGI, las descargas intericitales se activan durante fases de sueño inestable (CAP>NCAP), sin consecuencias evidentes en la macroestructura del sueño, pero con efectos signficativos sobre la estabilidad del despertar.
- En los pacientes con epilepsia, los ciclos CAP que incluyen al menos una descarga son más largos que aquéllos sin descargas (31.2 versus 25.4 s; P=0:007). El alargamiento selectivo de los ciclos CAPcon descargas y el aumento de la tasa CAP apoya la hipótesis de que ambos comparten mecanismos comunes que vinculan un fenómeno fisiológico (CAP) con un evento patológico (descargas intericitales).

Fotosensibilidad: fisiopatología

- El primer planteo de asociar un estímulo visual con una respuesta exagerada de neuronas corticales, capaces de generar crisis epilépticas, sería la existencia de un foco epileptógeno o grupo neuronal hiper-excitable en la corteza visual primaria o de asociación (dependiendo de las características del estímulo implicadas en cada individuo), cuya activación fisiológica en el proceso de percepción visual determina una respuesta exagerada, hiper-sincrónica, patológica.
- Sin embargo, las crisis parciales simples visuales, ilusorias o alucinatorias, son poco frecuentes, y rara vez fotosensibles. Si bien el córtex visual debe estar involucrado de una u otra forma, estos hechos nos llevan de la mano a la necesidad de comprender mejor la fisiología de las redes neuronales involucradas en la percepción visual y sus códigos de interrelación.

FS en modelos animales

❖ **Baboon Papio papio** –

- **FS** con RFP desencadenada por ELI a 20-30Hz, acompañada de **mioclonias y clonias**.
- **RFP** de distribución **frontocentral y rolándica** con generalización.
- En baboons FS se demostró que bajo ELI, **neuronas corticales frontales** son activadas progresivamente antes de que se distingan descargas paroxísticas en el EEG de superficie, y ambas terminan con el fin de la ELI.
- La infusión bilateral prolongada (7 días) de GABA en la corteza motora (área 4) de los baboons FS o alternativamente en la corteza occipital, bloquea completamente las manifestaciones clínicas y EEG inducidas por ELI durante la infusión. No así la infusión en área 6 u 8.
- Los generadores de las manifestaciones epilépticas en los baboons se situarían en el córtex motor, y las aferencias visuales provenientes del córtex occipital serían necesarias para disparar estos generadores

❖ **Baboon Papio hamadryas spp.** –Szabó C et al. 2003a2007.

- Factores asociados a epilepsia: **edad** < 4 a; sex ratio igual.
- **FS** se asoció con **base genética**: híbridos P.h.anubis/cynocephalus vs P.h. anubis (p=0.004)
- Estimulación: Consistentemente sensibles a 25 Hz igual que P.h. papio, se indujeron descargas y crisis a otras frecuencias, incluyendo 3, 6, 9, 12, 15, 18 y 27 Hz.
- Respuesta **EEG**: descargas 4-6 Hz; en los más jóvenes a 2-3 Hz.
- **PET** en ELI: FS mostraron mayor **activación en cíngulo anterior derecho y órbito-frontal**, sin activación del córtex occipital vs controles (activación bilateral, occipital y cerebelosa). Se sugiere inhibición de córtex occipital durante fotoestimulación en individuos fotosensibles.

❖ **Pollo FEpi (Fayoumi epileptic)** –

- mutación AR y forma de epilepsia refleja con crisis generalizadas en respuesta a la luz o sonido, EEG interictal con descargas paroxísticas.
- en ambas respuestas el iniciador de las crisis parece estar localizado en el tronco cerebral, con refuerzo de estructuras visuales telencéfalicas para desencadenar convulsiones generalizadas fotogénicas.

Estudios en humanos

- **Objetivos –**
  - Rol de la frecuencia temporal de la estimulación visual
  - Vías y circuitos extra-estriados involucrados. Facilitación e inhibición
- **Población –**
  - Pacientes con epilepsias fotosensibles
  - Individuos sanos -fisiología de vía visual y procesamiento cortical
- **Metodología –**

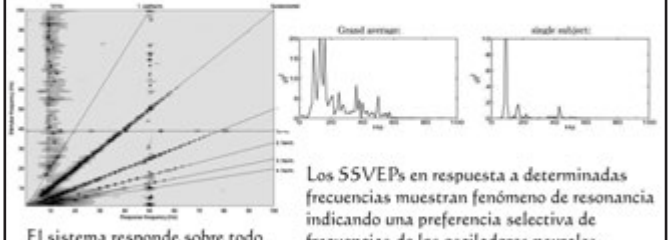
EEG	SSVEP
TMS	fMRI
SPECT	PET

Stimulus rate dependence of regional cerebral blood flow in human striate cortex demonstrated by positron emission tomography. Fox PT, 1984.

- Objetivo : determinar la relación entre el índice de repetición de un estímulo visual simple y el FSCr en el cerebro humano (voluntarios sanos).
- Entre 0 y 61Hz, el **FSCr en el córtex estriado varió como función de la frecuencia temporal** del estímulo fótico, formando una curva de respuesta unimodal con un **máximo entre 7.8 y 15.5 Hz**.
- La localización anatómica de la región con pico de respuesta vascular fueron los lóbulos occipitales a nivel mesial, a lo largo de la cisura calcarina (córtex visual primario) para todos los sujetos estudiados
- Ninguna otra área cerebral mostró un cambio consistente.

Human EEG responses to 1-100Hz flicker - Herrmann C. 2001

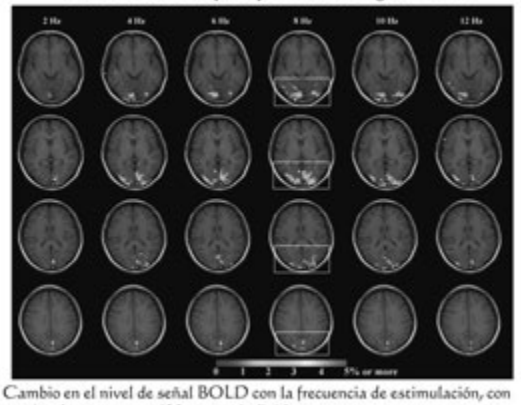
- Estudio en 10 individuos sanos.
- Muestra **frecuencias evocadas preferidas frente a distintas frecuencias de estimulación fótica.**



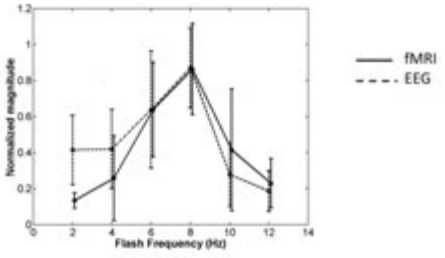
El sistema responde sobre todo con frecuencia igual a la de la estimulación y con frecuencias subarmónicas a la estimulación.

Los SSVEPs en respuesta a determinadas frecuencias muestran fenómeno de resonancia indicando una preferencia selectiva de frecuencias de los osciladores neurales. **Fenómenos de resonancia ocurrieron a frecuencias de 10, 20, 40 y 80 Hz.**

Correlation Between BOLD-fMRI and EEG Signal Changes in Response to Visual Stimulus Frequency in Humans Singh M - 2003



Cambio en el nivel de señal BOLD con la frecuencia de estimulación, con un pico de respuesta a 8Hz, en un individuo.

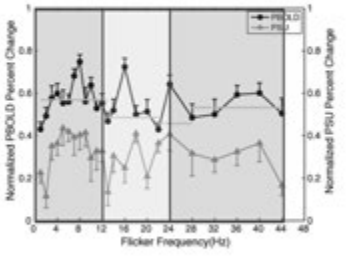


- Estudio en 8 sujetos sanos con estimulación flash 2-12 Hz.
- **Ambas modalidades muestran un cambio de señal similar con la frecuencia de estimulación, con un pico en ambos casos a 8Hz.**
- Picos a similar frecuencia se encontraron en estudios con PET y fMRI BOLD, para paradigma con damero.

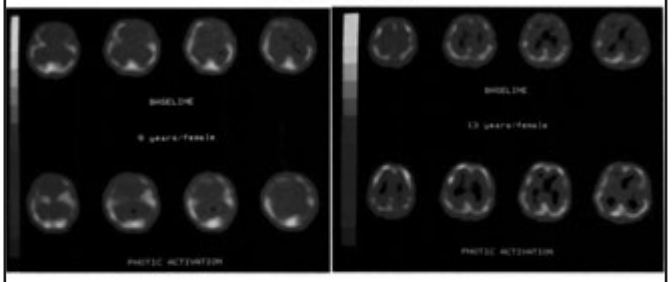
Changes in BOLD transients with visual stimuli across 1–44Hz
Uzay E. Emir – 2008

- fMRI en cada ELI a diferentes frecuencias de 1 a 44Hz, en sujetos sanos

- El **pico global para la respuesta BOLD fue a 8Hz**, con picos secundarios a 16 y 24 Hz, y un pico más amplio de 36-40Hz.
- **3 bandas de diferentes perfiles de respuesta** según correlaciones entre positive BOLD signal and post-stimulus undershoot (PSU).
- el aumento en la actividad excitatoria amplifica tanto PBOLD como PSU
- el aumento en la actividad inhibitoria evoca un descenso en la señal PBOLD sin alterar PSU



Brain SPECT evaluation of patients with pure photosensitive epilepsy – L.O. Kapucu 1996



SPECT INTERICTAL vs ICTAL (crisis inducidas porTV)
SPECT INTERICTAL: HIPOPERFUSIÓN FRONTAL en 6/7 pacientes + 1 normal
SPECT ICTAL: HIPERPERFUSIÓN FRONTAL en 7/7
Patrón de alteraciones del FSCr FRONTAL relativamente consistente, sugiriendo que los lóbulos frontales están involucrados en las crisis asociadas a FS en estos pacientes.

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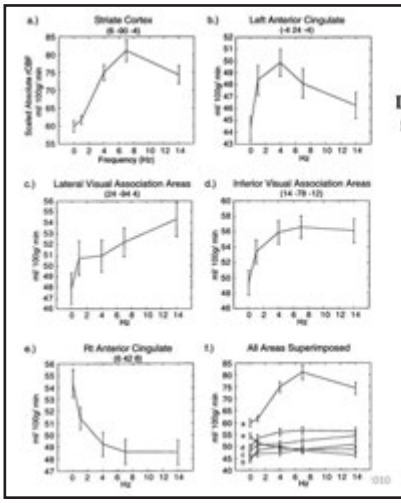
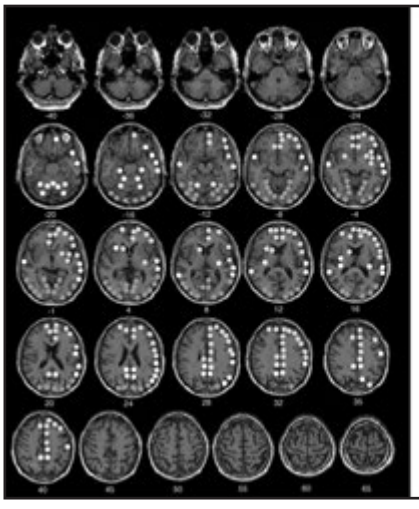


Frequency Variation of a Pattern-Flash Visual Stimulus during PET Differentially Activates Brain from Striate through Frontal Cortex. M. J. Mentis - 1997

Evaluación del FSCr en 19 adultos sanos con PET $H_2{}^{15}O$ frente a estímulo visual monocular alternante a diferentes frecuencias (0,1,4,7,14).



● Respuestas bifásicas:
Aumento en el córtex estriado hasta un pico en 7Hz
Aumento en cíngulo anterior izquierdo (pico 4 Hz)

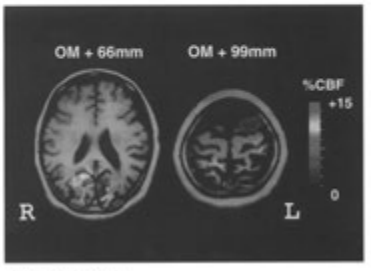
Respuetas monotónicas:
● Aumento en áreas posteriores
○ Descenso en áreas anteriores y cíngulo derecho

○ Otros patrones de respuesta frecuencia-dependiente
Activación específica de la circunvolución temporal media izquierda a 1 Hz

Central pathway of photic reflex myoclonus. Kanouchi T et al. 1997

- Datos anatómicos en primates muestran que proyecciones del área visual terminan en el área premotora y precentral
- Se plantea una vía central para el mioclonus fótico reflejo: un estímulo visual activa primero el córtex occipital, pasando el impulso al cortex motor primario ipsilateral, desencadenando una sacudida mioclónica contralateral a través del tracto córtico-espinal.

H2o-PET images corregistradas con MRI (1Hz flash vs reposo) en un paciente con mioclonus fótico reflejo del MSD (sin clínica durante PET)



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fMRI responses in medial frontal cortex that depend on the temporal frequency of visual input. Srinivasan R - 2007

- Objetivo: **patrones de activación en fMRI** a nivel occipital y por fuera del córtex visual, **en función de la frecuencia temporal del estímulo**.
- Metodología:
  - Estudio en 6 **sujetos sanos**.
  - Estímulo damero reversible con frecuencias de **3 a 14 Hz**.
- **Resultados:**
  - Cada sujeto mostró activación de las áreas corticales visuales en lóbulos occipitales acorde a lo esperado.
  - Se observó activación en un número elevado de vóxeles occipitales, y en un número menor de vóxeles en la región mesial de los lóbulos frontales.
  - Encuentran un **cluster de voxels en el cortex frontal mesial que responde a la frecuencia preferida en el rango 3.5-5 Hz**
  - Los resultados del presente experimento apoyan la hipótesis de que la **conectividad del cerebro humano es frecuencia-dependiente.**

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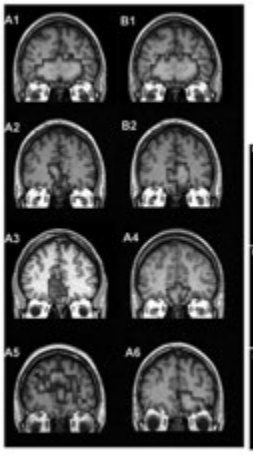
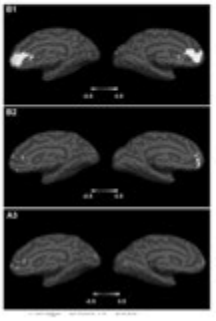
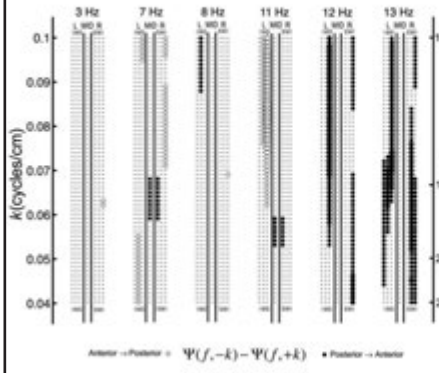




•Cluster de voxeles frontales en giro recto y órbito-frontal mesial.
•**Las respuestas a nivel frontal eran claramente frecuencia dependientes, con un pico a frecuencia de 4.5 Hz, replicada en 2 protocolos.**
•La respuesta media de activación occipital parece ser relativamente independiente de la frecuencia.

•Los voxeles frontales casi siempre estaban correlacionados positivamente entre sí en un mismo sujeto, y la localización era muy similar entre sujetos.
•A nivel occipital, se encontraban voxeles correlacionados positiva y negativamente entre sí, y con los frontales.

SSVEPs: distributed local sources and wave-like dynamics are sensitive to flicker frequency. Srinivasan R et al. 2006



- SSVEPs registrados en 110 electrodos durante tarea visual con patrones de puntos al azar a frecuencias 3-30 Hz.
- En la **banda α alta** se evidencia la presencia de **ondas en movimiento propagándose de los electrodos occipitales a pre-frontales.**
- En la banda α baja y δ se observan patrones estáticos de estas ondas.

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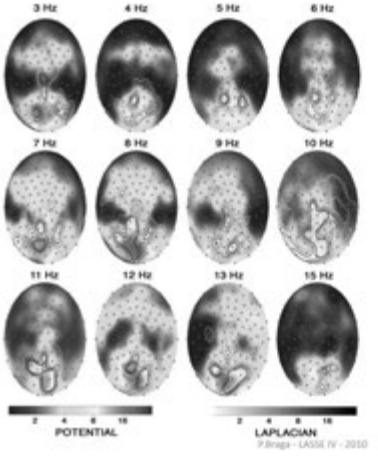

- SSVEPs son sensibles a la frecuencia de flicker
- **cambios en 1Hz pueden modular la respuesta en los canales frontales**
- Con estímulo en bandas alfa baja y delta se observan respuestas frontales bilaterales, en tanto que con frecuencias de 12-13 Hz se evidencia sólo en electrodo frontal derecho.
- Laplacian SSVEP –a nivel frontal sólo a 8-10 Hz de estimulación.
- Los canales occipitales muestran SSVEP robustos a todas las frecuencias de estimulación inferiores a 20Hz.

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- En este estudio se proporciona evidencia de configuraciones dinámicas de distribución de las fuentes subyacentes a los SSVEPs. Estas fuentes estarían organizadas en pequeña escala (2-3 cm) y gran escala (10-15 cm).
- Los potenciales de superficie de Laplace son menos sensibles a fuentes profundas, distantes o amplias, captando preferentemente los dipolos de las capas próximas al electrodo.
- **Las propiedades espaciales de ambos sistemas dependen fuertemente de la frecuencia del input visual.**
- Para la mayoría de frecuencias de estimulación, las respuestas frontales se deben a un dipolo profundo o a una fuente de distribución amplia sobre los lóbulos frontales, explicando la escasa contribución a los potenciales de Laplace.
- **Existe una excepción a *f* = 10 Hz, en que la distribución espacial de ambos SSVEP (potencial y Laplace) es muy similar, sugiriendo la contribución o sincronía de varias fuentes.**

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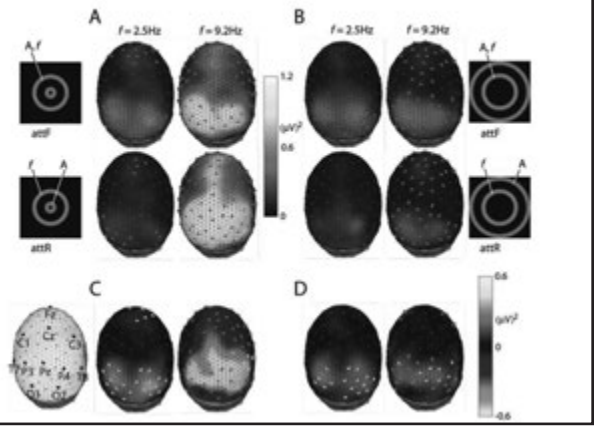
Attentional modulation of SSVEP power depends on the network tagged by the flicker frequency. Jian Ding et al, 2006

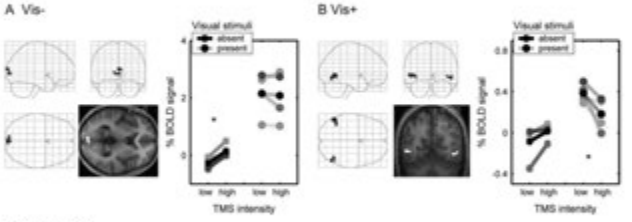


- Todas las frecuencias determinaron respuesta occipital
- Banda δ (1-4 Hz)
  Banda α alta (10-11 Hz) ⟹ vía occipital-frontal, potenciada cuando la atención se centra en el flicker, y en fase
- Banda α baja, **específicamente a 9.2 Hz** (y menos a 10 Hz)
  ⟹ Independientemente del componente atencional
  SSVEP de mayor poder en electrodos occipitales y frontales-prefrontales
  ⟹ Cuando la atención es dirigida a un estímulo en la fóvea, desatendiendo el estímulo intermitente
  SSVEP de muy alto poder en áreas frontales póstero-mediales y parietales, que no registran poder SSVEP significativo en ninguna otra frecuencia de estimulación

- **La atención parece modular la respuesta SSVEP en forma dependiente de la frecuencia del estímulo visual.**
- Algunas redes corticales activadas por frecuencia serían sensibles a la atención, en tanto que otras serían relativamente insensibles a la misma.

Distinct causal influences of parietal vs frontal áreas on human visual cortex: evidence from concurrent TMS—fMRI. Ruff C. et al. 2007

Estudio en 4 voluntarios sanos, con estimulación en el surco intraparietal del hemisferio derecho por TMS, y fMRI simultánea con un coil de superficie occipital para evaluar activación cerebral en corteza visual según el contexto visual (patrón aleatorio intermitente)



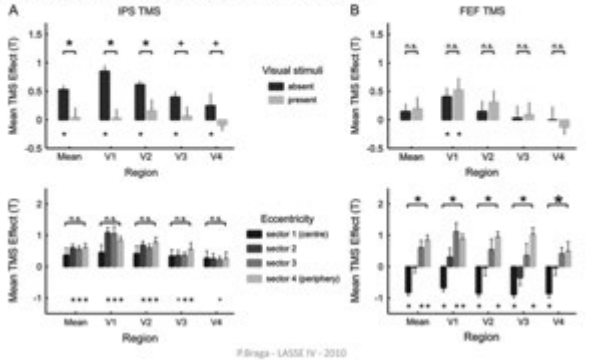
2 patrones:
A -cúneo bilateral incluyendo la cisura calcarina (V1-V4)– ↑actividad sólo en ausencia de estímulo visual
B -corteza occipital lateral bilateralmente (V5 /MT+) - ↓ actividad sólo en presencia de un estímulo visual en movimiento

Análisis retinotópico de las áreas individuales V1-V4.

•El efecto de la TMS en IPS (no en FEF) depende del contexto visual.

•TMS en FEF (no en IPS) discrimina el campo visual periférico y central, con efectos opuestos sobre los mismos.

•Todos los efectos en ambas condiciones son bilaterales.



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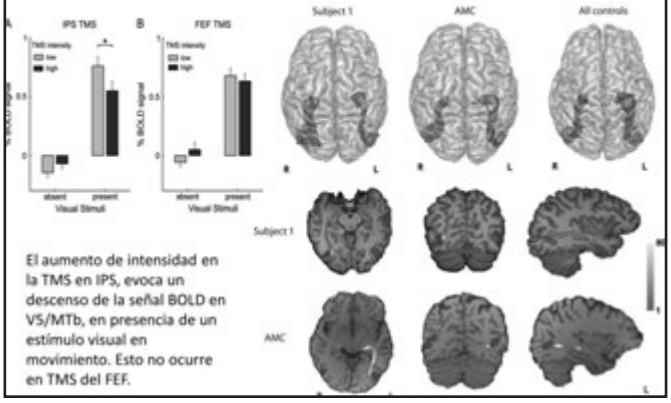
Análisis de efecto sobre V5/MT

Mediante DTI , se observó que existe una vía directa entre núcleo geniculado lateral y el área MT+/V5 ipsilateral, bypasseando V1. Holly Bridge. 2008

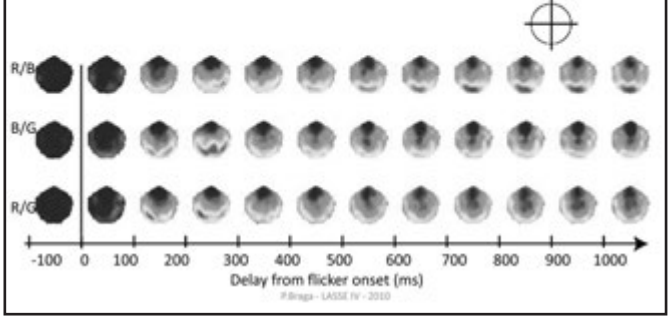


El aumento de intensidad en la TMS en IPS, evoca un descenso de la señal BOLD en V5/MTb, en presencia de un estímulo visual en movimiento. Esto no ocurre en TMS del FEF.

Neuromagnetic responses to chromatic flicker: implications for photosensitivity. Watanabe K - 2002

•En sujetos sanos, evaluación de la respuesta MEG a flickers cromáticos (3 combinaciones de colores) a 10 Hz, con igual intensidad lumínica y distancia, para determinar la existencia de una FS color-dependiente.

•Activación parieto-occipital bilateral precoz, y en polo occipital más tardía



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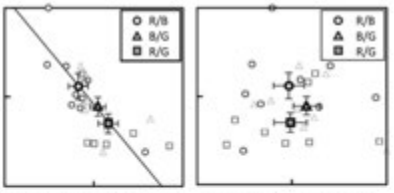
Respuesta MEG tardía en electrodos occipitales



Respuesta temprana P-O izquierda Respuesta temprana PO derecha

- La correlación negativa lleva al planteo de que **la actividad PO temprana directa o indirectamente suprime el desarrollo de la actividad tardía en el córtex visual.**
- La activación PO podría ser un mecanismo defensivo que suprime la hiperactividad cortical y la ausencia de este mecanismo puede ser la causa de la excitación anormal en pacientes con FS.
- La actividad temprana PO **sería menos pronunciada en algunos pacientes FS** en comparación con no FS.

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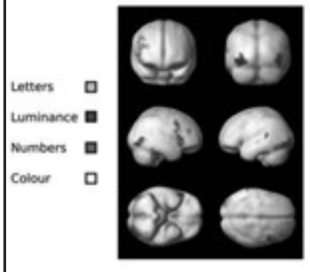
The Encoding of Temporally Irregular and Regular Visual Patterns in the Human Brain. Zeki S et al- 2008

- **Objetivo:** evaluar si el cerebro tiene sistemas para registrar secuencias de estímulos visuales en términos de su relación temporal de regularidad e irregularidad.



- Se identificaron diferentes zonas de activación, uni o bilaterales, para distintas características del estímulo (color, luminancia, contraste, etc)
- Luego, se determinó si la actividad producida en un área especializada es modulada de acuerdo a si el estímulo visual se presentó en una secuencia regular o impredecible.
- Los resultados sugieren la existencia de un proceso de abstracción en el registro de irregularidades temporales.

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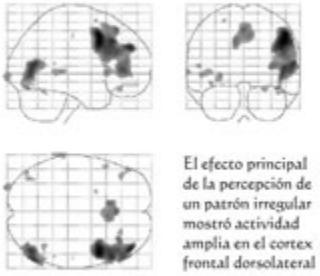
The Encoding of Temporally Irregular and Regular Visual Patterns in the Human Brain. Zeki S et al- 2008



El efecto principal de la percepción de un patrón irregular mostró actividad amplia en el cortex frontal dorsolateral

- La corteza pr-efrontal dorso-lateral contiene una confluencia de regiones, cada una selectiva para la irregularidad de diferentes sub-modalidades visuales. Dentro de esta confluencia de regiones, existe una región sensible a la irregularidad temporal, independientemente de la modalidad desde la cual se define la irregularidad (cambio de color, o forma, o luz). Para patrones regulares, regiones dispersas son reclutadas sin un área común.

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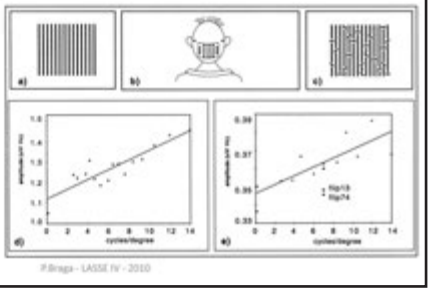
Contextualización de la información visual banda gamma

- En experimentación animal se vio que descargas de puntas en frecuencia gamma 30-80 Hz, s/t aprox. 40Hz, se asocian a las funciones de fusión de información referente a características individuales de un estímulo complejo, o sincronización de información procesada por diferentes grupos neuronales específicos para una información contextual o global (Gestalt).
- Experimentos en humanos mostraron que oscilaciones gamma inducidas están presentes en el EEG cuando dos partes de una barra en movimiento se perciben como un objeto coherente.

Different frequencies for different scales of cortical integration: from local gamma to long range alpha-theta synchronization. Von Stein A et al-2000.

- Análisis espectral del EEG frente a estímulos visuales de frecuencia creciente. Estudio de coherencia.
- Observa un aumento de la amplitud del componente gamma en el EEG lineal con el aumento de barras en el estímulo visual.
- El poder gamma disminuyó frente al estímulo de igual frecuencia con elementos "incoherentes".
- Estos resultados sugieren que, en forma similar a lo hallado en el gato, la sincronización cortical en el rango de frecuencias gamma puede ser medido en el EEG en humanos y refleja un criterio Gestáltico de coherencia visual.



Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception?
J. Parra; S. N. Kalitzin; J. Iriarte; W. Blanes; D. N. Velis; F. H. Lopes da Silva. 2003.

- pacientes con epilepsia FS idiopática evaluados con MEG durante ELI a 10, 15 y 20 Hz, en comparación con controles.
- PHASE CLUSTERING INDEX (PCI) -medida de la dispersión de fase de los diferentes componentes de frecuencias.
- rPCI - Para cada frecuencia de estimulación, la diferencia de fase de sus armónicos en función de la frecuencia fundamental.
- Períodos antes de una **ELI con RFP** vs períodos previos a ELI sin RFP: PCI **banda gamma** (30-120Hz) > PCI a la frecuencia fundamental
- Cuando la estimulación no provocó un RFP, la PCI en la banda de armónicos gamma no excedió el valor PCI para la frecuencia fundamental (rPCI igual que controles normales).
- **La dinámica de la actividad en frecuencias gamma puede ser predictor de RFP y crisis FS.**

FS y frecuencias gamma

•**distribución espacial-**
- –ELI sin RFP - mayores valores en regiones occipitales.
- –ELI con RFP - valores mayores más allá de las regiones occipitales, distribuidas sobre todo en las regiones parietales, centrales y temporales.

•**tipo de crisis -**
- –paciente con mioclonias: aumento esp. frontal y central
- –paciente con ausencias: aumento rPC1 dominante en sensores parietales

•Plantean hipótesis de que el aumento de la sincronía en la banda gamma de pacientes FS puede reflejar una pérdida del control cerebral sobre procesos oscilatorios de alta frecuencia que normalmente operan para conectar transitoriamente redes neuronales.

•La evolución temporal del rPC1, sugiere que la ELI inicialmente involucra poblaciones neuronales responsables de frecuencias gamma, pero que en condiciones normales existe un mecanismo de control que contrarresta esta sincronía, ausente o disfuncional en estos pacientes.

Hiperexcitabilidad y simetría

❑ **Hiperexcitabilidad -**

- Los pacientes con crisis fotosensibles tienden a tener PEV al flash o damero aumentados.
- En pacientes fotosensibles, se ve un mayor incremento del tamaño del PEV con el aumento del contraste del estímulo (Porciatti)
- La amplitud de los PEV disminuye bajo VPA

❑ **Bilateralidad y simetría -**

- Aunque grandes áreas de la corteza visual parecen ser equipotenciales para evocar crisis, el umbral en un hemisferio puede diferir marcadamente del otro, aún en pacientes con EGI
- La asimetría en algunas pruebas funcionales, aún en EGI (TMS; arrastre fótico y PEV asimétricos), permite plantear un rol de un disbalance interhemisférico en la excitabilidad cortical o umbral de activación de diferentes vías.
- Si bien las manifestaciones clínicas habituales asociadas a FS son simétricas o globales, los cambios metabólicos y vasculares evocados frecuentemente no lo son.

¿Qué es Fotosensibilidad en Epilepsia?

- cambio **cualitativo** en los **patrones de activación de determinados grupos neuronales**, desencadenado por un **estímulo luminoso** o algunas características del mismo, y que ocurre en pacientes predispuestos, probablemente por un aumento en la excitabilidad de toda o parte de la red involucrada
- asociación temporal implica factores ontogénicos de especialización cerebral y formación de redes, involucra la plasticidad cerebral e implica el compromiso de una delicada sincronía témporo-espacial de mecanismos excitatorios e inhibitorios.

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Future needs :Photosensitivity, visually sensitive seizures and epilepsies

Dorothée G.A. Kasteleijn-Nolst Trenité Epilepsy Research 70S (2006)

I. **Large-scale multinational epidemiological studies in the general population**
   -incidence and prevalence of FS, sensitivity and specificity of photic, pattern and TV stimulation in the laboratory, impact of longer duration of stimulation, occurrence of a PPR in non-affected persons and to follow-up

II. **Epidemiological studies in neurological and epilepsy patients in general:**
   -distribution among epilepsy syndromes and ethnic groups, compare follow-up

III. **Epidemiological studies in visually sensitive patients:**
   -prognosis, pure FS epilepsy, video game seizures; value of asymmetric findings; visual priming; role of sex.

IV. **Double-blind placebo-controlled trials to determine the efficacy of all AEDs and non-drug preventive measures in visual sensitive patients.**

V. **Imaging, functional and genetic studies to unravel the pathophysiology.**
   -fMRI studies and MEG studies, genetic studies

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Programa – 09.02.2010

08:30 – 09:30	Timing of AED application – Peter Wolf (Denmark)
09:30 – 10:30	Chronic effects of the antiepileptic drugs over time – Luisa Rocha (México)
10:30 – 11:00	Coffee-break
11:00 – 12:00	Expectations and results of epilepsy surgery in children – Helio Machado (Brazil)
12:00 – 14:00	Lunch
14:00 – 15:00	Expectations and results of epilepsy surgery in adults with MTLE – Mario A. Alonso (México)
15:00 – 16:00	Expectations and results of epilepsy surgery in adults with extra-temporal epilepsies – Manuel Campos (Chile)
16:00 – 16:30	Coffee-break
16:30 – 17:30	Expectations and results of epilepsy surgery: why, when and how to withdraw the pharmacological treatment – Americo Sakamoto (Brazil)
19:30 – 21:00	Dinner

Timing of AED application
Peter Wolf (Denmark)

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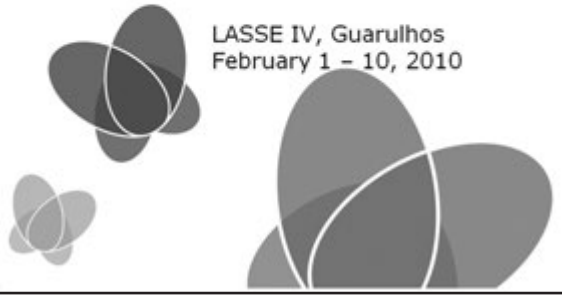
Timing of AED application
Peter Wolf (Denmark)



LASSE IV, Guarulhos
February 1 – 10, 2010

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Aspects of timing

Timing of AEDs: like with any other drug, a daily AED dose can be given in a single or in distributed doses

This can be done following some routine but it is often worth while to give timing some consideration

Several aspects deserve to be considered:

1. Compliance (adherence)
2. Diurnal distribution of seizures
3. Pharmacokinetics
4. Pharmacodynamics

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1. Compliance (adherence)

- Regular drug intake in chronic treatment needs some organisation to prevent forgotten doses
- The more single doses there are, the higher is the risk that some can be forgotten
- Dosage schemes and compliance rates (Cramer 1991):
  - 1/day 86%
  - 2/day 80%
  - 3/day 76%
  - 4/day 53%

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Conclusion about adherence

- AED administration in one or two daily doses is the best precondition for adherence
- The decision to prescribe 1 or 2 doses may be taken considering pharmacokinetics and patterns of seizure repetition
- Often it will be a matter of convenience depending on individual circumstances like a patient's daily time-table etc
- A single dose needs to be remembered only once in a day
- One forgotten dose in a twice-daily scheme produces an intake interval of ~24 hrs but in a once-daily scheme, of ~48 hrs which results in a higher risk of seizure recurrence
- The shorter a drug's half life, the more this difference counts
- "Once-daily" is the smallest possible burden for the patient but requires quasi-perfect adherence

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2. Diurnal distribution of seizures

- It has long been noticed that in many patients seizures do not occur at random but following certain patterns
- Gowers (1881, 1905)
- Langdon-Down & Brain (1929)
- Patry (1931)
- Hopkins (1939)
- Griffiths & Fox (1938)
- Janz (1953: GM in sleep ./. on awakening)

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Examples

- Seizures at falling asleep
  - Early epileptic encephalopathies
- Seizures during sleep including naps
  - Some patients with TLE
- Seizures towards end of sleep or at awaking
  - FLE, hypermotor szs
- Seizures soon after awaking
  - Idiopathic Generalised Epilepsies, in particular EGMA

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Consequences of diurnal seizure distribution

- Nosology: syndromatic relations
- EEG diagnostics
- Pathophysiology: conclusions about ictogenesis
  - Diurnal fluctuations of seizure threshold / seizure propensity
  - Consequence: in some patients the risk to have a seizure is highest at well-defined times of the day, and drug administration could and should take care of this

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Bickford R & Klass D: *Sensory Precipitation and Reflex Mechanisms*. In: Jasper HH, Ward AA & Pope A (ed): *Basic Mechanisms of the Epilepsies*. Little, Brown 1969, pp 543-564

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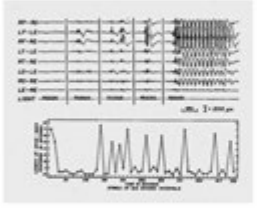
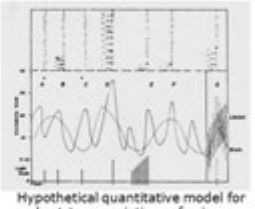


Variable responses to identical light stimuli delivered repeatedly over 520 sec



Hypothetical quantitative model for short-term variations of seizure propensity, with 3 components: 1) general excitability of the brain, 2) excitability of seizure generator, 3) different stimuli

Seizure threshold arbitrarily assumed at 40 units

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Consequences of diurnal sz distribution (cont)

- Social: consequences for work, driving etc.
- Therapy: adaptation of administration of AEDs
  - Principle: to achieve the maximal pharmacological AED action at the time of highest seizure propensity
  - Problems:
    - to identify the right moment but also the correct site of application
    - to get the drug there at the right time

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3. The contribution of pharmacokinetics

- An immediately convincing thought is to make the time of maximal AED concentration (t^{max}) coincide with the time of maximal seizure propensity.
- Example:
  - A patient has seizures habitually when falling asleep.
  - The AED has its C^{max} 2 – 2 1/2 hours after ingestion: ?
  - The patient is advised to take his entire daily dose 2 hours before going to bed
  - Afternoon naps are not allowed
  - The patient may become seizure free at a dose which was insufficient earlier when used without timing

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A more difficult example

- A patient with Frontal Lobe Epilepsy who has some seizures almost every morning just before or after awakening
- He is treated with Carbamazepine (t^{max} after 1 ½ - 2 ½ hours, serum half life of ca. 12 hours). With a b.i.d or t.i.d. schedule after 7 - 8 hrs sleep he is approaching the minimal morning concentration (C^{min}, trough level)

What do you propose?

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Another advantage with nocturnal seizures

Toxicity

- If a patient
  - at a certain dose has a C^{max} above the toxic threshold producing ataxia and diplopia, and
  - has a t^{max} coinciding with deep sleep, and
  - is on a drug with a reasonably short half-life:
- this patient may be treated with this dose (which may be the individual therapeutic dose) without experiencing toxic symptoms

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Restrictions of this logical approach

- Pharmacokinetics (PK) are not always simple
  - The administered drug may be a pro-drug
    examples?
  - There may be active metabolites
    what else?
- PK are not only what can be measured in the circulating blood
- Blood-brain barrier
  what else?
- Receptor binding (prototype: BZD)
- And: PK is only part of the matter

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4. The aspect of pharmacodynamics

- The mode of action of different AEDs is not uniform
- A close time relation between drug concentration (as measured by plasma levels) and therapeutic action clearly exists for the sodium channel blockers (...
- Other modes of action are more extended over time
- Acidosis by carboanhydrase inhibition (ZNS, TPM, STM, acetazolamide)
- BZD: receptor binding
- Levetiracetam: ...
- Vigabatrine: enhancement of endogenous GABA by competitive blockade of GABA-transaminase

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Conclusion

- Timing is important but not for all AEDs

Can you think of another situation in the treatment of epilepsy when timing of drug administration has a role?

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[case discussion]

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Acute administration of AEDs

- A special case of timing of drug delivery: the prevention of a predictable seizure
- For this indication, in most cases effective and rapidly acting drugs are needed
- For self-administration at home, non-injectable formulations are required
- Benzodiazepines, Acetazolamide, Chloral hydrate
- Routes of administration: oral, rectal, buccal, nasal

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Indications for acute AED administration (ADA)

- Febrile convulsions
  - at fever (prevention of seizures)
  - after onset (prevention of status)
- Catamenial seizures (periodic administration)
- Clusters of seizures (individually after 1st, 2nd sz; one dose or more)
- Prevention at prodrome / aura
- Some reflex epilepsies (e.g. hot water)
- Situations of high seizure risk (transcontinental travel, wet party)
- Situations of high social risk (prevent szs in public)
- AED withdrawal

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Choice of drug and route depends on timing

- When is the (next) seizure expected?
  1. Seizure still ongoing: rectal DZM (unconscious patient), buccal MZM, nasal LZP (conscious patient)
  2. Within 5 min: same
  3. 5 – 20/30 min: same; rectal chloral hydrate
  4. 20 min – hours (same day): oral CLB, DZM, CLZ, ACZ
  5. Same or next days: oral CLB, ACZ
- Repetitive acute dosing:
  1. clusters lasting >1 day
  2. catamenial epilepsy
  3. jet lag
  4. AED withdrawal

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Own use of ADA in treatment of epilepsy

- 24 patients followed for 12+ months
- 3 indications
  - Intervention at "warning" (absences, myoclonic szs, prolonged aura, twilight state ..)
  - Seizure prevention at perceived risk (trigger factors)
  - Prevention of serial seizures in disposed ptt
- Compliance?
  - Full: 10
  - Partial: 7
  - No: 7
- Outcome re prevention:
  - applicable 19, applied 13, successful 10

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Intervention at "warning", n=8

- Syndromes
  - IGE: 5, focal 2; migraine-epilepsy 1
- ADA
  - 10 mg oral CLB: 7, 10 mg rectal DZP: 1
- Outcomes
  - Sz free: 3
  - Reduction > 50%: 2
  - Unimproved: 3

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Prevention at perceived risk, n=8

- Syndromes
  - IGE 4
  - Focal 4
- ADA
  - 10 mg oral CLB
- Outcomes
  - Seizure free 2
  - Reduction < 50% 3
  - Unimproved 3

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Prevention of clusters, n = 8

- Syndromes
  - Focal 8 (all)
- ADA
  - 10 mg oral CLB
  - Could be repeated, sometimes increase to 20 mg CLB
- Outcomes
  - Free of disabling szs 1
  - Reduction > 50% 1
  - Unimproved 6

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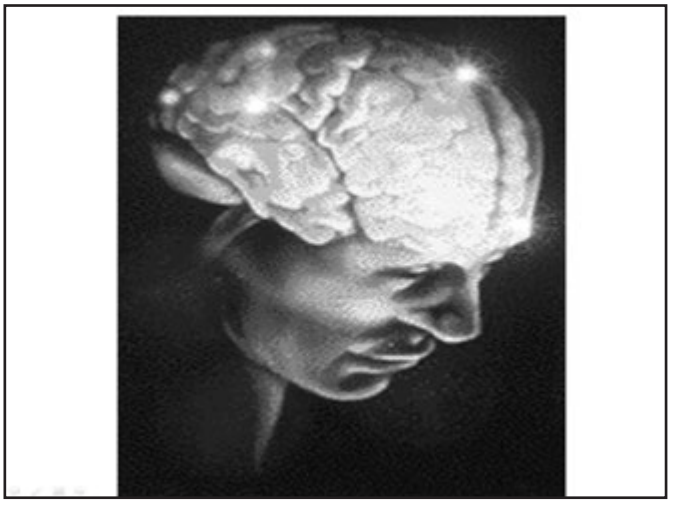
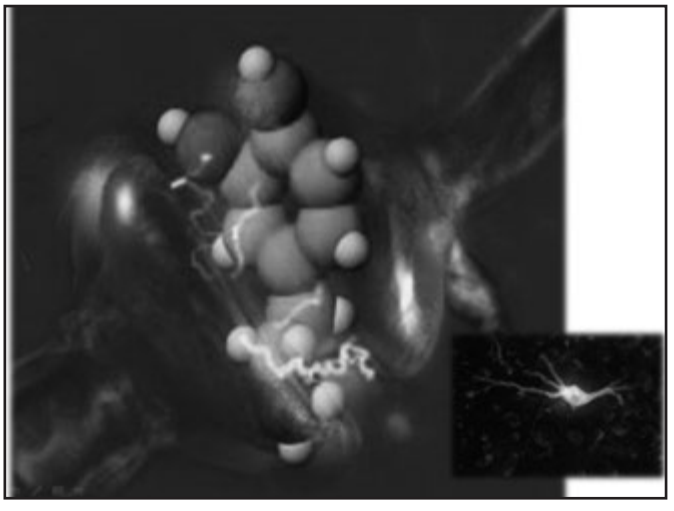
Chronic effects of the antiepileptic drugs over time

Luisa Rocha (México)





Droga Antiepiléptica (DAE)

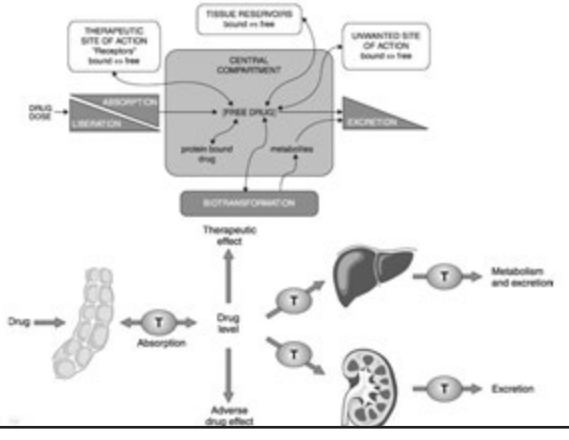
- Una droga que disminuye la frecuencia y/o severidad de las crisis epilépticas en personas con epilepsia
- Trata los síntomas de las crisis epilépticas, pero no la causa que origina a la epilepsia
- No previene el desarrollo de epilepsia en individuos que han adquirido un riesgo para presentar crisis epilépticas (e.g., después de un trauma cráneo-cerebral, embolia, hemorragia, tumor)
- La meta es optimizar la calidad de vida minimizando la incidencia de las crisis epilépticas y los efectos adversos de las drogas

Mecanismos de Neuromodulación de las DAEs

DAE	Bloqueo de canales de Na^+	Bloqueo de canales de Ca^{++}	Antagonista del receptor a Glutamato	Potenciación del GABA	Inhibición de la Anhidrasa Carbónica
PHT	X				
CBZ	X				
VPA	X	X		X	
Felbamato	X	X	X	X	
GBP		X		X	
LTG	X	X	X		
TPM	X	X	X	X	X
TGB				X	
OXCBZ	X	X			
ZNS	X	X			X
Pregabalina		X			

White HS. Pediatric Epilepsy: Diagnosis and Therapy. 2001:301-316

Principios de Farmacocinética



Principios de Farmacocinética

- Absorción: entrada de la droga al torrente sanguíneo
  - En general es completa para todas las DAEs
    - Excepción = Gabapentina con un sistema de transporte de aminoácidos saturable.
  - El tiempo en el que se realiza varía ampliamente dependiendo de la droga, formulación y características del paciente
  - Generalmente es lenta cuando hay alimento en el estómago (la Carbamazepina puede ser excepción)
  - Usualmente toma varias horas (es importante para interpretar los niveles sanguíneos)

Principios de Farmacocinética

- Eliminación: remoción de la droga activa de la sangre por su metabolismo y excreción
  - Metabolismo/biotransformación - generalmente hepática; dependiente del tiempo
  - Excreción - principalmente renal
  - Metabolitos activos e inactivos
  - Cambios en el metabolismo a lo largo del tiempo (auto-inducción con Carbamazepina) o con politerapia (inducción enzimática o inhibición)
  - Diferencias en el metabolismo por edad o enfermedades sistémicas

Enzimas Metabolizadoras de Drogas: UDP- Glucuroniltransferasa (UGT)

- Vías importantes para el metabolismo/ inactivación de drogas
- Generalmente menos descritas que la CYP
- Varias isoenzimas que están involucradas en el metabolismo de DAEs incluyen:
  - UGT1A9 (VPA)
  - UGT2B7 (VPA, Lorazepam)
  - UGT1A4 (LTG)

El Sistema de Isoenzimas Citocromo P-450

- Son las enzimas más involucradas en el metabolismo de drogas
- Su nomenclatura se basa en la homologia de la secuencia de aminoácidos
- Las enzimas tienen una especificidad de substratos amplia y las drogas individuales pueden ser substrato de varias enzimas
- Las principales enzimas involucradas con el metabolismo de las DAEs involucran a CYP2C9, CYP2C19 & CYP3A4

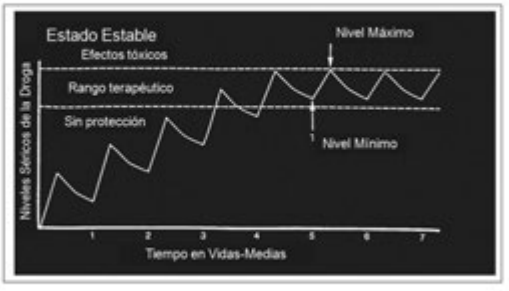
Isoenzimas Metabolizadoras de Drogas y DAEs

DAE	CYP3A4	CYP2C9	CYP2C19	UGT
CBZ	+			
PHT		+	+	
VPA		+		+
PB		+		
ZNS	+			
TGB	+			
OXC	+		+	
LTG				+
TPM	+		+	

Indice Terapéutico

- I.T. = DE 5O% /DT 50%
- "Rango terapéutico" de concentraciones séricas de DAEs
  - Datos limitados
  - Generalización amplia
  - Diferencias individuales

Estado Estable y Vida Media



Modificado de Engel, 1989

Concentraciones Séricas de DAEs

- **Las concentraciones séricas son útiles para la optimización de la terapia con DAEs, evaluando la combinación, o probando las interacciones entre drogas.**
- **Se deben usar para monitorear las interacciones farmacodinámicas y farmacocinéticas.**
- **Las concentraciones séricas deben de documentarse aún cuando un paciente está bien controlado.**

Rangos Potenciales para las Concentraciones Séricas de DAEs

DAE	Concentración Sérica (µg/ml)
Carbamazepina	4 - 12
Etosuximida	40 - 100
Fenobarbital	20 - 40
Fenitoína	5 - 25 (10 - 20mg/L)
Ac. Valproico	50 - 100
Primidona	5 - 12

Farmacocinética Comparada de DAEs Tradicionales

Droga	F %	Unión %	Cl	t ½ (hrs)	Causa interacción?
CBZ	80	75-85	100% H*	6-15	Si
PB	100	50	75% H	72-124	Si
PHT	95	90	100% H**	12-60	Si
VPA	100	75-95**	100% H	6-18	Si

* autoinducción
** no-lineal

Problemas:
Poca solubilidad en el agua
Unión protéica importante
Metabolismo oxidativo extenso
Múltiple interacción droga-droga

Factores Farmacocinéticos en Pediatría

Factores Farmacocinéticos en Pediatría

- **Neonatos** – con frecuencia requieren dosis bajas por kg
  - Baja unión a proteínas
  - Baja velocidad metabólica
- **Niños** – dosis altas y más frecuentes
  - Metabolismo más rápido

Farmacocinética en el Embarazo

Farmacocinética en el Embarazo

- Aumento en el volumen de distribución
- Baja albúmina sérica
- Metabolismo rápido
- Dosis altas, pero probablemente menores que las previstas para el nivel total (medida del nivel libre)
- Considerar dosis más frecuentes
- Rápido regreso a las condiciones pre-embarazo (2 semanas aproximadamente) después del parto

Factores Farmacocinéticos en Pacientes Ancianos

Factores Farmacocinéticos en Pacientes Ancianos

- **Absorción** – pocos cambios
- **Distribución**
  - Disminución en la masa corporal importante para las drogas altamente liposolubles
  - Decremento de la albúmina induciendo un aumento de la fracción libre
- **Metabolismo** – disminución del contenido enzimático hepático y flujo sanguíneo
- **Excreción** – decremento de la depuración renal

Cambios Metabólicos de las DAEs

- **Enfermedades Febriles**
  - ↑ velocidad metabólica y ↓ concentraciones séricas
  - ↑ proteínas séricas que pueden unirse a DAEs ↓ niveles libres de DAEs a nivel sérico
- **Enfermedades Hepáticas Severas**
  - Altera metabolismo ↑ niveles séricos de DAEs
  - ↓ proteínas séricas y ↑ niveles libres de DAEs a nivel sérico
  - Con frecuencia es difícil predecir los niveles séricos en esta situación

Cambios Metabólicos de DAEs

- **Enfermedades Renales**
  - ↓ la eliminación de algunas DAEs
  - Gabapentina, Pregabalina, Levetiracetam
- **Enfermedades Renales Crónicas**
  - ↑ pérdida proteica y ↑ fracción libre de DAEs con alta unión a proteínas
  - Puede ser útil administrar dosis menores y más frecuentes para ↓ efectos adversos
  - Fenitoína, Ac. valproico, Tiagabina

Efectos Adversos Agudos y Dependientes de las Dosis de las DAEs

- **Neurológicos/psiquiátricos: más comunes**
  - **Sedación, fatiga**
    - Todas las DAEs, y poco frecuentes con LTG y FBM
    - Más pronunciadas con las DAEs tradicionales
  - **Inestabilidad, incoordinación, vértigo**
    - Principalmente las DAEs tradicionales
    - Puede ser signo de toxicidad con varias DAEs
  - **Tremor – Acido valproico**

Efectos Adversos Agudos y Dependientes de las Dosis de las DAEs

- **Parestesia (Topiramato, Zonisamida)**
- **Diplopia, visión borrosa, distorsión visual (Carbamazepina, Lamotrigina)**
- **Actividad mental/motora lenta o daño (Topiramato a dosis altas)**
- **Cambios conductuales o del temperamento (Levetiracetam)**
- **Cambios en el libido o función sexual (Carbamazepina, Fenitoina, Fenobarbital)**

Efectos Adversos Agudos y Dependientes de las Dosis de las DAEs

- **Gastrointestinales** (náusea, ardor de pecho)

- **Cambios bajos a moderados en pruebas de laboratorio**
  - Hiponatremia: Carbamazepina, Oxcarbazepina
  - Aumento en ALT o AST
  - Leucopenia
  - Trombocitopenia

Efectos Adversos a Largo Plazo de las DAEs

- Efectos Endocrinos/Metabólicos
  - **Osteomalacia, osteoporosis**
    - **Carbamazepina**
    - **Fenobarbital**
    - **Fenitoina**
    - **Oxcarbazepina**
    - **Valproato**
  - **Folato (anemia, teratogénesis)**
    - **Fenobarbital**
    - **Fenitoina**
    - **Carbamazepina**
    - **Valproato**
  - **Metabolismo o crecimiento del tejido conectivo alterado (alteraciones faciales, hirsutismo, hiperplasia gingival o contracturas)**
    - **Fenitoina**
    - **Fenobarbital**
- Neurológicos
  - **Neuropatía**
  - **Síndrome Cerebelar - fenitoína**
- Alteraciones Sexuales
  - **Fentoína**
  - **Carbamazepina**
  - **Fenobarbital**
  - **Primidona**

¿Qué es la Epilepsia Refractaria a medicamentos?

Se caracteriza por la resistencia a un gran número de fármacos sin relación estructural y funcional alguna.

Lo anterior sugiere la participación de mecanismos de resistencia no específicos que evitan la acción de diversos fármacos

(Löscher, 2005)

Epilepsia y Respuesta a DAEs

CBZ-Responsive Chronic Epilepsy

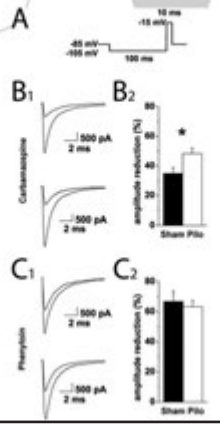
Potent inhibition of seizure activity

CBZ-Resistant Chronic Epilepsy

Reduced inhibition of seizure activity

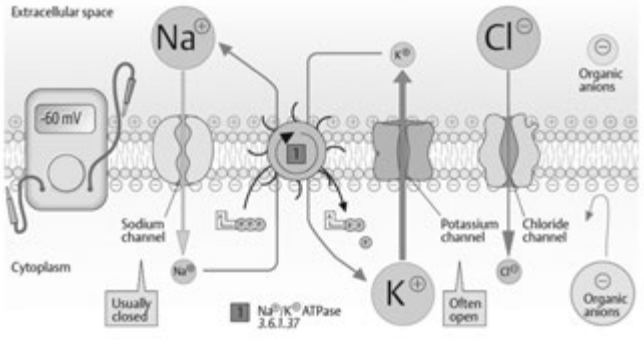
Remy et al., 2003

Epilepsia y Respuesta a DAEs

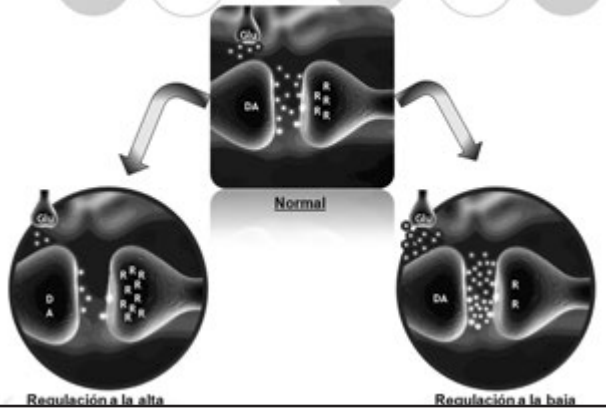


Schaub et al., 2007

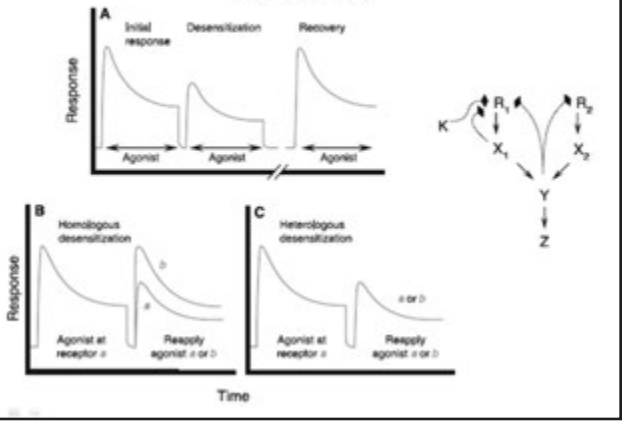
Epilepsia y Respuesta a DAEs



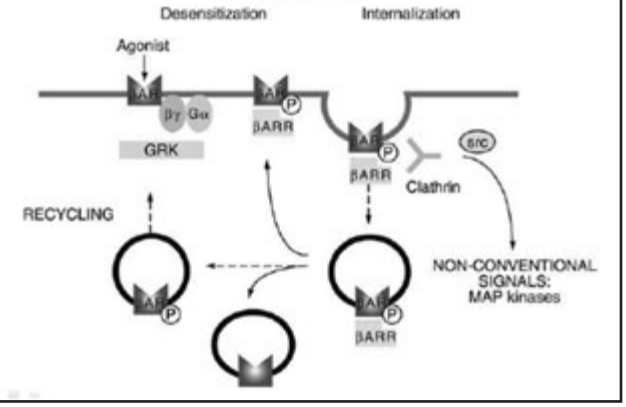
Efectos de la Administración Repetida de Fármacos



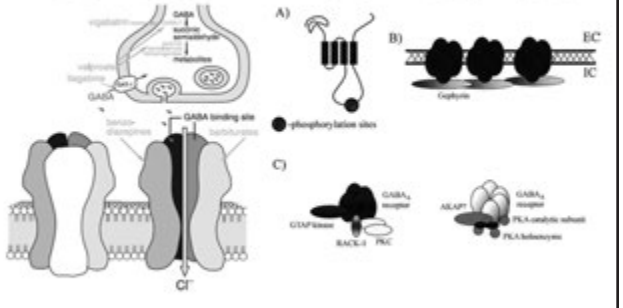
Efectos de la Administración Repetida de Fármacos



Efectos de la Administración Repetida de Fármacos

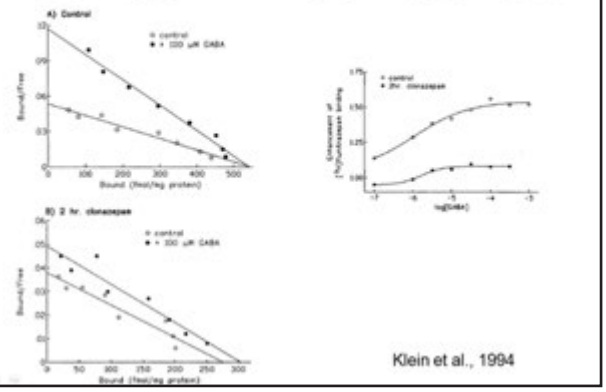


Receptores $GABA_A$



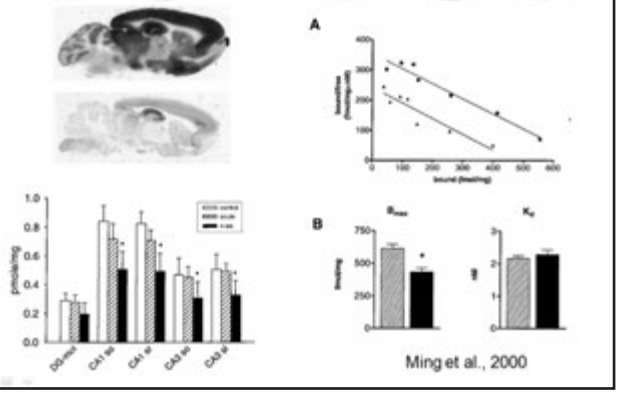
Brandon et al., 2000

El Tratamiento con BDZ produce Desacople de los Receptores $GABA_A$



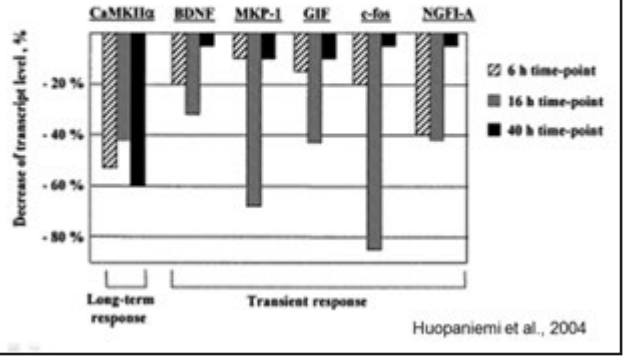
Klein et al., 1994

La Administración Crónica de BDZ Regula a la Baja a la Subunidad 5α



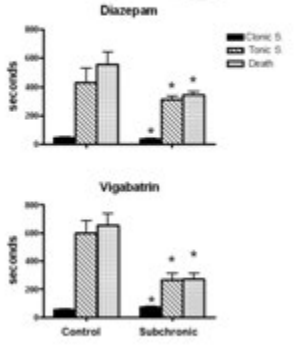
Ming et al., 2000

La Administración de Diazepam Produce Cambios Transcripcionales



Huopaniemi et al., 2004

Efectos de la Administración Repetida de DAEs

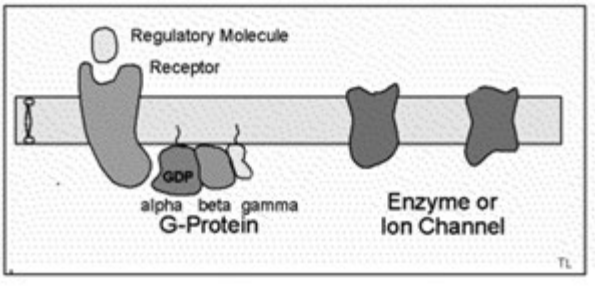


Brain Area	Saline	Diazepam
Motor Cortex	524.7 ± 27.0	352.0 ± 61.0*
Sensorimotor Cortex	501.4 ± 34.2	367.6 ± 62.4*
Cingulate Cortex	542.1 ± 35.1	334.4 ± 60.0*
Caudate Putamen	199.2 ± 49.0	143.7 ± 9.6
Nucleus Accumbens	253.8 ± 38.1	210.9 ± 34.9
CA1 -CA3 Fields	435.7 ± 57.1	286.1 ± 47.7*
Dentate Gyrus	564.3 ± 62.1	375.0 ± 69.4*
Medial Amygdala	552.7 ± 58.2	322.8 ± 58.6 *
Basolateral Amygdala	468.2 ± 60.6	276.3 ± 56.8*
Thalamus	290.6 ± 37.7	206.8 ± 34.7
Hypothalamus	421.5 ± 53.4	280.3 ± 57.3*

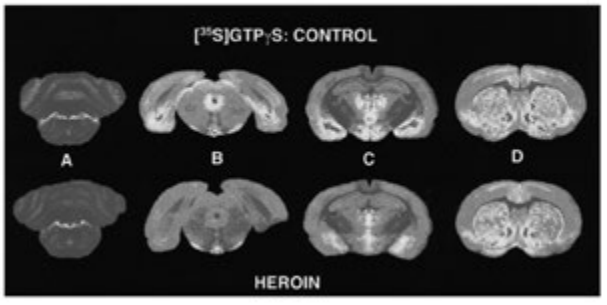
Brain Area	Saline	Vigabatrin
Motor Cortex	439.7 ± 52.4	388.9 ± 33.8
Sensorimotor Cortex	390.3 ± 50.6	369.9 ± 36.3
Cingulate Cortex	409.6 ± 51.5	386.6 ± 33.6
Caudate Putamen	160.4 ± 21.9	147.4 ± 13.6
Nucleus Accumbens	190.7 ± 26.6	168.6 ± 14.6
CA1 -CA3 Fields	263.1 ± 36.7	272.6 ± 23.6
Dentate Gyrus	365.8 ± 43.2	331.5 ± 36.6
Medial Amygdala	334.5 ± 46.2	379.6 ± 31.8
Basolateral Amygdala	288.5 ± 29.4	295.1 ± 34.0
Thalamus	245.1 ± 31.5	277.8 ± 26.9
Hypothalamus	296.9 ± 36.4	292.6 ± 24.7

Rocha et al., 2008

Efectos de la Administración Repetida de DAEs



La Administración Repetida de Heroína Desacopla los Receptores a Opioides de la Proteína G



Sim-Selley et al., 2000

Receptores a Opioides en Cerebro de Pacientes Epilépticos

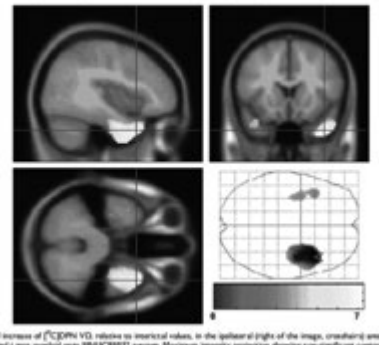


Fig. 1. Parietal increase of [^{11}C]DPN VD, relative to interictal values, in the ipsilateral (right of the image, crossthairs) anterior temporal lobe. Thresholded t map overlaid onto MNI/ICBM152 average. Maximum intensity projection showing non-significant contralateral increases and absence of changes elsewhere. Colour bar, t scores.

Hammers et al., 2007

Receptores a Opioides en Cerebro de Pacientes Epilépticos

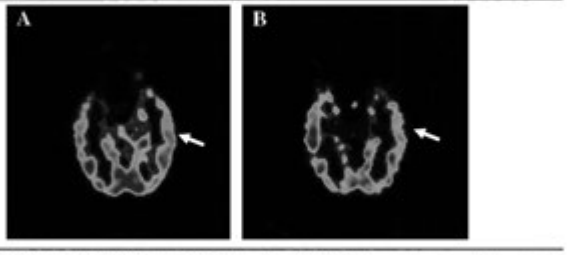
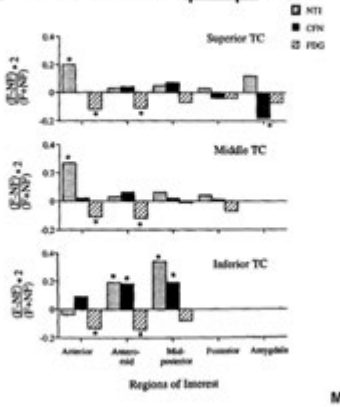


Fig 1. [^{11}C]Methylnaltrindole ([^{11}C]MeNTI) and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomographic images in a 35-year-old woman with a right-sided temporal lobe epileptic focus. In the [^{18}F]FDG study, there is approximately 25% reduction in [^{18}F]FDG uptake. In the [^{11}C]MeNTI study, there is a 35% increase in [^{11}C]MeNTI binding in the temporal lobe in a region corresponding the hypometabolic region and a 17% decrease in the ipsilateral amygdala.

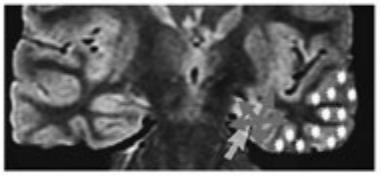
Frost et al., 1988

Receptores a Opioides en Cerebro de Pacientes Epilépticos

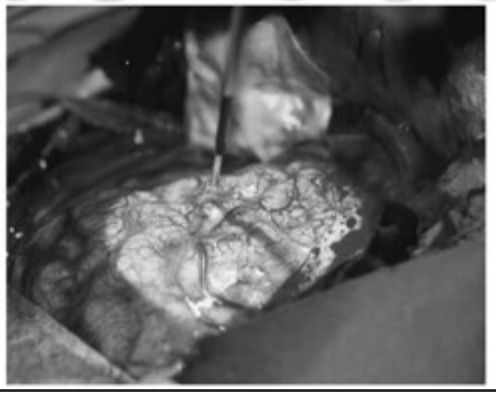


Madar et al., 1996

Receptores a Opioides en Cerebro de Pacientes Epilépticos

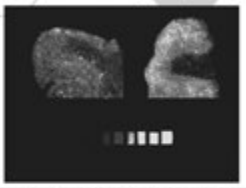


Cirugía de Epilepsia



Receptores a Opioides en Cerebro de Pacientes Epilépticos

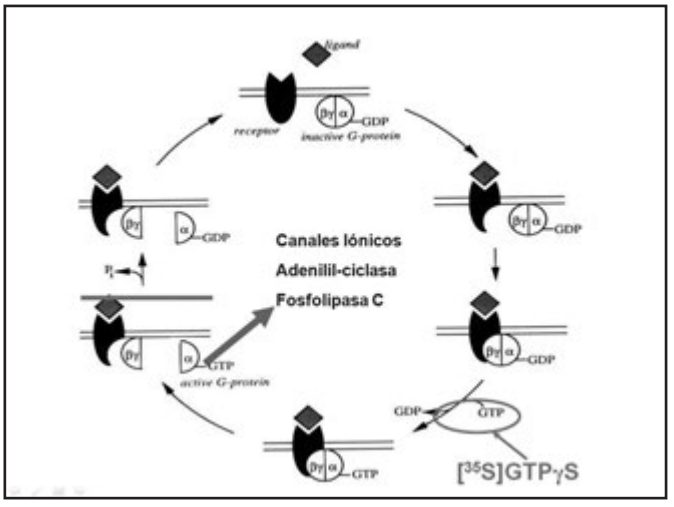
^{3}H-DAMGO



Capas	Autopsia	ELTM	Tumor/ Lesión
I-II	102±4	133±7 *	134±8 *
III-IV	102±5	139±8 **	144±8 *
V-VI	88±5	109±5 *	122±4 *

Valores expresados como promedio ± EE: *p<0.05, **p<0.01

Rocha et al., 2009

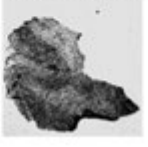


Receptores a Opioides en Cerebro de Pacientes Epilépticos

^{35}S-GTPγS

^{35}S-GTPγS+DAMGO

^{35}S-GTPγS+NOCICEPTIN



Efectos de DAMGO y Nociceptina en la Unión de [^{35}S]GTPγS

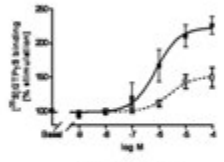
AGONISTA	AUTOPSIA	ELTM	TUMOR/ LESION
DAMGO			
I-II	16.5±2.5	6.6±1 *	8.1±1.1 *
III-IV	16.2±1.8	5.5±0.9 *	5.6±0.3 *
V-VI	17.4±1.3	8.9±2 *	7.2±0.7*
NOCICEPTINA			
I-II	11.6±2	15.8±4.4	15.1±4
III-IV	13.2±1.2	12.0±4	14.4±3
V-VI	14.8±2.2	17.2±4	19.2±5

Los valores representan el promedio ± EE del porcentaje de unión especifica [^{35}S]GTPγS con respecto a la unión basal (100%).
ANOVA y prueba post hoc Dunnet. *p<0.05.

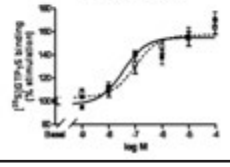
Rocha et al., 2009

Efectos de DAMGO y Nociceptina en la Unión de [^{35}S]GTPγS

DAMGO



NOCICEPTIN



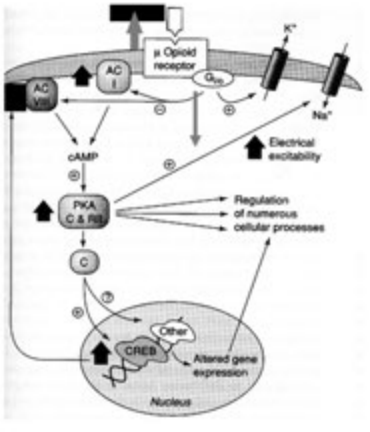
Rocha et al., 2009

Eficacia y potencia de DAMGO y Nociceptina para estimular a la unión de [^{35}S]GTPγS en membranas de corteza cerebral de autopsia y de pacientes con epilepsia

GROUPO	DAMGO	NOCICEPTINA
Autopsia		
Emax	122.9 ± 10	55.3 ± 3.5
pEC50	6.1 ± 0.2	7.44 ± 0.2
Pacientes epilépticos		
Emax	51.5 ± 8.5 *	57.3 ± 3.4
pEC50	5.57 ± 0.3 *	6.99 ± 0.1

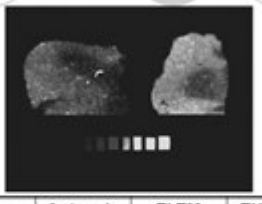
Los valores de E_{max} (expresados en % de estimulación de la unión a [^{35}S]GTPγS) y de pEC_{50} (expresados como $-logEC_{50}$) se calcularon por un análisis de regresión no-linear de concentración-efecto.
*p<0.05 comparedo con las muestras de autopsia usando prueba T de Student.

Rocha et al., 2009



Unión a la Adenilil-ciclasa en Cerebro de Pacientes Epilépticos

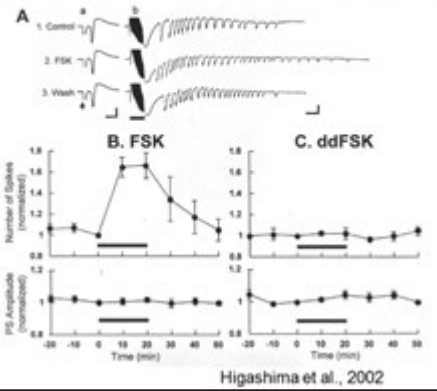
^{3}H-Forskolina



Capas	Autopsia	ELTM	TUMOR/ LESION
I-II	142±6	248±18**	224±19 *
III-IV	142±7	250±21**	200±18 *
V-VI	129±10	240±18**	205±16 *

Valores expresados como promedio ± EE: *p<0.05, **p<0.01

La Forskolina Facilita la Generación de la Posdescarga



Higashima et al., 2002

Journal of Neurochemistry
Lippincott-Raven Publishers, Philadelphia
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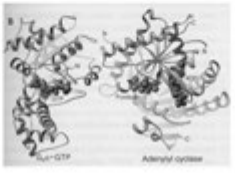
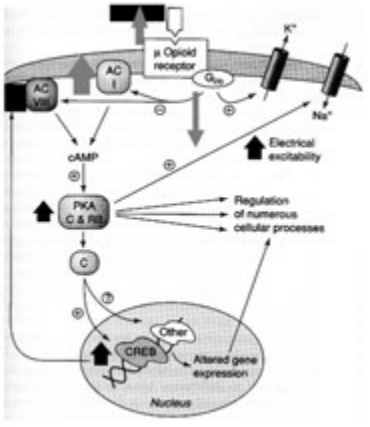
Attenuation of Cyclic AMP Production by Carbamazepine

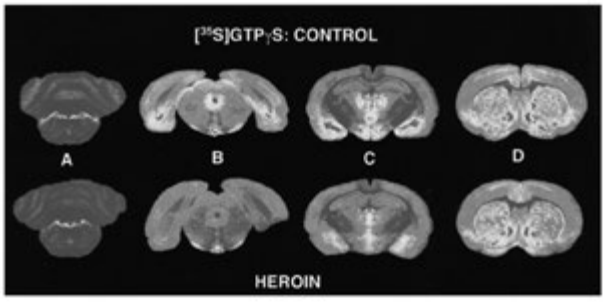
*Guang Chen, ‡Baishen Pan, ‡David B. Hawver, ‡Clinton B. Wright, ‡William Z. Potter, and *†Husseini K. Manji

*Molecular Pathophysiology Program, Schizophrenia and Mood Disorders Clinical Research Division, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine; †Neuropsychiatric Research Unit, Detroit Receiving Hospital, Detroit, Michigan; and ‡Section on Clinical Pharmacology, National Institute of Mental Health, Bethesda, Maryland, U.S.A.





La Administración Repetida de Heroína y la Epilepsia Desacoplan los Receptores a Opioides de la Proteína G



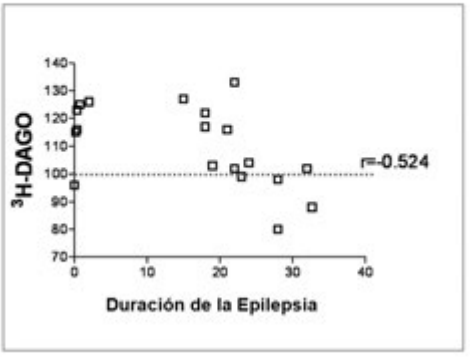
Sim-Selley et al., 2000

Correlación de Datos Clínicos con la Unión de [3H]ligandos y [35S]GTPγS

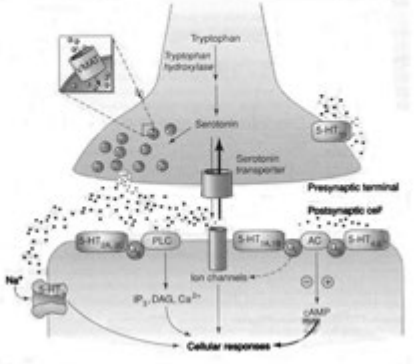
Datos Clínicos	Capas Corticales	[3H]DAMGO	DAMGO-[35S]GTPγS	[3H]Nociceptina	Nociceptina [35S]GTPγS	[3H]Paroxetina
Edad del Paciente	I-II	+0.287	+0.169	+0.020	-0.110	-0.062
	III-IV	+0.287	+0.028	+0.046	-0.205	-0.027
	V-VI	+0.005	+0.030	-0.140	-0.272	+0.070
Edad de inicio de la epilepsia	I-II	+0.581**	+0.052	+0.154	-0.056	+0.070
	III-IV	+0.572**	+0.502*	+0.155	+0.083	-0.046
	V-VI	+0.457*	+0.126	+0.102	+0.019	-0.275
Duración de la epilepsia	I-II	-0.531**	+0.090	-0.350*	+0.002	+0.378*
	III-IV	-0.539**	-0.335	-0.370*	-0.080	+0.498**
	V-VI	-0.524*	+0.114	-0.388*	-0.031	+0.531**
Frecuencia de Las crisis	I-II	-0.186	-0.272	-0.119	-0.305	-0.023
	III-IV	-0.303	-0.072	-0.174	-0.189	+0.080
	V-VI	-0.420	-0.227	-0.297	-0.262	+0.074

Los valores representan la r de Pearson. * p<0.05; ** p<0.01

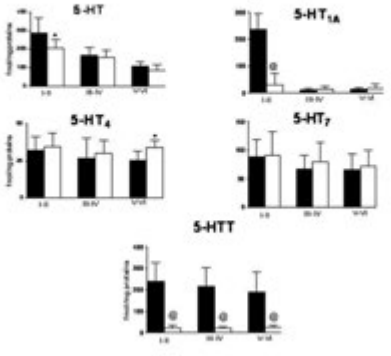
Receptores Mu Opioides en las Capas Corticales V-VI y Duración de la Epilepsia



Sistema Serotoninérgico

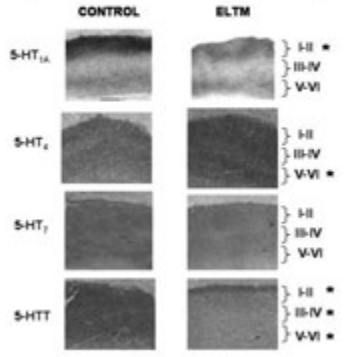


Receptores a Serotonina en Corteza de Pacientes Epilépticos



Rocha et al., 2007

Receptores a Serotonina en Corteza de Pacientes Epilépticos



Rocha et al., 2007

Correlación de Datos Clínicos y Receptores a Serotonina en Corteza de Pacientes Epilépticos

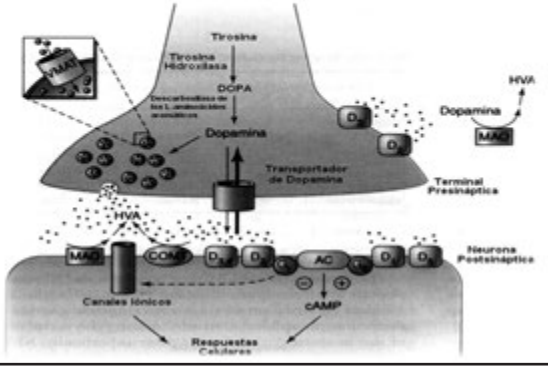
TABLE 3. Correlaciones entre datos clínicos y la unión a receptores o cuenta celular

Receptor/ Transportador/ Cuenta celular	Edad	Edad de primera convulsión	Duración de la epilepsia	Frecuencia de convulsiones	Duración del tratamiento antiepiléptico
5-HT (^{3}H-5-HT)					
Capas I-II	-0.4987	-0.4554	-0.4333	+0.0039	+0.3554
Capas III-IV	-0.3718	-0.6566	+0.6566	+0.6771	+0.6566
Capas V-VI	-0.6480	-0.4833	+0.4883	-0.3391	+0.2831
5-HT$_{1A}$ (^{3}H-8-OH-DPAT)					
Capas I-II	+0.4334	+0.2651	-0.1277	+0.4034	+0.1762
Capas III-IV	-0.0400	+0.0179	-0.0381	+0.1546	-0.3885
Capas V-VI	-0.0939	+0.1696	-0.1595	+0.0668	+0.1165
5-HT$_4$ (^{3}H-GR113808)					
Capas I-II	-0.5390	+0.0266	-0.5767	+0.5716	-0.6264
Capas III-IV	-0.5825	+0.1106	-0.6921 *	+0.2437	-0.6662 *
Capas V-VI	+0.6499	+0.3122	+0.1220	+0.4191	+0.7047 *
5-HT$_7$ (^{3}H-SB269970)					
Capas I-II	+0.2777	+0.6475 *	-0.4375	-0.3951	-0.4388
Capas III-IV	+0.1636	+0.6703 *	-0.6662 *	-0.4177	-0.6663 *
Capas V-VI	+0.1623	+0.6374 *	-0.6570 *	-0.3516	-0.6542 *
5-HTT (^{3}H-Citalopram)					
Capas I-II	-0.2093	+0.2235	-0.3335	-0.1608	-0.3473
Capas III-IV	+0.4178	+0.2272	+0.0255	+0.3347	-0.0350
Capas V-VI	+0.1099	-0.0182	+0.1315	+0.3775	+0.0936
Cuenta celular					
Capas I-II	-0.0103	-0.1848	+0.0910	+0.4473	+0.1897
Capas III-IV	+0.1403	-0.3414	+0.3685	-0.0974	+0.4176
Capas V-VI	-0.1298	-0.0362	-0.1072	+0.0571	+0.1134

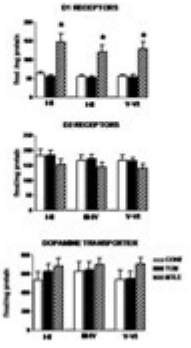
Los valores representan los coeficientes de correlación de Pearson. *p<0.05

Rocha et al., 2007

Sistema Dopaminérgico



Receptores Dopaminérgicos en Corteza de Pacientes Epilépticos



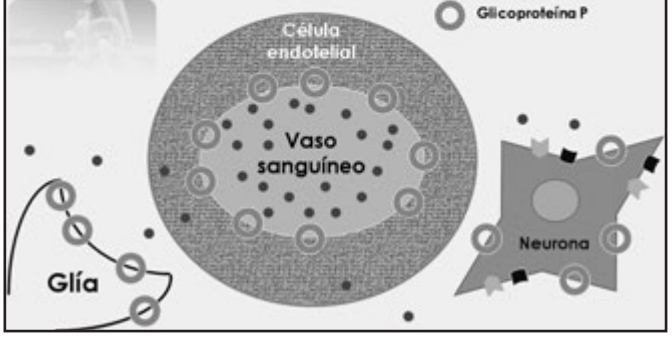
Correlación de Datos Clínicos y Receptores a Dopamina en Corteza de Pacientes Epilépticos

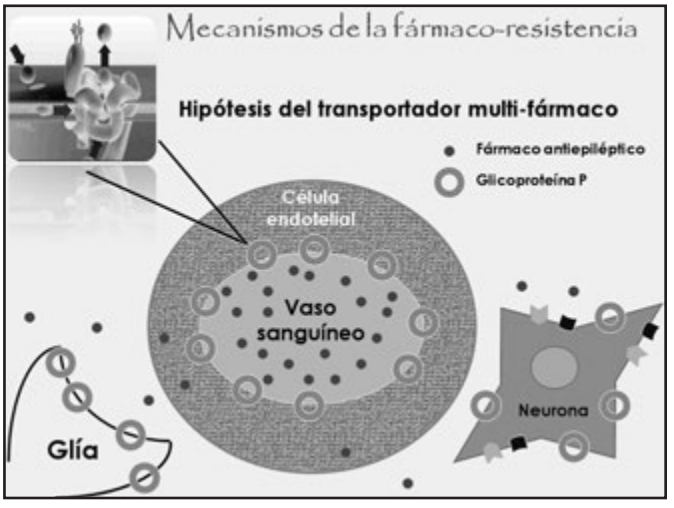
Unión	Edad	Edad de inicio	Duración epilepsia	Frecuencia crisis	Duración tratamiento
D1 (^{3}H-SCH23390)					
Capas I-II	0.1989	-0.0797	0.2406	-0.3867	0.3376
Capas III-IV	0.1566	-0.4416	0.4258	*-0.6502	*0.5119
Capas V-VI	0.2766	-0.1446	0.3556	*-0.7057	0.4304
D2 (^{3}H-Raclopride)					
Capas I-II	*0.5961	0.1153	*0.4997	-0.2689	*0.5070
Capas III-IV	*0.5732	-0.0480	*0.5797	-0.2621	*0.5963
Capas V-VI	0.4562	-0.0364	0.4603	-0.2258	0.4713
Transporter (^{3}H-Mazindol)					
Capas I-II	0.2192	0.0841	0.1577	-0.4198	0.1650
Capas III-IV	0.2777	0.2215	0.1281	-0.2707	0.1242
Capas V-VI	0.3127	0.3629	0.0734	-0.0677	0.0534

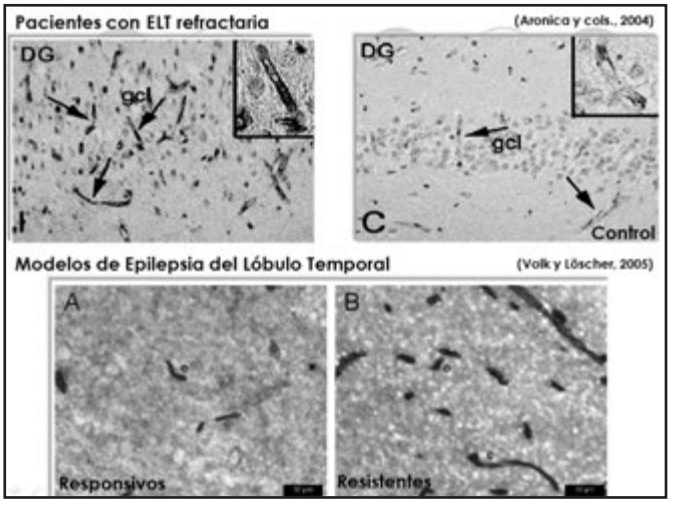
Los valores representan la r de Pearson. * $p<0.05$

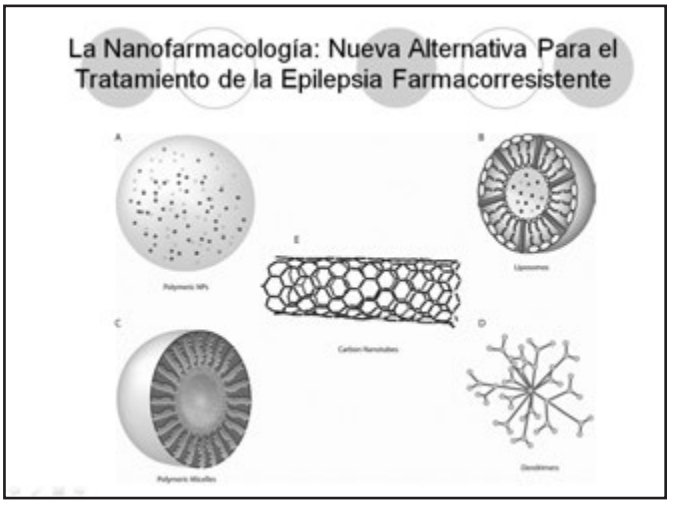
Mecanismos de la fármaco-resistencia

Hipótesis del transportador multi-fármaco

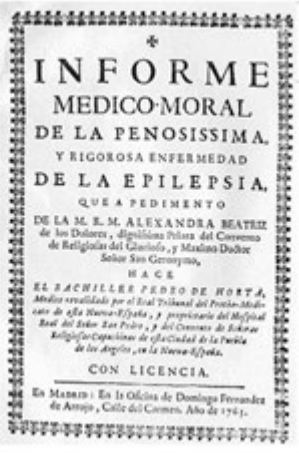



Mecanismos de la fármaco-resistencia
Hipótesis del transportador multi-fármaco
Fármaco antiepiléptico
Glicoproteína P
Célula endotelial
Vaso sanguíneo
Neurona
Glía


Pacientes con ELT refractaria
(Aronica y cols., 2004)
DG
gcl
DG
gcl
C
Control
Modelos de Epilepsia del Lóbulo Temporal
(Volk y Löscher, 2005)
A
B
Responsivos
Resistentes


La Nanofarmacología: Nueva Alternativa Para el Tratamiento de la Epilepsia Farmacorresistente

K'inich Ajaw Dios del Tiempo Maya



INFORME
MEDICO-MORAL
DE LA PENOSISSIMA,
Y RIGOROSA ENFERMEDAD
DE LA EPILEPSIA,
QUE A PEDIMENTO
DE LA M. R. M. ALEXANDRA BEATRIZ
de los Dolores, difinidora Prima del Convento
de Religiosas del Glorioso, y Mistico Doctor
Señor San Geronymo,
HACE
EL BACHILLER PEDRO DE HORTA,
Medico revalidado por el Real Tribunal del Proto-Medicato de esta Nueva-España, y propietario del Hospital Real del Señor San Pedro, y del Convento de Señoras Religiosas Capuchinas de esta Ciudad de la Puebla de los Angeles, en la Nueva-España.
CON LICENCIA.
En Madrid: En la Oficina de Domingo Fernandez de Arevajo, Calle del Carmen. Año de 1761.

DEPT. FARMACOBIOLOGIA
CINVESTAV. MEXICO

ACADEMIA DE CIENCIAS DE HUNGRIA
Dra. Anna Borsodi

CENTRO INTERNACIONAL DE
RESTAURACION NEUROLOGICA. CUBA
Dra. Lilia Morales Chacón
Dra. Lourdes Lorigados Pedre

INSTITUTO NACIONAL DE
NEUROLOGIA Y NEUROCIRUGIA
"Manuel Velasco Suárez"
Dr. Mario Alonso Vanegas
Dra. Juana Villeda

INSTITUTO MEXICANO DEL SEGURO SOCIAL
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Dra. Ana Luisa Velasco
Dr. Francisco Velasco

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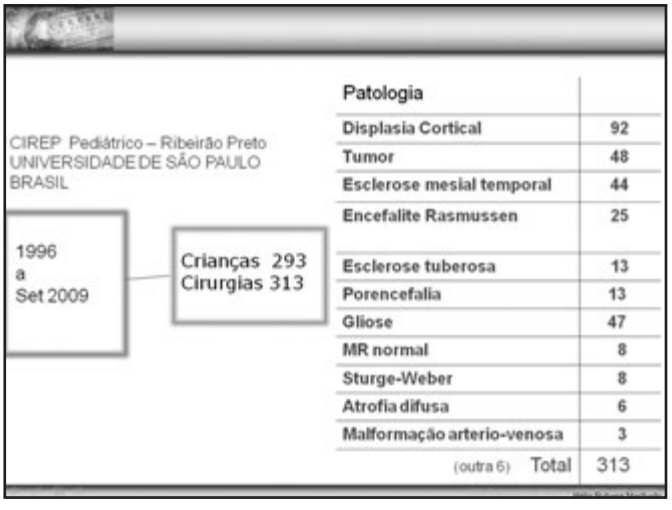
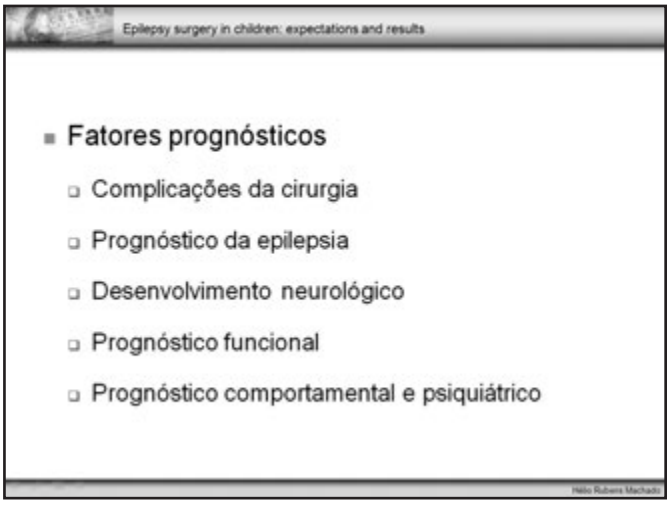
"Ramón de la Fuente"
Dr. Eduardo Calixto

HOSPITAL INFANTIL DE MEXICO
"Federico Gómez"
Dr. Eduardo Barragán
Dra. Marisela Hernández

EXPECTATIONS AND RESULTS OF EPILEPSY SURGERY IN CHILDREN
HELIO MACHADO (BRAZIL)





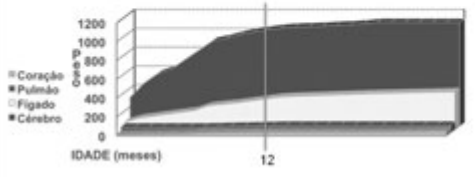
- Fatores prognósticos
  - Complicações da cirurgia
    - Período intra-operatório
      - Perda sanguínea
      - Problemas de coagulação
      - Distúrbio hidro-eletrolítico

- Peculiaridades da cirurgia na infância
  - Crianças pequenas X grandes cirurgias

  - Neuro-anestesia, cuidado intensivo, monitorização...

- Peculiaridades da cirurgia na infância
  - Crianças pequenas X grandes cirurgias

Idade (anos)	Encéfalo	Peso corporal
2	70 %	12%
10	95 %	50 %



Peculiaridades da cirurgia na infância

- Crianças pequenas X grandes cirurgias
- Volemia

Idade	Peso (kgs)	Volemia (ml)
6 me	6 - 10	450 – 750
1 a	8 – 12	600 – 900
2 a	10 – 15	750 – 1100
3 a	11.5 – 17.8	850 – 1300
10 a	23 – 51	1700 - 3800

- Perda sanguinea esperada

Ressecção focal/ lobar	200 – 500 ml
Hemisferectomia	1500 ml
Hemisferotomia	500 ml

Helio Rubens Machado

Fatores prognósticos

- Complicações da cirurgia
  - Período pós-operatório
    - Fístula LCR
    - Hematomas (intracerebral / extra ou subdural)
    - Hidrocefalia
    - Infecção superficial ou do retalho ósseo
    - Meningite (química ou bacteriana)

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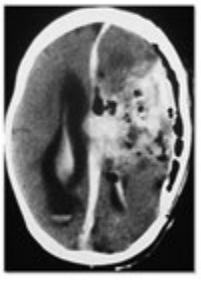
Peculiaridades da cirurgia na infância

- Riscos
  - Novos deficits, hidrocefalia
  - Anestesia, perda sanguinea, infecção
  - mortalidade



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- Fatores prognósticos
  - Complicações da cirurgia
  - Prognóstico da epilepsia
  - Desenvolvimento neurológico
  - Prognóstico funcional
  - Prognóstico comportamental e psiquiátrico

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FINALIDADES DA CIRURGIA

- Alívio da epilepsia catastrófica
- Desenvolvimento neurológico normalizado
- Melhora comportamental

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- Prognóstico
  - Substrato patológico
  - Extensão da lesão
  - Qualidade da ressecção
  - Tipo de cirurgia

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- Epilepsia catastrófica
  - Síndrome Sturge Weber
  - Hemimegalencefalia
  - Encefalite Rasmussen
  - Esclerose Tuberosa
  - Displasia Cortical
  - Porencefalia

Síndromes epilépticas catastróficas

Epilepsia Refratária — *Média 666,9 crises/ mês; Status epilepticus 40,7%*

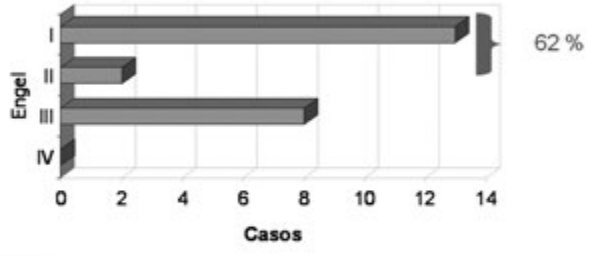
Deficit Neurológico Progressivo

hemiplegia espástica

Retardo Mental

Distúrbio de comportamento

Resultados



62 %

Engel

I Livre de crises II Raras crises III Considerável melhora IV Sem melhora

- Fatores prognósticos
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  - Desenvolvimento neurológico
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Inicio precoce epilepsia refratária → retardo de desenvolvimento

Pós-op
Melhora Cognitiva – 13,3 %
Inalterado – 71,5 %
Battaglia et al, 2006

Helio Rubens Machado

Ressecções focais	Cognição	Memória
Temporal	Inalterada Declinio	Melhora Declinio Inalterada Deficit reversivel
Frontal	Melhora	Inalterada
Córtex posterior	Inalterada (frequente deficit pré-op	

	Cognição
Hemisferotomias	Melhora Inalterada Declinio (Rasmussen)

Battaglia et al, 2006;Duchowny et al, 1998; Westerveld et al, 2000; Lah et al, 2002; Szabo et al, 1998; Adams et al, 1990; Lou Smith et al, 2006; Gleissner et al, 2005; Lendt et al, 1999 & 2002; Pulsifer et al, 2004; Vasconcelos et al, 2001; Vigevano et al, 1989; Wyllie et al, 1996.

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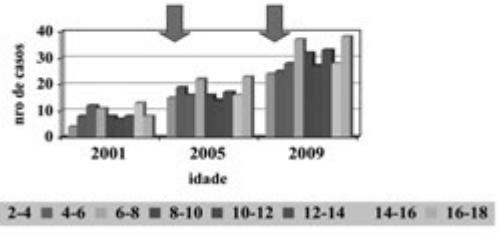
- Idade na cirurgia



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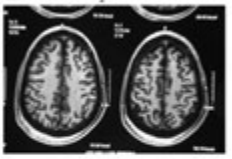
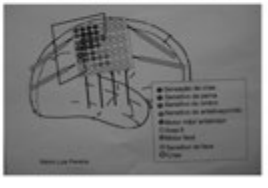
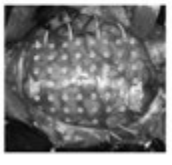
RISCO DE DEFICIT NEUROLÓGICO

- Definir o córtex eloquente (motor e linguagem)
- Monitorização invasiva / "mapa"cortical
- Imagem funcional

Helio Rubens Machado

- Localização de áreas eloqüentes



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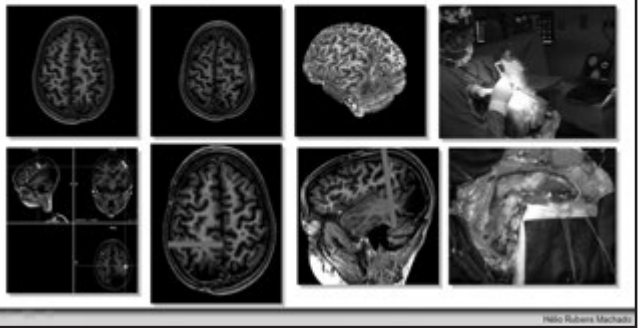
- **Monitorização Invasiva em Crianças**
  - **Indicações**
    - **Video EEG não oferece dados suficientes**
    - **Video EEG mostra dados discordantes com outros exames (RM)**
    - **Necessidade de mapas funcionais**
      - **MOTORES**
      - **SENSITIVOS**
      - **LINGUAGEM**

Cirurgias 281
Monitorização invasiva 147

- **Monitorização invasiva (em geral)**
- **ECoG: 103 pacientes (36,5 %)**
- **ECoG + eletrodos subdurais: 44 pacientes**

- Novas tecnologias
  - RM 3 T ; DTI (tratografia) ; fMRI
  - Neuronavegação



- Fatores prognósticos
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  - Desenvolvimento neurológico
  - Prognóstico funcional
  - Prognóstico comportamental e psiquiátrico

Distúrbios comportamentais e psquiátricos

↓

Alta prevalência

↓

Cirurgia – efeito positivo

McLellan et al, 2005; Davies et al, 2003; Szabo et al, 1999

K G Mckenzie

R A Krynauw

- McKenzie KC: The present status of a patient who had the right cerebral hemisphere removed. JAMA 111:168,1938
- Krynauw RA: Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatry 13:243, 1950

↓

Melhora significativa

White, 1961; Wilson, 1970; Lendt et al,2000

CONCLUSÕES

- **Cirurgia da epilepsia deve ser indicada o mais precocemente possível, antes do aparecimento de déficits irreversíveis.**
- **A criança deve ser atendida em ambiente especializado e por equipe treinada para este fim.**
- **Os resultados cirúrgicos são encorajadores apesar da complexidade da abordagem.**

Expectations and results of epilepsy surgery in adults with MTLE

Mario A. Alonso (México)

Expectativas y resultados de la cirugía de epilepsia a lo largo de la vida en adultos con ELTM

Dr Mario A Alonso Vanegas

EXPECTATIVAS

- Para el paciente
- Para los familiares
- Para el médico y equipo multidisciplinario

Expectativas = Realidad

Selección adecuada pacientes y técnicas

ÉXITO

"Ideales"

- Libertad de crisis
- Ninguna morbilidad asociada
- Mejora en la calidad de vida
- Regreso o inicio de empleo
- Posibilidad de desarrollo educativo
- Aceptación social

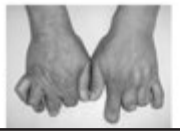
Las "medidas" finalmente, dependen de las condiciones biosicosociales previas y, por lo tanto, son totalmente individuales para cada paciente

Medidas de resultados

- Médicas
  - Reducción de crisis
  - Morbilidad asociada
- Socio-Psicológicas
  - Calidad de vida
  - Estado civil
  - Empleo
  - Educación

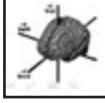
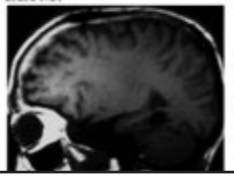
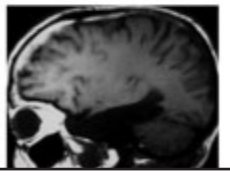
Epilepsia de Difícil Control

- **Incapacidad para obtener control de las crisis**
  - Con tres o más fármacos antiepilépticos (FAE) mayores
  - En un periodo no menor de 2 años de tratamiento continuo
  - Con supervisión adecuada para la ingesta y/o manejo de medicamentos, bajo estándares de dosificación adecuados
  - Y/o seguimiento con niveles plasmáticos dentro del rango terapéutico
  - A costa de efectos adversos intolerables

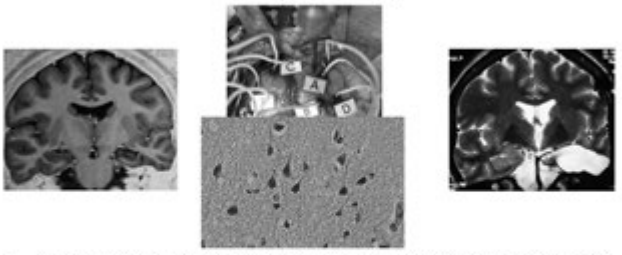



Repercusión Socioeconómica y Justificación de Abordaje Quirúrgico

- La epilepsia de difícil control o refractaria a tratamiento farmacológico se define, como aquella que ***provoca imposibilidad del paciente para llevar un estilo de vida acorde a su capacidad individual*** por la presencia de crisis, efectos secundarios del tratamiento y/o problemas psicosociales.
- La ELTM es la forma más común de epilepsia (25% en población infantil)
- La ELTM es la formas más refractaria de epilepsia (10% control de crisis)
- Las crisis de difícil control causan alteración conductual progresiva e irreversible
- **En pocos pacientes** se logra control de crisis después del fallo de 2 ensayos clínico-terapéuticos adecuados
- ¿Deberá la intervención quirúrgica temprana ser el tratamiento de elección para la ELTM?

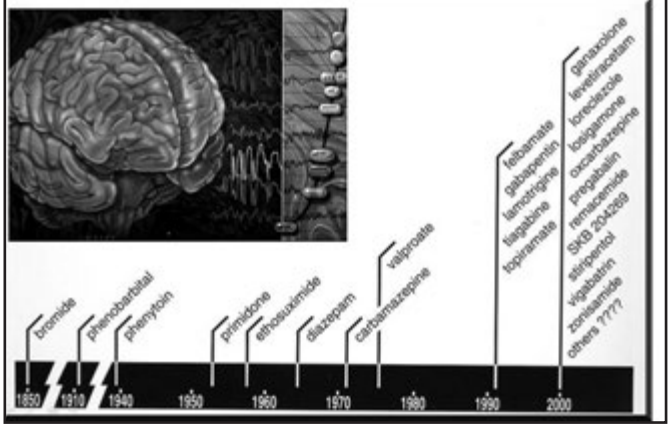




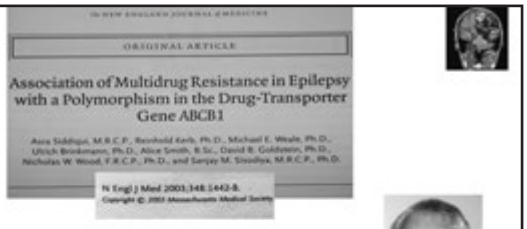
Repercusión Socioeconómica y Justificación de Abordaje Quirúrgico



- Se estima que alrededor del **2%** de la población sufre epilepsia en México, lo que equivale a **2.2 millones** de pacientes.
- Considerando que **20%** son epilepsias de difícil control, aproximadamente **440,000** pacientes son portadores de epilepsia de difícil control (candidatos quirúrgicos).
- De la mano del alto costo social se encuentra el alto costo económico. P.e. en EEUU el costo total directo é indirecto para todos los pacientes con ERTM fue de **9.9** billones de dólares (1995).

Los nuevos FAEs NO juegan un papel importante en mejorar el control de las crisis



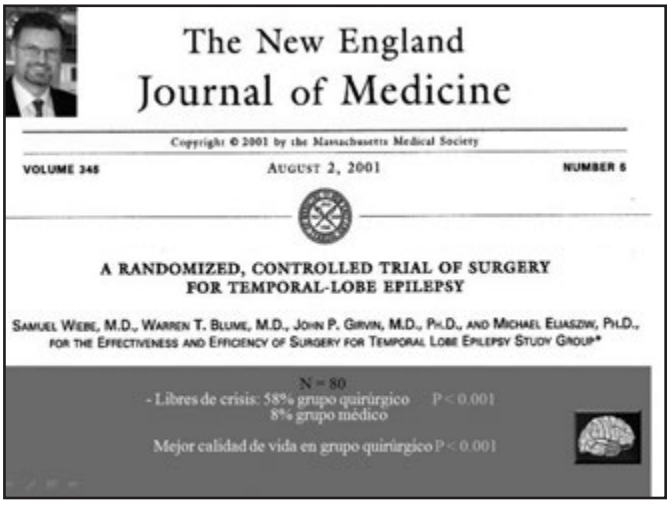


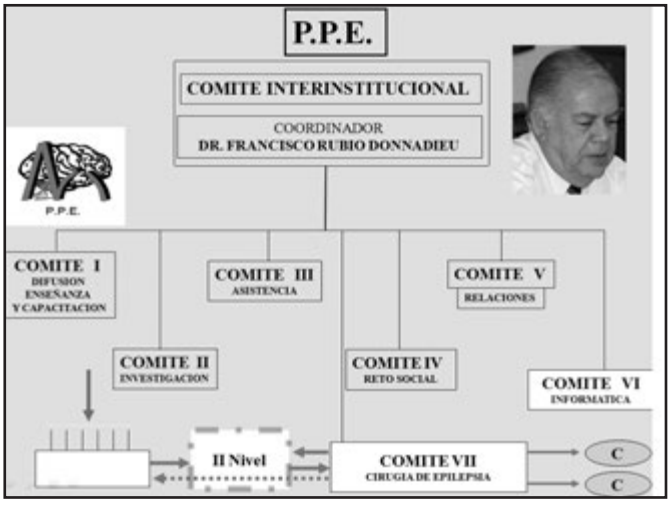
Control de Crisis

- 47% sin crisis con un fármaco (monoterapia)
- 13% sin crisis al agregar 2° fármaco
- 4% libres con politerapia

36% de los pacientes persisten con al menos una crisis por año

(Kwan and Brodie, NEJM 2000)

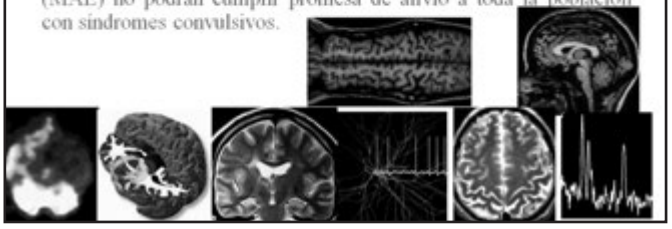

The New England
Journal of Medicine
Copyright © 2001 by the Massachusetts Medical Society
VOLUME 345
AUGUST 2, 2001
NUMBER 6
A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY
SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*
N = 80
- Libres de crisis: 58% grupo quirúrgico P < 0.001
8% grupo médico
Mejor calidad de vida en grupo quirúrgico P < 0.001


P.P.E.
COMITE INTERINSTITUCIONAL
COORDINADOR
DR. FRANCISCO RUBIO DONNADIEU
P.P.E.
COMITE I
DIFUSION ENSEÑANZA Y CAPACITACION
COMITE III
ASISTENCIA
COMITE V
RELACIONES
COMITE II
INVESTIGACION
COMITE IV
RETO SOCIAL
COMITE VI
INFORMATICA
II Nivel
COMITE VII
CIRUGIA DE EPILEPSIA
C
C


TEMA DEL DÍA
ESPERANZA PARA EPILÉPTICOS
REPORTAJE: CIRUGÍAS DE EPILEPSIA
Históricas operaciones
Programa Prioritario de Epilepsia
Cirugía de Epilepsia en el CAE No. 47
LAS DOS CIRUGÍAS FUNCIONALES DE EPILEPSIA EFECTUADAS EN EL Hospital General de Culiacán "Bernardo J. Gastélum", HAN SIDO EXITOSAS EN EL CORTO PLAZO
PRODUCTO DEL ESFUERZO COOPERATIVO DE NEURÓLOGOS, NEUROCIRUJANOS, ELECTROFISIÓLOGOS, PSICÓLOGOS, ENFERMERAS DE ÉSTE HOSPITAL Y DEL Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez"
POSIBLE GRACIAS A LA SOLIDARIA E INVALUABLE COOPERACIÓN DE:
DR. MARIO A. ALONSO VANEGAS INNN
M. C. CARLOS CASTILLO MONTOYA INNN

Resurgimiento de la Cirugía de Epilepsia

- Gran avance en la detección de crisis mediante tecnologías computarizadas aplicadas a la electrofisiología.
- Definición de blancos quirúrgicos mediante nuevas técnicas de imagenología, cuyo sustrato histológico era conocido previamente sólo después de la resección quirúrgica.
- Desarrollo de las técnicas microquirúrgicas, de la resección subpial y el desarrollo del disector ultrasónico (CUSA).
- Realidad latente de que los nuevos medicamentos antiepilépticos (MAE) no podrán cumplir promesa de alivio a toda la población con síndromes convulsivos.



Aspectos Históricos de la Cirugía de Epilepsia

¿ PORQUÉ ES IMPORTANTE LA CIRUGÍA DE EPILEPSIA DEL LÓBULO TEMPORAL?

FRECUENCIA ⟷ **COSTO PAISES EN DESARROLLO**

CONTROL DE CRISIS

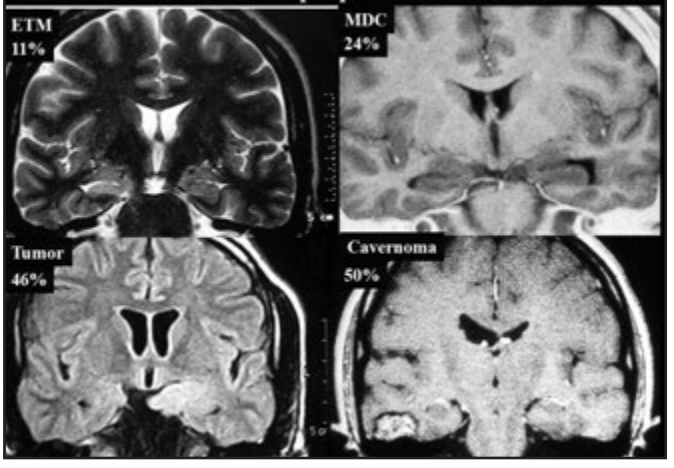
Es la cirugía de la epilepsia más frecuente en el mundo

Es la que logra los mejores resultados en el control de crisis post-operatoria

El 80% los estudios pre-quirúrgicos son NO-INVASIVOS

El 64% de todas las cirugías de la epilepsia

Factores Predictivos: Epilepsias Fármaco Resistente

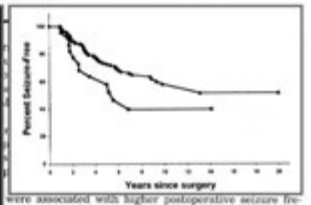


¿ De qué dependen los resultados?

Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery

H.H. Yoon, MD; H.L. Kwon, MPH; R.H. Mattson, MD; D.D. Spencer, MD; and S.S. Spencer, MD

- Evolución prolongada de crisis (> 10 años) y estudio histopatológico normal se asocian a mal pronóstico en el control de crisis

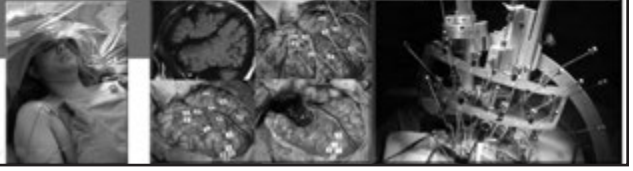


were associated with higher postoperative seizure free-
year after resective epilepsy surgery, the likelihood of
remaining seizure-free declined to 66% over 10 years, but half of patients who relapsed had at most one seizure per year.
Longer preoperative illness and normal pathology predicted poorer outcome.

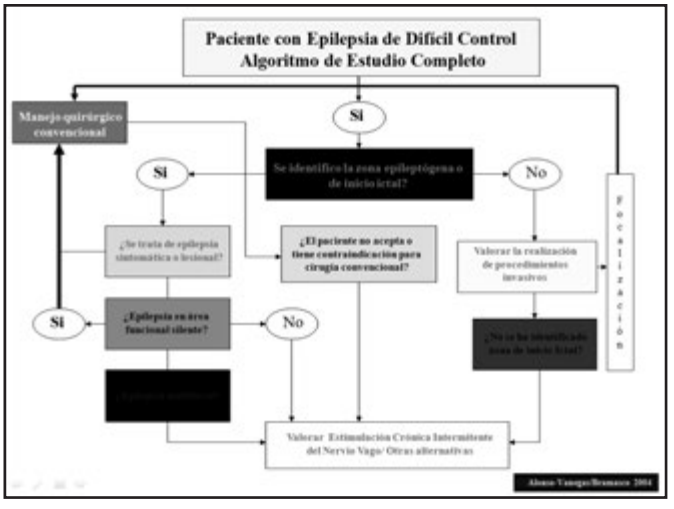
NEUROLOGY 2003;61:445–450

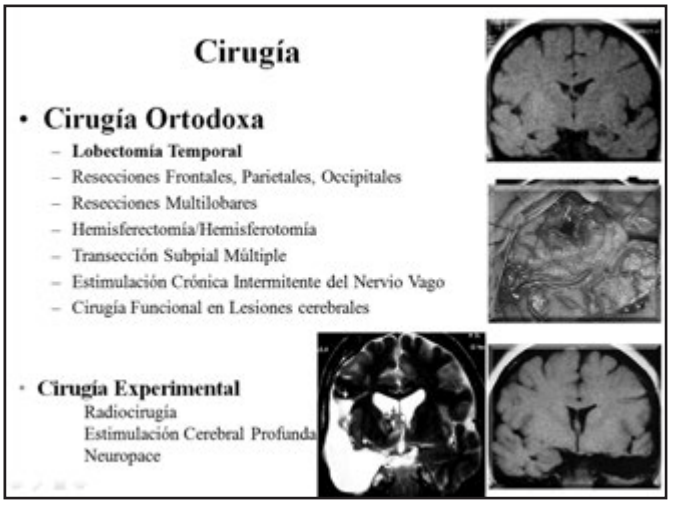
Equipo de Trabajo
(multidisciplinario)

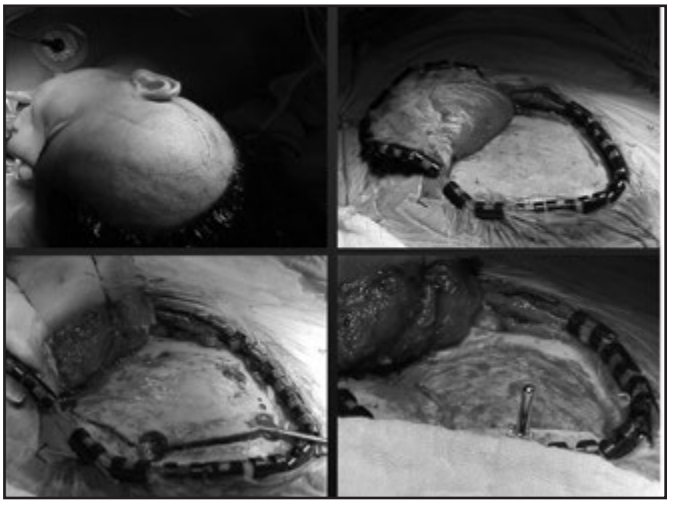
- Neurólogo epileptólogo
- Neurofisiólogo con interés clínico
- Neuropsicólogo
- Neuroimagenólogo
- Neuropsiquiatra
- Neuropatólogo
- **Neuroanestesiólogo**
- Ingeniero biomédico
- Técnicos en neurofisiología e imagenología
- Personal de enfermería y trabajo social
- **Neurocirujano especializado en cirugía de epilepsia**

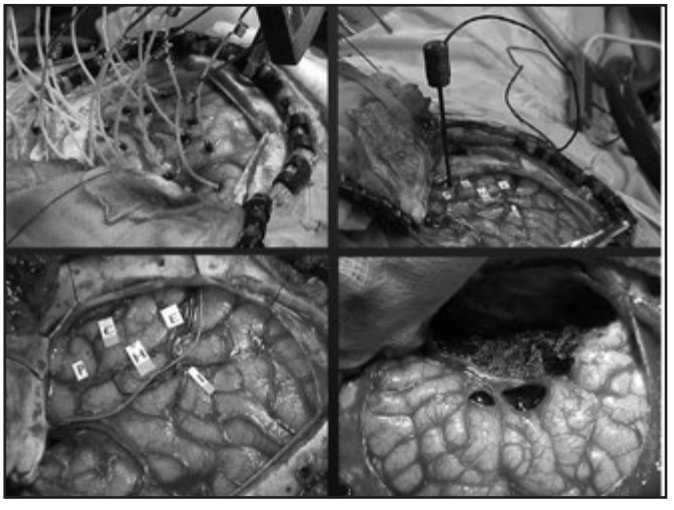


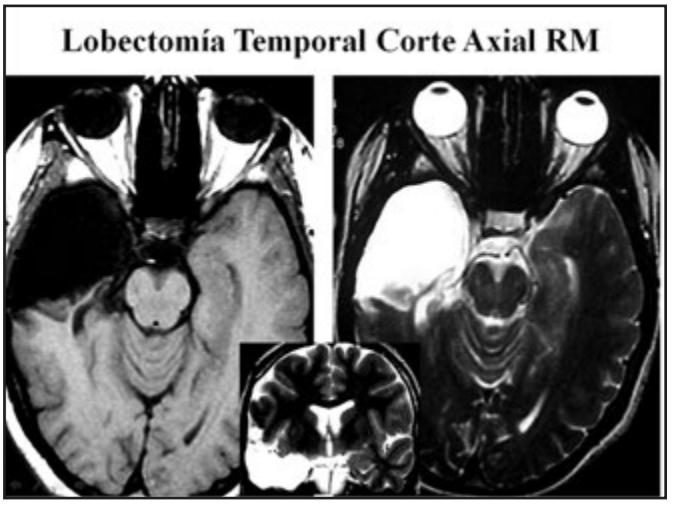

Algoritmo de Estudio
Revisión estudios previos
Historia clínica completa
Estudios Neurofisiológicos
Evaluación Neuroimagen
Neuropsiquiatría Neuropsicología
Prueba de Wada
Evaluación invasiva
Comité de cirugía de epilepsia
NO candidato quirúrgico
Candidato quirúrgico
Comité de cirugía de epilepsia
Cirugía de epilepsia Temporal/Extratemporal Lesional/No Lesional
Procedimientos paliativos
Estimulación vagal
Neuroestimulación (experimental)
Radiocirugía Gamma/Linac
Alonso-Vanegas 2003


Paciente con Epilepsia de Difícil Control
Algoritmo de Estudio Completo
Manejo quirúrgico convencional
SI
Se identifica la zona epileptógena o de inicio ictal?
SI
No
¿Se trata de epilepsia sintomática o lesional?
¿El paciente no acepta o tiene contraindicación para cirugía convencional?
Valorar la realización de procedimientos invasivos
Focalización
SI
¿Epilepsia en área funcional elocuente?
No
Valorar Estimulación Crónica Intermitente del Nervio Vago/ Otras alternativas


Cirugía
• Cirugía Ortodoxa
– Lobectomía Temporal
– Resecciones Frontales, Parietales, Occipitales
– Resecciones Multilobares
– Hemisferectomía/Hemisferotomía
– Transección Subpial Múltiple
– Estimulación Crónica Intermitente del Nervio Vago
– Cirugía Funcional en Lesiones cerebrales
• Cirugía Experimental
Radiocirugía
Estimulación Cerebral Profunda
Neuropace





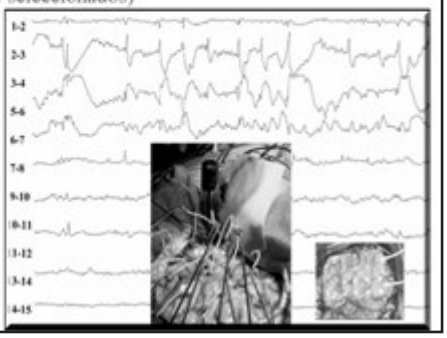

Lobectomía Temporal Corte Axial RM

Cirugía de Epilepsia: Objetivos

Eliminar la zona epileptogénica

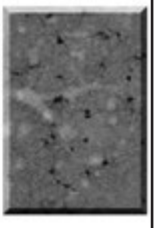
Interrumpir las vías de propagación de actividad anormal

Aumentar el umbral de las crisis (lesiones o estimulación eléctrica de blancos seleccionados)



Objetivos Secundarios

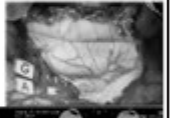
- En las últimas décadas y gracias a la experiencia de varios centros neuroquirúrgicos, se ha reconocido que los objetivos de la cirugía de la epilepsia deben incluir <u>además</u> del **control de las crisis:**
  - Mejoría en otros aspectos de la integridad bio-sico-social del individuo (alt. siquiátricas, emocionales, conductuales, etc)
  - Integración o mejor adaptación a la vida escolar o laboral
  - Mejoría en la calidad de vida individual, familiar y social
  - Reducción o modificación de daño neuronal secundario

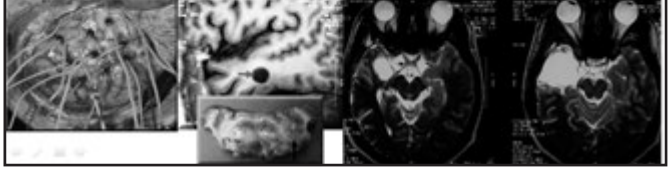


Cirugía de Epilepsia

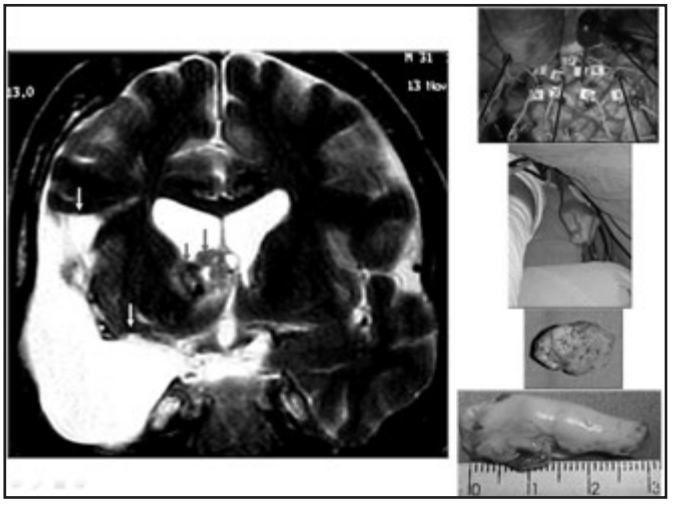
Consideraciones quirúrgicas

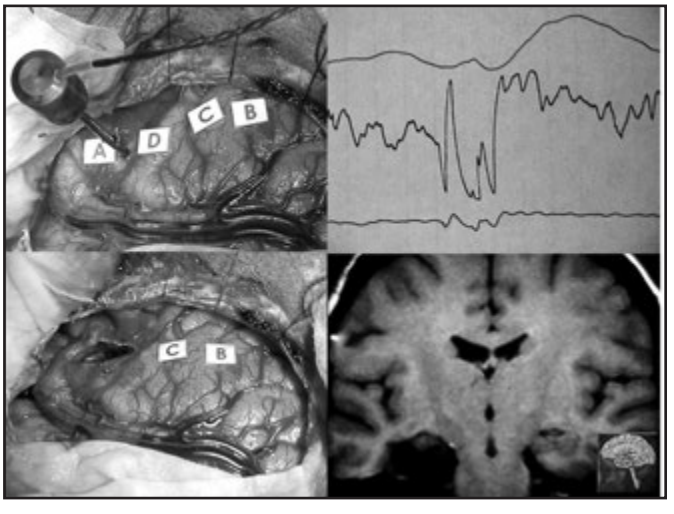
- Resecciones quirúrgicas encaminadas a:
- Epilepsia del Lóbulo Temporal Mesial
- Epilepsia del Lóbulo Temporal relacionada a lesión
- Epilepsia Neocortical del Lóbulo Temporal

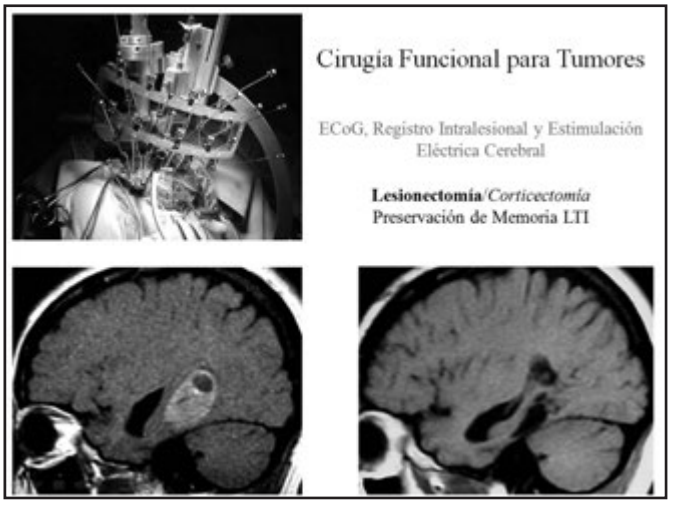


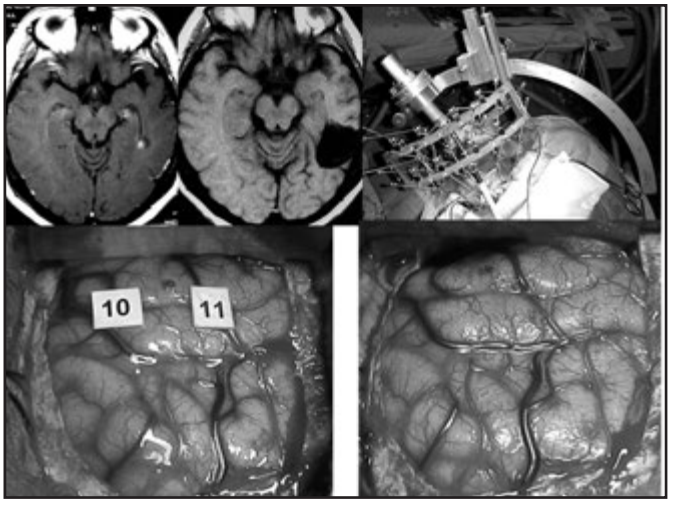


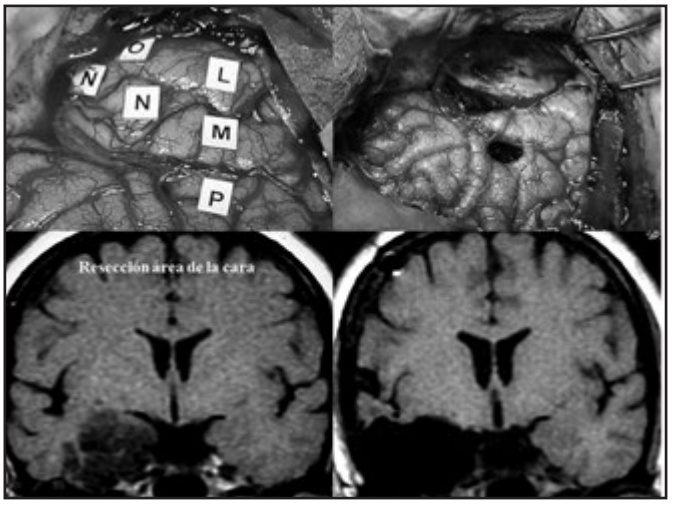

Candidatos óptimos para Cirugía del Lóbulo Temporal
Se logra lateralizar el origen de las crisis con estudios de EEG de superficie
Existe buen correlato entre imágenes, video-EEG y neuropsicología

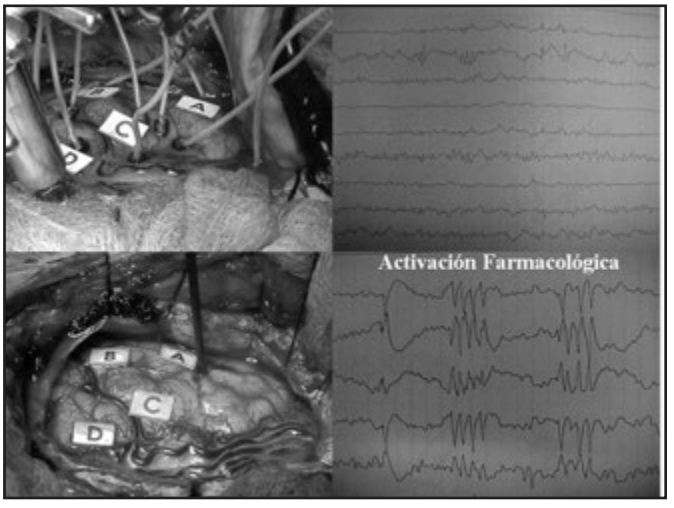



A
D
C
B
C
B


Cirugía Funcional para Tumores
ECoG, Registro Intralesional y Estimulación Eléctrica Cerebral
Lesionectomía/*Corticectomía*
Preservación de Memoria LTI

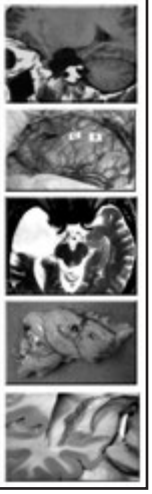

10
11

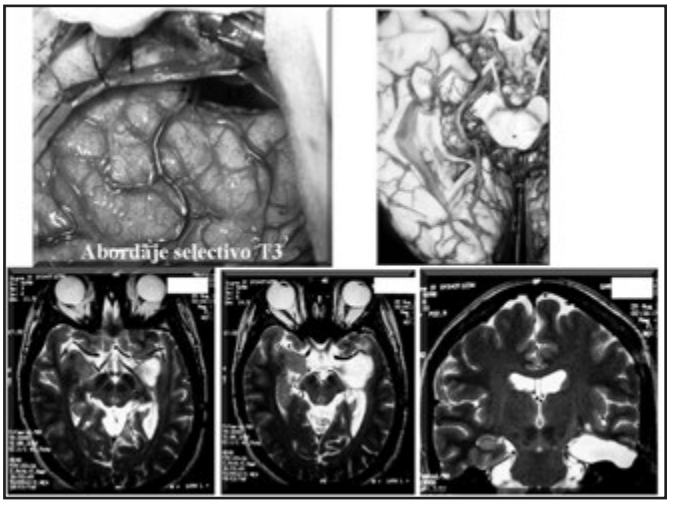

O
N
N
L
M
P
Resección area de la cara



Cirugía de Epilepsia

PROCEDIMIENTO	AUTOR
Neocorticectomía temporal	Penfield 1947
Neocorticectomía y Uncus-Hipocampectomía	Penfield 1950, 1954
Lobectomía temporal en bloque	Falconer 1955
Lobectomía temporal y Amígdala y Uncus-Hipocampectomía	Morris 1956
Abordaje transventricular y Amigdalo-Hipocampectomía	Niemeyer 1958
Abordaje transilviano y Amigdalo-Hipocampectomía	Yasargil 1982
Lobectomía subpial y Amigdalo-Hipocampectomía	Olivier 1983
Abordaje transulcal y Amigdalo-Hipocampectomía selectiva	Olivier 1988
Reoperaciones	Awad 1991
Endoscopia transventricular o Hipocampectomía	Silbergeld 1995
Abordaje subtemporal transparahipocampal y Amigdalo-Hipocampectomía	Park 1996
Abordaje transilviano-transcisternal y Amigdalo-Hipocampectomía	Vajkoczy 1998
Amigdalo-hipocampectomía selectiva guiada por Neuronavegación	Wurm 2000
Amigdalo-hipocampectomía selectiva a través del Surco temporal inferior por estereotaxia	Miyagi 2003
Abordaje Subtemporal transventricular / Transcoroideo	Miyamoto 2004





Abordajes Selectivos para Epilepsia del Lóbulo Temporal

* Seguimiento de un año, posterior a la cirugía.

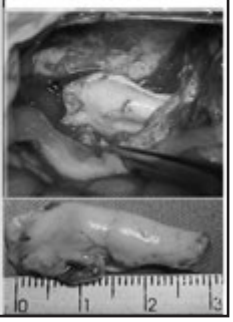
AUTOR	N° Pacientes	Libre de Crisis (%)*	Complicaciones
Yasargil 1993	100	69%	1 Hemiparesia transitoria 1 Osteomielitis
Wurm 2000	16	70%	1 Vasoespasmo severo / Hemiparesia
Miyagi 2003	7	100%	1 cuadrantanopsia 1 delirio
Alonso-Vanegas 2006	40	78%	5 Cuadrantanopsias

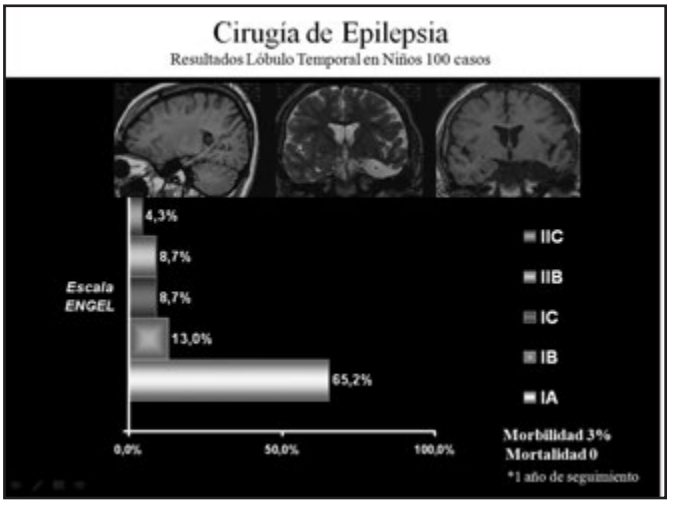
Clasificación de ENGEL

Clase I: Libre de crisis	a. Completamente libre de crisis desde la cirugía
	b. Solamente crisis parciales simples no discapacitantes desde la cirugía
	c. Algunas crisis discapacitantes después de la cirugía, pero libre de crisis en por lo menos los últimos 2 años
	d. Crisis generalizadas después del retiro de los fármacos anticonvulsivos
Clase II: Crisis infrecuentes (casi libre de crisis)	a. Inicialmente libre de crisis discapacitantes, pero con crisis de manera infrecuente actualmente
	b. Crisis discapacitantes infrecuentes desde la cirugía
	c. Crisis ocasionales discapacitantes desde la cirugía, pero infrecuentes en los últimos 2 años
	d. Solamente crisis nocturnas, que no provocan discapacidad
Clase III: Mejoría sigtnificativa	a. Reducción significativa de las crisis
	b. Períodos libres de crisis prolongados que acumulan más de la mitad del tiempo de seguimiento, pero no mayores de 2 años
Clase IV: Sin mejoría significativa	a. Reducción significativa de las crisis (del 60 al 90% de reducción)
	b. Sin cambios apreciables (menos del 60% de reducción)
	c. Empeoramiento de las crisis

Resultados Cirugía de Epilepsia LT

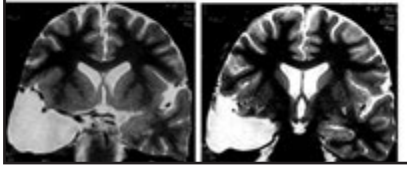
Referencia	Resultado
Kim R, Spencer D. Epilepsy Surgery: Surgery for mesial temporal sclerosis. Epilepsia 2001; 72: 643-652	Res neocortical: 54.2% LC Res mesial: 67.6% LC
Sperling MR; *et al.* Temporal Lobectomy for refractory epilepsy. JAMA 1996; 276: 470-5.	69% Libre de Crisis
Foldvary N; *et al.* Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. Neurology 2000; 54: 630-4.	63% Libre de Crisis
Becti C, Robitaille Y; *et al.* The Pathological Basis of Temporal Lobe Epilepsy in Childhood. Neurology 2003;60(2):191-195	41% LC y 14% Auras
Franzon RC, Guerreiro MM. Temporal Lobe Epilepsy in Childhood: Review Article. J Epilepsy Clin Neurophysiol 2006; 12(1 suppl. 1):26-31	73-100% LC
Dlugos DJ. Long Term Outcome after Temporal Lobe Epilepsy Surgery in Children. European J. Clinical Research 2003; 9: 10 – 13	0-100% LC Depende de patología





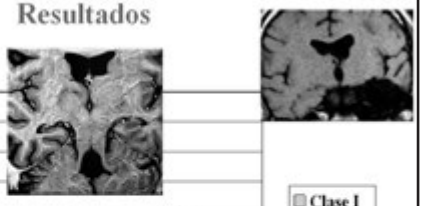
Resultados Obtenidos con Abordaje Microquirúrgico en ELT

- En 100 pacientes con seguimiento mayor de dos años, el 84% se encuentra libres de crisis, 10 % con mejoría y 6% ninguna mejoría.
- Sin mortalidad y la siguiente morbilidad: hemiparesia transitoria 2%, quadrantanopsia 43%, hemianopsia 1 paciente, infección menos del 1%, anomia transitoria en 4 %, anomia 1%.



Cirugía Lóbulo Temporal

Resultados



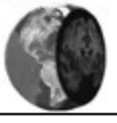
Arruda, *et al.* Ann Neurol '96

Cirugía para el Manejo de la Epilepsia

- **Conferencia de Epilepsia en Palm Desert (1992)**
  91 Centros/5746 casos
  (1986 a 1990)
- 66% Estructuras Límbicas
- **18% Extratemporales**
- 6% Hemisferectomías
- 10% Callosotomías

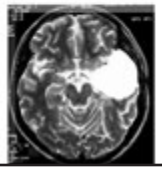
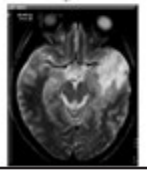
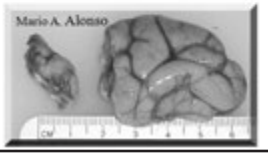
CONCLUSIONES

- **La cirugía es el mejor tratamiento para la epilepsia refractaria del lóbulo temporal, con control total de crisis, con medicamentos superior al 58%**
- **La cirugía de la epilepsia es una necesidad en Latinoamérica y requiere de centros básicos y avanzados**
- **Lamentablemente no es considerada por las autoridades, ni por muchos profesionales de las neurociencias**
- **La pobre cultura neuroquirúrgica obedece a sus antecedentes históricos y la insuficiente cantidad de neurocirujanos adiestrados en estas técnicas**



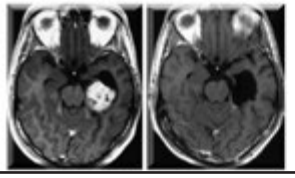
COROLARIO

Si la cirugía falla, el área resecada era incorrecta o fue removida de manera incompleta, o bien, era una de más regiones cerebrales responsables para provocar las crisis. *Sólo existen dos condiciones: selección inapropiada de pacientes y/o resecciones insuficientes*

Cirugía de Epilepsia

"El verdadero reto de la cirugía de epilepsia continua siendo la selección de los pacientes y en menor grado el tipo de procedimiento quirúrgico a realizarse."




Expectations and results of epilepsy surgery in adults with extra-temporal epilepsies

Manuel Campos (Chile)

¿Qué es la Epilepsia?

Nota: Definición con visión neuroquirúrgica

EPILEPSIAS- DEFINICIÓN

1- La epilepsia generalmente es un síndrome, es decir, un conjunto de síntomas y signos que obedece a distintas etiologías (enfermedades).

2- NO existe la epilepsia, sino, las "epilepsias", ya que hay múltiples tipos de crisis y con distintos pronósticos.

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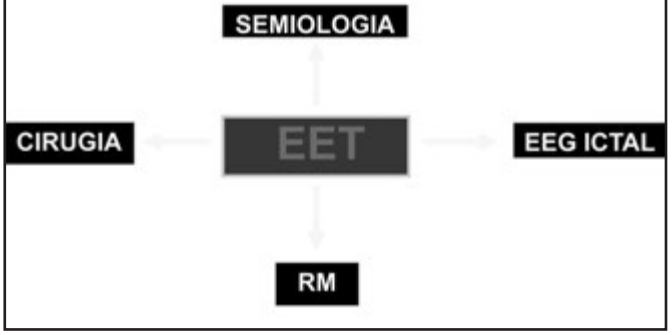
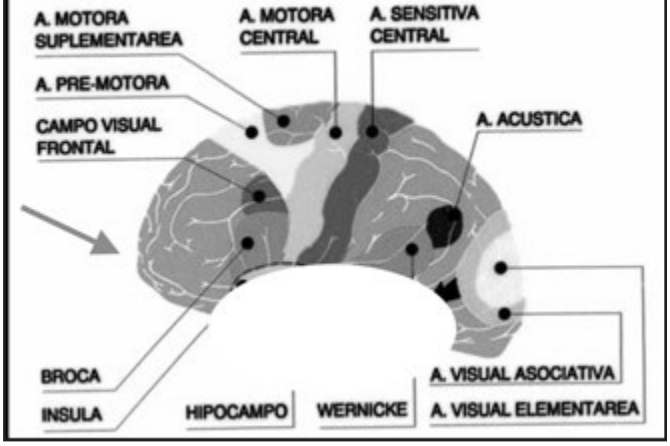
EPILEPSIA EXTRATEMPORAL



Zonas elocuentes por estimulación cortical

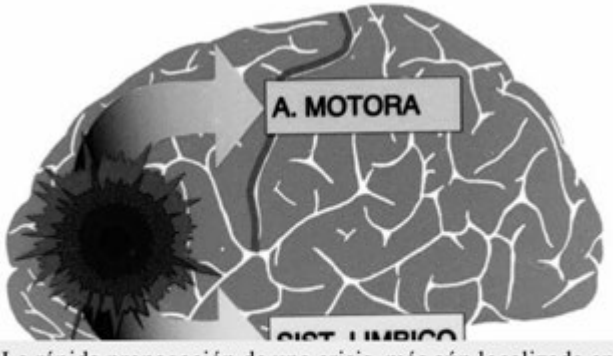


PROBLEMAS CLINICOS

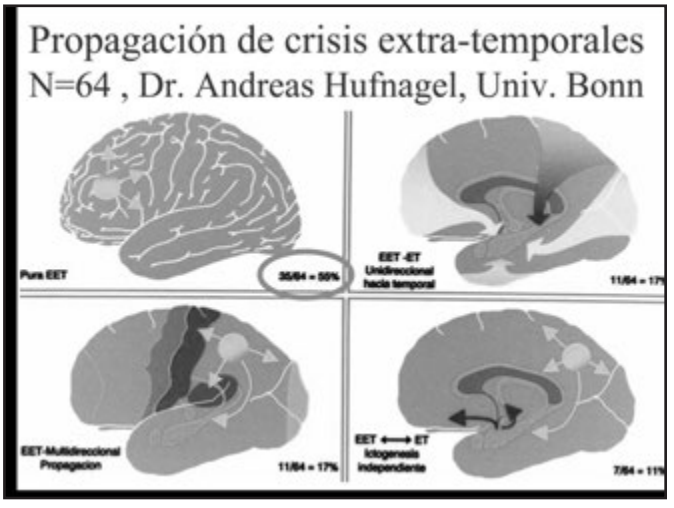
FALSA LOCALIZACION SEMIOLOGICA

Nota: Recordar que le 20% del sistema Límbico está en el L. Frontal

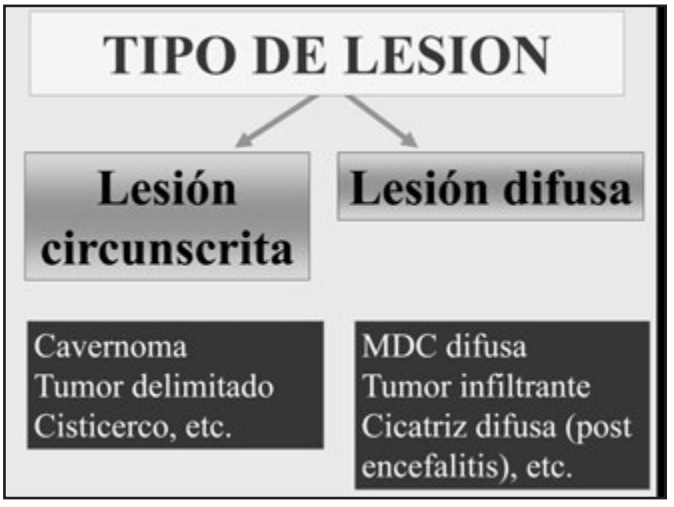
Crisis del Lóbulo Frontal
Automatismos complejos

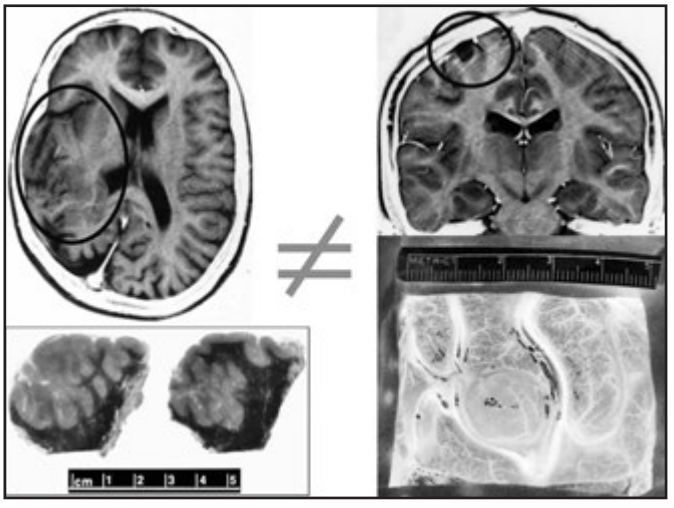


La rápida propagación de una crisis, más aún localizada en área no-elocuente, nos puede dar falsa localización semiológica. Y si la actividad eléctrica es muy rápida en propagarse, también lo puede hacer en el EEG de superficie.

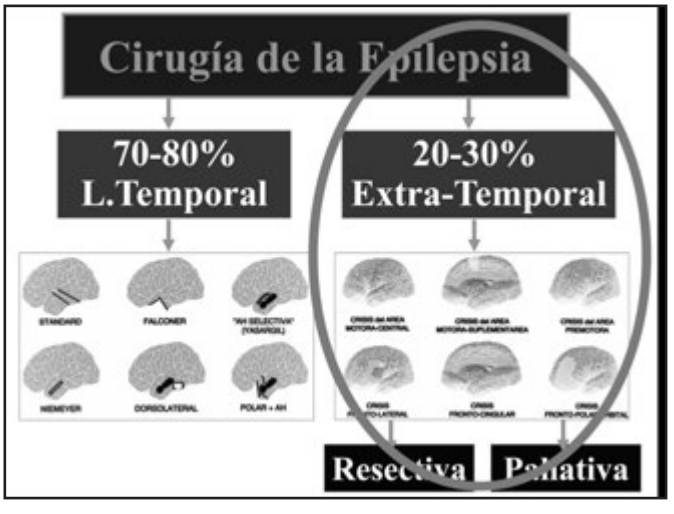


TIPO DE LESION ASOCIADA A LA EPILEPSIA EXTRATEMPORAL





¿Qué tan frecuente es la cirugía de la Epilepsia Extratemporal?

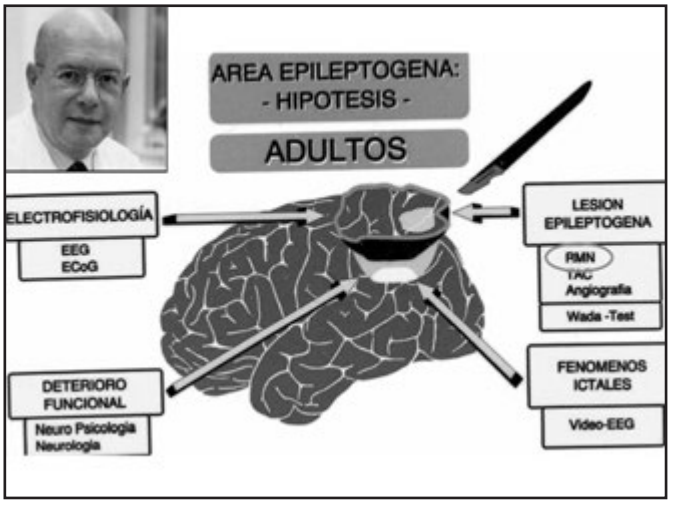


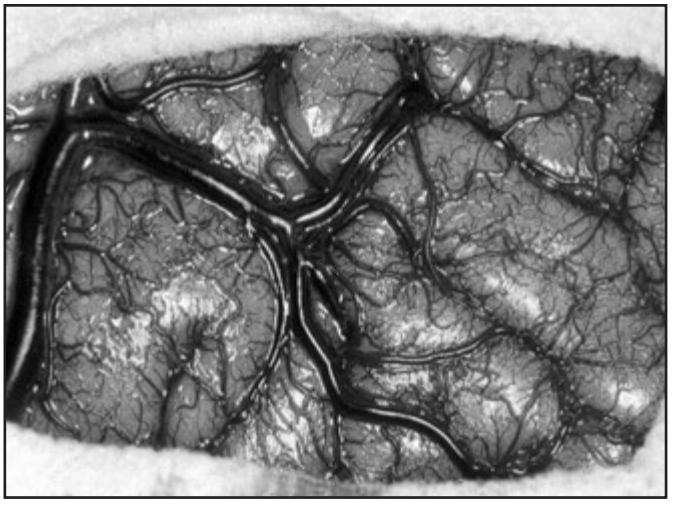
¿Qué tipos de cirugía de Epilepsia Extratemporal existen?

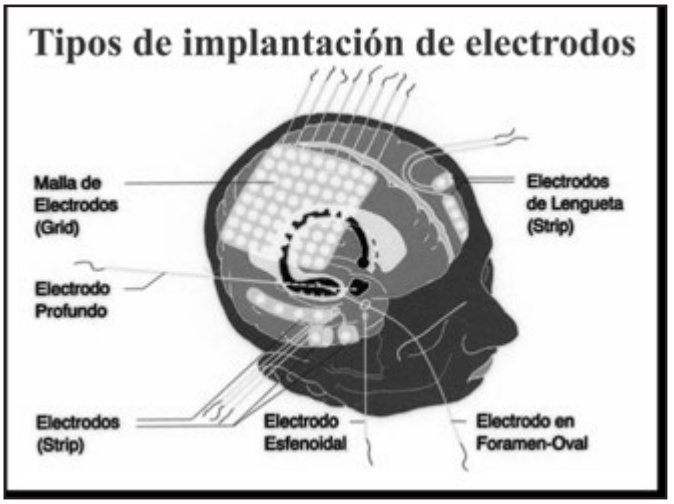
Tipos de Cirugías Extratemporales

Cirugía resectiva	• Cortectomia (topectomia) • Lobectomia • Multilobectomia • Hemisferectomia
Cirugía No-resectiva	•Transección Subpial múltiple •Callosotomia •Estimulador Vagal •Radiocirugía •Estimulación Profunda (experimental)

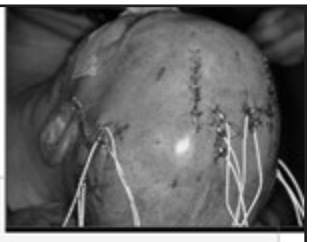
RESECCIONES FOCALES Y LOBECTOMIAS


AREA EPILEPTOGENA:
- HIPOTESIS -
ADULTOS
ELECTROFISIOLOGÍA
EEG
ECoG
LESION
EPILEPTOGENA
RMN
TAC
Angiografía
Wada -Test
DETERIORO
FUNCIONAL
Neuro Psicología
Neurología
FENOMENOS
ICTALES
Video-EEG




Tipos de implantación de electrodos
Malla de
Electrodos
(Grid)
Electrodos
de Lengueta
(Strip)
Electrodo
Profundo
Electrodos
(Strip)
Electrodo
Esfenoidal
Electrodo en
Foramen-Oval

PROBLEMAS



- Alto costo.
- 2 cirugías.
- Idiosincrasia de la población.
- ECoG crónica v/s intra-operatoria.
- Personal entrenado.
- Equipamiento.

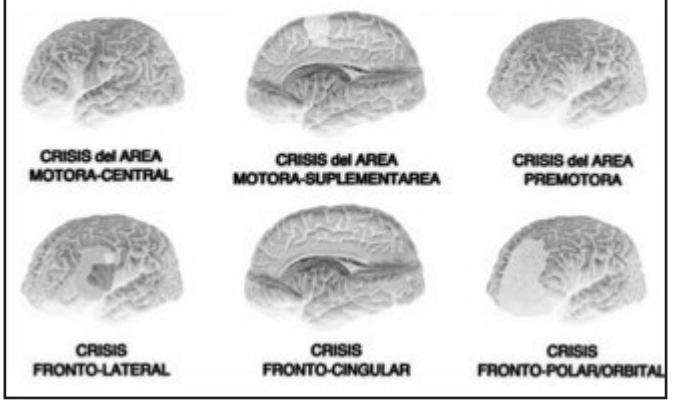
Practical problems when defining the epileptogenic zone

- Invasive electrodes can also not localize the seizure onset zone with precision
  - Only a very small fraction of the brain can be covered with invasive electrodes (depth and/or subdural electrodes)
  - Invasive electrodes are usually recruited progressively at seizure onset. It is totally arbitrary which of the electrodes involved early during a seizure initiation are considered as part of the seizure onset zone

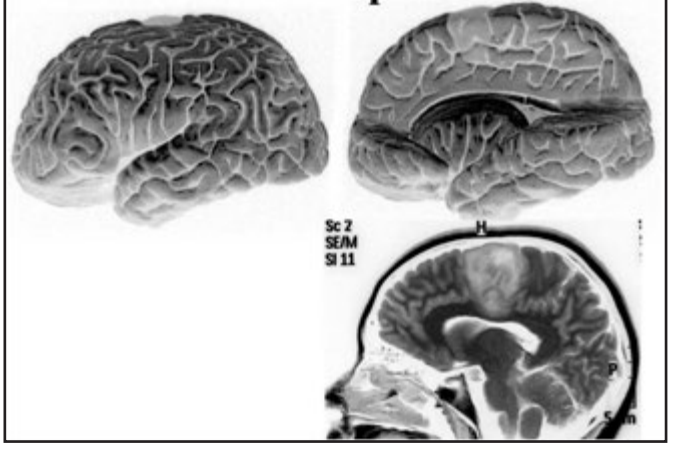
TIPOS DE EPILEPSIAS EXTRATEMPORALES

- FRONTALES
- PARIETALES
- OCCIPITALES
- MULTILOBARES

Tipos de crisis frontales

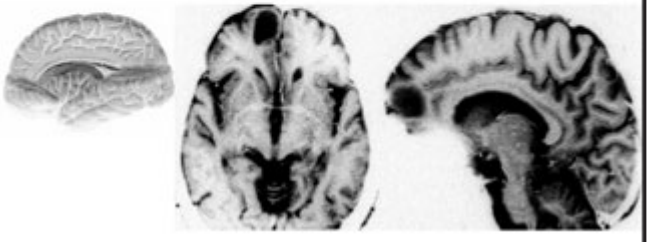


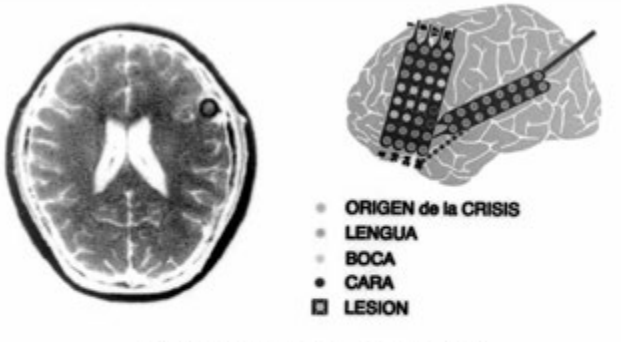
Área motora suplementaria



Crisis del Lóbulo Frontal
- Cíngulo -

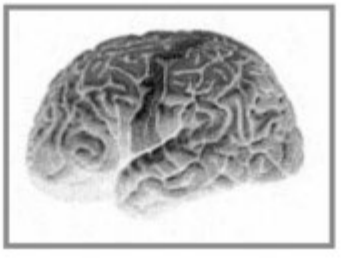
Síntomas del paciente con la lesión mostrada en la RM: afectivos e hiper-motores, confundido por años como paciente psiquiátrico.

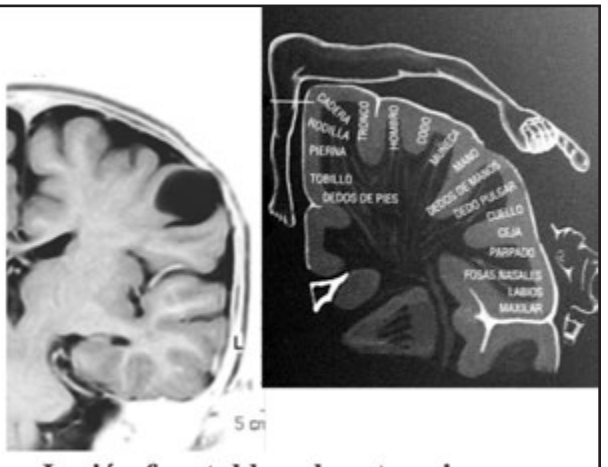




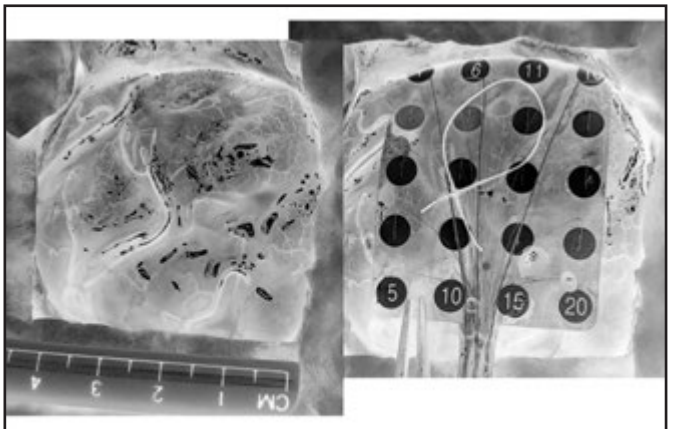
Crisis pre-motoras:
Ganglioglioma
G°I (OMS)

CRISIS ROLANDICAS



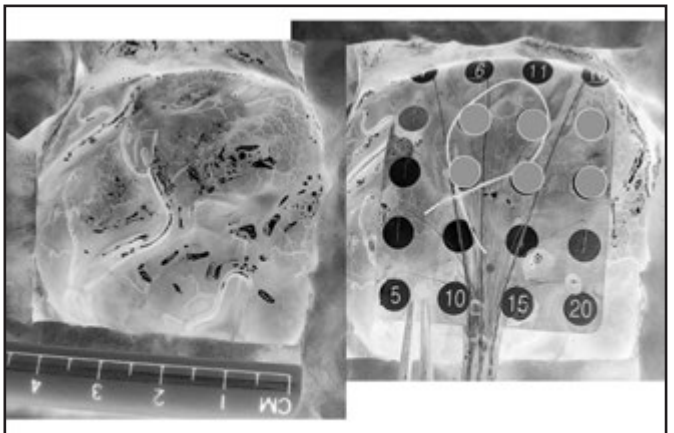


Caso: Lesión frontal basal motora izq.

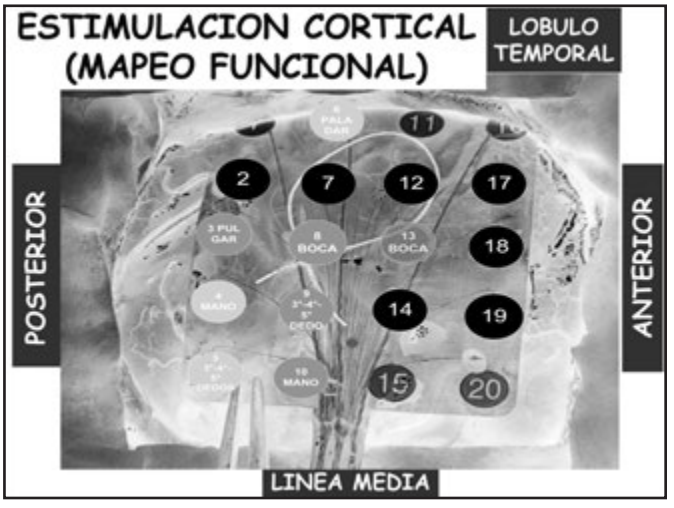


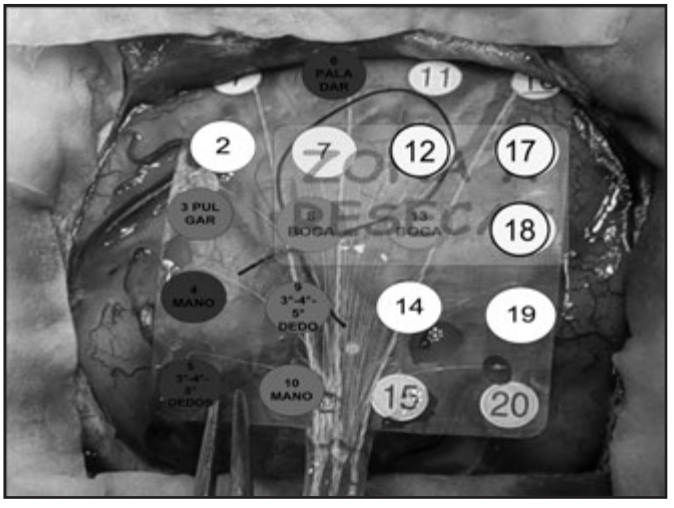
Caso: Lesión frontal basal motora izq.

ACTIVIDAD INTERICTAL



ACTIVIDAD ICTAL


ESTIMULACION CORTICAL
(MAPEO FUNCIONAL)
LOBULO TEMPORAL
POSTERIOR
ANTERIOR
LINEA MEDIA
2
7
12
17
18
14
19
15
20
11


2
7
12
17
18
14
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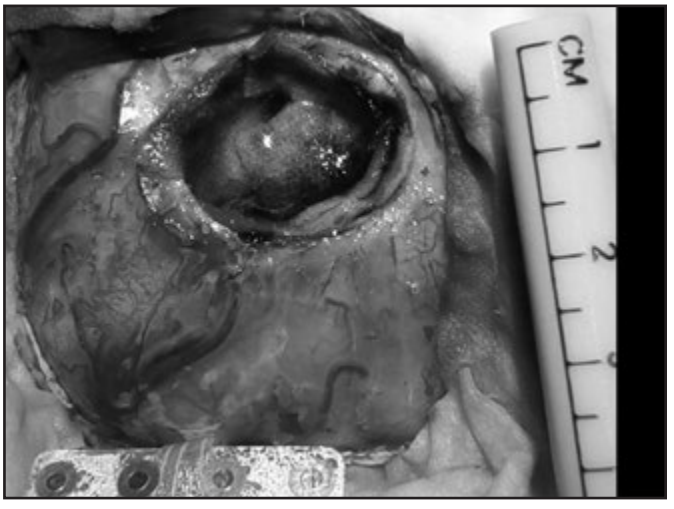
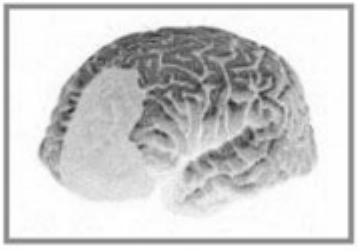
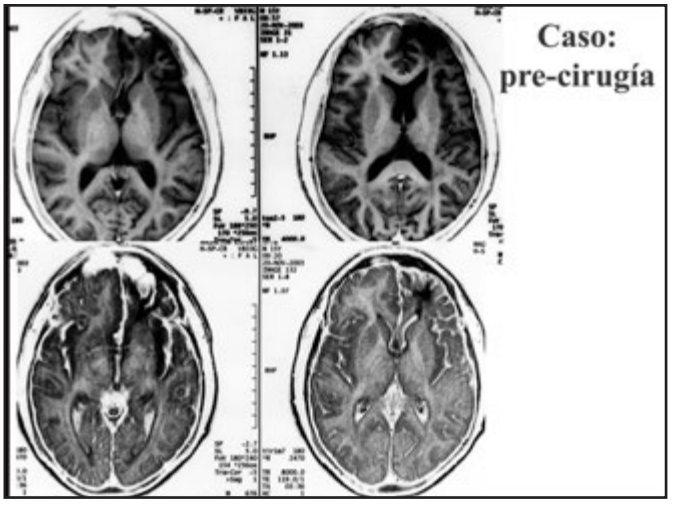
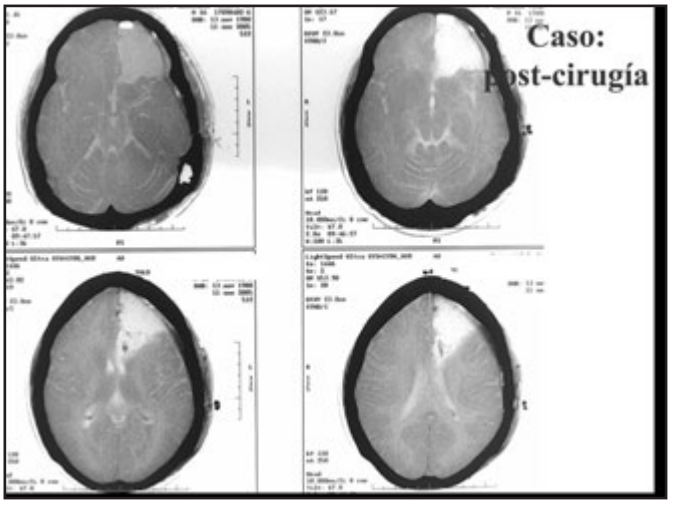
20
11


CM
1
2

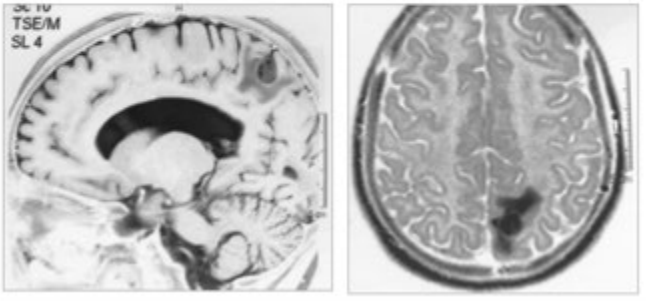
CRISIS FRONTO POLARES



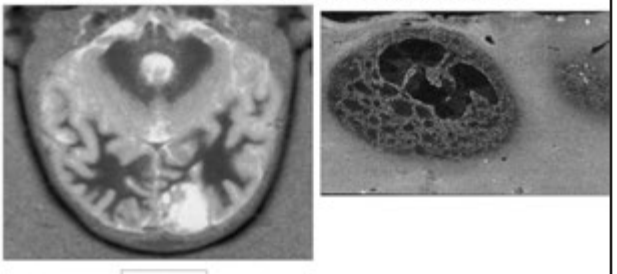




CRISIS PARIETALES



CRISIS OCCIPITALES



DNT

LESIONES Y EPILEPSIA

LA LESION (TUMOR)

- [illegible]
- [illegible]
- Histología

LA EPILEPSIA (ZONA ICTAL)

- No invasivo
  - EEG Scalp
- Invasivo
  - ECoG

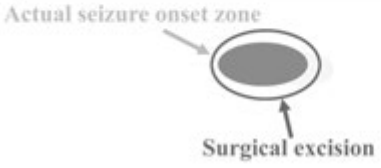
Otros: SPECT, MEG, RMs.

CEREBRO FUNCIONAL (ELOCUENTE)

- RM funcional
- PET
- Potenciales evocados
- Estimulación
  - Peri o intra operatoria

Practical problems when defining the epileptogenic zone (1)

- **Electroencephalography can only measure the actual seizure onset zone → "the epileptogenic zone " which includes the potential seizure onset zone can not be measured directly**



LESIONES Y EPILEPSIA

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- RM
- TAC
- Histología

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CEREBRO FUNCIONAL (ELOCUENTE)

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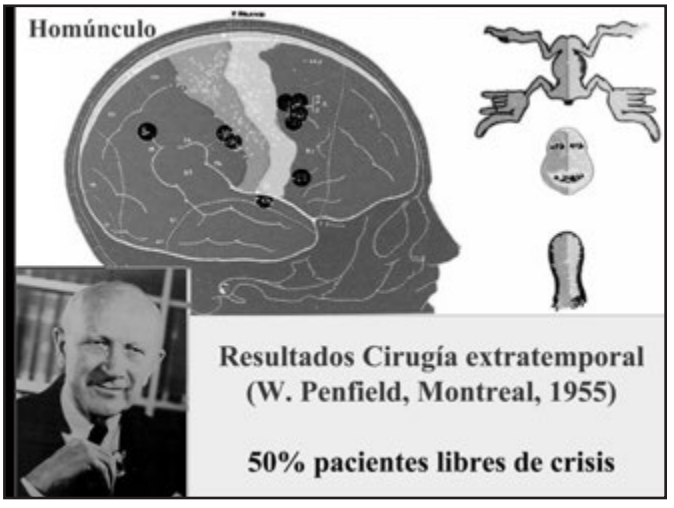
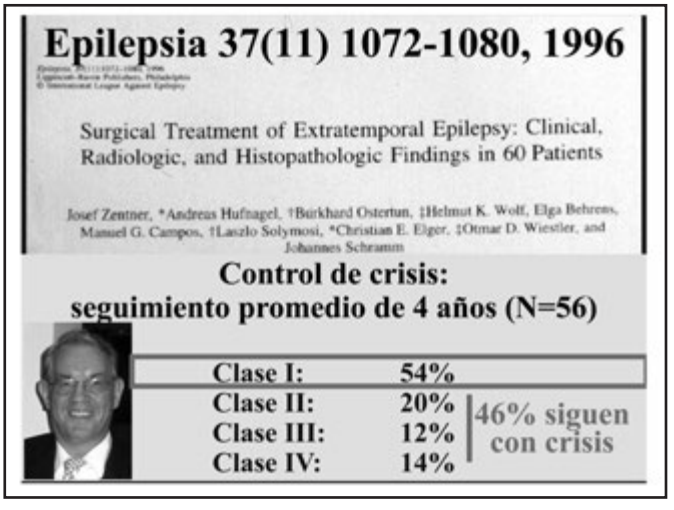
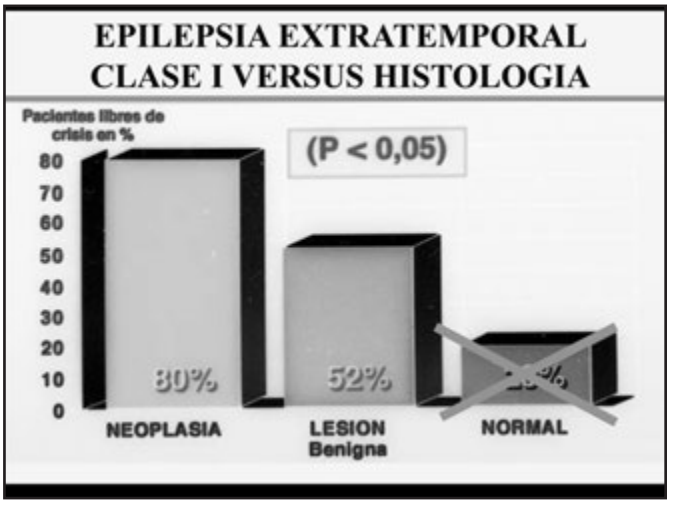
  - Peri o intra operatoria

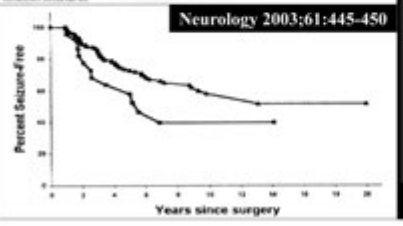
RESULTADOS


Homúnculo
Resultados Cirugía extratemporal
(W. Penfield, Montreal, 1955)
50% pacientes libres de crisis


Epilepsia 37(11) 1072-1080, 1996
Surgical Treatment of Extratemporal Epilepsy: Clinical, Radiologic, and Histopathologic Findings in 60 Patients
Josef Zentner, *Andreas Hufnagel, †Burkhard Ostertun, ‡Helmut K. Wolf, Elga Behrens, Manuel G. Campos, †Laszlo Solymosi, *Christian E. Elger, ‡Otmar D. Wiestler, and Johannes Schramm
Control de crisis:
seguimiento promedio de 4 años (N=56)
Clase I: 54%
Clase II: 20%
Clase III: 12%
Clase IV: 14%
46% siguen con crisis


EPILEPSIA EXTRATEMPORAL
CLASE I VERSUS HISTOLOGIA
Pacientes libres de crisis en %
(P < 0,05)
80
70
60
50
40
30
20
10
0
80%
52%
NEOPLASIA
LESION Benigna
NORMAL

Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery

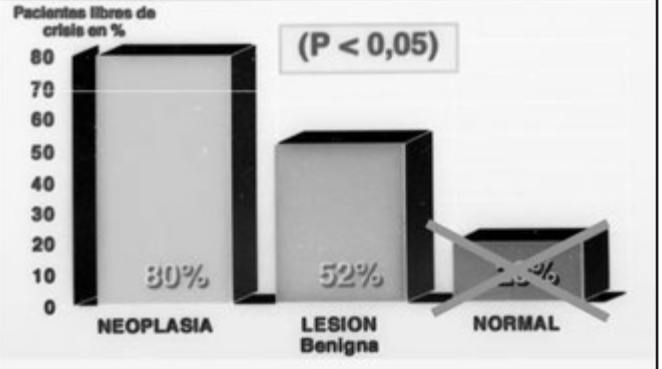


Neurology 2003;61:445-450

FACTORES PRONOSTICOS NEGATIVOS

- Más de 10 años de historia de crisis.
- Histología normal del tejido resecado (extirpado)

EPILEPSIA EXTRATEMPORAL CLASE I VERSUS HISTOLOGIA



Results by surgical topography, including all age groups

	Non lesional			Lesional		
Extratemporal (n of studies)	Total N patients	Seizure Free %	95% CI	Total N patients	Seizure Free %	95% CI
Overall (n=13)	156	34	27-41	350	66	61-70
Using MRI (n=9)	124	35	27-42	225	60	54-66
Using Histology (N=4)	35	32	18-47	125	74	67-82

Tellez et al. SURGICAL OUTCOMES IN LESIONAL AND NON-LESIONAL EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSYS. IN: Epilepsy Research (no published)

CONCLUSIONES

- **Es difícil localizar exactamente el área ictal.**
- **Se debe saber si existe compromiso de áreas elocuentes.**
- **Frecuentemente se deben usar electrodos sub-durales.**

CONCLUSIONES

- **El éxito post-cirugía es muy pobre en ausencia de lesión en la RM o histología!**
- **Por lo tanto recomiendo que en centros básicos de cirugía de la epilepsia, se comience por casos asociados a lesiones bien delimitadas.**

CONCLUSIONES

- **Un camino alternativo, en cirugía de la epilepsia, para países en vías de desarrollo, puede ser una cirugía lesional en pacientes con lesiones bien delimitadas (tumores, cavernomas) y ubicadas fuera de tejido elocuente.**

CONCLUSIONES

- **Una cirugía que tiene un resultado paliativo en un primer tiempo quirúrgico, puede tener una alternativa curativa en una segunda cirugía.**

MUCHAS GRACIAS

(Equipo de Centro de Epilepsias. Clínica Las Condes, Santiago de Chile)

Programa – 10.02.2010

Students presentations