6ª. ESCOLA LATINO-AMERICANA DE VERÃO EM EPILEPSIA
6ª. ESCUELA LATINO-AMERICANA DE VERANO EN EPILEPSIA
6th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 24 FEVEREIRO-3 MARÇO DE 2012
Centro de Convenções Santa Mônica

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SYMPTOMATIC EPILEPSY: A CRITICAL UPDATING

A 6ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) é uma atividade da *International League Against Epilepsy* (ILAE) e da Academia Latino Americana de Epilepsia (ALADE) com o apoio da Liga Brasileira de Epilepsia (LBE).

Com início em 2002, as "Escolas de verão em epilepsia", organizadas pela *International League Against Epilepsy* (ILAE) têm se tornado uma referência como experiência didática. Como professores e alunos permanecem em contato bastante próximo por quase duas semanas consecutivas, esse tipo de Escola tem facilitado a integração entre pesquisadores e alunos permitindo uma melhor compreensão das novas descobertas para o beneficio das pessoas com epilepsia. A sexta edição "Escola Latino-Americana de Verão em Epilepsia (LASSE)" realizada em Guarulhos entre 24 de fevereiro e 03 de março de 2012 aborda um dos temas mais relevantes em epileptologia: as epilepsias focais sintomáticas.

Agradecendo aos professores e tutores que de forma tão generosa abandonam seus afazeres e nos oferecem seu tempo damos boas-vindas aos alunos da LASSE-VI, razão maior do nosso trabalho.

A Comissão Organizadora

6TH. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY (LASSE VI)
"SYMPTOMATIC EPILEPSY: A critical updating"

PROGRAM

24 Feb 2012

25 Feb 2012

26 Feb 2012

27 Feb 2012

28 Feb 2012

29 Feb 2012

01 March 2012

02 March 2012

03 March 2012

Peter Wolf (DK)

THE NEW ILAE PROPOSAL FOR CLASSIFICATION OF SEIZURES AND SYNDROMES

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The new ILAE proposal for classification of seizures and syndromes
Peter Wolf (Denmark)

LASSE VI, Guarulhos
February 24 – March 3, 2012

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History of ILAE classifications (in EPILEPSIA)

- 1964 First draft of a seizure classification, 5:297-306
- 1970 International Classification of Epileptic Seizures, 11: 102-113
- 1970 First draft of a syndrome classification, 11:114-119
- 1981 Revision of I.C. of Seizures, 22:489-501
- 1985 Proposal for syndrome classification, 26: 268-278
- 1989 Rev. Class.Epilepsies a. Ep. Syndromes, 30:389-399
- 2001 "A proposed diagnostic scheme", 42:796-803
- 2006 Report of the ILAE Class.Core Group, 47:1558-68
- 2010 Berg: Report of the Comm Classif Terminol 51:676

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Reference

- Berg A et al: Revised terminology and concepts for organization of seizures and epilepsies: report of the Commission on Classification and Terminology.

  (Epilepsia 2010; 51(4): 676-685)

- Recommendation: read also the discussions in
- *Epilepsia 2010;51 and 2011;52*

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Classifications

Classifications are about classes

What classes of epileptic seizures and syndromes do you know?

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The 4 – field system of the International Classification of epilepsies and epileptic syndromes (1989)

Localisation-related idiopathic	Generalised idiopathic
Localisation-related symptomatic	Generalised symptomatic

The loose ends:
Cryptogenic
Undetermined a) + b)
Special syndromes

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Nosological concepts behind the dichotomies: 1) idiopathic vs. symptomatic

- pathos (**πυθος**) means disease
- idios (**ιδιος**) means self, proper, own
- idiopathic disease: a disease proper, with its own etiology and pathogenesis
- Oxford dictionary: "Idiopathy: Disease not preceded or occasioned by another."
- The term is used in all fields of medicine, not just in epilepsy
- The above definition was incorporated in the ILAE Classification of Epileptic Syndromes and Epilepsies of 1989

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Idiopathic and symptomatic epilepsy: history

- Epilepsy has its origin in the brain and is a hereditary disease (Hippocrates ca. 400 B.C.)
- Galen (129 – ca. 200 A.D.): all seizures due to affections of the brain which can be
  - primary or direct: epilepsy the presentation of an "idiopathic" or "protopathic" (**πρωτος** = first, primary) brain disease
  - indirect from another part of the organism: "sympathetic" (= concomitant) involvement of the brain

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William AldrenTurner (1907): "Epilepsy – A Study of the Idiopathic Disease"

The term idiopathic seemed not to require a definition.
"The dominant predisposing cause of epilepsy is ancestral epilepsy."

Discussion of the pathophysiology of idiopathic epilepsy:
Ictogenesis vascular? Autointoxication?

New proposal: replace "idiopathic" by "genetic"
What do you think of that?

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Nosological concepts behind the dichotomies: 1) idiopathic vs. symptomatic

- The distinction of idiopathic (protopathic, primary, genuine, essential, proper) epilepsy as a disorder with a genetic background ,
- and symptomatic (secondary) epilepsy with many possible etiologies affecting the brain in various ways:
- has been around, with many adjustments to developing knowledge, for 2 millennia.

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Nosological concepts behind the dichotomies: 2) focal vs. generalized

- For hundreds of years epilepsy was synonymous with generalized tonic-clonic seizures
- Other seizure types start to be mentioned occasionally in the 18th century but become mostly described during the 19th century
- Beyond mere description, J.H.Jackson (1835-1911) starts to analyse seizure semiology

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Focal seizures

At Queen Square, London, Jackson together with the neurosurgeon Victor Horsley (1857-1916) identified anatomical sites of epileptogenic lesions by semiological analysis, and in 1886 operated upon this.

Horsley coined the term "focal" for this kind of seizures.

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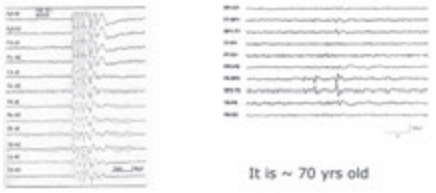
The dichotomy focal ./. generalized is based upon the EEG



It is ~ 70 yrs old

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Focal seizures and anatomical clues

- The 1981 ICES abstained from including anatomical informations because the Commission decided that these were well-established only in few instances
- Later commissions including the 2005-2009 Commission also did not do this
- The Commission report of 2006 addressed the issue of anatomy in a different way: different types of generation and propagation of focal seizures in anatomical sites of different structure
- Not followed up in 2010 report

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New developments: focal ictogenesis

- Traditional view: there is an epileptic focus, i.e. a small aggregate of abnormally functioning neurons that start to produce spikes which spread from there.
- Usually there is also a local lesion, the more likely to be found the better your imaging outfit
- More recent view: in focal lesional epilepsies seizures originate in consequence of an interplay of ictogenic tissues in or adjacent to the lesion, with normal tissue more or less close by.
- There is excess of excitation in the shape of epileptic discharge, and there is inhibition (which also may be in excess) that contributes to the synchronisation which is a central feature of ictogenesis.

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Focal ictogenesis: investigation methods

- SPECT (interictal vs ictal)
- Intracranial EEG recordings during preoperative monitoring
- EEG combined with MEG
- Connectivity study by graph analysis of ECoG
- fMRI
  - combined with EEG source analysis
  - sequential analysis
  - Diffusion tensor imaging / tractography

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Focal ictogenesis in idiopathic LREs

- There is no lesion or constant epileptic focus
- Seizures can be generated in alternate sides
- Very little investigated
- Primary Reading Epilepsy: fMRI study of orofacial reflex myocloni (ORM) triggered by reading

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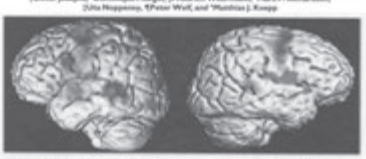
Primary Reading Epilepsy: the findings

FULL-LENGTH ORIGINAL RESEARCH

Imaging seizure activity: A combined EEG/EMG-fMRI study in reading epilepsy



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 functions." (Salek-Haddadi et al. Epilepsia 2009; 50:256-264)

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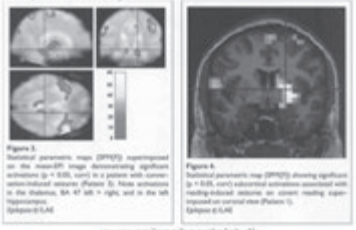
Thalamus involved in JME case with ORM



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Commission Report 2010

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"Focal ep. sz. are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal sz may originate in subcortical structures. For each seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere. In some cases, however, there is more than one network, and more than one seizure type, but each individual sz type has a consistent site of onset."

This applies only to symptomatic (=lesional) focal epilepsies

No attention paid to focal ictogenesis in idiopathic localization-related epilepsies

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The concept of generalized epilepsy

- "Generalized seizures are commonly thought to involve the entire brain homogeneously" (*McNally KA, Blumenfeld H Epilepsy & Behavior 2004; 5:3-12*)
  - How correct is this (EEG – based) common view?

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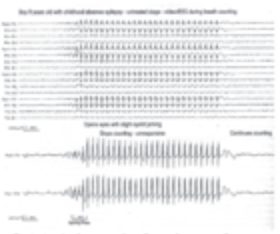
Generalised SW discharges typically are symmetric, synchronous and widespread -

but typically also have a frontal accentuation, especially at onset



Prototypical example of an absence, from Loiseau et al. *Childhood Absence Epilepsy*. In: Roger et al, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2002

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TV-induced seizures: photoparoxysmal EEG response

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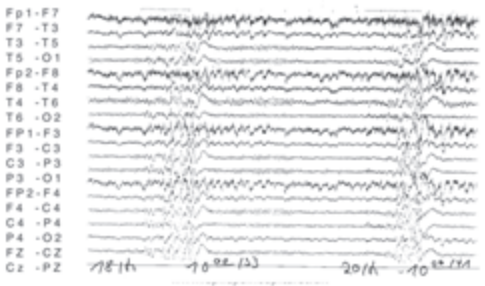

"pseudofocal" discharge

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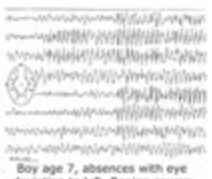
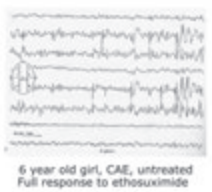


Boy age 7, absences with eye deviation to left. Benign course.



6 year old girl, CAE, untreated Full response to ethosuximide

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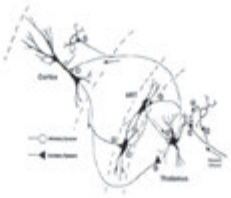
Thalamo-cortical hypothesis of generalised ictogenesis (Gloor 1969)



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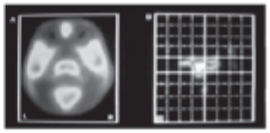
Thalamic changes in IGE:$H_2{}^{15}O$-PET

- Absences: global ~15% rCBF increase
  Thalamus: additional +4 - 8%



Prevett et al., Neurology 1995; 45(7):1396-402

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Generalized ictogenesis: further studies: 1) what is involved?

- EEG source analysis
- MEG (combined with EEG or not)
- Quantitative MRI
  - Morphometry / EEG source analysis: Campinas
- MR spectroscopy
- PET
  - FDG
  - FMZ
  - Fallyprid (dopamine ligand)
- fMRI (EEG – triggered)

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"Frontal" changes in JME: ^{11}C-FMZ PET

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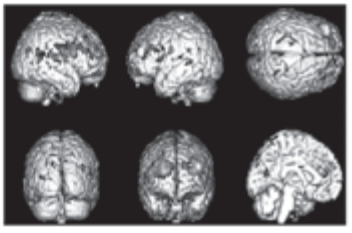
JME:
Global ⇑ of FMZ binding ($GABA_A$ receptors), especially in dorso-lateral pre-frontal cortex -

but also PO



Koepp MJ & Duncan JS. PET in IGE: Imaging beyond structure. In: Juvenile myoclonic epilepsy: The Janz syndrome. Schmitz B, Sander T (Eds). Wrightson, London, 2000: 91-99.

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Functional diagnostics: local findings in IGE

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	thalamus	frontal	parieto-occipital
PET	⇧ rCBF	⇧ FMZ dorso-lat. prefrontal	⇧ FMZ TPO post cingulum
EEG-fMRI (BOLD)	⇧ > ⇩	⇩ > ⇧	⇩ > ⇧ (10/15) post cingulum
quantitative MRI	normal volumina	⇧ Gray matter (GM) density	occipital: ⇧ GM
^{1}H-MR spectroscopy	⇩ NAA	⇩ NAA, ⇧GLX ⇔GABA	Occipital: ⇧ GABA, GLX ⇧ in gray matter

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Generalized ictogenesis: further studies: 2) what's going on?

- Investigations of reflex seizures in IGE
  - Clinical analysis
  - Ictal EEG
  - Other functional studies
- fMRI
  - Spontaneous seizures
  - Reflex seizures
    - Photosensitivity
    - Others

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Absence seizures: Individual patterns revealed by EEG-fMRI

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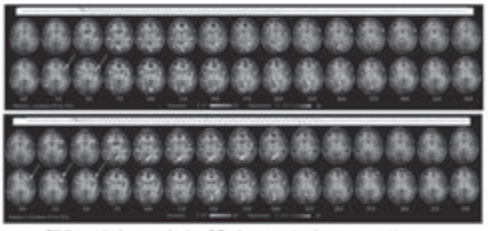

Sliding window analysis of 2 absences in the same patient

From: Moeller F et al. Epilepsia 2010

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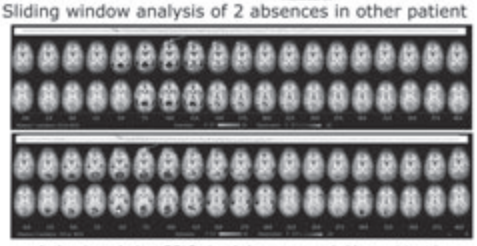
Sliding window analysis of 2 absences in other patient



Authors' conclusion: BOLD signal changes remarkably consistent in space and time in different absences of one patient but different from patient to patient despite similar EEG patterns and clinical semiology

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TV-induced seizures:
photoparoxysmal EEG response

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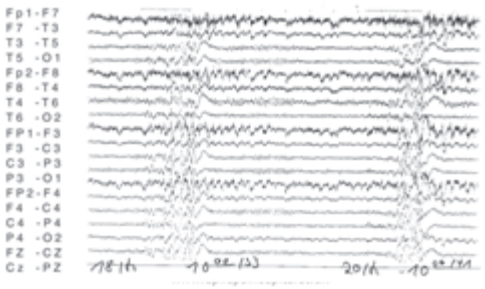

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Moeller et al (NeuroImage 2009) fMRI activation during spike and wave discharges evoked by photic stimulation

Comparison of BOLD signal 3 sec before photoparoxysmal response (PPR), i.e. at phase of synchronisation of cortical gamma oscillations preceding PPR

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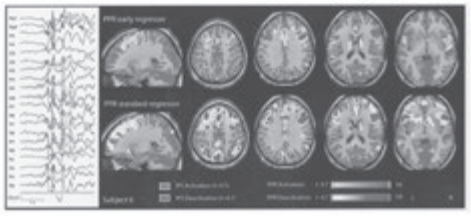
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2 years. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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Authors' conclusion

- "In contrast to spontaneous GSW, these results suggest that PPR (photoparoxysmal response) is a cortical phenomenon with an involvement of the parietal and frontal cortices."

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Thalamus, FS + absence: fMRI

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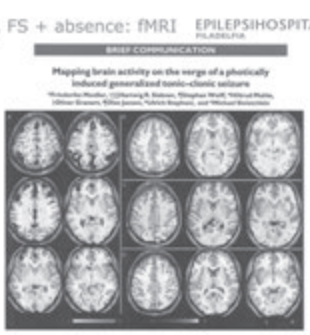
BRIEF COMMUNICATION

Mapping brain activity on the verge of a photically induced generalized tonic–clonic seizure

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Other reflex epileptic traits in IGE: - orofacial reflex myocloni (ORM)

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- Phenotypically identical with ORM in Primary Reading Epilepsy (PRE)
- 25 – 30% of JME patients
- Pathophysiology: interaction of complex functional anatomical network subserving formal processes of (written) language with short reflex loop = proprioception from speech musculature ⇒ myocloni in speech musculature
- No direct functional studies but probably largely identical with PRE

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Praxis induction

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- Pecipitation of seizures by cognition-guided complex motor tasks
- Most typical: complex visuo-motor coordination
- Matsuoka et al (2000): closely related to IGE. Found in 50% of JME patients in Japan
- 25 – 35% of JME patients in Germany (Mayer et al 2006) and Brasil (Sao Paolo group: Yacubian et al)
- Pathophysiology: interaction of complex functional anatomical network subserving visuomotor coordination with short reflex loop (proprioception ⇒ myocloni) in active musculature
- First functional studies available

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Vollmar et al. Motor system hyperconnectivity in JME: a cognitive fMRI study. Brain 2011; 134:1710-1719

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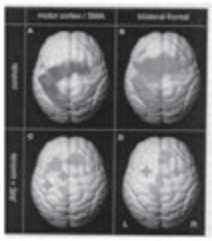

Study: fMRI with an executive frontal lobe paradigm

Findings:

A+B: motor connectivity and working memory network in healthy controls

C+D: inreased connectivity in JME patients

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Reflex epileptic traits in IGE and their significance

- Photosensitivity (40-50%)
  - occipital ⇒ motor cortex
- Eye closure sensitivity (4-5%)
  - sensorimotor reflex loop (role of occipital cortex?)
- Praxis induction (30%; Japan: 50%)
  - complex visuomotor coordination as "tuner" ⇒
  - sensorimotor reflex loop
- Orofacial reflex myoclonias (25-30%)
  - complex visuo-audio-motor "tuner" ⇒
  - sensorimotor reflex loop

Conclusion: All reflex epileptic traits suggest interactions of functional anatomic networks or subsystems of the CNS

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Moeller et al Absence seizures: individual patterns revealed by EEG-fMRI. *Epilepsia* 2010

- 17 absences from 9 patients studied
  - Identical findings in all absences of one individual
- Thalamic activation: 16 abs / 8 pts
- Default mode areas deactivation: 15 abs / 8 pts
- Caudate nucleus deactivation: 10 abs / 5 pts
- Cortical activation: 10 abs / 6 pts
  - Frontal: 5 pts
  - Parietal: 1 pt.
  - (no cortical activation: 3 pts)

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Conclusion on IGE: areas involved in corticothalamic and intracortical networks

- Thalamus (in particular nc. reticularis)
- Frontal cortex (frontopolar; ventromedial; motor +?)
- Parietal cortex
- Occipital cortex (photosensitive patients +?)
- Colliculi superiores (photosensitive patients)
- Lateral geniculate body (photosensitive patients)
- Precuneus
- Default mode areas

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Conclusion on concepts and terms

- The concepts behind the terms "focal" and, in particular, "generalized" have fundamentally changed, both regarding generation and propagation of seizures
- The term "generalized" has become meaningless
- Idiopathic LREs and IGEs have common characteristics of widespread bilateral networks essentially using pre-existent functional anatomical circuits. These networks are much studied at present and getting identified.
- These are different from symptomatic focal epilepsies where pathological circuits emerge around an epileptogenic lesion (but pre-existing networks are used for seizure propagation).

www.epilepsihospitalet.dk

EPILEPSIHOSPITALET PILADELFIA

New concepts need new terms

- In the 1st Monreale Workshop of 2008 it was proposed to use the term "system epilepsies" for ILREs and IGEs because
- ILREs are based upon the epileptic susceptibility of a given system on either side of the brain, and there is no evidence of any structural abnormality,
- in IGEs the involvement of central nervous functional subsystems have been demonstrated,
- and it is common in neurology to distinguish local pathologies from system disorders.

(Capovilla et al, Epilepsia 2009; 50: 1645-1656)

Commission Report 2010

EPILEPSIHOSPITALET PILADELFIA

"Generalized ep. sz. are conceptualized as originating at some point within, and rapidly engaging, bilateral distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not ~~necessarily~~ include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric."

Commission Report 2010

EPILEPSIHOSPITALET PILADELFIA

"Generalized ep. sz. are conceptualized as originating at some point within, and rapidly engaging, bilateral distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not ~~necessarily~~ include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric."

No change of terms proposed
Falls short of the progress made

EPILEPSIHOSPITALET PILADELFIA

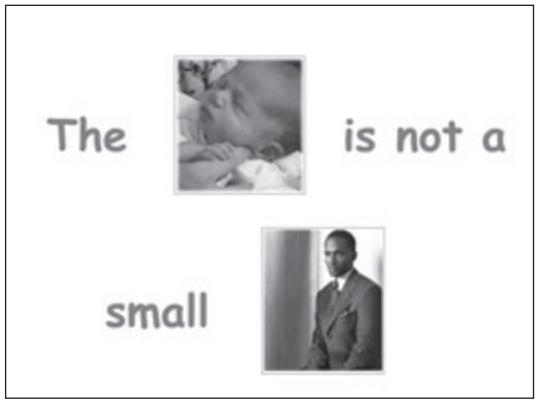
Commission Report 2010

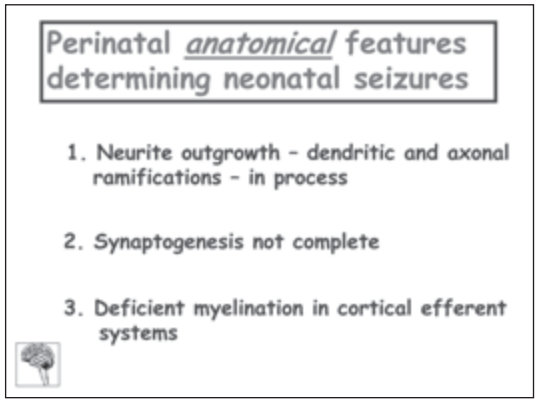
- Proposed changes of terms:
  - Idiopathic ⇒ genetic
  - Symptomatic ⇒ structural/metabolic
  - Cryptogenic ⇒ unknown cause
- Concepts unchanged

- Conclusion: The commission report proposes
  - change of terms where there is no change of concept
  - no change of terms where there is change of concept.
  - It takes a significant but small step towards a revision of our classification

Maria Chiara Stefanini (Italy)

NEONATAL SEIZURES





Perinatal *physiological* features determining neonatal seizures

1. Immature hippocampal and cortical neurons more susceptible to seizure activity than mature neurons
2. Impaired propagation of electrical seizures, and synchronous discharges recorded from surface EEG may not correlate with behavioral seizure phenomena

Clinical definition of seizures

All the paroxysmal alterations in neurological function,i.e.behavioral, motor,or autonomic function.

Neonatal seizures: definition

1

Some clinically identified motor and behavioural phenomena characterized as seizures do not have a simultaneous EEG seizure correlate.

↓

Overestimation of the number of seizures

Neonatal seizures: definition

2

Many EEG seizures are not accompanied by clinically observable alterations in motor and behavioral functions.

↓

Underestimation of the number of seizures

Subtle seizures

- Ocular phenomena
  - Tonic horizontal deviation of eyes with or without jerking of eyes
  - Sustained eye opening with ocular fixation

- Oral-buccal-lingual movements
  - Chewing
  - Others (swallowing, tongue movements, cry, grimaces, etc.)

Subtle seizures: major manifestations

- Extremity movements
  - Pedalling, stepping
  - "Boxing", "hooking"

- Autonomic phenomena
  - Tachycardia
  - Vasomotor phenomena

- Apnoeic spells
  - Usually with other subtle phenomena

Common etiologies of neonatal seizures

1. Hypoxic-ischemic encephalopathy (pre and postnatal onset)
2. Infection: meningitis/encephalitis (congenital and postnatal), sepsis without meningitis
3. Vascular disease: stroke, venous trombosis
4. Intracranial hemorrhage, intraparenchymal and subarachnoid

Common etiologies of neonatal seizures

5. Metabolic encephalopathy (transient metabolic disturbance and inborn error of metabolism)
6. Cerebral dysgenesis, migration disorders, and major malformations
7. Trauma (delivery-related and non accidental)
8. Idiopathic
9. Epileptic syndromes, including familial epilepsies

Idiopathic neonatal seizures	Symptomatic neonatal seizures	Nonepilepstic neonatal seizures
Benign Familial Neonatal Seizures (BFNS)	Early Infantile Epileptic Encephalopathy (EIEE-Otahara)	Benign Neonatal Sleep Myoclonus
Benign Idiopathic Neonatal Seizures (BINS)	Early Myoclonic Encephalopathy (EME)	Hyperekplexia
	Migrating Partial Seizures in Infancy (MPSI)	

Idiopathic neonatal seizures as chronic epilepsy

1. Benign Familial Neonatal Seizures [BFNS]
2. Benign Idiopathic (non-familial) Neonatal Seizures [BINS] (5th day fits)

Symptomatic neonatal seizures as chronic epilepsy

1. Early Infantile Epileptic Encephalopathy [EIEE] with suppression bursts (Otahara syndrome)
2. Early Myoclonic Encephalopathy [EME]
3. Migrating partial seizures in infancy (MPSI)

(Yamamoto H. et Al., 2011)

Nonepileptic neonatal seizures

1. Benign Neonatal Sleep Myoclonus
2. Hyperekplexia

(Plouin P. et Al., 2002)

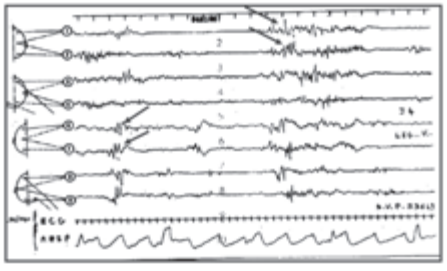
Epileptic Idiopathic Syndromes of Neonatal Seizures: BFNS

- Onset in the 2nd-3rd postnatal day
- 10-20 seizures/day
- EEG: a brief initial period of flat EEG (apnoea + tonic actvity), followed by a bilateral discharge of spikes and slow waves (clonic activity)
- Self limited and the seizures end in 1-6 months
- Only 10% of infants exhibit subsequent seizures, requiring treatment
- Mutation of two genes KCNQ2 and KCNQ3 encoding voltage-gated potassium channel subunits (60-70%)

Epileptic Idiopathic Syndromes of Neonatal Seizures: BINS (5th day fits)

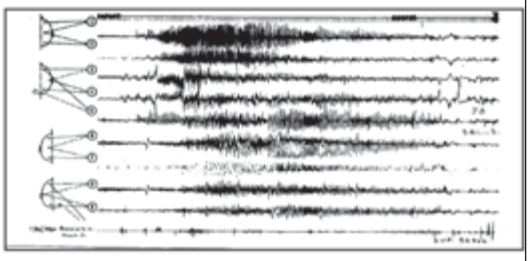
- Onset between the 4th and the 6th postnatal day
- Seizures are multifocal clonic, usually with apnoea
- Seizures are very frequent, but lasts <24 h
- Interictal EEG: "théta pointu alternant pattern" – burst of theta rhythms mostly in rolandic areas.
- Usually all seizures cease in 15 days

BINS



Interictal EEG: "théta pointu alternant pattern" – burst of theta rhythms mostly in rolandic areas.

BINS



Ictal EEG: recorded seizure starting from right rolandic areas. Left hand clonic jerks

Early Infantile Epileptic Encephalopathy (EIEE) – Otahara Syndrome

- Onset within the first 10 days of life
- Seizures are very frequent (100-300/day): mostly tonic spasms, partial motor seizures, hemiconvulsions
- Early development of severe neurological abnormalities
- EEG: suppression bursts in both awake and sleep, which evolves to hypsarrhythmia (3-4 months)
- Etiology: structural abnormalities of the brain
- Evolution: → West S. → Lennox Gastaut S.

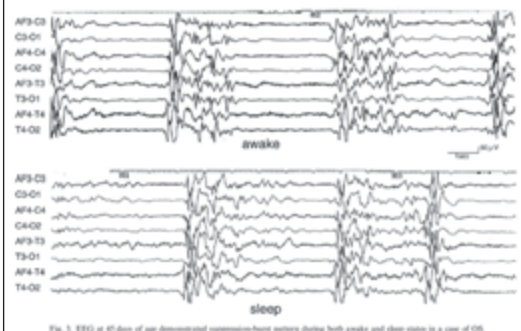


Fig. 3. EEG at 45 days of age demonstrated suppression-burst pattern during both awake and sleep states in a case of OS.

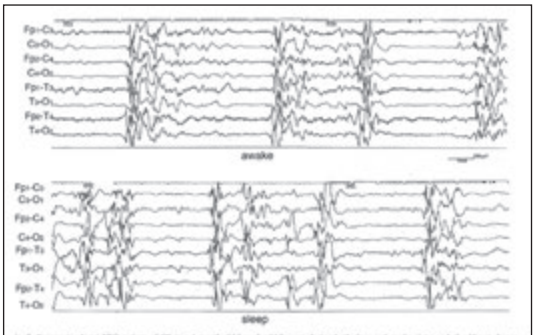


Fig. 7. Suppression-burst EEG pattern of OS in a 1-month-old boy should be seen during both sleep and awake states and should not change according to the sleep-wake cycle.

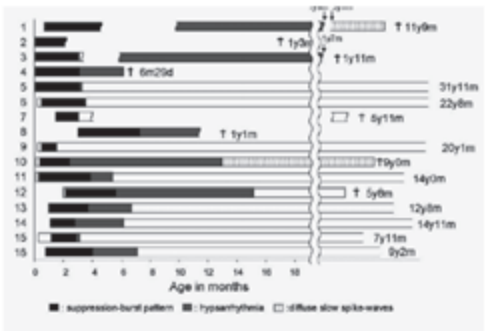
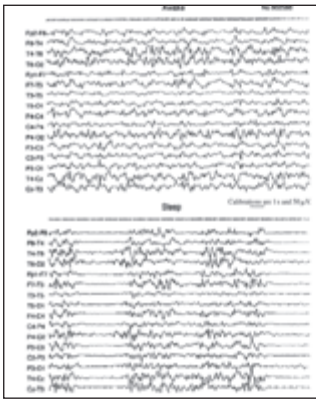


Fig. 3. Changing pattern of suppression-burst in patients with Ohtahara syndrome.

(Ohtahara et al., 2006)

Early Myoclonic Encephalopathy (EME)

- Onset within the first 3 months of life
- Seizures: mostly fragmentyary myoclonias, erratic partial seizures, massive myoclonias.
- Early development of severe neurological abnormalities
- EEG: Suppression Bursts more evident during sleep, which evolves to hypsarrhythmia (3-4 months)
- Etiology: unknown, frequent familial cases
- Evolution: → long lasting SB



Interictal EEG of a 6-months-old girl with EME: hypsarrhythmic pattern during wakefulness

Interictal EEG of a 6-months-old girl with EME: Suppression Bursts pattern during sleep

(Ohtahara et al., 2006)

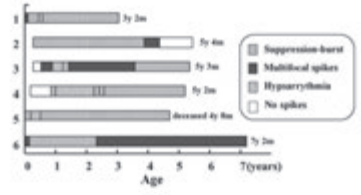


Fig. 5. Follow-up of the EEG in patients with early myoclonic encephalopathy.

(Ohtahara et al., 2006)

Nonepileptic Idiopathic Syndromes: Benign Neonatal Sleep Myoclonus

- Onset in the first week of life
- Myoclonic jerks, usually bilateral, synchronous, and repetitive, involving upper and/or lower extremities
- Episodes occur exclusively during sleep
- EEG: normal
- Spontaneous resolution within 2 months

Nonepileptic Idiopathic Syndromes: Hyperekplexia (Startle Disease)

- It is characterized by two abnormal forms of response to unexpected visual, auditory or somesthetic stimuli:

1. Sustained tonic spasm sometimes mimicking a generalized tonic seizure
2. Exaggerated startle response

- Additional features: hypertonia, nocturnal myoclonus
- EEG: normal
- Episodes disappear spontaneously by the age of 2 years

Neonatal Status Epilepticus (se)

CONVENTIONAL DEFINITION OF SE:

Any continuous clinical seizure activity lasting longer than 30' or 2 or more seizures without interictal resumption of baseline mental status

DEFINITION OF SE IN NEWBORN:

- Any electrographic recording with seizure activity >50% of the length of the recording time

(Siverstein et al., 2007)

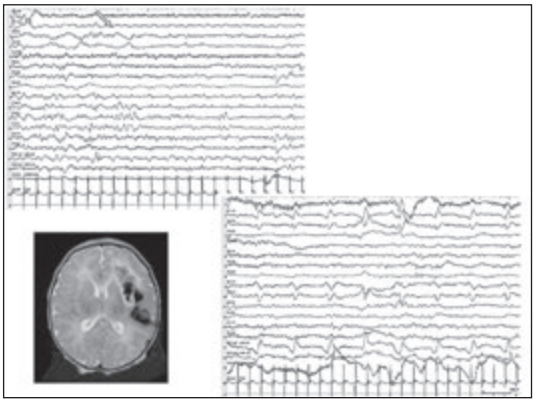
Neonatal Status Epilepticus (se)

CONVENTIONAL DEFINITION OF SE:

Any continuous clinical seizure activity lasting longer than 30' or 2 or more seizures without interictal resumption of baseline mental status

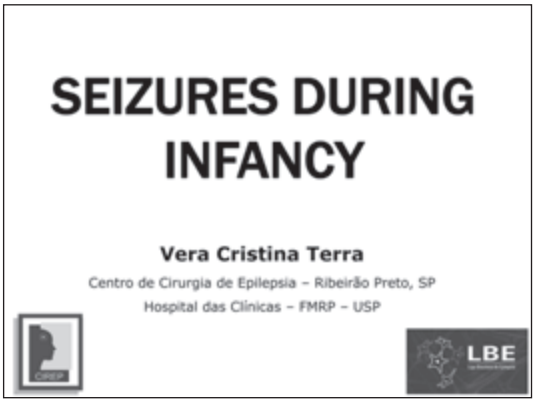
DEFINITION OF SE IN NEWBORN:

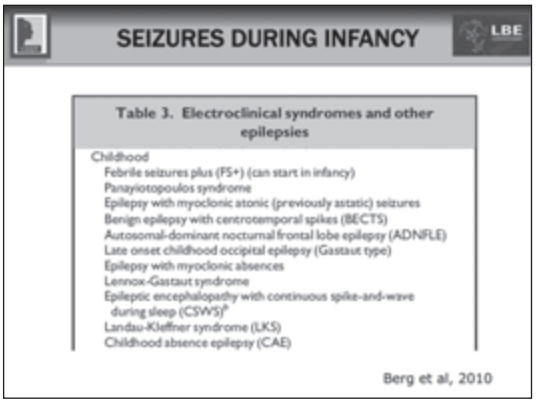
- Any electrographic recording with seizure activity >50% of the length of the recording time
- Recurrent and prolonged seizure activity

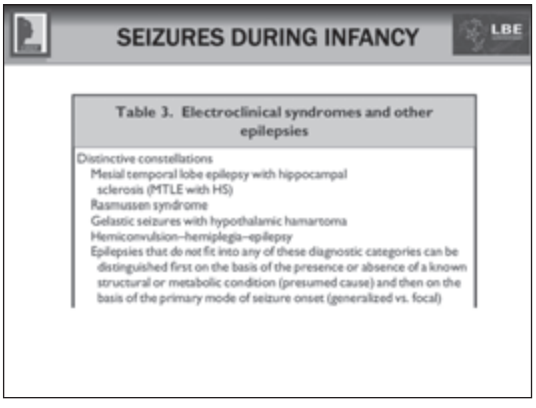


Vera Cristina Terra (Brazil)

SEIZURES DURING INFANCY

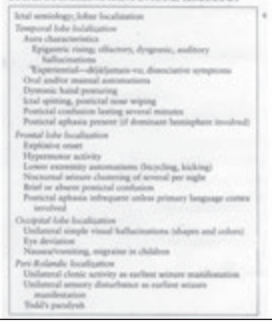






SEIZURES DURING INFANCY

SEMIOLOGIA


LOBAR LOCALIZING SIGNS IN ICTAL SEMIOLOGY

Ictal semiology; lobar localization

Temporal lobe localization
- Aura characteristics
  - Epigastric rising, olfactory, dysgeusic, auditory hallucinations
  - "Experiential—déjà/jamais-vu; dissociative symptoms
- Oral and/or manual automatisms
- Dystonic hand posturing
- Ictal spitting, postictal nose wiping
- Postictal confusion lasting several minutes
- Postictal aphasia present (if dominant hemisphere involved)

Frontal lobe localization
- Explosive onset
- Hypermotor activity
- Lower extremity automatisms (bicycling, kicking)
- Nocturnal seizure clustering of several per night
- Brief or absent postictal confusion
- Postictal aphasia infrequent unless primary language cortex involved

Occipital lobe localization
- Unilateral simple visual hallucinations (shapes and colors)
- Eye deviation
- Nausea/vomiting, migraine in children

Peri-Rolandic localization
- Unilateral clonic activity as earliest seizure manifestation
- Unilateral sensory disturbance as earliest seizure manifestation
- Todd's paralysis

SEIZURES DURING INFANCY

SEMIOLOGIA

Até 3-6 anos

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

SEIZURES DURING INFANCY

SEMIOLOGIA

Após os 7 anos

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

SEIZURES DURING INFANCY

EPILEPSIAS IDIOPÁTICAS

(GENÉTICAS)

SEIZURES DURING INFANCY

Epilepsia generalizada idiopática
Epidemiologia

TABLE 1. *Frequency of generalized idiopathic epilepsies in some cohorts studies*

Authors (yr)	Country	Population	Frequency (%)	IP	Comments
Gastaut (1975)	France	4591 (C/A)	28.4		"Primary GE"
Jacinto (1986)	Faroes islands	194	34.5	P: 2.18; 14.8	"Primary GE"
Loiseau (1981)	France	1004 (C/A)	16.3 vs. 35.8		University hospital versus private practice
Manford (1992)	England	567 (C/A)	6.8		
Avanzini (1996)	Italy	1027 (C/A)	17.4 vs. 3.1		Definite cases versus uncertain
King (1998)	Australia	300 (C/A)	22.3		Consecutive cases
Zarelli (1999)	Rochester	157 (C/A)	15.7	I: 3.7	4 yr inclusion
Jallon (2000)	France	1942 (C/A)	16 vs. 27.4		Single seizure versus index seizures
Senanayake (1995)	Sri Lanka	1250 (C/A)	17.2		
Murthy (1998)	South India	2531 (C/A)	6.4		
Osuntokun (1985)	Nigeria	945 (C/A)	20.4		

Jallon & Latour, 2005

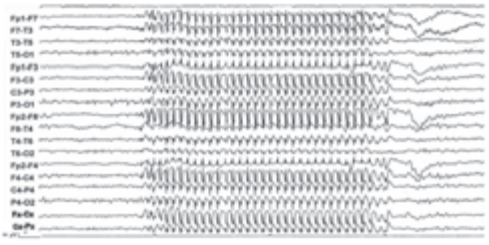
SEIZURES DURING INFANCY

Epilepsia ausência da infantil

- Início: 2-8 anos, pico 6-7 anos
- Crises de ausência muito freqüentes
- Sexo feminino
- Predisposição genética
- EEG: CEO regulares a 3 Hz
- Crises TCG na adolescência

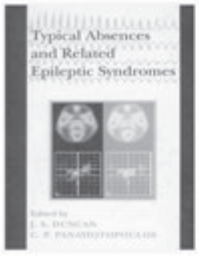
SEIZURES DURING INFANCY

Epilepsia ausência da infantil



SEIZURES DURING INFANCY

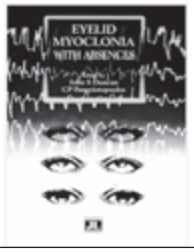
Panayiotopoulos et al., 1989



- Todas as epilepsias ausência são iguais?

SEIZURES DURING INFANCY

Epilepsia ausência com mioclonias palpebrais



Jeavons, 1977. *Dev. Med. Child Neurol.*, 19: 3-8.

SEIZURES DURING INFANCY

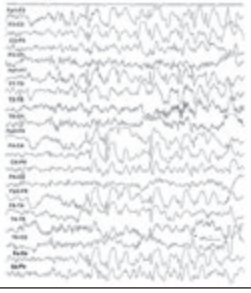
Epilepsia com ausências mioclônicas

Tassinari et al., 1969.

- Início: 2-9 anos
- Ausências com mioclonias maciças do segmento cefálico e membros superiores e contração tônica
- Refratariedade a drogas antiepilépticas
- EEG: ponta-onda a 3 Hz

SEIZURES DURING INFANCY

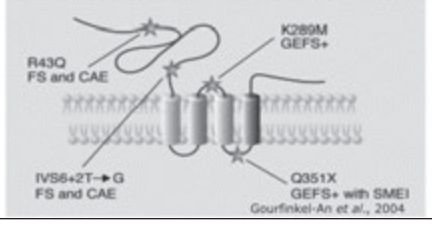
Ausência Atípica



SEIZURES DURING INFANCY

Epilepsias Generalizadas Genética

- Epilepsia generalizada com CF plus

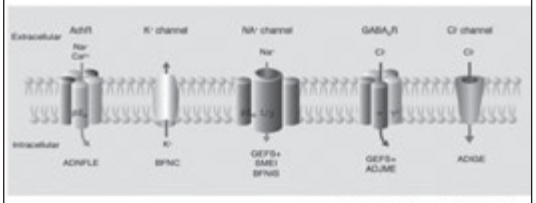


Gourfinkel-An *et al.*, 2004

SEIZURES DURING INFANCY

Epilepsias Generalizadas Genética

- Alterações descritas



Gourfinkel-An *et al*., 2004

SEIZURES DURING INFANCY

Ausências Genética

- Subunidade γ2 do receptor GABAA (GABRG2) (Wallace *et al*., 2001; Kanaura *et al*. 2002; Marini *et al*., 2003)
- Subunidade β1 do canal de sódio voltagem dependente (SCN1B) (Audenaert *et al*., 2003)
- Mutações dos canais de cálcio (CACNA1H) em pacientes da China (Chen *et al*., 2003) (não confirmados em pacientes europeus (Chioza *et al*., 2006))

SEIZURES DURING INFANCY

Tratamento

Duron *et al*., 2005

SEIZURES DURING INFANCY

EPILEPSIAS FOCAIS IDIOPÁTICAS

- EBI – forma rolândica.
- Ep. occipital de início precoce – tipo Panayiotopoulos.
- Ep. Occipital forma tardia – tipo Gastaut.
- Ep. Benigna Atípica

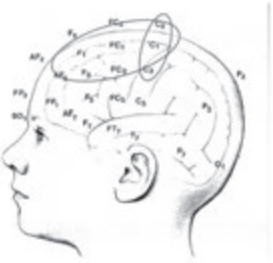
SEIZURES DURING INFANCY

EBI – FORMA ROLÂNDICA

- Afetam 22% das crianças com crises não febris.
- Crianças clinicamente normais / imagem normal.
- Evolução clínica favorável: considerar frequência de crises e aspectos cognitivos.

SEIZURES DURING INFANCY

EBI – FORMA ROLÂNDICA



SEIZURES DURING INFANCY

EBI – FORMA ROLÂNDICA

- Prognóstico – EBI com pontas centro-temporais:
  - 10-20% dos casos com crises frequêntes.
  - 1% evolui para síndromes mais graves.

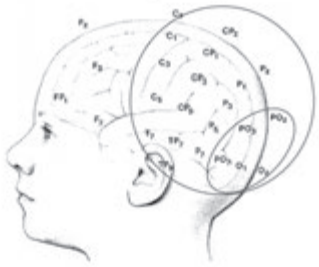
SEIZURES DURING INFANCY

EBI OCCIPITAL DE INÍCIO PRECOCE
(tipo Panayiotopoulos)

- Forma mais precoce (2-8 anos).
- Predomínio no sexo feminino.
- Crises raras, noturnas.
- Desvio tônico dos olhos, vômitos, generalização secundária.

SEIZURES DURING INFANCY

Síndrome de Panayiotopoulos.



SEIZURES DURING INFANCY

EBI OCCIPITAL DE INÍCIO PRECOCE
(tipo Panayiotopoulos)

- **Prognóstico**

  - **25% dos casos com crises frequêntes.**

  - **10% dos casos com crises por maior período de tempo.**

  - **Evolução atípica em < 3% dos casos.**

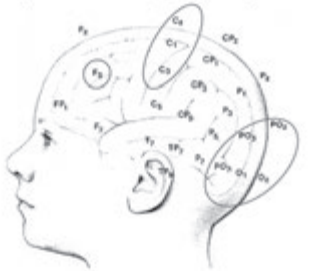
SEIZURES DURING INFANCY

EBI OCCIPITAL – INÍCIO TARDIO
(tipo Gastaut)

- **Crises com sintomas visuais, com ou sem generalização secundária.**
- **Crises com predomínio na vigília.**
- **Início das crises com pico entre 7 e 9 anos.**

SEIZURES DURING INFANCY

EBI com pontas occipitais tipo Gastaut.



SEIZURES DURING INFANCY

EBI OCCIPITAL – INÍCIO TARDIO
(tipo Gastaut)

- **Prognóstico:**
  - **40 - 50% dos casos mantém CPS e CTCG raras.**
  - **Evolução atípica rara.**
  - **Boa resposta terapêutica.**

SEIZURES DURING INFANCY

EBI ATÍPICA

- Início entre 2 e 6 anos.
- Vários tipos de crises: focais motoras, ausências atípicas, mioclonias, crises atônicas.
- Exame neurológico e cognitivo normal.
- EEG sono: POCS.
- EEG vigília: descargas multifocais e CPO.

SEIZURES DURING INFANCY

EBI ATÍPICA

- Resposta terapêutica ruim.
- Pode haver piora das crises com a CBZ.
- Boa resposta a IGIV e VGB.

SEIZURES DURING INFANCY

Table 6. Comparison of recommendations for the treatment of pediatric epilepsy.

Seizure type or epilepsy syndrome	U.S. pediatric expert consensus opinion[a]	European pediatric expert consensus opinion[b]	ILAE[c]	NICE[d]	SIGN[e]	French study[f]	FDA approved[g]
Partial-onset	CBZ, OXC	CBZ, OXC	A: CBZ, B: none C: CBZ, PB, PHT, TPM, VPA	PHT, VPA, CBZ, LTG, TPM, OXC, VGB, CLB	CBZ, VPA, LTG, OXC, TPM	OXC, CBZ, LTG (adult studies)	PB, PHT, CBZ, OXC, TPM
BECT	CBZ, OXC	VPA	A, B: none C: CBZ, VPA	Not specifically mentioned	CBZ, OXC, LTG, VPA	Not surveyed	None
Childhood absence epilepsy	ESM	VPA	A, B: none C: ESM, LTG, VPA	VPA, ESM, LTG	VPA, ESM, LTG	VPA, LTG	ESM, VPA
Juvenile myoclonic epilepsy (JME)	VPA, LTG	VPA	A, B, C: none	VPA, LTG, TPM	VPA, LTG	VPA, LTG	TPM, LTG, LEV
Lennox-Gastaut syndrome	VPA, TPM	VPA	Not reviewed	Not specifically mentioned	LTG, VPA, TPM	Not surveyed	FLB, TPM, LTG
Infantile spasms	VGB, ACTH	VGB	Not reviewed	Not specifically mentioned	VGB, corticosteroids	Not surveyed	None

Wheless et al, 2007

SEIZURES DURING INFANCY

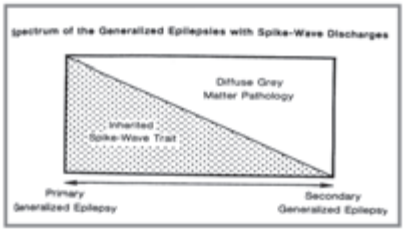
EPILEPSIAS

SINTOMÁTICAS

(ESTRUTURAL / METABÓLICA)

SEIZURES DURING INFANCY

Epilepsias generalizadas
"Continuum biológico"



Berkovic et al., 1987

SEIZURES DURING INFANCY

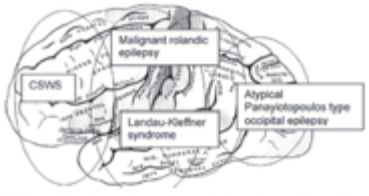


Figure 1 Epileptic encephalopathies or malignant epilepsies with electrical status epilepticus during sleep. Pathophysiology is quite the same, but symptoms are defined by the driver focus: prefrontal and frontal area in continuous spike-waves syndrome (CSWS), central region in malignant rolandic epilepsy, temporo-parietal location in Landau-Kleffner syndrome or more posterior in atypical Panayiotopoulos type occipital epilepsy.

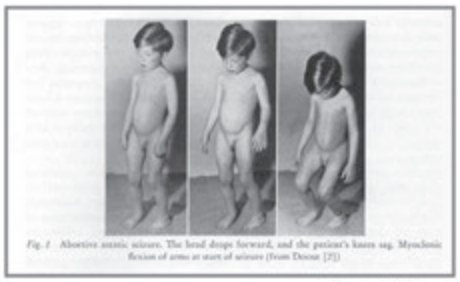
K. van Rijckevorsel, Seizure (2006) 15, 227—234

SEIZURES DURING INFANCY

Epilepsia com crises mioclônico-astáticas

- Doose, 1964: "*Centrencefalic myoclonic-astatic petit mal*".
- Início desde 7 meses de vida até 6 anos
- Crises mioclônicas seguidas por queda abrupta, várias vezes ao dia, ausências atípicas, TCG
- EEG interictal: ondas 4-7Hz e surtos de EO e PEO generalizada
- Evolução variável

SEIZURES DURING INFANCY



Doose, 1964

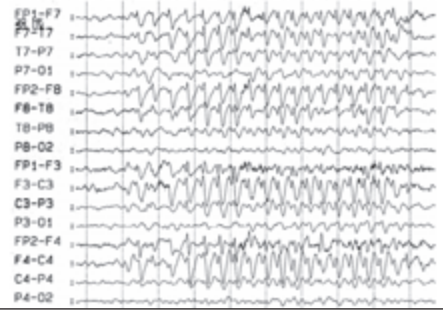
SEIZURES DURING INFANCY

Síndrome de Lennox-Gastaut

- Início 1-8 anos
- Retardo mental ou involução psíquica
- Crises tônicas, atônicas, ausências atípicas, mioclônicas, TCG, parciais
- EEG interictal: atividade de base lenta; espícula-onda lenta generalizada <3Hz, paroxismos focais, multifocais; sono ritmo rápido (10 Hz)
- EEG ictal: atividade rápida 10Hz, espícula-onda lenta generalizada

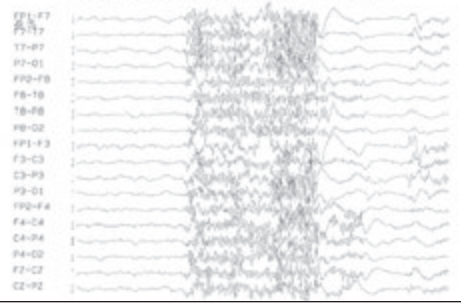
SEIZURES DURING INFANCY

Síndrome de Lennox-Gastaut



SEIZURES DURING INFANCY

Síndrome de Lennox-Gastaut



SEIZURES DURING INFANCY

Síndrome de Doose ou Epilepsia Mioclonico-Astática

Tipo de queda	Astática	Tônica
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

SEIZURES DURING INFANCY

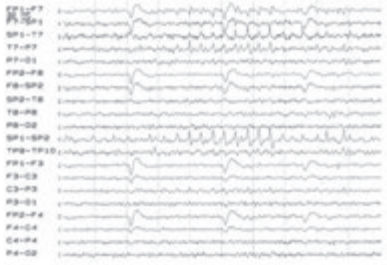
Epilepsias focais provavelmente ou indubitavelmente sintomáticas

Epilepsias límbicas

- **Epilepsia medial do lobo temporal por esclerose hipocampal.**
- **Epilepsia medial do lobo temporal definida por etiologias específicas.**

SEIZURES DURING INFANCY

Epilepsias temporal mesial – EH

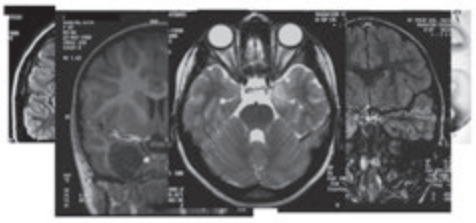


SEIZURES DURING INFANCY

Epilepsias temporal mesial – EH

SEIZURES DURING INFANCY

Epilepsias temporal mesial – EH



SEIZURES DURING INFANCY

Epilepsias focais provavelmente ou indubitavelmente sintomáticas

Epilepsias neocorticais

- Do lobo frontal
- Do lobo temporal
- Do lobo parietal
- Do lobo occipital
- Epilepsias focais com formas específicas de precipitação

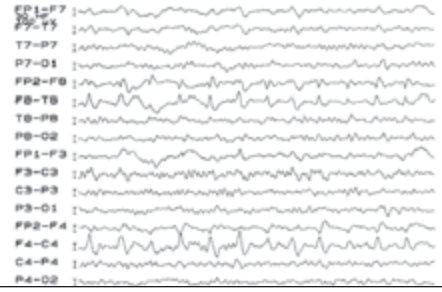
SEIZURES DURING INFANCY

Epilepsias do lobo frontal

- Área motora suplementar.
- Cíngulo.
- Fronto-polar.
- Órbito-frontal.
- Dorso-lateral.
- Opercular.
- Córtex motor.

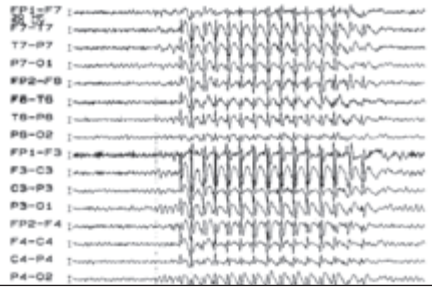
SEIZURES DURING INFANCY

Epilepsias do lobo frontal



SEIZURES DURING INFANCY

Epilepsias do lobo frontal

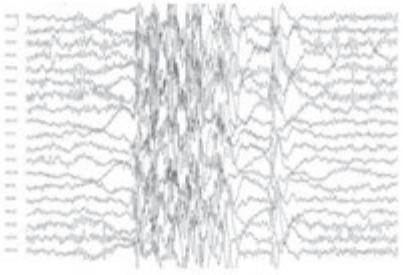


SEIZURES DURING INFANCY

Epilepsias do lobo frontal

SEIZURES DURING INFANCY

Epilepsias do lobo temporal neocortical



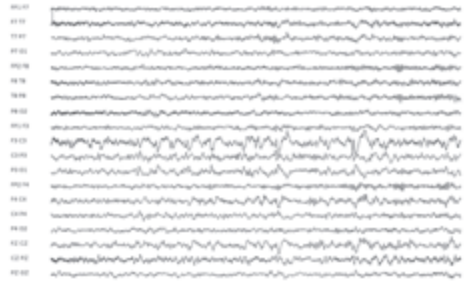
SEIZURES DURING INFANCY

Epilepsias do lobo temporal neocortical

SEIZURES DURING INFANCY

LBE

Epilepsias do lobo parietal



SEIZURES DURING INFANCY

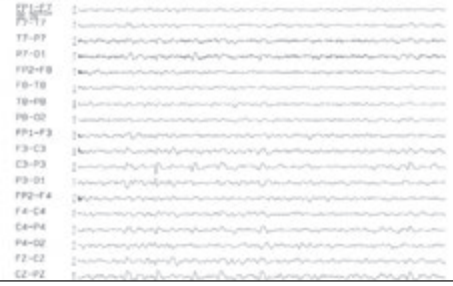
LBE

Epilepsias do lobo parietal

SEIZURES DURING INFANCY

LBE

Epilepsias do lobo occipital



SEIZURES DURING INFANCY

LBE

Epilepsias do lobo occipital

SEIZURES DURING INFANCY

Table 3. Electroclinical syndromes and other epilepsies

Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.

SEIZURES DURING INFANCY

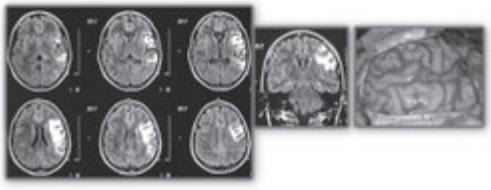
Epilepsias focais provavelmente ou indubitavelmente sintomáticas

Epilepsias neocorticais

- **Síndrome de Rasmussen**
- **Síndrome de hemiconvulsão-hemiplegia**
- **Outros tipos definidos pela localização e etiologia**
- **Crises parciais migratórias da infância precoce**

SEIZURES DURING INFANCY

Encefalite de Rasmussen



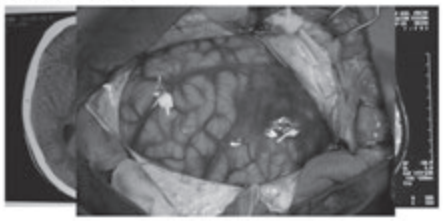
SEIZURES DURING INFANCY

Encefalite de Rasmussen

SEIZURES DURING INFANCY

LBE

Outras etiologias



SEIZURES DURING INFANCY

LBE

ESCLEROSE TUBEROSA

Critérios diagnósticos para Esclerose Tuberosa segundo o consenso da conferência do complexo esclerose tuberosa de 1998 (dois critérios maiores ou um critério maior e dois menores).

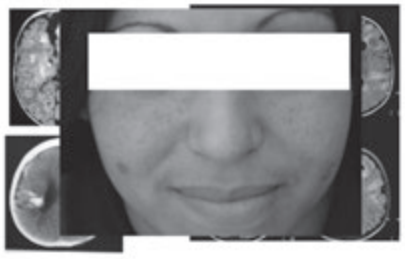
Critérios maiores	Critérios menores
Angiofibromas faciais ou placas fibrosas	Manchas múltiplas na dentina
Fibroma periungueal ou ungueal não traumáticos	Pólipos hamartomatosos retais
Máculas hipomelanóticas (três ou mais)	Cistos ósseos
Placa de shagrém (nevus de tecido conjuntivo)	Linhas de migração radial na substância branca do sistema nervoso central (três ou mais lesões radiais)
Hamartomas retinianos nodulares múltiplos	Fibromas gengivais
Tubers corticais	Hamartomas não renais
Nódulos subependimários	Placas retinianas acromáticas
Astrocitoma subependimário de células gigantes	Lesões cutâneas em confete
Rabdomioma cardíaco único ou múltiplo	Cistos renais múltiplos
Linfangiomatose	
Angiomiolipoma renal	

1. Associação de DC e alterações da migração neuronal ocorrem associadas, são considerados como apenas um critério.
2. Associação de linfangiomatose e angiomiolipomas renais, outro critério do ET deve ser considerado para o diagnóstico.

SEIZURES DURING INFANCY

LBE

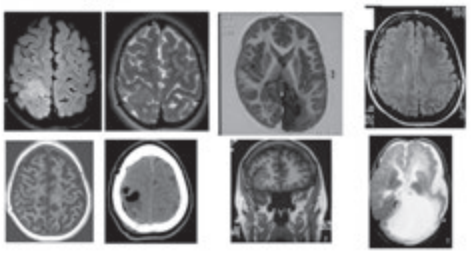
Outras etiologias



SEIZURES DURING INFANCY

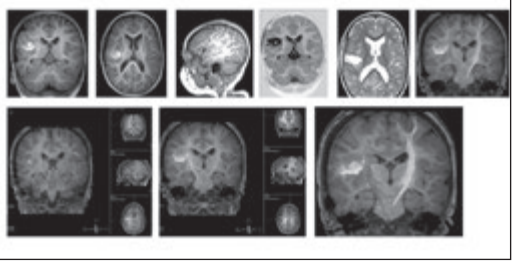
LBE

Outras etiologias



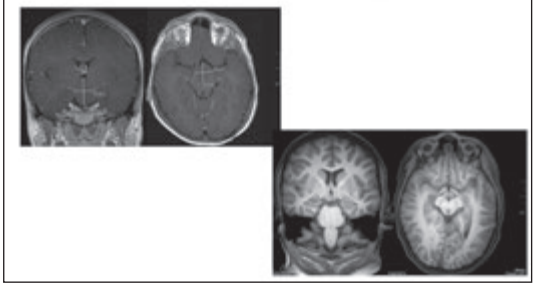
SEIZURES DURING INFANCY

Outras etiologias



SEIZURES DURING INFANCY

HAMARTOMA HIPOTALÂMICO



SEIZURES DURING INFANCY

SEIZURES DURING INFANCY

HISTÓRIA NATURAL DA EPILEPSIA

- **Mortalidade – causas:**

***Relacionadas à epilepsia**: suicidio, efeitos adversos das DAE, reações idiossindráticas das DAE, relacionadas às crises (traumas, queimaduras, afogamento), estado de mal epiléptico, asfixia, aspiração, pneumonia após uma crise, SUDEP.*

SEIZURES DURING INFANCY

COMORBIDADES

16 a 72% dos casos:

- Dificuldade de aprendizado.
- Retardo mental.
- Distúrbios de comportamento.
- Dificuldades sociais.
- Relação com o controle de crises???

SEIZURES DURING INFANCY

TAMANHO DO PROBLEMA!!

Em crianças com diagnóstico de epilepsia:

- TDAH: 14 a 38%.
- Desordens afetivas e ansiedade: 16 a 31%.
- Ideação suicida: 20%.
- Desordens do espectro autista: 9 a 32%.

INCIDÊNCIAS MENORES EM PACIENTES CONTROLADOS

SEIZURES DURING INFANCY

Epilepsy is more than seizures. An ongoing epileptogenic process can irreversibly damage the brain, especially maturing brain, even if seizures are controlled or missing, and causes persistent cognitive changes and finally global intellectual deficits.

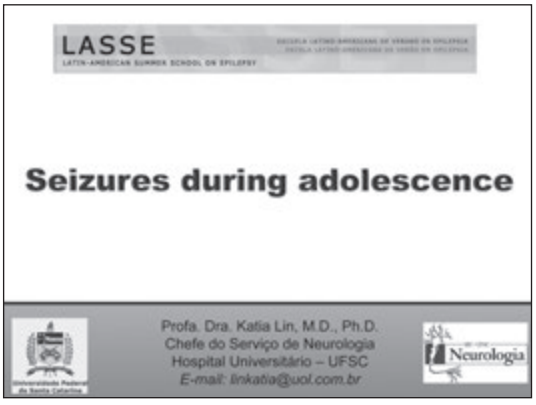
K. van Rijckevorsel; Seizure (2006) 15, 227—234

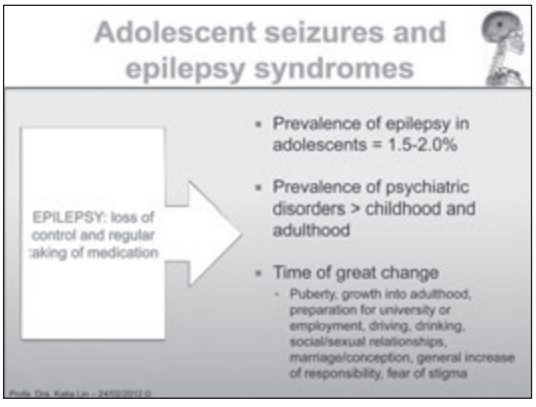
SEIZURES DURING INFANCY

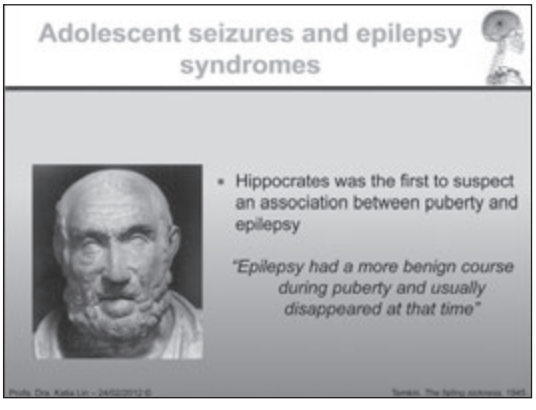
Obrigada!

Katia Lin (Brazil)

SEIZURES DURING ADOLESCENCE







Adolescent seizures and epilepsy syndromes

TABLE 1. *Childhood-onset epilepsy syndromes that usually remit before or during adolescence*

- Benign childhood epilepsy with centrotemporal spikes
- Benign childhood epilepsy with occipital paroxysms, Panayiotopoulos type (early onset)
- Childhood absence epilepsy
- Acquired epileptic aphasia (Landau–Kleffner syndrome)

TABLE 2. *Childhood-onset epilepsy syndromes that may persist into adolescence*

- Benign childhood epilepsy with occipital paroxysms, Gastaut type (late onset)
- Benign myoclonic epilepsy in infancy
- Lennox–Gastaut syndrome
- Generalized epilepsy with febrile seizures plus
- Childhood absence epilepsy
- Epilepsy with myoclonic absences (Tassinari syndrome)
- Eyelid myoclonia with absences (Jeavons syndrome)
- Myoclonic astatic epilepsy of early childhood (Doose syndrome)

TABLE 3. *Epilepsy syndromes with onset in adolescence*

- Reading epilepsy
- Photosensitive epilepsies
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with grand mal on awakening
- Progressive myoclonic epilepsies
- Mesial temporal lobe epilepsy
- Nonepileptic seizures

Report of the ILAE Commission on Classification and Terminology, 2005-2009

Table 1. Classification of seizures[a]

- Generalized seizures
  - Tonic–clonic (in any combination)
  - Absence
    - Typical
    - Atypical
    - Absence with special features
      - Myoclonic absence
      - Eyelid myoclonia
  - Myoclonic
    - Myoclonic
    - Myoclonic-atonic
    - Myoclonic-tonic
  - Clonic
  - Tonic
  - Atonic
- Focal seizures
- Unknown
  - Epileptic spasms

[a]Seizure that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category, however.

Berg, et al. Epilepsia. 2010

Report of the ILAE Commission on Classification and Terminology, 2005-2009

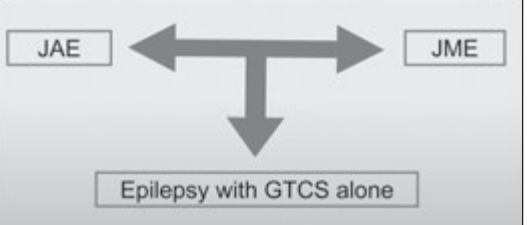
Table 3. Electroclinical syndromes and other epilepsies

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

Berg, et al. Epilepsia. 2010

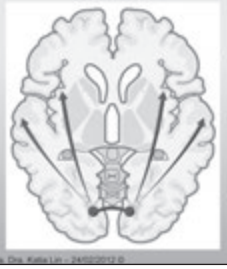
Idiopathic/Genetic Generalized Epilepsies

Idiopathic/Genetic Generalized Epilepsies



The most frequent group with adolescent seizure onset.
Neurobiological continuum: clinical and EEG overlapping features & not all sz types manifest right away at presentation.

"Idiopathic / Genetic Epilepsies"
"System epilepsies"



- Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks.
- Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex.
- Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another.
- Generalized seizures can be asymmetric.

Berg, et al. Epilepsia, 2010
Capovilla, et al. Epilepsia, 2009

Idiopathic/Genetic Generalized Epilepsies

"The onset of IGEs is unusual over the age of 25."

Epilepsy with GTCS alone

JME

CAE JAE

0 5 10 15 20 years

Age at onset

Wheless and Kim. Epilepsia, 2003
Cutting et al. Epilepsia, 2001

Juvenile Absence Epilepsy

- Onset: 9-13 years (peak 10-12)
- No gender preference
- Similarity to the absence sz seen in CAE
  - Less frequent – 9-10x/dia (Spanioleptic)
  - Milder consciousness impairment, automatisms
  - Longer duration (4-30sec.)
- Infrequent GTCS (morning) in most patients
- Mild myoclonic jerks (1/5 subjects)
- Intermediate syndrome between CAE and JME

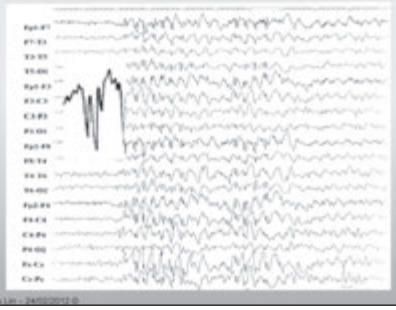
Juvenile Absence Epilepsy

Juvenile Absence Epilepsy

Courtesy: Dra. Elza Márcia Yacubian – UNIPETE/UNIFESP

Profa. Dra. Katia Lin – 24/02/2012 ©

EEG background: normal. Interictal and ictal: bursts of generalized spike- or polyspike-wave discharges (fragmented or not) with slightly faster repetition rate (3-4 Hz).

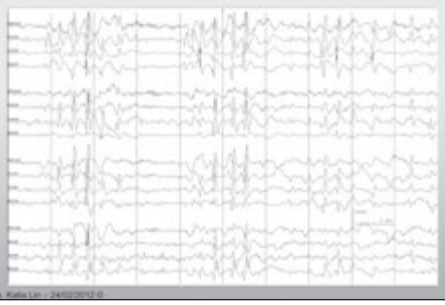


Profa. Dra. Katia Lin – 24/02/2012 ©

Longer duration (16.3 ± 7.1sec. JAE; 12.4 ± 2.1sec. CAE; 6.6 ± 4.2sec. JME)

Profa. Dra. Katia Lin – 24/02/2012 ©

Maximally over frontal head regions.
Precipitated by hyperventilation, sleep deprivation, and infrequently by photic stimulation.



Profa. Dra. Katia Lin – 24/02/2012 ©

Juvenile Absence Epilepsy

- Genetics
  - Strong genetic component – polygenic
  - Chromosome linkage to chromosomes 5, 8, 18 and 21
- Prognosis
  - Sz control in most patients (70-80%)
    - Avoid precipitants, VPA, ESM, LTG
  - Absence severity usually decreases with time

Juvenile Myoclonic Epilepsy

- Janz's syndrome

Prof. Dieter Janz
Impulsiv-Petit mal (1957)

Janz & Christian. Disch Z Nervenheilk. 1957

Juvenile Myoclonic Epilepsy

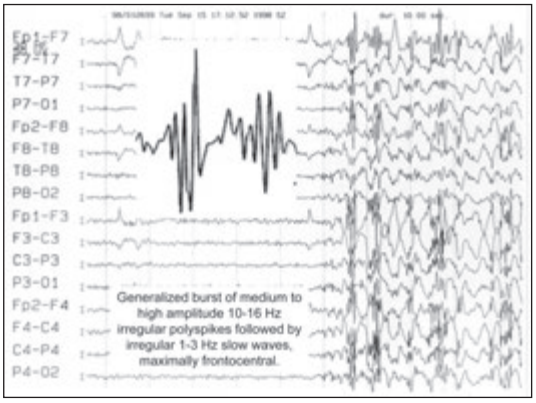
- 5-10% of all epilepsies
- 20-27% of IGEs
- No gender preference
- Onset: 12-18 years (mean age = 14.2)
  - Myoclonus 100% / GTCS 95% / Absence sz 30%
- Precipitated by sleep deprivation, fatigue, or alcohol
- Photosensitivity in 30%
- Normal neurologic examination and intelligence

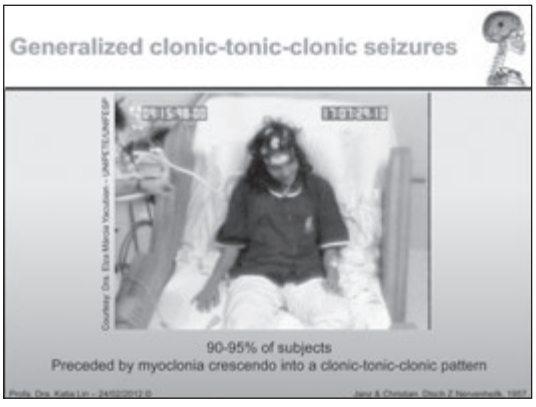
Myoclonia

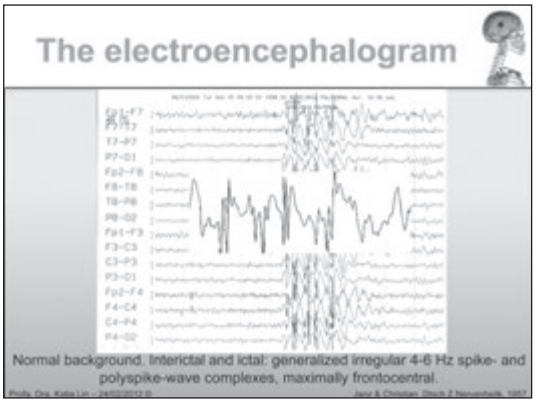
Courtesy: Dra. Elza Márcia Yacubian – UNIPETE/UNIFESP

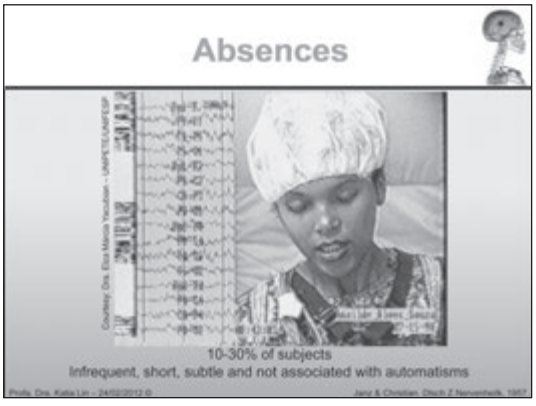
Essential to diagnosis.
Early morning – sudden drop of objects.
Neck, shoulder, **arms**, legs – extensor.
No alteration of consciousness.

Blume, et al. Epilepsia. 2001


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
Generalized burst of medium to high amplitude 10-16 Hz irregular polyspikes followed by irregular 1-3 Hz slow waves, maximally frontocentral.


Generalized clonic-tonic-clonic seizures
90-95% of subjects
Preceded by myoclonia crescendo into a clonic-tonic-clonic pattern


The electroencephalogram
Normal background. Interictal and ictal: generalized irregular 4-6 Hz spike- and polyspike-wave complexes, maximally frontocentral.


Absences
10-30% of subjects
Infrequent, short, subtle and not associated with automatisms

Juvenile Myoclonic Epilepsy

- Genetics
  - Linkage to several chromosomes
  - Genetic heterogeneous disorder – mutations in several genes
    - GABRA1 gene, CACNB4 gene, CLCN2 gene, EFHC1 gene, ...
- Prognosis
  - Remarkable response to treatment (90%)
    - Avoid precipitants, VPA, CZP, TPM
  - Lifelong treatment

Epilepsy with GTCS Alone

- GTCS at various times of the day
  - Infrequent sz
- 6-47 years (peak 16-17)
- Slightly more prominent in men
- Sleep deprivation and alcohol increase sz
- Photosensitivity (13%)
- EEG
  - Normal background
  - Generalized irregular and fast spike- and polyspike-wave complexes at 3-4 Hz
- Good sz control

Epilepsy with GTCS Alone

- Genetics
  - Genetic component – polygenic
- Prognosis
  - Sz control in most patients
    - Avoid precipitants, VPA, PB, LTG, TPM
  - Lifelong disease
    - High (83%) incidence of relapse on withdrawal of treatment

Other syndromes

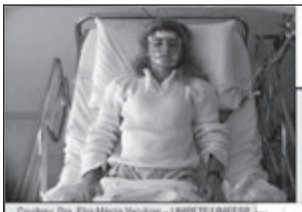
Benign partial seizures in adolescence

- ¼ of focal sz in adolescence
- Age of onset = 10-20 years (peak 13-14)
- Male predominance
- No family history
- No cognitive or neurological impairment
- Simple or complex partial seizures, frequently with secondary generalization
  - Somatosensitive, clonic or tonic motor sz, versive, no jacksonian march
  - SINGLE SZ in 75%; or cluster of 2-4 sz in 36-48hr.
- EEG is typically normal or shows only mild abnormality
- Avoid treatment – benign course and isolated sz

Loiseau et al. 1972;
Loiseau & Orgogozo, 1978;
Loiseau & Loubert, 1992

Photosensitive epilepsies

- All forms of heterogeneous epilepsies in which sz are triggered by photic stimulation (videogames, television)
- Photosensitive sz and epilepsies affect 1:4000 of the population
- Maximal expression during puberty (peak 12-14).
- Female predominance (2/3)
- Do not constitute a single syndrome
  - Important to define the syndrome in which the photosensitivity occurs (JME, JAE, etc.)
- Treatment: avoid precipitants, VPA, CLB, CZP
- Good prognosis

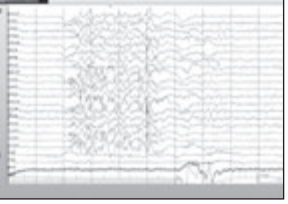


Sz and discharges precipitated by photic stimuli

Courtesy: Dra. Elza Márcia Yacubian – UNIFESP/UNIFESP

Photosensitivity

- Genetically determined trait
- Clinical manifestations depend on the underlying syndrome and severity of photosensitivity (pure photosensitive epilepsy or associated with spontaneous sz: generalized sz > occipital sz)



Photosensitive epilepsies

Reading epilepsy

- Mean age of onset of 17–18 years
- Male predominance
- Strong genetic predisposition
- Motor/sensory aura: after reading for a period, abnormal sensations or movements occur (with full consciousness), involving the tongue, throat, jaw, lips and face
  - If the patient does not stop reading, this aura may progress to GTCS
- Avoid precipitants, treatment with AEDs may not be necessary (VPA, CZP)
- EEG is usually normal
- Good prognosis

Wolf, 1992

Reading epilepsy

Sousa et al. Epilepsia Disord. 2005

Investigation

Diagnosis

FEATURES SUGGESTING IGE

- Childhood or teenage onset
- Triggered by sleep deprivation & alcohol
- Early morning tonic-clonic sz or myoclonic jerks
- Short absence sz
- Photoparoxysmal response on EEG
- Generalized 3 per sec spike-and-wave or polyspike and wave on EEG

FEATURES SUGGESTING FOCAL EPILEPSIES

- Hx of potential cause
- Aura
- Focal motor activity during sz
- Automatisms

Tonic-clonic sz without any focal features or any positive features of an IGE cannot be confidently classified!

Investigation

- **Accurate diagnosis**
  - Important physical, psychosocial and economic implications for the patient
  - Hx of sz depends on the account of a witness
  - *"Art of listening"*
- **EEG** should be performed in young people with generalized sz to aid classification and to detect a photoparoxysmal response
- **Brain imaging** is not routinely required when there is a confident diagnosis of an IGE and if there is rapid and complete response to the first-line AEDs

Management Issues

Adolescence and seizures

- Transient deterioration in sz control secondary to rapid growth and suboptimal AEDs levels.
- More frequent laboratory evaluation of AEDs may be necessary until pubertal changes are complete

Menarche and seizures

- Some women with epilepsy experience changes in sz patterns at times of hormonal fluctuations
  - Menarche, over the menstrual cycle and with menopause
- Catamenial epilepsy refers to seizure exacerbation related to the menstrual cycle
  - Most common pattern is an increased tendency for seizures just before, or at the onset of menstruation
- Evaluate therapeutic interventions including progesterone therapy or adjunctive AEDs

Sexuality and epilepsy

All commonly used birth control methods, including hormonal contraceptives, barrier devices or substances, and timing techniques, can be used by women with epilepsy, but the choice of contraceptive method can be influenced by the AED that is used.

AEDs interfering with OC	AEDs non-interfering with OC
Carbamazepine	Benzodiazepines
Phenobarbital	Gabapentine
Phenytoin	Lamotrigine
Oxcarbazepine	Valproate
Topiramate (> 200 mg/day)	Vigabatrin

Adolescence behavior and epilepsy

- Normal adolescent behavior can be unpredictable and inconsistent
- Seizures may affect cognition and emotional responses
- Side effects of AEDs may also cause changes in cognition and physical abilities
  - Irritability, difficulty with balance or coordination, confusion and lethargy may occur if AED blood levels are too high
- Education about epilepsy and realistic expectations
- Professional counseling may be necessary for some adolescents and their families.

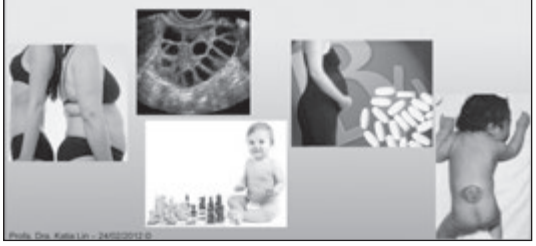
Independence X safety for adolescents with epilepsy

- Alcohol and drug abuse and destructive behaviors may be common among adolescents
- A driver's license is regarded by many adolescents as essential to freedom and independence – state laws vary
- Sports with the potential of head injury should be undertaken with caution – activities that may result in injury if a seizure occurs should be carefully monitored, especially involving water
- Showers should be encouraged over tub baths and safety devices to prevent shower scalding

Pharmacological treatment

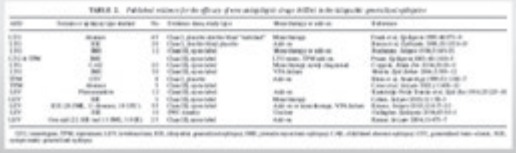
Management dilemmas

Sodium valproate – drug of choice



Practical Management Issues for Idiopathic Generalized Epilepsies

Selim R. Benbadis



Practical Management Issues for Idiopathic Generalized Epilepsies

Selim R. Benbadis

TABLE 1. *Published evidence that some antiepileptic drugs (AEDs) are not effective in idiopathic generalized epilepsies and may exacerbate some seizure types (Modified with permission [1])*

AED	Seizure or epilepsy type studied	Reference
CBZ	IGE	*N Engl J Med* 1983;313:926-21
CBZ	IME	*Neurology* 2000;55:1106–9
CBZ	Unclear	*Epilepsia* 1994;35:1154–8
GBP	Childhood absence	*J Child Neurol* 1996;11:470–5
TGB	IGE	*Seizure* 1999;8:314–7
CBZ	Unclear	*Neurology* 1983;33:1487–9
CBZ	Mixed	*Pediatr Neurol* 1986;2:340–5
CBZ	Unclear	*Epilepsia* 1994;35:1026–8
CBZ	Unclear	*Epilepsia* 1994;35:1154–8
PHT	IGE	*Neurology* 1965;15:716–22
PHT, CBZ	IME	*Epilepsia* 1994;35:285–96
PHT, CBZ	IME	*Neurology* 2000;55:1106–9
OXC	IGE	*Epilepsia* 2002;43(suppl 7):208 [abstract]
OXC	IGE	*Epilepsia* 2004;45:1282–6

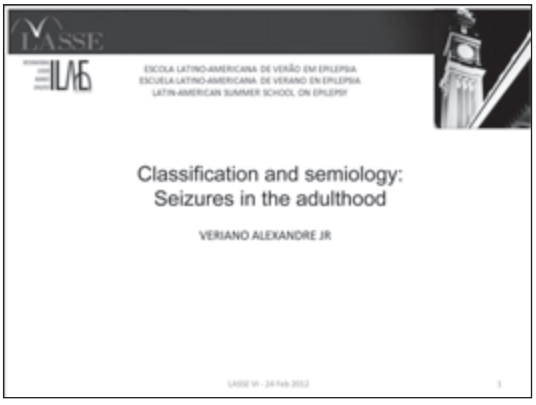
Suggested reading

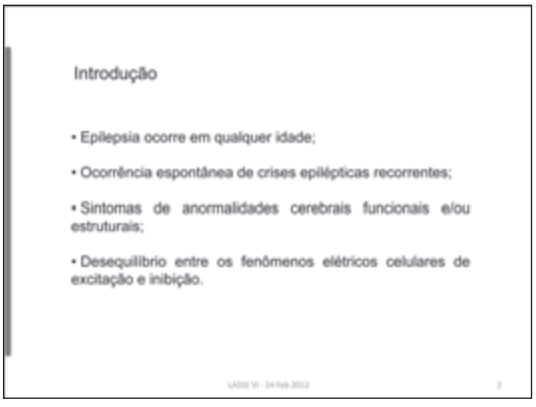
- Berg AT, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission oon classification and terminology, 2005-2009. Epilepsia 2010; 51:676-685.
- Nordli Jr DR. Idiopathic generalized epilepsies recognized by the International League Against Epilepsy. Epilepsia 2005; 46:S48-S56.
- Wheless JW & Kim HL. Adolescent seizures and epilepsy syndromes. Epilepsia 2002; 43:S33-S52.
- Shahwan A, et al. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. Lancet Neurol 2005; 4:239-248.
- Goebel HH & Wisniewski K. Current state of clinical and morphological features in human NCL. Brain Pathol 2004; 14:61-69.
- Benbadis SR. Practical management issues for idiopathic generalized epilepsies. Epilepsia 2005; 46:S125-S132.

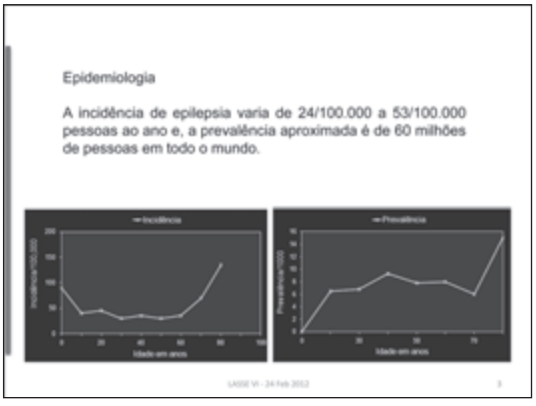

Thank you! Obrigada! Gracias!
Neurologia
"Without clinical expertise, practice may become tyrannized by evidence, for even excellent external evidence may be applicable to or inappropriate for an individual patient."
D.L. Sackett

Veriano Alexandre Junior (Brazil)

SEIZURES IN THE ADULTHOOD

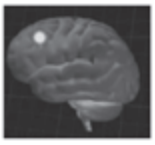


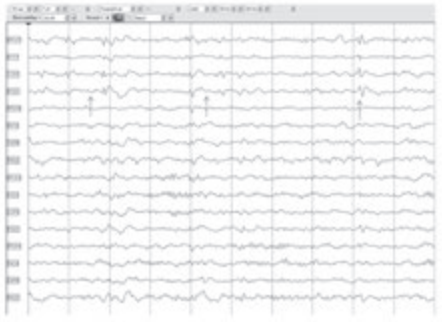




Epilepsias focais

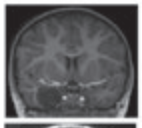
- Ocorrência de crises que se iniciam em um grupo localizado de neurônios;
- A atividade anormal pode se propagar e envolver cada vez mais outras regiões do cérebro;
- Manifestações clínicas dependem das áreas acometidas.
- Lesões localizadas são implicadas nesse mecanismo fisiopatológico



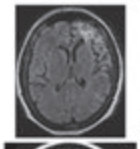


Etiologia

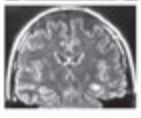
- Criptogênicas (~50% dos casos)
- Idiopáticas
- Sintomáticas



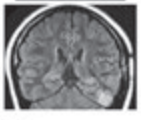
Neoplásicas



Gliose



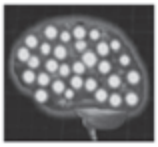
Esclerose mesial temporal

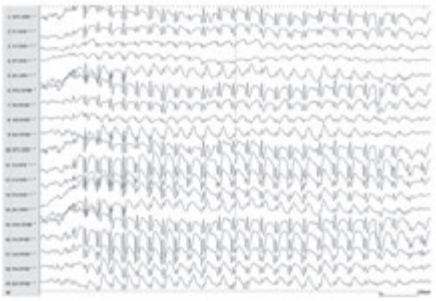


Displasia cortical focal

Epilepsia Generalizada

- Epilepsias generalizadas;
- Ocorrência de crises que se iniciam com sincronização simultânea da atividade paroxística em ambos os hemisférios cerebrais;
- As manifestações clínicas são bastante características, como por exemplo, crises de ausência, mioclônicas, espasmos, tônicas, atônicas, tônico-clônicas;
- Apresentam mais frequentemente causas determinadas geneticamente.





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Diagnóstico

- Predominantemente clínico, baseado na história clínica e exame físico;
- Diagnóstico diferencial com distúrbios cardíacos, psicológicos, psiquiátricos ou metabólicos devem ser consideradas;
- Exames complementares.

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Diagnóstico diferencial

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Vídeos

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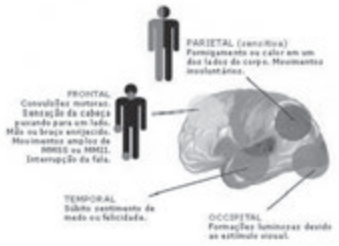
Semiologia

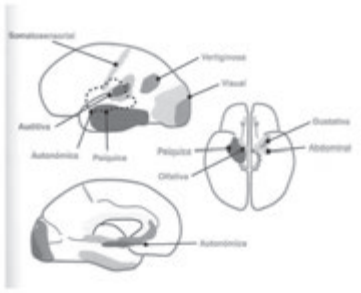


O homúnculo de Penfield

Auras

Fenômeno ictal subjetivo que pode preceder uma crise observável:

- Auras somato-sensitivas
- Auras visuais
- Auras auditivas
- Auras olfativas
- Auras gustativas
- Auras autonômicas
- Auras abdominais
- Auras psíquicas



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Vídeos

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Comprometimento da consciência

Pode ser a principal manifestação (crises de ausência) ou ocorrer associada a fenômenos motores (parciais complexas e generalizadas).

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Vídeos

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Automatismos

Atividade motora repetitiva, mais ou menos coordenada, geralmente acompanhada de alteração da consciência

Manifestações Motoras

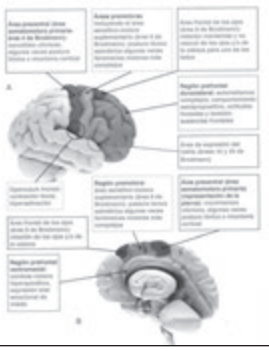
As manifestações motoras são muito características de tipos específicos de crises, cujas manifestações variam desde movimentos relativamente simples até movimentação mais complexa.

- Crises mioclônicas
- Crises clônicas
- Crises tônicas
- Crises versivas
- Crises tônico-clônicas
- Crises hipermotoras
- Crises psicomotoras

Espasmos
Crises gelásticas
Crises atônicas, astáticas, hipomotoras, acinéticas, mioclônicas negativas
Crises afásicas

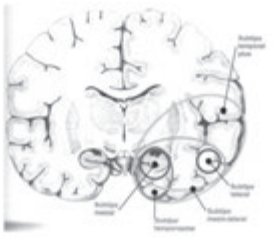
Vídeos

Crises de lobo frontal



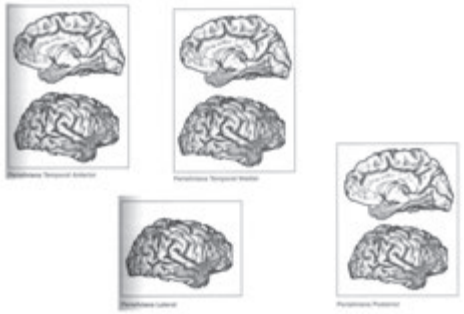
Vídeos

Crises de lobo temporal



Vídeos

Crises Perisilvianas



Vídeos

Crises parietais

- Crises parciais simples sensitivas
  - Fenômenos positivos: parestesias, sensações dolorosas
  - Fenômenos negativos: afasia, asomatognosia, vertigem
  - Sintomas pela propagação para lobos frontal, temporal ou occipital

Vídeos

Crises occipitais

Vídeos

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

Vídeos

Caso Clínico 1

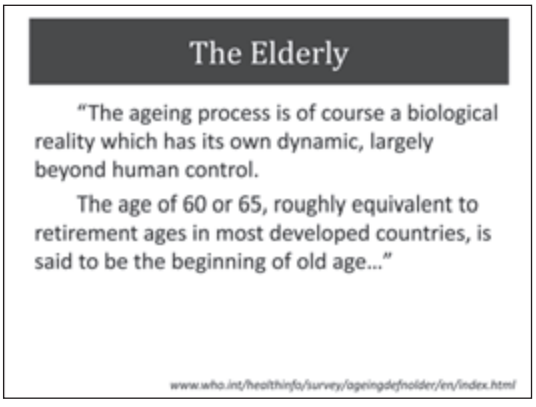
Crise de origem não epiléptica

Caso Clínico 2

Crise de origem epiléptica

Carlos Silvado (Brazil)

SEIZURES IN THE ELDERLY



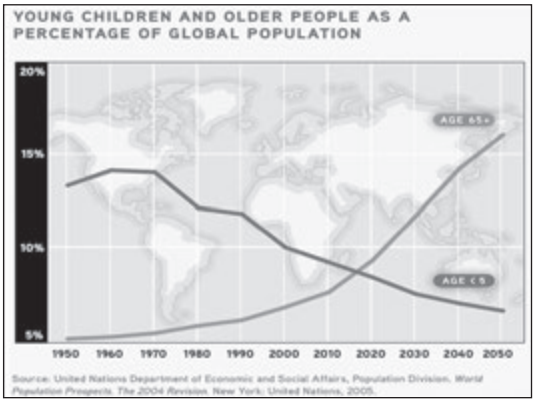
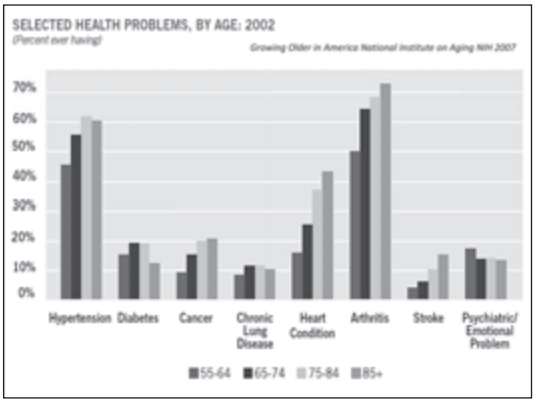



Gráfico 2 - Proporção de pessoas de 60 anos ou mais de idade em países selecionados - 1990/1999
Venezuela 6,4
México 6,5
Equador 6,6
Colômbia 6,8
Peru 7,0
Brasil 8,6
Chile 10,1
China 10,8
Cuba 13,0
Argentina 13,2
Estados Unidos 15,9
Canadá 16,3
Uruguai 17,1
França 19,7
Reino Unido 20,4
Alemanha 21,8
Japão 22,3
Itália 23,1
Demographic yearbook 1999. New York: United Nations, 1999
IBGE, Censo Demográfico 2000


HEALTH STATUS, BY AGE: 2002
(Percent in each health category)
Growing Older in America - National Institute on Aging NIH 2007
100%
80%
60%
40%
20%
0%
55-64 65-74 75-84 85+
Excellent Very Good Good Fair Poor


SELECTED HEALTH PROBLEMS, BY AGE: 2002
(Percent ever having)
Growing Older in America National Institute on Aging NIH 2007
70%
60%
50%
40%
30%
20%
10%
0%
Hypertension Diabetes Cancer Chronic Lung Disease Heart Condition Arthritis Stroke Psychiatric/ Emotional Problem
55-64 65-74 75-84 85+


Perfil de Idosos Responsáveis por Domicílios no Brasil 2000 - IBGE
1990 – 7.3%
2000 – 8.6%
2020 – 13%

Incidence of Epilepsy in Elderly

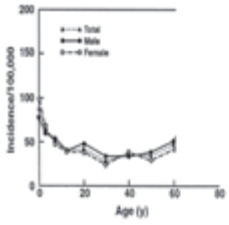


Figure 1. Incidence of epilepsy by age, Rochester, MN, 1935–1984. (Reproduced from Hauser,[1] with permission.)

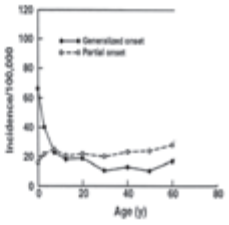
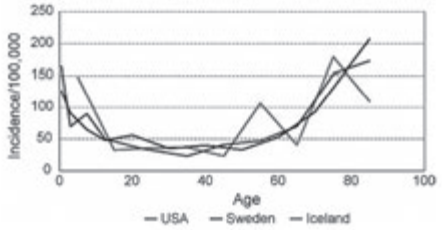


Figure 2. Incidence of seizure by type and age, Rochester, MN, 1935–1984. (Reproduced from Hauser,[1] with permission.)

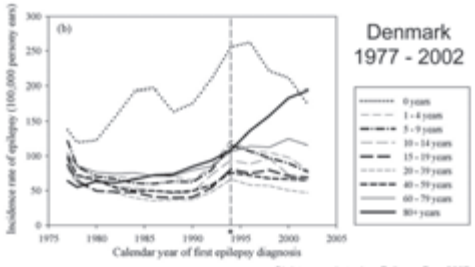
Incidence of Epilepsy in Elderly

Incidence of epilepsy in developed countries



Hauser et al. 1993; Sidenvall et al. 1993; Forsgren et al. 1996; Olafsson et al. 2005

Incidence of Epilepsy in Elderly



Christensen J et al. – Epilepsy Res. 2007

Incidence of Epilepsy in Elderly

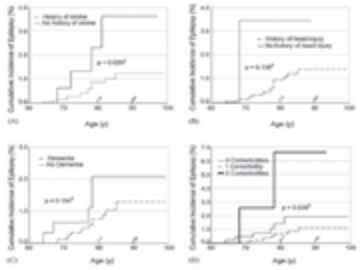
- Brasil:
  - Elderly Population:
    2000 – 8,6% ***2020 – 13%***

    IBGE 2002
- Campinas and São Jose do Rio Preto:
  - 60 years or more
  - Active Epilepsy Prevalence = 8,5 / 1.000
  - "Treatment Gap" = 51%

Noronha AL et al. – Epilepsia 2007

Why they have more seizures ?

Incidence of epilepsy in a racially diverse, community-dwelling, elderly cohort: Results from the Einstein aging study. - 11919 elderly ≥ 70 y, Bronx USA. *Hussain AS et al. – Epilepsy Res 2006*



Epilepsy in the Elderly

- Main Issues
  - Challenging diagnosis
  - Increase risk of trauma during seizure
  - Potential for loss of functional independence
  - Cognitive dysfunction is usual and could be increased by the effects of seizures or side effects of medication.
  - Increase susceptibility to side effects
  - Various drugs in use for treatment of comorbidities
  - Patient condition is more important than age

Epilepsy in the Elderly

Concomitant Diseases	%
Hypertension	64
Cerebrovascular Disease	53
Cardiophaty	49
Diabetes	27
Cancer	23

Co-medications	Nº
Types	0 - 15
Mean	6.7

Cooperative Study VA 428
Ramsay RE et al - Neurology 2004; , Rowan AJ et al – Neurology 2005

Epilepsy in Elderly

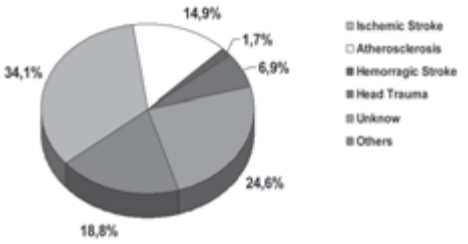
AEDs + Co-Medications

4 291 nursing home residents using AEDs - USA

Category	Use with AED (%)
Antidepressants	18.9
Antipsychotics	12.7
Benzodiazepines	22.4
Thyroid Medications	14.0
Antacids	8.0
Calcium Channel Blockers	6.9
Warfarin	5.9
Cimetidine	2.5

Lackner T et al – Epilepsia 1998

Etiology of Epilepsy in the Elderly



Ramsay RE et al. Neurology 2004

Table 1 The territorial involvement in patients with post-stroke and post-ischemic epilepsy

	Whole population (1,428 patients)		Post-ischemic epilepsy (36 patients)	
Territorial classification	*n*	Percentage	*n*	Percentage
MCA	1,045	73.2	23	63.9
PCA	147	10.3	5	13.8
ACA	103	7.2	4	11.1
Borderline between MCA and PCA	83	5.8	2	5.6
ICA	50	3.5	2	5.6

MCA middle cerebral artery; posterior cerebral artery; *ACA* anterior cerebral artery; *ICA* internal carotid artery.

Table 3 The etiological distribution in stroke patients with or without epilepsy

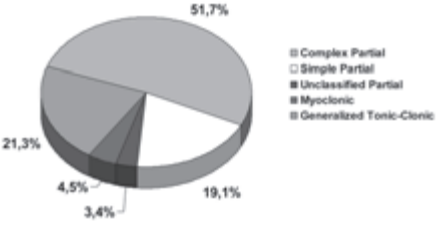
	Patients			
	With epilepsy (*n* = 51)		Without epilepsy (*n* = 1,377)	
Stroke subtypes	*n*	Percentage	*n*	Percentage
Ischemic*	36	70.6	1291	93.8
Hemorrhagic*	11	21.6	75	5.4
Venous infarctions*	4	7.8	11	0.8

*$P < 0.001$, paired *t*-test.

Benbir G et al. - Acta Neurol Scand 2006

Epilepsy in Elderly

Types of Epileptic Seizures



Epileptic Seizures in the Elderly

	Adults	Elderly
Seizure Type	many/GTC	SP/CP
Location of Focus	temporal	frontal/parietal
Frequency	variable	low
Aura	well defined	unespecific
Automatisms	usual	rare
Pos Ictal	brief	prolonged
Potential to Harm	low	high
Seizure Control	variable	usually easy

Epilepsy in Elderly

Why the diagnosis is difficult ?

- Fall with Loss of Consciousness
  - Syncope ?
  - Epileptic seizure ?
  - Head trauma ?
- Transient Confusional State
  - Complex partial seizure ?
  - Long post-ictal confusion ?
  - Drug side effect ?
  - Non convulsive status epilepticus ?
  - Metabolic disorder ?

Cooperative Study VA # 428

128 epileptic patients

Initial Diagnosis	%
Altered mental status	42
Confusion	37,5
Blackout spells	29
Memory disturbance	17
Sincope	17
Dizziness	10
Dementia	7

Cooperative Study VA 428
Ramsay RE et al - Neurology 2004; Rowan AJ et al – Neurology 2005

VEEG in Elderly

94 patients > 60 years admitted to Epilepsy Monitoring Unit
Mean length of stay Video-EEG = 3,8 days

ICTAL EVENTS	*%*
Epileptic Seizures	49
Non Epileptic Seizures	29
Physiologic	*15*
Psychogenics	*14*
Epileptic and Psychogenic	0,4
No Events	14

McBride et al. - Epilepsia 2002

Non Epileptic Seizure in Elderly

Late onset psychogenic nonepileptic attacks

%	Early Onset	Late Onset	"p"
Number of Cases	241	26	
Male	23	42	0,029
Concomitant epilepsy	10	26	0,309
Antecedent sexual abuse	32	4	0,002
Antecedent physical abuse	28	15	0,173
Other traumatic experience	70	73	0,754
Health-related traumatic experiences	4	47	0,001

Duncan R et al – Neurology 2006

Epilepsy in Elderly

- Which diagnostic tests ?
  - EEG during sleep → VEEG
  - ECG → Holter
  - CT at Emergency Room and/or MRI
  - Evaluate others probable diseases (presence and severity)

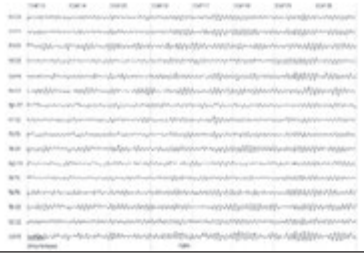
Epilepsy in Elderly

Elderly Normal EEG

- Background activity 9 Hz (+ temporal e + left)
- Intermitent focal slowing (no more than 1-2 % of record)
  - Benign Temporal Transients of Elderly
  - Theta (17 a 36%) and/or Delta (12%)
- Abrupt onset of sleep with frontally dominat rhytmic delta activity, reduced number of grapho-elements of sleep
- Benign Variants
  - "Wicket spikes"
  - SREDA (subclinical rhythmic electrographic discharge of adult)

Epilepsy in Elderly

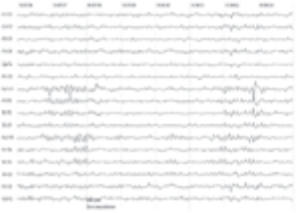
Normal EEG



PM, 67 y, male

Epilepsy in Elderly

"Wickets Spikes"



BR, 69 y, female

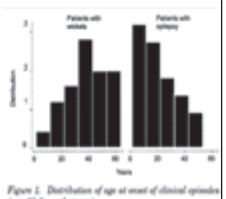


Figure 1. Distribution of age at onset of clinical episodes (n = 35 for each group).

Krauss GL et al. - Neurology 2005

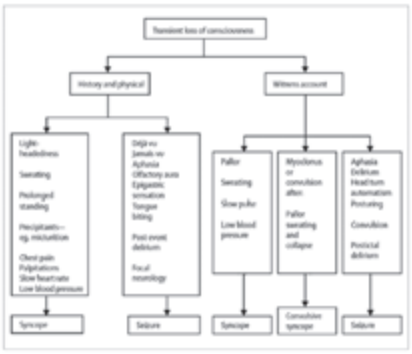
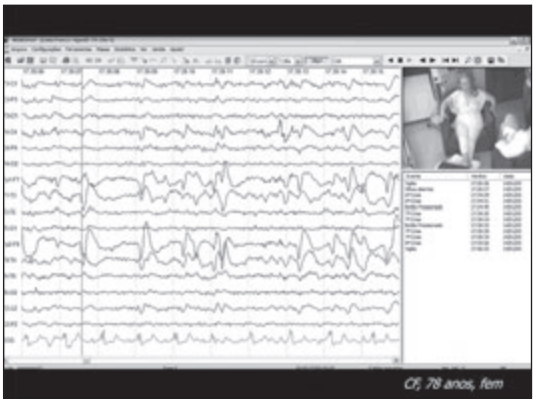


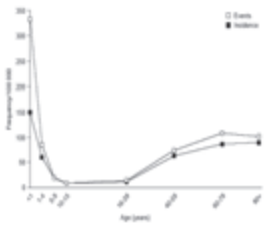
Figure 1: Clinical features distinguishing seizure from syncope

McKean et al – Lancet Neurol 2006



CF, 78 anos, fem

Status Epilepticus in Elderly



Etiology

Stroke = 40%

Low compliance = 21%

Mortality

>65 y= 38%

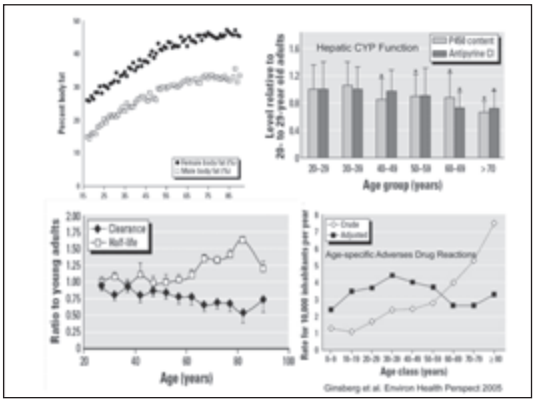
>80y = 50%

Stroke =14%

SE = 4%

Acute stroke + SE = 39%

De Lorenzo et al. - Neurology 1996



Ginsberg et al. Environ Health Perspect 2005

Table 1 Average reduction in apparent oral clearance (CL/F) of old-generation AEDs in old age. Quoted values should be regarded as indicative because inter-individual variability related to actual age, comorbidity and comedication may be considerable

Drug	Mean % difference in CL/F vs non-elderly adults
Phenytoin	Probably moderate decrease (complexity of phenytoin pharmacokinetics makes assessment of effect of age difficult)
Carbamazepine	−25–40
Valproate	−40*
Phenobarbital	−22

*Differences calculated on clearance of unbound drug (differences may not be apparent from total plasma concentration measurements).

Perucca E et al. Acta Neurol Scand 2006

Drug	Mean % difference in CL/F (vs adults)	Comments
Felbamate	−10–20	
Gabapentin	−30–50	
Lamotrigine	−37	
Levetiracetam	−20–40	
Oxcarbazepine	−25–35	Assessment based on the serum levels of the active metabolite monohydroxy-carbazepine
Pregabalin	No data	
Tiagabine	−30	
Topiramate	−20	
Vigabatrin	−50–90	Studies included patients with pathologically and severely impaired renal function
Zonisamide	No change (?)	Studies in subjects older than 71 years were not conducted

Perucca E et al. Acta Neurol Scand 2006

Antiepileptic Drugs in the Elderly

AED	Hepatic (%)	Renal (%)
VAL	>95	
CBZ	>90	
PHT	>90	
LMT	90	
FB	75	25
TPM	30-50	50-70
OXC mhd	45	45
GAB		100
LEV		66

French J & Gidal B – Epilepsia 2000; 41(suppl 8):S30-36

Table I. Summary of clinical guidelines and clinical recommendations for antiepileptic drugs (AEDs) in older patients with epileps

Guideline/clinical recommendation	Date	Specific geriatric AED recommendation	Level of evidence
Systematically derived guidelines			
Scottish Intercollegiate Guidelines Network[30,31,38]	1997, 2001, 2003	LTG may be advantageous (favourable adverse effect profile, few drug interactions)	1[a]
National Institute for Health and Clinical Excellence[39]	2004	Same as for other adults	1
International League Against Epilepsy[29]	2006	LTG and GBP preferred first-line AEDs	1
		CBZ alternative first-line AED	1
		Weak efficacy/effectiveness data to support use of VPA or TPM as first-line AED	3[b]
Professional organisation or policy statements			
American Academy of Neurology and the American Epilepsy Society (new diagnosis)[34]	2004	No	NA
American College of Emergency Physicians[37]	2004	No	NA
Expert consensus process			
Karceski et al.[33,41]	2001, 2005	AED of choice: LTG[c] Other first-line AEDs: LEV, GBP, CBZ, OXC[c]	4[d]
Semah et al.[36]	2004	AEDs of choice: GBP, LTG	4

Pugh MJ et al – Drugs Aging 2006

Cooperative Study VA # 428

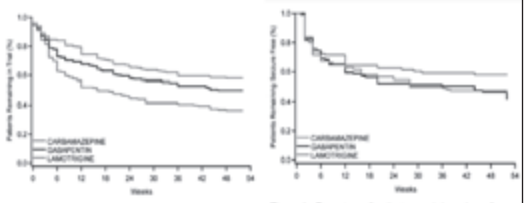


Figure 2. Percentage of patients remaining in the trial over time (52 weeks).

Figure 4. Percentage of patients remaining seizure-free over time (time to first seizure).

Rowan AJ et al . Neurology 2005

Clinical Trials

LTG 25 → 500 mg/day x CBZ 100 → 2000 mg/day

Age ≥ 65 years, recém diagnosticado, randomized, double-blind, multicentric, parallel group, 40-weeks

	LTG	CBZ
Number of cases	93	92
Completed the 40-week	73%	67%
Seizure free	52%	57%
Adverse events withdrawal	14%	25%

Saetre E et al – Epilepsia 2007

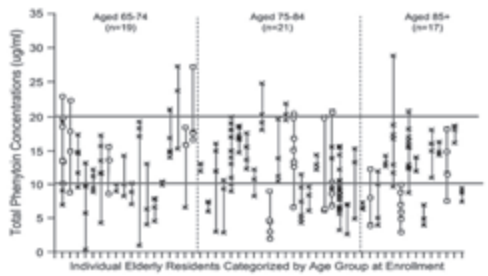
Clinical Trials

LTG 25 → 500 mg/day x CBZ 100 → 2000 mg/day

	Lamotrigine (n = 93)	Carbamazepine (n = 92)
Subjects with any drug-related adverse event	51 (55%)	51 (55%)
Dizziness	13 (14%)	9 (10%)
Rash/skin reaction	5 (5%)	12 (13%)
Headache	10 (11%)	10 (11%)
Somnolence/sedation/ hypersomnia	7 (7%)	9 (10%)
Asthenia/fatigue	9 (10%)	9 (10%)
Nausea/vomiting	7 (7%)	4 (4%)
Diarrhea	4 (4%)	5 (5%)

Saetre E et al – Epilepsia 2007

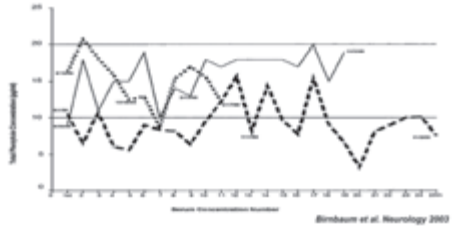
Phenytoin in Elderly



Birnbaum et al. - Neurology 2003

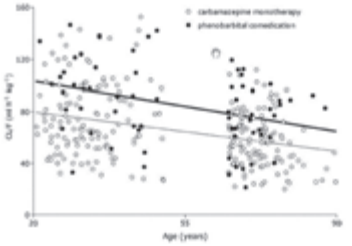
Phenytoin in the Elderly

Individual total phenytoin serum concentrations in 3 subjects with at least 10 phenytoin concentrations.



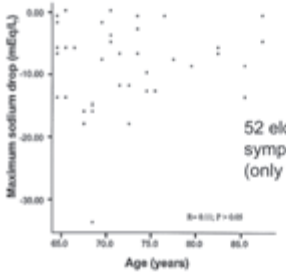
Birnbaum et al. Neurology 2003

Carbamazepine in Elderly



Batino D et al – Epilepsia 2003

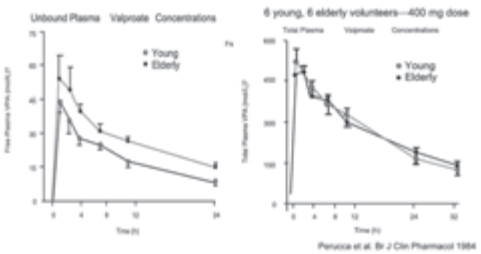
Oxcarbazepine in the Elderly



52 elderly with epilepsy
symptomatic hyponatremia = 3
(only one bellow 125 mEq/l)

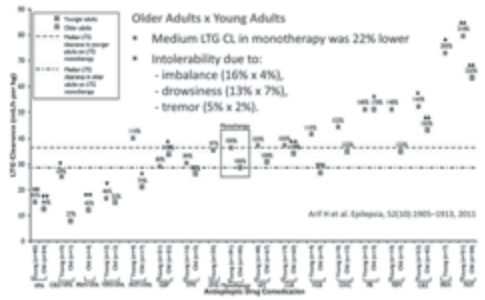
Kutluay et al. Epilepsy & Behav 2003

Valproate in Elderly



Perucca et al. Br J Clin Pharmacol 1984

Lamotrigine in the Elderly



Older Adults x Young Adults

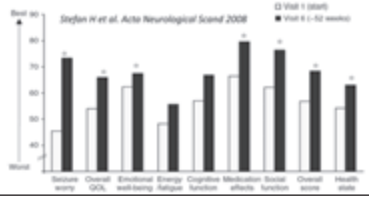
- Medium LTG CL in monotherapy was 22% lower
- Intolerability due to:
  - imbalance (16% x 4%),
  - drowsiness (13% x 7%),
  - tremor (5% x 2%).

Arif H et al. Epilepsia, 52(10):1905–1913, 2011

Topiramate in Elderly

Seizure response rates (%)	All patients (ITT) *N* = 102	Patients, duration of epilepsy <1 year *N* = 51	Patients, duration of epilepsy ≥1 year *N* = 51
≥50	78.4	78.4	78.4
≥75	69.6	74.5	64.7
100	44.1	58.8	29.4[1]

[1]Mean score

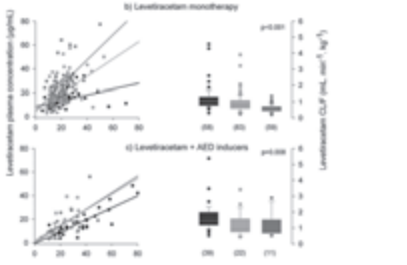


Stefan H et al. Acta Neurological Scand 2008

Seizure worry · Overall QOL · Emotional well-being · Energy fatigue · Cognitive function · Medication effects · Social function · Overall score · Health state

Levetiracetam in Elderly

Elderly dose must be 30% and 50% below the usual adult dose



Contin M et al. Epilepsy Research (2011) xxx

Table 2 Dose-Related Reactions Associated with Individual AEDs (Most Common Association)

Arrhythmias	CBZ and PHT
Hyponatremia and water intoxication	CBZ and OXC
Metabolic acidosis, paresthesias, and oligohydrosis	ZNS and TPM
Macrocytosis and anemia related to folate deficiency	CBZ, PHT, and PHB
Tremor	VPA
Leukopenia	CBZ and PHT
Thrombocytopenia and abnormal platelet function	VPA
Insomnia	LTG and PHB

AEDs, antiepileptic drugs; CBZ, carbamazepine; PHT, phenytoin; OXC, oxcarbazepine; ZNS, zonisamide; TPM, topiramate; VPA, valproic acid; LTG, lamotrigine; PHB, phenobarbital.

Toledano R, Gil-Nagel A – Sem Neurol 2008

Epilepsy in Elderly

Reason to Choice the AED

- Potential to Drug Interaction
- Side Effects Profile
- Global Healthy Condition
- Evidences, Clinical Trials and Day-to-Day Practice

What is the best AED ?

Evidences, Clinical Trials and Day-to-Day Now in Brazil

1ª. Lamotrigine or Gabapentine or Carbamazepine

2ª. Valproate or Oxcarbazepine or Topiramate

3ª. Phenytoin or Phenobarbital

Epilepsy in the Elderly

- Optimize the Treatment
  - Choose AED with adjuvant side effect to the other comorbidities / drugs
  - Start low, increase slowly
  - One daily dose, no more than 2
  - Many small side effects could result in a big problem
  - Always look for not informed side effects

Liverpool Adverse Events Profile (LAEP)

During the past 4 weeks, have you had any of the problems or side effects listed below ?

Symptoms	Always or often	Sometimes	Rarely	Never
Unsteadiness	4	3	2	1
Tiredness	4	3	2	1
Restlessness	4	3	2	1
Feelings of aggression	4	3	2	1
Nervousness and/or aggression	4	3	2	1
Headache	4	3	2	1
Hair loss	4	3	2	1
Problems with skin, e.g., acne, rash	4	3	2	1
Double or blurred vision	4	3	2	1
Upset stomach	4	3	2	1
Difficulty in concentrating	4	3	2	1
Trouble with mouth or gums	4	3	2	1
Shaky hands	4	3	2	1
Weight gain	4	3	2	1
Dizziness	4	3	2	1
Sleepiness	4	3	2	1
Depression	4	3	2	1
Memory Problems	4	3	2	1
Disturbed sleep	4	3	2	1

Martins H et al. The Portuguese–Brazilian validation of the Liverpool Adverse Events Profile - Epilepsy Behav 2011

Don´t forget ...

- Make clear:
  - Goal of treatment
  - Regular use of AED
  - How to deal with the seizures
  - Need of active life, if possible independent
- Make easy:
  - Treatment schedule
  - Medications box
- Bring ALL medication package in use at next visit

No more seizures. What to do ?

- Seizure Free ?
  - Seizure free after 1 year 61 - 89%
  - Only 1 - 3 seizures in 68% patients
- AED Withdrawal ?
  - No clinical trials, but the cause is still present and neuroplasticity is almost zero
  - Keep AED
- Independent Life
  - Try to keep previous way of life
  - Do not add ineffective restritions because the family ask for them

Epilepsy Surgery in Elderly

Medically Refractary Epilepsy

- Lesionectomy
  - If possible, always
- Anterior Temporal Lobectomy
  - Same indications and almost same results

Epilepsy in the Elderly

- Jose, 76 years old
  - Probable seizure during sleep last week
  - MRI and EEG "normal" for age
  - Arterial hypertension well controlled
  - losartan 50 mg/day, aspirin 100 mg/day
  - Very active and independent life

Jose, 76 years old

Possible Epileptic Seizure

- What should we do ?
  - Define as a epileptic seizure and high risk of recurrence ?
  - Look for other causes of "seizure" ?
  - Try a "therapeutic test with AED" ?

Jose, 76 years old

Possible Epileptic Seizure

- What I did ?
  1. Investigation other causes loss of conscience
  2. Epileptic seizure not confirmed, so do not start AED
  3. Orientation to patient and family what to do in case of another seizure
  4. Do not drive for at least 30 days

Epilepsy in the Elderly

- Beatriz, 82 years old
  - Rare partial complex and TCG seizures since stroke two years ago
  - MRI sequel of right media cerebral artery infarcts
  - EEG slow activity on right temporal lobe
  - Discreet right hemiparesis
  - Diabetes, arterial hypertension, dyslipidemia, osteoporosis, peptic acid reflux, insomnia, depression
  - Metformin, hydrochlorothiazide, sinvastatin, clopidogrel, omeprazole, clonazepan, citalopram, bisphosphonate (8 drugs)
  - Phenytoin 300 mg/day

Beatriz, 82 years old

Symptomatic Localized Epilepsy

- What should we do ?
  - Adjust PHT dose ?
  - Change AED ? OXC ? LMT ? VAL ? LEV ?
  - Supplemental calcium and vitamin D ?

Beatriz, 82 years old

Symptomatic Localized Epilepsy

- What I did ?
  - Started valproate 250 → 500 mg/day in 30 days
  - Reduced phenytoin. Stopped it in 30 days
  - Vitamin D 400 IU daily

Asla Pitkanen (Finland)

CIRCUITRY MECHANISMS IN SYMPTOMATIC EPILEPSY

Molecular Mechanisms
- Symptomatic Epilepsy -

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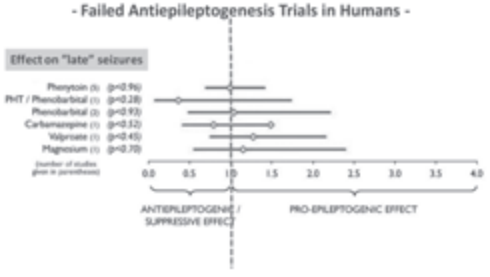
1. Introduction - The Challenge
2. Target Identification – 'Omics
3. A Journey from Array to Functional Characterization of "Epileptogene"
4. How To Get Further

The "Driving Force"
- Failed Antiepileptogenesis Trials in Humans -



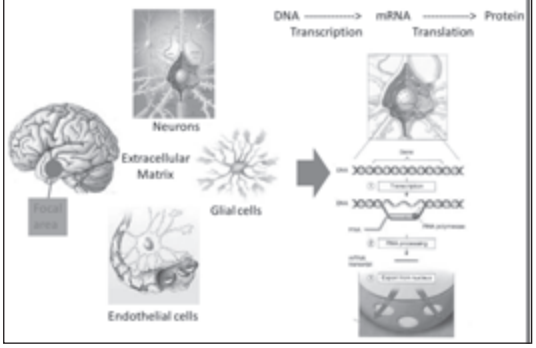
No evidence of favorable effect

Identification of AEG Treatments

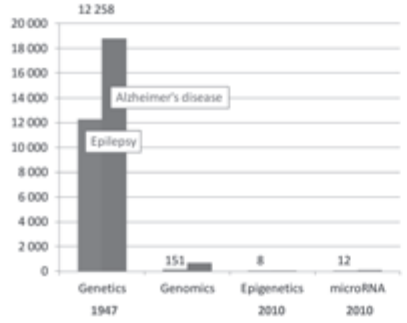
- A 5-Step Path From Lab To Clinic -

NINDS Workshop 8/2010

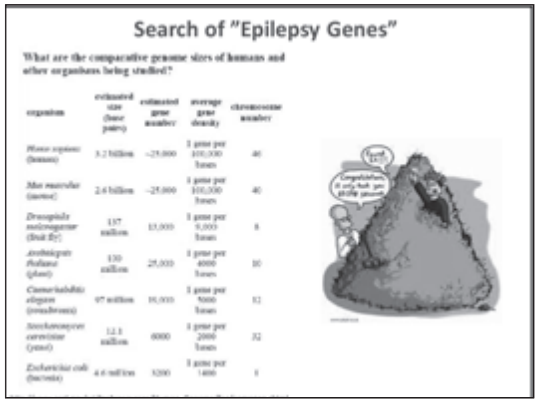
The Challenge



PubMed Search (2/2012)

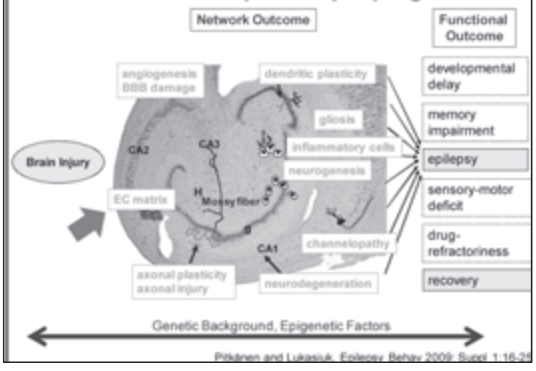


Search of "Epilepsy Genes"



Contents

Anatomics of Acquired Epileptogenesis



Pitkänen and Lukasiuk, Epilepsy Behav 2009; Suppl 1:16-25

Transcriptomics

	Status epilepticus (chemically induced)			
	Okamoto et al[24]	Becker et al[25]	Elliott et al[26]	Lauren et al[27]
Species	Rat	Rat	Rat	Juvenile rats
Induction method/drug	Pilocarpine	Pilocarpine	Pilocarpine	Kainic acid
Video-EEG monitoring	Yes	No	No	No
Gene expression platform?	CodeLink	Affymetrix	Affymetrix	Illumina
Day of tissue sampling	7	14	14	7
Brain structure	Hippocampus	Dentate gyrus or CA1	Dentate gyrus	CA1
Regulated genes (n)	328	50 in dentate gyrus, 400 in CA1	129	1592
Immune response	Yes	No	Yes	No
Inflammatory response	Yes	No	No	Yes
Response to wounding	No	No	Yes	No
Regulation of cell death/cell damage	Yes	Yes	No	Yes
Signal transduction	Yes	Yes	Yes	Yes
Lipid metabolism	No	No	No	No

Caveats

- species
- injury type
- age
- time of sampling
- brain area
- analysis
- platform
- analysis
- algorithm
- bioinformatics

Transcriptomics (SE, TBI models)

Function	Number of genes	Official gene symbol
cell-cell signaling	12	C1QA, GABRD, NPY, GRIA2, SLC6A1, SYT4, NPTX2, APOE, GRIN2C, CAMK2G, GABRA5, GABARAP
ion transport	12	KCNC2, GABRD, NPY, GRIA2, SCN3B, GRIN2C, CAMK2G, SCN2A, GABRA5, CAMK1B, CACNG2, KCNK1
synaptic transmission	10	GABRD, NPY, GRIA2, SLC6A1, SYT4, NPTX2, APOE, GRIN2C, GABRA5, GABARAP
regulation of cell proliferation	9	PTPN6, PPP3R1B, PTGS2, APOE, GRN, CLU, CD81, IL6R, SPARC
response to wounding	8	C1QA, PTPN6, C1QB, GRIN2C, CLU, IL6R, CTSB, C1QC
immune response	8	C1QA, C1QB, CLU, IL6R, CTSB, C1QC, CD74, B2M
behavior	7	PTGS2, NPY, SLC6A1, S100B, GABRA5, IL6R, CALB1
regulation of apoptosis	7	PTGS2, APOE, CLU, DNAJC3, IL6R, CTSB, CD74
leukocyte mediated immunity	6	C1QA, C1QB, CLU, IL6R, C1QC, CD74
regulation of synaptic transmission	6	PTGS2, GRIA2, SLC6A1, APOE, GRIN2C, CALB1
adaptive immune response	5	C1QA, C1QB, CLU, C1QC, CD74
learning or memory	5	PTGS2, SLC6A1, S100B, GABRA5, CALB1
inflammatory response	5	C1QA, C1QB, CLU, IL6R, C1QC
cell proliferation	5	RPS27, NPY, S100B, CD81, CD74
regulation of phosphorylation	5	PPP3R1B, APOE, CD81, IL6R, CD74
complement activation	4	C1QA, C1QB, CLU, C1QC
regulation of synaptic plasticity	4	PTGS2, APOE, GRIN2C, CALB1
response to steroid hormone stimulus	4	C1QB, PTGS2, SLC6A1, IL6R
lipid transport	3	NPC2, APOE, CLU
response to oxidative stress	3	PTGS2, APOE, CLU

Total 46 common genes

Regulated both by SE and TBI (17/46)

"Molecular Noise"

Epigenetics - Definitions

The interaction of genes with their **environment** which bring the phenotype into being

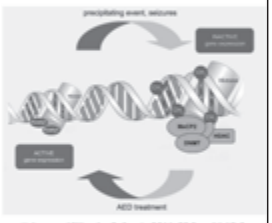
(Conrad Hal Waddington, 1940)

Mitotically and/or meiotically **heritable** variations in gene expression that are **not caused by changes in DNA sequence**

(Russo et al., 1996)

Structural adaptation of chromosomal region so as to register, signal, or perpetuate altered activity states

(Bird, 2007)



Kobow and Blümcke, Epilepsia 2011: 52 Suppl 4:15-9

Epigenetics

Epigenetic pathway	Observation	Experimental model
DNA methylation	⇧ or ⇩	Rat TBI
		Human TLE
Histone methylation	H3 methylation ⇩	TBI in immature rats
Histone acetylation	H3 acetylation ⇩	TBI in rats, mice
	H4 acetylation at c-fos and BDNF promoters ⇧	EC seizures in rat
	H4 acetylation at GluR2 promoter ⇩	Pilocarpine induced SE in rat
	H4 acetylation at BDNF P2 promoter ⇧	
	H4 acetylation ⇧	Kainate induced SE
Histone phosphorylation	H3 phosphorylation ⇧	Pilocarpine or kainate induced SE in mice

Issue of VPA (HDAC inhibition)

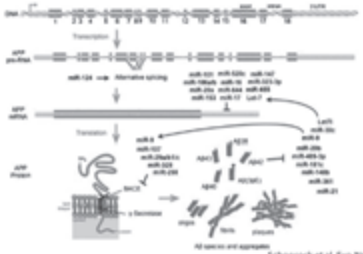
Antiepileptogenesis and Co-morbidity modification?

- inflammatory response
- neurodegeneration
- learning and memory
- motor recovery

microRNAs

- short non-coding RNAs that bind mRNAs through partial base-pair complementarity with their target genes, resulting in post-transcriptional **repression** of gene expression

An Example from AD (~8% have epilepsy)

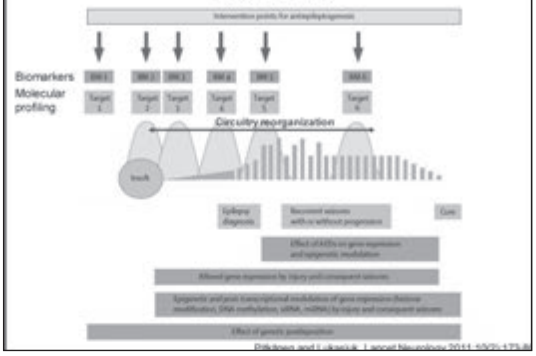


microRNAs in Epilepsy

Model	Time point	Tissue	microRNA	Target	Reference
SE Pilocarpine	< 8 h	HC	miR-132	Dendritic plasticity	Nudelman et al., 2010
SE Kainate	24 h TaqMan microRNA array (381)	HC blood	HC: 21 Blood: 31		Liu et al. 2010
SE el. stimulation	1 wk, 3-4 months	HC	miR-146a	Inflamamtion	Aronica et al., 2010
Human TLE		HC	miR-146a	Inflammation	Aronica et al., 2010
SE Li-pilocarpine	24 h Rat microRNA array (113)	HC blood	19⇩, 7⇧ 4		Hu et al., 2011
SE Li-pilocarpine	≤50 d µParaflo™ microRNA array (125)	HC blood	23⇩, 5⇧		Song et al., 2011
SE i.a. kainate	24 h TaqMan microRNA array (381)	CA3	21⇩, 12⇧		Jimenez-Mateos et al., 2011
SE Li-pilocarpine	< 3wk Exicon 10.2 array	HC	miR-21 miR-21*	NT-3-3	Risbud et al., 2011
SE kainate	2 h NCode™ microarray (258)	HC			Casas et al., 2012

Epileptogenic Molecular Reorganization

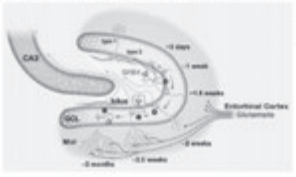
"Epileptogenomics"



Pitkänen and Lukasiuk. Lancet Neurology 2011;10(2):173-86

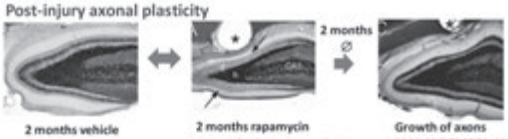
Time Schedule for Circuitry Repair - Examples

Intergration of newly-born neurons into network



Zhang et al.
Cell 2008;132:645-660

Post-injury axonal plasticity



Buckmaster et al. J Neurosci 2009;29(26):8259-69

Where Are We?

"Like a Kid in a Candystore"

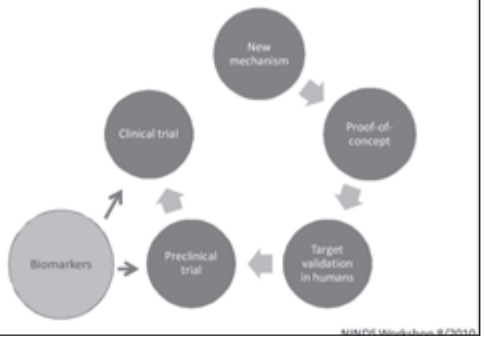
Are populations of Rats w/Epilepsy Any Easier to Study Than Humans?

... they all look the same, but...

Contents

Identification of AEG Treatments

- A 5-Step Path From Lab To Clinic -



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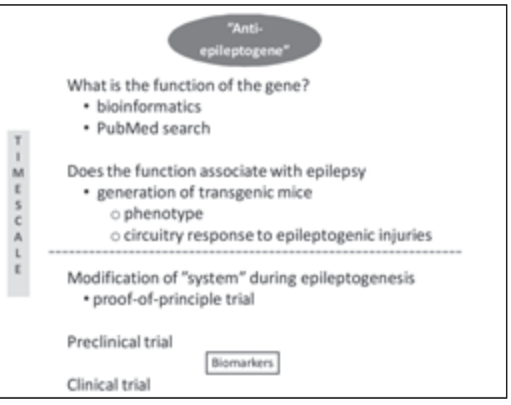


Cantidate Epileptogenes

Cystatin C
Urokinase-type plasminogen activator
Secreted phosphoprotein 1 (osteopontin)
Tweety homolog 1
Sodium channel type 7 subunit A
Transforming growth factor β
Prostagrandin G/H synthase 2 (COX-2)
Ferritin

Most targets no rigorously tested in animal models

Conclusion

☹

Pitkänen and Lukasiuk, Lancet Neurology 2011;10(2):173-86

Gene ice-fishing in March 1999 (Kuopio, Finland)

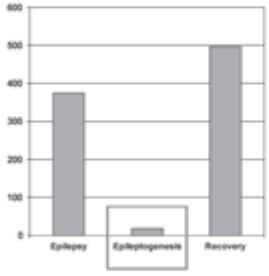
gene

uPA (urokinase-type plasminogen activator) – 7-fold increase

gene

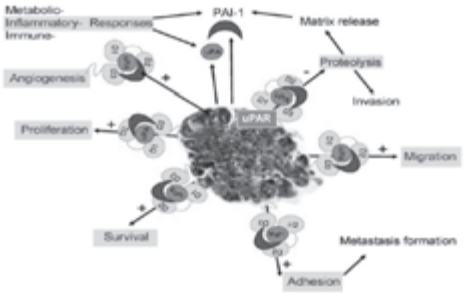
PubMed Search (9/2009)

Proteinase and ...

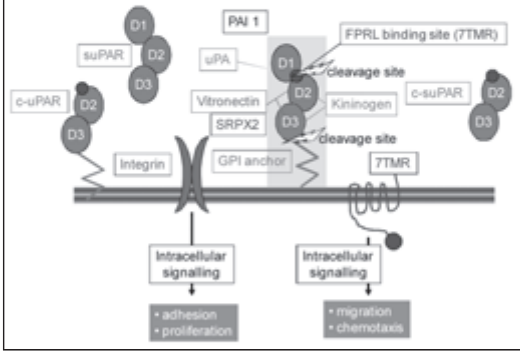


Urokinase-type Plasminogen Activating System

Pleiotrophic Function in Cancer Cells



uPAR Interactome



- Previous studies -

uPA and uPAR expression ⇧
during the 2 wk post-SE in rat

also in human epileptic tissue

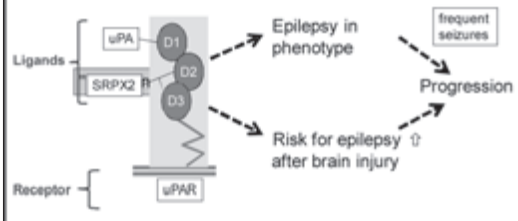
- Question -

Does uPAR interactome
modify tissue remodeling after
epileptogenic injury?

Lukasiuk et al. Eur J Neurosci 2002;17(2):271-9; Lahtinen et al. Eur J Neurosci 2006;24(7):1935-41; Lahtinen et al. Neuroscience 2009;163(1):316-28; Lahtinen et al., Neurobiol Dis 2010;37(3):692-703; Louet et al. J Neurosci Res 2010;88(13):2447-54; Iwaki et al., Neuroscience 2010;168(3):797-810;

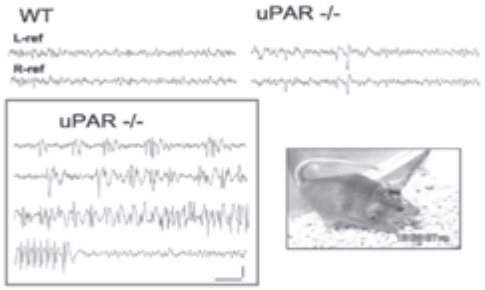
Hypothesis

"Bad gene" in uPAR system



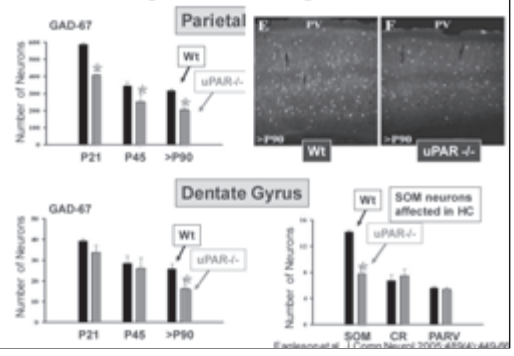
uPAR -/-

Spontaneous Seizures in 4% of Mice



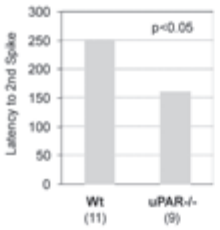
uPAR -/-

Reduced Migration of GABAergic Interneurons



uPAR -/-
Increased Excitability and Behavioral Activity

PTZ Seizure Threshod Test



Behavioral Testing

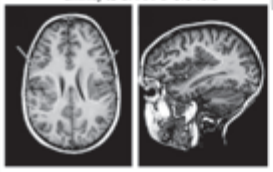
- increased activity in open-field
- poor learning of contextual fear-conditioning
- spatial memory normal

Rantala and Pitkänen (unpublished)

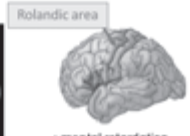
SRPX2 Mutation in Humans
Sushi-Repeat Protein, X-linked 2 (uPAR ligand)

Rolandic epilepsy with bilateral perisylvian polymicrogyria

- glycosylation ⇧
- affinity to uPAR ⇧ 5.8-fold



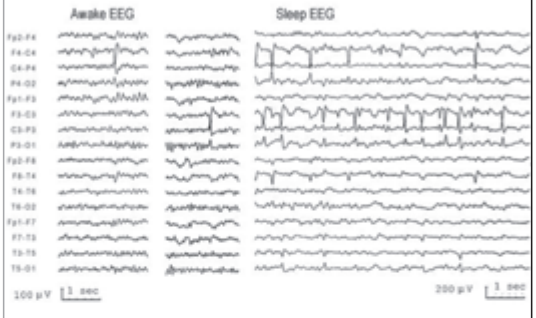
Rolandic epilepsy with speech dyspraxia (RESDX syndrome)



- mental retardation
- attention defect
- visuo-spatial impairment
- MRI normal

Rollet al., Hum Mol Genet. 2006;15(7):1195-207; Royer-Zemmour et al. Hum Mol Genet 2008;17(23):3617-30

SRPX2 Mutation in Humans
Sushi-Repeat Protein, X-linked 2 (uPAR ligand)



Summary I

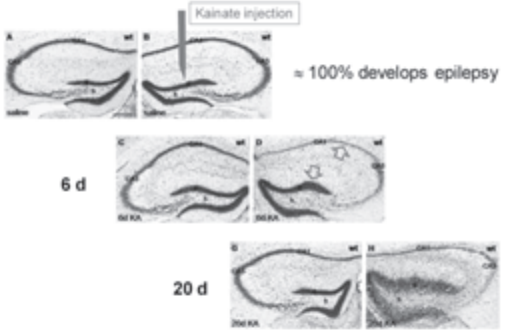
Mutations in uPAR system associate with epilepsy or increased seizure susceptibility in mouse and human

Next Question

"Bad gene" in uPAR system

Study Design

i.h. Kainate Model



Boulleret V et al. Neuroscience 1999;89(3):717-29; Lahtinen et al., Neurobiol Dis 2010;37(3):692-70

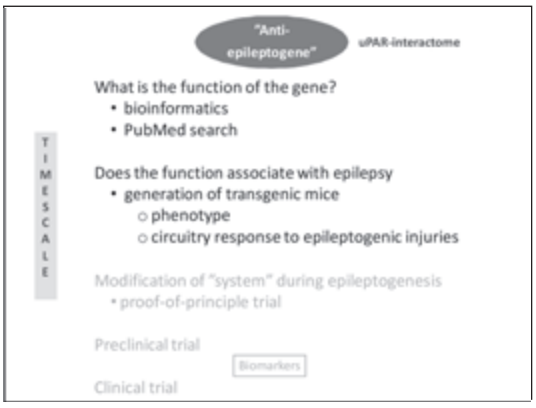
Unpublished data not included in slide handout

Candidate Epileptogene - Summary

1. Mutation(s) in uPAR-system associate with epilepsy
2. uPAR-system affects several components of post-injury circuitry reorganization
3. uPAR-system has a disease-modifying effect on acquired epileptogenesis

---

4. What are the downstream molecular mechanisms of uPAR-system activation in post-injury brain?
5. How are the interactions with other components of proteolytic system coordinated
6. Drug targets and biomarkers?



How To Get Further?

- ❑ Define the clinical need
- ❑ Find a target: Hypothesis-driven or not?
- ❑ Functional analysis: Do not give up
- ❑ Optimization of proof-of-principle and preclinical study designs
  - ❑ to avoid false negative findings
- ❑ Definition of criteria to move from lab to clinic
  - ❑ to convince the clinician
  - ❑ to convince the regulatory officer
- ❑ Can the target be used for biomarker development
- ❑ Contribute to efforts which aim at ensuring research funding

Epilepsy Research Group

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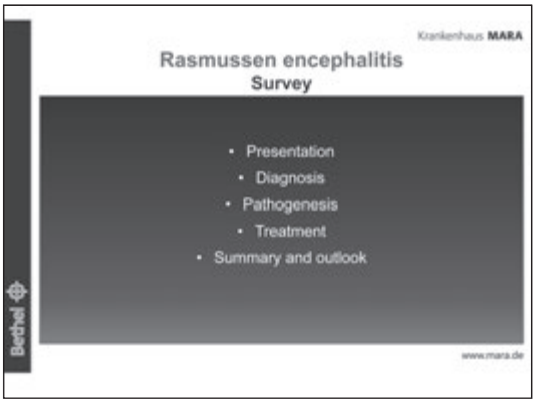
Funding
- **Academy of Finland**
- **Sigrid Juselius Foundation**
- **The Finnish Technology Fund**
- **NIH/NINDS** (R21 NS049525)
- **EU (EpiCURE)** (LSH-CT-2006-037315)
- **CURE (USA)**
- **ESF EpiGENet**

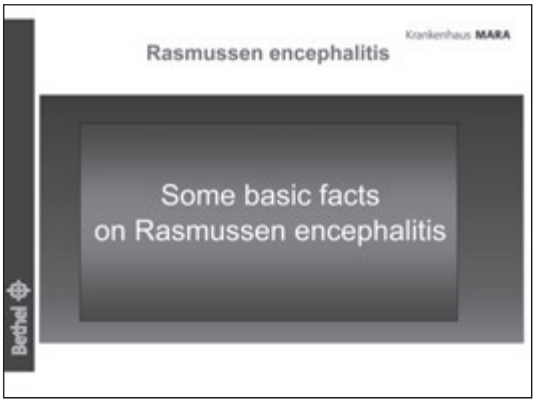
Fernando Lopes da Silva (Netherlands)

NEURONAL HYPEREXCITABILITY: BIOMARKERS OF EPILEPTOGENICITY

Christian Bien (Germany)

RASMUSSEN'S ENCEPHALITIS

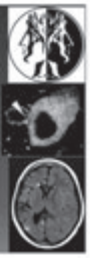




Krankenhaus **MARA**

Rasmussen encephalitis
- Three basic facts -

1. RE has two faces:
   - The progressive monohemispheric neurological deficit
   - The intractable epilepsy
2. Cytotoxic T cells are pathogenic key players.
   They kill neurons and astrocytes
   T cells can be suppressed
3. RE is a monohemispheric disease.
   Hemispherectomy is highly effective against seizures



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Krankenhaus **MARA**

Rasmussen encephalitis

Presentation

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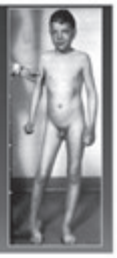
Rasmussen encephalitis
- Characteristics -

- Rare disorder, mainly of children:
  85% < 10 years
- Pharmacoresistant epileptic seizures,
  unilateral Epilepsia partialis continua
- Progressive cerebral hemiatrophy
- Progressive unilateral deficit
- Histology: chronic encephalitis,
  neuronal loss



Rasmussen et al. 1958. Montreal Series, 1958

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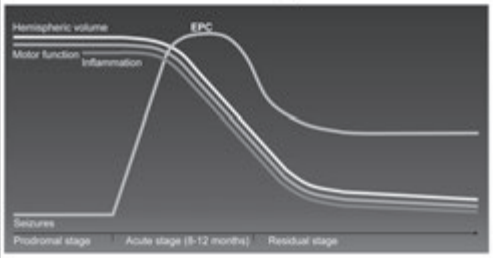
Rasmussen encephalitis
- Natural history -



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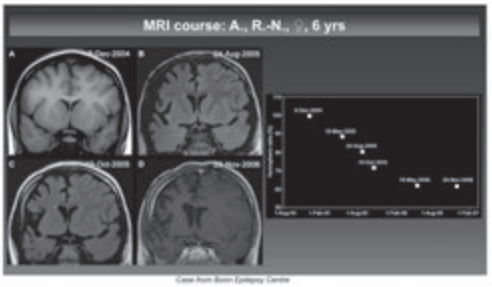
Rasmussen encephalitis



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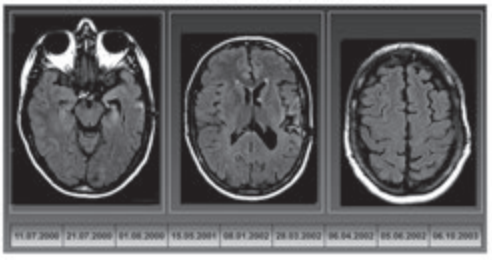
Rasmussen encephalitis

- Patient T.,P.,♀, *04.08.1961: MRI course -



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Rasmussen encephalitis

Diagnosis

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Rasmussen encephalitis

Pathogenesis, diagnosis and treatment of Rasmussen encephalitis
A European consensus statement

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Rasmussen encephalitis
- European Consensus: Diagnostic criteria -

Part A (all 3 must be fulfilled):		
1.	Clinical	Focal szs (+/- EPC) *and* unilateral cortical deficit(s)
2.	EEG	Unihemispheric slowing +/- ED *and* unilateral sz onset
3.	MRI	Unihemispheric focal cortical atrophy *and* ≥ 1 *of the following:* (1) GM or WM T2/FLAIR hyperintense signal, (2) Hyperintense signal or atrophy of ipsilateral caudate head
Part B (2 must be fulfilled):		
1.	Clinical	EPC or progressive unilateral cortical deficit(s)
2.	MRI	Progressive unihemispheric focal cortical atrophy
3.	Histopathology	T cell dominated encephalitis with activated microglial cells and reactive astrogliosis

Bien, Granata et al., Brain 2005

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Rasmussen encephalitis

Pathogenesis

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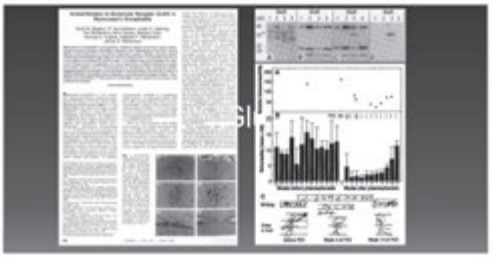
Rasmussen encephalitis
GluR3 antibodies



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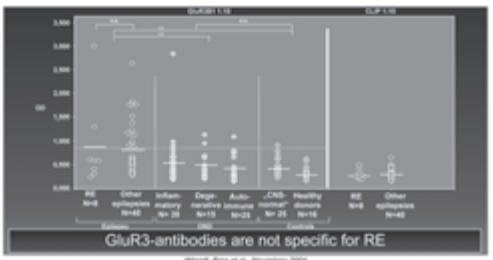
Rasmussen encephalitis
GluR3 antibodies



GluR3-antibodies are not specific for RE

Wandi, Bien et al., Neurology 2001
Similar: Mantegazza, J Neuroimmunol 2002, Watson, Neurology 2004

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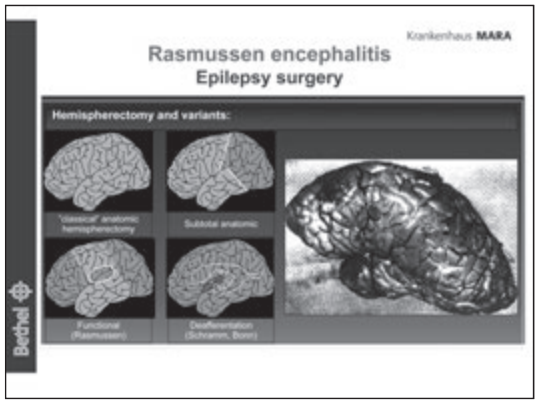
Krankenhaus MARA
Rasmussen encephalitis
Epilepsy surgery
Hemispherectomy and variants:
"classical" anatomic hemispherectomy
Subtotal anatomic
Functional (Rasmussen)
Deafferentation (Schramm, Bonn)
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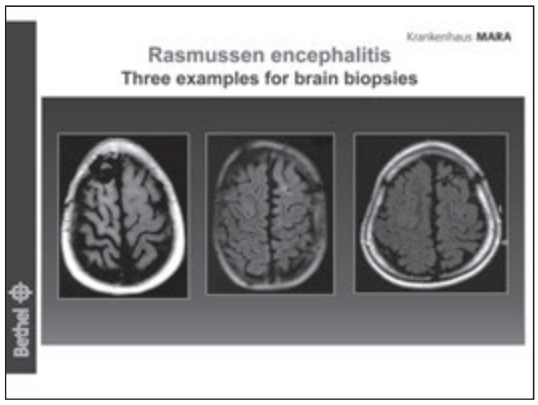
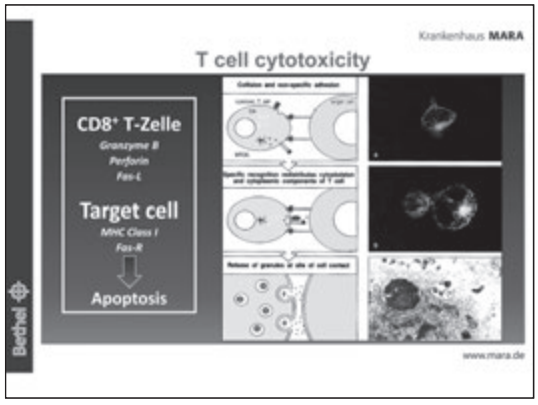

Krankenhaus MARA
Rasmussen encephalitis
Three examples for brain biopsies
Bethel


Krankenhaus MARA
T cell cytotoxicity
CD8+ T-Zelle
Granzyme B
Perforin
Fas-L
Target cell
MHC Class I
Fas-R
Apoptosis
www.mara.de
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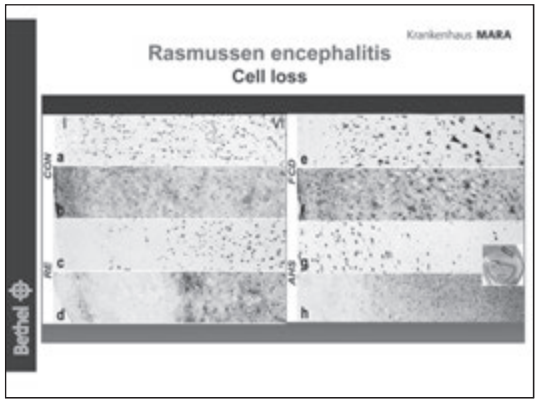
Krankenhaus MARA
Rasmussen encephalitis
Cell loss
CON
FCD
INF
AHS
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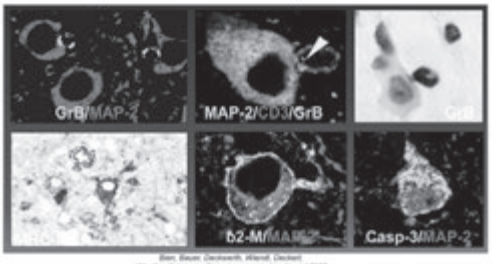
Rasmussen encephalitis: Pathomechanisms
- Cytotoxic T cell attack against neurons -



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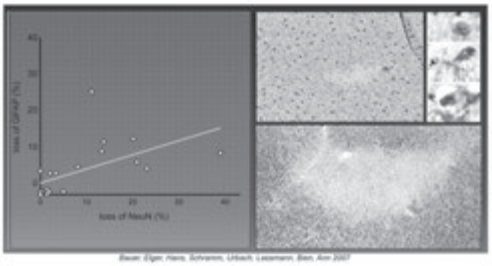
Rasmussen encephalitis: Pathomechanisms
- Astrocyte loss -



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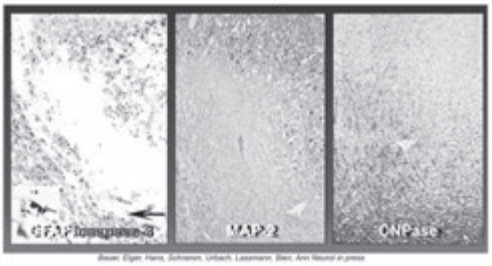
Rasmussen encephalitis: Pathomechanisms
- Cortical astrocyte loss -



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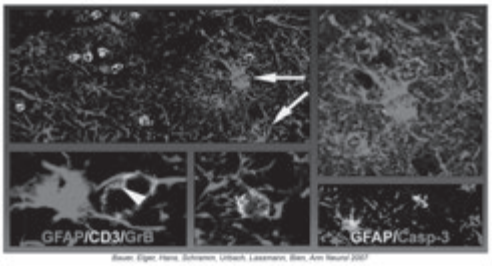
Rasmussen encephalitis: Pathomechanisms
- Cytotoxic T cell attack against astrocytes -



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Rasmussen encephalitis

Treatment

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Rasmussen encephalitis
- Its two faces -

The progressive neurological deficit	The drug-resistant epilepsy
Cause: Progressive hemiatrophy	**Cause:** unclear
Duration: 8-12 months	**Duration:** Whole disease course
Age: Children > Adults	Not in all cases!
Immunotherapy	**Hemispherectomy**

Bien et al., under review

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Rasmussen encephalitis
Conservative treatment

	N	Median age at disease onset (yrs)	Median duration until treatment (yrs)	Seizures	Neurological functions	Complications
IVIG	7	11,5	3	↓ - ↓↓	↑	-
Steroids	18	~5	~3	↓ - ↓↓	partly ↑	++
IVIG + Steroids	19	5,5	~3	temp ↓↓	partly ↑	++
Cyclophosphamide	1	15	14	temp ↓	temp ↑	-
Intraventricular IFN-α	2	3,7	1,2	↓↓	↑/=	+
Plasmapheresis/ IgG-Immunoadsorption	6	~7	~4	partly, temp ↓	partly, temp ↑	+/++
Ganciclovir	4	6,5	1,8	partly, temp ↓	partly, temp ↑	-
Zidovudine (AZT)	1	14	4	temp ↓ ↓	=	+

Bien & Wiendl, Expert Op Exp Drugs 2002

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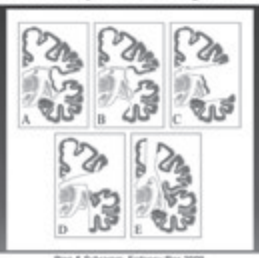
Rasmussen encephalitis
Functional hemispherectomy techniques



Bien & Schramm, Epilepsy Res 2009

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Rasmussen encephalitis
Consequences of hemispherectomy

Motor function

- Upper extremity: Use of fine finger movements of day-to-day relevance?
- Lower extremity: ambulatory prior to HE → ambulatory after HE

Language

- Disease onset before age 4(-6): high chance of transfer
- Language deterioration during disease course: incomplete language transfer?

→ Wada test!

Visual field

- Examination often not possible (cooperation)
- Rarely a relevant contraindication for HE

Bien & Schramm, Epilepsy Res 2009

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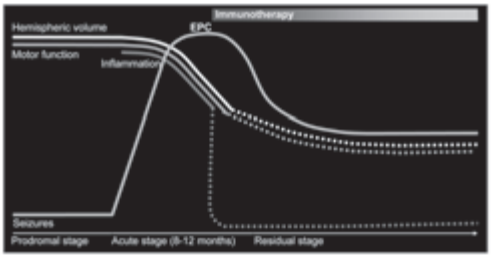
Rasmussen encephalitis
- Natural course and expected effect of immuno-tx-



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Rasmussen encephalitis
- Therapeutic consequences -

Functional deficit	Refractory epilepsy	Non-refractory epilepsy
High-grade	Hemispherectomy (≥80% sz freedom rate)	0-1 AED
Low-grade	Try immuno-tx. If unsatisfactory: Consider hemispherectomy	0-1 AED + long-term IVIG or tacrolimus

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Krankenhaus **MARA**

Rasmussen encephalitis

Summary and outlook

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Rasmussen encephalitis
Summary and outlook

Disease cause?

- Which antigen do the T cells recognize?

Causative treatment?

- Depending on antigenic target

Early treatment

- Long-term tacrolimus or IVIG for pats. with less severe epilepsy
- In cases with refractory epilepsy: consider hemispherectomy

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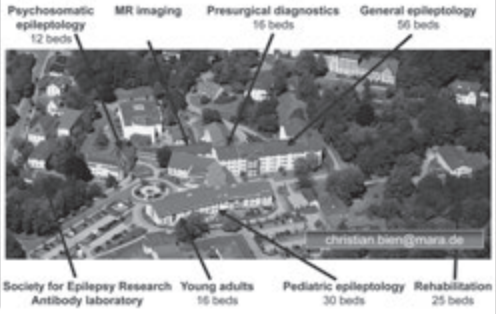
Epilepsy Centre Bethel: Hospital



Bethel

Marco de Curtis (Italy)

ICTAL AND INTERICTAL PROCESSING MECHANISMS

Ictal and interictal mechanisms

FONDAZIONE IRCCS ISTITUTO NEUROLOGICO CARLO BESTA

Marco de Curtis

Unit of Neurophysiology and Experimental Epileptology

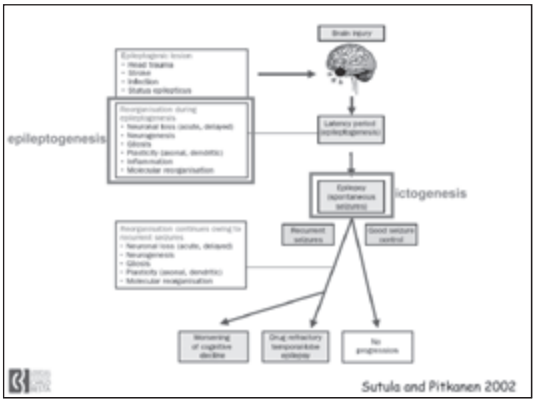
Research priorities in epilepsy for the next decade—A representative view of the European scientific community: Summary of the ILAE Epilepsy Research Workshop, Brussels, 17–18 January 2008

ILAE Commission on European Affairs Task Force

W Beuter, E Aronica, Y Ben-Ari, C Bernard, M Brodie, C Chiron, M de Curtis, J Duncan, A Friedman, JM Fritschy, O Grohn, A Gueltrini, O Kuhlmann, R Kate, R Kjeling, H Lerche, W Lyashet, M Kokaia, T Manson, J Mifsud, C Odhana, A Pitkanen, P Rydin, L Sander, F Semah, J Serratosa, S Shorvon, T Tomson, A Vezzani.

Box 5. Research priorities to understand mechanisms of seizure generation (ictogenesis)

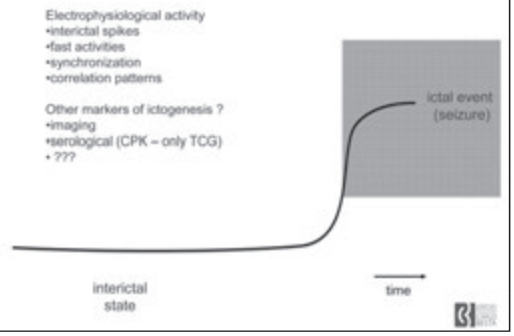
- Identify seizure patterns and study the underlying mechanisms in different forms of human epilepsy by using advanced neurophysiologic and functional imaging tools
- Reproduce the ictal patterns observed in humans in animal models and in postsurgical human tissue in order to study network, cellular and molecular changes that correlate to the ictal transition (focus on neurons, glia, and neurovascular interactions)
- Utilize the identified mechanisms to develop novel strategies to detect or prevent progression to seizures—that is, either new drugs or functional interventions
- Organize and reinforce epilepsy surgery and functional interventional centers in Europe to improve presurgical diagnostic assessment and treatment of drug-resistant epilepsies, with particular emphasis on refractory pediatric forms



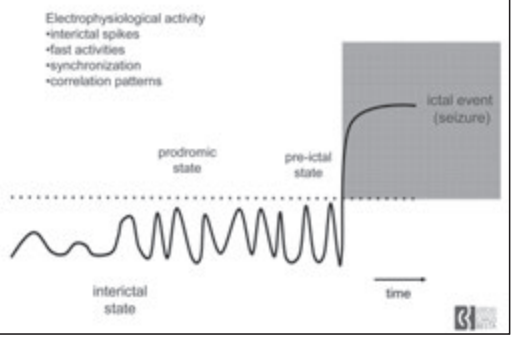
interictal / ictal

- ictal events = seizures
- interictal state = the condition of an "epileptic" brain between seizures
- defined by clinical means
- assessed by EEG (and other diagnostic tools?)
- the identification of interictal-ictal EEG patterns has a diagnostic and prognostic value
- the study of the mechanisms of ictogenesis (and the interictal state) is usefull to develop new therapeutic strategies

interictal / ictal



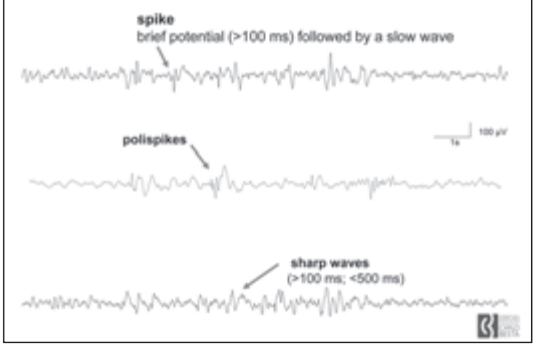
interictal / ictal



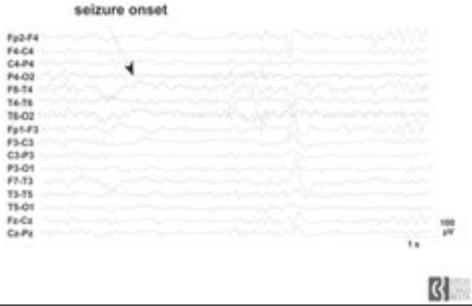
study of ictogenesis in focal epilepsies

- video EEG recordings: electroclinical correlates
- intracranial recordings: direct access to cortical generators during pre-surgical studies
- animal models: test hypotheses on ictogenesis

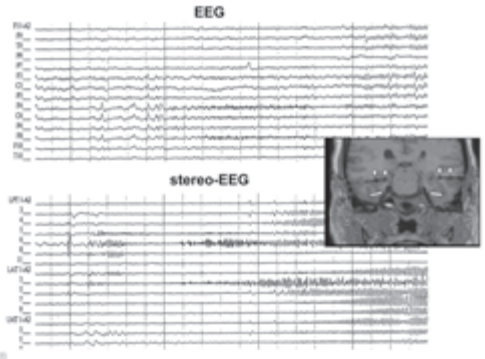
focal interictal EEG patterns



focal ictal EEG patterns

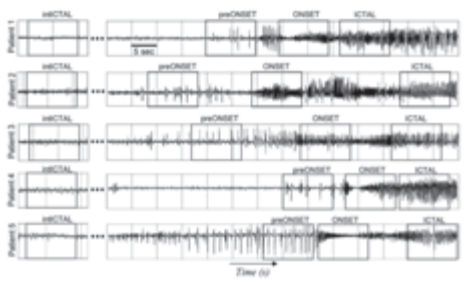


EEG

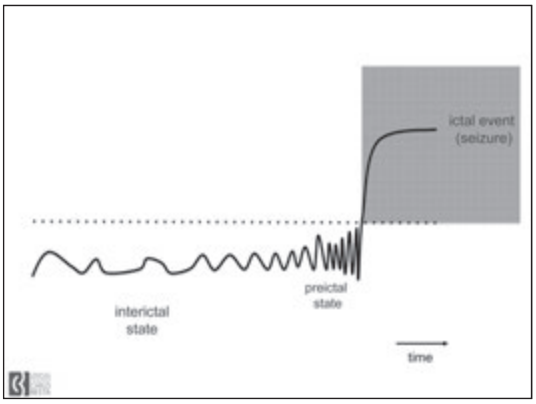


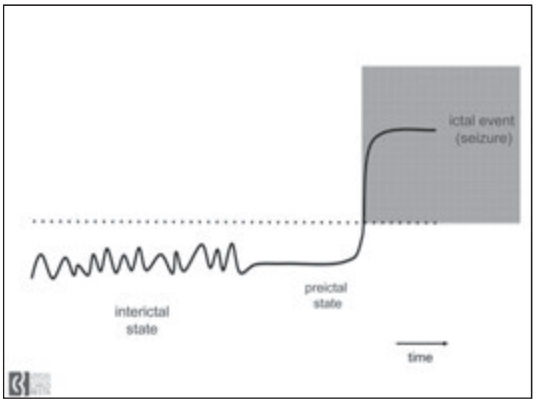
Pacia and Ebersole 1997

temporal lobe epilepsy



Wendling et al., 2004



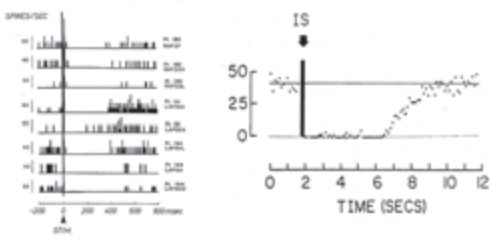


interictal spikes and pre-ictal state

- Pre-ictal patterns may correlate with
  - reinforcement of interictal spikes
  - a marked decrease in interictal spike frequency
- Interictal spikes are not required to initiate a seizure
- Interictal spikes and ictal discharges can be generated in different cortical areas
- The induction of interictal spikes may prevent seizure generation

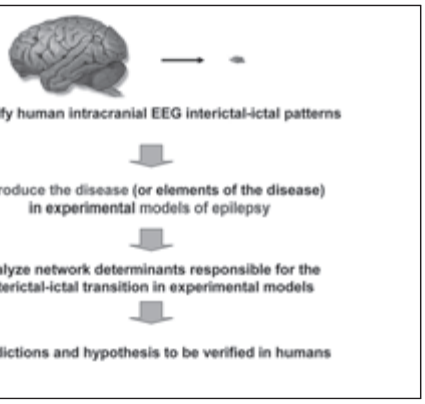
reviewed in de Curtis and Avanzini 2001

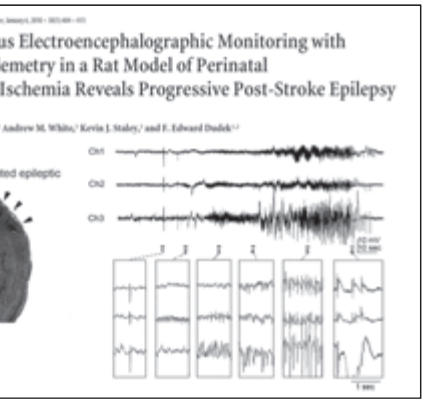
interictal spikes are followed by a period of inhibition

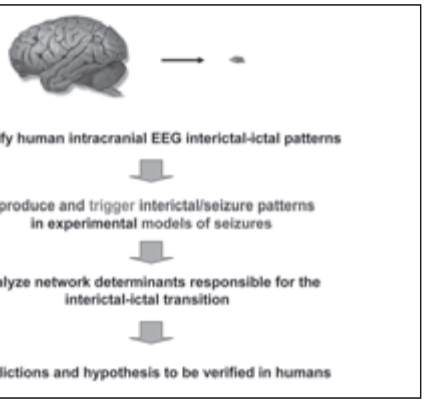


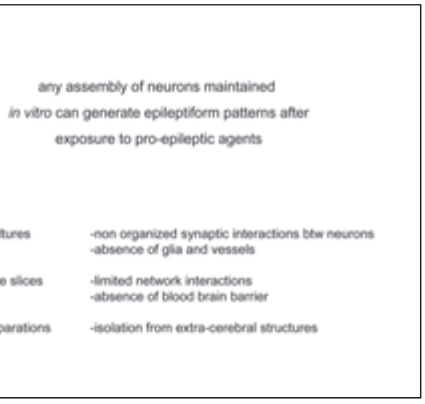
Isokawa-Akesson et al., 1989

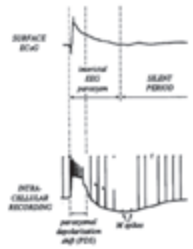
Lebovitz, 1979


identify human intracranial EEG interictal-ictal patterns
reproduce the disease (or elements of the disease) in experimental models of epilepsy
analyze network determinants responsible for the interictal-ictal transition in experimental models
predictions and hypothesis to be verified in humans


Continuous Electroencephalographic Monitoring with Radio-Telemetry in a Rat Model of Perinatal Hypoxia–Ischemia Reveals Progressive Post-Stroke Epilepsy
C Right/HI-treated epileptic
Ch1
Ch2
Ch3
1 sec

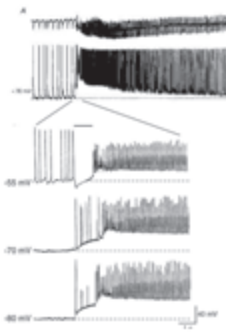

identify human intracranial EEG interictal-ictal patterns
reproduce and trigger interictal/seizure patterns in experimental models of seizures
analyze network determinants responsible for the interictal-ictal transition
predictions and hypothesis to be verified in humans


any assembly of neurons maintained
in vitro can generate epileptiform patterns after
exposure to pro-epileptic agents
Neuron cultures
-non organized synaptic interactions btw neurons
-absence of glia and vessels
Brain tissue slices
-limited network interactions
-absence of blood brain barrier
In toto preparations
-isolation from extra-cerebral structures



Ayala et al., 1970

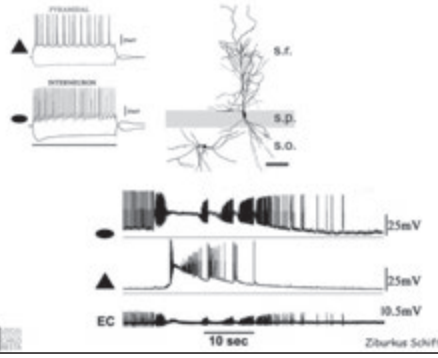
in vitro rodent brain slices



ictal events
in vitro
can be initiated
by inhibition

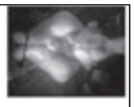
Avoli et al, 2002

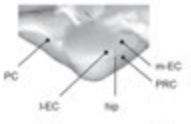
in vitro rodent brain slices

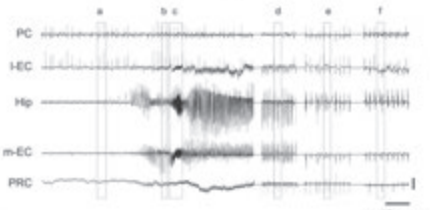


Ziburkus Schiff et al 2006

isolated *in vitro* guinea pig brain

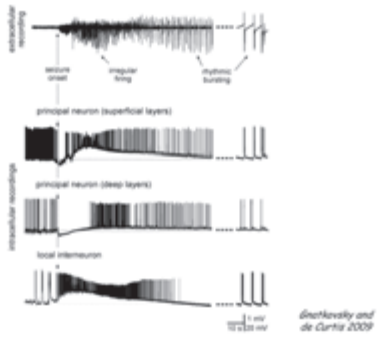






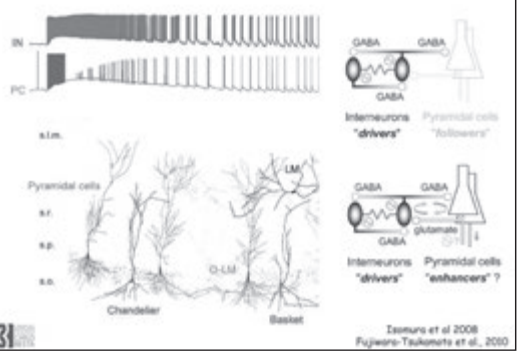
Uva PPSI, 2006

isolated *in vitro* guinea pig brain



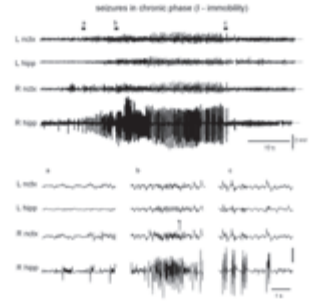
Gnatkovsky and de Curtis 2009

in vitro rodent brain slices

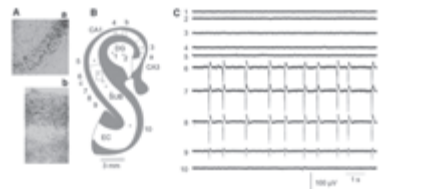


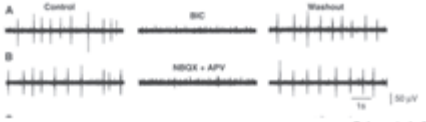
Isomura et al 2008
Fujiwara-Tsukamoto et al., 2010

focal ictal EEG pattern in vivo



human post-surgical tissue *in vitro*





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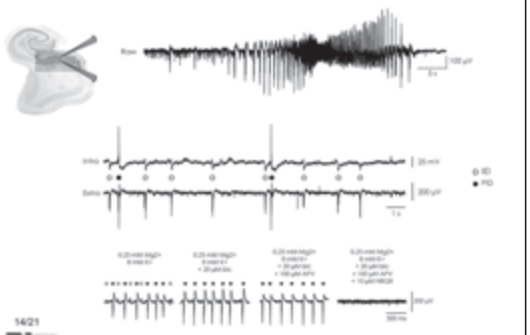
Cohen et al., 2002

human post-surgical tissue *in vitro*



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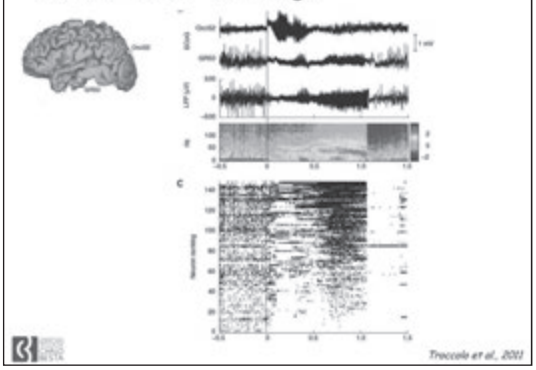
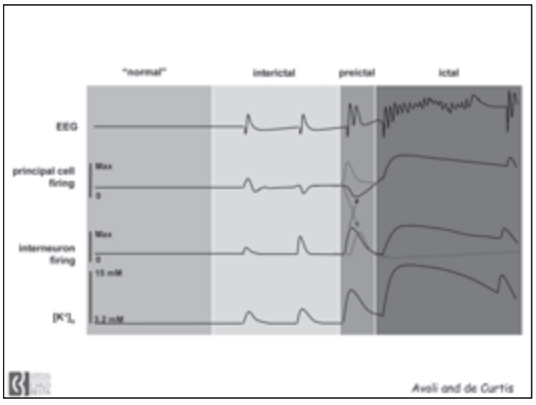
Huberfeld et al., 2011

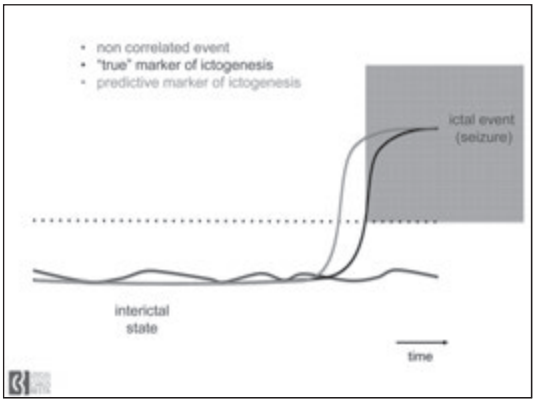
human "in vivo" recordings



Trevelyan et al., 2011



Avoli and de Curtis



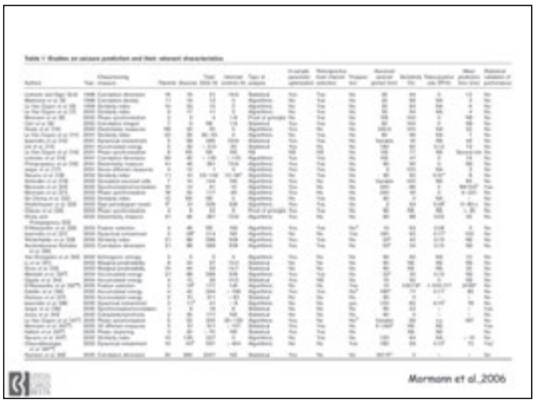


Table 1 Studies on seizure prediction and their relevant characteristics

Mormann et al. 2006

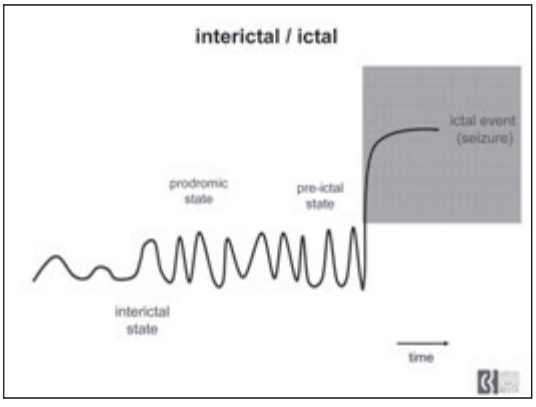
doi:10.1093/brain/awl241 Brain (2007), 130, 314–333

REVIEW ARTICLE

Seizure prediction: the long and winding road

Florian Mormann,[1] Ralph G. Andrzejak,[2] Christian E. Elger[1] and Klaus Lehnertz[1,2]

While most of the studies published in the 1990s and around the turn of the millennium yielded rather promising results, more recent evaluations could not reproduce these optimistic findings, thus raising a debate about the validity and reliability of previous investigations. In this review, we will critically discuss the literature on seizure prediction



References (reviews)

Avoli M, Biagini G, de Curtis M. (2006) Do interictal spikes sustain seizures and epileptogenesis? *Epilepsy Curr* 6:203-7.

de Curtis M, Avanzini G. (2001) Interictal spikes in focal epileptogenesis. *Progr Neurobiol* 63:541-567.

de Curtis M and Gnatkovsky V (2009)) Re-considering the mechanisms of focal ictogenesis: the role of l low-voltage fast activity. *Epilepsia* 50; 25

Engel J Jr, Bragin A, Staba R, Mody I: High-frequency oscillations: what is normal and what is not? Epilepsia 2009;50:598–604.

Gotman J: Relationships between interictal spiking and seizures: human and experimental evidence. Can J Neurol Sci 1991;18:573-576.

Mormann F, Andrzejak FG, Elger CE and Lehnertz K (2007) Seizure prediction: the long and winding road. Brain (2007), 130, 314–333

Pitkanen A, Sutula TP. Is epilepsy a progressive disorder? Prospect for new therapeutic approaches in temporal-lobe epilepsy. *Lancet Neurol* 2002; 1: 173–81.

References (data manuscripts)

Derchansky M et al. (2008) Transition to seizures in the isolated immature mouse hippocampus: a switch from dominant phasic inhibition to dominant phasic excitation. *J Physiol* 586:477-94.

Fujiwara-Tsukamoto Y, et al. (2004) Synaptic interactions between pyramidal cells and interneurone subtypes during seizure-like activity in the rat hippocampus. *J Physiol* 557:961-79.

Gnatkovsky V, et al. (2008) Fast activity at seizure onset is mediated by inhibitory circuits in the entorhinal cortex in vitro. *Ann Neurol* 64:674-86.

Gotman J, et al. (1995) Frequency of the electroencephalographic discharge in seizures of focal and widespread onset in intracerebral recordings. *Epilepsia* 36:697-703.

Huberfeld G, et al. (2011) Glutamatergic pre-ictal discharges emerge at the transition to seizures in human epilepsy. *Nature Neurosci* in press.

Lopantsev V, Avoli M. (1998) Laminar organization of epileptiform discharges in the rat entorhinal cortex in vitro. *J Physiol* 509 (Pt 3):785-96.

Matsumoto H, Ajmone-Marsan CA. (1964) Cortical cellular phenomena in experimental epilepsy: interictal manifestations. *Exp Neurol* 80:286-304.

Schindler K, et al. (2007) Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. *Brain* 130:65-77.

Wendling F, et al. (2002) Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. *Eur J Neurosci* 15:1499-508.

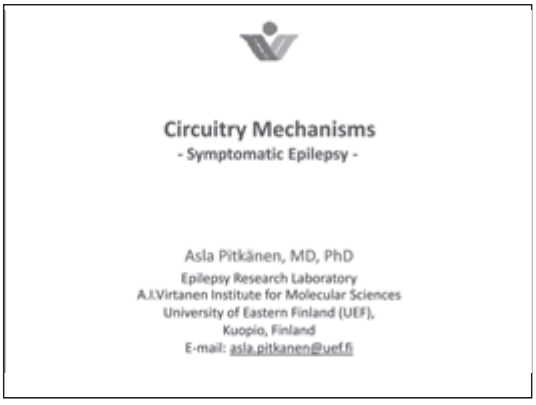
Zburkus J, et al. (2006) Interneuron and pyramidal cell interplay during in vitro seizure-like events. *J Neurophysiol* 95:3948-54.

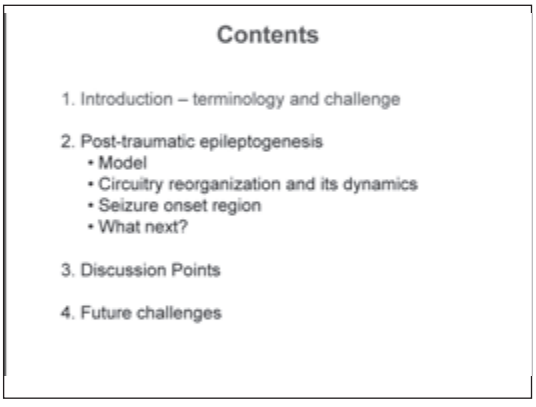
Raman Sankar (USA)

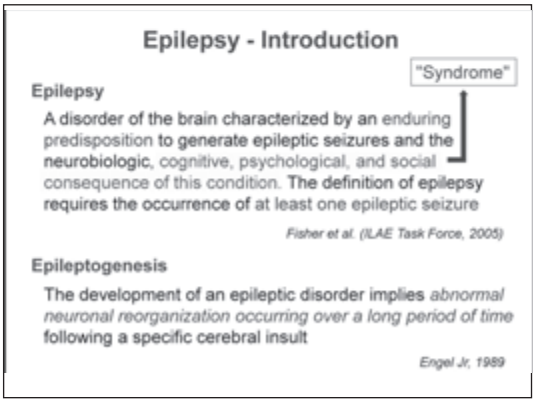
EXPERIMENTAL MODELS OF EARLY SEIZURES GIVING RISE TO CHRONIC EPILEPSY

Asla Pitkanen (Finland)

MOLECULAR MECHANISMS IN SYMPTOMATIC EPILEPSY



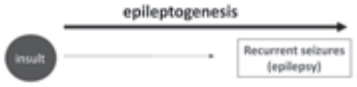




Epileptogenesis

The development and extension of tissue capable of generating spontaneous seizures, including

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



Pitkänen, Epilepsia 2010;51(Suppl 3):2-17; Galanopoulou et al., Epilepsia: 2012, in press

Antiepileptogenesis

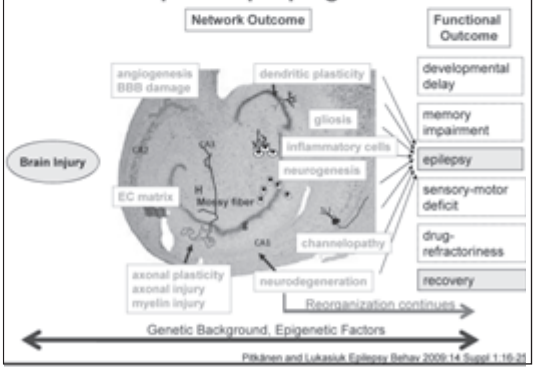
A process that counteracts the effects of epileptogenesis, including

-
-
-

  - complete and permanent reversal of epilepsy such that no seizures occur after treatment withdrawal

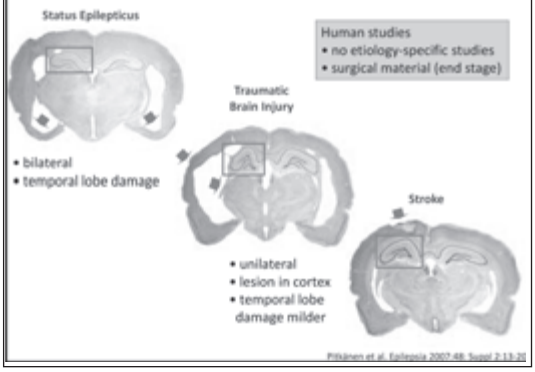
Pitkänen, Epilepsia 2010;51(Suppl 3):2-17; Galanopoulou et al., Epilepsia: 2012, in press

Acquired Epileptogenesis



Pitkänen and Lukasiuk Epilepsy Behav 2009;14 Suppl 1:16-25

Distribution of Pathology Depends on Etiology in Rat



Pitkänen et al. Epilepsia 2007;48 Suppl 2:13-20

Epileptogenesis

- What is the critical molecular and cellular pathology? -

- Where? -

Contents

1. Introduction -- terminology and challenge

2. Post-traumatic epileptogenesis
   - Model
   - Circuitry reorganization and its dynamics
   - Seizure onset region
   - What next?

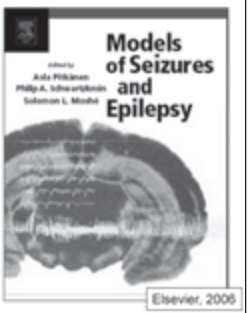
3. Discussion Points

4. Future challenges

Animal Models of PTE

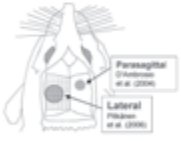
Pitkänen and McIntosh, J Neurotrauma 2006:23(2):241-61)

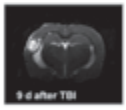
- ❑ metals
  - Fe, Al, (Co)
- ❑ cortical undercut
- ❑ fluid percussion injury
  - parasagittal
  - lateral
- ❑ controlled cortical impact



Fluid-Percussion TBI

McIntosh et al., Neuroscience 1989:28(1):233-44

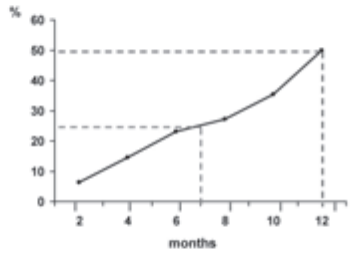




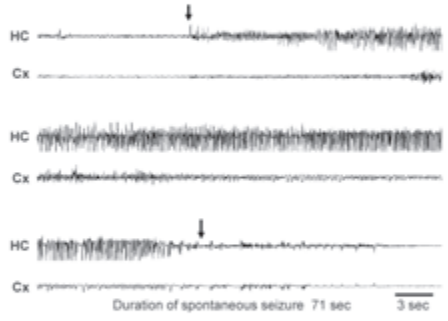
- PubMed: "fluid percussion injury" 946 publications (5/2010)
- most widely used model of TBI
-
-

Cumuative % of Rats with Epilepsy

Data from 2 experiments

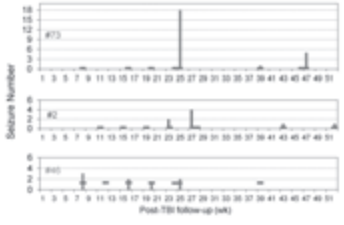


Secondarily Generalized Seizure in Rat with PTE



Kharatishvili et al. Neuroscience 2006;140(3):685

Seizure Occurrence - Each Rat Is An Individual



In PTE model spontaneous seizures are infrequent!

Use of seizure threshold as a surrogate for epileptogenesis

PTZ Test

PTZ administration

- 9 a.m. - 2 p.m.
- 30 mg/kg or 25 mg/kg, i.p.
- under video-EEG control

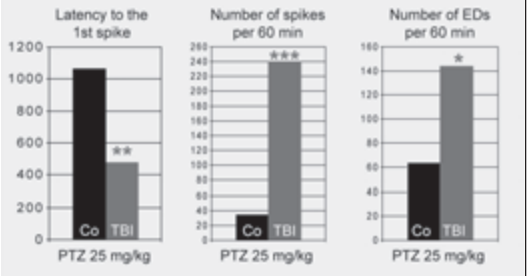
Markers of hyperexcitability

- latency to the first spike
- total number of spikes
- total number of epileptiform discharges (ED)
- time to occurrence of first behavioral events

60 min post-PTZ

Indicators of Lowered Seizure Threshold

Rats with TBI



Kharatishvili et al. Brain 2007;130(Pt 12):3155-68

Summary - Epilepsy Phenotype

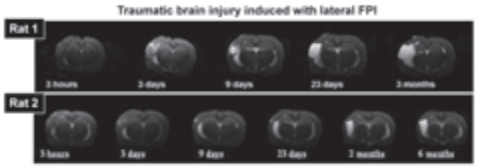
Post-TBI vs. Post-SE

Epileptogenesis	TBI lateral fluid-percussion	SE amygdala stimulation
duration of latency	several months	days -1 mo
% of rats with seizures	50%	80-100%
mean seizure frequency	0.3/day	8/day
maximal seizure frequency	up to 1/day	up to 30/day
mean seizure duration	104 sec	49 sec
day-night cycle	44% lights on	57% lights on
response to AEDs	?	yes
Epilepsy: memory impairment	yes	yes
Co-morbidities: sensory-motor impairment	yes	?
Co-morbidities: drug-refractoriness	?	yes

Contents

Does Location or Size of Cortical Lesion Associate with Epilepsy?

Each Injured Animal is An Individual
- Which one develops epilepsy?



Distribution of Pathology in Rat PTE

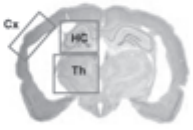
BBB damage

Neurodegeneration

Gliosis
- inflammation

Angiogenesis

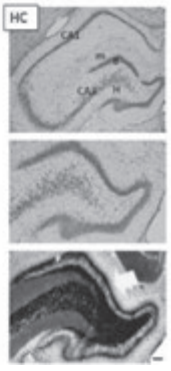
Axonal injury



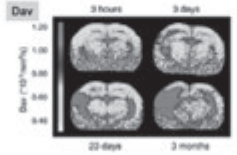
- unilateral

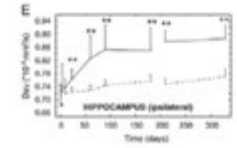
- cortex
- hippocampus
- thalamus

Hippocampal Pathology and Epilepsy?

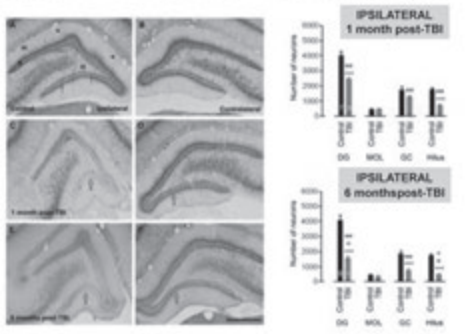


Progression of Hippocampal Pathology

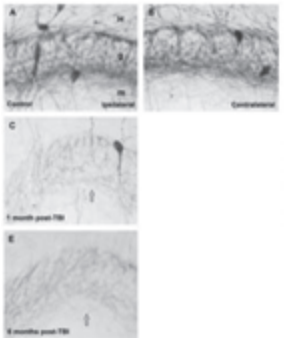




Loss of PARV-ir Neurons in the Dentate Gyrus



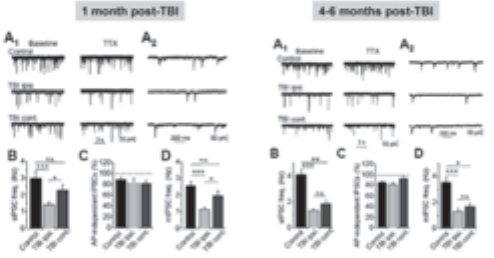
Progression of Pathology in Dentate Gyrus



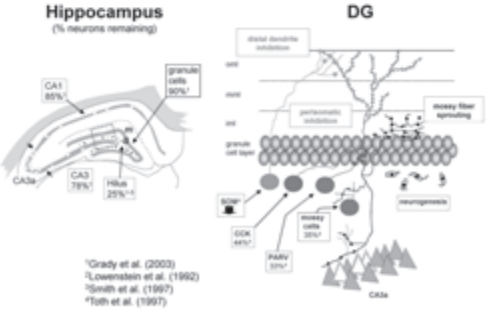
Electrophysiology

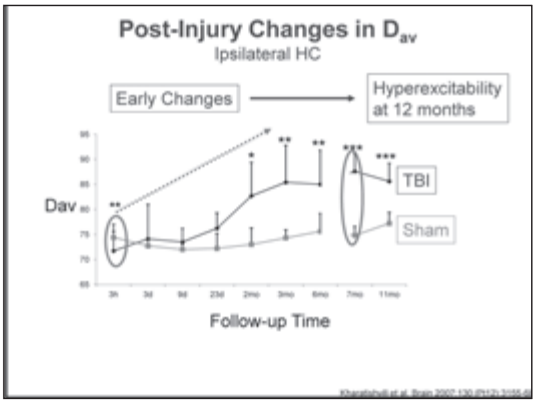
- progressive loss of phasic inhibition of dentate granule cells
- at 6 months also contralaterally

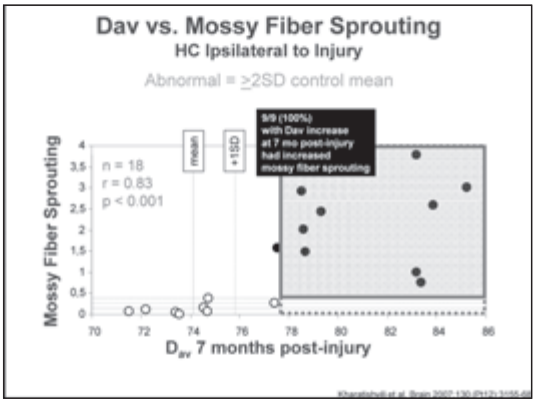
Granule Cells Receive Less Spontaneous Inhibitory Synaptic Inputs

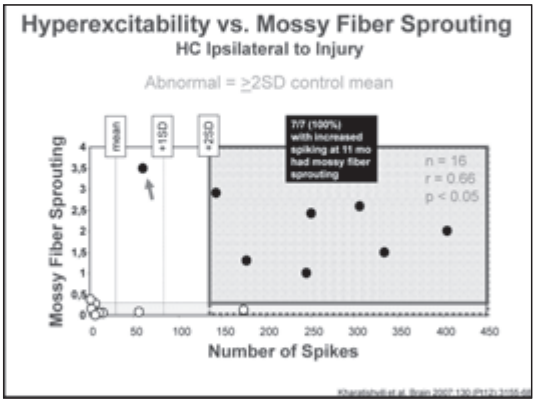


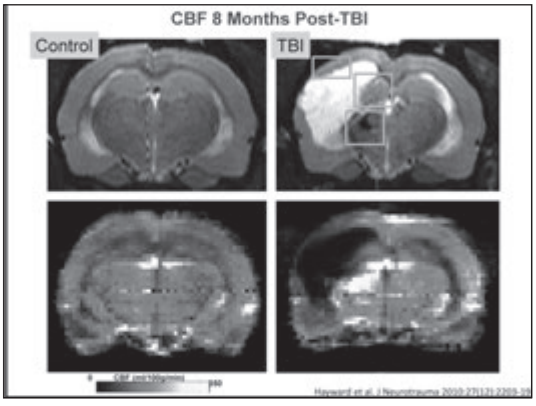
Hippocampus and Dentate Gyrus in Rat TBI



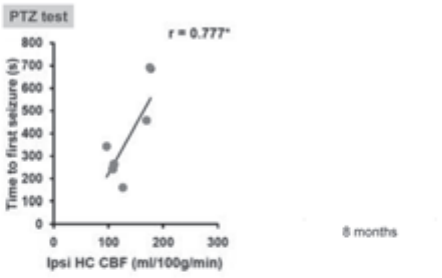

Post-Injury Changes in D_{av}
Ipsilateral HC
Early Changes
Hyperexcitability at 12 months
Dav
TBI
Sham
Follow-up Time


Dav vs. Mossy Fiber Sprouting
HC Ipsilateral to Injury
Abnormal = ≥2SD control mean
9/9 (100%) with Dav increase at 7 mo post-injury had increased mossy fiber sprouting
mean
+1SD
n = 18
r = 0.83
p < 0.001
Mossy Fiber Sprouting
D_{av} 7 months post-injury


Hyperexcitability vs. Mossy Fiber Sprouting
HC Ipsilateral to Injury
Abnormal = ≥2SD control mean
7/7 (100%) with increased spiking at 11 mo had mossy fiber sprouting
mean
+1SD
+2SD
n = 16
r = 0.66
p < 0.05
Mossy Fiber Sprouting
Number of Spikes


CBF 8 Months Post-TBI
Control
TBI

Hippocampal Hypometabolism



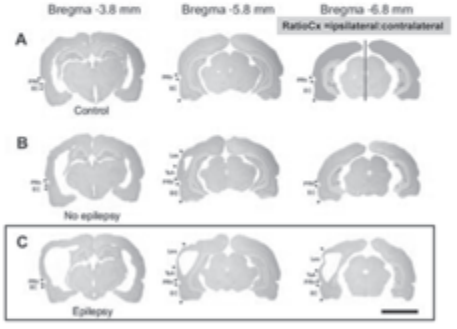
Hayward et al. J Cereb Blood Flow Metab 2011;31(1):166-77; Hayward et al. J Neurotrauma 2010;27(12):2203-19

Conclusion

Magnitude of diffusion changes & development of hypometabolism in the hippocampus
associate with later development of lowered seizure threshold

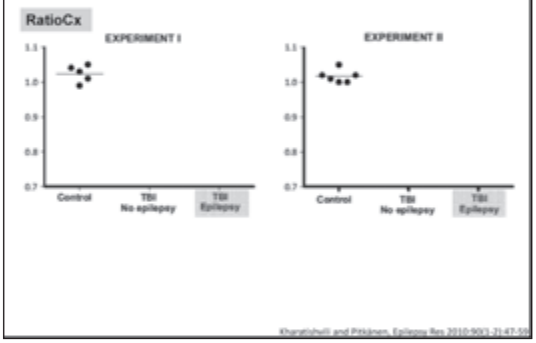
Cortical Pathology and Epilepsy?

Is the Size of Cortical Lesion Associated With Epilepsy?



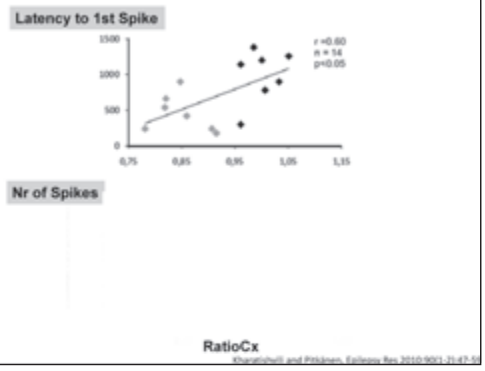
Kharatishvili and Pitkänen, Epilepsy Res 2010;90(3-2):147-58

Is the Size of Cortical Lesion Associated With Epilepsy?



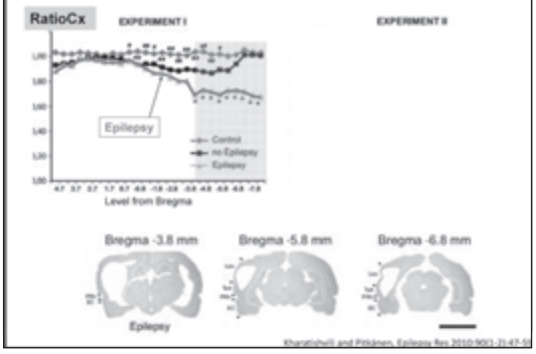
Kharatishvili and Pitkänen, Epilepsy Res 2010;90(3-21:47-59

Cortical Lesion and Lowered Seizure Threshold



Kharatishvili and Pitkänen, Epilepsy Res 2010;90(3-21:47-59

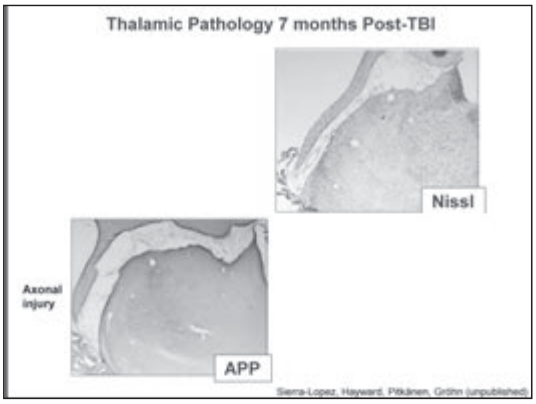
Is the Location of Cortical Lesion Associated With Epilepsy?



Kharatishvili and Pitkänen, Epilepsy Res 2010;90(3-21:47-59

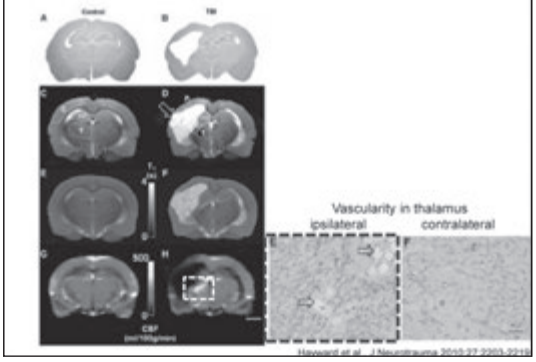
Thalamus and Epilepsy

Thalamic Pathology 7 months Post-TBI



Sierra-Lopez, Hayward, Pitkänen, Gröhn (unpublished)

Increased Thalamic Blood Flow in ASL 7 months Post-TBI



Hayward et al., J Neurotrauma 2010;27:2203-2218

Contents

1. Introduction – terminology and challenge
2. Post-traumatic epileptogenesis
   - Model
   - Circuitry reorganization and its dynamics
   - Seizure onset region
   - What next?
3. Discussion Points
4. Futute challenges

Where Do Seizures Begin?

- hippocampus
- cortex
- thalamus

(slides noy included in handout)

Contents

1. Introduction – terminology and challenge
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   - Model
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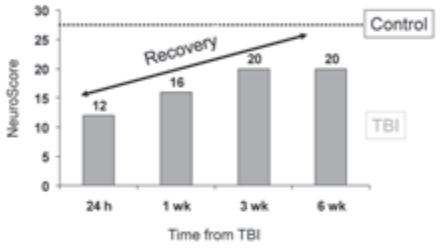
Epileptogenesis *vs.* Recovery

Somato-Motor Recovery

Composite NeuroScore



Modified from Raka et al. Eur. J Neurosci 2006;23:2119-2134

Post-TBI Brain Faces Many Challenges

Acute damage → Secondary damage and circuitry alterations

Somato-motor recovery

Epileptogenesis ····· Epilepsy

"epileptogenesis" *vs.* "repair"

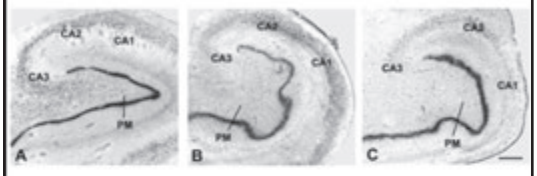
Pitkänen et al., Epilepsia 2009;50 Suppl 2:21-9

Translation

Circuitry Reorganization
- Human PTE -

Hippocampal Damage in PTE

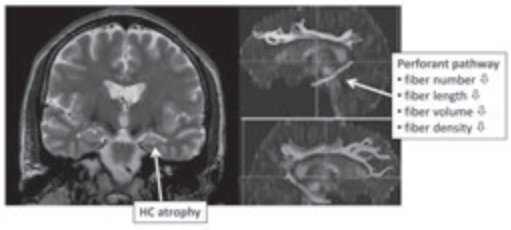
Mathern et al., 1994; Swartz et al. 2006



- cell loss (hilus, CA subfields)
- mossy fiber sprouting

Axonal and Myelin Injury

DTT in Post-traumatic Epilepsy



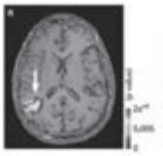
Díaz-Arrastia et al. Epilepsia 2009;50(suppl. 2):14-20

Blood-Brain-Barrier Damage

Human Post-Traumatic Epilepsy

Gd-DTPA

Volume (cm^3)



Tomkins et al. JNNP 2008;79:774–777

Future Challenges

- to continue to develop clinically relevant animal models which respond to clinical needs
- to understand the cellular and network changes that are critical for epileptogenesis and their molecular basis in that particular syndrome
  - functional analysis of molecular findings
  - epilepsy vs. co-morbidity
  - epileptogenesis vs. recovery
- can targets be generalized?
- out-of-the-box thinking

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- **Academy of Finland**
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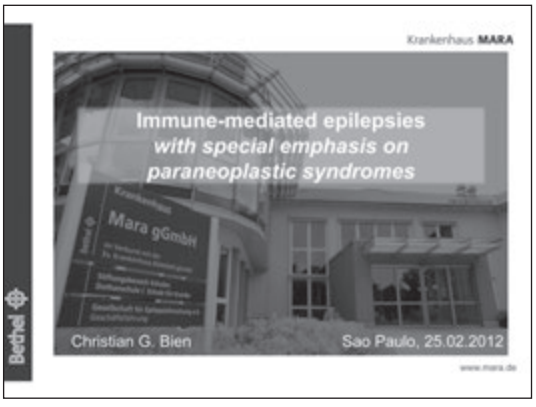
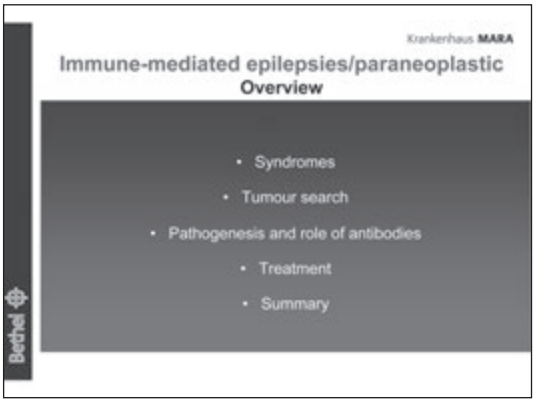
- **The Finnish Technology Fund**
- **EU (EpiCURE)** (LSH-CT-2006-037315)
- **COST (ECMNet)**
- **CURE**
- **ESF EpiGENet**

Christian Bien (Germany)

PARANEOPLASIC ENCEPHALITIS AND EPILEPSY





Krankenhaus **MARA**

Immune-mediated epilepsies/paraneoplastic

The syndromes

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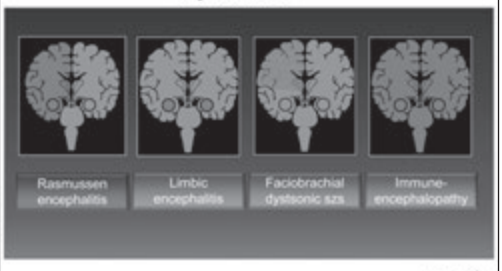
Krankenhaus **MARA**

Immune-mediated epilepsies/paraneoplastic

- Syndromes -



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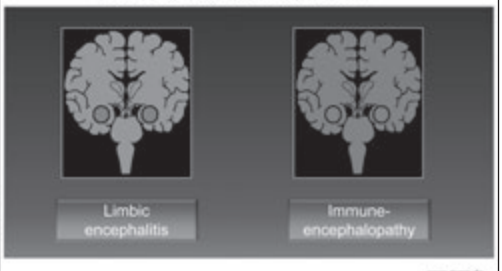
Immune-mediated epilepsies/paraneoplastic

- Potential paraneoplastic origin -



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Krankenhaus **MARA**

Immune-mediated epilepsies/paraneoplastic

Limbic encephalitis

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Limbic encephalitis
- Diagnostic criteria -

- Recent onset (< 5 yrs) temporomedial signs and symptoms
- +/- temporomedial T2/FLAIR hypersignal (otherwise unexplained)

plus ≥1:

- Peripheral tumour (paraneoplastic disease)
- Antibody
- Encephalitic histopathology

Bien & Elger, Epilepsy & Behavior 2007

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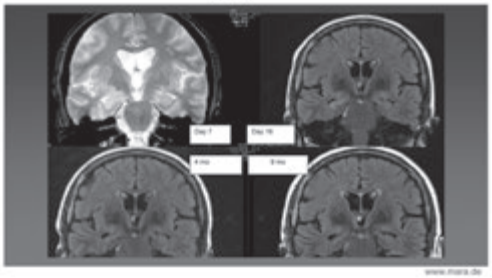
Krankenhaus **MARA**

Patientin H., G.
MRI



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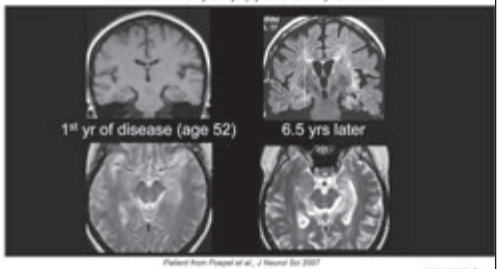
Limbic encephalitis defined by antibody targets
Patient S., R., ♀, Hu ab⁺, SCLC



Patient from Poepel et al., J Neurol Sci 2007

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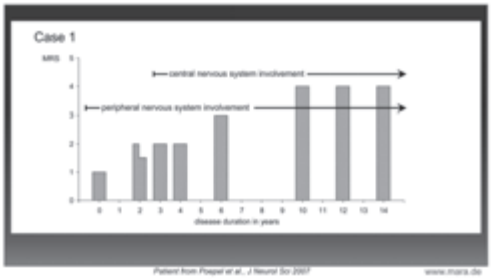
Krankenhaus **MARA**

Encephalitides defined by antibody targets
- Patient S., R., ♀, Hu ab⁺, SCLC -



Patient from Poepel et al., J Neurol Sci 2007

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Krankenhaus **MARA**

Adult-onset TLE-HS after limbic encephalitis

- Inclusion criteria and methods -

1. Manifestation of temporal lobe epilepsy >20 yrs of age
2. Time between onset of epilepsy and investigation <6 yrs
3. Initial assessment at our centre between 1999 and 2005
4. Hippocampal sclerosis on brain MRI

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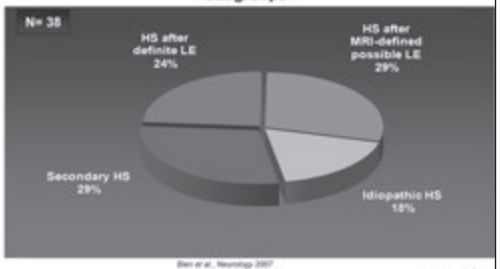
Adult-onset TLE with hippocampal sclerosis

- Subgroups -



Bien et al., Neurology 2007

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Adult-onset TLE with hippocampal sclerosis

- (Post-) LE subgroups (53%) -

Definite limbic encephalitis: N= 9 (24%)

- 5 patients with paraneoplastic LE (2 with abs against intracellular antigens)
- 4 patients with VGKC abs

5 patients had bilateral hippocampal sclerosis (56%)

MRI defined LE (ab⁻, nonparaneoplastic): N= 11 (29%)

- Typical MRI evolution from hippocampal swelling to atrophy
- **Abnormal CSF standard parameters: 8/13**
- **Bilateral hippocampal sclerosis: 12/20**

Bien et al., Neurology 2007

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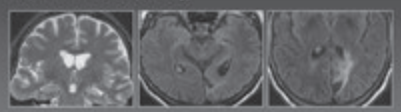
Temporal lobe epilepsy

- Hippocampal sclerosis -

Secondary hippocampal sclerosis: N= 11 (29%)

- 6 patients with dual pathology



- 9 patients with initial precipitating injury (trauma, febrile seizures, status, meningitis)

Idiopathic hippocampal sclerosis: N= 7 (18%)

Bien et al., Neurology 2007

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Krankenhaus MARA

Immune-mediated epilepsies/paraneoplastic

Encephalopathies

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Encephalopathy
Definition

Prerequisite:

- Cognitive impairment [recent & rapid onset]

and ≥1 of the following:

- Neuropsychiatric features (eg, hallucinations, delusions, or paranoia)
- Myoclonus
- Generalized tonic-clonic or partial seizures
- Focal neurologic deficit

Adapted from Castillo et al., Arch Neurol 2006

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Krankenhaus MARA

Anti-NMDAR encephalitis
Features

- Mostly young females
- Encephalopathy, monophasic or relapsing-remitting (≈20%)
- MRI usually normal or non-specifically altered
- Tumours, mostly teratomas of the ovary, in ≈ ¼- ½ of patients
- Antibodies to NMDA receptor (NR1 subunit)
- Substantial improvement under immunotherapy in >75%

Dalmau et al., Lancet Neurol 2011, Irani et al., Brain 2010

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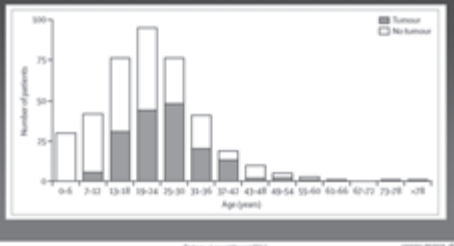
Anti-NMDAR-Encephalitis
Age, tumours



Dalmau, Lancet Neurol 2011

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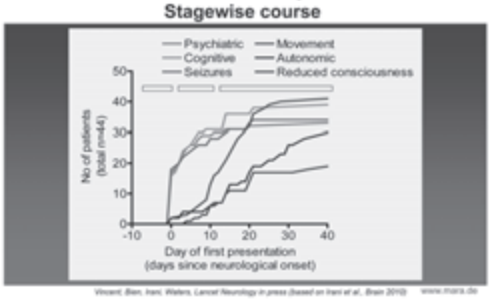
Anti-NMDAR encephalitis
Stagewise course



Vincent, Bien, Irani, Waters, Lancet Neurology in press (based on Irani et al., Brain 2010)

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Immune-mediated epilepsies/paraneoplastic

Pathogenesis and role of antibodies

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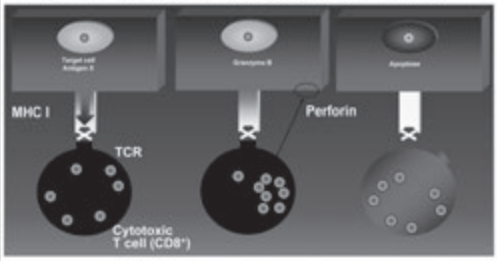
Immune-mediated epilepsy
- Perforin-Granzyme B mediated T cell cytotoxicity -



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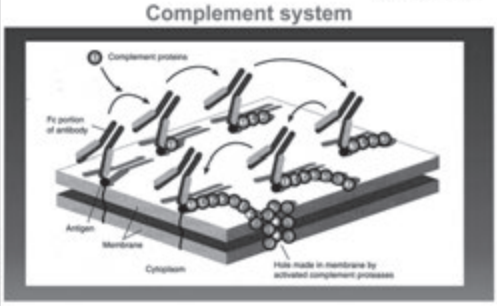
Complement system



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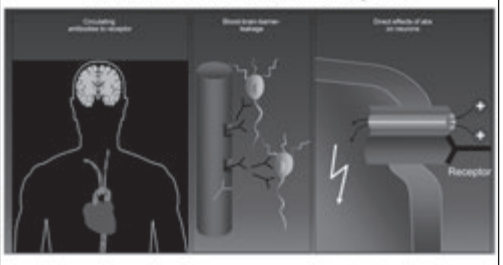
Immune-mediated epilepsy
- Direct functional effect on receptors -



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Immune-mediated epilepsy
- Reduction in receptor density -

Drachman et al., NEJM 1978; http://www.macalester.edu

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Antibody-associated conditions
- Overview of autoantibodies -

	Intracellular antigen			Surface antigen "Neuropil antibodies"						
	Onconeural		GAD	?	mGluR1	VGKCc	NMDAR	AMPAR	$GABA_BR$	mGluR5	?
	Hu	Ma	other			LGI1	CASPR2	?			
Description	1980/90s		1990		2000	2001/ 2010	2007	2009	2010	2011	
Published patients	>400		≈50		3	>200	>400	12	25	2	
Tumour	>90%		<10%		100%	0%/<25%	40%	50%	60%	100%	

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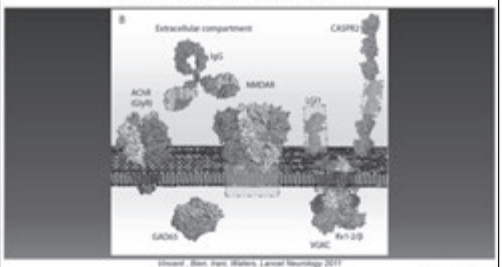
Limbic encephalitis
- Location of antibody targets -



Vincent , Bien, Irani, Waters, Lancet Neurology 2011

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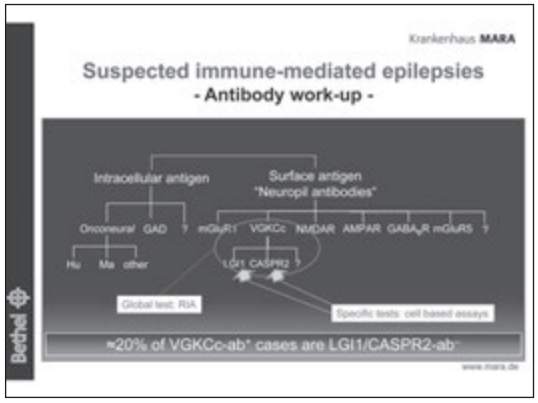
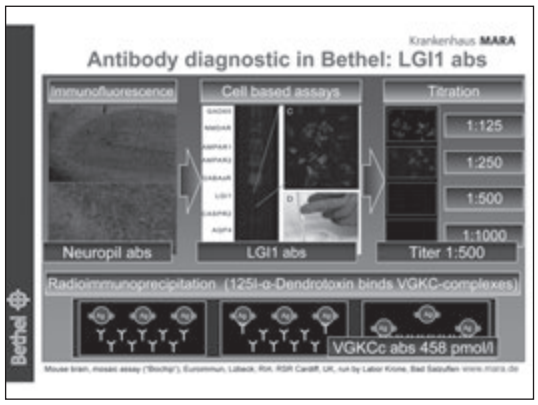
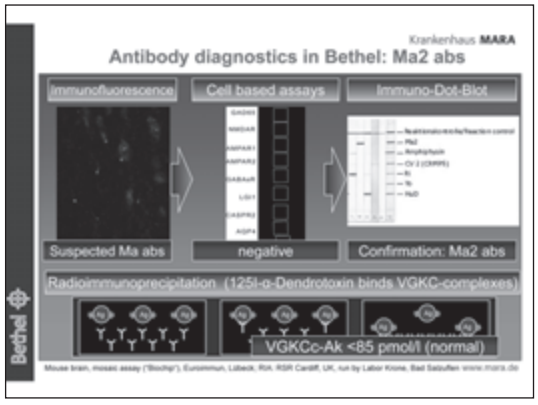
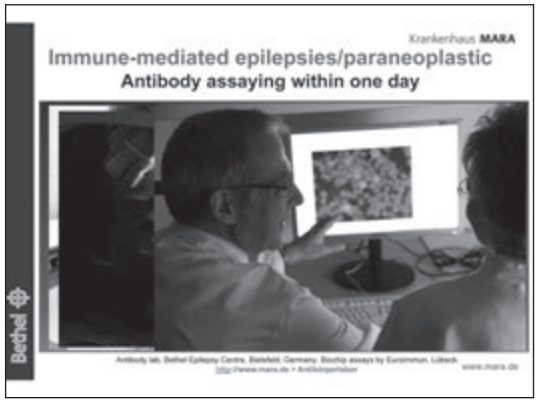
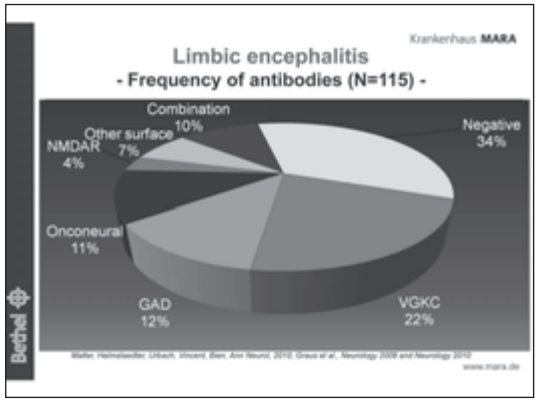

Krankenhaus MARA
Suspected immune-mediated epilepsies
- Antibody work-up -
Intracellular antigen
Surface antigen
"Neuropil antibodies"
Onconeural GAD ? mGluR1 VGKCc NMDAR AMPAR GABA$_B$R mGluR5 ?
Hu Ma other
LGI1 CASPR2 ?
Global test: RIA
Specific tests: cell based assays
≈20% of VGKCc-ab$^+$ cases are LGI1/CASPR2-ab$^-$
Bethel


Krankenhaus MARA
Antibody diagnostic in Bethel: LGI1 abs
Immunofluorescence
Cell based assays
Titration
1:125
1:250
1:500
1:1000
Neuropil abs
LGI1 abs
Titer 1:500
Radioimmunoprecipitation. (125I-α-Dendrotoxin binds VGKC-complexes)
VGKCc abs 458 pmol/l
Bethel


Krankenhaus MARA
Antibody diagnostics in Bethel: Ma2 abs
Immunofluorescence
Cell based assays
Immuno-Dot-Blot
Suspected Ma abs
negative
Confirmation: Ma2 abs
Radioimmunoprecipitation. (125I-α-Dendrotoxin binds VGKC-complexes)
VGKCc-Ak <85 pmol/l (normal)
Bethel


Krankenhaus MARA
Immune-mediated epilepsies/paraneoplastic
Antibody assaying within one day
Bethel


Krankenhaus MARA
Limbic encephalitis
- Frequency of antibodies (N=115) -
Combination 10%
Other surface 7%
NMDAR 4%
Negative 34%
Onconeural 11%
GAD 12%
VGKC 22%
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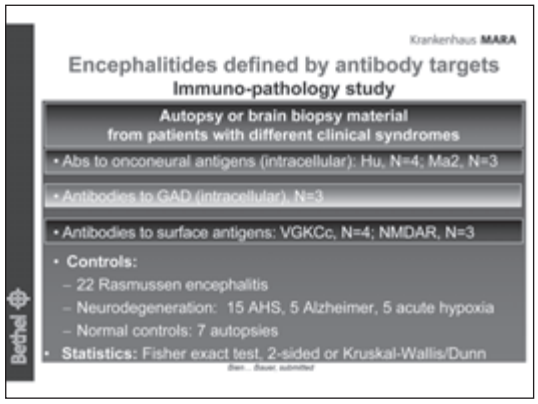
Bethel


Krankenhaus MARA
Encephalitides defined by antibody targets
Immuno-pathology study
Autopsy or brain biopsy material
from patients with different clinical syndromes
• Abs to onconeural antigens (intracellular): Hu, N=4; Ma2, N=3
• Antibodies to GAD (intracellular), N=3
• Antibodies to surface antigens: VGKCc, N=4; NMDAR, N=3
• Controls:
– 22 Rasmussen encephalitis
– Neurodegeneration: 15 AHS, 5 Alzheimer, 5 acute hypoxia
– Normal controls: 7 autopsies
• Statistics: Fisher exact test, 2-sided or Kruskal-Wallis/Dunn
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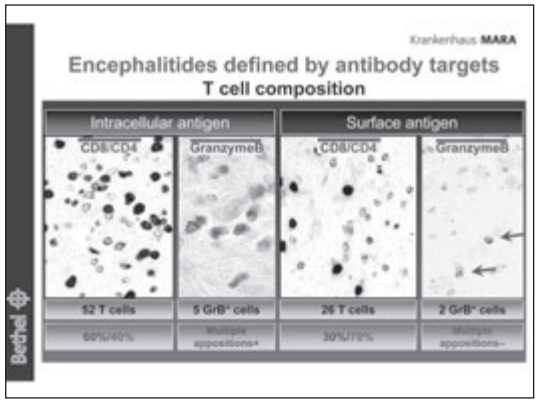
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Encephalitides defined by antibody targets
T cell composition
Intracellular antigen
Surface antigen
CD8/CD4
GranzymeB
52 T cells
5 GrB+ cells
26 T cells
2 GrB+ cells
60%/40%
30%/70%
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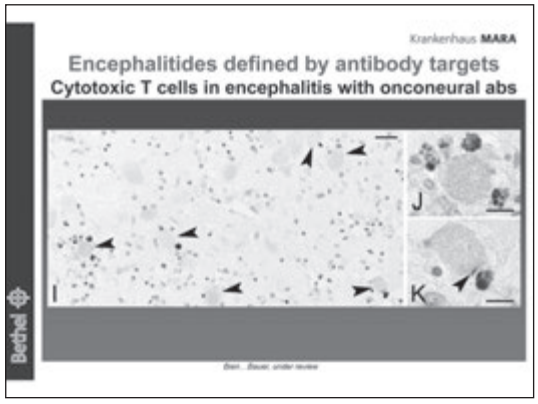
Krankenhaus MARA
Encephalitides defined by antibody targets
Cytotoxic T cells in encephalitis with onconeural abs
I
J
K
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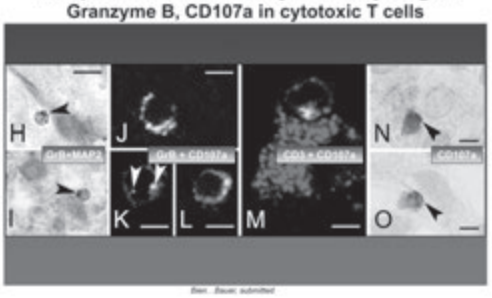
Encephalitides defined by antibody targets

Granzyme B, CD107a in cytotoxic T cells



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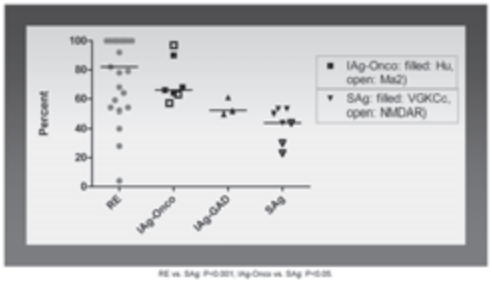
Encephalitides defined by antibody targets

- CD8/CD3 ratio-



RE vs. SAg: P=0.001, IAg-Onco vs. SAg: P=0.05.

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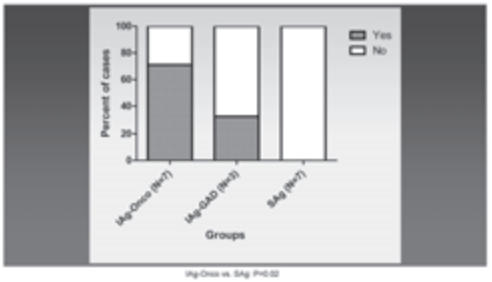
Encephalitides defined by antibody targets

- Cases with multiple appositions -



IAg-Onco vs. SAg: P=0.02

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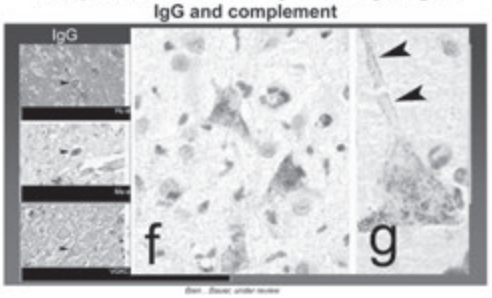
Encephalitides defined by antibody targets

IgG and complement



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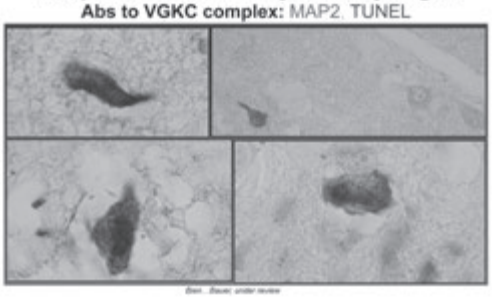
Encephalitides defined by antibody targets

Abs to VGKC complex: MAP2, TUNEL



Bien ... Bauer, under review

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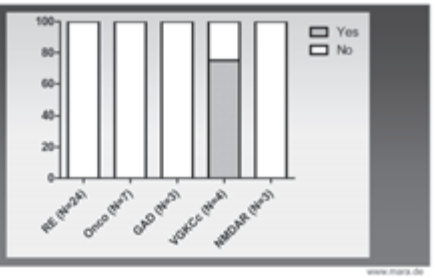
Encephalitides defined by antibody targets

- Cases with complement deposition on neurons -



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Encephalitides defined by antibody targets

Discussion of this human tissue study

Advantages

1. Direct study of immune reactions in brains of affected humans
2. Making use of archived tissue and serum from the time prior to regular antibody testing

Limitations

1. Disease duration in all cases >1 month (mean 21 months)
2. Biopsies or epilepsy surgery (11/17): Potential sampling errors
3. Prior immunosuppressive treatment (6/15)
4. No serial brain MRIs from all patients

Bien ... Bauer, under review

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Encephalitides defined by antibody targets

Summary of human tissue study

	Onconeural	GAD	VGKCc	NMDAR
Antigen localisation	Intracellular	Intracellular	Surface	Surface
T-cell density	↑	++	++	↓
CTL attached to neurons	+	+/-	-	-
Complement on neurons	-	-	+	-
Neuronal loss	yes	yes	yes	no
Mechanism	Cytotoxic T cells		IgG & complement	*Direct effect of ab to receptors*
Epilepsy/cognition outcome	↓	↓	↔	↑

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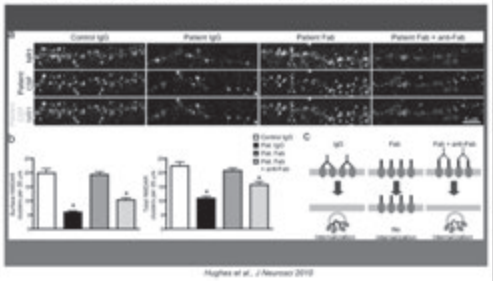
Anti-NMDAR encephalitis

- Antibodies bind, cross-link and internalise NMDARs -



Hughes et al., J Neurosci 2010

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Immune-mediated epilepsies/paraneoplastic

Clinical management

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Krankenhaus **MARA**

Immune-mediated epilepsies/paraneoplastic

Management pathway

Epilepsy of unknown cause with features suggestive of active immune-mediated disorder

Antibody diagnostics | Tumor search

Make diagnosis: 1) Antibody specificity
2) Paraneoplastic/non-paraneoplastic
3) Syndrome [limbic encephalitis…]

Immunotherapy

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Immune-mediated epilepsies/paraneoplastic

- When to do antibody diagnostics -

- **Syndrome:**
  - Limbic encephalitis
  - Encephalopathy
  - FBDS
- **Evolution:** subacutely (days-12 wks)
  - Early high sz-frequency
  - Concomitant cognitive deficits
- **MRI:** T2/FLAIR hyperintense lesion(s), suggestive of encephalitis
- **CSF:** Oligoclonal bands or elevated cell count
- **Histopathology:** Encephalitis

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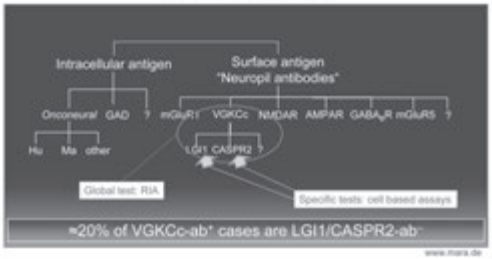
Immune-mediated epilepsies/paraneoplastic
- Antibody work-up -



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Immune-mediated epilepsies/paraneoplastic
Suggested tumour search

If ≥1 of the following is present ...

- Known onconeural antibody
- "Classical" paraneoplastic syndrome: limbic encephalitis, brainstem encephalitis, subacute cerebellar degeneration
- Risk factor present: onconeural antibody, known tumour (2nd tumor?), age >60, B symptoms (unexplained fever, night sweat, weight loss)

... do the following tests:

A.	All	Chest and abdominal CT with contrast
B.	Women	Gynecological examination. Mammography
C.	Men <50 years	Urological examination (testicular cancer?)
D.	Men >50 years	Urological examination (prostate cancer?)
E.	If 1of the following is fulfilled: - Onconeural antibody - Clinical suspicion of cancer	Whole body FDG-PET-/CT scan

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Antibody-associated epilepsies
- Treatment suggestions -

Tumour:

- If present, first treatment aim

Immunotherapy:

- VGKCc and NMDAR abs: bring down abs as quickly and effective as possible.
  (NMDAR abs: early use of rituximab/cyclophosphamide*)
- GAD abs
- Onconeural abs
- Ab negative

→ ?

*Dalmau, Lancet Neurol 2011 and personal communication

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Immune-mediated epilepsies/paraneoplastic

Summary

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Immune-mediated epilepsies/paraneoplastic
- Summary -

- Paraneoplastic conditions can manifest as epilepsy
- Antibody diagnostics and tumour search in suspected immune-mediated epilepsies recommended
- Antibodies inform us about
  - Diagnosis
  - Prognosis
  - Treatment choice
- Onconeural or GAD abs, often resistant to AEDs and to immuno-tx (T cell diseases!)
- Abs to surface Ags: frequently good outcome on immuno-tx (Antibody-mediated diseases!)

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Thanks to

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Epileptology
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John Radcliffe Hospital
A Vincent
S Irani

Medical University Vienna
Centre for Brain research
J Bauer
H Lassmann

Euroimmun, Lübeck
W Stöcker
KP Wandinger

christian.bien@mara.de

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Epilepsy Centre Bethel: Hospital

Krankenhaus MARA

Psychosomatic epileptology 12 beds
MR imaging
Presurgical diagnostics 16 beds
General epileptology 56 beds

christian.bien@mara.de

Society for Epilepsy Research Antibody laboratory
Young adults 16 beds
Pediatric epileptology 30 beds
Rehabilitation 25 beds

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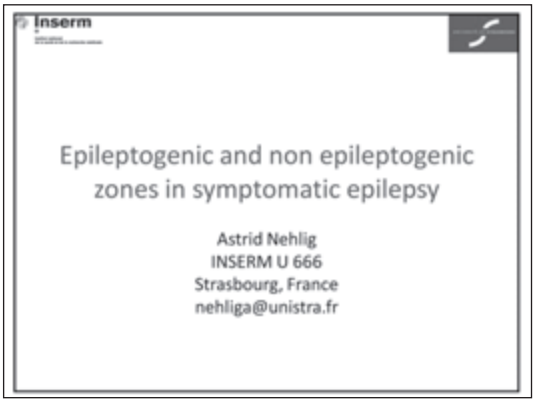
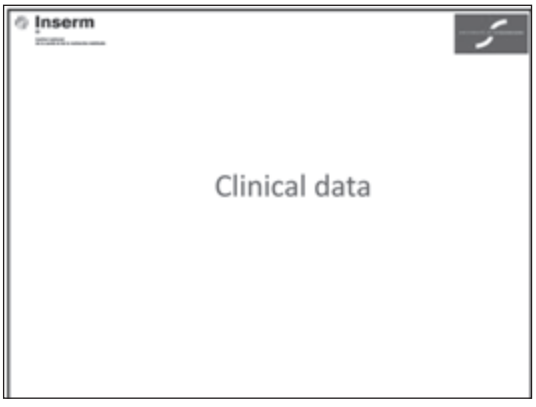
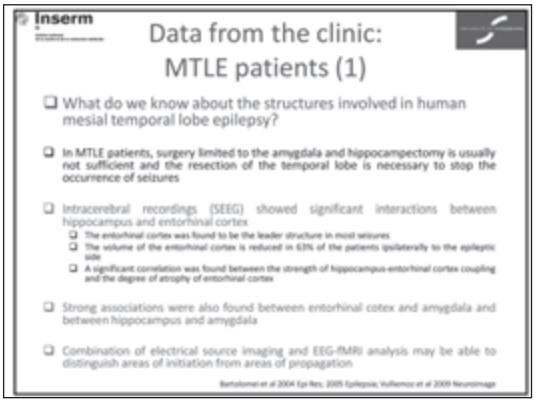
Astrid Nehlig (France)

EPILEPTOGENIC AND NON-EPILEPTOGENIC ZONES IN SYMPTOMATIC EPILEPSY

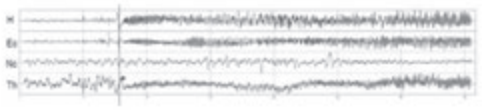






Data from the clinic: MTLE patients (2)

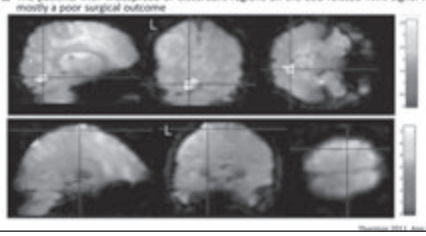
- Synchronization and variable degrees of coupling were also found between thalamus and remote cortical areas in MTLE patients
  - the surgical prognosis is better in patients with low values of thalamo-cortical coupling at the onset of seizures
  - The extension of the epileptogenic network to the thalamus is a potential important factor predicting surgical prognosis



Guye et al, 2006, Brain

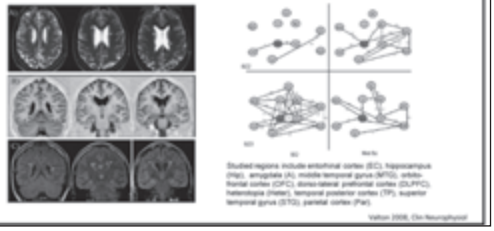
Data from the clinic: cortical dysplasia

- In focal cortical dysplasia, surgery is most successful if all epileptogenic tissue is resected
  - EEG-fMRI provides useful information about the zone of origin of seizures
  - In these patients, the correct location of the zone of origin of seizures is related with a good surgical outcome
  - The patients with widespread or discordant regions on the EEG-related fMRI signal had mostly a poor surgical outcome



Data from the clinic: diffuse periventricular heterotopia

- In bilateral diffuse periventricular heterotopia (BDPH), SSEG in one patient showed
  - Large initial network involving both heterotopia and cortical structures
  - Stimulation of heterotopia induced responses in remote cortical regions
  - In BDPH a vast epileptogenic network including heterotopic and cortical neurons is recruited. This may explain surgical failures in this syndrome (Vallon 2008, Clin Neurophysiol)



Studied regions include entorhinal cortex (EC), hippocampus (Hip), amygdala (A), middle temporal gyrus (MTG), orbito-frontal cortex (OFC), dorso-lateral prefrontal cortex (DLPFC), heterotopia (Heter), temporal posterior cortex (TP), superior temporal gyrus (STG), parietal cortex (Par).

Vallon 2008, Clin Neurophysiol

Animal studies

Animal studies

- Many groups studied how to modify/prevent epileptogenesis in temporal lobe epilepsy
- Not many data available on other types of epilepsy

➢ Review available studies on epileptogenesis and prevention in animal models of TLE induced by SE

The role of hippocampus in epileptogenesis

Use of antiepileptic drugs in experimental SE

Drug and model	Treatment onset	Epileptic outcome	Protection in hippocampus
Fluorofelbamate (PPS)	10 or 40 min (1 dose)	↓ SRS freq-interictal spikes	+
Lamotrigine (PPS)	2 h (2 w)	no effect	+ hip
Levetiracetam (pilo)	30 min (21 d)	no effect	0
(PPS)	40 min (1 dose)	↑ latency, ↓ SRS frequency	N.D.
Phenytoin (HS)	1-4 h (1 dose)	↓ epileptogenesis	N.D.
Fos-phenytoin (AS)	3 h (1 dose)	no effect	N.D.
Topiramate (k-pilo)	10 min at P28 (1 dose)	↓ SRS freq-interictal spikes	
	1 h in adults (7 d)	no effect	+ hip
Valproate (KA)	24 h at P35 (40 d)	no animals with SRS	N.D.
(AS)	8 h in adults (4 w)	no effect	+ hip
Vigabatrin (AS)	2 days (10 w)	no effect	0
(k-pilo)	10 min after SE (45 d)	no effect	+ hip

- Interpretation difficult, the effect varies with age, timing and duration of treatment
- No apparent link between the mechanism of action of AEDs and their effect on epileptogenesis
- Better effect when AEDs are given early

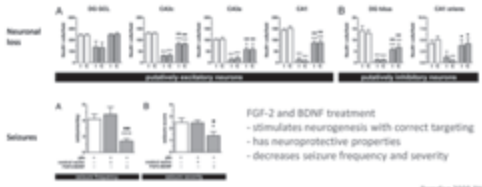
André 2001, 2003, Bolanos, 1998, Brandt 2006, François 2006, Halonen 2001, Klitgaard 2001, Macaraï 2000, 2004, Niebauer 1999, Pitkanen & Kubova, 2004, Rigoulot 2003

Other therapies

- Immunosuppressants
  - Rapamycin
    - acts on the mTOR pathway
    - suppresses epileptogenesis in genetic epilepsies in which the mTOR pathway is activated (tuberous sclerosis, cortical dysplasia)
    - In the KA and pilocarpine model rapamycin reduces seizure frequency and mossy fiber sprouting
- Proconvulsants
  - Atipamezole: selective α_2-adrenergic antagonist
    - No effect on the number of rats with seizures but reduced seizure frequency, hippocampal pathology and mossy fiber sprouting

Role of growth factors

- NGF, BDNF and FGF-2
  - SE is associated with increased expression of BDNF
  - Decreased BDNF signaling (mice overexpressing the trunkated TrkB receptor) is associated with delayed SE-induced epileptogenesis
- Treatment with both FGF2 and BDNF starting 4 days after SE



FGF-2 and BDNF treatment
- stimulates neurogenesis with correct targeting
- has neuroprotective properties
- decreases seizure frequency and severity

Paradiso 2009 PNAS

Peptides

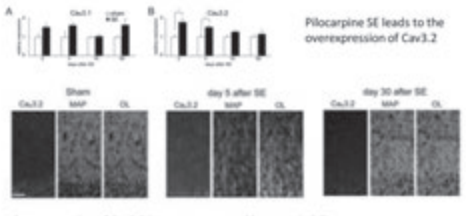
- NPY, somatostatin, dynorphin, galanin, substance P
  - NPY: initial seizure activity triggers the expression of BDNF which enhances the expression of the endogenous anticonvulsant NPY
  - Overexpression of NPY in the hippocampus by adenoviral transfection increases seizure threshold and delays the development of epilepsy in the kainate model

Heinrich 2006, Kokaia 1995, Lahtinen 2002

Gene modifications

- During the initial insult, reorganization at the gene and protein level
- This leads to largely disturbed functional activity
- Problems
  - how to identify the critical genes involved in the process?
  - at the moment not many pathways and genes have been identified

The Cav3.2 gene



Pilocarpine SE leads to the overexpression of Cav3.2

Overexpression of Cav3.2 increases neuronal hyperexcitability
In Cav3.2 KO mice, epilepsy onset is retarded and severity decreased

Becker et al. 2008

Epigenetic studies
Acetylation and metylation

- Increased promoter methylation and sustained down-regulation of hippocampal mGluR2 after SE in rats
- Increased promoter methylation of reelin in hippocampus of TLE patients (maintenance of laminar organization)

Kobow 2009, Bluemcke 2010

The neuron silencing restricting factor (NSRF)

- Alternative strategy: try to identify the mechanisms controlling changes in the expression of genes
- Some proteins can control the expression of numerous genes
  - Fixation of the protein on the promoter region of the gene
  - Result: the gene can be expressed or not
- One possible candidate: NSRF has the capacity of controlling about 1800 genes and is overexpressed after SE
- This type of genes could play a critical role in switching genes on or off and leading to epileptogenesis

Bernard, 2011 Ann Neurol

Epigenetic regulation

- NRSF and its physical binding to the Hcn1 gene were augmented after SE, resulting in repression of HCN1 expression and HCN1-mediated currents (Ih).
- Chromatin changes typical of epigenetic gene repression were apparent at the Hcn1 gene within a week after SE.
- Administration of decoy ODNs comprising the NRSF DNA-binding sequence reduced NRSF binding to Hcn1, prevented its repression, and restored Ih function.
- In vivo, decoy NRSE ODN treatment restored theta rhythm and altered the initial pattern of spontaneous seizures.

Bernard, 2011 Ann Neurol

Conclusions on the hippocampus

- Hippocampus is involved in the spontaneous seizure circuit
- Interventions at the hippocampal level can modify the disease
  - Reduce seizure frequency and severity
- No treatment leading to hippocampal protection is able to suppress the occurrence of spontaneous seizures
- Do we need to protect other structures?
  - Alone
  - In conjunction with hippocampal protection

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The role of other structures: study in the lithium-pilocarpine model of SE-induced TLE

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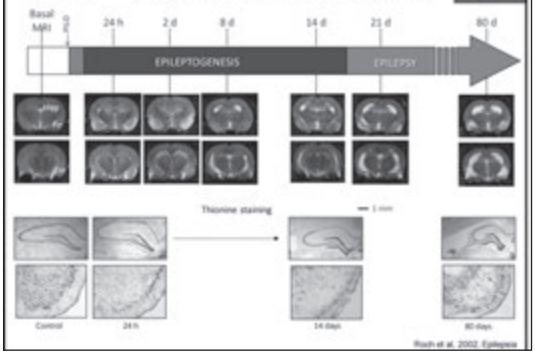
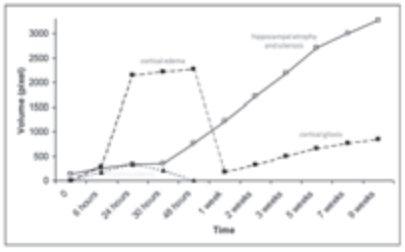
Anatomical MRI in adult rats (4.7 T)



Roch et al. 2002, Epilepsia

Inserm

Li-Pilo SE: T2 signal in adult rats



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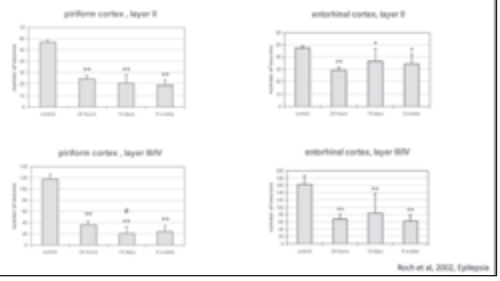
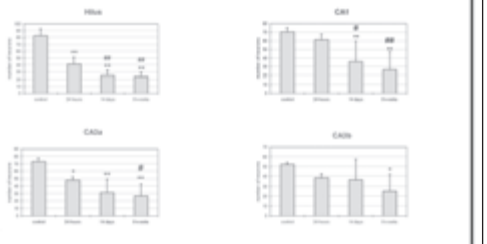
Li-Pilo SE: neuronal damage in cerebral cortex of adult rats



Roch et al. 2002, Epilepsia

Li-Pilo SE: neuronal damage in hippocampus of adult rats



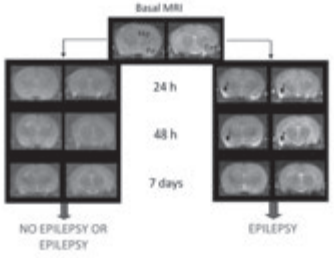
Roch et al, 2002, Epilepsia

MRI studies after Li-Pilo SE: adult rats

- Piriform, entorhinal cortex
  - rapid appearance of a signal (6 h)
  - high reactivity and fast involvement of these structures after the onset of SE
- Hippocampus
  - signal appearing later (36-48 h)
  - delayed and progressive enhancement: in favor of a secondary and not primary role in epileptogenesis?

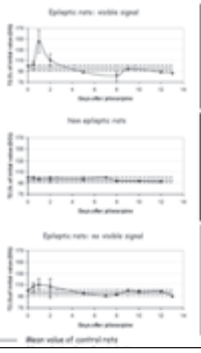
MRI in PN21 rats

All PN21 rats develop SE but only 60% become epileptic



- The early signal in temporal cortices is predictive of epilepsy at this age
- How to make sure that we identify all the animals that will develop epilepsy?

T2 relaxometry in PN21 rats



Visible and measurable signal: epilepsy

No visible signal: two situations

➡ Non measurable signal: no epilepsy

➡ Measurable signal: epilepsy

MRI signal in the cortex can be used as a predictive factor for epilepsy in this age group. Why are parahippocampal cortices so reactive?

Mean value of control rats

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Other antiepileptogenic strategies

Inflammation and BBB leakage

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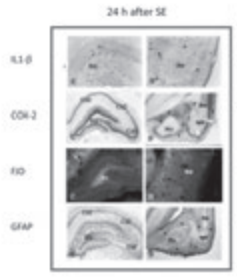
Inflammation and neuronal death in the lithium-pilocarpine model of SE



Rapid onset of cytokines in different cell types: neurons, astrocytes and microglial cells

IL1-β is enhanced in astrocytes in the dentate gyrus and entorhinal cortex

Strong induction of COX-2 labeling in neurons of CA1-CA3, dentate gyrus, entorhinal cortex and amygdala

Fluoro-Jade positive neurons associated with inflammation factors during SE

Glial reactivity in damaged areas

Vezzani-Porcher et al, 2004, NBDI

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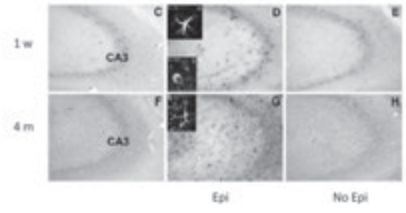
SE-induced inflammation in P21 rats: Implications for epileptogenesis?



At 1 week post-SE two groups of rats: the first one with IL-1β expression in neurons, the second one with no difference compared to controls
At 4 months post-SE marked inflammatory reaction in astrocytes only in rats with SRS

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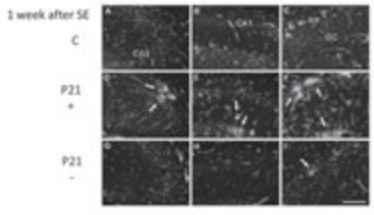
SE-induced BBB leakage in P21 rats: Implications for epileptogenesis?



In control rats only the inside of the vessels is labelled by the dye
In rats with SE, large areas of leakage outside the vessels in one group and only discrete leakage in the other group

Marcon et al, 2009 NBDI

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Summary

- Participation of inflammation and BBB leakage in hyperexcitability and epileptogenesis
- Treatment with celecoxib
  - In the li-pilo model celecoxib reduces seizure frequency, duration, hippocampal degeneration

Could anti-inflammatory treatments and prevention of BBB leakage be used as strategies against epileptogenesis?

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Role of the entorhinal cortex in epileptogenesis

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Non conventional neuroprotection strategies

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Modulation of damage by brief repeated seizures: preconditioning

- Brief seizures do not induce lesions
- They modify
  - neuronal excitability (receptors, ionic channels)
  - cell survival, division and neuronal connections (BDNF, NGF, c-fos, c-jun)
- Beneficial or deleterious consequences?
- Comparison of amygdala kindling (limbic) or electroshocks (brainstem)

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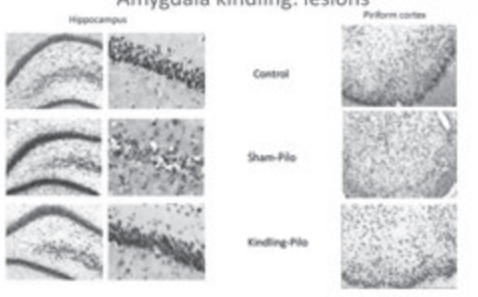
Amygdala kindling: lesions



The lateral entorhinal cortex is the only structure not protected

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Amygdala kindling: epileptic outcome

	Sham-Pilo rats	Kindling-pilo rats
Rats with recurrent seizures	100%	100%
Latency of occurrence of recurrent seizures	54 ± 34 d	53 ± 17 d

- The protection of all structures except the entorhinal cortex does not prevent seizure occurrence

→ Critical role of the entorhinal cortex in epileptogenesis?

André et al, Neuroscience 2000

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Electroshock-Pilo: lesions and epilepsy

- No structure was protected
- Lesions destroyed totally the entorhinal and perirhinal cortices
- Recurrent seizures occurred only in 20% of the rats, after more than 105 d vs 40 d in sham-Pilo rats

Entorhinal and/or perirhinal cortices play a key role in epileptogenesis

André et al, Neuroscience 2000

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Use of antiepileptic strategies for antiepileptogenic purposes: attempts to identify critical structures for epileptogenesis

Neuroprotection in the lithium-pilocarpine model

Drug	Treatment onset	Neuronal loss	Epilepsy
Vigabatrin	10 min pilo (45 days)	↓CA1=CA3, Tentcx =0 hilus	no change in latency or severity
Caffeine	15 d prior (21 days)	↓CA1, ↑pircx =0 hilus	no change in latency or severity
Topiramate	1 h SE (7 days)	↓CA1=CA3 =0 hilus, entcx, pircx	no change in latency or severity
Pregabalin	20 min pilo (40 days)	=0 hippocampus ↓entcx, pircx	increased latency no change in severity
Carisbamate	1 h SE (7 days)	↓CA1=CA3, entcx, pircx, thalamus, amygdala, =0 hilus	increased latency disease-modification seizure suppression

⇨ Protection of Ammon's horn has no effects per se on epileptogenesis
⇨ Protection of cortices delays epilepsy
⇨ Protection of both areas combined plus thalamus and amygdala delays epilepsy or suppresses seizure occurrence and hence has striking disease-modifying effects

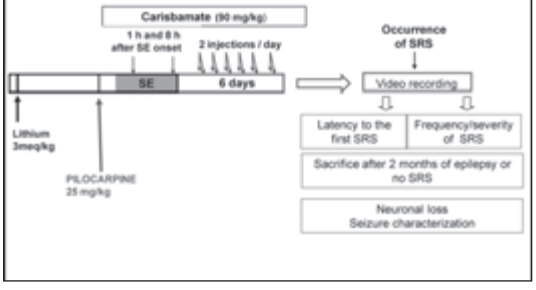
André 2001 Epi Res, 2003 Epilepsia, Rigoulot 2003 JPET, François 2011 Neuropharmacol

Protection and mechanisms of action

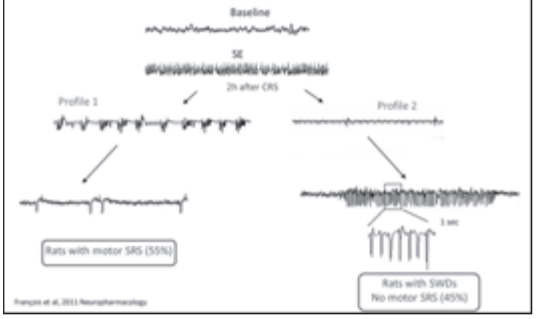
Drug	Protection	Epilepsy	Mechanism of action
Vigabatrin	Ammon's horn	no effect	Inhibition of GABAT
Caffeine	Ammon's horn	no effect	Antagonism of adenosine receptors
Topiramate	Ammon's horn	no effect	AMPA/KA Rs; Na^+ and Ca^{++} (L,N or P/Q) voltage-dependent channels
Pregabalin	Temporal cortices	↑ latency	GAT1 GABA transporter (redistribution to membranes); ↑ GAD; L, N or P/Q Ca^{++} voltage-dependent channels
Carisbamate (CRS)	Ammon's horn + Temporal cortices	↑ latency or no SRS ↓ severity	Mechanism of action largely unknown; action on Na^+ channels

⇨ No relationship between the mechanisms of action of drugs and the outcome of SE (protection and/or epilepsy)

Carisbamate protocol

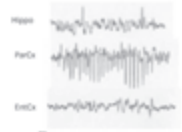


Disease-modifying effect of CRS (90 mg/kg): EEG



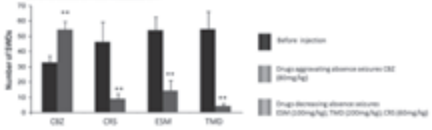
François et al. 2011 Neuropharmacology

Effect of CRS on EEG: depth recordings and pharmacology



SWDs observed only in the parietal cortex

Indication of absence-like epilepsy?



Same pharmacology for SWDs in rats treated with CRS and typical absence seizures

Antiepileptogenesis: Which structures do we need to protect?

Data: Carisbamate is neuroprotective in the whole epileptic circuit and is able to delay the occurrence of motor SRS or induce remarkable disease-modifying effects

TREATMENT	PROTECTION	EPILEPTOGENESIS
TOPIRAMATE ± DZP	HIPPOCAMPUS (CA1 and CA3)	No Effect
VIGABATRIN	HIPPOCAMPUS (CA1 et CA3)	No Effect
PREGABALIN	ENTORHINAL AND PIRIFORM CORTICES	Delays the occurrence of SRS
CARISBAMATE	ENTORHINAL AND PIRIFORM CORTICES + CA1 + THALAMUS + AMYGDALA	Delays the occurrence of motor SRS, reduces severity or transforms the disease into a milder form

Neuroprotection of the ventral cortices alone is not sufficient to prevent epilepsy

Is the protection of the whole epileptic circuit necessary?

Summary on the use of AEDs in the lithium-pilocarpine model

- The putative mechanism of action of current AEDs is not sufficient to explain why some AEDs are protective and others are not
- Carisbamate appears to be the first available drug with striking disease-modifying effects but its mechanism of action remains largely unknown

Conclusions

- Epileptogenesis is a very complex process involving a multiple array of cellular and molecular changes
- Up to now, most strategies focusing on one target (growth factors, inflammation, gene expression…) have been at the best able to reduce seizure frequency and severity
- Carisbamate protects the whole epileptic circuit
- Carisbamate has a strong disease-modifying action but its molecular mechanism of action remains largely unknown
- Combining different strategies would be a good choice
- Necessity of identifying and targeting the very early events

Marco de Curtis (Italy)

MECHANISMS OF FOCAL EPILEPTOGENESIS

Mechanisms of focal epileptogenesis

FONDAZIONE IRCCS ISTITUTO NEUROLOGICO CARLO BESTA

Marco de Curtis

Unità di Neurofisiologia ed
Epilettologia Sperimentale

Fondazione Istituto Neurologico *Carlo Besta*
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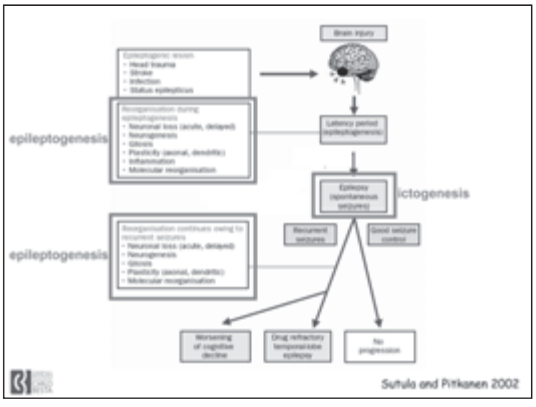
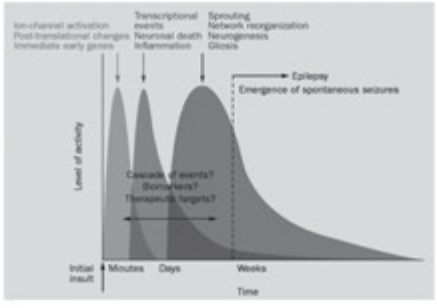


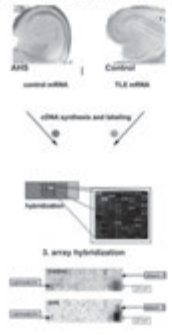
Time-course of Epileptogenesis



Rakhade & Jensen, Nat Rev Neurol 2009

Gene expression

Microarray gene expression profiling



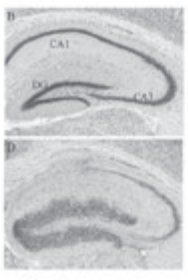
Gene expression

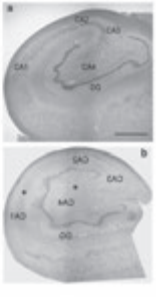
Gorter et al., 2006

Pitkanen Lukasiuk 2011

	Status epilepticus (chemically induced)				Status epilepticus (induced by electrical stimulation)			Traumatic brain injury	
	Okazaki et al.[a]	Becker et al.[b]	Elliott et al.[c]	Lauren et al.[d,e]	Lerche et al.[f]	Hirabayashi et al.[g]	Lukasiuk et al.[h,i]	Kobow et al.[j,k]	Conedera et al.[l]
Species	Rat	Rat	Rat	Juvenile rats	Rat	Rat	Rat	Mouse	Mice (overexpressing APOE3)
Induction methodology	Pilocarpine	Pilocarpine	Pilocarpine	Kainic acid	Angular bundle stimulation	Angular bundle stimulation	Angular stimulation	Controlled cortical impact	Controlled cortical impact
Video-EEG monitoring	Yes	No	No	No	Yes	Yes	Yes	No	No
Gene expression platform	CodeLink	Affymetrix	Affymetrix	Illumina	Affymetrix	SAGE	Research Genetics	Incyte Genomics	Affymetrix
Day of tissue sampling	7	14	14	7	7	8	14	14	28
Brain structure	Hippocampus	Dentate gyrus vs CA1	Dentate gyrus	CA1	CA1 vs entorhinal cortex	Hippocampus	Hippocampus vs temporal lobe	Cerebral cortex	Hippocampus vs cortex
Regulated genes (n)	109	12 (vs dentate gyrus, 449 vs CA1)	178	1520	1409 in CA1, 1168 in entorhinal cortex	78	12 in hippocampus, 10 in temporal lobe	19	285 in hippocampus, 52 in cortex
Hormone response	Yes	No	Yes	No	Yes	No	No	Yes	Yes
Inflammatory response	Yes	No	No	Yes	Yes	No	No	No	Yes
Response to wounding	No	No	Yes	No	Yes	No	No	No	Yes
Regulation of cell death/cell damage	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Signal transduction	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Lipid metabolism	No	No	No	No	Yes	No	No	No	No
Protein transport and processing	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Regulation of transcription	No	No	No	Yes	Yes	Yes	No	Yes	No
Regulation of translation	No	No	No	No	Yes	Yes	No	No	Yes
Cell growth, proliferation, and differentiation	Yes	No	Yes	No	Yes	Yes	No	No	Yes
Cell motility	Yes	No	No	No	No	No	No	No	Yes
Energy metabolism	No	No	No	No	No	No	Yes	No	No
Synaptic transmission and plasticity	No	Yes	Yes	No	Yes	No	No	No	Yes
Structural plasticity	No	Yes	Yes	No	No	Yes	No	No	No
Neurotransmitter synthesis and secretion	No	Yes	No	No	Yes	No	No	No	Yes
Ion transport	No	No	No	No	Yes	No	No	No	Yes
Protein phosphorylation	No	No	No	No	Yes	No	No	No	No
Adhesion of neurons	No	No	Yes	Yes	No	No	No	No	Yes

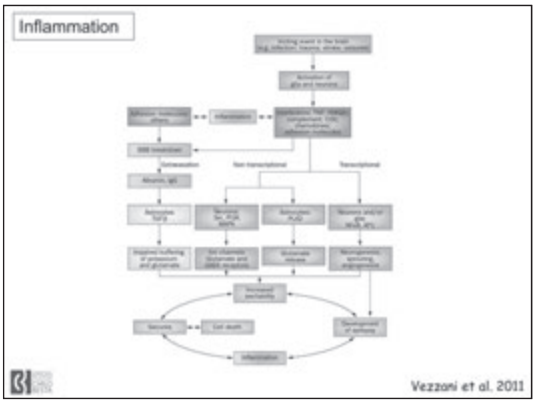
Neuronal loss

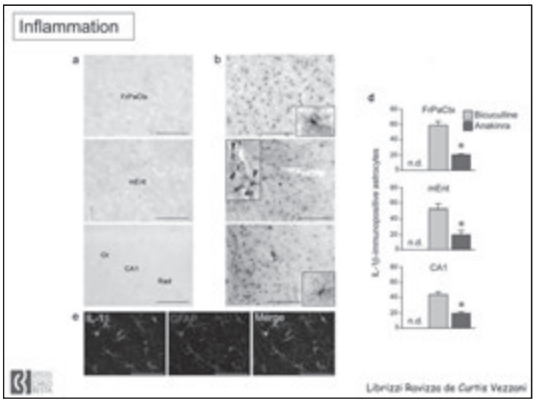


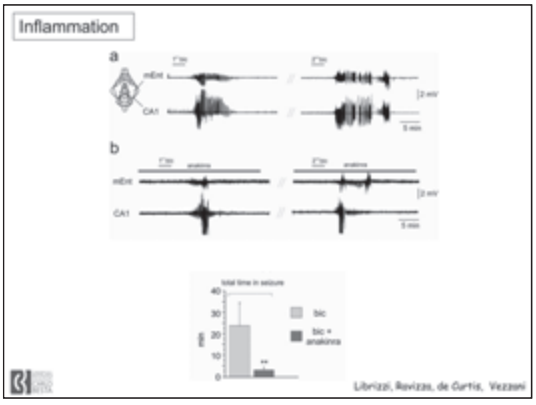


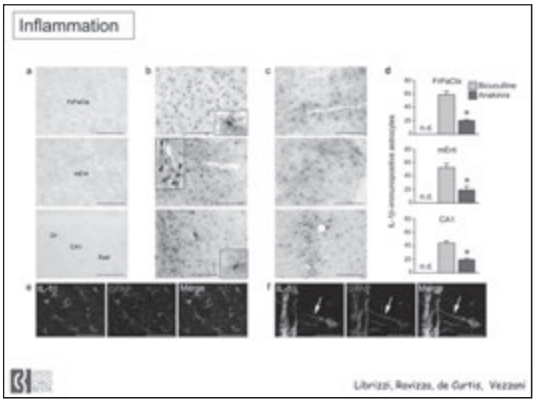
Arabadzisz et al. 2005

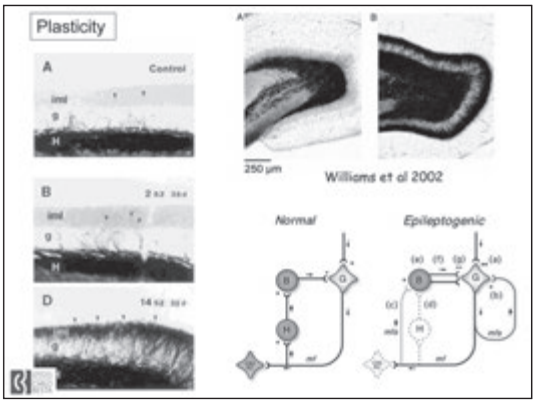
Blumcke et al. 2007

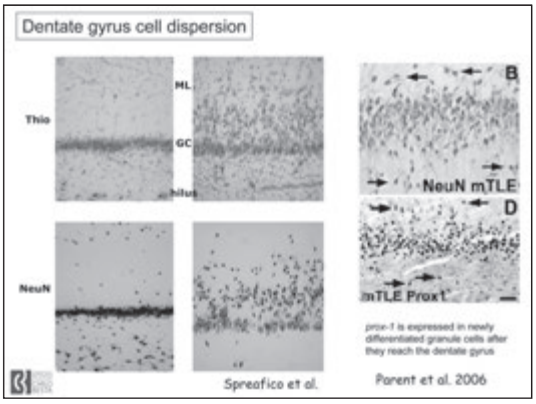

Inflammation
Vezzani et al. 2011

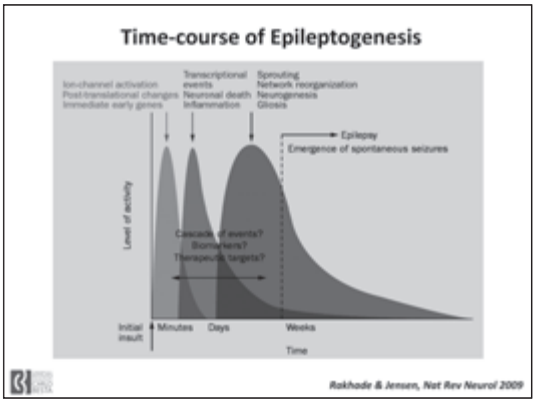

Inflammation
Librizzi Rovizzo de Curtis Vezzani

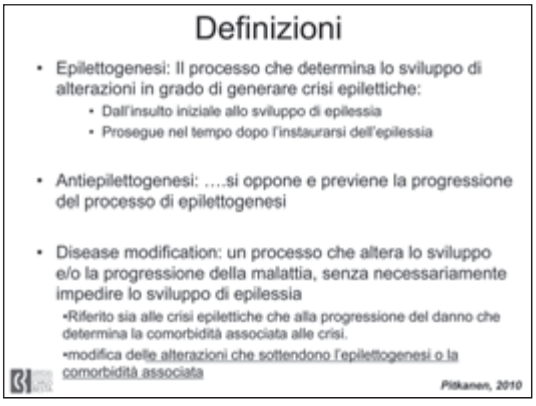

Inflammation
Librizzi, Rovizzo, de Curtis, Vezzani

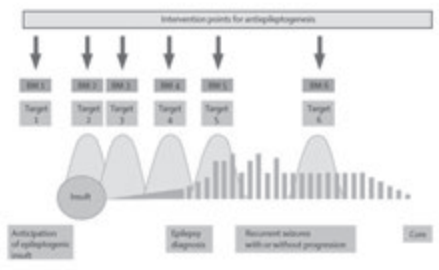

Inflammation
Librizzi, Rovizzo, de Curtis, Vezzani


Plasticity
A
Control
B
D
250 μm
Williams et al 2002
Normal
Epileptogenic


Dentate gyrus cell dispersion
Thio
HL
GC
hilus
NeuN
Spreafico et al.
B
NeuN mTLE
D
mTLE Prox1
prox-1 is expressed in newly differentiated granule cells after they reach the dentate gyrus
Parent et al. 2006


Time-course of Epileptogenesis
Ion-channel activation
Post-translational changes
Immediate early genes
Transcriptional events
Neuronal death
Inflammation
Sprouting
Network reorganization
Neurogenesis
Gliosis
Epilepsy
Emergence of spontaneous seizures
Level of activity
Cascade of events?
Biomarkers?
Therapeutic targets?
Initial insult
Minutes
Days
Weeks
Time
Rakhade & Jensen, Nat Rev Neurol 2009

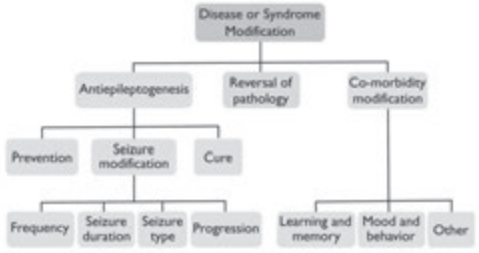

Definizioni
• Epilettogenesi: Il processo che determina lo sviluppo di alterazioni in grado di generare crisi epilettiche:
• Dall'insulto iniziale allo sviluppo di epilessia
• Prosegue nel tempo dopo l'instaurarsi dell'epilessia
• Antiepilettogenesi: ….si oppone e previene la progressione del processo di epilettogenesi
• Disease modification: un processo che altera lo sviluppo e/o la progressione della malattia, senza necessariamente impedire lo sviluppo di epilessia
•Riferito sia alle crisi epilettiche che alla progressione del danno che determina la comorbidità associata alle crisi.
•modifica delle alterazioni che sottendono l'epilettogenesi o la comorbidità associata
Pitkanen, 2010



Pitkanen Lukasiuk 2011

Anti-epilettogenesi - problemi

- L'insulto iniziale non sempre determina lo sviluppo di epilessia
- E' possibile definire quando e quale popolazione trattare in seguito ad un insulto iniziale?
- E' possibile identificare il rischio di sviluppare epilessia?
- Esistono markers in grado di predire lo sviluppo di epilessia?



Pitkanen 2010

Predittori di epilettogenesi: definizioni

Fattori di rischio - predispongono allo sviluppo di epilessia. Possono avere diversi gradi di attendibilità.

Per es: geni a penetranza variabile
Convulsioni fabbrili
Trauma cranic o infezioni pregresse
Altre lasioni cerebrali
Anomalie EEG (fotoparossistiche, fotosensibilità etc)

Fattori precipitanti – fenomeni transienti che causano crisi epilettiche.

Per es: farmaci convulsivanti
privazione di sonno
Febbra
stimolazione luminosa in pz. Sensibili

Biomarkers – fattori che si modificano dinamicamente nel tempo e identificabno un processo epilettogeno con un discreto grado di attendibilità

biomarkers di epilettogenesi

Identificano lo sviluppo di alterazioni tissutali in grado di generare attività epilettiforme

Localizzano in aree cerebrali in grado di generare crisi epilettiche

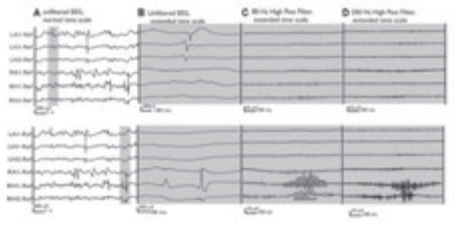
Identificano la tendenza alla progressione di una condizione epilettica

Possono determinare farmacoresistenza

potenziali biomarkers

- Modifiche RM dell'ippocampo
- Interictal spikes identificabili con EEG o fRM
- high-frequency oscillations (pHFOs) patologiche
- Modifiche di eccotabilità corticale caratterizzabili con TMS
- Imaging PET
- Profili di espressione genica

high frequency oscillations



Jacobs et al 2008

biomarkers di sviluppo di epilettogenesi

Possono aiutare a predire se individui con fattori di rischio svilupperanno epilessia con un livello di attendibilità sufficiente per instituire un trattamento preventivo

biomarkers di progressione di epilettogenesi

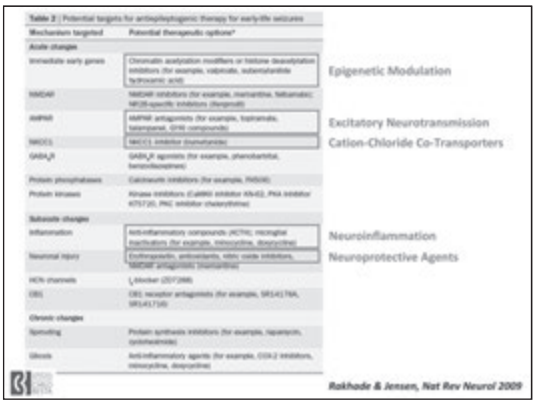
Contribuiscono a predirre quali pazienti con epilessia avranno una progressione di malattia con un alto grado di attendibilità, tale da permettere trattamenti agressivi (chirurgia) che prevengano un'aggravamento della disabilità.

biomarkers di farmacoresistenza

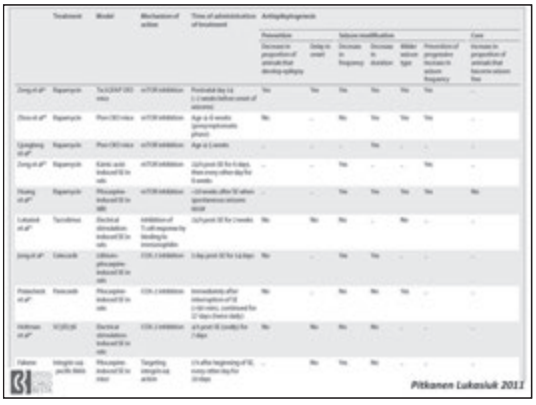
Identificano la presenza di farmacoresistenza e facilitano la decisione di trattamenti alternativi a quello farmacologico

possibili targets per studiare i biomarkers di epilettogenesi

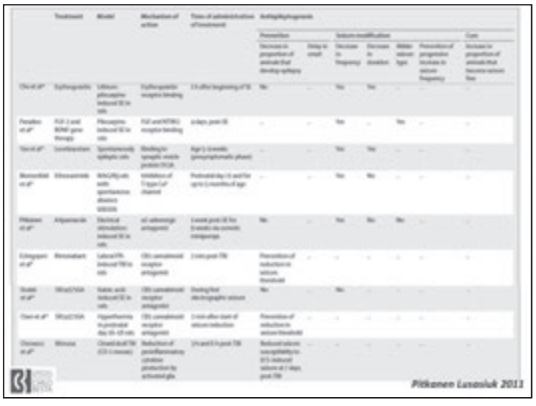
- Cell loss (per es atrofia ippocampale)
- Axonal sprouting
- Ri-organizzazione sinaptica
- Alterazioni di espressione genica o di produzione di proteine etc.
- Neurogenesi
- Gliosi ed alterazioni della funzione della glia
- Modifiche infiammatorie
- Angiogenesi
- Alterazioni di eccitabilità e sincronizzazione



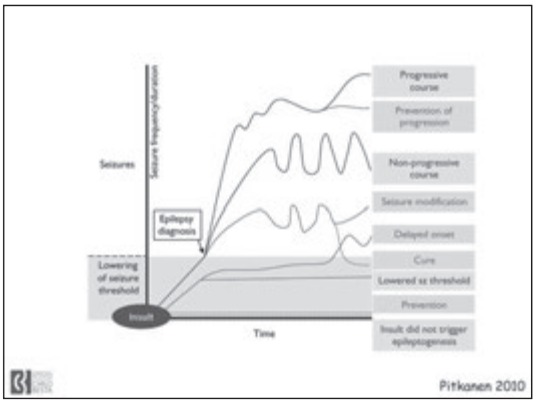
Rakhade & Jensen, Nat Rev Neurol 2009



Pitkanen Lukasiuk 2011

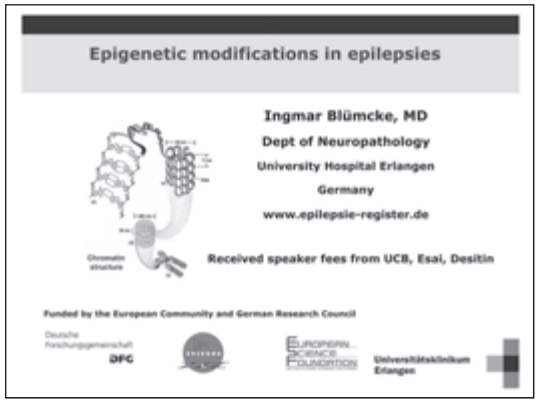


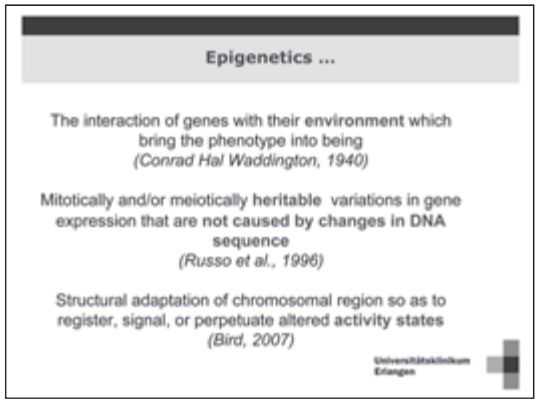
Pitkanen Lusosiuk 2011

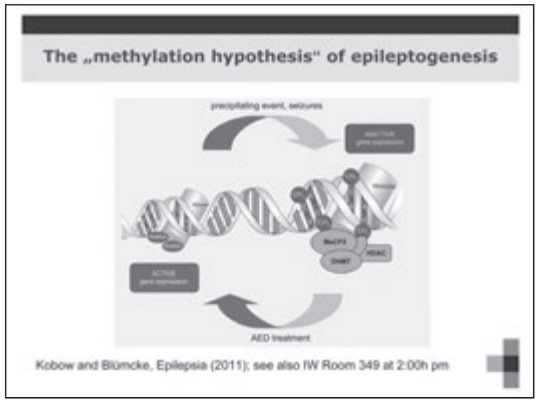

Seizures
Seizure frequency/duration
Epilepsy diagnosis
Lowering of seizure threshold
Insult
Time
Progressive course
Prevention of progression
Non-progressive course
Seizure modification
Delayed onset
Cure
Lowered sz threshold
Prevention
Insult did not trigger epileptogenesis
Pitkanen 2010

Ingmar Blümcke (Germany)

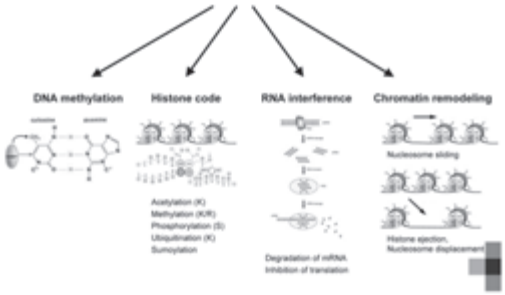
EPIGENETIC MODIFICATIONS IN NON-LESIONAL EPILEPSIES





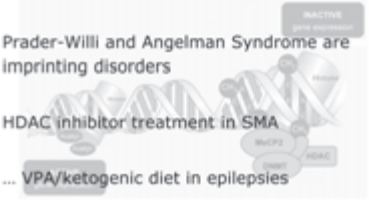


Short and long – term epigenetic mechanisms



Epigenetics in neurological disorders

- MeCP2 mutations associate with Rett syndrome
- Prader-Willi and Angelman Syndrome are imprinting disorders
- HDAC inhibitor treatment in SMA
- … VPA/ketogenic diet in epilepsies



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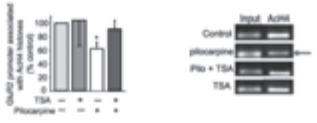
SE – induced histone deacetylation

Trichostatin A inhibited SE-induced histone deacetylation at the GluR2 (AMPA) promoter



Huang and Dingledine, J. Neurosci. 2002

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Increased promoter methylation in human mTLE - HS

Methylation specific PCR of the Reelin promoter in mTLE patients with granule cell dispersion

Kobow et al, J. Neuropathol Exp. Neurol. 2009

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Sustained down-regulation of gene expression

SE-induced and long-lasting alterations in gene expression (Affymetrix-Chipanalyse)

Becker et al., Eur. J. Neurosci. 2003

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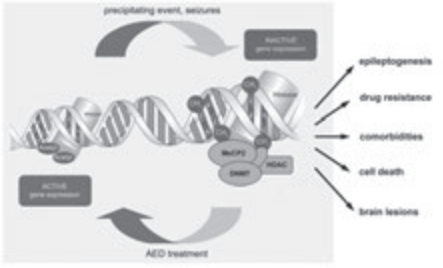
Summary – II -



Raman Sankar (USA)

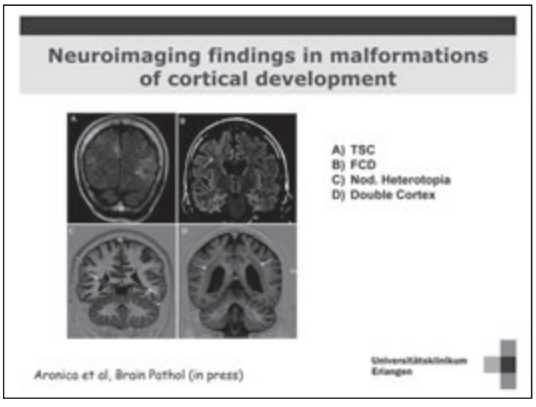
EXPERIMENTAL MODELS OF EARLY SYMPTOMATIC AND CATASTROPHIC EPILEPSY

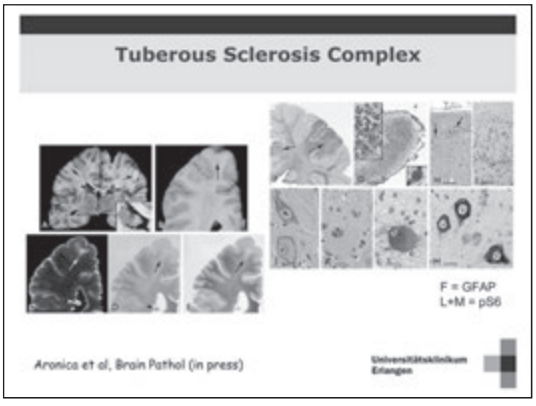
Laura Tassi (Italy)

INVASIVE EEG EVALUATION AND ITS RELEVANCE FOR THE UNDERSTANDING OF EPILEPTOGENIC ZONE

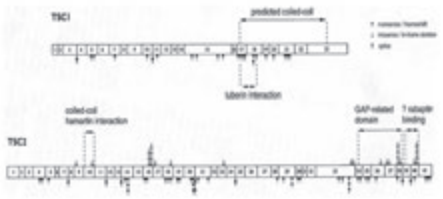
Ingmar Blümcke (Germany)

NEUROPATHOLOGY OF MALFORMATIONS OF CORTICAL DEVELOPMENT





Tuberous Sclerosis Complex



Jones et al, Am J Hum Genet (1999)

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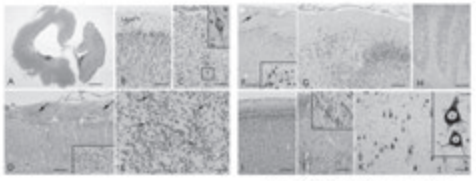
Hemimegalencephaly



F-H = NeuN, I-J = NFM, K = pS6

Aronica et al, Brain Pathol (in press)

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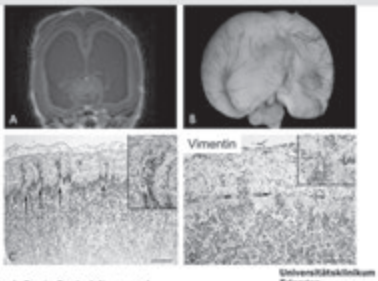
Lissencephaly



Aronica et al, Brain Pathol (in press)

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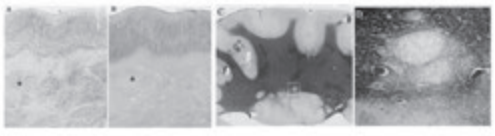
Nodular Heterotopia



Aronica et al, Brain Pathol (in press)

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European Epilepsy Brain Bank

www.epicure-bank.org

MCD	Number	Age	Onset	Duration
Heterotopia	11	2.2	0	2.2
Polymicrogyria	33	7.7	2.0	5.5
FCD-type I	75	11.6	3.5	6.8
FCD-type IIa	36	16.7	2.6	12.8
FCD-type IIb	182	18.6	4.3	14.6
FCD (NOS)	133	20.8	7.9	13.3
mMCD	46	28.0	10.1	17.6
Hamartia/-toma	34	25.1	8.9	16.0
Nodular heterotopia	9	29.6	13.0	18.5

FCD: focal cortical dysplasia; NOS: not otherwise specified; mMCD: mild malformation of cortical development; Age: OP mean (in years); Onset: mean (in years); Duration: mean (in years).

Blümcke et al. Epileptic Disorders 2009

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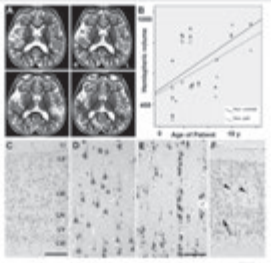
The new ILAE consensus classification of Focal Cortical Dysplasias

FCD Type I (isolated)	*Focal Cortical Dysplasia with abnormal radial cortical lamination* (FCD Ia)		*Focal Cortical Dysplasia with abnormal tangential cortical lamination* (FCD Ib)	*Focal Cortical Dysplasia with abnormal radial and tangential cortical lamination* (FCD Ic)
FCD Type II (isolated)	*Focal Cortical Dysplasia with dysmorphic neurons* (FCD IIa)		*Focal Cortical Dysplasia with dysmorphic neurons and balloon cells* (FCD IIb)	
FCD Type III (associated with principal lesion)	*Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis* (FCD IIIa)	*Cortical lamination abnormalities adjacent to a glial or glio-neuronal tumor* (FCD IIIb)	*Cortical lamination abnormalities adjacent to vascular malformation* (FCD IIIc)	*Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis* (FCD IIId)

FCD Type III (not otherwise specified, NOS):
if clinically/radiologically suspected principal lesion is not available for microscopic inspection

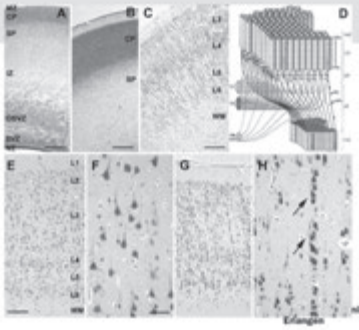
Blümcke et al. Epilepsia 2011

FCD - ILAE Type Ia
(abnormal radial cortical lamination)

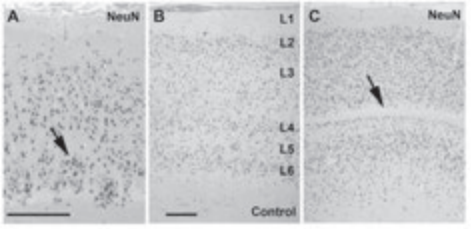


Blümcke and Spreafico, Acta Neuropathol 2010

Universitätsklinikum Erlangen



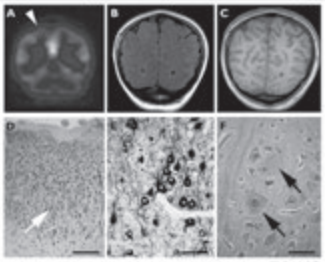
FCD – ILAE Type Ib
(abnormal tangential cortical lamination)



Blümcke et al. Epilepsia 2011

Universitätsklinikum Erlangen

FCD – ILAE Type IIa
(with dysmorphic neurons)



Blümcke et al. Epilepsia 2011

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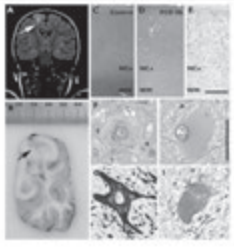
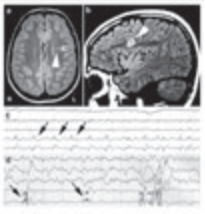
FCD – ILAE Type IIb
(dysmorphic neurons and balloon cells)



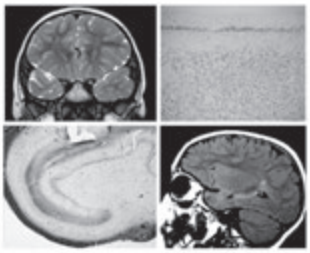


Blümcke and Spreafico 2010
Acta Neuropathol

Blümcke et al. Epilepsia 2011

Universitätsklinikum Erlangen

FCD – ILAE Type IIIa (with MTS)



Courtesy of Dr. R. Spreafico (Milan)

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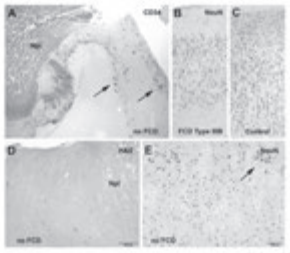
FCD – ILAE Type IIIb (with neoplasia)



Blümcke et al. Epilepsia 2011

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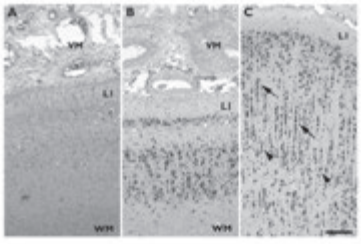
FCD – ILAE Type IIIc (with vascular malformation)



Blümcke et al. Epilepsia 2011

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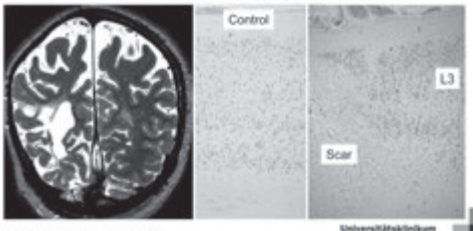
FCD – ILAE Type IIId (with perinatal infarction)

17 year old female patient with perinatal temporo-occipital infarction and focal epilepsy since age 4 years



Blümcke et al. Epilepsia 2011

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Different clinical presentation and outcome in isolated vs. associated FCDs

Histology	No. of patients (%)	Males (%)	Females (%)	Age at epilepsy onset* (SD)	Duration of epilepsy (SD)	Age at surgery (SD)	Monthly seizure frequency (SD)	Auto-cydents (%)	PS (%)	Negative MRI (%)	SEIG (%)
FCD isolated	66 (31)	41 (62)	25 (38)	8 (10)	33 (9)	23 (12)	113 (208)	25 (38)	3 (5)	22 (33)	47 (71)
FCD + MCD	34 (?)	11 (64)	3 (33)	10 (?)	18 (?)	28 (?)	21 (?)	6 (18)	1 (3)	0	12 (?)
FCD + tumour	49 (23)	33 (?)	14 (29)	8 (6)	17 (12)	25 (14)	30 (29)	11 (?)	4 (8)	1 (2)	11 (?)
FCD + HS	76 (35)	48 (63)	36 (47)	8 (8)	25 (18)	34 (?)	10 (?)	32 (42)	41 (54)	2 (3)	11 (15)
FCD + other	8 (4)	5 (62)	3 (38)	6 (3)	12 (?)	18 (10)	45 (18)	7 (88)	1 (13)	0	7 (88)
Total	213	132 (62)	81 (38)	8 (8)	19 (11)	27 (13)	47 (128)	81 (39)	50 (23)	25 (12)	98 (62)

Histology	Class Ia + Ib (%)	Class I (%)	Class II (%)	Class III (%)	Class IV (%)	Therapy stopped (%)
FCD isolated	33 (50)	80 (66)	7 (11)	10 (15)	19 (29)	9 (14)
FCD + MCD	12 (63)	12 (80)	0	1 (8)	1 (8)	1 (8)
FCD + tumour	18 (78)	40 (82)	1 (4)	1 (?)	1 (?)	17 (?)
FCD + HS	50 (66)	62 (82)	7 (9)	3 (4)	4 (5)	18 (24)
FCD + other	5 (63)	7 (?)	1 (?)	1 (?)	1 (?)	1 (?)
Total	123 (57)	148 (69)	19 (9)	21 (10)	27 (13)	46 (23)

Tassi et al., Epileptic Disord 2010

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Conclusions

FCDs are the most frequent entities in MCD -associated focal epilepsies

FCD Type I (isolated FCDs) remains enigmatic. There are probable „hidden" clinico-pathological entities (or even syndromes) which need better characterization and presurgical detection by imaging and electrophysiology.

FCD Type II is histopathologically well characterized, which allows good outcome prediction (>75% seizure control) as well as therapy/pathogenesis-related scientific studies

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Conclusions

FCD Type III (associated FCDs) need to be characterized clinically, radiologically, neurophysiologically and histopathologically,

FCD Type III is maybe a result of the principal pathology rather than of independent pathogenesis … (*acquired ?*)

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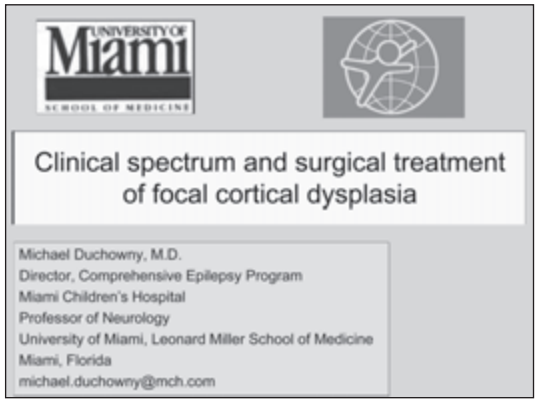
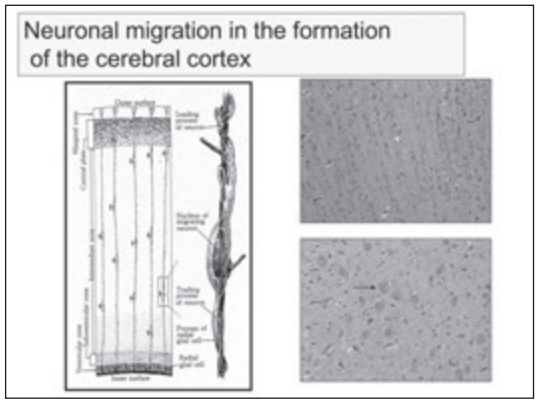
Ruben Kuzniecky (USA)

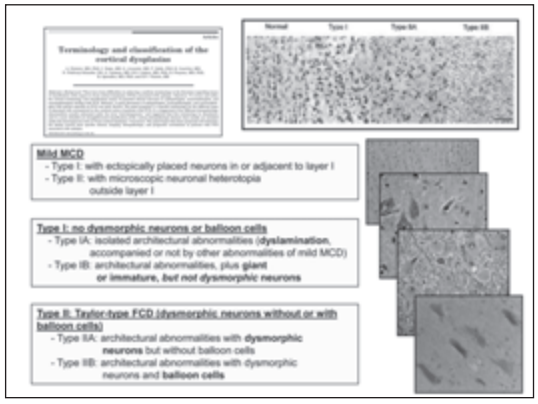
MTS – MRI

Michael Duchowny (USA)

CLINICAL SPECTRUM AND SURGICAL TREAMENT OF FOCAL CORTICAL DYSPLASIA







SPECIAL REPORT

The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission†

[*]Ingmar Blümcke, [†]Maria Thom, [‡]Eleonora Aronica, [§]Donna D. Armstrong, [¶]Harry V. Vinters, [#]Andre Palmini, [**]Thomas S. Jacques, [††]Giuliano Avanzini, [‡‡]R. James Barkovich, [§§]Giorgio Battaglia, [¶¶]Albert Becker, [##]Carlos Cepeda, [***]Fernando Cendes, [†††]Nadia Colombo, [‡‡‡]Peter Crino, [§§§]J. Helen Cross, [¶¶¶]Viktor Delalande, [###]François Dubeau, [****]John Duncan, [††††]Renzo Guerrini, [‡‡‡‡]Philippe Kahane, [§§§§]Gary Mathern, [¶¶¶¶]Imad Najm, [####]Ojetun Ozkara, [*****]Charles Raybaud, [††††]Alfonso Represa, [‡‡‡‡]Steven M. Roper, [§§§§]Marike Salamon, [¶¶¶¶]Andreas Schulze-Bonhage, [####]Laura Tassi, [*****]Annamaria Vezzani, and [††]Roberto Spreafico

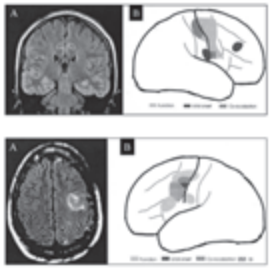
Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

FCD Type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)
FCD Type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)
FCD Type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)	Cortical lamination abnormalities adjacent to glial or glioneuronal tumor (FCD Type IIIb)	Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc)	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId)

FCD Type III is not a histopathologically separate entity but is not suitable for neurosurgical resection. Please note that the non-association between FCD Type IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variants.

FCD Type 2: which cell types are epileptogenic?

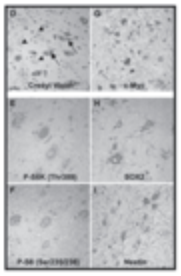
- Seizure onset and interictal discharges found only in cortical regions with large dysmorphic neurons
- No seizures in neocortical areas with balloon cells
- Absence of functionality in regions characterized by FLAIR abnormalities and balloon cells



Marusic et al, Epilepsia, 2002
Boonyapisit et al, Epilepsia, 2003

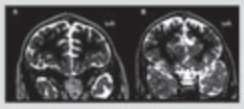
Early Progenitor Cell Marker Expression Distinguishes Type II From Type I Focal Cortical Dysplasias

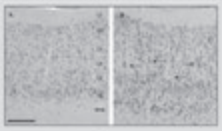
- Immunohistochemistry/immunocytochemistry of Types 1 and 2 FCD (n=20) and TSC (n=8)
- Expression of neuroglial progenitor protein (nestin) and stem cell proteins (c-Myc, SOX2, SOX3, OCT-4, FOXG1, KLF4, Nanog) only in FCD Type 2 and TSC
- Protein expression phenotype similar to pleuripotential stem cells. Nestin, vimentin, CD133, Mem2 also identified. May assist in stratifying subgroups of FCD in absence of balloon cells
- Enhanced phosphorylation of downstream signaling proteins (S6, S6K1) suggests hyperactivity in mTOR complex 1

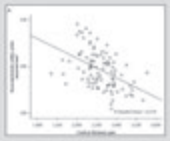


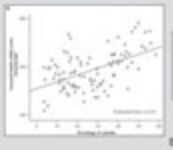
Original article

A distinct variant of focal cortical dysplasia type I characterised by magnetic resonance imaging and neuropathological examination in children with severe epilepsies









Increased neuronal density correlates with:
- decreased cortical thickness
- abundance of neuronal microcolumns

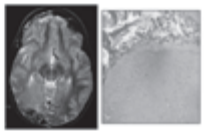
Blumcke et al, Epilep Disord , 2010

FCD Type 1 and the temporal lobes

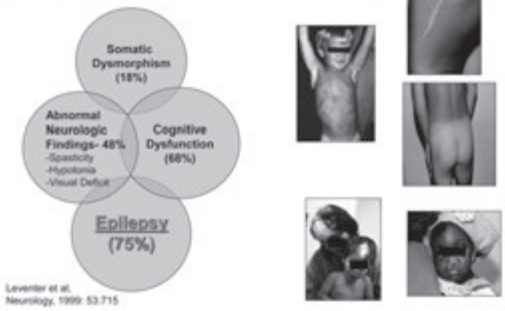
- Seizures in patients with Grade 1 FCD more likely to arise in the temporal lobes (Tassi et al, 2002; Bautista et al, 2003; Fauser et al, 2004; Widdess-Walsh et al, 2005)
- MRI evaluation- normal; hypoplasia and atrophy (volumetric). No radiologic feature distinguishes Types 1a and 1b (Krsek et al, 2008)
- Highly correlated with other neuropathological findings
  - HS ("dual pathology") (Tassi et al, 2002; Kral et al, 2007; Krsek et al, 2008).
  - Developmental tumors, neoplasms (Honovar et al,1999; Park et al, 2006)
  - Sturge-Weber syndrome (Maton et al, 2010)
  - Pre/Perinatal pathology (Krsek et al, In Press)
  - Rasmussen's syndrome (Takei et al, 2010)

MRI-Negative Studies

STUDY	FCD Type 1 (%)	FCD Type 2 (%)
Kim et al, 2000	87	18
Tassi et al, 2002	35	33
Krsek et al, 2008a	17	0
Krsek et al, 2008b	63	10

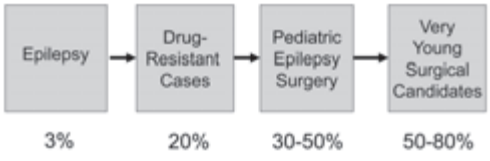


Clinical correlates of cortical malformations in childhood



Leventer et al, Neurology, 1999; 53:715

MCD and Epilepsy: spectrum of involvement



Outcome of early epilepsy surgical series for focal cortical dysplasia

Study	N	Ages	SF (%)
Taylor et al, 1971	10	17-46	2 (20)
Palmini et al, 1991	24	2-31	2 (8)
Hirabayashi et al, 1993	17	1-38	3 (18)
Raymond et al, 1995	35*	15-63	15 (43)

* 21 DNETs

Surgical failure in focal cortical dysplasia

Why do so many children with FCD fail epilepsy surgery?

- *Failure rate for FCD* - exceeded other known pathological substrates. Seizure-freedom for HS, AVMs, tumors between 60-90%
- *Younger patients* - especially failure-prone despite large procedures such as multilobar resection and hemispherectomy

➢ ***Even with well-documented lesions, seizure-freedom in FCD only marginally better than for non-lesional cases***

Surgical failure in focal cortical dysplasia

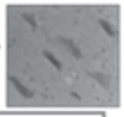
Possible Explanations

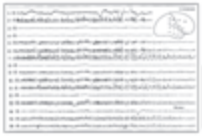
Patient-related factors (e.g. age at surgery, IQ, seizure type) - no significant influence on outcome (*Goldstein et al, 1992*)

Technical issues unlikely to influence outcome (possible exception: hemimegalencephaly)

Lesion size *Are children with larger and more complex dysplastic lesions more failure-prone?* Failure rate for smaller lesions- similar or possibly higher than for larger lesions. Small, subtle dysplastic lesions- most likely to fail. MRI advances have helped, but not eliminated the problem

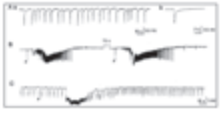
FCD- why is the epilepsy so severe?





Intrinsic Hyperexcitability

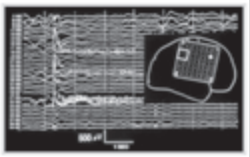
Palmini et al, 1995: Recording of continuous epileptiform discharges (CEDs) on the ECoG of patients with focal cortical dysplasia



Mattia et al, 1995: In vitro dysplastic tissue has intrinsic ability to generate spontaneous ictal-like events in response to 4-aminopyridine challenge

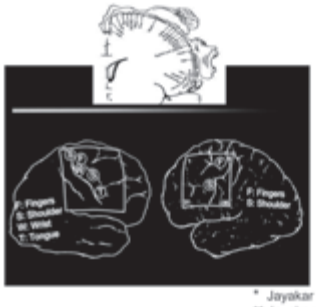
Epilepsy in FCD …the neuron or the network?

EEG in FCD - Atypical Features
hyperexcitability, complex spike and propagation fields with unexpected interactions- often at non-contiguous sites:
- Cortico-cortical propagation
- Intra-ictal activation
- Multi-lobar spread
- "Immediate" secondary generalization



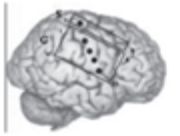
Neural systems for hyper-excitability in FCD - ***widespread and dysfunctional***

Surgical failure in focal cortical dysplasia
- anomalous functional representation

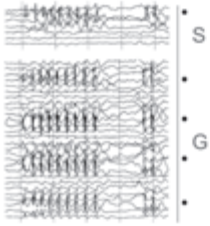


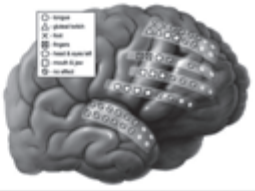
- Direct cortical stimulation studies utilizing a dual-stimulation paradigm* reveal anomalous motor homunculi in patients with FCD**
- Cortical mapping in infants <1 yr confirms the existence of motor anomalies, indicating that altered functionality is already present at birth**

* Jayakar et al, J Clin Neurophys, 1992
** Jayakar & Duchowny, Adv Neurol, 1993



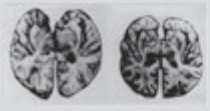
Epilepsy and FCD: is the epileptic network functionally isolated or functionally integrated?

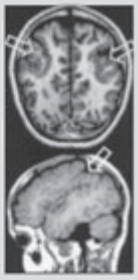


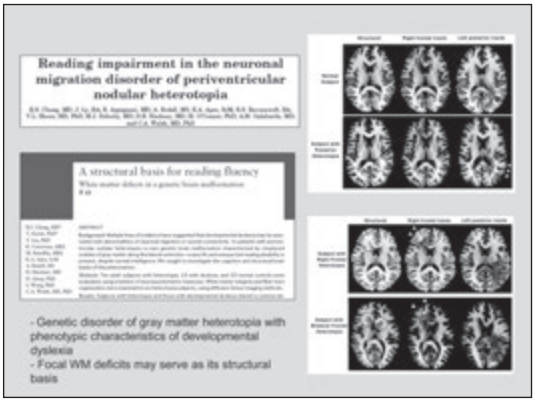


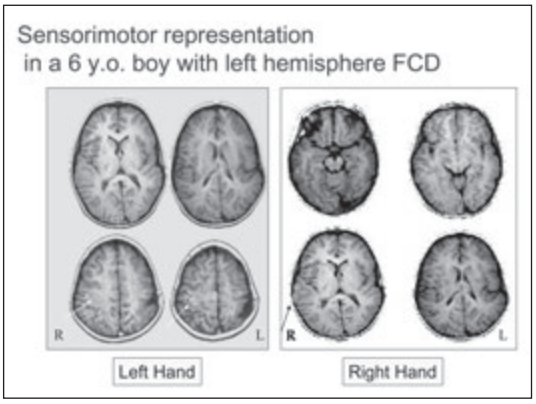
Dysplastic tissue frequently located directly within, contiguous to or in close proximity to eloquent cortical regions

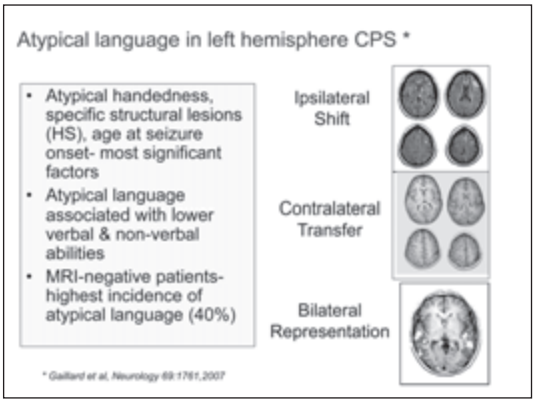
Over-representation of FCD in sensorimotor and language cortex compared to other epilepsy substrates

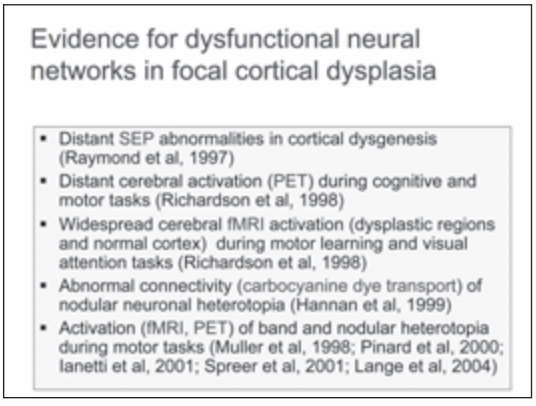




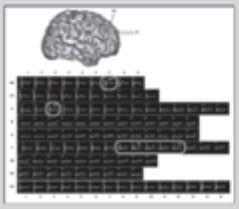

Reading impairment in the neuronal migration disorder of periventricular nodular heterotopia
A structural basis for reading fluency
White matter deficits in a genetic brain malformation
- Genetic disorder of gray matter heterotopia with phenotypic characteristics of developmental dyslexia
- Focal WM deficits may serve as its structural basis


Sensorimotor representation
in a 6 y.o. boy with left hemisphere FCD
R
L
R
L
Left Hand
Right Hand


Atypical language in left hemisphere CPS *
• Atypical handedness, specific structural lesions (HS), age at seizure onset- most significant factors
• Atypical language associated with lower verbal & non-verbal abilities
• MRI-negative patients- highest incidence of atypical language (40%)
Ipsilateral Shift
Contralateral Transfer
Bilateral Representation
* Gaillard et al, Neurology 69:1761,2007


Evidence for dysfunctional neural networks in focal cortical dysplasia
• Distant SEP abnormalities in cortical dysgenesis (Raymond et al, 1997)
• Distant cerebral activation (PET) during cognitive and motor tasks (Richardson et al, 1998)
• Widespread cerebral fMRI activation (dysplastic regions and normal cortex) during motor learning and visual attention tasks (Richardson et al, 1998)
• Abnormal connectivity (carbocyanine dye transport) of nodular neuronal heterotopia (Hannan et al, 1999)
• Activation (fMRI, PET) of band and nodular heterotopia during motor tasks (Muller et al, 1998; Pinard et al, 2000; Ianetti et al, 2001; Spreer et al, 2001; Lange et al, 2004)

Investigation of heterotopic and remote cortical structures at seizure initiation in a patient with BPNH

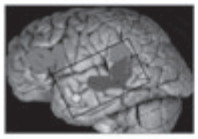


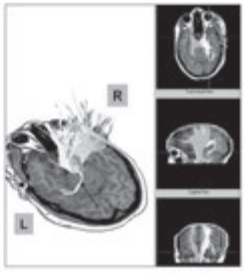
Signal analysis of two seizures reveal large initial network involving both heterotopia and cortical structures

- Stimulation of heterotopia- induced responses in remote cortical structures
- Distinct epileptogenic networks identified- leader structures either heterotopic nodules or mesial temporal structures. Functional connections between heterotopic and cortical areas

Valton *et al.* Clin Neurophysiol 2008; 119: 21

Fiber tractography in a 13 y.o. girl with dual pathology





Neurology 2006;67:258–260
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Articles

Cognitive outcome of children with epilepsy and malformations of cortical development

Beth Klein, PhD, Bonnie E. Levin, PhD, Michael S. Duchowny, MD and Maria M. Llabre, PhD

From the Miami Children's Hospital Dev. Neur. and Psychology and the Departments of Neurology (Dr. Levin) and Psychology (Dr. Llabre), University of Miami, FL.

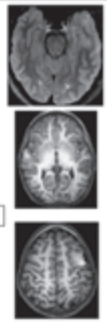
- 54 children with refractory seizures due to unilateral developmental lesions. Lesions classified as circumscribed or diffuse and graded according to histopathology. Subjects received either the WISC-R, WISC-III or WAIS-R
- Circumscribed - less deleterious for cognitive development
  - R sided lesions- Non-verbal measures
  - L sided lesions- Verbal measures
- Left hemisphere lesions - greater compromise of both ipsilateral and contralateral measures

→ No relationship between severity of graded histopathology (or interaction of lesion grade/ laterality) and IQ

childhood TLE: unique influences on language organization? *

- Evaluation of language networks by fMRI and neuropsychological performance in 30 right-handed subjects ages 9-20 years with intractable partial epilepsy due to FCD or HS
- Temporal lesions associated with atypical organization of receptive language (and diminished neuropsychological performance) in 60% of subjects and atypical expressive language organization in 22%. Pathology-independent
- No instances of atypical receptive language organization associated with left frontal lesions

Prenatal and early postnatal pathologic lesions in the dominant temporal lobe strongly promote atypical language organization and diminished receptive language performance. The contribution of histopathological substrate is minimal



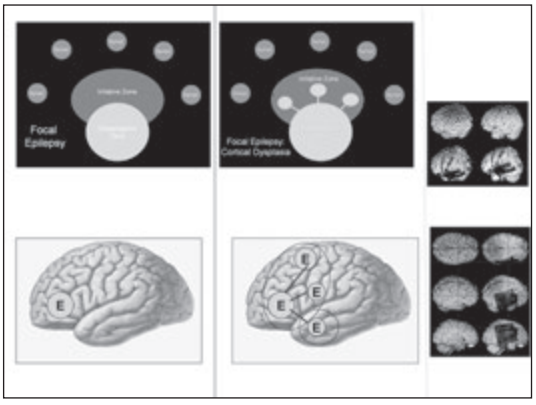
* Korman et al. J Child Neurol. 2010

Childhood TLE: specific influences on cognition and language organization

- Intellectual disability (IQ<79) in 57% of children; 82.4% if age of onset in in first year. Pathology-independent (Cormack et al, 2007).
- Language development significantly delayed in pediatric temporal lobectomy candidates (Lendt et al, 1999; deKoning et al, 2009)
- Children with TLE show high incidence of atypical language lateralization (Briellmann et al, 2006)
- Memory deficits in children with TLE show no clear evidence of lateralization (Gonzalez et al, 2007)
- Children with TLE exhibit neuropsychological deficits indicative of extra-temporal dysfunction (attention, visuoconstructive praxis, executive function) (Guimaraes et al, 2007)

Focal cortical dysplasia: neural networks and epilepsy surgery

- *Prediction: aberrant physiological networks and anomalous functional representation in children with FCD are the primary variables complicating surgical planning, and compromising outcome. Smaller lesions, non-lesional cases- most challenging.*
- *Surgery on a "dysfunctional network" rather than an epileptogenic lesion.*




Predictors of outcome in pediatric epilepsy surgery

- 75 patients < 12 yrs. (40 M, 35 F)
- 35 non-lesional, 40 lesional
- "lesional" - focal signal change, gyral anomaly, HS
- "non-lesional" - non-specific changes (e.g. cortical atrophy)
- **55 (73%) had extra-operative monitoring**

Outcome:
1 SF (n = 44, 59%)
2 > 90% reduction (n =14, 19%)
3 > 50 % reduction
4 < 50 % reduction

Mean follow-up 5 yrs. (range: 1-10 yrs.)

Stepwise, multiple logistic regression and univariate analyses for seizure-freedom:
No significant difference
- Age of seizure onset, duration of epilepsy
- Temporal vs. extra-temporal resection
- Lesional vs. non-lesional MRI

Completeness of resection
Only significant variable (p<.001) Odds ratio=11 (probability of a poor outcome 11 times greater after incomplete resection)

Surgical therapy for FCD: the 21st century

STUDY	N	AGES	S.F. (%)	Intracr
Edwards et al, 2000	35	3m-47y	49	+
Hong et al, 2000	36	1-58 y	72	+
Tassi et al, 2002	52	2-42 y	54	+
Kral et al, 2003	53	5-46 y	72	+
Bautista et al, 2003	55	17-57 y	65	
Cohen-Gadal et al, 2004	22	9-43 y	63	+
Widdess-Walsh et al, 2007	48	1-56 y	45	+
Kloss et al, 2002	68	5m- 16 y	50	-
Hudgins et al, 2005	15	3m- 17 y	66	+

Surgical therapy- FCD subtypes

STUDY	N	mMCD	1a	1b	2a	2b
Fauser et al, 2004	67	63	67	55	43	50
Lawson et al, 2005	31	-	-	-	44	80
Widdess-Walsh et al, 2005	145	-	61	38	67	80
Krsek et al, 2008	200	52	49	45	61	75

Surgical therapy- non-lesional cases

STUDY	N	SF-2 yrs (%)	SF- 2 yrs (%)	SF- 10 yrs (%)
Jayakar et al, 2008*	101	44	44	38

* Significant:
- Resection (complete v incomplete) p< .0005
- Inter-ictal spikes (focal v non-focal) p< .005

NEUROLOGY®

Predictors of seizure-freedom after incomplete resection of the epileptogenic zone in children.
Perry MS, Dunoyer C, Dean P, Bhatia S, Ragheb J, Miller I, Resnick T, Jayakar P, Duchowny M. ***Neurology,*** In Press

- 48 lesional patients with complete resection
- 65 patients with incomplete resection- 44% SF

	Sz-free	Non- Sz-free	p-value*
MRI/EEG complete*	**37 (77%)**	**11 (23%)**	**0.0005**
MRI incomplete/EEG complete	**13 (57%)**	**10 (43%)**	
MRI complete/EEG incomplete	**11 (52%)**	**10 (48%)**	
MRI incomplete/EEG incomplete	**5 (24%)**	**16 (76%)**	

- Complete resection of the MRI and EEG-defined EZ is the best predictor of seizure freedom; however, patients incomplete by EEG or MRI alone have better outcome compared to patients incomplete by both
- More than one-third of patients with incomplete resection (by either EEG or imaging) criteria can still become SF- contiguous MRI lesion a predictor of SF outcome

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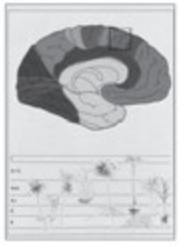
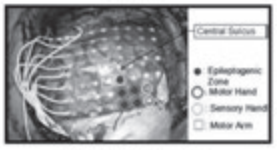
FCD: where do we go from here?



Better understanding of developmental epileptogenesis and disorders of cortical specification



Detailed clinical observations

Epilepsy: The Team Approach

Francois Dubeau (Canada)

PERIVENTRICULAR NODULAR HETEROTOPIA

6th Latin-American Summer School on Epilepsy (LASSE VI) – Sao Paulo 2012

Symptomatic Epilepsy along the Life:

periventricular nodular heterotopia

François Dubeau, md
Montreal Neurological Hospital and Institute
McGill University, Montréal, Canada

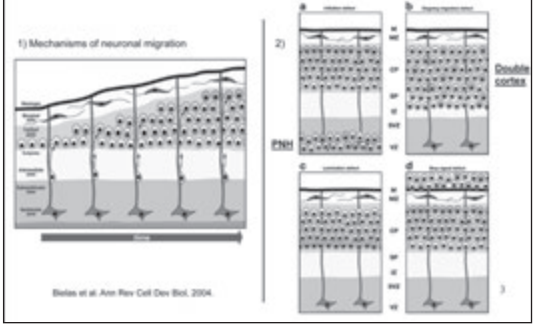
1

periventricular neuronal heterotopia
definition

- Neuronal heterotopia can be found anywhere from the subependyma along the lateral ventricles to the cortical mantle.
- PNH or periventricular nodular heterotopia (also sub-ependymal = SEH or periventricular = PVH or periventricular nodular = PVNH) are collections of gray matter located in abnormal position within the cerebral hemispheres. They are caused by a primary failure of neuronal migration resulting in ectopic neuronal nodules lining the lateral ventricles beneath a normal appearing cortex.

2

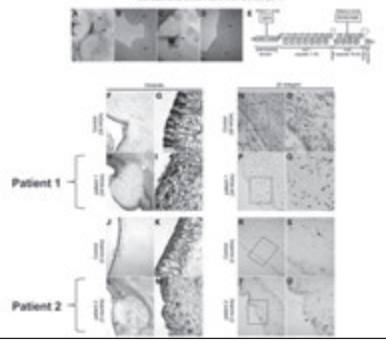
Cortical migrating neurons and various cortical migration defects.



3

Alteration of the radial glia scaffold in human PNH brains (patients 1 and 2) harboring distinct FLNA mutations.

Carabalona et al. Hum Mol Genet 2011



Summary of genetic associations of PNH

Leeflang, 2003; Sheen, 2003; Lu, 2005; Parland, 2006; Hehr, 2006; Moro, 2006; Neal, 2006; Parrini, 2006; Kantarci, 2007; Pang, 2008; Cardoso, 2008.

Region	Gene	Phenotype
Xq28	FLNA	Predominantly female with normal to borderline IQ; coagulopathy, cardiovascular abnormalities, Ehlers-Danlos syndrome and fronto-metaphyseal dysplasias.
20q13.1	ARFGEF2	Microcephaly; profound MR and spastic quadriparesis.
Xq27.3	FMRI	Same as fragile-X syndrome.
3q23.3-31.1	LRP2	Donnai-Barrow syndrome.
1p36 (deletion)	Uncertain	Dysmorphism; developmental delay.
7q11.23 (deletion)	Uncertain	Williams Syndrome features.
5p15 (duplication and trisomy)	Uncertain	Normal to mildly impaired MR; dysmorphism; cardiac defects (atrial septal defects, tricuspid regurgitation).
5q14 (deletion)	Uncertain	Severe MR
t(1;6) (p12;p12.2)	Interruption of mannosidase alpha (MAN1A2)AA and glutathione S-transferase (GSTA2)	Infantile spasms and myoclonis seizures; dysmorphism.
t(2;9) (p24;q32)	Disruption of KIAA1803 and ASXL2	Hearing loss; dysmorphism; hemangiomas.

periventricular nodular heterotopia
overview

- A frequent type of MCD
  - ~ 15-20% of cortical genesis series
- Normal looking neurons in an abnormal position with an abnormal synaptic organization
  - Metabolically active
  - May be involved in normal cognitive processing
  - Ectopic neurons show senescence degeneration
- Interconnected among themselves and with overlying cortex
- Generating normal and epileptic activity
- Overlying or distant cortex may also be reorganized and epileptic

6

Tassi et al. *Brain* 2005

• Nodular heterotopia

No laminar organization.

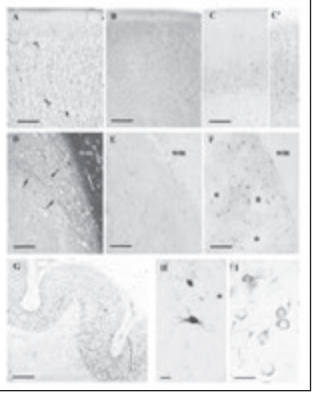
Haphazardly oriented pyramidal-like cells.

GABAergic interneurones.

Small fusiform bipolar cells at the borders of the nodules.

• 9/10 pts showed an overlying dysplastic cortex (abnormal layering).

• no Hc sclerosis but may be associated with abnormal Hc shape and malrotation.



periventricular nodular heterotopia
classification

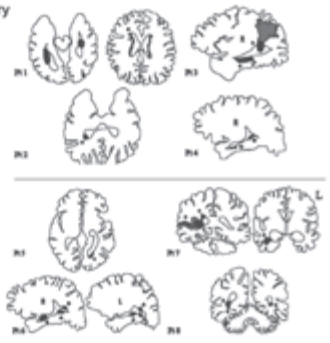
- genetic or acquired basis
- typically nodular
- isolated, scattered and focal or diffuse and contiguous
- uni- or bilateral
- symmetrical or asymmetrical
- Along the wall of the lateral ventricles sparing the 3rd and the 4th, usually protruding into the lumen
- sub-cortical to cortical extension
- part of ± complex brain malformations involving archi- or allocortex

5

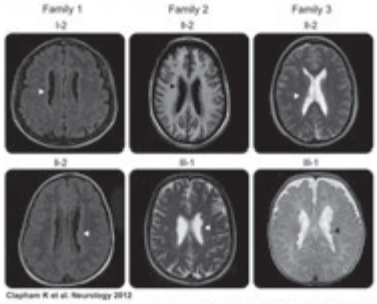
Topographic distribution of PNH in 8 pts with refractory focal epilepsy

from Aghakhani et al., Brain 2005

- bil symmetrical PNH
- bil symmetrical PNH
- bil focal PNH
- Uni PNH without cortical involvement
- Uni PNH with cortical involvement



PNH may be classified according to anatomic distribution



Clapham K et al. Neurology 2012

3 distinct families (all ♀) with bilateral symmetrical diffuse PNH due to *FLNA* deletions

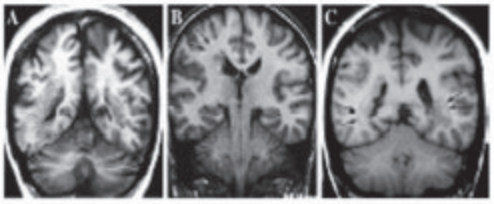
Bilateral symmetrical PNH

- Multiple, contiguous nodules of GM lining the ventricular walls symmetrically.
- Mutations in the *FLN1* gene are responsible in a number of cases, and a definite ♀ preponderance exists.
- mega cisterna magna, cerebellar hypoplasia, thin corpus callosum and asymmetrical hippocampal formations.
- Filamin A plays a role in vascular development and blood coagulation. Up to 20 % patients may have cardiovascular and hematological disorders (aortic insufficiency, patent ductus arteriosus and idiopathic thrombocytopenia).
- The majority of patients are neurologically normal.
- Focal and refractory epilepsy develops in the 2nd decade of life. GTC szs are easily controlled with medication and status epilepticus is not seen.

11

cont'd

bilateral asymmetrical



from Battaglia and Granata, 2008

12

Bilateral asymmetrical PNH

- Bilateral but clearly asymmetrical and coalescent. R-sided preponderance (related to the later completion of neuroblast migration during development?).
- Frequent cortical extension.
- FLN1 mutations are rarely observed though the ♀ predominance remains.
- Mildly abnormal neurological or cognitive function occurs in ~ 40% patients.
- Focal epilepsy is seen in all such patients, often medically refractory.

13

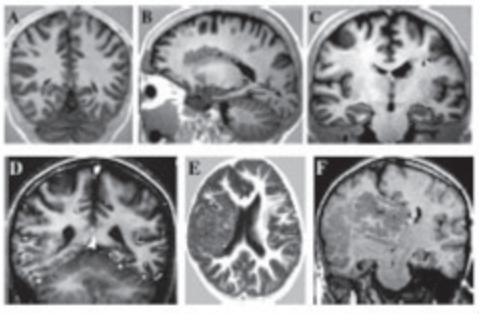
Bilateral focal PNH

- Nodules are isolated, non-confluent and small.
- This group appears to be unrelated to the FLN1 mutation and is more commonly seen in ♂.
- Up to 70 % patients have normal cognition though the remainder can have significant MR, particularly in association with ventricular enlargement.
- Non-specific facial dysmorphisms occasionally seen.
- The epilepsy, which presents itself by the second decade of life and focal, is often easily controlled.

14

cont'd

unilateral with or without cortical extension



15

Unilateral PNH with no cortical involvement

- Nodules are unilateral and often extend into the white matter. The right side appears to be preferentially involved, possibly via the same mechanism as for bilateral asymmetrical.
- No direct extension of the nodules into the cortex, but neocortical malformations of varying degrees are seen in up to 30% cases.
- A minority of patients have mild MR.
- Focal seizures occur frequently and can be medically refractory, but generalized convulsions are rare.

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Unilateral PNH with cortical involvement

- Large heterotopic nodules extend into the neocortical region occasionally with involvement of entire lobes and hemispheres.
- The extent of the cortical involvement determines the severity of the neurological and mental deficits.
- Frequent and refractory focal seizures are the common pattern.

17

PNH may be classified based on anatomical distribution and associated malformations

- Classical bilateral PNH (54%)
- Additional 14 sub-types (46%):
  - Bilateral PNH:
    - with Ehlers-Danlos syndrome
    - T-O PNH and Hc malformation and cerebellar hypoplasia
    - fronto-sylvian PNH and polymicrogyria
    - posterior PNH and polymicrogyria
    - posterior PNH with hydrocephalus
    - with microcephaly
    - with frontonasal dysplasia
    - with limb abnormalities
    - with fragile-X syndrome
    - with ambiguous genitalia
    - micronodular PNH
  - Unilateral diffuse PNH
  - Diffuse bilateral linear PNH
  - PNH with ribbon-like aspect

Parrini et al. *Brain* 2006

18

periventricular nodular heterotopia
clinical features

- Often no apparent impact on brain function except to cause epilepsy.
- Patients with "pure" PNH often have normal intelligence or borderline IQ, they usually don't have neurological deficits, but the majority have seizures or epilepsy.
- The proportion of patients with epileptic manifestations is smaller than in patients with other types of MCDs.

19

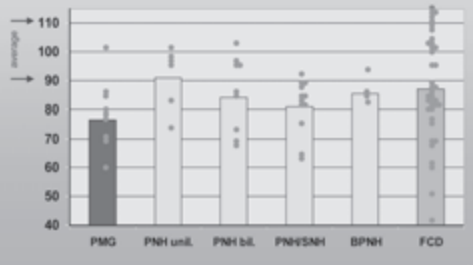
periventricular nodular heterotopia

epilepsy and epileptogenesis

- When present the epilepsy is usually focal, but PNH has been associated with generalized seizures. The age at seizure onset is late compare to other MCD types.
- Usually the epilepsy is focal and refractory, often with a semiology suggesting a TL origin (pseudo-temporal epilepsy) Li et al., *Ann Neurol* 1997.
- The prognosis of the epilepsy disorder depends on type of PNH, and is worsened by the presence of other brain anomalies.

20

FSIQ in patients with PMG, nodular heterotopia or FCDs



from MNI/MNH series

21

Proportion of patients with seizures and age at onset in malformations of cortical development

Type	extent of malformation	szs (%)	age at onset	EEG
hemimegalenc.	fo, multifo	100	< 1	multifo
band heterotopia	diffuse (fo)	92	5	gen, multifo, fo
FC dysplasia	fo	100	< 6	fo
polymicrogyria	fo, multifo, diff.	92	11	fo, multifo, gen
subcortical NH	fo	90	15	fo
focal PNH	**fo, multifo**	**93**	**16**	**multifo, fo**
BPNH	**diffuse**	**80**	**14**	**fo, gen**

from MNI/MNH series

22

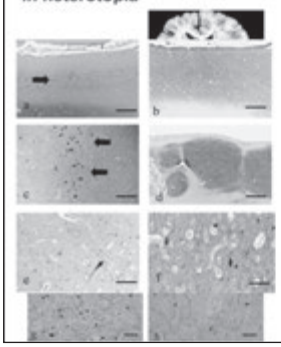
periventricular nodular heterotopia

mechanisms of epileptogenesis.

- nodules show altered GABAergic representation Hannan, 1999; Kakita, 2002; Thom, 2004; Ben-Ari, 2006
- altered expression of Ca^{++}/CaMKII kinase and NR2A/B subunit of NMDA receptor complex in cortex Bellaglia, 2002
- abnormal metabolism of tryptophan Natsume, 2008
- reciprocal connections between nodules and with neocortex Hannan, 1999; Kakita, 2002; Valton, 2007
- often associated with a structural disorganization of the overlying neocortex or of distant areas such as the hippocampal formation Baulac, 1998; Hannan, 1999; Aghakhani, 2005; Bernasconi, 2005; Tassi, 2005; Meroni, 2008

23

Immunohistochemistry demonstrated inhibitory neurons in heterotopia



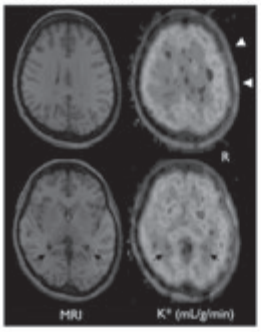
- rudimentary patterns of laminar organization within heterotopia
- small reelin-IR neurons, but not large neurons, identified within heterotopia
- interneurons randomly oriented with densities similar to those in overlying cortex
- major inhibitory interneurones present in heterotopia

→ abnormal representation and connectivity of interneuronal populations in heterotopia may explain or contribute to epileptogenicity of PNH

24

Thom et al. *Epilepsia* 2004

Abnormal metabolism of tryptophan in overlying neocortex but not in heterotopic nodules



Example: Patient 1

BPNH focal and posterior, with R>L post TL EA and increased uptake of α-MTrp R FT

- serotonin-mediated compensatory mechanism to reduce cortical excitability?
- increased activity of the kynurenine pathway that may increase epileptogenicity?

Natsume et al. *Epilepsia* 2008

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periventricular nodular heterotopia

mechanisms of epileptogenesis cont'd

- Human studies using acute or chronic intracranial EEG recordings showed that heterotopia can generate normal electrical activity, spikes and seizures.

  Francione, 1994; Preul, 1997; Kothare, 1998; Aghakhani, 2005; Tassi, 2005; Scherer, 2005; Stefan, 2007; Valton, 2008

- There are reciprocal connections between nodules and with neocortex. PNH are often associated with a structural disorganization of the overlying neocortex or of distant areas such as the hippocampal formation.

  Baulac, 1998; Hannan, 1999; Kakita, 2002; Aghakhani, 2005; Bernasconi, 2005

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periventricular nodular heterotopia

mechanisms of epileptogenesis cont'd.

- EEG/fMRI measures blood flow changes and demonstrated BOLD changes correlated to intracranial findings in patients with MCDs.

  Kobayashi, 2006; Tyvaert, 2008

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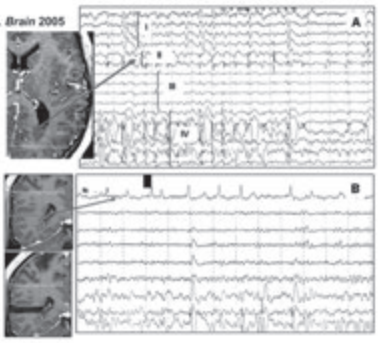
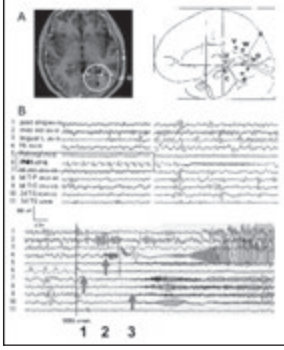
Intrinsic epileptogenicity: frequent high voltage spikes recorded from heterotopia

Tassi et al. *Brain* 2005



28

Intrinsic epileptogenicity of isolated focal PNH



Patient with TL semiology and L post TL spikes

- interictal spikes in heterotopia
- ictal onset in heterotopia with propagation to adjacent Hc and overlying neocortex
- seizure-free after lesionectomy

Scherer et al., *Neurology* 2005

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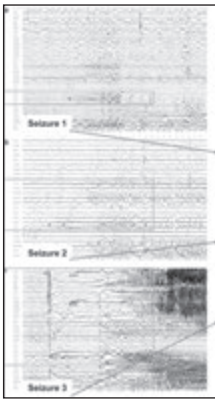
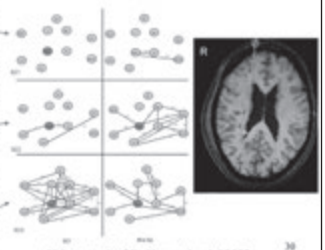


Patient with TL semiology and classical BPNH

Early interactions between heterotopia and cortical structures at seizure onset



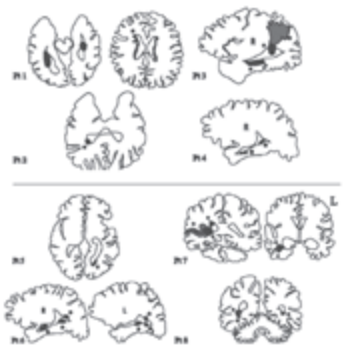
Valton et al., *Clin Neurophysiol* 2008

30

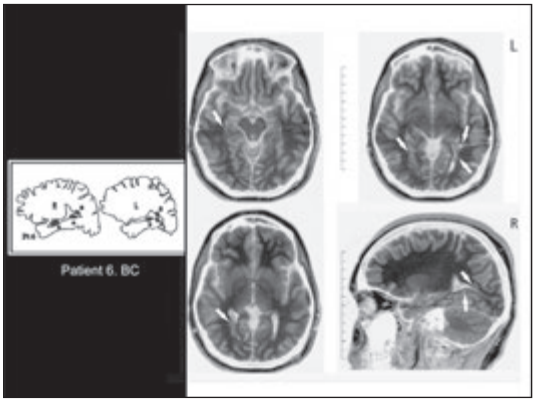
The role of PNH in epileptogenesis.

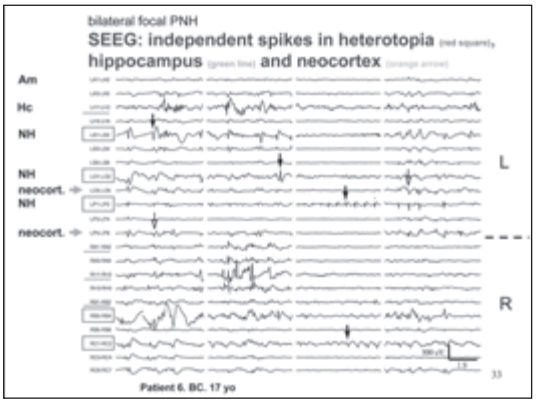
Interictal EA can be generated in heterotopia but seizures are more likely generated by the cortex overlying the malformation.

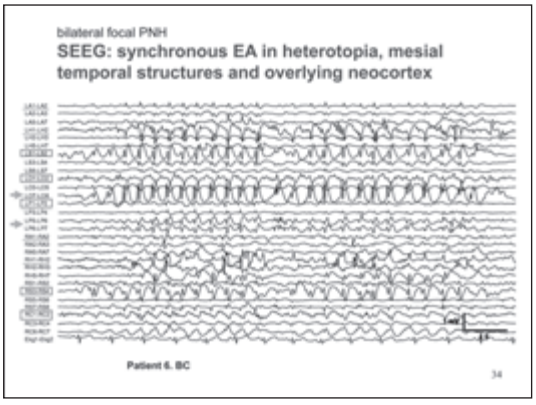
Aghakhani et al., *Brain* 2005

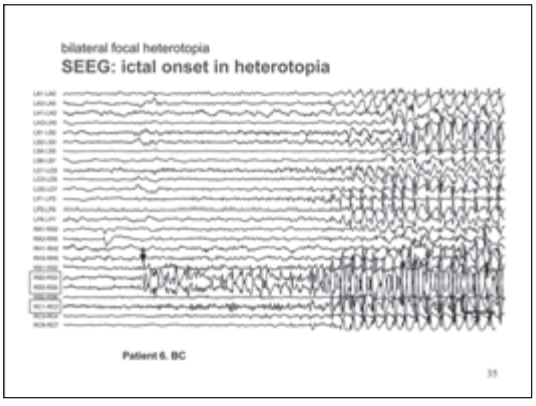


31


L
R
Patient 6. BC

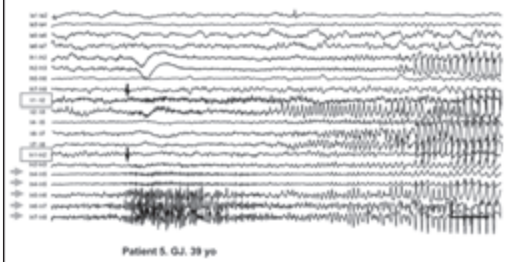

bilateral focal PNH
SEEG: independent spikes in heterotopia (red square), hippocampus (green line) and neocortex (orange arrow)
Am
Hc
NH
NH
neocort.
NH
neocort.
L
R
Patient 6. BC. 17 yo
33


bilateral focal PNH
SEEG: synchronous EA in heterotopia, mesial temporal structures and overlying neocortex
Patient 6. BC
34


bilateral focal heterotopia
SEEG: ictal onset in heterotopia
Patient 6. BC
35

unilateral focal PNH

SEEG: ictal onset in overlying cortex



Patient 5. GJ. 39 yo

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periventricular nodular heterotopia

mechanisms of epileptogenesis cont'd.

- In a rat model of PNH (methylazoxymethanol – MAM – rat), the aberrant structure is not more excitable than the hippocampus and neocortex and does not initiate or lead EA.
- There is structural connectivity between the nodule and surrounding brain tissue.
- The aberrant nodule provides a bridge that facilitates communication between brain regions that in normal brain do not communicate directly.

Tschuluun, 2011

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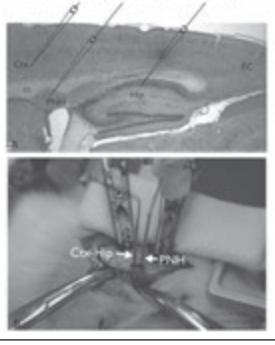
Recording of epileptiform activity in MAM-rat model of PNH

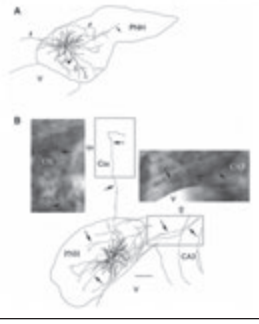


Sagittal slice

In vivo recording

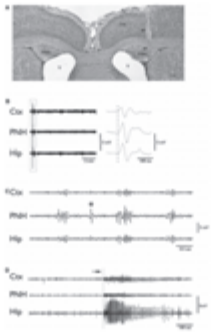
from Tschuluun, et al. 2011

Biocytin-filled neuron in PNH with morphology similar to pyramidal cells of the neocortex, and with axonal projections into the adjacent cortex (Ctx) and hippocampus (CA3).



from Tschuluun, et al. 2011

In vivo electrophysiological recordings in 12 MAM-exposed rats



Spontaneous EA with bicuculline

Coincidence of EA in the 3 regions with rare independent discharges in PNH

Ictal onset simultaneous in the 3 regions

from Tachuloun, et al. 2011

Blood flow changes during ictal and interictal discharges in PNH

- EEG/fMRI technique measures BOLD changes related to an event, reflecting *indirectly* the neuronal activity through blood flow modification.
- It can measure epileptic activity with a good temporal and spatial resolution providing that the electrophysiological signal is detectable on scalp.
- Heterotopic and normal cortices are involved in BOLD changes during interictal and ictal epileptic events in patients with nodular heterotopia.

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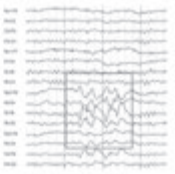
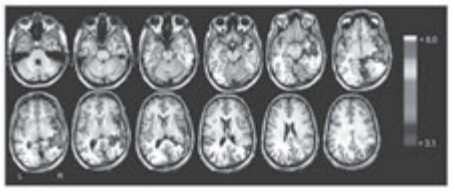
Patient 9

BOLD activation in a pt. with R O periventricular and subcortical NH and R TL runs of SSW





Kobayashi et al., *Brain* 2006

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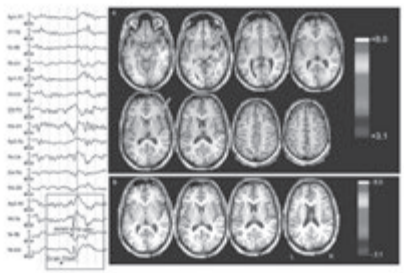
Patient 6

BOLD activation in a pt. with R trigone PNH and R TL spikes



Kobayashi et al., *Brain* 2006

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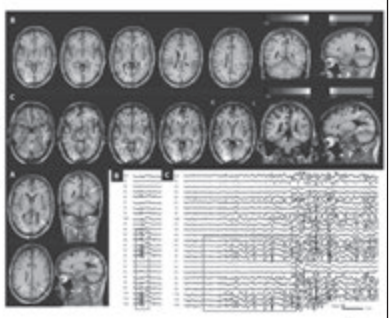
Unilateral focal PNH

Patient 2. LS

BOLD responses during R mid-post T seizure in a pt. with R O and trigone PNH and R post TL spikes

1 event, 22 sec. duration

Tyvaert, Brain 2008

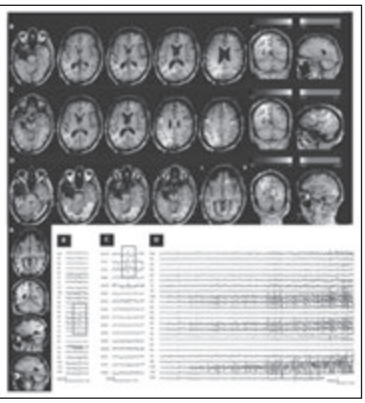


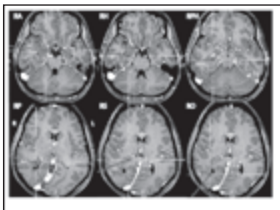
Patient 3

BOLD responses during R FT seizure in a pt. with bil trigone PNH and R and L TL spikes

1 event, 65 sec. duration

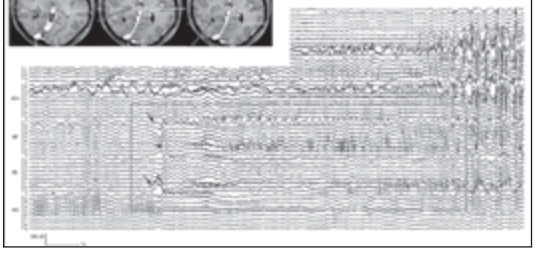
Tyvaert et al., *Brain* 2008





Patient CA, 17 yo

SEEG: R O-T seizures and uni focal PNH with cortical involvement



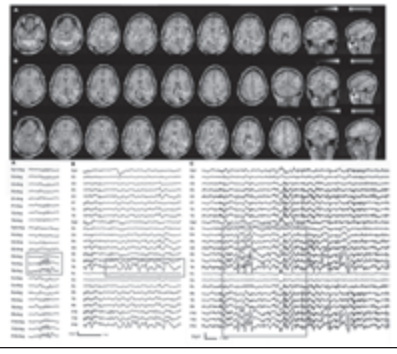
BOLD responses (activation and deactivation)

T4-T6 spiking

T4-T6 ssw

T4-T6 seizure

Patient CA



Summary of max BOLD responses (activations) during interictal and ictal discharges in 4 patients with periventricular nodular heterotopia

		Areas of the max BOLD response			
		Max t-value	Lesion	Overl Cx	Dist
Interictal EA	1	5.6	Y	–	–
	2	6.3	Y	–	–
	3	5.2	–	–	Y
		4.8	–	–	Y
	4	4.3	–	Y	–
		8.2	–	–	Y
Ictal EA	1	22.8	–	Y	–
	2	6.8	–	Y	–
	3	10.6	–	Y	–
	4	10.6	–	Y	–

Tyvaert et al., *Brain* 2008

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periventricular nodular heterotopia
surgery results

from 1995 to 2010, MNH series

- 25 patients with PNH and refractory seizures
- 15 underwent SEEG evaluations — n pts (or, class 1-2)
  - bil symmetrical PNH — 1 (1, 1)
  - bil focal PNH — 3 (2, 0)
  - uni without cortical involvement — 7 (6, 6)
  - uni with cortical involvement — 4 (3, 2)
- 12 operated

Class I-II 9 (75%)
Class III-IV 3 (25%)

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Surgical outcome (1995 to 2003)

Agha Khani et al., *Brain* 2005

pts	Heterotopia	neocortex	Am and Hc	outcome
1, F	-	-	+	II (BPNH)
2, M	-	-	+	I (uni focal)
3, M	+ synchro. with Am/Hc	+	+	I (uni focal +)
4, M	+ synchro. with Am/Hc	-	+	I (uni focal)
5, M	+ synchro. with neocortex	+	+	I (uni focal)
6, F	+ synchro. with Am/Hc, neocort. or independent	+	+	IV (bil focal)
7, F	+ synchro. with neocortex	+	+	- (uni focal +)
8, F	+	+	+	- (bil focal)

Red = resected areas

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Surgical outcome (2003 to 2010)

pts	Heterotopia	neocortex	Am and Hc	outcome
9, M	-	+	+	I (uni focal)
10, M	+ synchro with Am/Hc	+	+	I (uni focal)
11, F	+ synchro with neocortex	+	-	III (uni focal +)
12, M	-	-	+	II (uni focal)
13, M	-	+	+	IV (bil focal)
14, F	+ synchro. with Am/Hc, neocort. or independent	+	+	I (uni focal +)
15, F	+ synchro. with neocortex	+	+	- (uni focal)

Red = resected areas

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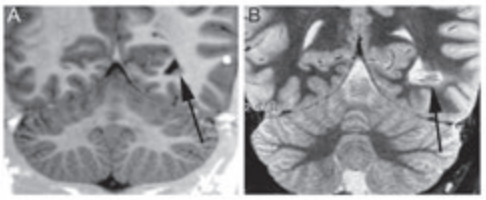
Pre- and post-radiofrequency thermocoagulations in a patient with L TO nodular heterotopia



SEEG-guided RF-thermocoagulation of epileptic foci: A therapeutic alternative for drug-resistant non-operable partial epilepsies.

Catenoix et al., *Neurology* 2008 and

Guénot et al., *Adv Tech Stand Neurosurg* 2011

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conclusions

- MCD are commonly complicated by intractable, often focal, epilepsy. Epileptogenesis in these disorders is not well understood but depends on the type of MCD.
- Cellular mechanisms involved in genesis of interictal and ictal discharges are likely different and influenced independently by the type of MCD.
- PNH is a frequent (15 to 20% of cortical dysgenesis series) and clinically heterogenous type of MCD.

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conclusions cont'd

- Interictal EA can be generated by nodular heterotopia, but seizures are more likely to be generated by the overlying cortex. The connections between nodules and with adjacent or distant structures may play a role in amplification and synchronization of EA and may explain the widespread epileptogenic networks often found in these patients.
- for PNH SEEG and EEG/fMRI are generally in good agreement providing overlapping information on EA.

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Michael Duchowny (USA)

TUBEROUS SCLEROSIS, HEMIMEGALENCEPHALY AND STURGE-WEBER SYNDROME

Tuberous Sclerosis, Hemimegalencephaly and Sturge-Weber Syndrome

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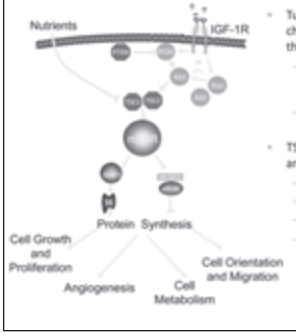
Tuberous Sclerosis: Overview

Organ Involvement in TS

- Characterized by the presence of hamartomas in multiple organs, especially:
  - Numerous cutaneous lesions[1]
  - Lesions of the brain, kidneys, and lungs that contribute significantly to morbidity and mortality[1,2]
- Also characterized by neurologic dysfunction, i.e., epilepsy and cognitive/behavioral dysfunction[1,2]
- Wide clinical spectrum of disease[2]
  - Patients with *TSC2* mutations tend to have more severe disease[3]
- Treatment[1,4]
  - Current treatment is local and symptomatic

[1]Baskin HJ. *Pediatr Radiol.* 2008;38:936-952. [2]Crino PB, et al. *N Engl J Med.* 2006;355(13):1345-1356. [3]Curatolo P, et al. *Lancet.* 2008;372:657-668. [4]Schwartz RA, et al. *J Am Acad Dermatol.* 2007;57:189-202.

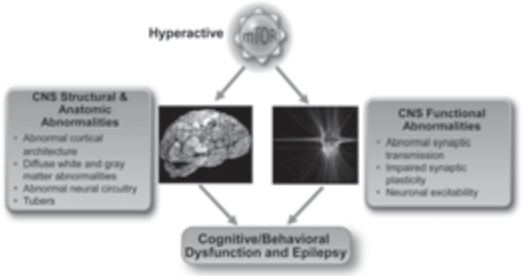
mTOR in Tuberous Sclerosis



- Tuberous sclerosis (TS) is a genetic disorder characterized by multiple benign tumors throughout the body
  - Mutations of *TSC1* or *TSC2*, resulting in constitutive mTOR activation, are found in 80-85% of patients with TS[1]
  - 2/3 due to sporadic genetic mutations, 1/3 inherited in autosomal dominant fashion[2]
- TS has an estimated prevalence of 1:6,000 and affects 1.5 million people worldwide[3]
  - 90% have early-onset epilepsy
  - 60% have developmental delays
  - 50% have mental retardation
  - 25-50% have autism

1) Crino, et al. *N Engl J Med.* 2006;355:1345-1356.
2) Au K-S, et al. *J Child Neurol.* 2004;19:699-709.
3) Baskin. *Pediatr Radiol.* 2008;38:936-952.

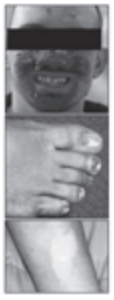
mTOR-induced Structural and Functional Abnormalities May Underlie the Pathogenesis of Neurologic Dysfunction in TS



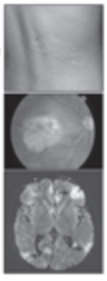
[1]de Vries PJ. Howe CJ. *Trends Mol Med.* 2007;13:319-328. [2]Ehninger D, et al. *Nat Med.* 2008;14:843-848. [3]Crabtree GR, et al. *Trends Genet.* 2008;24:488-510. [4]Moavero R, et al. *Childs Nerv Syst Epub Apr 1 2010.* [5]Napolioni V, et al. *Brain Dev.* 2009;31:104-113. [6]Swiech L, et al. *Biochim Biophys Acta.* 2008;1784:116-132. [7]Tavazoie SF, et al. *Nat Neurosci.* 2005;8:1727-1734. [8]Hong M. *Epilepsia.* 2008;49:8-21. [9]Hong M. *Epilepsia.* 2010;51:27-36. [10]Zang LH, et al. *J Neurosci.* 2009;29:6964-6972.

TS manifestations: Major signs

- Facial angiofibromas or forehead plaque[1]
- Nontraumatic ungual/ periungual fibroma[2]
- Hypomelanotic macules (> 3)[3]



- Shagreen patch (connective tissue nevus)[3]
- Multiple retinal nodular harmartomas[3]
- Cortical tuber[4]

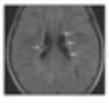


All figures used with permission

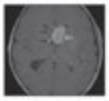
1. Korol et al. *J Periodontol.* 2008;79:759-763.
2. Dacumha. *N Engl J Med.* 2008;359:1381.
3. Curatolo et al. *Lancet.* 2008;657-668.
4. Crino et al. *N Engl J Med.* 2006;355:1345-1356.

TS manifestations: Major signs

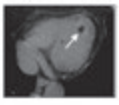
Subependymal nodule



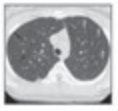
Subependymal giant cell astrocytoma



Cardiac rhabdomyoma: single or multiple

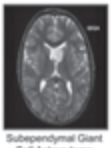


Lymphangio-myomatosis (LAM)



Renal angiomyolipoma

Central Nervous System Abnormalities Are the Primary Cause of Morbidity and Mortality in TS[1]



Subependymal Giant Cell Astrocytoma (SEGA)*

Epilepsy

Anatomic Lesions	Frequency
Subependymal giant cell astrocytomas (SEGAs)[1,2]	10–20%
Subependymal nodules (SENs)[3]	95%
Cortical tubers[1,4]	80–90%

Neurologic Dysfunction	Frequency
Epilepsy[5]	80–90%
Cognitive impairment[1,6,7]	50%
Autism and autism spectrum disorders[6,8]	25–50%
Attention deficit/hyperactivity disorder (ADHD)[9]	30–60%

[1]Baskin HJ. *Pediatr Radiol.* 2008;38:936-952.
[2]Adriaensen ME,APM, et al. *Eur J Neurol.* 2009;16:691-696.
[3]O'Callaghan FJK, et al. *Arch Dis Child.* 2008;93:751-754.
[4]Crino PB, et al. *N Engl J Med.* 2006;355:1345-1356.
[5]Thiele EA. *J Child Neurol.* 2004;19:680-686.
[6]Prather P, de Vries PJ. *J Child Neurol.* 2004;19:666-674.
[7]Ehninger D, et al. *J Intellect Disabil Res.* 2009;53:838-851.
[8]Wamboer NI. *J Child Neurol.* 2004;19:675-679.
[9]Ercan E, et al. *J Child Neurol.* 2009;24:1282-1287.

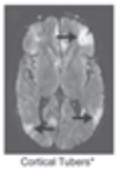
Epilepsy affects most TS patients

Epilepsy

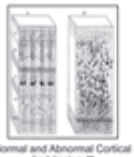
- Affects 80-90% of TS patients[1]
- Most seizures types seen, particularly complex partial seizures[1,2]
- Infantile spasms occur in at least 1/3 of children and confer a poor prognosis[3]
- Seizures tend to increase in frequency and severity[4]
- Associated with cognitive/behavioral dysfunction[5]
- Traditional view of pathogenesis is that tubers and peri-tuberal cortex contain epileptogenic foci[1–4]
- **Often refractory to pharmacologic treatment[1,3]**
  - Newly approved vigabatrin, a GABA transaminase inhibitor, is effective for infantile spasms but may cause visual field loss
- Non-pharmacologic therapies with efficacy include vagus nerve stimulation, ketogenic diet, and surgical resection of tubers[1]

[1]Thiele EA. *J Child Neurol.* 2004;19:680-686.
[2]Holmes GL, et al. *Epilepsia.* 2007;48:617-630.
[3]Jacobs J, et al. *Epilepsia.* 2008;49:816-825.
[4]Wong M. *Epilepsia.* 2008;49:8-21.
[5]Curatolo P, et al. *Lancet.* 2008;372:657-668.

Cortical tubers are in part responsible for epilepsy



Cortical Tubers*



Normal and Abnormal Cortical Architecture**

- Firm "potato-like" hamartomas that arise in developing cortical gyri in the fetus[1,2]
- Contain dysplastic neurons, proliferating glial cells, and giant cells of neural/glial origin[1,2]
- Exhibit abnormal cortical architecture[1–3]
  - Loss of normal 6-layer lamination pattern
  - Aberrant columnar orientation
- Found in 80–90% of patients[1,2]
- Surrounding peri-tuberal cortex may contain epileptogenic foci[4]
- Surgical removal to treat refractory epilepsy[5]

Crino PB, et al. *N Engl J Med.* 2006;355:1345-1356.
**Bentivoglio M, et al. *Epileptic Disord.* 2003;5(Suppl 2):S27-S34.

[1]Baskin HJ. *Pediatr Radiol.* 2008;38:936-952.
[2]Crino PB, et al. *N Engl J Med.* 2006;355(13):1345-1356.
[3]DiMario FJ. *J Child Neurol.* 2004;19:650-657.
[4]Major P, et al. *Epilepsia.* 2009;50(1):147-154.
[5]Weiner HL, et al. *J Child Neurol.* 2004;19:687-689.

Tuberous sclerosis and Infantile Spasms

FULL-LENGTH ORIGINAL RESEARCH

The underlying etiology of infantile spasms (West syndrome): Information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification*

FULL-LENGTH ORIGINAL RESEARCH

The natural history of epilepsy in tuberous sclerosis complex

Seizure types among 117 epilepsy patients with TSC

Seizure Phenotypes

- Hypoxic–ischemic encephalopathy (HIE) 21 (10%),
- Chromosomal 16 (8%),
- Malformations 16 (8%),
- Stroke 16(8%),
- **Tuberous sclerosis complex (TSC) 15 (7%)**
- Periventricular leukomalacia or hemorrhage 11 (5%)

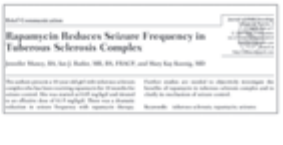
- Cognitive impairment in 75% with IS compared to 40% without IS
- IS more likely to lead to LGS (39% vs 14%)
- IS more common in TSC2 mutation (56%) compared to TSC1 mutation (10%)

Rapamycin therapy in Tuberous sclerosis

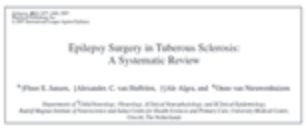
Rapamycin Prevents Epilepsy in a Mouse Model of Tuberous Sclerosis Complex

Novel Proteins Regulated by mTOR in Subependymal Giant Cell Astrocytomas of Patients with Tuberous Sclerosis Complex and New Therapeutic Implications

Rapamycin Reduces Seizure Frequency in Tuberous Sclerosis Complex



Surgical treatment of Tuberous Sclerosis



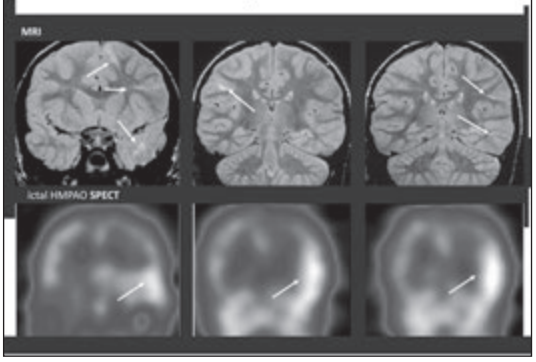
Epilepsy Surgery in Tuberous Sclerosis:
A Systematic Review

Developmental outcome of epilepsy surgery in tuberous sclerosis complex

Metanalysis of 177 patients/25 studies (Jansen et al, 2007)
- Mean age at surgery: 8.6 years
- 12 patients with normal intellect
- 101 patients (57%)-SF; 32 patients (32) >90% improved
-Risk factors for seizure recurrence: tonic seizures , moderate-severe intellectual disability

- Cognitive deterioration may be prevented; improved behavior and socialization
- Good outcome related to seizure relief
- (Zaroff et al, 2005)

Tuberous Sclerosis – multiple cortical tubers



Tuberous sclerosis, intractable epilepsy and eloquent cortex

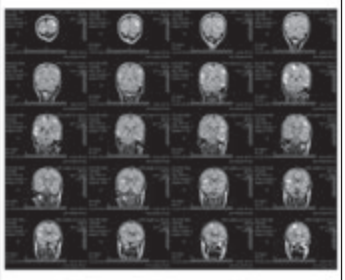
Eric: 10 year old boy with TSC and long-standing pharmaco-resistant partial epilepsy.

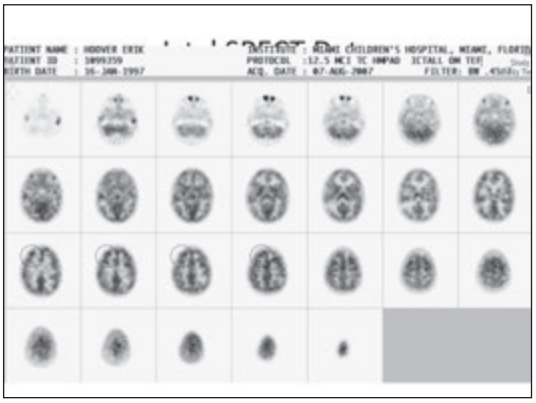
Seizures- usually several per day, stereotyped. Typically begin with "vibratory" sensation in L arm followed by L facial jerking. Often progress to forced L head deviation, L arm stiffening. Last 1-2 minutes.

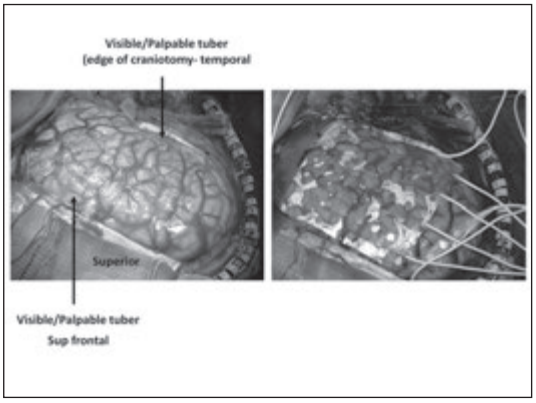
Scalp EEG

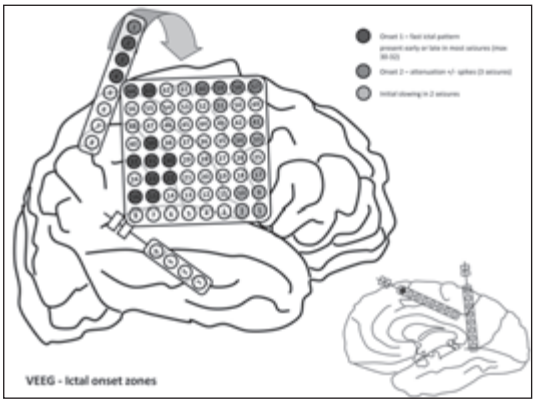
Interictal: R frontal, parietal spikes, sharp waves. Field may include L fronto-central electrodes

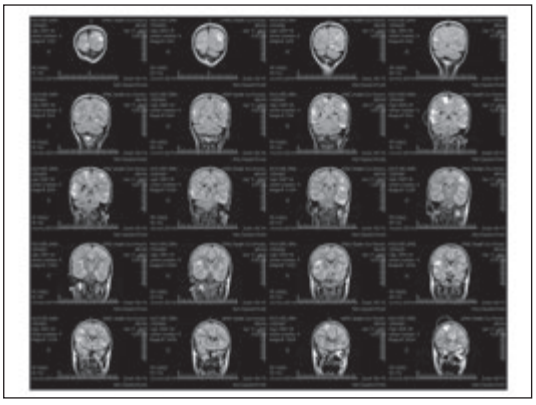
Ictal: R fronto-central seizure onset

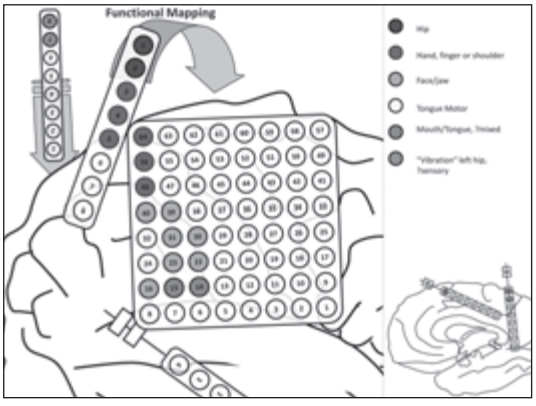


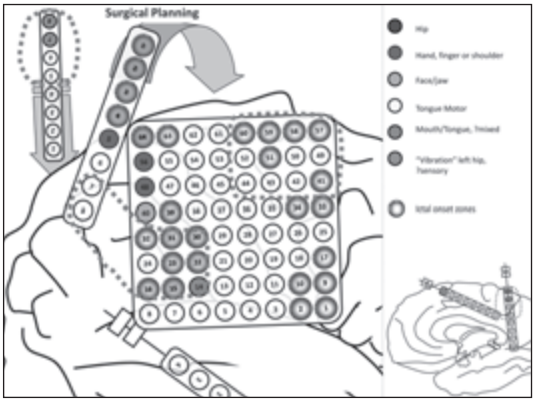



Visible/Palpable tuber
(edge of craniotomy- temporal
Superior
Visible/Palpable tuber
Sup frontal

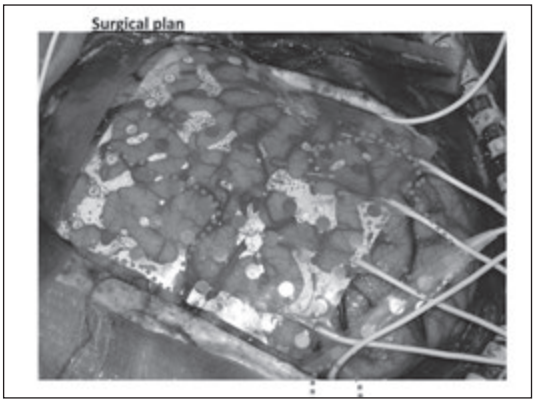

VEEG - Ictal onset zones

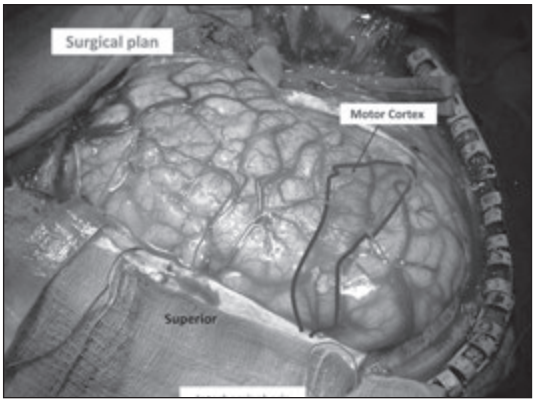


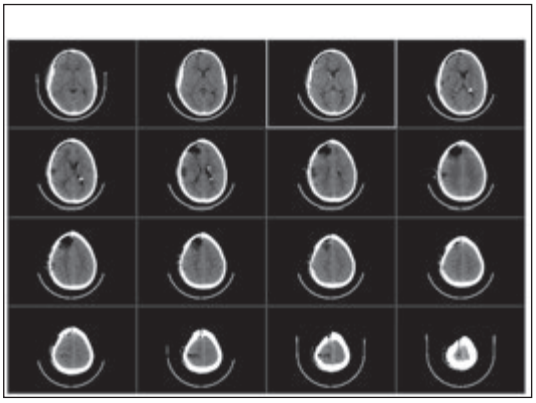

Functional Mapping
Hip
Hand, finger or shoulder
Face/jaw
Tongue Motor
Mouth/Tongue, Trivaid
"Vibration" left hip,
Twinsory


Surgical Planning
Hip
Hand, finger or shoulder
Face/jaw
Tongue Motor
Mouth/Tongue, Tmload
"Vibration" left hip, Tremory
Ictal onset zones


Superior


Surgical plan

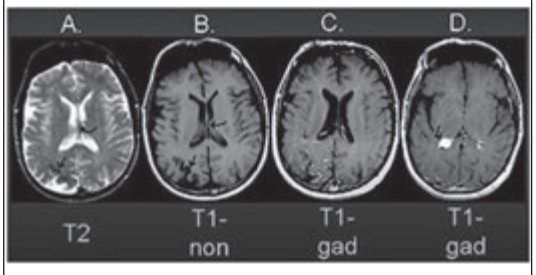

Surgical plan
Motor Cortex
Superior



Sturge-Weber Syndrome

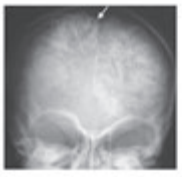
- Sturge-Weber syndrome (encephalofacial/encephalotrigeminal angiomatosis) is characterized by a facial "port wine" nevus and leptomeningeal angiomatosis of the brain. Typically parieto-occipital
- Skin lesion- usually purple to pink in appearance; involves one side of upper face, including the eye.
- Higher risk for developing glaucoma
- Underlying brain lesion- venous anomaly with a reduced number of superficial cortical veins in a cortical region, usually ipsilateral to the skin lesion

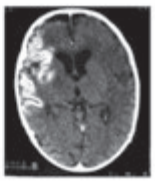
Neuroimaging in Sturge-Weber syndrome



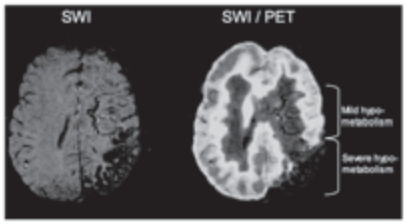
Calcification in Sturge-Weber Syndrome

- Underly angiomatosis
- Present early, progress, then stabilize
- Conventional MRI may lack the sensitivity to detect cortical and pial calcification.
- Longer TEs, gradient echo techniques, or CT are more sensitive in detecting these calcifications.
- Gyriform cortical calcification may also be seen in a variety of other brain disorders including infection, infarction, gliomatosis cerebri, chemotherapy or celiac disease





Sturge-Weber Syndrome: functional imaging



- Early hyperperfusion (PET) followed by hypoperfusion (PET/SPECT)
- Extensive unilateral involvement implicates contralateral abnormalities

Sturge-Weber syndrome: Clinical presentation and natural history

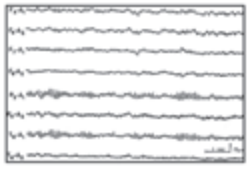
Risk of SWS with facial PWS *	9%
SWS without facial nevus	13%
Bilateral cerebral involvement *	15%
Seizures *	72-93%
Hemiparesis	25-56%
Hemianopia	44%
Headaches	44-62%
Developmental delay and mental retardation *	50-75%
Glaucoma *	30-71%
Choroidal hemangioma *	40%

- 37 cases (16M/21F) followed for 6-25 years
- Normal or borderline IQ- 53% (2 in college)
- Severe motor or mental handicap- 22%
- No weakness- 30%
- Transient hemiparesis - 25%

- Erba & Cavazzutti, 1990

Epilepsy in Sturge-Weber syndrome

- 75% of cases present in the first year; 86% by age 2 years
- Occur with unilateral (72-80%) and bilateral (93%) involvement
- Arise focally & secondarily generalize
- Early and/or refractory seizures increase risk of cognitive impairment



- Voltage attenuation- localized to region of cerebral angiomatosis
- Polymorphic slowing- may be ipsilateral or bilateral
- Interictal spiking-rare, poorly correlated with angiomatosis
- Ictal discharges- periphery of lesion

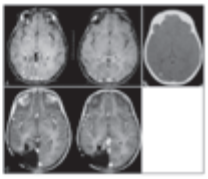
-Sassower et al, 1994

High seizure intensity in young patients with Sturge-Weber syndrome is a prognostic marker for mental deterioration

Outcome of infants with unilateral Sturge-Weber syndrome and early onset seizures

- 15 patients with unilateral Sturge-Weber syndrome and early onset seizures, five of whom underwent epilepsy surgery
- mean follow-up period of all the patients was 15 years
- six patients had normal intelligence, four had borderline cognitive level, three had mild mental retardation and two had moderate mental retardation
- Cognitive delay was significantly correlated with seizure intensity in the early period, but not with the age of seizures onset, the degree of hemiparesis, or the presence of ongoing seizures

Surgical treatment of epilepsy in Sturge–Weber syndrome in children



- Retrospective review of 27 children who underwent surgery
- Seventeen children (63%) experienced seizure onset before 1 year of age
- Younger patients - significantly more likely to have hemiparesis and status epilepticus and be developmentally delayed

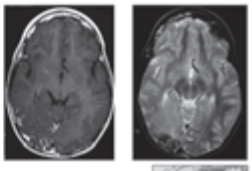
Developmental and seizure-related outcome depending on type of epilepsy surgery in 27 children with SWS

	Epilepsy (%)		Developmental Status (%)		
Type of Op	No Seizures	Seizures	Improvement	No Improvement	Total
hemispherectomy	8 (100)	0 (0)	6 (75)	2 (25)	8
complete resection	8 (89)	1 (11)	6 (67)	3 (33)	9
incomplete resection	3 (30)	7 (70)	4 (40)	6 (60)	10
total	19 (70)	8 (30)	16 (59)	11 (41)	27

* Hemispherectomy should not be performed early solely because of the diagnosis of SWS

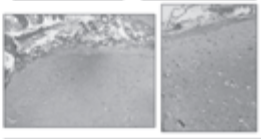
Sturge-Weber syndrome and FCD Type 1*

Medically intractable epilepsy in Sturge-Weber syndrome is associated with cortical malformation: Implications for surgical therapy



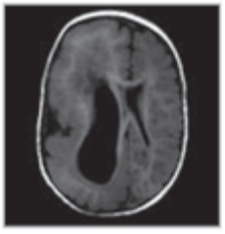
- Review of imaging features and histopathology in 12 consecutive children with SWS and pharmaco-resistant seizures. Mean age of seizure onset = 11.1 mos. Developmental delay in 11; hemiparesis in 8
- FCD, PMG noted in cortex underlying vascular malformation; retrospective review of imaging studies reveals radiologic evidence of cortical malformation
- Strong association with FCD Type 1

* Maton et al, Epilepsia, 2010



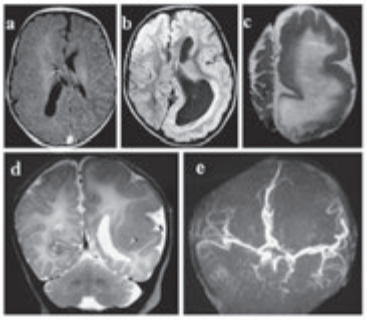
H&E stained sections (40X/100X) showing leptomeningeal angiomatosis, dysplamination and ectopic neurons

Hemimegalencephaly



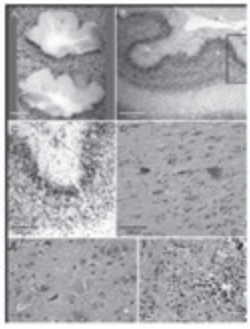
- Rare congenital brain malformation characterized by excessive growth of one cerebral hemisphere- frequently associated with hemiparesis, hemianopia, psychomotor retardation, and refractory epilepsy.
- Often presents in early infancy: either cerebral hemisphere affected; occurs in every ethnic group and both genders, (Flores-Sarnat, 2002).
- Between 1-3 cases per 1000 children with epilepsy and up to 14% of those with abnormalities of cortical development have hemimegalencephaly (DiRocco, et al 2006).

Neuroimaging in Hemimegalencephaly



Neuropathological correlates of Hemimegalencephaly

- Affected hemisphere is enlarged and malformed (agyria, polymicrogyria, pachygyria, lissencephaly), with involvement of the entire hemisphere or individual lobes interspersed with apparently normal brain (DiRocco, et al, 2006).
- The cortex lacks normal lamination with heterotopic giant neurons abnormally organized within the cortical layers, as well as ectopically present within the white matter (DiRocco, et al, 2006; Flores-Sarnat, 2003).
- Pathologically, there are no distinct characteristics which can differentiate the various subtypes and associated syndromes of hemimegalencephaly, thus suggesting hemimegalencephaly may be a common result of several genetic disorders (Flores-Sarnat, 2003).



Disorders associated with Hemimegalencephaly

Hypomelanosis of Ito

Epidermal nevus syndrome

Incontinentia pigmenti

Tuberous sclerosis

Ipsilateral hemifacial hypertrophy

Linear nevus sebaceous of Jadassohn

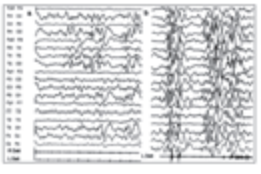
Proteus syndrome

Klippel-Trenaunay-Weber syndrome

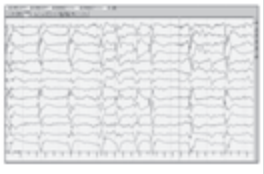
Epilepsy in Hemimegalencephaly

- Epilepsy in up to 93% of patients with hemimegalencephaly; seizures often begin within the first days of life- onset rare after 6 months of age (Vigevano, et al, 1996).
- Partial seizures, seldom with secondary generalization- most frequent initial seizure type, often presenting as contralateral hemi-body motor seizures, eye deviation, or oral automatisms. Tonic seizures, infantile spasms, and myoclonic seizures may also be encountered.
- Seizures- frequent, often daily, notoriously refractory to AEDs.
- Etiology of several epilepsy syndromes:
  - Ohtahara syndrome,
  - West syndrome (infantile spasms present in up to 50% of patients (Dulac, et al, 1994).
  - Lennox-Gastaut syndrome (DiRocco, et al, 2006; Flores-Sarnat, 2002).
- Older children with the isolated subtype may exhibit a more benign presentation with partial seizures that are more easily controlled by AEDs.

EEG in Hemimegalencephaly

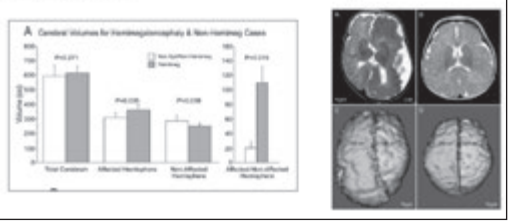


Typical waking and sleep EEG in HME.
Waking- asymmetric background attenuation and paroxysmal activity.
Sleep- Diffuse spike-wave activation



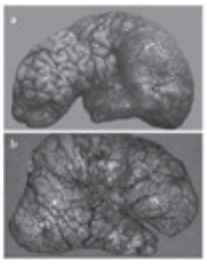
EEG pattern of triphasic complexes often present early in patients with epilepsy and hemimegalencephaly.

Contralateral hemimicrencephaly and clinical–pathological correlations in children with hemimegalencephaly



Hemimegalencephaly: clinical implications and surgical treatment

- Series of 20 patients followed for mean of 10.5 years
- 75% achieved Engel Class 1 outcome
- 3 patients with suboptimal outcome-all had EEG activity in contralateral hemisphere
- High incidence of complication



Hemispheric Procedures:
- Anatomic hemispherectomy
- Functional hemispherectomy
- Hemispherotomy
- Hemispheric decortication

Surgical Challenges:
- Large hemisphere
- Distorted surgical landmarks
- Malformed vasculature

Conclusions

- TSC, SWS and HME are neurocutaneous (or neurocutaneous- associated) disorders that present with severe and often medically refractory seizures
- Seizure onset typically occurs in very early life
- TSC and HME are highly linked to epileptic encephalopathy
- Aggressive treatment indicated; early surgery is a consideration in TSC and HME patients

Ruben Kuzniecky (USA)

BILATERAL PERISYLVIAN POLYMICROGYRIA AND SCHIZENCEPHALY

Fernando Cendes (Brasil)

HHE AND VASCULAR INSULTS IN EARLY LIFE

Laura Tassi (Italy)

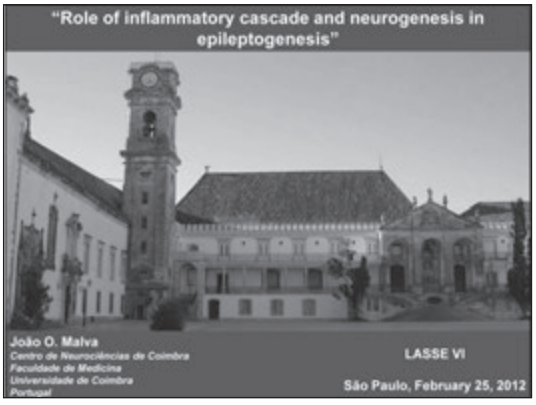
STEREO-ELECTROENCEPHALOGRAPHY (SEEG) IN EXTRATEMPORAL EPILEPSIES

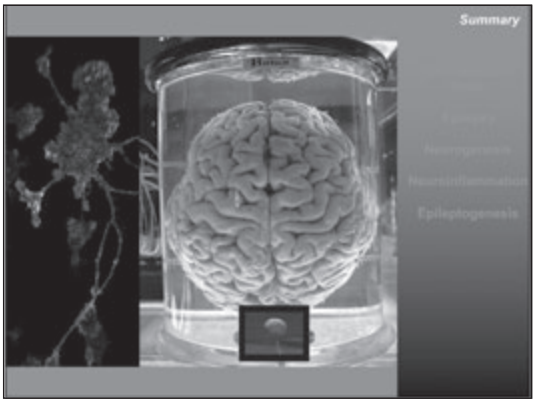
Philippe Ryvlin (France)

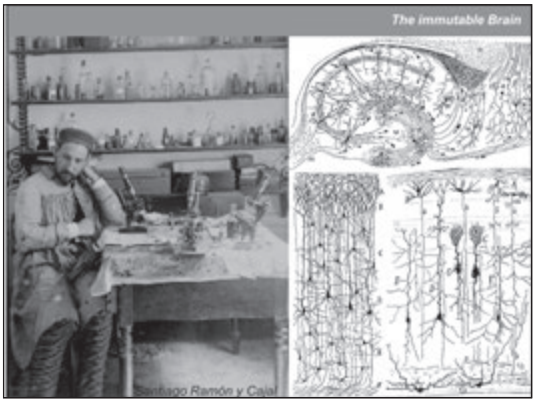
AUTO-IMMUNE ENCEPHALITIS

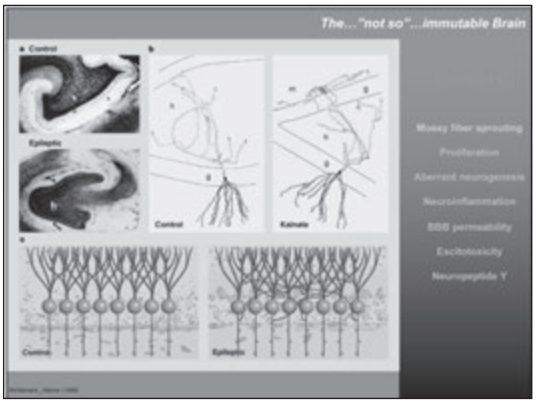
João Malva (Portugal)

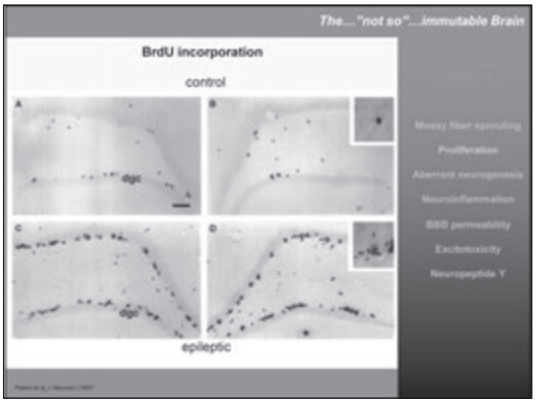
ROLE OF INFLAMMATORY CASCADE IN EPILEPTOGENESIS

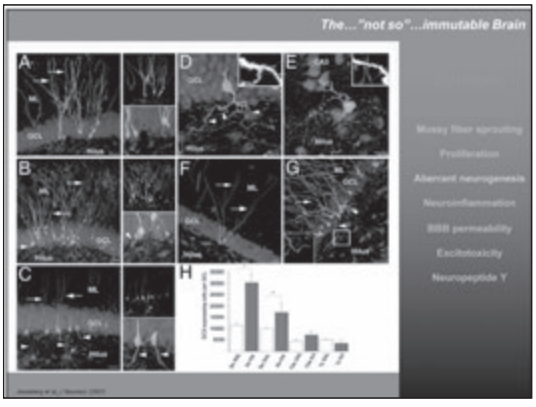


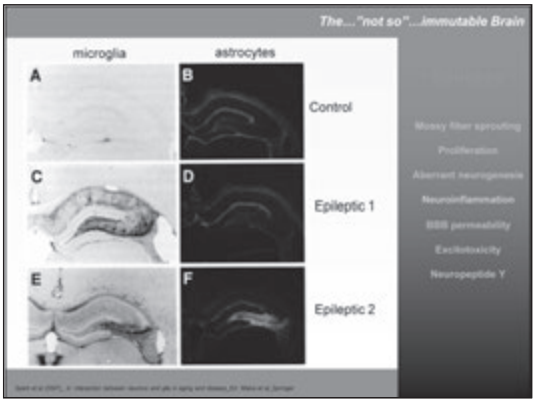


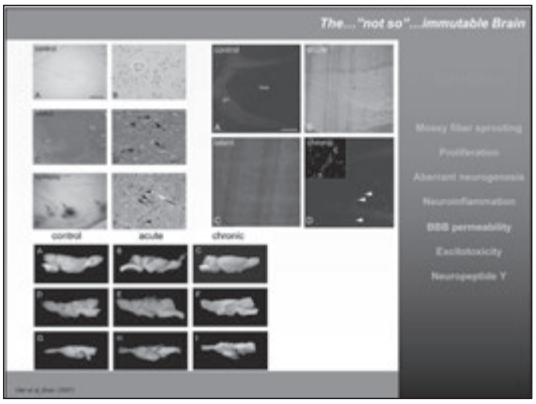


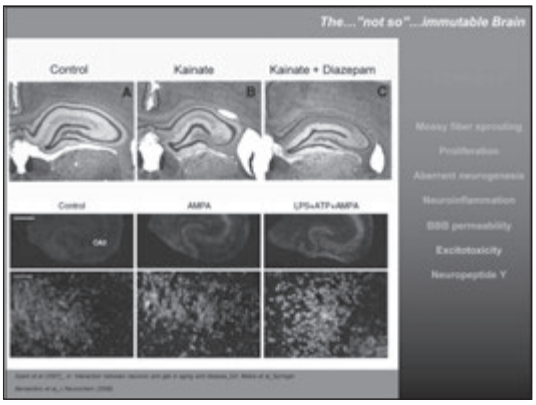

The…"not so"…immutable Brain
Control
Epileptic
Control
Kainate
Control
Epileptic
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y

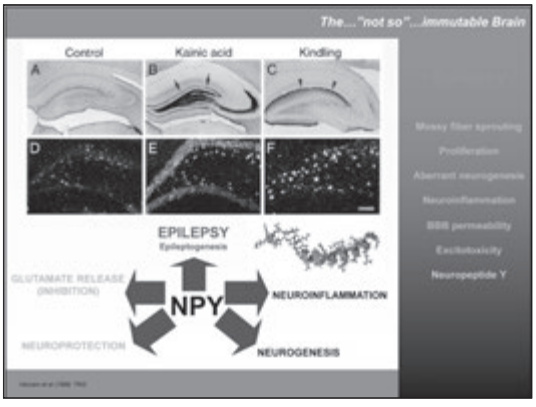

The…"not so"…immutable Brain
BrdU incorporation
control
dgc
epileptic
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y

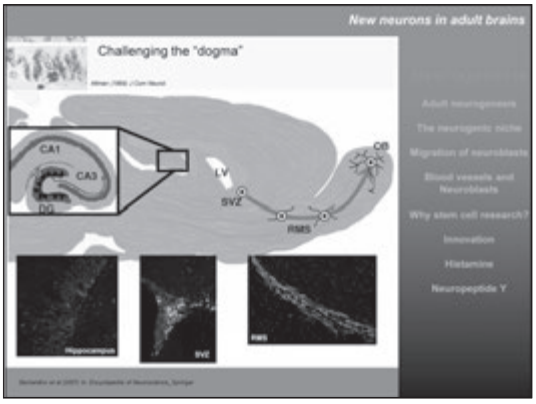

The…"not so"…immutable Brain
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y


The…"not so"…immutable Brain
microglia
astrocytes
Control
Epileptic 1
Epileptic 2
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y


The…"not so"…immutable Brain
control
acute
chronic
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y


The…"not so"…immutable Brain
Control
Kainate
Kainate + Diazepam
A
B
C
Control
AMPA
LPS+ATP+AMPA
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y


The…"not so"…immutable Brain
Control
Kainic acid
Kindling
EPILEPSY
Epileptogenesis
GLUTAMATE RELEASE
(INHIBITION)
NPY
NEUROINFLAMMATION
NEUROPROTECTION
NEUROGENESIS
Mossy fiber sprouting
Proliferation
Aberrant neurogenesis
Neuroinflammation
BBB permeability
Excitotoxicity
Neuropeptide Y


New neurons in adult brains
Challenging the "dogma"
CA1
CA3
DG
LV
SVZ
RMS
OB
Hippocampus
SVZ
RMS
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innervation
Histamine
Neuropeptide Y

New neurons in adult brains

The neurogenic niche – **A combination of signaling molecules and cellular interactions allowing the maintenance of an undifferentiated state of neural stem cells that proliferate and generate progenitors and new neurons.**

*Intrinsic factors

(ex1: transcription factors; Hes, SOX-2, Tlx, Ngn, Mash1, Dlx2, Pax6, Olig2, NeuroD, Prox1…
ex2: histone and chromatin modulators…histone acetyltransferases and deacetylases;
Methylation of DNA and histones…)

*Extrinsic factors

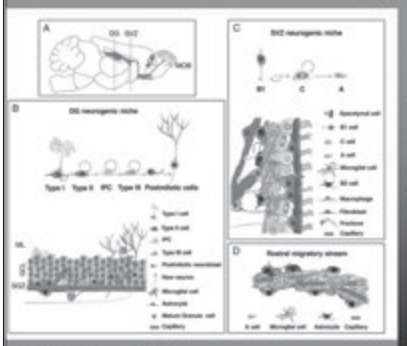
(Notch, Shh, Wnt, BMP, Slit-Robo, growth factors, neurotransmitters, endothelia, astroglia, ependymal cells, extracellular matrix)

*Environment factors

(voluntary exercise, rich environment, stress, depression…)

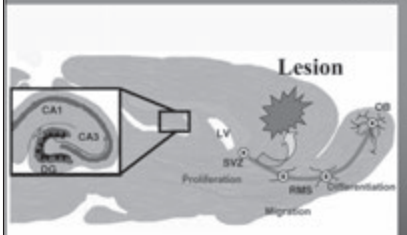
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

New neurons in adult brains



Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

New neurons in adult brains

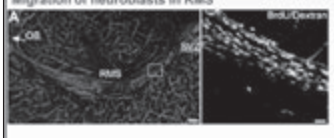


*Lesion promotes re-routing of neuroblast to damaged areas.
*However, Brain repair is not efficient

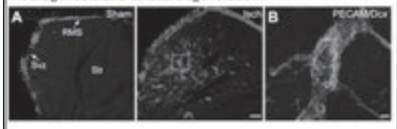
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

New neurons in adult brains

Migration of neuroblasts in RMS



Neurogenesis and striatal degeneration



Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

Neural stem cells

REGENERATIVE MEDICINE

*Endogenous resources
*Transplantation…
*Treating diseases?
-the case of epilepsy-

RESEARCH

*Self-renewal
*Proliferation
*Migration
*Integration
*Functional maturation
*Pathogenesis
-epileptogenesis-

European Brain Council
…the real impact of Brain research…

(European Brain Council - 28 european countries)

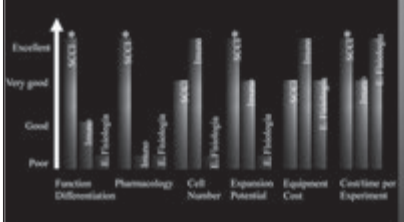
*Drug addiction	9 millions
*Mood disorders	21 millions
*Anxiety	41 millions
*Brain tumors	0.135 millions
*Dementia	5 millions
*Epilepsy	3 millions
*Migraine	41 millions
*Multiple sclerosis	0.38 millions
*Parkinson's disease	1.2 millions
*Squizophrenia	3.7 millions
*Stroke	1 million
*Trauma	0.7 millions

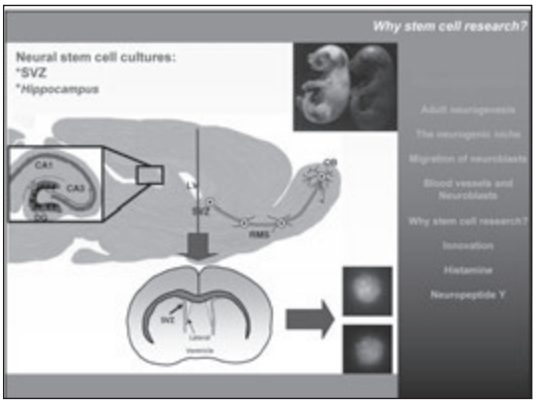
REGENERATIVE MEDICINE STEM CELL RESEARCH

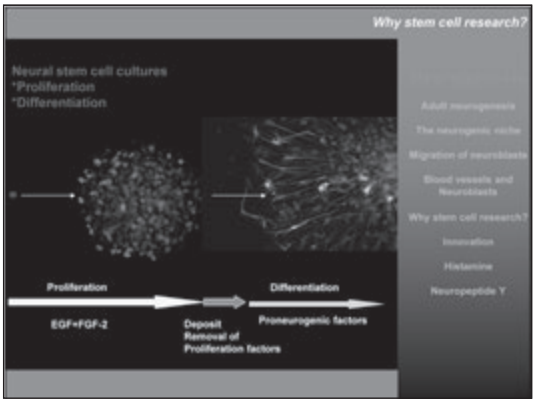
Lack of good methods for functional studies

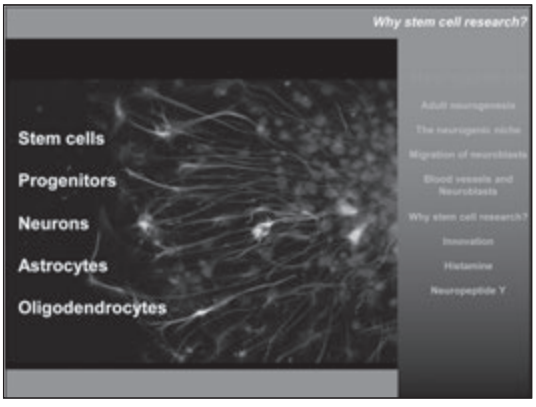
*Viability
*Pharmacology
*Differentiation

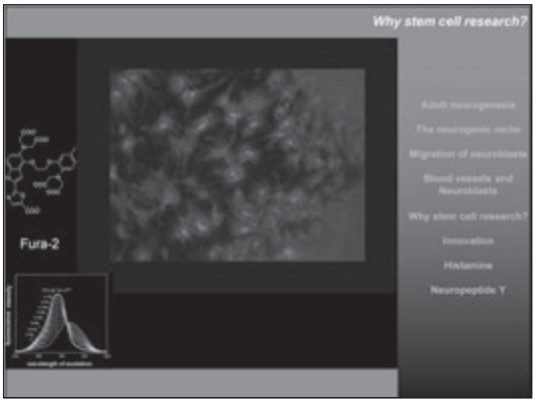
Single cell calcium imaging (SCCI)

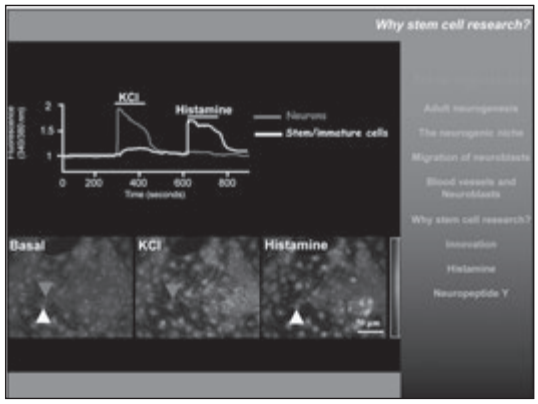


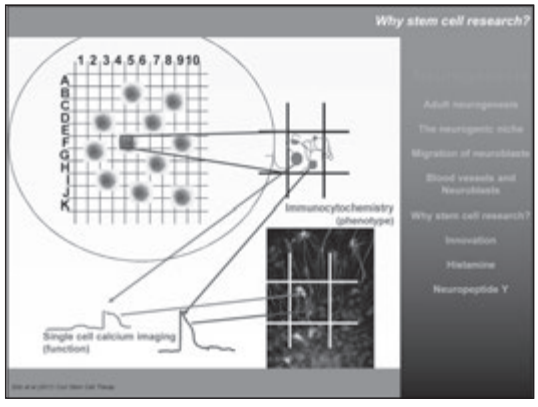

Why stem cell research?
Neural stem cell cultures:
*SVZ
*Hippocampus
CA1
CA3
DG
SVZ
RMS
OB
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

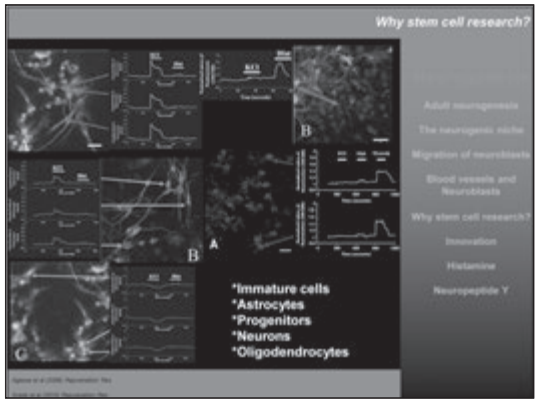

Why stem cell research?
Neural stem cell cultures
*Proliferation
*Differentiation
Proliferation
EGF+FGF-2
Deposit
Removal of
Proliferation factors
Differentiation
Proneurogenic factors
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

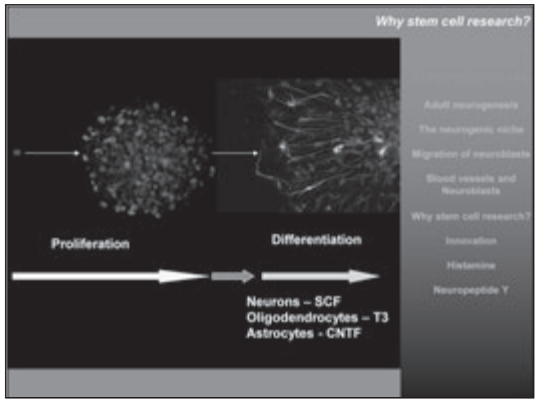

Why stem cell research?
Stem cells
Progenitors
Neurons
Astrocytes
Oligodendrocytes
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

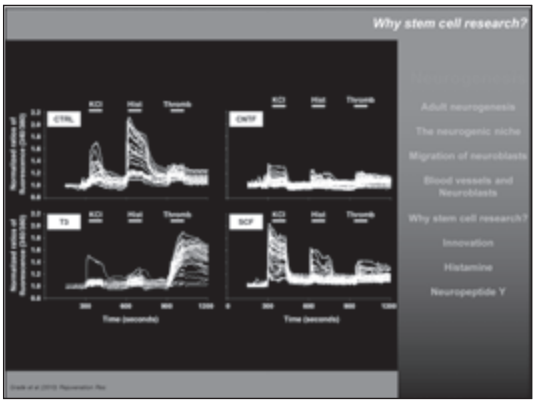

Why stem cell research?
Fura-2
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

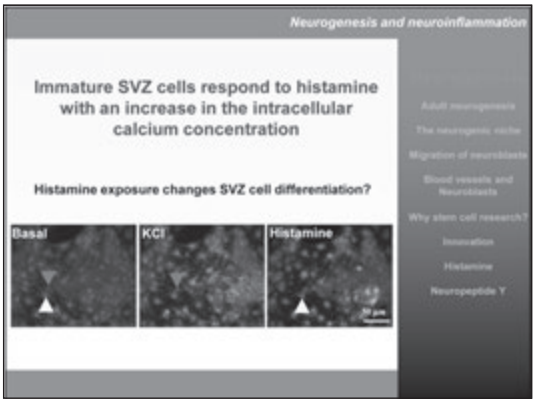

Why stem cell research?
KCl
Histamine
Neurons
Stem/immature cells
Time (seconds)
Basal
KCl
Histamine
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

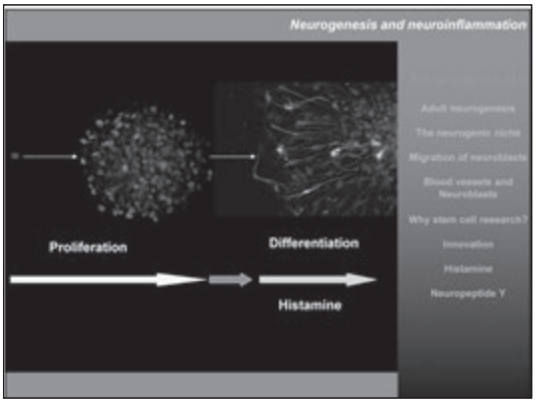

Why stem cell research?
1,2,3,4,5,6,7,8,910
A
B
C
D
E
F
G
H
I
J
K
Immunocytochemistry (phenotype)
Single cell calcium imaging (function)
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

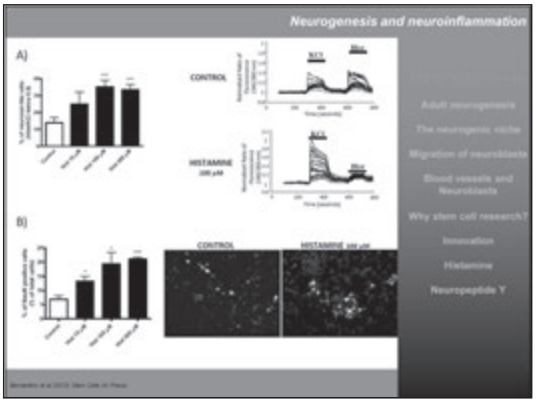

Why stem cell research?
A
B
B
*Immature cells
*Astrocytes
*Progenitors
*Neurons
*Oligodendrocytes
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

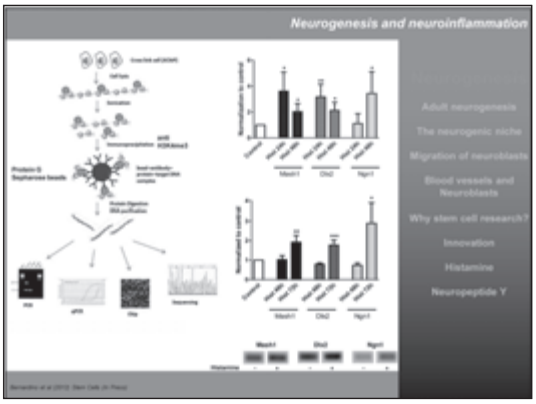

Why stem cell research?
Proliferation
Differentiation
Neurons – SCF
Oligodendrocytes – T3
Astrocytes - CNTF
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

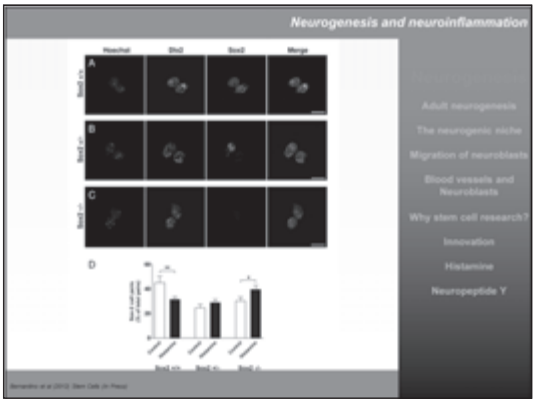

Why stem cell research?
KCl
Hist
Thrombi
CNTF
T3
SCF
Time (seconds)
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

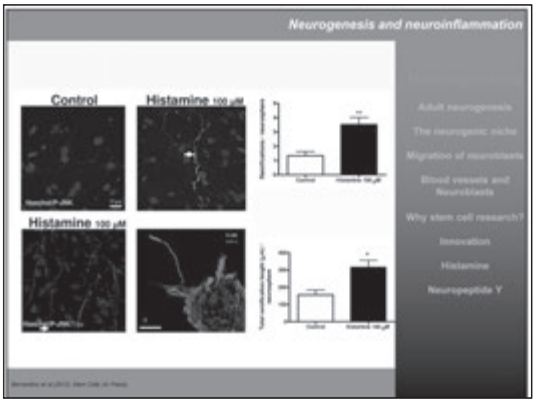

Neurogenesis and neuroinflammation
Immature SVZ cells respond to histamine with an increase in the intracellular calcium concentration
Histamine exposure changes SVZ cell differentiation?
Basal
KCl
Histamine
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

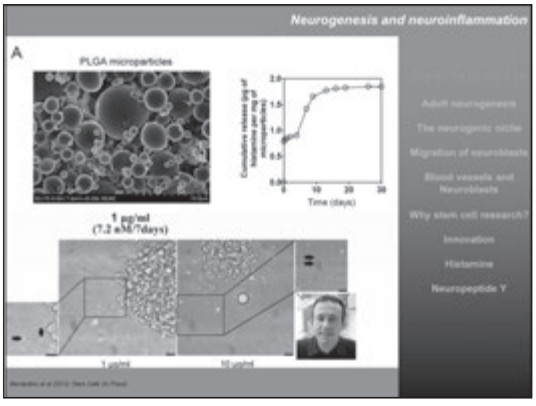

Neurogenesis and neuroinflammation
Proliferation
Differentiation
Histamine
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

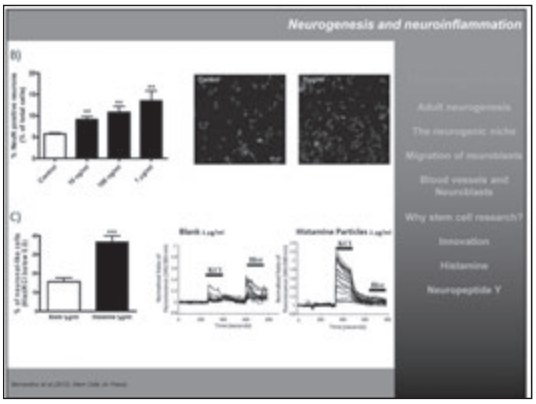

Neurogenesis and neuroinflammation
A)
CONTROL
HISTAMINE
B)
CONTROL
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

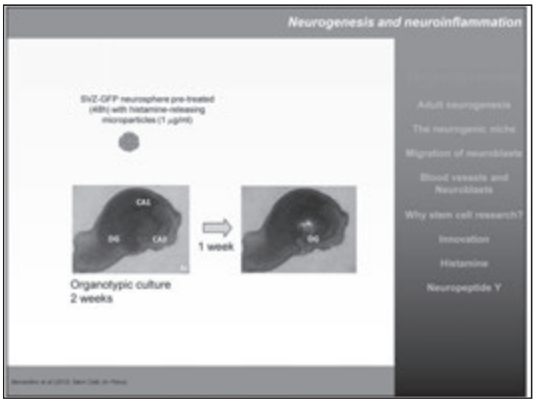

Neurogenesis and neuroinflammation
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

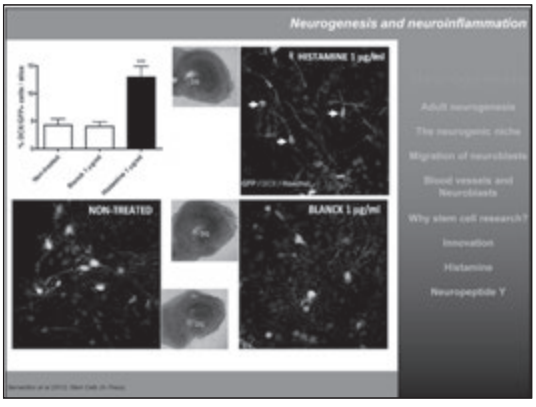

Neurogenesis and neuroinflammation
Hoechst
Dlx2
Sox2
Merge
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

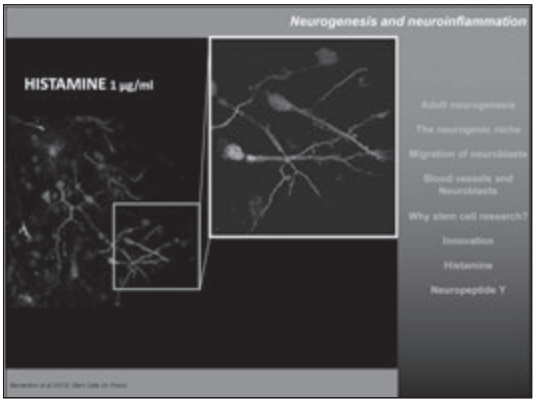

Neurogenesis and neuroinflammation
Control
Histamine 100 µM
Histamine 100 µM
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

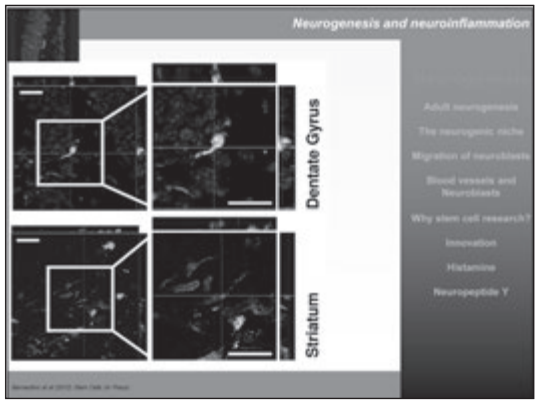

Neurogenesis and neuroinflammation
A
PLGA microparticles
1 µg/ml
(7.2 nM/7days)
Time (days)
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

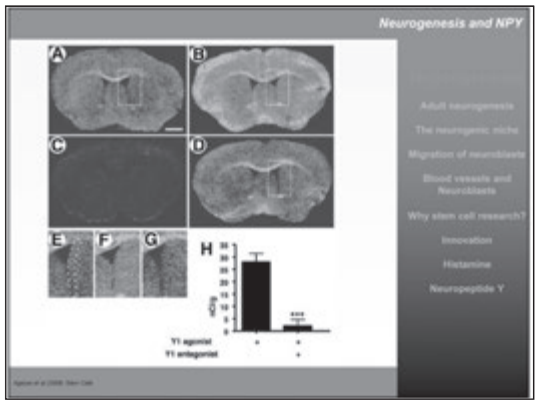

Neurogenesis and neuroinflammation
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

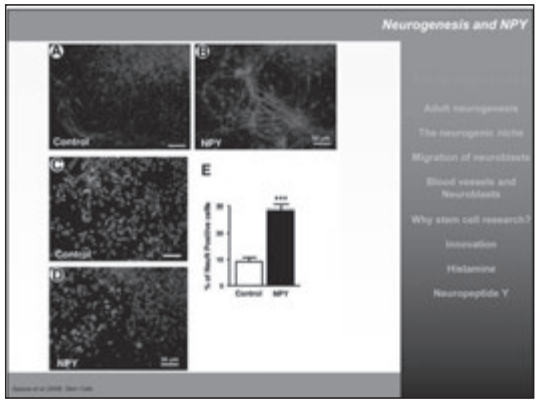

Neurogenesis and neuroinflammation
SVZ-GFP neurosphere pre-treated (48h) with histamine-releasing microparticles (1 µg/ml)
CA1
DG
CA3
1 week
DG
Organotypic culture
2 weeks
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

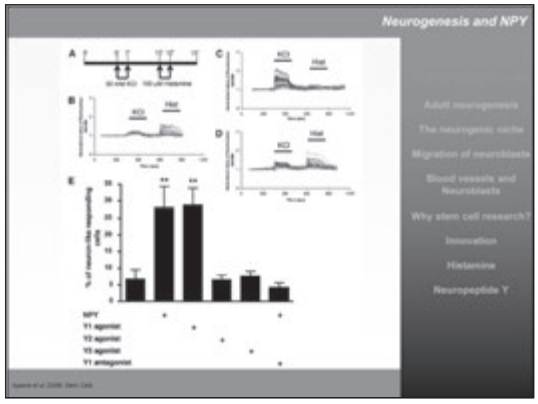

Neurogenesis and neuroinflammation
HISTAMINE 1 µg/ml
NON-TREATED
BLANCK 1 µg/ml
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

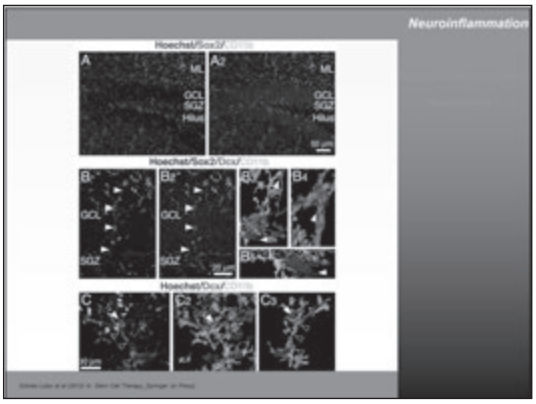

Neurogenesis and neuroinflammation
HISTAMINE 1 µg/ml
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

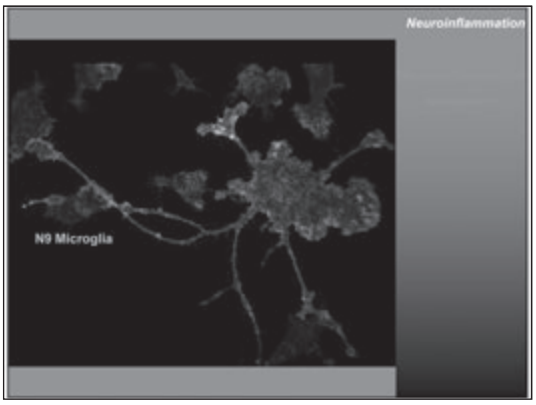

Neurogenesis and neuroinflammation
Dentate Gyrus
Striatum
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

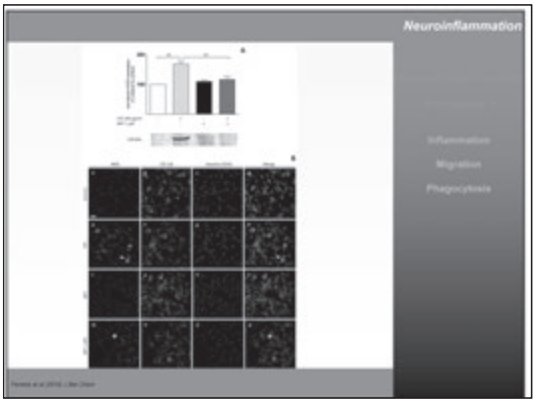

Neurogenesis and NPY
A
B
C
D
E
F
G
H
Y1 agonist
Y1 antagonist
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

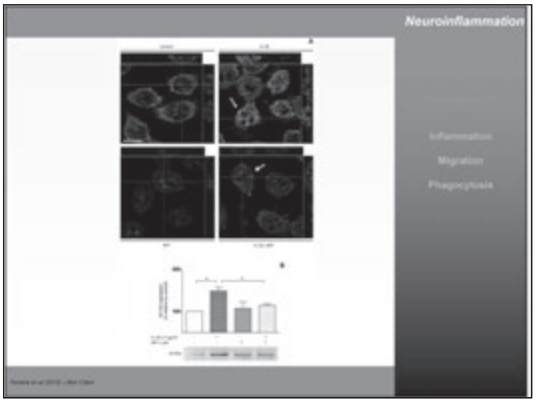

Neurogenesis and NPY
Control
NPY
E
Control
NPY
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

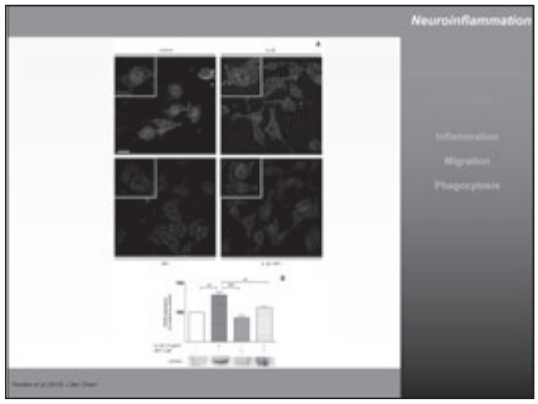

Neurogenesis and NPY
A
B
C
D
E
KCl
Hist
NPY
Y1 agonist
Y2 agonist
Y5 agonist
Y1 antagonist
Adult neurogenesis
The neurogenic niche
Migration of neuroblasts
Blood vessels and Neuroblasts
Why stem cell research?
Innovation
Histamine
Neuropeptide Y

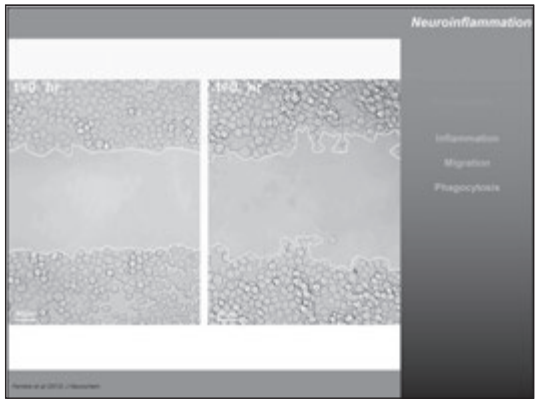

Neuroinflammation
Hoechst/Sox2/
A
A2
ML
GCL
SGZ
Hilus
Hoechst/Sox2/Dcx/
B1'
B2'
B3
B4
B1
C
C2
C3
Hoechst/Dcx/

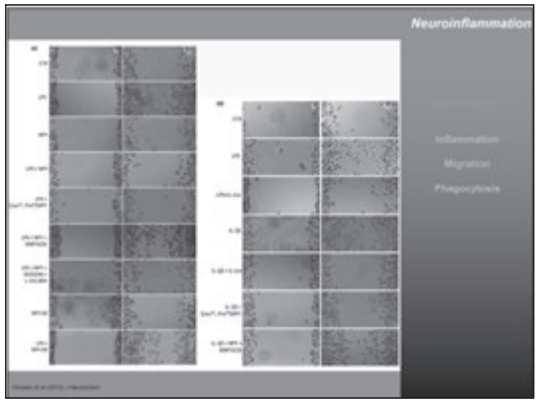

Neuroinflammation
N9 Microglia

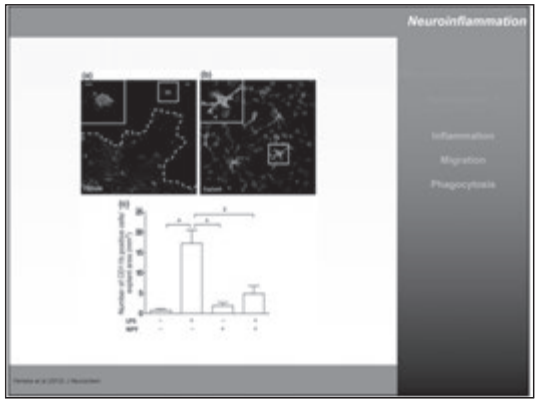

Neuroinflammation
Inflammation
Migration
Phagocytosis

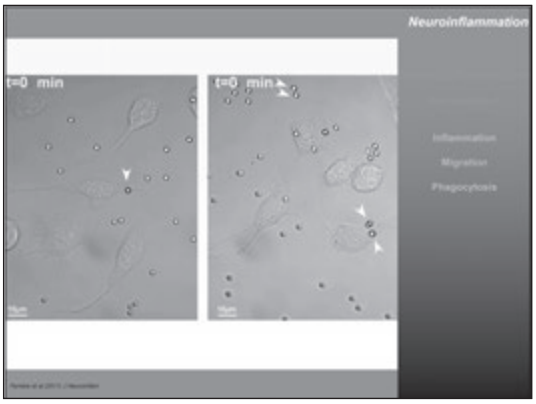

Neuroinflammation
Inflammation
Migration
Phagocytosis

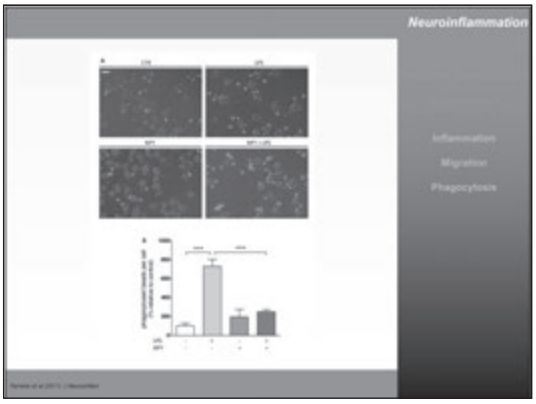

Neuroinflammation
Inflammation
Migration
Phagocytosis

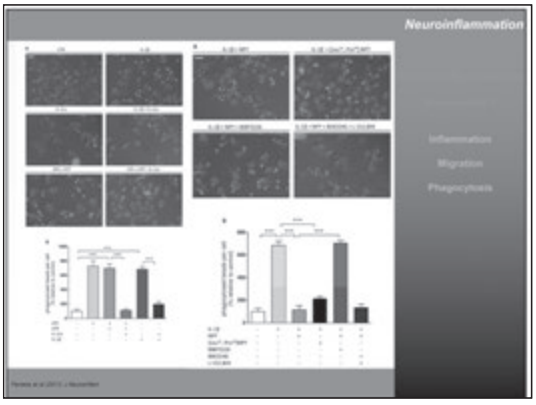

Neuroinflammation
Inflammation
Migration
Phagocytosis

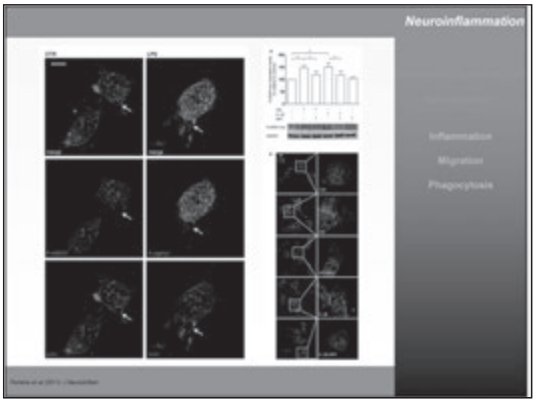

Neuroinflammation
Inflammation
Migration
Phagocytosis

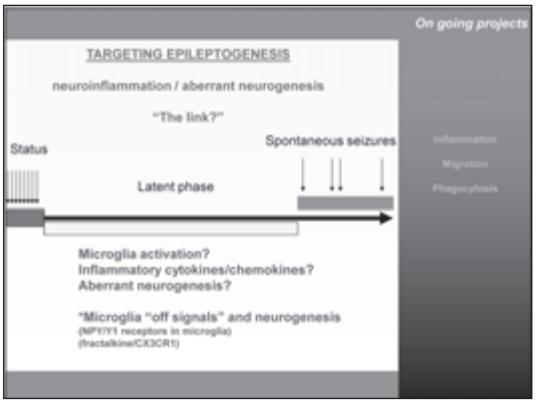

Neuroinflammation
Inflammation
Migration
Phagocytosis


Neuroinflammation
t=0 min
t=0 min
Inflammation
Migration
Phagocytosis


Neuroinflammation
Inflammation
Migration
Phagocytosis


Neuroinflammation
Inflammation
Migration
Phagocytosis

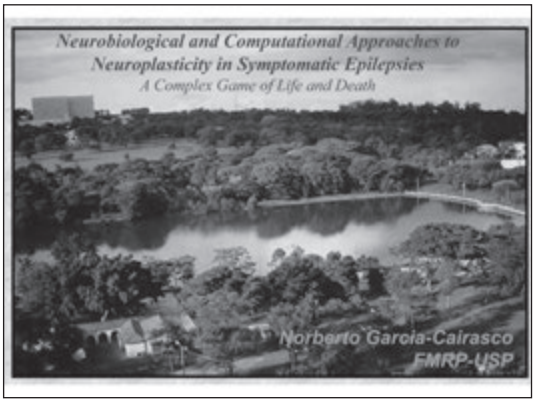

Neuroinflammation
Inflammation
Migration
Phagocytosis

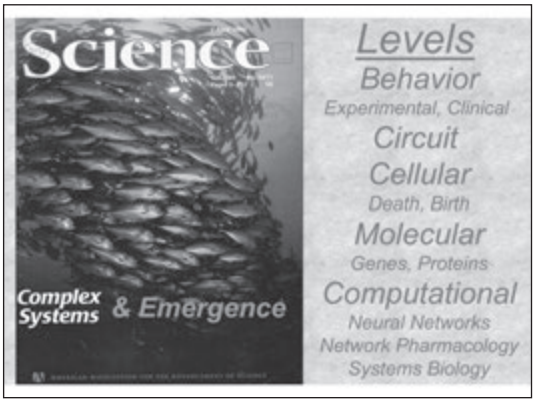

On going projects
TARGETING EPILEPTOGENESIS
neuroinflammation / aberrant neurogenesis
"The link?"
Status
Spontaneous seizures
Latent phase
Inflammation
Migration
Phagocytosis
Microglia activation?
Inflammatory cytokines/chemokines?
Aberrant neurogenesis?
"Microglia "off signals" and neurogenesis
(NPY/Y1 receptors in microglia)
(fractalkine/CX3CR1)


"Astronomy Domine"
Pynk Floyd
1969 – O ano da conquista da Lua

Norberto Garcia Cairasco (Brazil)

NEUROBIOLOGICAL AND COMPUTATIONAL APPROACHES TO NEUROPLASTICITY IN SYMPTOMATIC EPILEPSIES: A COMPLEX GAME OF LIFE AND DEATH





Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies

A Complex Game of Life and Death

Behavior Level I

Definitions & Concepts


INFORME

MEDICO MORAL

DE LA PENOSISSIMA,

Y RIGOROSA ENFERMEDAD

DE LA EPILEPSIA,

QUE PADECIENDO

DE LA M. S. M. ALEXANDRA MATHE

HACE

EL BACHILLER PEDRO DE MARTA,

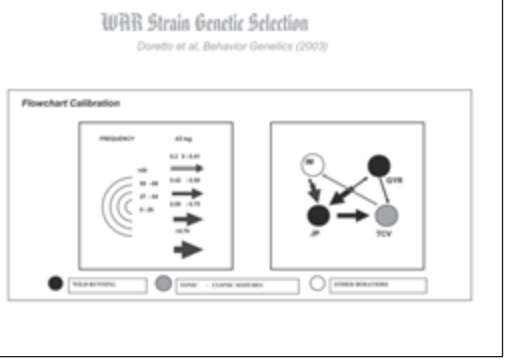
CON LICENCIA.

Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies

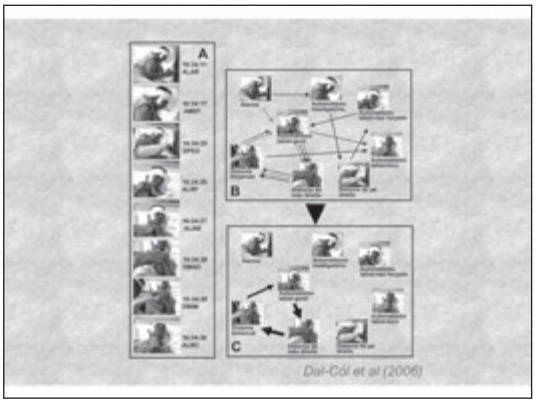
A Complex Game of Life and Death

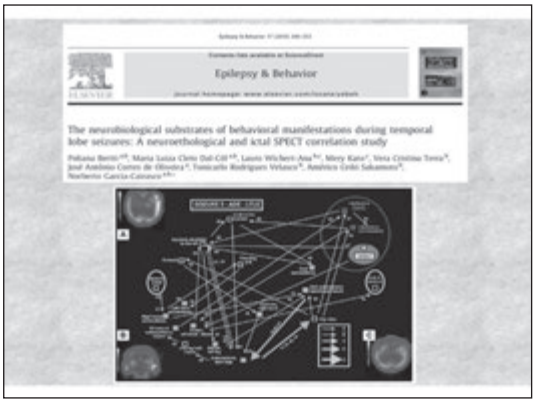
Behavioral Level II

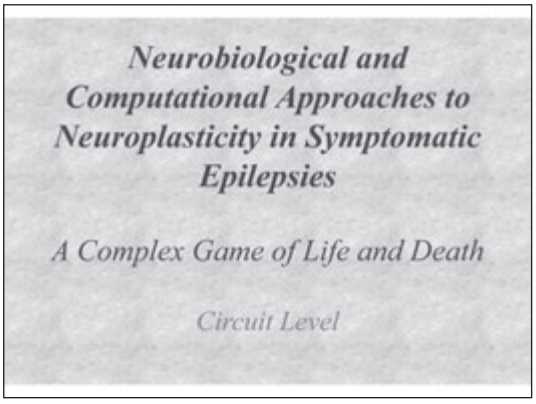
Models & Clinical Seizures

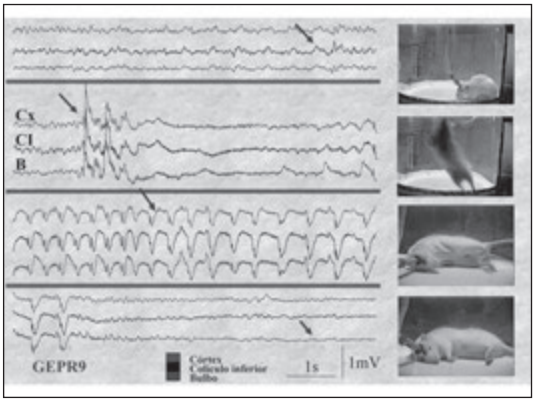


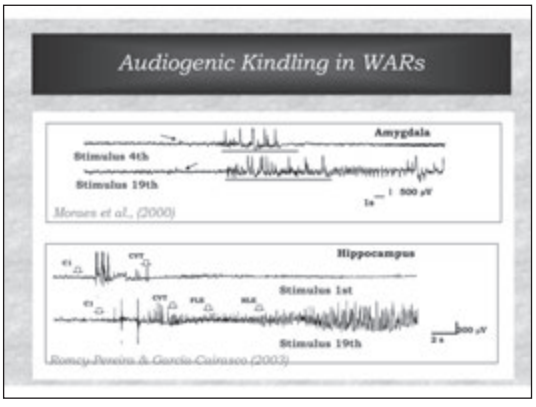

Before Selection
20th Generation
The WRR Strain
Doretto et al (2003)
Pre
Sound
Post

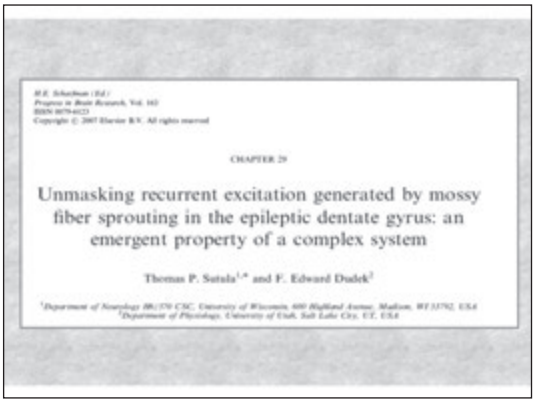

A
B
C
Dal-Cól et al (2006)

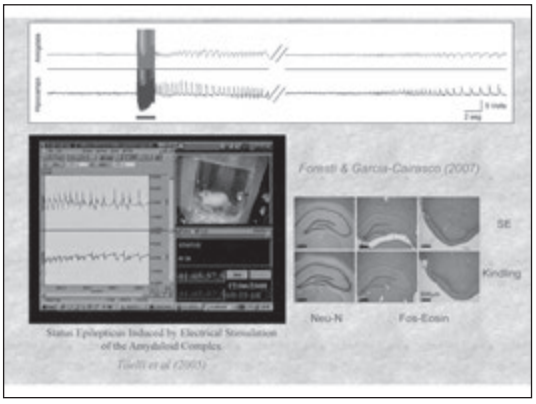

Epilepsy & Behavior
The neurobiological substrates of behavioral manifestations during temporal lobe seizures: A neuroethological and ictal SPECT correlation study

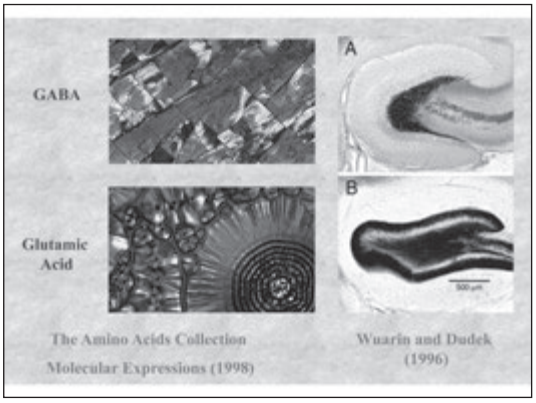

Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies
A Complex Game of Life and Death
Circuit Level

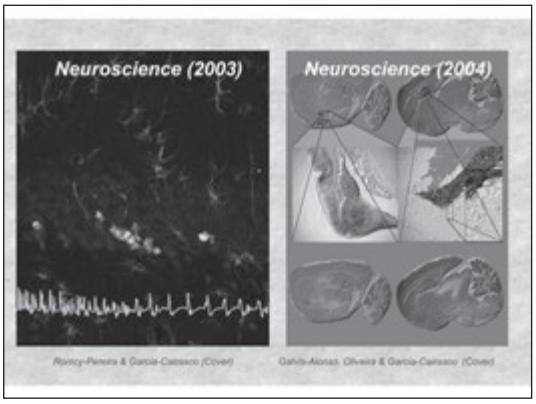

Cx
Cl
B
GEPR9
Cortex
Colliculo inferior
Bulbo
1s
1mV

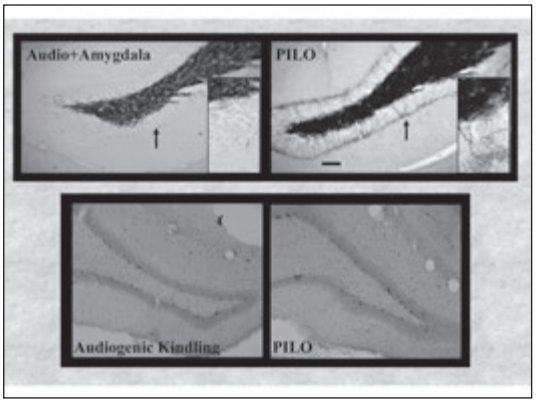

Audiogenic Kindling in WARs
Amygdala
Stimulus 4th
Stimulus 19th
500 μV
Moraes et al., (2000)
Hippocampus
Stimulus 1st
Stimulus 19th
Roncy Pereira & Garcia-Cairasco (2003)

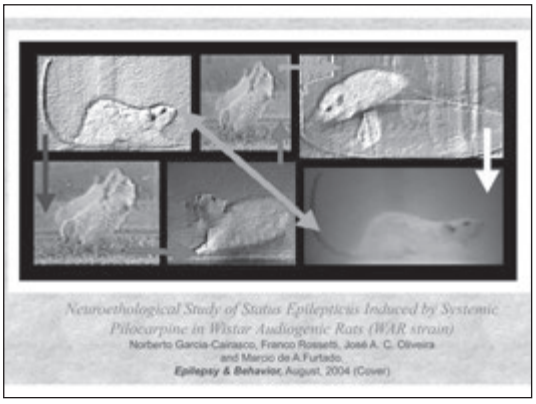

CHAPTER 29
Unmasking recurrent excitation generated by mossy fiber sprouting in the epileptic dentate gyrus: an emergent property of a complex system
Thomas P. Sutula and F. Edward Dudek


Foresti & Garcia-Cairasco (2007)
SE
Kindling
Neo-N
Fos-Eosin
Status Epilepticus Induced by Electrical Stimulation of the Amygdaloid Complex
Tuelli et al (2005)


GABA
Glutamic Acid
A
B
The Amino Acids Collection
Molecular Expressions (1998)
Wuarin and Dudek
(1996)


Neuroscience (2003)
Neuroscience (2004)


Audio+Amygdala
PILO
Audiogenic Kindling
PILO


Neuroethological Study of Status Epilepticus Induced by Systemic Pilocarpine in Wistar Audiogenic Rats (WAR strain)
Norberto Garcia-Cairasco, Franco Rossetti, José A. C. Oliveira and Marcio de A.Furtado.
Epilepsy & Behavior, August, 2004 (Cover)

Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies

A Complex Game of Life and Death

Cellular Level

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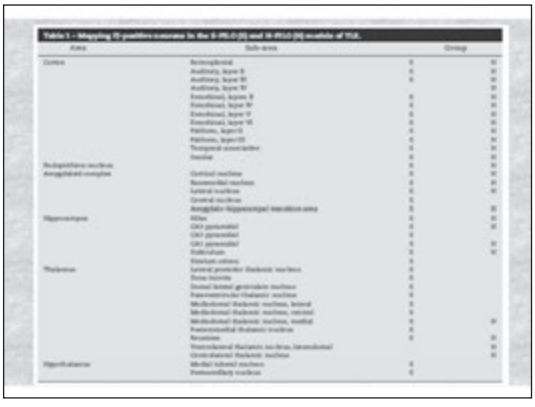
www.elsevier.com/locate/brainres

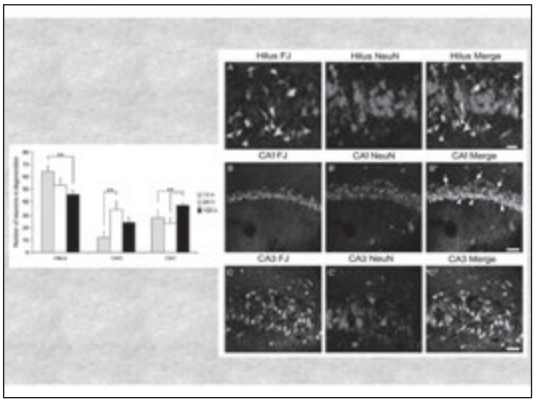
BRAIN RESEARCH

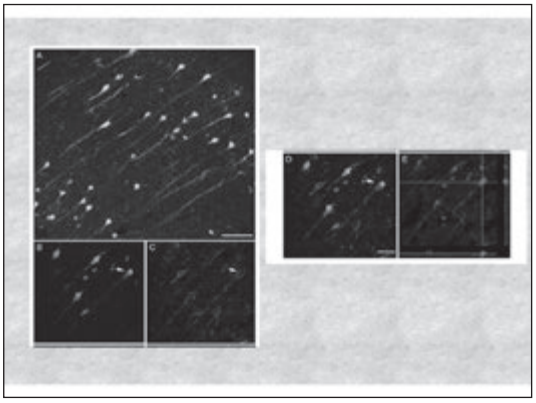
Research Report

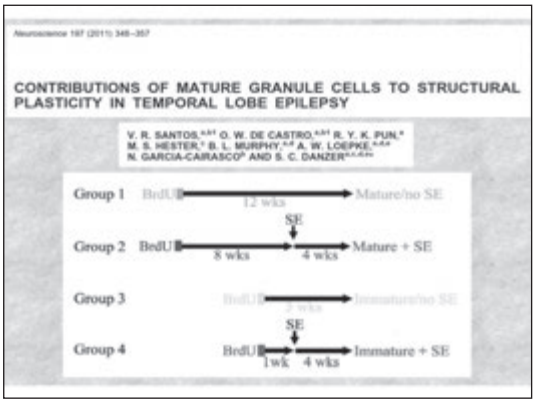
Comparative neuroanatomical and temporal characterization of FluoroJade-positive neurodegeneration after status epilepticus induced by systemic and intrahippocampal pilocarpine in Wistar rats

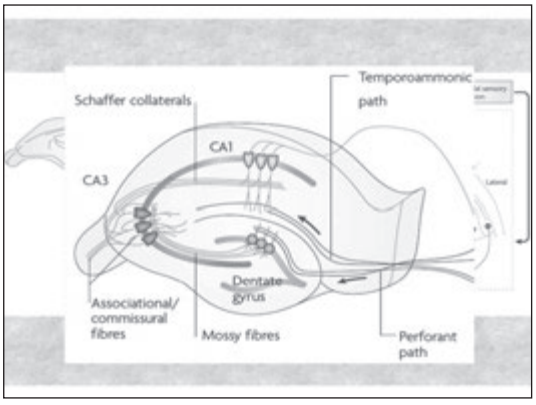
O.W. Castro, M.A. Furtado[1], C.Q. Tilelli[2], A. Fernandes, G.P. Pajolla, N. Garcia-Cairasco*

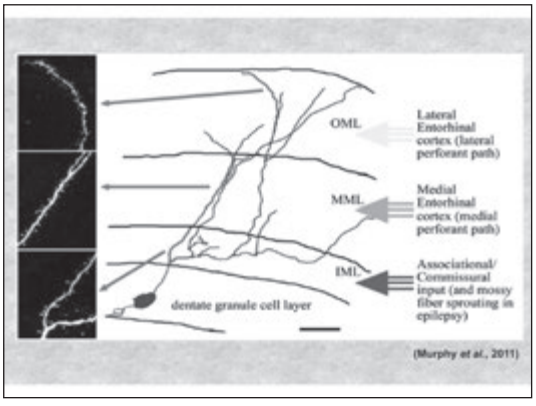


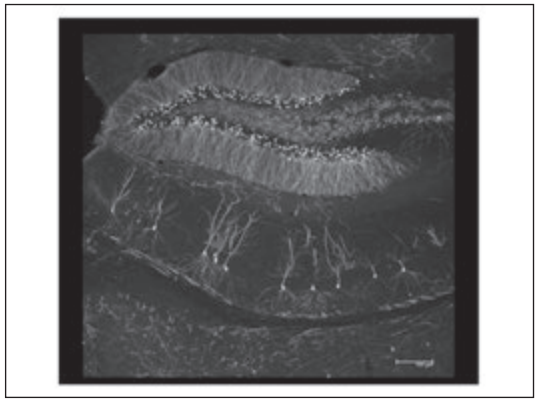


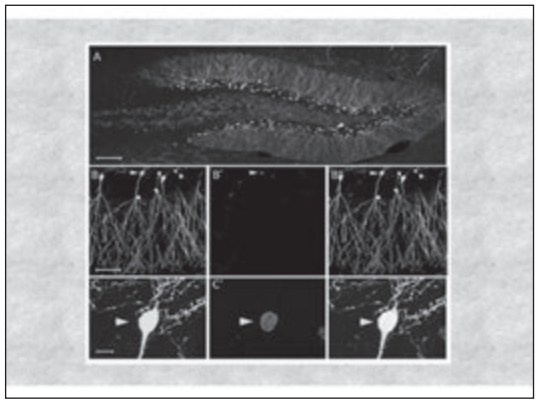


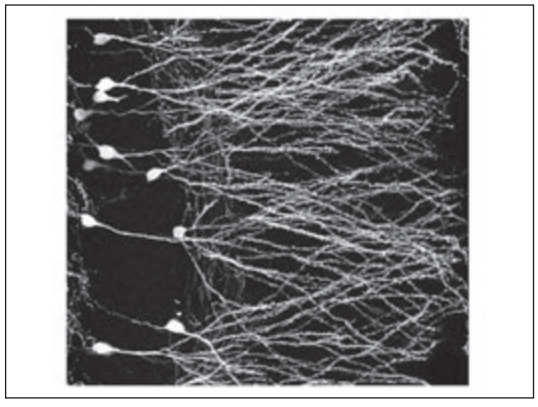

Neuroscience 197 (2011) 348–357
CONTRIBUTIONS OF MATURE GRANULE CELLS TO STRUCTURAL PLASTICITY IN TEMPORAL LOBE EPILEPSY
V. R. SANTOS, O. W. DE CASTRO, B. Y. K. PUN, M. S. HESTER, B. L. MURPHY, A. W. LOEPKE, N. GARCIA-CAIRASCO AND S. C. DANZER
Group 1 BrdU 12 wks Mature/no SE
Group 2 BrdU 8 wks SE 4 wks Mature + SE
Group 3 BrdU 2 wks Immature/no SE
Group 4 BrdU 1wk SE 4 wks Immature + SE

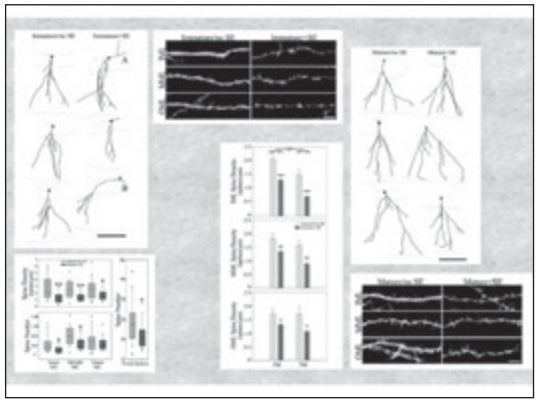

Schaffer collaterals
Temporoammonic path
CA1
CA3
Dentate gyrus
Associational/ commissural fibres
Mossy fibres
Perforant path


OML
Lateral Entorhinal cortex (lateral perforant path)
MML
Medial Entorhinal cortex (medial perforant path)
IML
Associational/ Commissural input (and mossy fiber sprouting in epilepsy)
dentate granule cell layer
(Murphy et al., 2011)





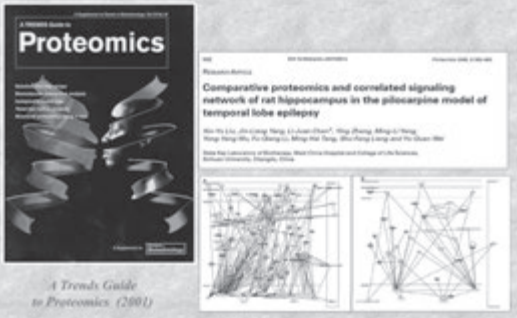




Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies

A Complex Game of Life and Death

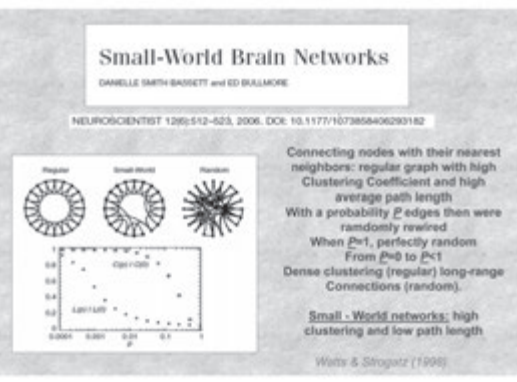
Molecular Level

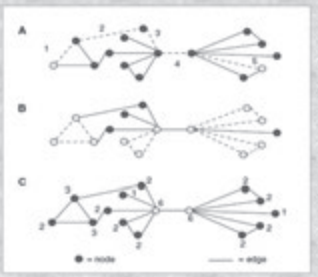


Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies

A Complex Game of Life and Death

Computational Level I
Definitions & Concepts





Nodes: circular objects
Edges: Connections
Path Length (L): Fewest number of edges – given nodes (5 in A)

Clustering Coefficient C (high): Number of connected triangles If two nodes are connected to a third one, probably they are also connected to each other

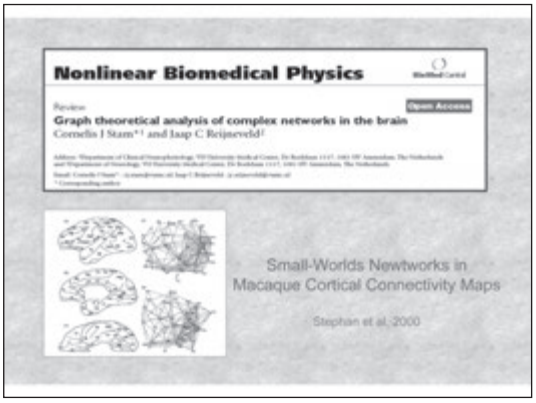
Degree of a node: Number of edges connected to it
Hub: Node with a degree larger than the average degree.
This network: A D=3.3. Therefore, nodes with degrees 6 are hubs

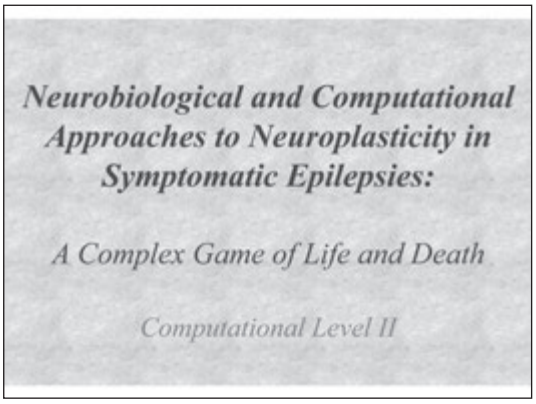
Many small-world networks in biology and sociology have been shown to have the economic property of delivering high global and local efficiency at relatively low cost (Latora and Marchiori 2003)

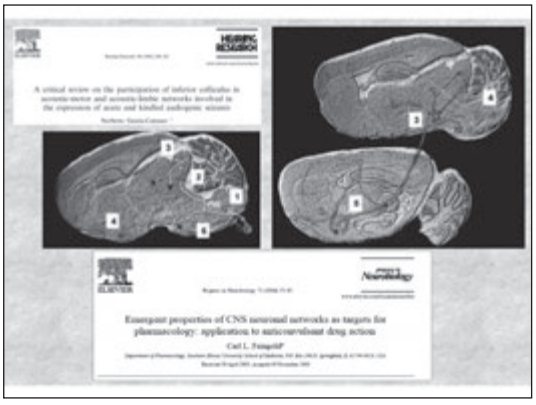
Since the discovery of **small-world and scale-free networks** the study of complex systems from a network perspective has taken an enormous flight. In recent years many important properties of complex networks have been delineated. In particular, **significant progress has been made in understanding the relationship between the structural properties of networks and the nature of dynamics taking place on these networks.**

For instance, the **'synchronizability' of complex networks of coupled oscillators** can be determined by **graph spectral analysis.** These developments in the theory of complex networks have inspired new applications in the field of neuroscience. **Graph analysis has been used in the study of models of neural networks, anatomical connectivity, and functional connectivity based upon fMRI, EEG and MEG.** These studies suggest that the human brain can be modeled as a complex network, and may have a *small-world structure* both at the level of anatomical as well as functional connectivity.

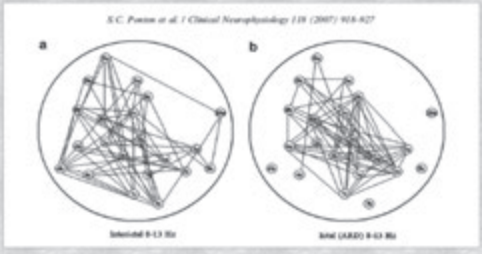
This small-world structure is hypothesized to reflect an optimal situation associated with rapid synchronization and information transfer, minimal wiring costs, as well as a balance between local processing and global integration. The topological structure of functional networks is probably restrained by genetic and anatomical factors, but can be modified during tasks. There is also increasing evidence that various types of brain disease such as **Alzheimer's disease, schizophrenia, brain tumours and** epilepsy may be associated with deviations of the functional network topology from the optimal small-world pattern.


Nonlinear Biomedical Physics
Review
Open Access
Graph theoretical analysis of complex networks in the brain
Cornelis J Stam*1 and Jaap C Reijneveld2
Small-Worlds Newtworks in
Macaque Cortical Connectivity Maps
Stephan et al, 2000


Neurobiological and Computational
Approaches to Neuroplasticity in
Symptomatic Epilepsies:
A Complex Game of Life and Death
Computational Level II


HIPPOCAMPUS
Emergent properties of CNS neuronal networks as targets for
pharmacology: application to anticonvulsant drug action


Small-world networks and epilepsy: Graph theoretical analysis
of intracerebrally recorded mesial temporal lobe seizures

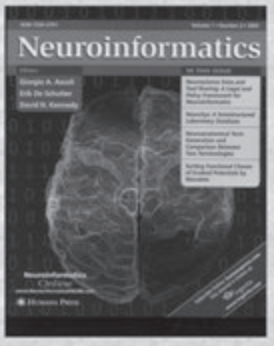


Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies:

A Complex Game of Life and Death
Computational Level III
e-Neuroscience & Neuroinformatics
Simulation & Modeling

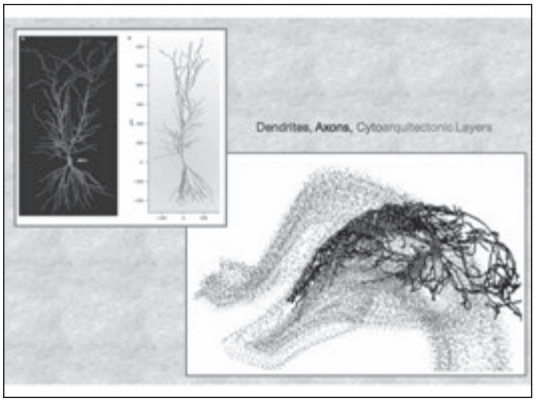
Neuroinformatics (NIH; 1998)

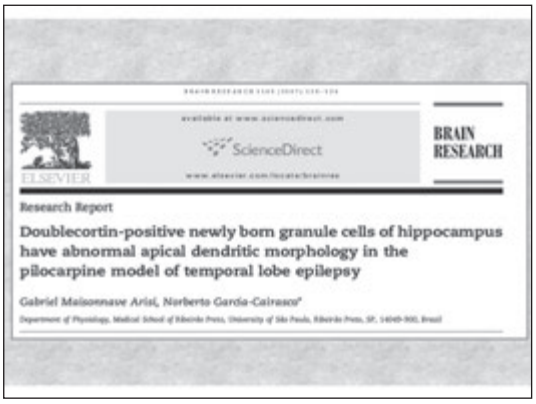
"Putting the Brain Back Together Again"

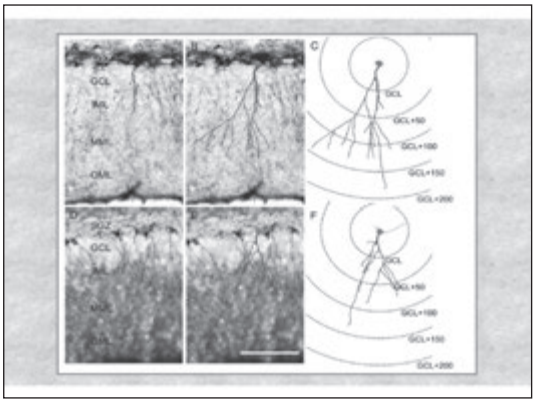


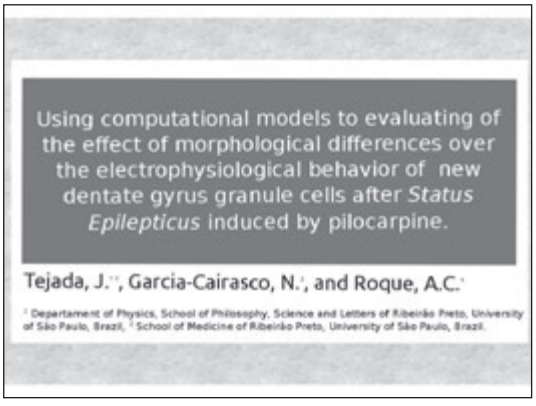
"Neuroscience Data and Tool Sharing: A legal and Policy Framework for Neuroinformatics"

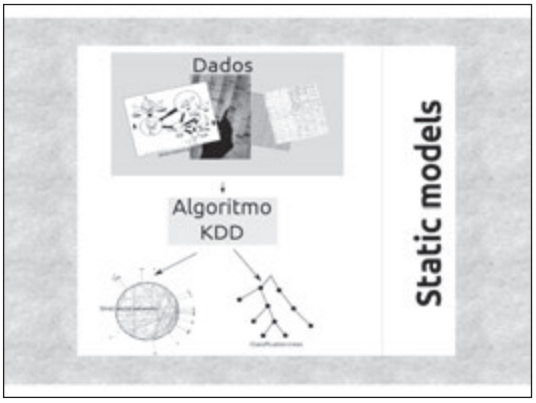
The OECD Working Group on Neuroinformatics (2003)

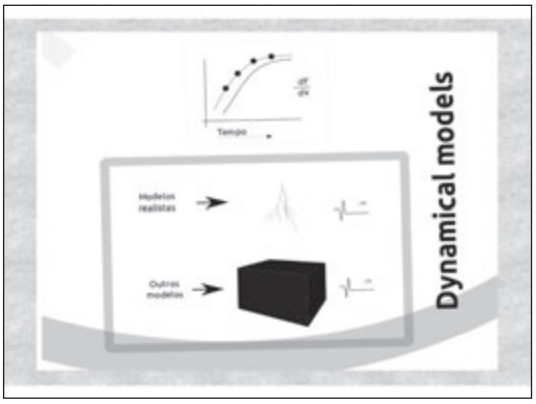

Dendrites, Axons, Cytoarquitectonic Layers

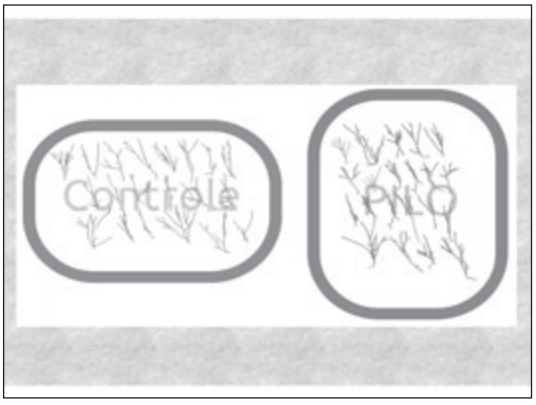

ScienceDirect
BRAIN RESEARCH
Research Report
Doublecortin-positive newly born granule cells of hippocampus have abnormal apical dendritic morphology in the pilocarpine model of temporal lobe epilepsy
Gabriel Maisonnave Arisi, Norberto Garcia-Cairasco*

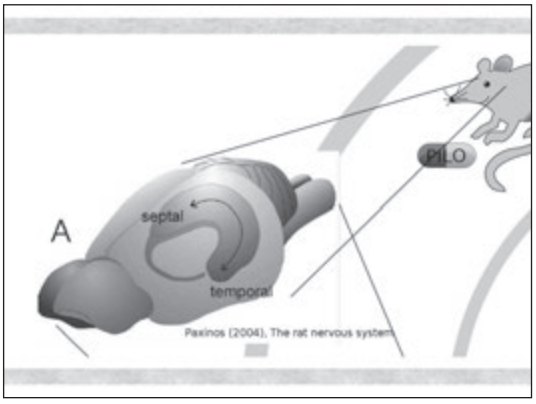

GCL
ML
HIL
OML
C
F

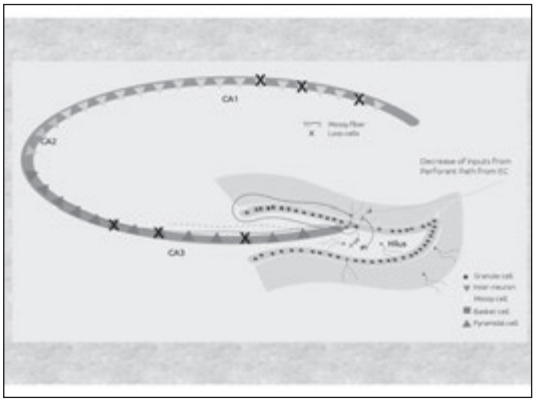

Using computational models to evaluating of the effect of morphological differences over the electrophysiological behavior of new dentate gyrus granule cells after *Status Epilepticus* induced by pilocarpine.
Tejada, J.[1], Garcia-Cairasco, N.[2], and Roque, A.C.[1]
[1] Departament of Physics, School of Philosophy, Science and Letters of Ribeirão Preto, University of São Paulo, Brazil, [2] School of Medicine of Ribeirão Preto, University of São Paulo, Brazil.

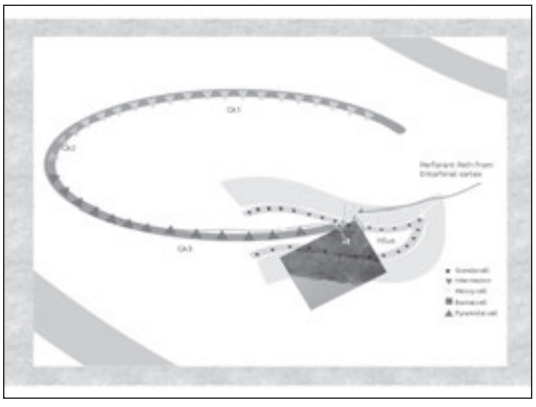

Dados
Algoritmo
KDD
Static models

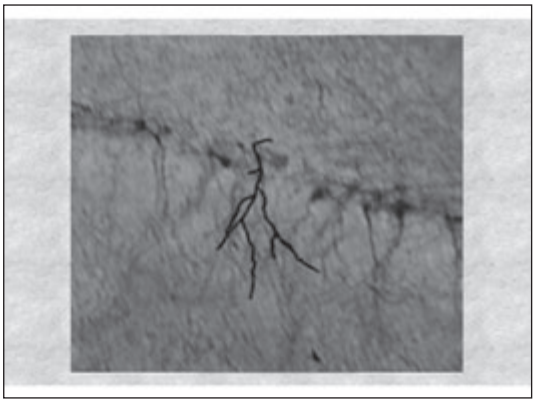

Tempo
Modelos realistas
Outros modelos
Dynamical models

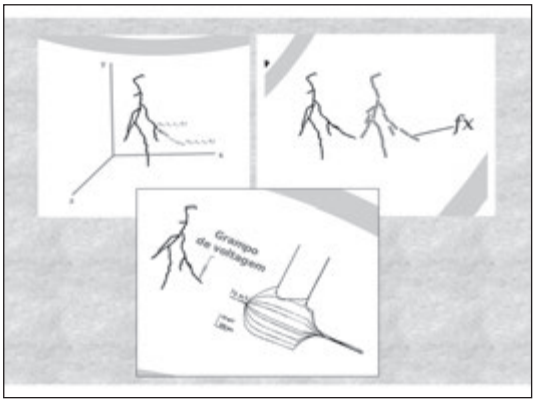

Controle
PILO

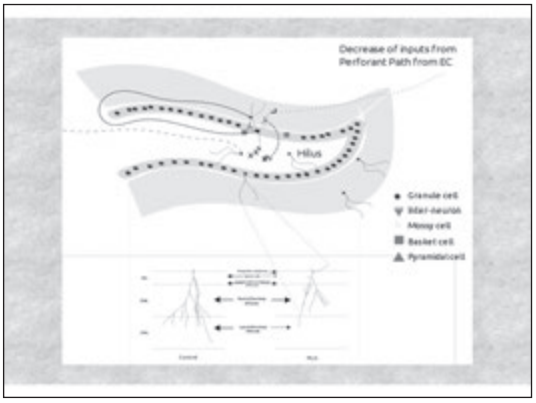

PILO
A
septal
temporal
Paxinos (2004), The rat nervous system

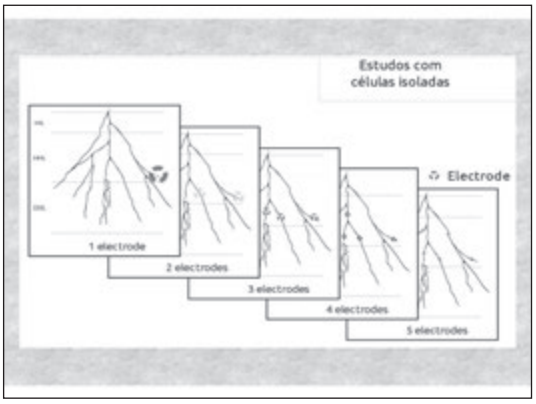

CA1
CA2
CA3
Hilus

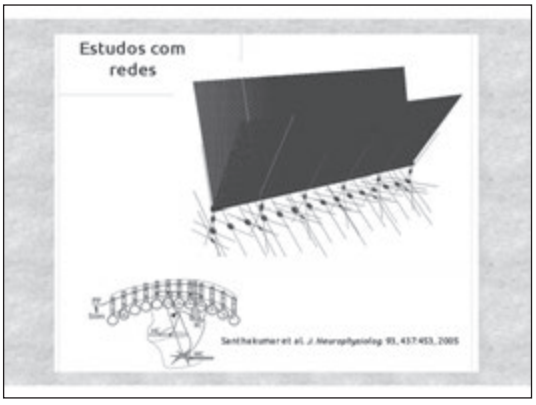

CA1
CA2
CA3
Hilus

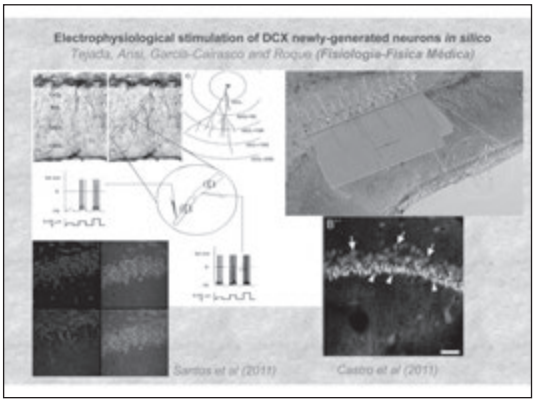



Grampo
de voltagem


Decrease of inputs from
Perforant Path from EC
Hilus
Granule cell
Mossy cell
Basket cell
Pyramidal cell

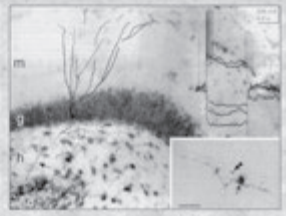

Estudos com
células isoladas
Electrode
1 electrode
2 electrodes
3 electrodes
4 electrodes
5 electrodes


Estudos com
redes


Electrophysiological stimulation of DCX newly-generated neurons in silico
Tejada, Arisi, Garcia-Cairasco and Roque (Fisiologia-Física Médica)
Santos et al (2011)
Castro et al (2011)

Functional Neurogenesis in the Adult Hippocampus

GABAergic Cells Are the Major Postsynaptic Targets of Mossy Fibers in the Rat Hippocampus



van Praag H, Schinder A F, Christie B R, Toni N, Palmer T D & Gage F H (2002)

J Acsády et al (1998)

Network: Computation in Neural Systems
September 2009; 20(3): 137–161

informa

Additive neurogenesis as a strategy for avoiding interference in a sparsely-coding dentate gyrus

PETER A. APPLEBY & LAURENZ WISKOTT

OPEN ACCESS Freely available online

PLOS COMPUTATIONAL BIOLOGY

The Role of Additive Neurogenesis and Synaptic Plasticity in a Hippocampal Memory Model with Grid-Cell Like Input

Peter A. Appleby[1*], Gerd Kempermann[2,3], Laurenz Wiskott[4]

Neurobiological and Computational Approaches to Neuroplasticity in Symptomatic Epilepsies:

A Complex Game of Life and Death

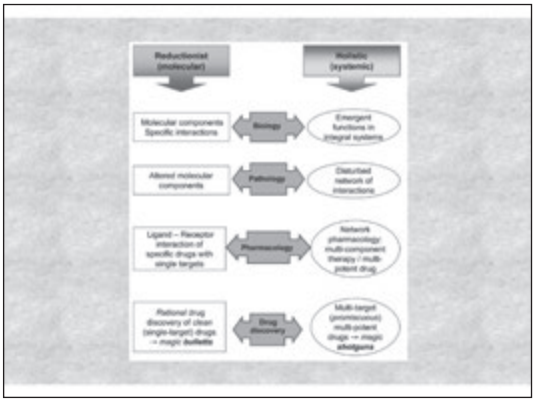
Computational Level IV
Systems Biology & Network Pharmacology

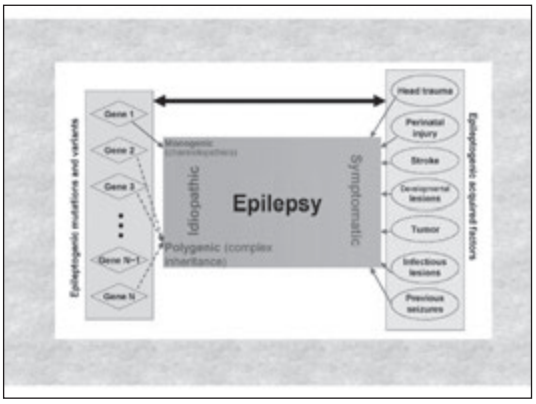
ARTICLE IN PRESS

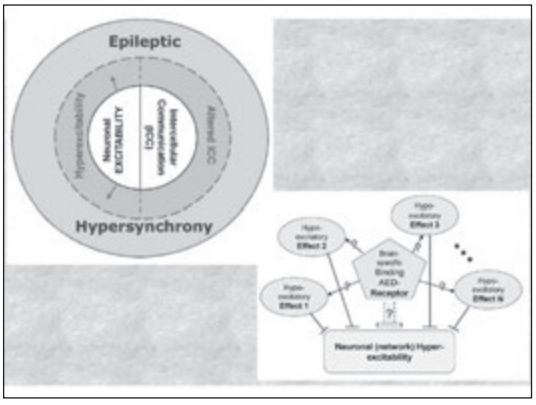
REVIEW

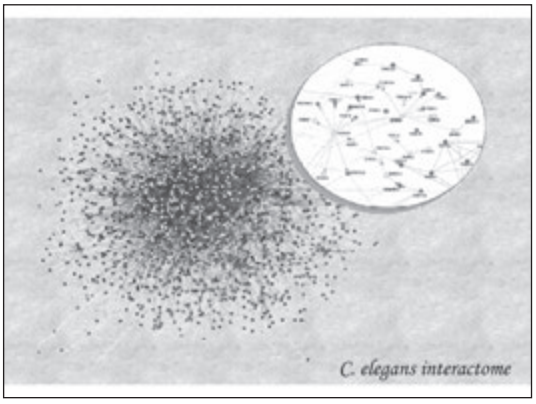
Systems biology impact on antiepileptic drug discovery

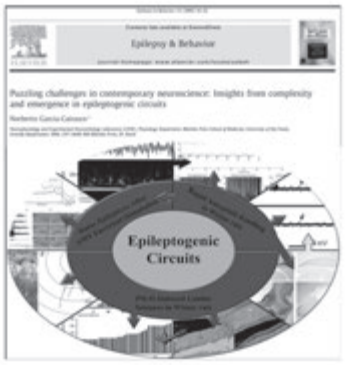
Doru Georg Margineanu*

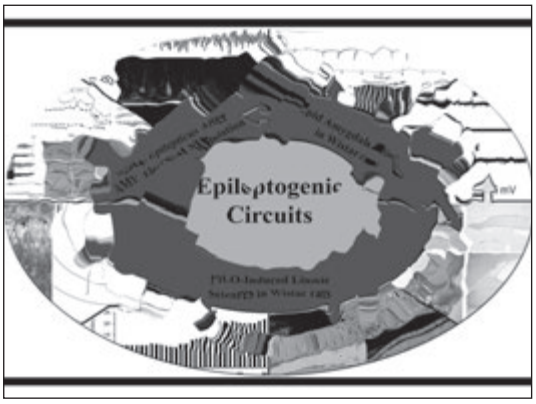

Reductionist (molecular)
Holistic (systemic)
Molecular components Specific interactions
Biology
Emergent functions in integral systems
Altered molecular components
Pathology
Disturbed network of interactions
Ligand – Receptor interaction of specific drugs with single targets
Pharmacology
Network pharmacology/ multi-component therapy / multi-potent drug
Rational drug discovery of clean (single-target) drugs → magic bullette
Drug discovery
Multi-target (promiscuous) multi-potent drugs → magic shotguns


Epileptogenic mutations and variants
Gene 1
Gene 2
Gene 3
Gene N−1
Gene N
Monogenic (channelopathies)
Idiopathic
Epilepsy
Symptomatic
Polygenic (complex inheritance)
Epileptogenic acquired factors
Head trauma
Perinatal injury
Stroke
Developmental lesions
Tumor
Infectious lesions
Previous seizures

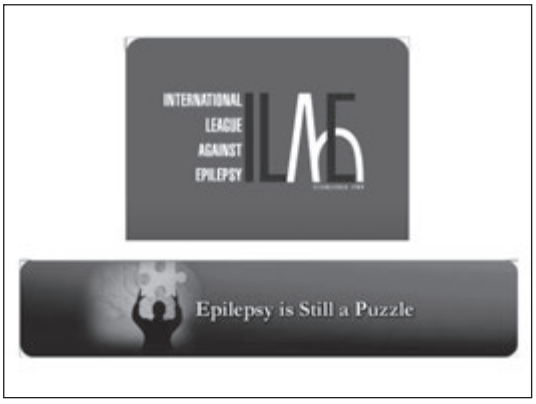

Epileptic
Hypersynchrony
Hyperexcitability
Neuronal EXCITABILITY
Transmembrane ECl
Altered ECl
Hypo-excitatory Effect 3
Hypo-excitatory Effect 2
Brain-specific Binding AED-Receptor
Hypo-excitatory Effect 1
Hypo-excitatory Effect N
?
Neuronal (network) Hyper-excitability


C. elegans interactome


Epileptogenic
Circuits


Epileptogenic
Circuits


Complexity
&
Emergence


INTERNATIONAL
LEAGUE
AGAINST
EPILEPSY
ILAE
Epilepsy is Still a Puzzle

Two Cultures: Scientific, Literary
C.P.Snow

The Structures of Scientific Revolutions
T.Kuhn

Consilience
The Unity of Knowledge
EO Wilson


THE END

Fernando Cendes (Brazil)

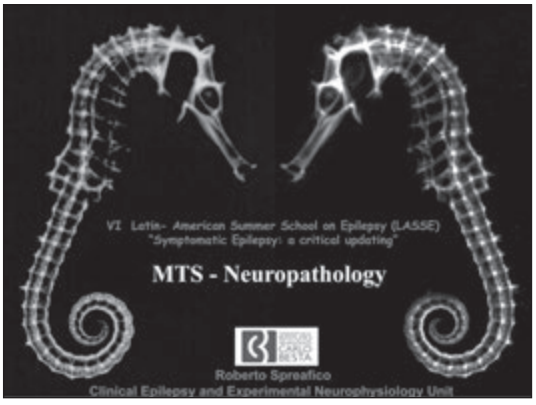
VIRAL ENCEPHALITIS AND ACUTE SEIZURES, DIAGNOSIS AND TREATMENT

Helen Cross (England)

USE OF CORTICOSTEROIDS AND OTHER IMMUNOMODULATION THERAPIES FOR SEIZURES

Roberto Spreafico (Italy)

MTS – PATHOLOGY



Many studies show a significant effect of the underlying etiology on the course of the disease, pharmacoresistance and post operative outcome

The prognosis of partial epilepsies is more closely related to the underlying pathology than to the localization of the epileptogenic zone (EZ) (Semah et al 1998)

The ILAE Commission on Classification and Terminology recommends a classification that puts more emphasis on the underlying structural or metabolic cause of focal epilepsies rather than concentrating on localization

Questions to be addressed

- Is TLE with MTS a unique epileptic condition different from other focal temporal lobe epilepsies based on neuro-pathological/pathogenesis evidence?
- Is HS specific to TLE?
- Need for a consistent definition of hippocampal anatomy

Pathology:

Spectrum of changes associated with HS includes:

- Variable extent of cell loss within the hippocampus.
- Long and short term structural and functional glial changes.
- Dentate dispersion in approximately 50% of cases
- Extra-hippocampal pathology:
  - Other mesial temporal lobe structures
  - Temporal lobe white matter

Pathology

- Definition of Hippocampal Sclerosis: minimal criteria
- What is the extent of cell loss
- Is HS an isolated lesion or is it associated with diffuse changes?
- Is this condition a progressive disease?
- Need for a precise definition of dual pathology.

Pathogenesis

- When does it occur?
- What causes the cell loss?
- HS can be a developmental disorder ?
- What is the evidence that febrile convulsions "cause" HS?

TERMINOLOGY

Temporal Lobe Epilepsy (**TLE**)

≠

Mesial Temporal Lobe Epilepsy (**MTLE**)

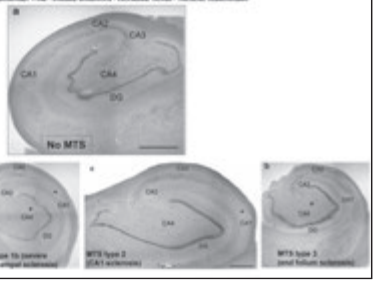
MTLE
can be determined by

- different pathologies *(Tumors, HS, Vascular malformations, Focal Dysplasia, etc.)*
- different mesial regions/structures involved (*Hippocampus, Amygdala, Parahippocampal cortex, mesial aspect of the neocortex)*

ORIGINAL PAPER

A new clinico-pathological classification system for mesial temporal sclerosis

Ingmar Blümcke · Elisabeth Pauli · Hans Clusmann · Johannes Schramm · Albert Becker · Christian Elger · Martin Merschhemke · Heinz-Joachim Meencke · Thomas Lehmann · Andreas von Deimling · Christian Scheiwe · Josef Zentner · Roman Stefan · Johann Romstöck · Hermann Stefan · Michelle Hildebrandt



Reliability of patterns of Hippocampal Sclerosis as predictors of postsurgical outcome

(modified) from Thom et al. : Epilepsia 51 (2010): 1801-1808

N° of Patients	HS Pattern	Mean age at IPI	Mean age at seizure onset	Mean duration of Epilepsy	Outcome (ILAE Classification)		
					I	II	III
9 (6%)	**CA1p** (CA2-3-4 preserved)	1.8	5.9	26.5	33	22	45
5 (3%)	**EFS** EndFoliumSclerosis (CA4 only)	2.4	18.2	15.2	100	-	-
60 (36%)	**CHS** (CA1+CA4; CA2 and Sub preserved)	1.7	9.3	24.2	69	9	22
39 (24%)	**THS** (all fields including CA2)	1.9	6.5	25.5	71	8	21
35 (21%)	**Indeterminate** (CA1+CA3; CA4 preserved)	3.7	10.8	24	56	23	21
17 (10%)	**No HS**	1.2	12.4	23.1	44	19	37
21	**Control**	-	-	-	-	-	-

Comparison among different classification systems

CA Subfield(s) Neuronal loss	Thom et al. (2010) Classification (N° of patients)	Outcome (ILAE-Class 1)	Blumcke et al. (2007) Classification (N° of patients)	Outcome (Engel Class 1)	Wyler et al. (1992)
CA1 only	CA1 p (9)	33%	Type 2 (10)	66.7%	
CA4 only	EFS (5)	100%	Type 3 (7)	28.6%	EFS
CA1=CA4	Classical HS (60)	69%	Type 1a CHS (33)	72 %	
CA1=CA3 (CA4 preserved)	Indeterminate HS (35)	56%			
CA1=CA3=CA4			Type 1b (severe) (94)	72.3%	Grade III*
CA1=CA2=CA3+ CA4	Total HS (THS) (39)	71%			Grade IV
No cell loss	NO HS (17)	44%	No HS (23)	72%	

* Grade I (mild) gliosis < 10% involving CA1+CA3+CA4
Grade II (moderate) gliosis=10-50% involving CA1+CA3+CA4

Outcome predictors for surgical treatment of temporal lobe epilepsy with Hippocampal Sclerosis

(S. Aull-Watschinger et al . Epilepsia 49 (2008): 1306-1316)

- **Short term surgical outcome of patients remain stable between 70% to 79%**
- **Positive predictors of short-term outcome do not predict long-term outcome**

Proposal for a semi-quantitative ILAE scoring system for HS in epilepsy patients [a]

	Pattern of neuronal loss and gliosis (complete samples)					Pattern of neuronal loss and gliosis (incomplete samples)	
SUB	0 - 1	0 - 1	0 - 1	0 - 1	0	0 - 1	n.a.
CA1	2	2	1 - 2	0	0	1 - 2	n.a.
CA2	0 - 1	0 - 2	0	0	0	n.a.	n.a.
CA3	0 - 1	2	0	0 - 1	0	n.a.	n.a.
CA4	1 - 2	2	0	1 - 2	0	n.a.	1 - 2
DG [b]	0 - 2	1 - 2	0 - 2	0 - 2	0 - 1	n.a.	0 - 2
Class.	ILAE Type 1a [c]	ILAE Type 1b [c]	ILAE Type 2 [c]	ILAE Type 3 [c]	No HS [d]	Probable HS [e]	Possible HS [e]

0 = No detectable/obvious neuronal loss or gliosis only
1= Neuronal loss or gliosis (GFAP) but moderate or patchy
2= Severe neuronal loss (majority of neurons) and fibrillary gliosis

a = microscopic examination based on formalin-fixed, paraffin-embedded surgical specimen (4-7 µm section thickness) , H&E, CV/LFB, NeuN (recommended) and GFAP stainings
b = granule cell layer is normal (score = 0), dispersed (score 1; can be focal) or shows severe granule cell loss (score 2; can be focal)
c = if surgical specimen is anatomically well-preserved (en bloc resection recommended)
d = minimal requirement for DX is presence of CA1 with transition to subiculum; n.a. = not available for histological examination;
DX of „probable HS" allowed only in the context of supportive electro-clinical and imaging findings
e = minimal requirement for DX is presence of CA4 and DG; n.a. = not available for histological examination;
DX of „possible HS" allowed only in the context of supportive electro-clinical and imaging findings

Indeterminate HS = rare cases where specimen is complete but the pattern of sclerosis does not fall into one of the three main types .

	Pattern of neuronal loss and gliosis (complete samples)					Pattern of neuronal loss and gliosis (incomplete samples)	
SUB	0 - 1	0 - 1	0 - 1	0 - 1	0	0 - 1	n.a.
CA1	2	2	1 - 2	0	0	1 - 2	n.a.
CA2	0 - 1	0 - 2	0	0	0	n.a.	n.a.
CA3	0 - 1	2	0	0 - 1	0	n.a.	n.a.
CA4	1 - 2	2	0	1 - 2	0	n.a.	1 - 2
DG [b]	0 - 2	1 - 2	0 - 2	0 - 2	0 - 1	n.a.	0 - 2
Class.	ILAE Type 1a [c]	ILAE Type 1b [c]	ILAE Type 2 [c]	ILAE Type 3 [c]	No HS [d]	Probable HS [e]	Possible HS [e]

Thom	CHS	THS	CA1p	EFS	No HS
Blumcke	Type 1a	Type 1b	Type 2	Type 3	No HS

Francois Dubeau (Canada)

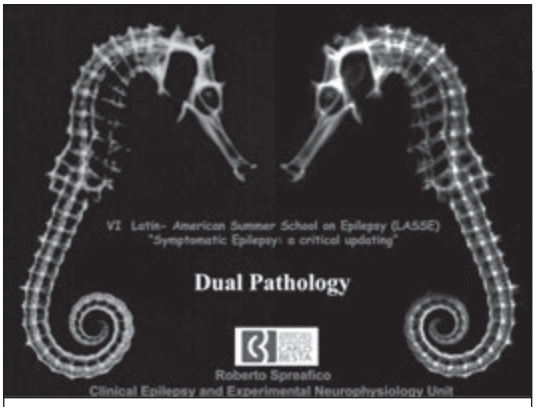
MTS – INVASIVE AND NON-INVASIVE EEG

Gregory Cascino (USA)

MTS- CLINICAL SPECTRUM AND SURGICAL TREATMENT

Roberto Spreafico (Italy)

DUAL PATHOLOGY



Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and in surgical series of patients with drug-resistant epilepsy, 60-75% of cases are reported to have TLE (Blümcke et al., 2002; Lahl et al., 2003).

However, pathological studies show that lesions correlated with TLE may be found well beyond the hippocampal formation and conventional MRI often identifies developmental or vascular malformations and tumors within the temporal lobe in TLE patients, which may or may not be associated with HS (Kuzniecky et al., 1999; Raymond et al., 1994; Lee et al., 1998).

Dual pathology is estimated to occur in 5-30% of TLE cases. The most common second alteration is a malformation of cortical development (MCD), most often focal cortical dysplasia (FCD)

Dual Pathology is not yet comprehensively defined (Cendes et al., 1995), and is still ambiguously used in clinical and histopathologic practice. Proposed definition:

Dual Pathology

refers only to patients with **hippocampal sclerosis**, who have a second principal lesion affecting the brain (which may be located also outside the ipsilateral temporal lobe), that is, tumor, vascular malformation, glial scar, limbic/Rasmussen encephalitis, or MCD (including FCD Type IIa/IIb).

Ipsilateral temporopolar atrophy with increased T2 signal changes on MRI is not included as its histopathologic correlate has yet to be specified.

Of note

histopathologically confirmed architectural abnormalities in the temporal lobe associated with HS should not be diagnosed as FCD Type I or "Dual Pathology" but FCD Type IIIa.

Blumcke et al. – ILAE classification of FCD – Epilepsia 2011

SPECIAL REPORT

The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

*†Ingmar Blümcke, †Maria Thom, ‡Eleonora Aronica, §Dawna D. Armstrong, ¶Harry V. Vinters, #Andre Palmini, **Thomas S. Jacques, ††Giuliano Avanzini, ‡‡A. James Barkovich, §§Giorgio Battaglia, ¶¶Albert Becker, ##Carlos Cepeda, ***Fernando Cendes, †††Nadia Colombo, ‡‡‡Peter Crino, §§§J. Helen Cross, ¶¶¶Olivier Delalande, ###François Dubeau, ****Jules Duncan, §§§§Renzo Guerrini, ‡‡‡‡Philippe Kahane, §§§§Gary Mathern, ¶¶¶¶Ismad Najm, ####Çiğdem Özkara, *****Charles Raybaud, §§§§§Alfonso Represa, ‡‡‡‡‡Steven N. Roper, §§§§§Noriko Salamon, ¶¶¶¶¶Andreas Schulze-Bonhage, ######Laura Tassi, *****Annamaria Vezzani, and ††Roberto Spreafico*

Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

FCD Type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)	
FCD Type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)	
FCD Type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIIb)	Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc)	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId)

FCD Type III (not otherwise specified, NOS): if clinical/radiologically suspected principal lesion is not available for microscopic inspection. *Please note that the rare association between FCD Types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variants.

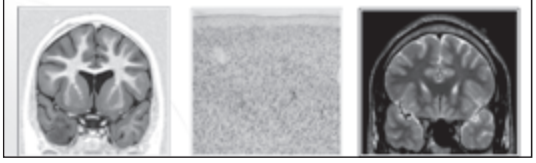
Dysplasia (synonymous of Dysgenesis and Malformation): general terms referred to any tissue that is imperfectly developed in embryonic or fetal life.

The etiology and pathogenesis of FCD type III remains to be determined but it is likely related to the pathogenesis or effects of the associated lesion acquired in early life

Epilepsia Disord 2004; 6 (2): 169-73

Are some focal cortical dysplasias post-migratory cortical malformations?

Roberto Spreafico



Hypothesis for FCD type III

- The etiology and pathogenesis of FCD type III remains to be determined but it is likely related to the pathogenesis or effects of the associated lesion acquired in early life

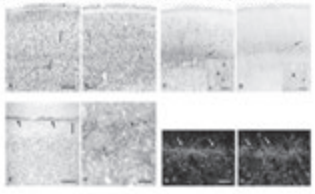
---

TLS as a peculiar form of FCD Type IIIa

Architectural (Type IA) Focal Cortical Dysplasia and Parvalbumin Immunostaining in Temporal Lobe Epilepsy

Temporal Lobe Sclerosis Associated with Hippocampal Sclerosis in Temporal Lobe Epilepsy: Neuropathological Features

TLS is likely an acquired process with accompanying re-organizational dysplasia and an extension of mesial temporal sclerosis rather than a separate pathological entity.



Double Pathology

refers to **two independent lesions** affecting one or multiple lobes, but **not including hippocampal sclerosis**.

This definition assumes that both lesions evolve from an independent pathogenesis, i.e. a cavernoma in one cerebral hemisphere and a ganglioglioma in the other.

Electrophysiology will be necessary to characterize the "most likely" epileptogenic lesion

Principal lesions

comprise **any anatomical lesion** with etiologically defined pathogenesis of either neoplastic, genetic, infectious, traumatic or metabolic origin.
This includes:

- the spectrum of epilepsy-associated tumors,
- vascular malformations,
- MCDs,
- encephalitis,
- traumatic scars,bleeding,
- vascular infarction,
- mitochondrial/metabolic dysfunctionand genetic syndromes.

Blumcke et al. - ILAE classification of FCD - Epilepsia 2011

HS + FCD I ---------- FCD IIIa

HS + second, distinct principal lesion --------- Dual Pathology

Two independent lesions ---------- Double pathology (affecting one or multiple lobes)

May 1996 – April 2010
941 patients operated on

234 pts with HS

Isolated HS 69 pts (30%)

165 pts HS "plus" (70%)

165 pts HS "plus"

HS + FCD I = FCD IIIa 67 pts (40%)

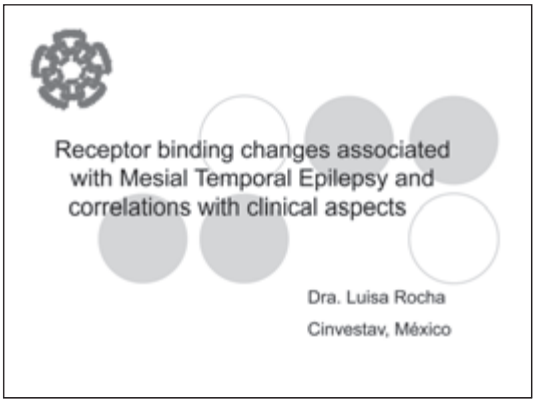
HS + "other"= Dual Pathology 98 pts (60%)

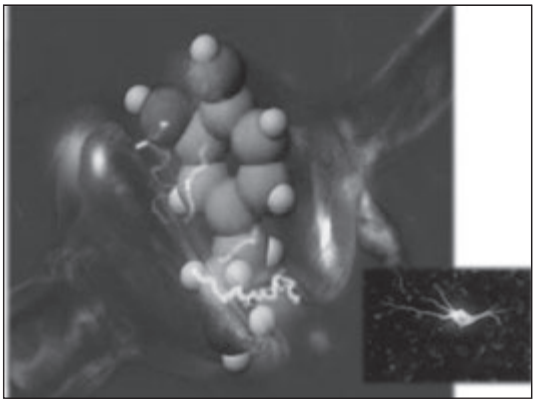
HS + TUM.	12 pts (13%)
HS + TUM+FCD I	7 pts (7%)
HS + Inf./Infl.	11 pts (12%)
HS + Malf.	68 pts (68%)

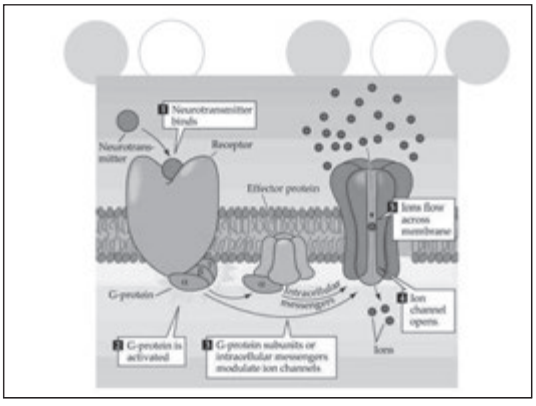
HS + cavernoma 4 pts
HS + mMCD 29 pts
HS + MCD 35 pts

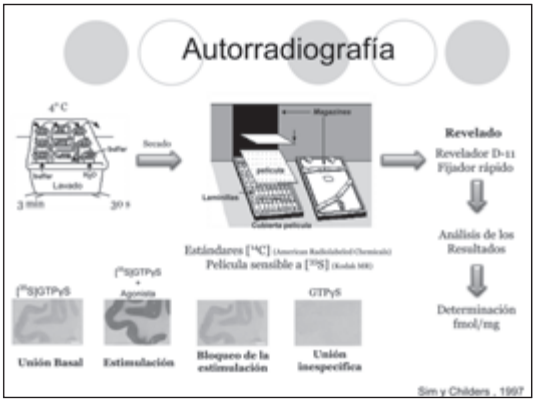
Luisa Rocha (México)

RECEPTOR BINDING CHANGES ASSOCIATED WITH MTE AND CORRELATION WITH CLINICAL ASPECTS





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Lavado
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30 s
Secado
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Laminillas
Cubierta película
Revelado
Revelador D-11
Fijador rápido
Análisis de los Resultados
Determinación fmol/mg
Estándares [14C]
Película sensible a [35S]
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GTPγS
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Estimulación
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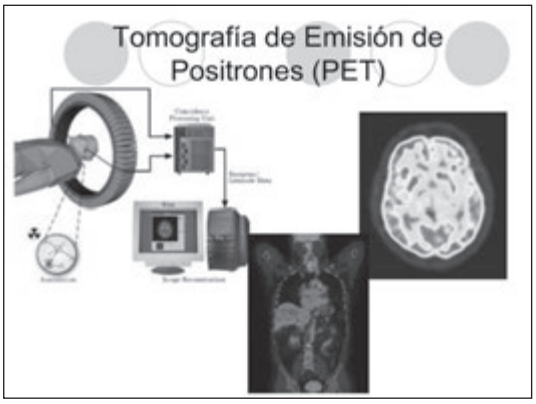
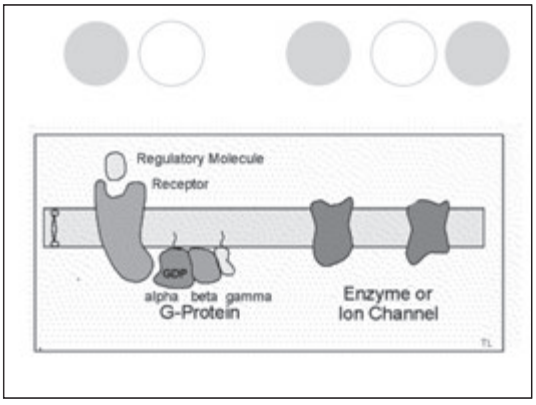
Unión inespecífica
Sim y Childers , 1997


Tomografía de Emisión de Positrones (PET)


Regulatory Molecule
Receptor
GDP
alpha beta gamma
G-Protein
Enzyme or Ion Channel

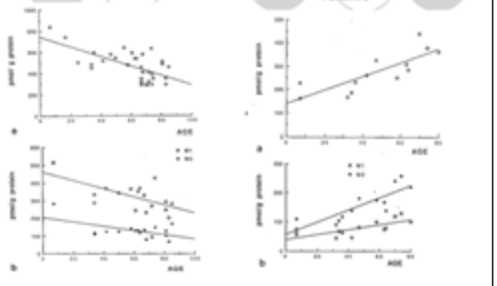

Receptores en Pediatría

Receptores en Pacientes de la Tercera Edad

Receptores Muscarínicos y Edad

Corteza Frontal

Tálamo

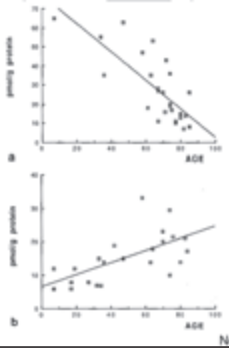


Nordberg et al., 1992

Receptores Nicotínicos en Cx. Cerebral y Edad

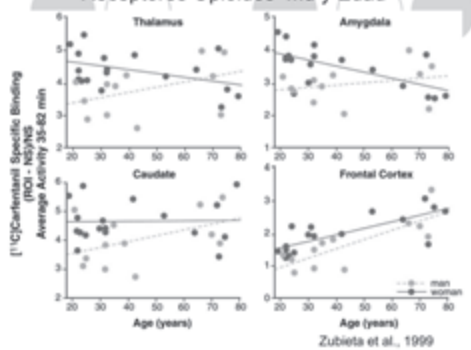
Corteza Frontal

Tálamo

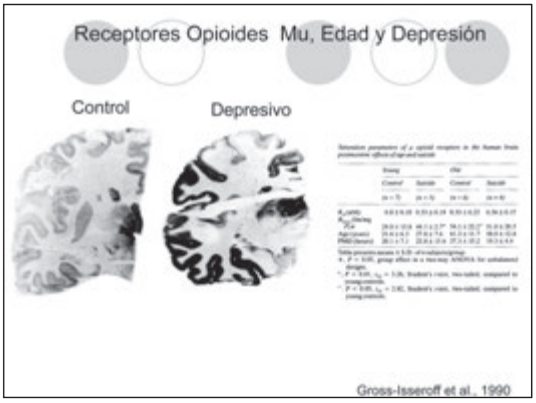


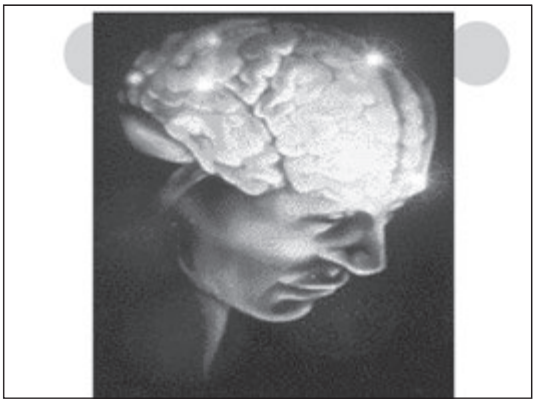
Nordberg et al., 1992

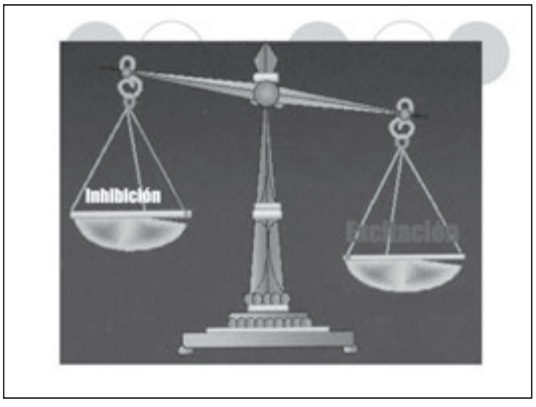
Receptores Opioides Mu y Edad

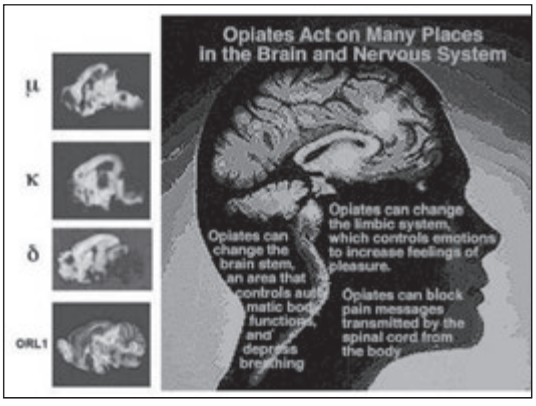


Zubieta et al., 1999

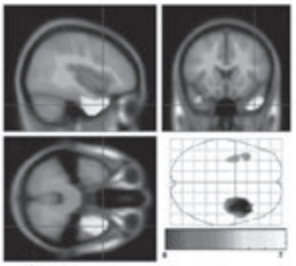

Receptores Opioides Mu, Edad y Depresión
Control
Depresivo
Gross-Isseroff et al., 1990




Inhibición
Excitación

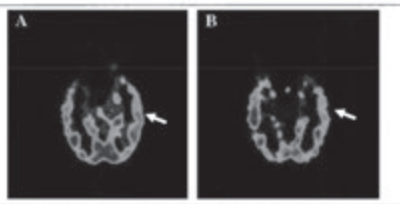

μ
κ
δ
ORL1
Opiates Act on Many Places in the Brain and Nervous System
Opiates can change the brain stem, an area that controls automatic body functions, and can depress breathing
Opiates can change the limbic system, which controls emotions to increase feelings of pleasure.
Opiates can block pain messages transmitted by the spinal cord from the body

Receptores a Opioides en Cerebro de Pacientes Epilépticos



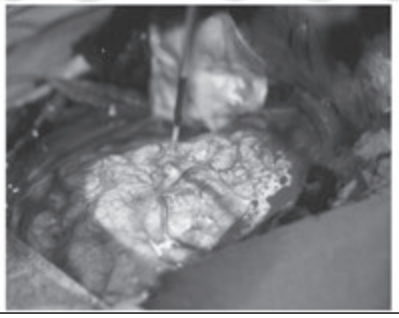
Hammers et al., 2007

Receptores a Opioides en Cerebro de Pacientes Epilépticos



Frost et al., 1988

Cirugía de Epilepsia



Características

	Autopsia	ELTM	Tumor o Lesión
Edad (años)	39.5 ± 3.4	35.53 ± 2.43	33.17 ± 2.94
Edad inicio (años)		7.54 ± 1.66	23.65 ± 4.99
* Duración de epilepsia (años)		27.99 ± 2.35	9.56 ± 2.98
Crisis al mes		12 ± 3.18	19.09 ± 9.18
Ansiedad y Depresión		58%	25%

Datos Clínicos de los Pacientes con ELTM

Paciente	Género	Edad (años)	Edad inicio crisis	Antecedentes	Lado del foco	Duración epilepsia (años)	Tipo de crisis	Frecuencia de crisis por mes	DAE	Hallazgos en la RMN
P56	M	27	4	Hipoxia Crisis febriles	Derecho	23	CPC	3	CBZ, LMG, CNZ	EMT derecha
P61	F	38	6	No	Izquierdo	32	CPC	3	OXCBZ	EMT izquierda
P68	F	29	8	No	Derecho	21	CPC	30	AVP, CLB	EMT derecha
P93	M	25	7	Hipoxia	Izquierdo	18	CPC	16	CBZ, CNZ	Hipotrofia hipocampal izquierda
P95	F	47	25	Trombosis cerebral postparto	Derecho	22	CPC MIOC	14	LMG, CNZ, ZNS	EMT derecha
P98	M	32	8	Hipoxia	Izquierdo	24	CPC	7.5	AVP, LMG, CLB	EMT izquierda
P104	M	60	6	No	Izquierdo	54	CPC	9	CBZ, LMT	EMT bilateral
P105	M	24	6	Hipoxia Crisis febriles	Derecho	18	CPC	4	AVP, TMP CNZ	EMT derecha
P107	M	34	6	TCE	Izquierdo	28	CPC	3	AVP, CBZ, CLB	EMT izquierda
P123	M	35	13	TCE	Izquierdo	22	CPC	12.5	AVP, CBZ, LMG	EMT izquierda
P125	M	45	17	No	Izquierdo	28	CPC CTCG	48	OXCBZ, TMP, CLB	EMT izquierda
P127	F	36	3	TCE Crisis febriles	Izquierdo	33	CPC EE	15	AVP, LMG OXCBZ,	EMT derecha

TCE, traumatismo craneoencefálico; MIO, Mioclonias; CPC, crisis parciales complejas; CTCG, Crisis tónico clónicas generalizadas; EE, estatus epiléptico; AVP, Acido Valpróico; CBZ, Carbamazepina; CLB, Clobazam; CNZ, Clonazepam; LMG, Lamotrigina; OXCBZ, oxcarbamazepina; TMP, Topiramato; ZNS, Zonizamida.

Datos Clínicos de los Pacientes con ELT Secundaria a Tumor o Lesión Cerebral

Paciente	Género	Edad (años)	Edad inicio crisis	Antecedentes	Lado del foco	Duración epilepsia (años)	Tipo de crisis	Número crisis (mes)	FAE	Diagnóstico final
P37	M	27	11	TCE	Derecho	16	CPC CTCG	32	DFH, CBZ	Astrocitoma
P54	F	34	1.33	TCE	Derecho	32.6	CPS CPC	36	CBZ, LMG	MAV
P92	F	27	27	TCE	Izquierdo	0.33	CTCG	1	DFH, AVP	Glioma temporal
P99	F	48	46	No	Izquierdo	2	CPC	16	AVP, CNZ	Lesión cerebral
P103	M	28	13	TCE Crisis febriles	Derecho	15	CPC	3	AVP, CBZ, CNZ	Neoplasia temporal
P112	M	40	40	No	Derecho	0.16	CTCG	1	DFH	Lesión frontal
P116	F	24	10	No	Izquierdo	14	CPC	102	CBZ	Glioma temporal
P119	M	32	28	No	Izquierdo	4	CPS CTCG	1	DFH, CBZ	Glioma temporal

TCE, traumatismo cráneoencefálico; CPC, crisis parciales complejas; CTCG, Crisis tónico clónicas generalizadas; DFH, difenilhidantoína, CBZ, Carbamazepina; LMG, Lamotrigina; AVP, Acido Valpróico; CNZ, Clonazepam; MAV, Malformación arteriovenosa

Receptores a Opioides en Cerebro de Pacientes Epilépticos

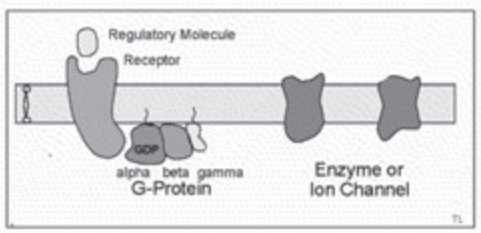
Receptores a Opioides Mu en Corteza de Pacientes Epilépticos

^{3}H-DAMGO

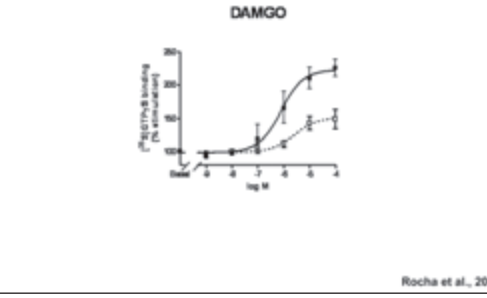
Capas	Autopsia	ELTM	Tumor/ Lesión
I-II	102±4	133±7 *	134±8 *
III-IV	102±5	139±8 **	144±8 *
V-VI	88±5	109±5 *	122±4 *

Valores expresados como promedio ± EE: *p<0.05, **p<0.01

Rocha et al., 2009

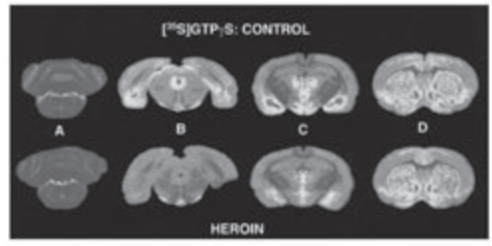


Efecto de la activación del receptor Mu en la activación de la proteína Gi



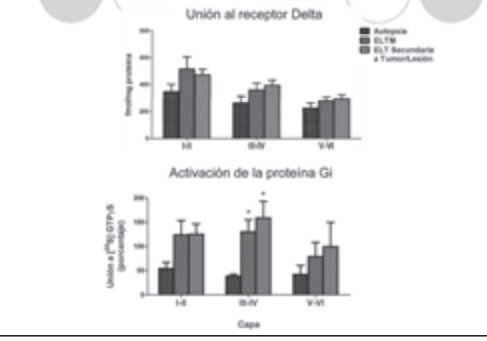
Rocha et al., 2009

La Administración Repetida de Heroína y la Epilepsia Desacoplan los Receptores a Opioides de la Proteína G

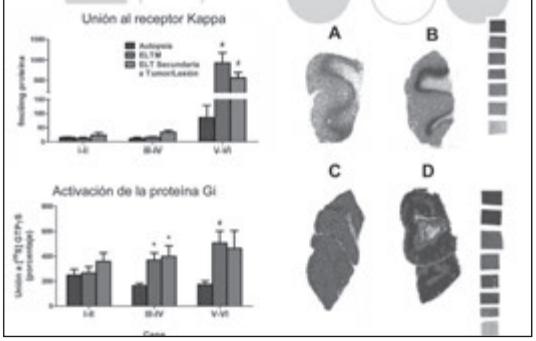


Sim-Selley et al., 2000

Receptores Delta Opioides en Corteza Cerebral



Receptores Kappa Opioides en Corteza Cerebral

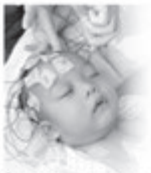


Correlación de Datos Clínicos con la Unión de Receptores a Opioides y Activación de Proteína G

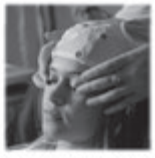
Datos Clínicos	Capas Corticales	MU	MU-[^{35}S]GTPγS	Delta	Delta [^{35}S]GTPγS	Kappa	Kappa [^{35}S]GTPγS
Edad del Paciente	I-II	+0.287	+0.169	+0.020	-0.110	-0.062	-0.236
	III-IV	+0.287	+0.028	+0.046	-0.205	-0.027	-0.112
	V-VI	+0.005	+0.030	-0.140	-0.272	+0.070	+0.321
Edad inicio epilepsia	I-II	+0.581**	+0.052	+0.226	-0.226	-0.297	-0.185
	III-IV	+0.572**	+0.502*	+0.372	-0.076	-0.224	-0.125
	V-VI	+0.457*	+0.126	+0.468*	+0.699*	+0.753*	-0.076
Duración epilepsia	I-II	-0.531**	+0.090	-0.394	+0.251	+0.136	+0.228
	III-IV	-0.539**	-0.335	0.006	+0.102	+0.346	+0.463
	V-VI	-0.524*	+0.114	0.082	-0.135	+0.296	+0.226
Frecuencia crisis	I-II	-0.186	-0.272	-0.159	-0.244	-0.226	-0.066
	III-IV	-0.303	-0.072	-0.022	0.065	-0.412	+0.068
	V-VI	-0.420	-0.227	-0.092	+0.262	-0.299	+0.023

Los valores representan la r de Pearson. * p<0.05; ** p<0.01

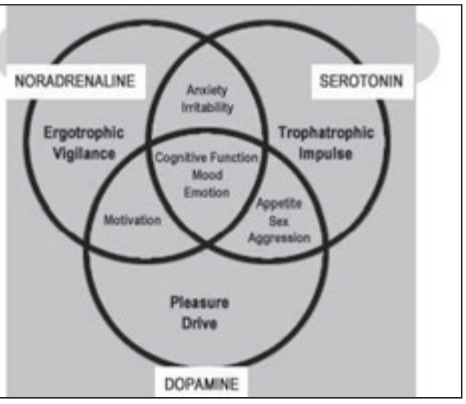
A mayor edad de adquisición de la epilepsia…

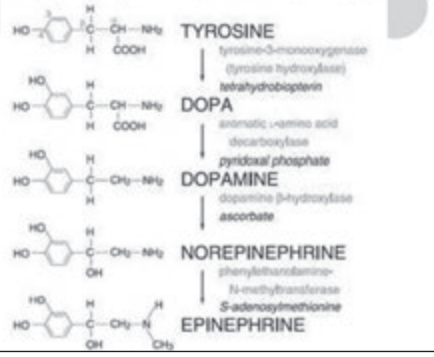


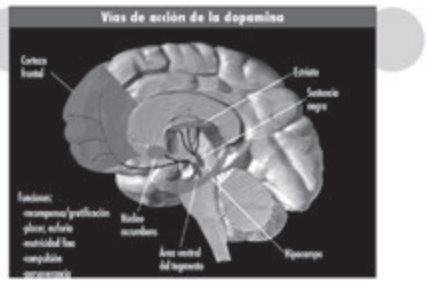
↑ Unión a receptores Mu, Delta y Kappa

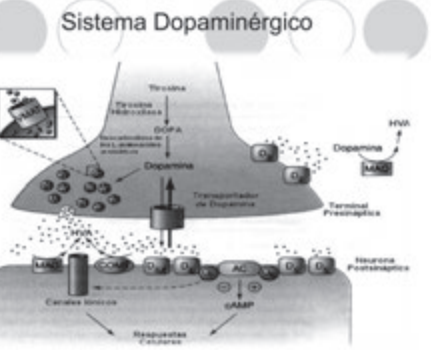


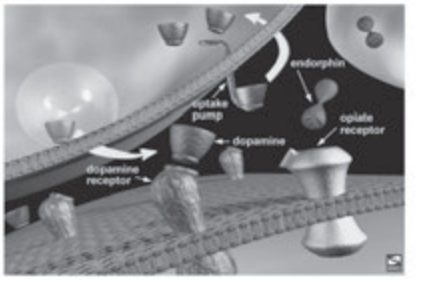
↑ Capacidad de estimulación de proteínas $G_{i/o}$ al activar los receptores Mu, Delta o Kappa



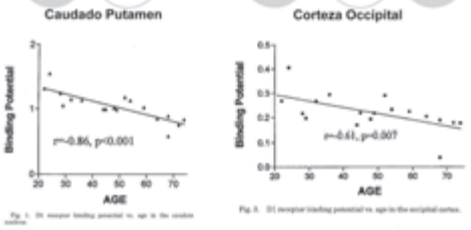

TYROSINE
tyrosine-3-monooxygenase
(tyrosine hydroxylase)
tetrahydrobiopterin
DOPA
aromatic L-amino acid
decarboxylase
pyridoxal phosphate
DOPAMINE
dopamine β-hydroxylase
ascorbate
NOREPINEPHRINE
phenylethanolamine-
N-methyltransferase
S-adenosylmethionine
EPINEPHRINE


Vías de acción de la dopamina
Cortex frontal
Estriado
Sustancia negra
Núcleo accumbens
Área ventral del tegmento
Hipocampo


Sistema Dopaminérgico
Tirosina
DOPA
Dopamina
HVA
Terminal Presináptica
Neurona Postsináptica
cAMP


endorphin
uptake pump
opiate receptor
dopamine
dopamine receptor

Receptores D1 y Edad



Wang et al., 1998

Receptores D2, Edad y Alteraciones Motoras y Cognitivas

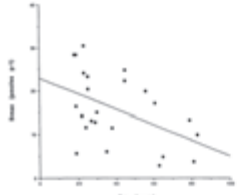
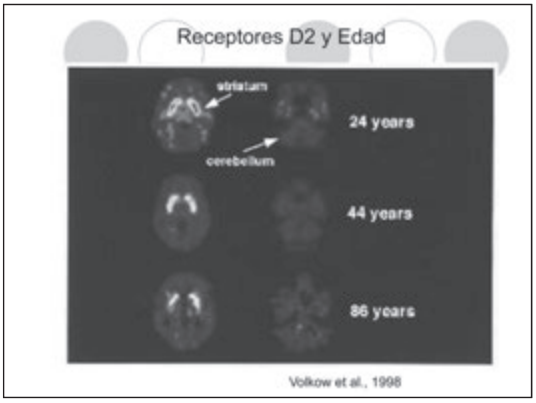
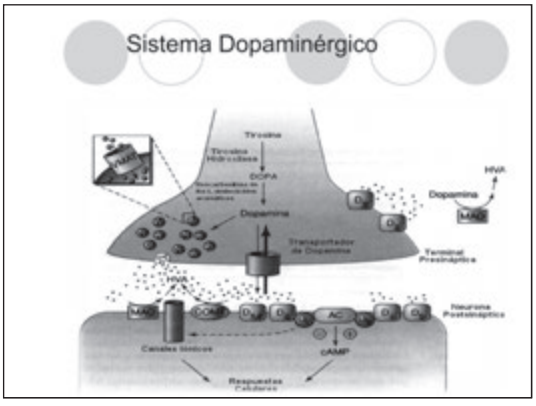


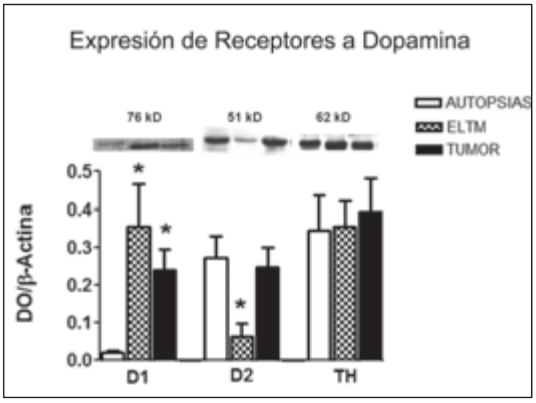
FIG. 4. B_{max} versus age of normal volunteers. The decline with age is clearly depicted (see text for details).

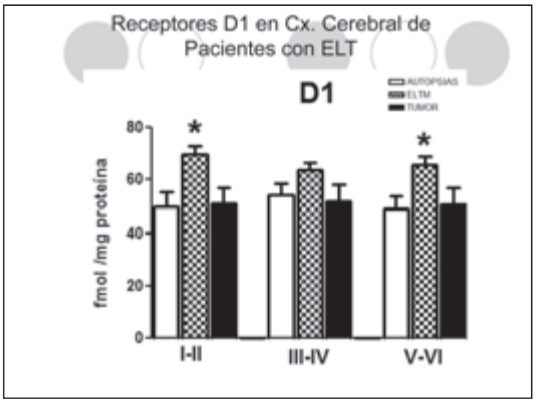
Wong et al., 1990

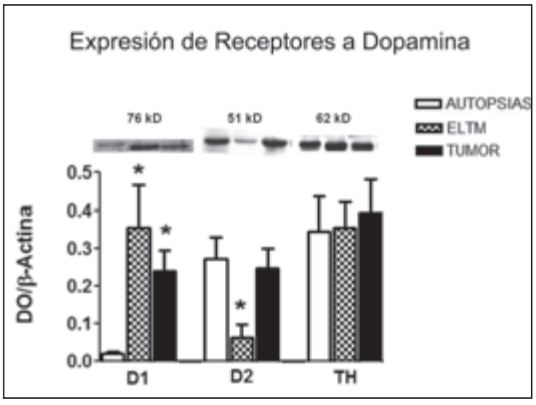
Volkow et al., 1998

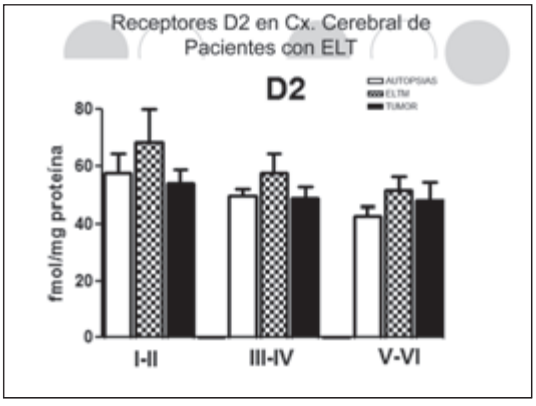

Receptores D2 y Edad
striatum
cerebellum
24 years
44 years
86 years
Volkow et al., 1998

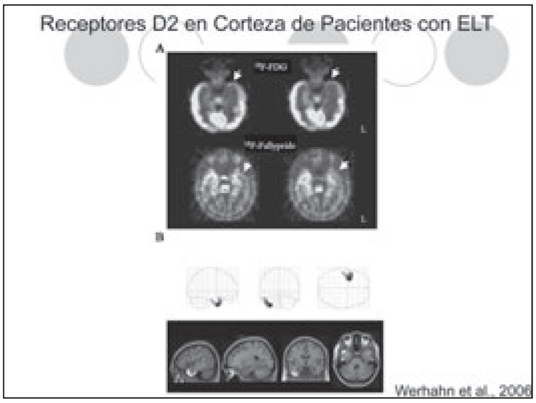

Sistema Dopaminérgico
Tirosina
DOPA
Dopamina
HVA
Transportador de Dopamina
Terminal Presináptica
Neurona Postsináptica
cAMP

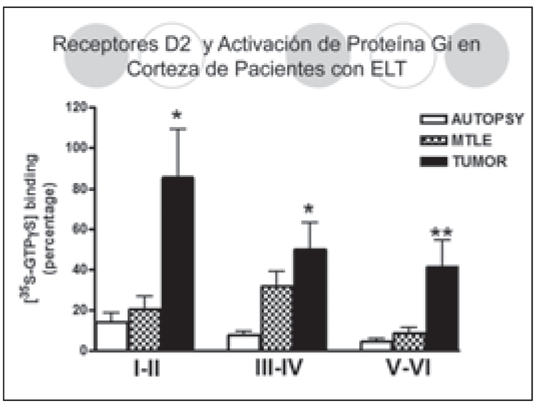

Expresión de Receptores a Dopamina
76 kD
51 kD
62 kD
AUTOPSIAS
ELTM
TUMOR
DO/β-Actina
0.5
0.4
0.3
0.2
0.1
0.0
D1
D2
TH


Receptores D1 en Cx. Cerebral de Pacientes con ELT
D1
AUTOPSIAS
ELTM
TUMOR
fmol /mg proteína
80
60
40
20
0
I-II
III-IV
V-VI


Expresión de Receptores a Dopamina
76 kD
51 kD
62 kD
AUTOPSIAS
ELTM
TUMOR
DO/β-Actina
0.5
0.4
0.3
0.2
0.1
0.0
D1
D2
TH


Receptores D2 en Cx. Cerebral de Pacientes con ELT
D2
AUTOPSIAS
ELTM
TUMOR
fmol/mg proteína
80
60
40
20
0
I-II
III-IV
V-VI

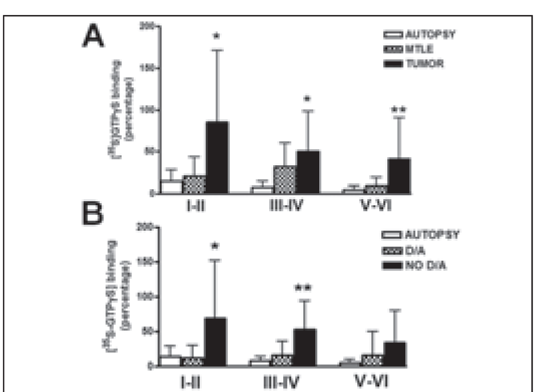




Correlaciones entre Datos Clínicos y la Unión a Receptores o al Transportador a Dopamina en Corteza de Pacientes con ELTM

Sitio de unión y ligando	Edad paciente	Edad inicio epilepsia	Duración epilepsia	Frecuencia de crisis epilépticas
D1 ^{3}H-SCH23390				
Capas I-II	-0.2768	-0.5261*	0.2568	-0.5503*
Capas III-IV	-0.3412	-0.5047*	-0.1467	-0.7180**
Capas V-VI	-0.1627	-0.6614**	-0.1718	-0.6740*
D2 ^{3}H-Raclopride				
Capas I-II	0.2799	0.6639*	-0.1467	-0.0951
Capas III-IV	0.0552	0.3602	-0.1718	-0.1580
Capas V-VI	0.2303	0.5718*	-0.0743	0.0232
D2 y Proteína G ^{35}S-GTPγS				
Capas I-II	0.184	-0.022	0.212	0.297
Capas III-IV	0.385	0.243	0.286	0.287
Capas V-VI	0.419	0.356	0.392	0.438

Los valores representan los coeficientes de correlación de Pearson.
* $p<0.05$, ** $p<0.01$



Correlaciones entre Datos Clínicos y la Unión a Receptores, al Transportador a Dopamina o activación de la proteína G en Corteza de Pacientes con ELTM y ansiedad y/o depresión.

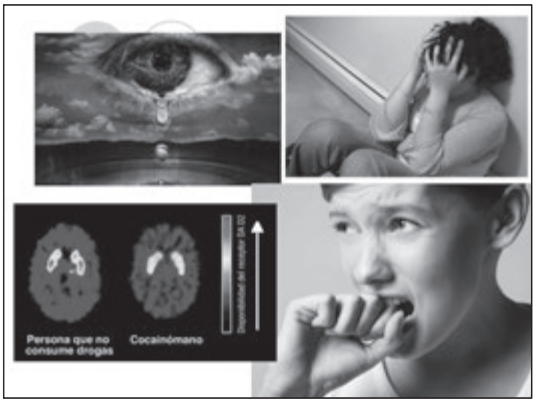
Unión y ligando	Edad del paciente	Edad de inicio	Duración epilepsia	Frequencia crisis
D1				
^{3}H-SCH23390				
Capas I-II	-0.0709	-0.5382	0.6093*	0.0290
Capas III-IV	0.0276	-0.2524	0.3335	-0.1158
Capas V-VI	-0.0790	-0.4785	0.5929*	-0.0224
D2				
^{3}H-Raclopride				
Capas I-II	0.4765	0.2854	0.0195	-0.0458
Capas III-IV	0.6629*	0.6148*	-0.0242	-0.0415
Capas V-VI	0.7186*	0.3586	0.1159	-0.0065
Transporter				
^{3}H-Mazindol				
Capas I-II	-0.0647	-0.3409	0.3705	0.0906
Capas III-IV	-0.0332	-0.5935*	0.7070*	0.0068
Capas V-VI	-0.0715	-0.3649	0.3948	0.1058
Proteina Gi				
^{35}S-GTPγS				
Capas I-II	-0.0761	-0.0227	-0.0313	-0.1337
Capas III-IV	0.4293	0.0042	0.4791	0.4807
Capas V-VI	-0.1026	0.3600	-0.4247	-0.3024

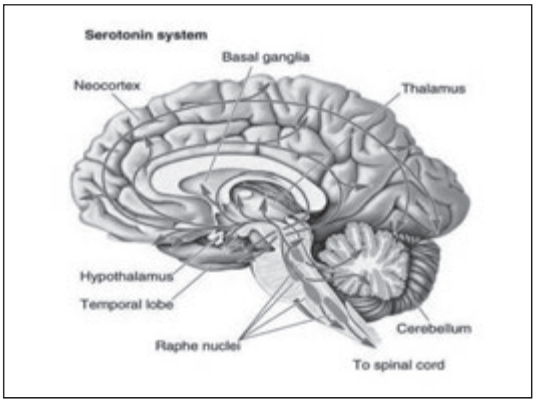
Los valores representan los coeficientes de correlación de Pearson.* p<0.05

Correlaciones entre Datos Clínicos y la Unión a Receptores, al Transportador a Dopamina o activación de la proteína G en Corteza de Pacientes con ELTM, sin ansiedad y/o depresión.

Unión y ligando	Edad paciente	Edad de inicio	Duración epilepsia	Frecuencia crisis
D1				
^{3}H-SCH23390				
Capas I-II	-0.0995	-0.2459	0.7333*	-0.0105
Capas III-IV	-0.3024	-0.0920	0.5810*	-0.1698
Capas V-VI	-0.0868	0.0070	0.4979*	-0.2982
D2				
^{3}H-Raclopride				
Capas I-II	-0.0994	0.0080	0.1682	-0.0590
Capas III-IV	-0.0557	0.0174	0.0945	-0.0663
Capas V-VI	0.0817	0.5085*	-0.2099	-0.2524
Transportador				
^{3}H-Mazindol				
Capas I-II	0.0885	-0.2371	-0.0536	0.4656*
Capas III-IV	0.0637	-0.3136	0.1346	0.6304*
Capas V-VI	0.1890	-0.2320	0.2188	0.3966
Proteina Gi				
^{35}S-GTPγS				
Capas I-II	0.1388	0.6633*	-0.5465*	-0.2739
Capas III-IV	0.5081*	-0.2191	-0.1876	-0.0840
Capas V-VI	0.5081*	-0.2959	-0.2401	-0.1941

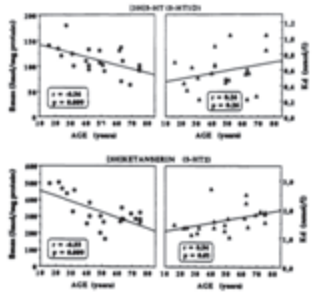
Los valores representan los coeficientes de correlación de Pearson.* p<0.05





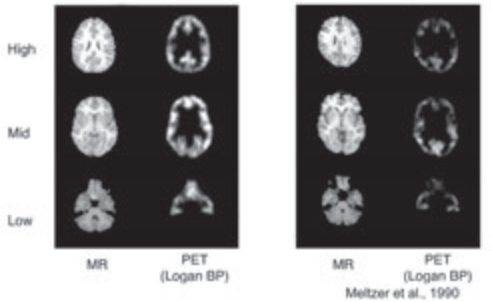
Receptores a Serotonina y Edad

Cx. Frontal



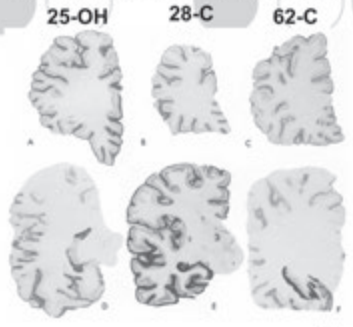
Arranz et al., 1993

Receptores 5-HT$_{2A}$ y Edad



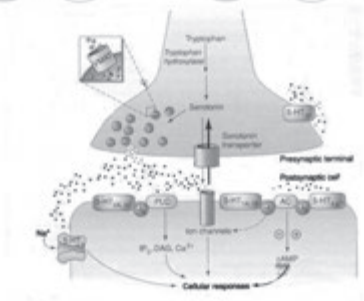
Meltzer et al., 1990

Receptores 5-HT$_{1A}$, Edad y Alcohol

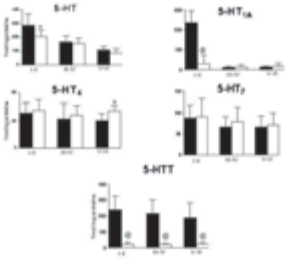


Dillon et al., 1991

Sistema Serotoninérgico

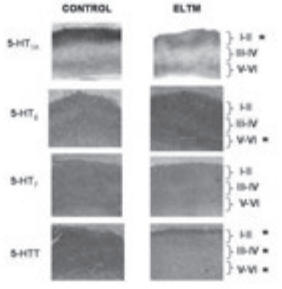


Receptores a Serotonina en Corteza de Pacientes con ELTM

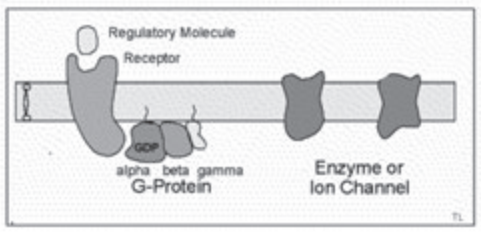


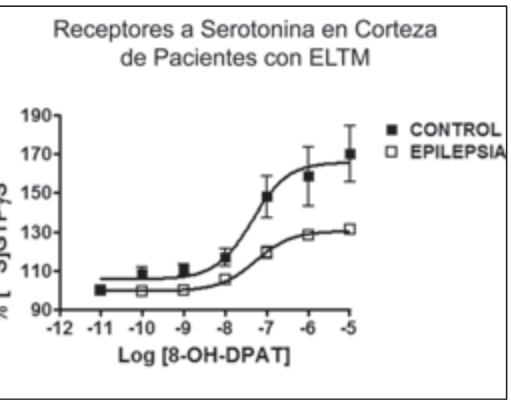
Rocha et al., 2007

Receptores a Serotonina en Corteza de Pacientes con ELTM

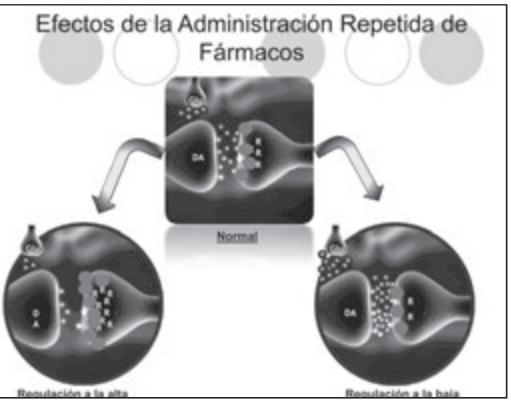


Rocha et al., 2007


Regulatory Molecule
Receptor
GDP
alpha beta gamma
G-Protein
Enzyme or
Ion Channel


Receptores a Serotonina en Corteza
de Pacientes con ELTM
CONTROL
EPILEPSIA
% [35S]GTPγS
190
170
150
130
110
90
-12 -11 -10 -9 -8 -7 -6 -5
Log [8-OH-DPAT]


Correlación de Datos Clínicos y Receptores a
Serotonina en Corteza de Pacientes con ELTM
Rocha et al. 2007


Efectos de la Administración Repetida de
Fármacos
DA
Normal
Regulación a la alta
Regulación a la baja

Tolerancia a los Efectos de Fármacos Antiepilépticos

TABLE 6. *Clinical evidence for tolerance to effect during prolonged administration of first-generation antiepileptic drugs*

Antiepileptic drug	Responder to nonresponder shift (in percentage of responders)	References
Acetazolamide	15% (3/20)	Lau et al. (185)
	55% (5/9)	Katayama et al. (186)
Benzodiazepines	36%	Robertson (111) (clobazam)
	27% (4/15)	Nanda et al. (189) (clonazepam)
	40% (52/175)	Sugai et al. (200) (clonazepam)
Carbamazepine	4% (2/48)	Canadian Study Group for Childhood Epilepsy (116)
Methsuximide	38% (3/8)	Browne et al. (176)
Phenytoin	7% (1/15)	Canadian Study Group for Childhood Epilepsy (116)
Phenobarbital	11% (2/18)	Mitchell and Chavez (187)
Sulthiame	19% (3/26)	Kragh et al. (184)
Valproate	58% (7/12)	Bonati et al. (177) (partial epilepsy)
	21% (6/28)	Klotz and Schweizer (183) (absence seizures)
	0 (0/11)	Feuerstein et al. (178) (idiopathic generalized epilepsy)

TABLE 7. *Clinical evidence for tolerance to effect during long-term administration of second- and third-generation antiepileptic drugs*

Antiepileptic drug	Responder-to-nonresponder shift (in percentage of responders)	References
Felbamate	11% (6/56)	Cilio et al. (175)
Gabapentin	7% (2/27)	McDonnell and Mizrahi (118)
	8% (1/12)	Stevanin et al. (139)
Lamotrigine	80% (12/15)	Kim-Weiler et al. (125)
	1% (1/127)	McDonnell and Mizrahi (118)
Levetiracetam	15% (6/26)	Brunetto et al. (174)
	5% (5/107)	Mouracks and Mimken-Jaggi (95)
	19% (68/362)	Abou-Khalil and Lacombe (122)
	27% (4/15)	Ben-Menachem et al. (114)
Oxcarbazepine	14% (51/356)	Novartis, data on file (190)
Pregabalin	12% (66/205)	Pfizer, data on file (192)
Stiripentol	16% (15/94)	Perez et al. (191)
Topiramate	20% (2/10)	Privitera (193)
	47% (7/15)	Mohamed et al. (188)
Vigabatrin	12% (12/100)	McDonnell and Mizrahi (118)
	33% (5/15)	Pellock et al. (123) at 5 years
Zonisamide	23% (8/35)	Kanazawa et al. (126)

Lösher and Schmidt, 2006

Tolerancia a los Efectos de Fármacos Antiepilépticos

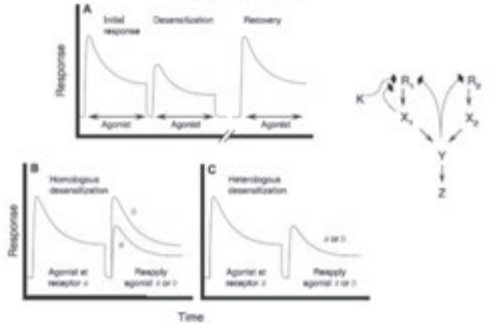
TABLE 2. *Evidence for loss of antiepileptic efficacy (i.e., tolerance) during prolonged treatment with AEDs in animal models*

AED	Evidence for functional tolerance in animal models: Kindled rats	Electrical or chemical seizure models in rodents	Epileptic rodents	Chemical seizure induction in dogs	Representative references
First-generation AEDs					
Benzodiazepines	Yes	Yes	Yes	Yes	Killam et al. (181); Frey et al. (179); File (63); Frey et al. (62a); Lescher and Schwab (96); Rosenberg et al. (71); Schmidt et al. (63); Lescher (56); Haigh and Feely (60); Schmidt et al. (64); Lescher and Rundfeldt (28); Schmidt et al. (195); Rundfeldt et al. (24); Pomes et al. (69); Lescher et al. (65)
Carbamazepine	Yes	Yes	?	?	Marcelis et al. (196); Wilensky and Lescher (52)
Ethosuximide	?	Yes	No	?	Frey and Kampmann (54); Wahle and Frey (39)
Phenobarbital	Yes	Yes	Yes	?	Frey and Kampmann (54); Marcelis et al. (196); Schmidt et al. (40); Bourgeois (30); Lescher and Wilensky (53); Leite and Cavalheiro (35)
Phenytoin	Yes	Yes	?	?	Frey and Kampmann (54); Marcelis et al. (196); Rundfeldt and Lescher (66)
Primidone	Yes	?	?	?	Lescher and Wilensky (53)
Valproate	Yes[a]	No	Yes/No[b]	?	Lescher and Nau (59); Lescher (56); Lescher et al. (56); Wahle and Frey (39); Leite and Cavalheiro (35)
Second- and third-generation AEDs					
Felbamate	?	No	?	?	Irwin et al. (202)
Gabapentin	?	?	?	?	
Lamotrigine	Yes	?	?	?	Kragh et al. (55); Zhang et al. (205)
Levetiracetam	Yes	Yes/No[c]	Yes	?	Klitgaard et al. (67); Lescher and Wilensky (53); Glien et al. (36); Zhang et al. (60)
Oxcarbazepine	?	No	?	?	Schmutz et al. (197)
Pregabalin	?	?	?	?	
Tiagabine	?	No	?	?	Smith (201)
Topiramate	?	?	?	?	
Vigabatrin	Yes	Yes	Yes	?	Lescher (55); Lescher and Frey (53); Rundfeldt and Lescher (25)
Zonisamide	Yes	?	?	?	Shimoda et al. (61)

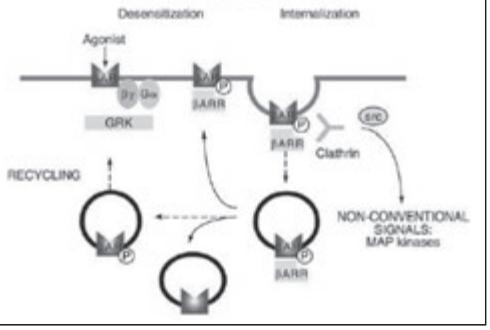
[a] no published data were found.
[b]Not much more complex pattern compared with other AEDs.
[c]Depending on seizure type studied (see text).
[d]Depending on the dose of levetiracetam being administered.

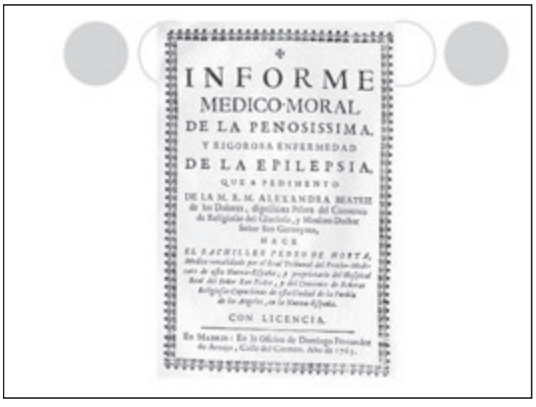
Losher and Schmidt, 2006

Efectos de la Administración Repetida de Fármacos



Efectos de la Administración Repetida de Fármacos




INFORME
MEDICO-MORAL
DE LA PENOSISSIMA,
Y RIGOROSA ENFERMEDAD
DE LA EPILEPSIA,
CON LICENCIA.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HOSPITAL GENERAL DE MEXICO
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Dra. Lilia Morales Chacón
Dra. Lourdes Lorigados Pedre

Gregory Cascino (USA)

TUMORS AND EPILEPSIES

Arturo Carpio (Ecuador)

ALADE CONFERENCE: NEUROCISTICERCOSIS AS ETIOLOGY OF SYMPTOMATIC EPILEPSY

6TH. Latin-American Summer School on Epilepsy (LASSE VI)

"Symptomatic epilepsy: A critical updating"

(São Paulo, 24 Feb-3 March 2012)

"Neurocysticercosis as etiology of symptomatic epilepsy"

Arturo Carpio, M.D.
School of Medicine
University of Cuenca, Ecuador

Carpio A, 2012 1

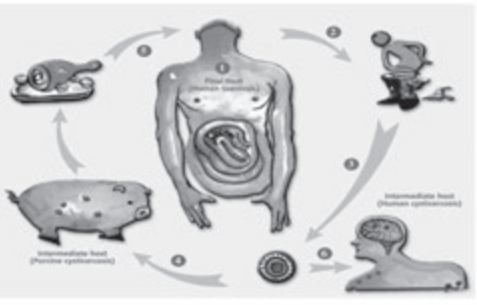
Neurocysticercosis and Epilepsy

- Epidemiology and definitions of NC and epilepsy
- Seizures, the main clinical manifestation of NC
- NC as an etiology of epilepsy in developing countries
- Does antihelmintic treatment improve seizures recurrence due to NC?
- Prognosis of epilepsy in patients with NC
- Conclusions and recommendations

Epidemiology of Cysticercosis

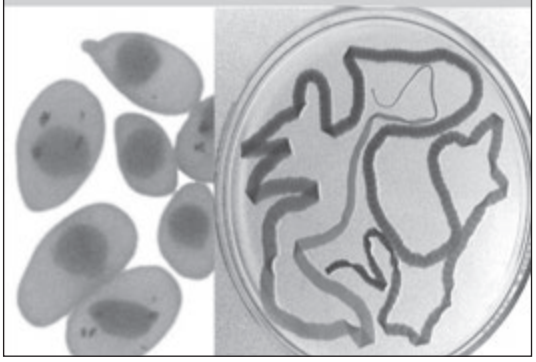
- Taeniasis/Cysticercosis are distributed worldwide
- Infection is imported by migrant workers into the USA, Spain, and other developed countries
- T/C is an emerging infection and a current public health problem

Lyfe Cicle of Taeniasis/Cysticercosis *

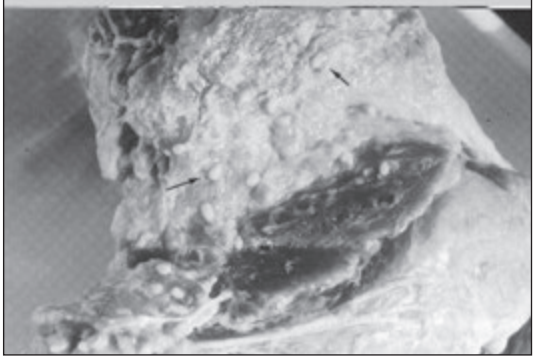


* Carpio A. Neurocysticercosis: An update. Lancet Infect Dis. 2002;2:751-762

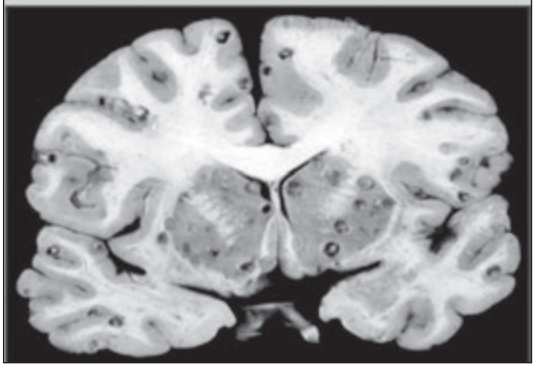
Taenia Solium & Cysticercus



Pork Cysticercosis



Human Brain Cisticercosis



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PLoS

A Systematic Review of the Frequency of Neurocysticercosis with a Focus on People with Epilepsy

Patrick C. Ndimubanzi[1], Hélène Carabin[1*], Christine M. Budke[2], Hai Nguyen[1], Ying-Jun Qian[1], Elisabeth Rainwater[1], Mary Dickey[1], Stephanie Reynolds[1], Julie A. Stoner[1]

Background: The objective of this study is to conduct a systematic review of studies reporting the frequency of neurocysticercosis (NCC) worldwide.

Methods/Principal Findings: PubMed, Commonwealth Agricultural Bureau (CAB) abstracts and 23 international databases were systematically searched for articles published from January 1, 1990 to June 1, 2008. Articles were evaluated for inclusion by at least two researchers focusing on study design and methods. Data were extracted independently using standardized forms. A random-effects-binomial model was used to estimate the proportion of NCC among people with epilepsy (PWE). Overall, 1,565 articles were retrieved and 290 (51%) selected for further analysis. After a second analytic phase, only 4.5% of articles, all of which used neuroimaging for the diagnosis of NCC, were reviewed. Only two studies, both from the US, estimated an incidence rate of NCC using hospital discharge data. The prevalence of NCC in a random sample of village residents was reported from one study where 9.1% of the population harboured brain lesions of NCC. The proportion of NCC among different study populations varied widely. However, the proportion of NCC in PWE was a lot more consistent. The pooled estimate for this population was 29.0% (95%CI: 22.9%–35.5%). These results were not sensitive to the inclusion or exclusion of any particular study.

Conclusions/Significance: Only one study has estimated the prevalence of NCC in a random sample of all residents. Hence, the prevalence of NCC worldwide remains unknown. However, the pooled estimate for the proportion of NCC among PWE was very robust and could be used, in conjunction with estimates of the prevalence and incidence of epilepsy, to estimate this component of the burden of NCC in endemic areas. The previously recommended guidelines for the diagnostic process and for declaring NCC an international reportable disease would improve the knowledge on the global frequency of NCC.

Citation: Ndimubanzi PC, Carabin H, Budke CM, Nguyen H, Qian Y-J, et al. (2010) A Systematic Review of the Frequency of Neurocysticercosis with a Focus on People with Epilepsy. PLoS Negl Trop Dis 4(11): e870. doi:10.1371/journal.pntd.0000870

Epidemiology of Cysticercosis *

- EITB +: 8% - 12% in Latin America
- Useful for identification of individuals who have had systemic contact with the parasite at some time.
- Seropositivity does not mean active systemic infection or CNS involvement

- Brain cysticercosis in autopsies: ~ 1%

Epidemiology of Epilepsy

Developing countries*	Developed countries **
Prevalence of active epilepsy: 7-12/1.000	Prevalence of active epilepsy : 5-7 /1.000
Incidence: ~ 120/100.000	Incidence: 50-70/100.000

* Carpio A, Hauser WA. Epilepsy in the developing world. Current neurology and neuroscience reports. 2009;9(4):319-26

** Hauser A, Epilepsy: frequency, causes and consequences. NY: Demos Press; 1990

Neurocysticercosis and Epilepsy: Definitions *

- Epilepsy is the name for a group of functional disorders of the brain that are characterized by repetitive seizures. Epilepsy is caused by abnormal, excessive electric discharges of the nerve cells or neurons in the brain.
- A first and single seizure should be clearly distinguished from "epilepsy," as this has important implications

* ILAE's Commission. Guidelines for epidemiological studies on epilepsy. Epilepsia 1993;34:592-596

Neurocysticercosis and Epilepsy: Definitions *

Acute symptomatic seizures are events, occurring in close temporal relationship with an acute CNS insult, which may be metabolic, toxic, structural, infectious, or due to inflammation. The interval between the insult and the seizure may vary according to the underlying clinical condition.

* Beghi E, Carpio A, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010 Apr;51(4):671-5.

Table A1. Examples of acute symptomatic seizures in association with disruption of the structural or functional integrity of the brain

Cause (Annegers et al., 1995; Beghi et al., 2010)	Period of occurrence	Notes/Exceptions
Cerebrovascular disease (Labovitz et al., 2001; Camilo & Goldstein, 2004; Haut[illegible] et al., 2009)	First 7 days	
Traumatic brain injury (Jennett, 1975a,b; Jennett et al., 1973; Frey, 2003; Haut[illegible] et al., 2009)	First 7 days	Includes intracranial surgery. Longer intervals are acceptable for subdural hematoma in the absence of known trauma or at first identification of new hematoma. Subsequent seizures are unprovoked.
CNS infection (Haut[illegible] et al., 2009; Beghi et al., 2010)	First 7 days	Includes seizures occurring after 7 days in patients with persistent clinical and/or laboratory signs of infection
Neurocysticercosis	Presence of parasites in transitional or degenerative phase by imaging	Includes seizures occurring in the presence of[illegible] forms. Seizures occurring with viable parasites (cystic phase) or calcified granuloma (calcified phase) are unprovoked
Hydrocephalus	Presence of[illegible] and motor symptoms	
Postinfarct neurologic syndrome	Clearance of parasitemia, associated with fever and psychosis	
Cerebral tuberculoma	During treatment	Seizures occurring after successful treatment are unprovoked
Brain abscess	During treatment	Seizures occurring after successful treatment are remote symptomatic
HIV infection	Acute infection or with severe metabolic disturbances	Seizures occurring in the absence of opportunistic CNS infections or severe metabolic disturbances are unprovoked
Arteriovenous malformations	In the presence of acute hemorrhage	All other seizures are unprovoked
Multiple sclerosis	First presenting symptom within 7 days of relapse	—
Autoimmune diseases	Signs or symptoms of activation	—

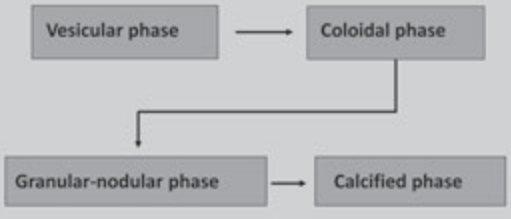
Thurman DJ, et al. ILAE Commission on Epidemiology. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia. 2011 Sep;52 Suppl 7:2-26.

Table A2. Comorbid conditions associated with epilepsy

Categories	
Psychiatric disorders (Hesdorffer et al., 2000; Gaitatzis et al., 2004; Hesdorffer et al., 2004; Qin & Nordentoft, 2005; Qin et al., 2005; Hesdorffer et al., 2006, 2007)	Mood disorders, anxiety disorders, alcohol related disorders, somatoform disorders, attention deficit hyperactivity disorders, schizophrenia and psychotic disorders, personality disorders, suicidality
Somatic disorders (Gaitatzis et al., 2004)	Stroke, cardiovascular disease, diabetes mellitus, migraine, asthma and other pulmonary conditions, celiac disease and other gastrointestinal disorders, osteoporosis and osteopenia
Infectious disease (Carpio et al., 1998)	Neurocysticercosis
Intoxications (Kubore et al., 1996; Mion et al., 2009)	Possibly onchocerciasis and toxocara
Cognitive disorders (Elger et al., 2004; Sillanpaa, 2004; Hermann & Seidenberg, 2007)	Cognitive impairment, learning disability
Disabilities (Gaitatzis et al., 2004)	Hearing and vision loss
Accidents (Tomson et al., 2004)	Accidents and injuries
Nutritional problems (Crepin et al., 2007)	Malnutrition

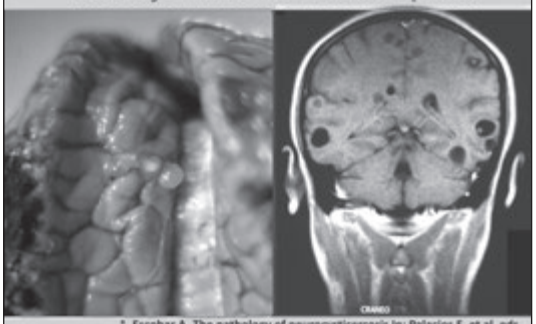
Thurman DJ, et al. ILAE Commission on Epidemiology. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia. 2011 Sep;52 Suppl 7:2-26.

Pathophysiology of Neurocysticercosis



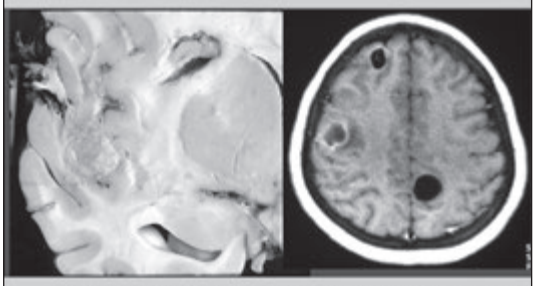
* .Escobar A. The pathology of neurocysticercosis In: Palacios E, et al, eds. Cysticercosis of Central Nervous System. Springfield: Charles C Thomas 1983:27-54.

Neurocysticercosis: Vesicular phase



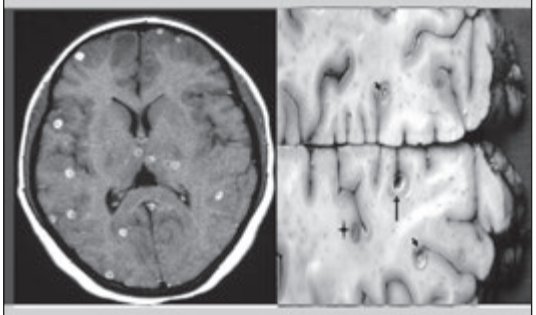
* .Escobar A. The pathology of neurocysticercosis In: Palacios E, et al, eds. Cysticercosis of Central Nervous System. Springfield: Charles C Thomas 1983:27-54.

Neurocysticercosis: coloidal phase*



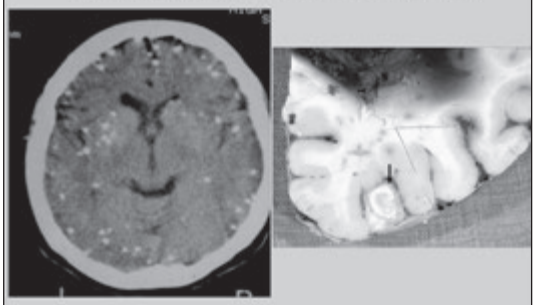
* .Escobar A. The pathology of neurocysticercosis In: Palacios E, et al, eds. Cysticercosis of Central Nervous System. Springfield: Charles C Thomas 1983:27-54.

NC: granular-nodular phase *



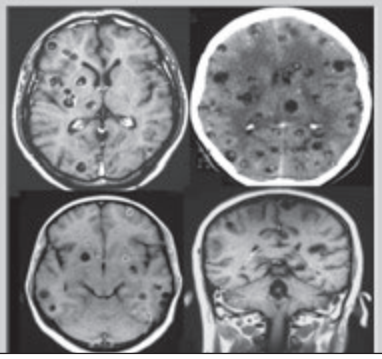
* .Escobar A. The pathology of neurocysticercosis In: Palacios E, et al, eds. Cysticercosis of Central Nervous System. Springfield: Charles C Thomas 1983:27-54.

Neurocysticercosis: Calcified phase



* .Escobar A. The pathology of neurocysticercosis In: Palacios E, et al, eds. Cysticercosis of Central Nervous System. Springfield: Charles C Thomas 1983:27-54.

Typical Images of Neurocysticercosis



Classification of Neurocysticercosis*

Viability

- **Active:** parasite is alive, vesicular phase
- **Transitional:** parasite in degenerative form
- **Inactive:** parasite is dead, calcified phase

Location

- **Parenchymal**
- **Extraparenchymal**

*

Carpio A, Placencia M, Santillán F, Escobar A. Proposal for a new classification of neurocysticercosis Can J Neurol Sci 1994;21:43-7.

Classification and Clinical Manifestations in 336 Patients with Neurocysticercosis.*

VIABILITY Location	Patients n (%)	Seizures n (%)	LH n (%)	M.A. n (%)	C.N.A * n (%) *
ACTIVE					
Parenchymal	90 (26.7)	74 (82)	9 (10)	22 (24)	14 (15)
Extraparenchymal	7 (2.1)	0	6 (86)	1 (14)	2 (10)
Parench. + Extraparen.	28 (8.3)	12 (43)	24 (86)	8 (28)	10 (38)
TRANSITIONAL					
Parenchymal	82 (24.4)	72 (88)	15 (18)	12 (14)	12 (14)
Meningeal	10 (2.9)	2 (20)	10 (100)	1 (10)	6 (60)
Parench. + Mening.	18 (5.3)	6 (33)	16 (89)	6 (33)	14 (78)
INACTIVE					
Parenchymal	87 (25.9)	66 (75)	0	3 (3)	7 (8)
Meningeal	14 (4.1)	7 (50)	12 (86)	2 (14)	6 (4)
TOTAL	336 (100)	239 (71)	92 (27)	55 (16)	71 (21)

Neurocysticercosis and Epilepsy

- Epidemiology and definitions of NC and epilepsy
- Seizures, the main clinical manifestation of NC
- NC as an etiology of epilepsy in developing countries
- Does antihelmintic treatment improve seizures recurrence due to NC?
- Prognosis of epilepsy in patients with NC
- Conclusions and recommendations

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Clinical Manifestations Associated with Neurocysticercosis: A Systematic Review

Hélène Carabin[1]*, Patrick Cyaga Ndimubanzi[1], Christine M. Budke[2], Hai Nguyen[1], Yingjun Qian[3], Linda Demetry Cowan[1], Julie Ann Stoner[1], Elizabeth Rainwater[4], Mary Dickey[5]

Abstract

Background: The clinical manifestations of neurocysticercosis (NCC) are poorly understood. This systematic review aims to estimate the frequencies of different manifestations, complications and disabilities associated with NCC.

Methods: A systematic search of the literature published from January 1, 1990, to June 1, 2008, in 24 different electronic databases and 8 languages was conducted. Meta-analyses were conducted when appropriate.

Results: A total of 1569 documents were identified, and 21 included in the analysis. Among patients seen in neurology clinics, seizures/epilepsy were the most common manifestations (78.8%, 95%CI: 65.1%–89.7%) followed by headaches (37.9%, 95%CI: 23.3%–53.7%), focal deficits (16.6%, 95%CI: 9.7%–23.6%) and signs of increased intracranial pressure (11.7%, 95%CI: 6.0%–18.9%). All other manifestations occurred in less than 10% of symptomatic NCC patients. Only four studies reported on the mortality rate of NCC.

Conclusions: NCC is a pleomorphic disease linked to a range of manifestations. Although definitions of manifestations were very rarely provided, and varied from study to study, the proportion of NCC cases with seizures/epilepsy and the proportion of headaches were consistent across studies. These estimates are only applicable to patients who are ill enough to seek care in neurology clinics and likely over estimate the frequency of manifestations among all NCC cases.

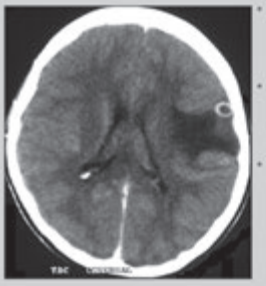
Citation: Carabin H, Ndimubanzi PC, Budke CM, Nguyen H, Qian Y, et al. (2011) Clinical Manifestations Associated with Neurocysticercosis: A Systematic Review. PLoS Negl Trop Dis 5(5): e1152. doi:10.1371/journal.pntd.0001152

Clinical heterogeneity of NC *

- Variability in the clinical forms of expression and evolution of NC are well recognized, but attempts in classification have been oriented more towards medical diagnosis and clinical management of NC than to its possible causes
- Factors that contribute to clinical heterogeneity of NC:
  - parasite: developmental phases, size, number and location, genetics of taenia solium
  - host: age, gender, genetics, immunological status and inflamation
  - environment

* Fleury A, et al. Clinical heterogeneity of human neurocysticercosis results from complex interactions among parasite, host and environmental factors. Trans R Soc Trop Med Hyg (2010)

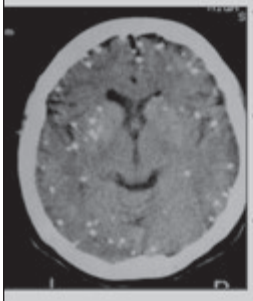
Neurocysticercosis and Seizures



- Seizures are the most common symptom of NC (60 – 90 %)
- Seizures may occur at any evolutionary stage of the parasite
- Acute seizures are more frequent with the transitional form due to the inflammatory brain reaction

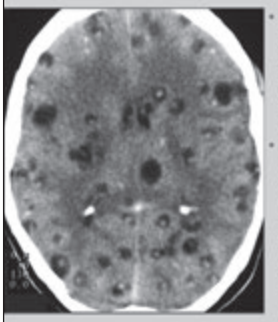
* Carpio A, Escobar A, Hauser WA. Cysticercosis and epilepsy: A critical review. Epilepsia 1998,39:1025-40

Neurocysticercosis and Seizures



- Risk of seizure recurrence (i.e. epilepsy), probably occurs in the inactive or calcified form
- This has been attributed to residual perilesional gliosis that results in chronic epileptogenic foci
- Parasite location may be remote from the apparent epileptogenic region

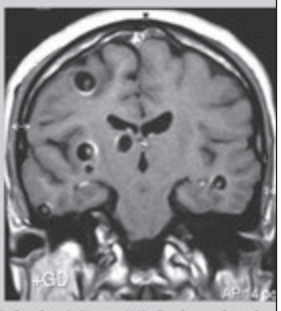
Relationship between NC and epilepsy



- There is no correlation between the NC burden of lesions and the severity of the epilepsy
- Patients with severe refractory seizures may have only one calcified lesion; on the other hand, there are patients with multiple cysts or calcifications but not epilepsy

Relationship between NC and epilepsy

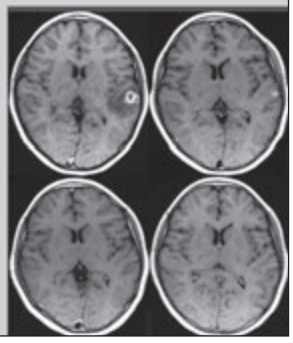
- There are inconsistencies in the link between epilepsy and NC
- NC and epilepsy are common diseases in most developing countries
- Because of their high prevalence, a causal as well as fortuitous relationship between the two conditions might independently exist



* Carpio A, Escobar A, Hauser WA. Cysticercosis and epilepsy: A critical review. Epilepsia 1998,39:1025-40

Single enhancing lesion and seizures

- The patients, mainly children and young adults, have some benign and transitory clinical manifestations, predominantly partial or partial secondary generalized seizures, and occasionally Todd's paresis or focal neurological deficits



Single enhancing lesion and seizures *

- SECTL are benign and tend to resolve spontaneously (3-6 months), without anticysticercal drugs or surgery
- The parasite is already in the degenerative phase and will eventually disappear or become calcified.
- Treatment should be limited to medication required to control the acute sympoms symptoms, such as antiepileptic medication

* Pal DK, Carpio A, Sander JWAS. Neurocysticercosis and Epilepsy. J Neurol Neurosurg Psychiatry 2000;68 137-143

- Kelvin EA, Carpio A, et al. Seizure in people with newly diagnosed active or transitional neurocysticercosis. Seizure. 2011 ;20:119-25

  Children, those with cysts in parenchymal locations, and those with a higher number of cysts appear to be more likely to experience seizure when they have NC cysts in the active or transitional stage
- Saenz B, et al. Neurocysticercosis: clinical, radiologic, and inflammatory differences between children and adults. Pediatr Infect Dis J 2006;25:801–3.

  Children more frequently suffer from a single degenerating parasite located in the parenchyma, while multiple viable parasites located in the basal SA cisterns are more common in NC adult patients

Kelvin EA, Carpio A, et al. Investigation of familial aggregation of seizures in neurocysticercosis patients. Epilepsy Res. 2009;84:67-71

We examined whether there is familial aggregation of seizures in first-degree relatives of NC patients with seizure versus NC patients without seizure : There was no trend toward familial aggregation of seizures in NCC patients

Velasco TR, et al Calcified cysticercotic lesions and intractable epilepsy: across sectional study of 512 patients. JNNP 2006;77:485–8.

NC is an uncommon cause of intractable epilepsy, even in an endemic region such as Brazil, and that it may only represent a coexistent pathology.

Kelvin EA, Carpio A, et al. The association of host age and gender with inflammation around neurocysticercosis cysts. Ann Trop Med Parasitol. 2009;103:487-99

- **In the Poisson model, the number of transitional cysts was found to be 1.8-fold higher in the female patients than in the male, and this gender effect was not only statistically significant (p >02) but also constant over time**
- **It therefore appears that there are significant gender and age differences in the local immune response to NCC, even after adjusting for differences in healthcare access.**

Nash TE et al. Perilesional brain oedema and seizure activity in patients with calcified neurocysticercosis: a prospective cohort and nested case–control study. *Lancet Neurol* 2008;7: 1099–105

- **110 patients with only calcified lesions and seizures were followed to assess seizure relapse. Perilesional oedema was assessed by MRI at the time of seizure in 110 symptomatic patients**
- **29 patients had an incident seizure during a median follow up of 32 months, with an estimated 5-year seizure incidence of 36%. Perilesional oedema was seen in 12 patients (50%)**
- **Perilesional oedema is common and associated with episodic seizure activity in patients with calcified NC.**

E.E.G. Abnormalities and NC

- EEG is abnormal in 30 to 50% of patients with NC
- Correlation between CT/MR lesions and localizing or lateralizing EEG abnormalities has been reported for only 15% to 30% of patients
- Calcifications are the origin of the epileptogenic lesion in < 50% of the cases
- A non-causal relationship between epilepsy and cysticercosis in some cases might explain these apparent discrepancies

Sakamoto AC et al. Cysticercosis and Epilepsy. In, Kotagal P, Luders HO, eds. The Epilepsies: Etiologies and Prevention. San Diego: Academic Press, 1999. 275-82.

Neurocysticercosis and Epilepsy

- Epidemiology and definitions of NC and epilepsy
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Frequency of NC as etiology of epilepsy

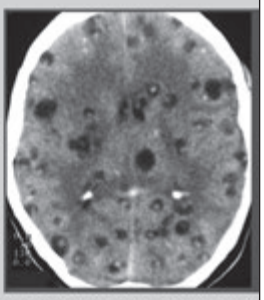
- It is extremely difficult to compare studies of epilepsy due to NC
- These studies are few, and mainly directed at single seizures, instead of epilepsy
- Almost all the studies are prevalent case-series, which are not useful for identifying etiology
- There are broad differences in the definition of epilepsy and NC (if any)
- What is the real burden of NC as a etiology of epilepsy?

Diagnosis of Neurocysticercosis

- Clinical features: focal neurological deficit and/or seizures, that appears and disappears spontaneously, over several years, according to the evolutionary phases of the parasite.
- CSF: inflammatory signs very similar to other granulomatous meningitis (Tb, mycosis, etc).
- Immunologic serum test (ELISA and EITB): limited utility in NC.

Diagnosis of Neurocysticercosis*

- CT scan and MRI are the main tools in NC diagnosis (gold standard) *
- MRI is superior for intraventricular or subarachnoid cysts, while CT is better for calcifications
- Typical image: viable cyst with a mural nodule (scolex) - multiple cysts in different pathological stages



* Carpio A. Neurocysticercosis: an update. Lancet Infect Dis. 2002;2:751-762

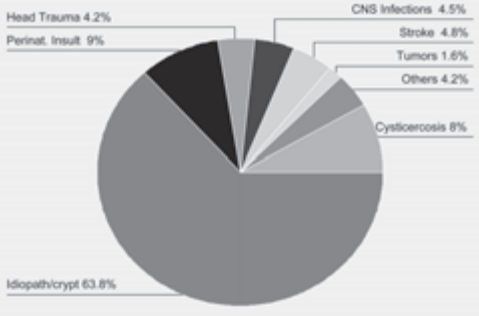
Neurocysticercosis as etiology of epilepsy: Hospital-based studies

Author Country/year	# Pts.	Case Ascertainment	Type of study	NC (%)
Medina et al México / 90	100	All seizures, CT scan	Prevalent cases	50%
DelBrutto et al Ecuador / 91	225	All seizures, CT scan	Prevalent cases	40%
Arruda et al Brasil / 91	210	All seizures, CT scan	Prevalent cases	27%

Neurocysticercosis as an etiology of epilepsy: Hospital-based studies

Author Country/year	No. of Pts	Case Ascertainment	Type of study	NC
Murthy et al India / 99	572	Acute seizures CT scan	Retrospect (SCTEL)	67 %
Sawhney et al India / 96	407	Single Sz. Excluded CT scan	Prevalent and incident cases	11 %
Singh G, et al India/2006	1026	Single, incident and prevalent seizures CT scan	Single Sz Prevalent cases Incident cases	59 % 2 % 0 %

Etiology of Epilepsy in 310 patients in Ecuador



Neurocysticercosis as an etiology of epilepsy: Community-based studies

Author Country/year	Patients with epilepsy	Inclusion criteria	Diagnosis of NC	NC No. (%)
Montano, et al Perú/ 2005	39	All seizures Prevalent cases	CT scan, > 50% only 1 calcification	15 (38)
Del Brutto, et al Ecuador/2005	19	Recurrent seizures Prevalent cases	CT scan, All pts had only 1 calcification	5 (26)
Medina et al Honduras/2005	100	Recurrent seizures Prevalent cases	CT scan,	37(37)

TABLE 3. *Diagnosis of neurocysticercosis[a] in eight patients with epilepsy in Atahualpa, Ecuador*

Age/Sex	Diagnostic criteria[b]	Degree of diagnostic certainty[c]
54 F	Two major (CT and immunoblot), one minor, one epidemiologic	Definitive neurocysticercosis
21 M	Two major (CT and immunoblot), one minor, one epidemiologic	Definitive neurocysticercosis
60 F	Two major (CT and immunoblot), one minor, one epidemiologic	Definitive neurocysticercosis
37 M	One major (CT), one minor, one epidemiologic	Probable neurocysticercosis
57 M	One major (CT), one minor, one epidemiologic	Probable neurocysticercosis
31 F	One major (immunoblot), one minor, one epidemiologic	Probable neurocysticercosis
22 M	One major (immunoblot), one minor, one epidemiologic	Probable neurocysticercosis
1 M	One major (immunoblot), one minor, one epidemiologic	Probable neurocysticercosis

NCC, neurocysticercosis; ELISA, enzyme-linked immunosorbent assay.
[a] According to Del Brutto et al. Proposed diagnostic criteria for neurocysticercosis. Neurology 2001; 57:177–83.
[b] Diagnostic criteria: *Major*: Lesions highly suggestive of NCC on imaging studies, positive serum immunoblot for the detection of anticysticercal antibodies, resolution of intracranial lesions after cysticidal therapy, and spontaneous resolution of small single enhancing lesions. *Minor*: Lesions compatible with NCC on imaging studies, clinical manifestations suggestive of NCC, positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens, and cysticercosis outside the CNS. *Epidemiologic*: Evidence of a household contact with *T. solium* infection, individuals coming from or living in an area where cysticercosis is endemic, and history of frequent travel to disease-endemic areas.
[c] Degrees of diagnostic certainty: *Definitive diagnosis*: Presence of two major plus one minor and one epidemiologic criteria. *Probable diagnosis*: Presence of one major plus two minor criteria, presence of one major plus one minor and one epidemiologic criteria, or presence of three minor plus one epidemiologic criteria.

Del Brutto OH, et al.: Epilepsy and neurocysticercosis in Atahualpa: a door-to-door survey in rural coastal Ecuador. *Epilepsia* 2005, 46:583–87.

Neurocysticercosis and Epilepsy

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Meta-Analysis of Cysticidal Drugs for Neurocysticercosis *

- Synthesis: 11 studies (among 764) were selected: 6 (464 pts) with viable cysts y 5 (478 pts) con coloidal cysts
- Quality: 5 good, 4 fair, 2 poor. No study used the intention-to-treatment analysis
- Results: - disappearance of viable cysts : albendazole 44% vs. placebo 19% (p <0.025); - disappearance of degenerative cysts : albendazol 72% vs. placebo 63% (p <0.38)

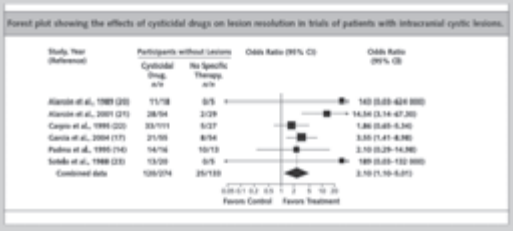
* Del Brutto et al, Ann Intern Med. 2006;145:43-51

Meta-Analysis of Cysticidal Drugs : "good" studies*

Study, year	Disign	Patients/ controls	Cystic lesions
Baranwal et al, 1998	Double-blind, Alb/Placebo	31/32	Single coloidal cysts
Carpio et al, 1995	Nonblinded Alb/Praz/Control	111/27	Viable cysts
Garcia et al, 2004	Double-blind, Alb/Placebo	55/54	Viable cysts
Cogia et al, 2003	Double-blind, Alb/Placebo	24/29	Coloidal cysts (2-3)
Singhi et al, 2004	Nomblinded Alb/corticoids	72/38	Single coloidal cysts

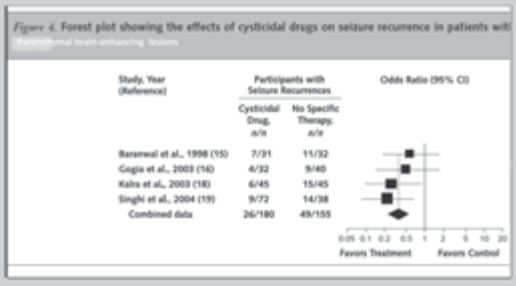
* Del Brutto et al, Ann Intern Med. 2006;145:43-51

Meta-Analysis of Cysticidal drugs for Neurocysticercosis *



* Del Brutto et al, Ann Intern Med. 2006;145:43-51

Meta-Analysis of Cysticidal drugs for Neurocysticercosis *



* Del Brutto et al, Ann Intern Med. 2006;145:43-51

Meta-Analysis of Cysticidal Drugs for Neurocysticercosis *

Conclusions of the Editors

- Context: **the efficacy of treatment with praziquantel and albendazole is controversial**
- Contribution: **the effects on neuroimaging end points were relatively small (OR <2.2) Treatment reduced the frequency of seizures (OR: 0.36)**
- Cautions: **the studies were small and heterogeneous, and only 5 of 11 were good quality**
- Implications: **these studies provide limited evidence of a modest effect of NC treatment**

* Del Brutto et al, Ann Intern Med. 2006;145:43-51

Anthelmintics for people with neurocysticercosis

Abba Katharine, et al. Cochrane - Systematic Reviews. 2009

Objective : To assess the effectiveness and safety of anthelmintics for people with NC.

Main results; For viable lesions in adults, no difference was detected for albendazole compared with no treatment for recurrence of seizures; but fewer participants with albendazole had lesions at follow up (RR 0.56, 95% CI 0.45 to 0.70)

Authors' conclusions: In patients with viable lesions, evidence from trials of adults suggests albendazole may reduce the number of lesions. In trials of non-viable lesions, seizure recurrence was substantially lower with albendazole, which is counter-intuitive.

Effects of Cysticidal drugs on resolution of Parenchymal viable cysts

Study / Reference	Treatment	Disapperance of cysts on CT scan at 6 m n/n %
Garcia H, et al. *N Engl J Med* 2004	Albendazole	21/55 (38%)
	Placebo	8/54 (15%)
Carpio A, et al J. Neurol Neurosurg Psychiat. 2008,	Albendazole	18/51 (35%)
	Placebo	6/50 (12%)
Das K, et al. J Clin Neurosci. 2007	Albendazole	10/148 (7%)
	Placebo	12/150 (8%)

Effects of Cysticidal drugs on seizures recurrence due to NC

Study / Reference	Treatment	Seizures Recurrence
Garcia H, et al. *N Engl J Med* 2004	Albendazole	32/57 (56%)
	Placebo	32/59 (54%)
Carpio A, et al. J Neurol Neurosurg Psychiat. 2008	Albendazole	19/51 (38%)
	Placebo	27/56 (48%)
Das K, et al. J Clin Neurosci. 2007	Albendazole	40/148 (27%)
	Placebo	24/150 (16%)

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- Conclusions and recommendations

Prognosis for seizure recurrence in patients with neurocysticercosis *

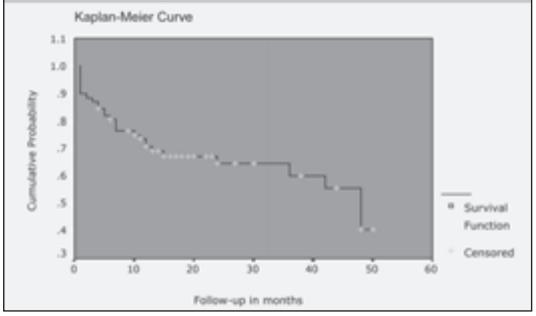
- **Objective: To determine the risk of seizure recurrence after a first seizure due to NC and to evaluate risk factors for seizure recurrence including the influence of antihelminthic treatment.**
- **Methods: We prospectively followed 77 patients with a first seizure and active or transitional NC for over 7 years (median 24 months)**

* Carpio A, Hauser WA. Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis. Neurology 2002;59:1730-1734.

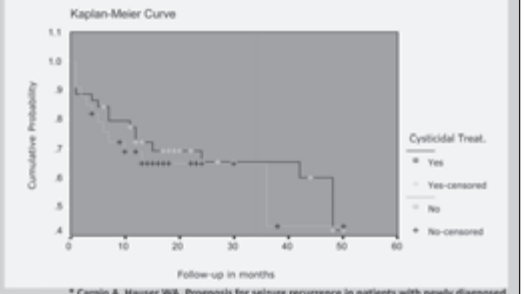
Seizure Recurrence after the First Seizure in 77 Patients with NC according to Antihelminthic Treatment

Follow-up	All patients	Group 1 (Albendazole)	Group 2 (no treat.)
No. of patients	77	44	33
Within 6 months	20 %	16 %	25 %
Within 12 months	29 %	28 %	35 %
Within 24 months	35 %	35 %	57 %
Within 48 months	60 %	58 %	60 %

Probability of Seizure Recurrence after a First Seizure in 77 Patients with Neurocysticercosis



Probability of Seizure Recurrence after a First Seizure in 77 Patients with NC as Function of Cysticidal Treatment



* Carpio A, Hauser WA. Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis. Neurology 2002;59:1730-1734

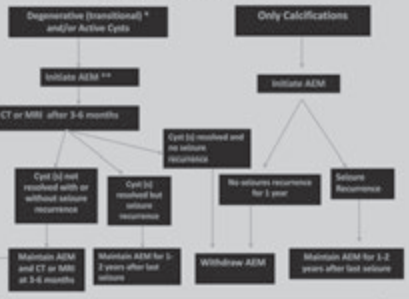
Prognosis for seizure recurrence in patients with neurocysticercosis *

Discussion:

- **Seizure recurrence is about 40% following a first acute symptomatic seizure due to NC, but this seems to be related to persistence of active brain lesions.**
- **Recurrence risk is low and in keeping with seizure risk following other brain insults leading to a static encephalopathy in those in whom the NC lesion clears**

* Carpio A, Hauser WA. Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis. Neurology 2002;59:1730-1734

Antiepileptic treatment for patients with first seizure due to neurocysticercosis *



•Carpio A. Neurocysticercosis: an update. Lancet Infect Dis. 2002;2:751-762

Neurocysticercosis and Epilepsy

- **Epidemiology and definitions of NC and epilepsy**
- **Seizures, the main clinical manifestation of NC**
- **NC as an etiology of epilepsy in developing countries**
- **Does antihelmintic treatment improve seizures due to NC?**
- **Prognosis of epilepsy in patients with NC**
- **Conclusions and recommendations**

Neurocysticercosis and Epilepsy Conclusions (1)

- **Seizures is the most frequent clinical manifestation of NC**
- **Seizures may occur at any evolutionary stage of the parasite, but acute symptomatic seizures are more frequent in the transitional form**
- **It is likely that most people with NC have acute symptomatic seizures that do not necessarily evolve into epilepsy. This is one of the reasons that epilepsy is overdiagnosed in some studies**

Neurocysticercosis and Epilepsy – Conclusions (2)

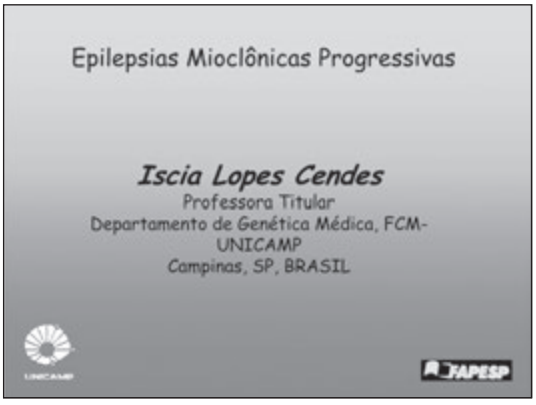
- Studies of NC as etiology of epilepsy are difficult to compare due to methodological differences
- According to recent studies (incidence epilepsy), NC is not necessarily the main cause of epilepsy, although it is one of the most frequent antecedents among adult patients with symptomatic epilepsy.
- Because of the high prevalence of each condition, a causal as well as fortuitous relationship between the two pathologies might exist.

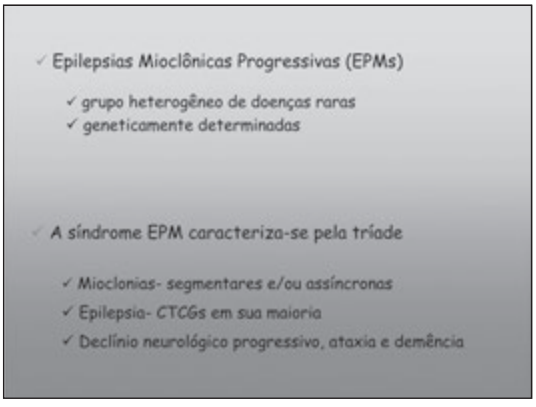
Neurocysticercosis and Epilepsy – Conclusions (3)

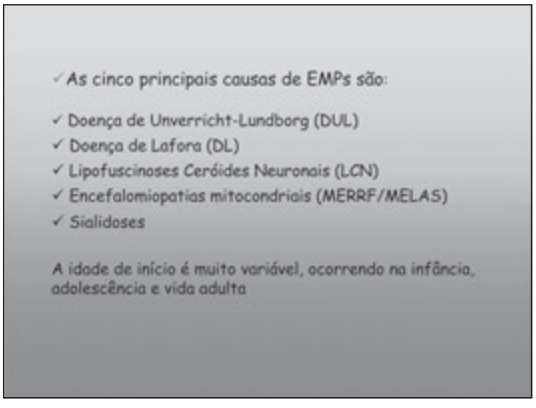
- Clinical heterogeneity of NC makes hard to compare reports each other
- There is not validated diagnoses criteria of NC
- Seizure recurrence is about 1/3 following a first acute symptomatic seizure due to NC
- The prognosis of seizure in patients with NC is good
- There is no correlation between treatment with antihelminthic agents and seizure recurrence

Iscia Lopes-Cendes

PROGRESSIVE MYOCLONIC EPILEPSIES







EPIDEMIOLOGIA

- A verdadeira freqüência não está definida
- EMPs menos de 1% de todos os casos de epilepsia
- Distribuição mundial com diferenças geográficas e étnicas
- DUL: Báltico e região ocidental do Mediterrâneo
- DL: sul da Europa e norte da África
- LCNs: Escandinávia

DOENÇA DE UNVERRICHT-LUNDBORG

- idade de início entre 6 e 15 anos
- mioclonias despertadas por estímulos como luz, barulho e movimento
- início lento e gradual do declínio neurológico, principalmente o comprometimento cognitivo
- sobrevida pode ocorrer até vida adulta
- biópsia de pele com a presença de vacúolos em glândulas sudoríparas écrinas (década de 90)

Aspectos genéticos

Cistatina B - 21q22.3

(ccccgcccccgcg) x 2 a 3

- mutações de ponto e/ou expansão do dodecâmero

DOENÇA DE LAFORA

- idade de início variando entre 11 a 18 anos
- alterações de comportamento e dificuldades escolares
- rápida progressão da doença com deterioração cognitiva
- evoluem para a morte após 2 a 10 anos de doença
- biópsias de pele, em glândulas sudoríparas, com corpúsculos de Lafora

aspectos genéticos

EPM2A - 6q23-25

- codifica a laforina
- cerca de 80% dos pacientes possuem mutação neste gene
- heterogeneidade alélica e não alélica (segundo gene identificado em 6p12, codifica a malina)

LIPOFUSCINOSES CERÓIDES NEURONAIS

- início dos sintomas varia desde meses até vida adulta
- involução do desenvolvimento neuropsicomotor e perda visual progressiva
- classificação das diferentes formas depende da idade de início, sinais clínicos e achados histopatológicos
- diagnóstico através de biópsia de pele, conjuntiva e reto

Quatro principais formas de LCN

Formas clínicas	Idade de início	Principais sintomas	Padrão de herança	Achados histopatológicos	Gene
Infantil	6 meses a 2 anos	atraso do desenvolvimento crises cegueira	autossômico recessivo	depósitos granulares osmiofílicos	*LCN1*
Infantil tardia	2 a 8 anos	involução amarose crises	autossômico recessivo	corpúsculos curvilíneares	*LCN2*
Juvenil	4 a 10 anos	involução amarose extra-piramidal	autossômico recessivo	impressões digitais	*LCN 3*
Adulta	15 a 50 anos	sem perda visual, alterações de comportamento	autossômico recessivo ou dominante	misto	desconhecido

ENCEFALOMIOPATIAS MITOCONDRIAIS

- início dos sintomas são variáveis, ocorrendo tanto em crianças quanto adultos
- padrão de herança mitocondrial, via materna
- doenças multissistêmicas, cuja expressão depende da heteroplasmia

MERRF e MELAS

MERRF

- 90% dos pacientes com MERRF: A8344G no mtDNA

MELAS

- episódios de acidentes vasculares que não respeitam a anatomia arterial, acidose lática
- 80-90% dos casos são devido a mutação A3243G
- biópsia de músculo: fibras vermelhas rajadas

SIALIDOSES

- doenças lisossomiais (deficiência da neuroaminidase)
- associada ou não a deficiência de beta-galactosidase
- característica marcante: mancha vermelho-cereja no fundo de olho
- herança autossômica recessiva com dois fenótipos principais

FORMAS RARAS DE EMP

Atrofia dentatorubropalidoluisiana (DRPLA)
Doença de Gaucher forma não-infantil
GM2 gangliosidose, forma infantil tardia e juvenil
Distrofia neuroaxonal, forma juvenil
Síndrome da falência renal com mioclonus
Doença de corpos de inclusão atípicos
Doença de Huntington, forma juvenil

Nível Diagnóstico I

Inicialmente avaliamos 25 pacientes/21 famílias não-relacionadas

9 pacientes / 6 famílias	DUL
4 pacientes / 4 famílias	DL
6 pacientes / 5 famílias	LCN
4 pacientes / 4 famílias	Encefalomiopatia Mitocondrial
1 paciente / 1 família	Dç de Depósito
1 paciente / 1 família	Dç Huntingnton juvenil

Nível Diagnóstico II

- ✓ EEG em todos os pacientes
- ✓ RNM de crânio em 23 pacientes e 2 TC de crânio

Nível Diagnóstico III

- ✓ Biópsia de pele ou músculo em 15 pacientes
- ✓ Teste molecular em 20 pacientes
- ✓ Testes bioquímicos em 6 pacientes

DOENÇA DE UNVERRCHIT-LUNDBORG
(n=9)

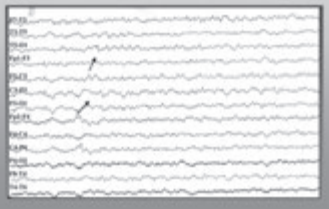
Nível diagnóstico I

- ✓ 9 pacientes/6 famílias
- ✓ idade de início variou entre 7 a 18 anos de idade
- ✓ longos períodos de evolução (entre 6 a 34 anos)
- ✓ ataxia cerebelar e mioclonias incapacitantes
- declínio cognitivo lento
- consanguinidade em 2 famílias

DOENÇA DE UNVERRCHIT-LUNDBORG

Nível diagnóstico II - EEG

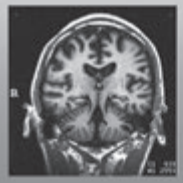
- ✓ achados inespecíficos

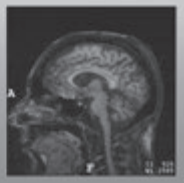


DOENÇA DE UNVERRCHIT-LUNDBORG

Nível diagnóstico II - RNM

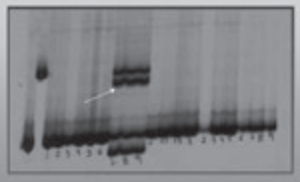
- ✓ achados inespecíficos - atrofia cortical e cerebelar





DOENÇA DE UNVERRCHIT-LUNDBORG

Nível diagnóstico III – Análise Molecular

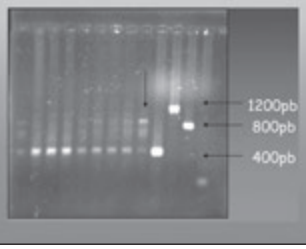


Cistatina B – exon 2 (3 pacientes relacionados)

DOENÇA DE UNVERRICHT-LUNDBORG

Nível Diagnóstico III- Análise molecular

Expansão do dodecâmero



DOENÇA DE LAFORA
(n=4)

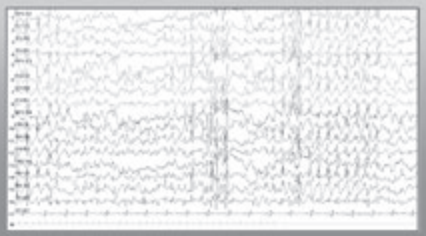
Nível diagnóstico I

- ✓ 4 pacientes/ 4 famílias
- ✓ Idade de início variou entre 9 a 14 anos
- ✓ Dificuldades escolares
- ✓ CTCGs desencadeadas por estímulo luminoso
- ✓ Mioclonias debilitantes
- Rápida deterioração neurológica

DOENÇA DE LAFORA

Nível diagnóstico II - EEG

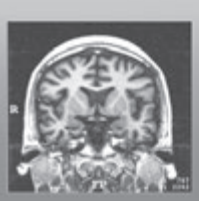
✓atividade epileptiforme generalizada e dist. atividade de base

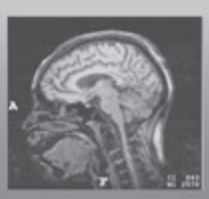


DOENÇA DE LAFORA

Nível diagnóstico II -RNM

- ✓ alterações discretas; atrofia cortical e cerebelar
- ✓ P. R. C., 14 anos, fem. 1 ano e meio de evolução

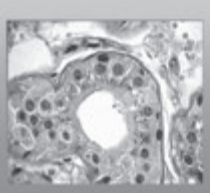


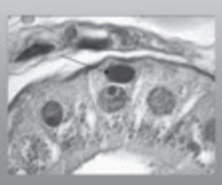


DOENÇA DE LAFORA

Nível diagnóstico III – biópsia de pele

✓corpúsculos de Lafora (PAS +) nos 4 pacientes

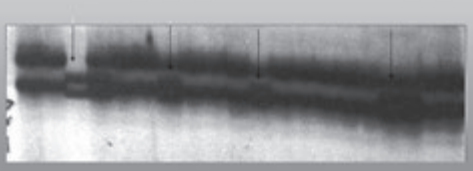




DOENÇA DE LAFORA

Nível diagnóstico III – análise molecular

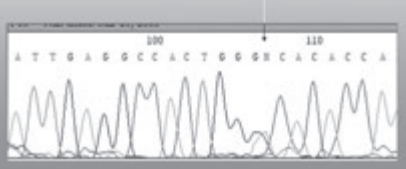
✓ gene *EPM2A*, através do SSCP revelou alteração no éxon 2, para os 3 pacientes do estudo



DOENÇA DE LAFORA

Nível diagnóstico III – análise molecular

✓Sequenciamento automático, exon 2 do gene *EPM2A*, comprovou a presença de mutação em 3 dos 4 pacientes



LIPOFUSCINOSES CERÓIDES NEURONAIS
(n=6)

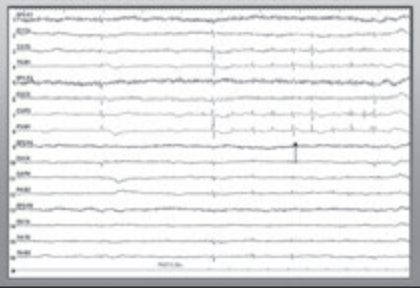
Nível diagnóstico I

- 6 pacientes/ 5 famílias
- início dos sintomas variou entre 1 a 5 anos
- alterações neurológicas:
  - mioclonias, alteração da marcha e alteração visual
- forma infantil tardia suspeita mais frequente

LIPOFUSCINOSES CERÓIDES NEURONAIS

Nível diagnóstico II- EEG

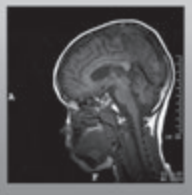
- EEG- V. C. P., 9 anos, fem., 5 anos de evolução

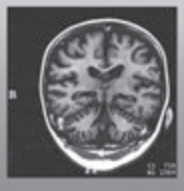


LIPOFUSCINOSES CERÓIDES NEURONAIS

Nível diagnóstico II- RNM

- todos exames alterados, como atrofia cortical e cerebelar

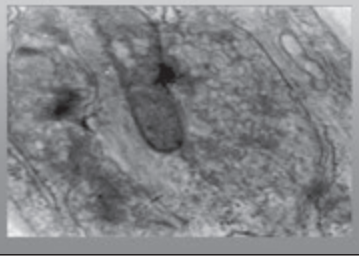




LIPOFUSCINOSES CERÓIDES NEURONAIS

Nível diagnóstico III- biópsia de pele

- definição diagnóstica em 2 pacientes:forma infantil tardia
- (corpúsculos curvelineares)



ENCEFALOMIOPATIAS MITOCONDRIAIS
(n=4)

Nível diagnóstico I- Avaliação clínica

✓ clínica e exame neurológico altamente sugestiva de MERRF e MELAS em 2 pacientes:

MERRF	MELAS
início 34 anos	início 6 anos
lipomas gigantes	microcefalia
surdez neurossensorial	amaurose pós-ictal
neuropatia periférica	hipoacusia

ENCEFALOMIOPATIAS MITOCONDRIAIS

Nível diagnóstico I- MERRF

✓ Paciente M. A . L., 41 anos, fem., com lipomatose giagnte

ENCEFALOMIOPATIAS MITOCONDRIAIS

Nível diagnóstico II-EEG

MELAS

✓ EEG – atividade epileptiforme focal nos quadrantes posteriores e generalizada pouco frequente

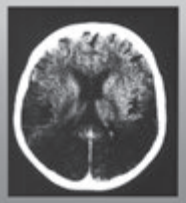
MERRF

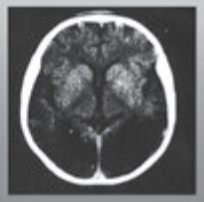
✓ EEG 1°-Ondas agudas generalizadas, correspondendo a mioclonias;
2°-lentificação difusa da atividade de base, ausência de atividade epileptiforme generalizada

ENCEFALOMIOPATIAS MITOCONDRIAIS

Nível diagnóstico II- TC de crânio

✓ R.R.P., 15 anos, mas., MELAS

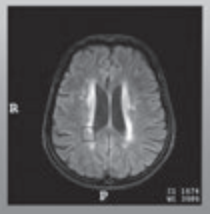


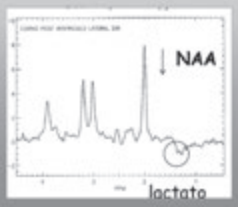


ENCEFALOMIOPATIAS MITOCONDRIAIS

Nível diagnóstico II- RNM

- M. A . L., 41 anos, fem., MERRF

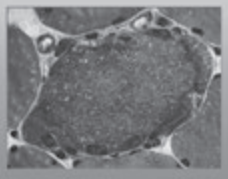




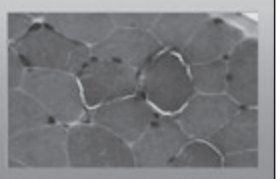
ENCEFALOMIOPATIAS MITOCONDRIAIS

Nível diagnóstico III- biópsia de músculo

- biópsia de músculo realizou-se em 2 pacientes, as RRF



Coloração de gomori

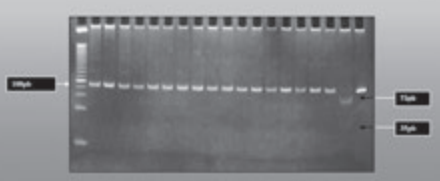


Coloração H. E .

ENCEFALOMIOPATIAS MITOCONDRIAIS

Nível diagnóstico III- análise molecular

- pesquisou os pontos de mutação A3243G e A8344G mt DNA responsáveis por MELAS e MERRF



Pesquisa da mutação de ponto A8344G- MERRF

SIALIDOSES
(n=1)

- Nível diagnóstico I- polimioclônus
  fácies grosseira (sinais dismórficos)
  escoliose
  cegueira
- Nível Diagnóstico II-EEG-ativ. epileptiforme generalizada
  (concomitante com as mioclonias)

  TC- atrofia cortical
- Nível Diagnóstico III- Teste bioquímico
  baixos níveis de sialidase

Diagnóstico: sialidose tipo I, forma juvenil

Formas Raras de EMP

Ataxia espinocerebelar tipo 7 (SCA-7) como EMP

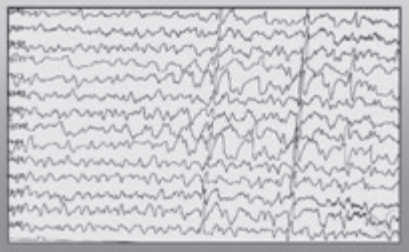
- Nível Diagnóstico I-início aos 6 anos
  ptose bilateral, oftalmoparesia
  baixa acuidade visual
  mioclonias
- Nível Diagnóstico II-EEG- ativ.epileptiforme generalizada, associada a mioclonias

  RNM de crânio-atrofia acentuada de cerebelo e tronco cerebral

Formas Raras de EMP

Nível Diagnóstico II-EEG

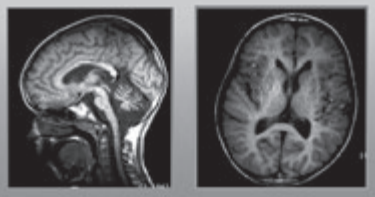
- Paciente M. O . B., 9 anos, mas. inicialmente caso isolado



Formas Raras de EMP

Nível Diagnóstico II-RNM

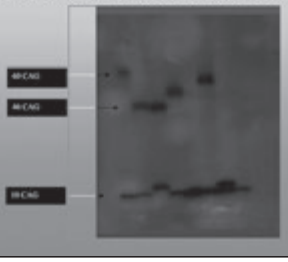
- RNM mostram intensa atrofia cerebelar e de tronco



Formas Raras de EMP

Nível Diagnóstico III- Análise molecular

- presença de alelos com 60 repetições(paciente) e sua mãe com 46



Resultados Finais

Diagnosticamos: 13 pacientes (52% dos pacientes)
11 famílias (52% das famílias)

DUL- 3 pacientes- teste molecular (9)

✓DL- 4 pacientes- biópsia de pele e 3 com confirmação molecular (somente gene *LAF* pesquisado) (4)

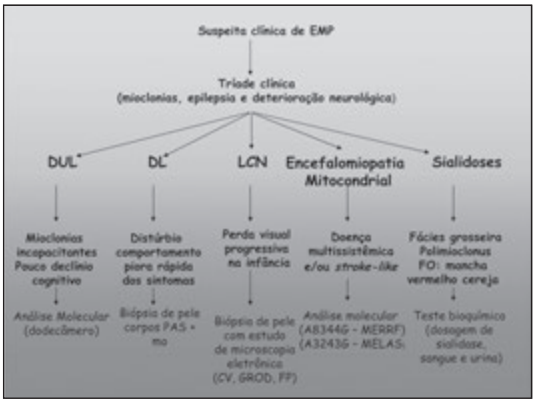
✓LNC- 2 pacientes- biópsia de pele (6)

✓MERRF- 1 paciente- teste molecular (1)

MELAS- 1 paciente- teste molecular (1)

Sialidose – 1 paciente- teste bioquímico (1)

SCA-7 – 1 paciente- teste molecular (0)



Helen Cross (England)

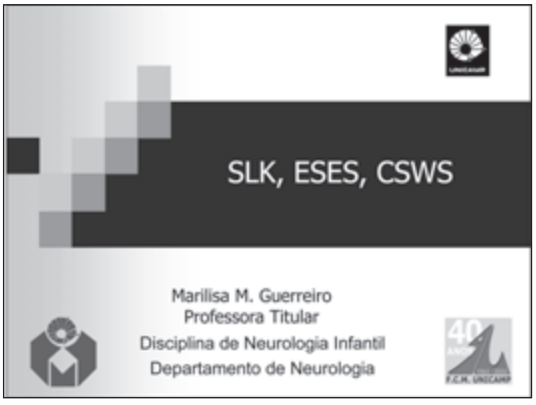
CHILDHOOD CATASTROPHIC EPILEPSIES

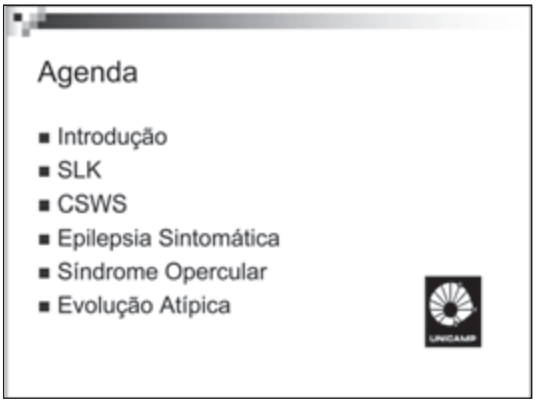
Marina Bentivoglio (Italy)

GLIAL RESPONSES TO ICTAL INSULTS

Marilisa Guerreiro (Brasil)

LANDAU-KLEFFNER SYNDROME, ELECTRICAL STATUS EPILEPTICUS DURING SLEEP, AND CONTINUOUS SPIKE-WAVES DURING SLEEP






Subclinical "Electrical Status Epilepticus"
Induced by Sleep in Children
A Clinical and Electroencephalographic Study of Six Cases

Definições

- **ESES** = encephalopathy with status epilepticus during sleep or electrical status epilepticus in sleep (85%)
- **CSWS** = continuous spike and waves during sleep
- **EMES** = estado de mal elétrico do sono
- **POCS** = ponta onda contínua do sono

ILAE, 2010

Fisiopatologia

- Hipótese: paroxismos epileptiformes podem interferir com funções fisiológicas e com neuroplasticidade
- O sono desempenha papel fundamental na consolidação do aprendizado e da memória
- A consolidação da memória reflete processos a nível molecular e celular que convertem a memória lábil em permanente
- O sono lento é fundamental para o processo da homeostasia sináptica

Walker and Stickgold, 2002-2011
Tononi and Cirelli, 1991-2011

John William Waterhouse, 1912

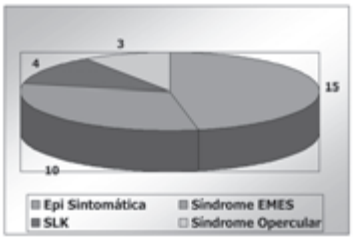
Síndrome de Penélope

- "*Spinning during the day, spiking during the night*"

- Tear = rede neuronal
- Desfazer = descargas elétricas durante o sono
  - Prejuízo neuropsicológico e comportamental

Tassinari et al, 2009

EMES
(padrão eletrencefalográfico)



Veggiotti et al, 1999

SLK

Neurology Volume 7 • Number 8

Syndrome of Acquired Aphasia with Convulsive Disorder in Children

William M. Landau, M.D. and Frank R. Kleffner, Ph.D.

Síndrome de Landau-Kleffner

- Distúrbio de linguagem
  - Deterioração da compreensão associada à redução progressiva da fala espontânea
- Epilepsia: 80%
- EEG: descargas epileptiformes em 100%

Shinnar et al, 2001; Stefanos et al, 2002; Guilhoto et al, 1997; Guerreiro et al, 1998

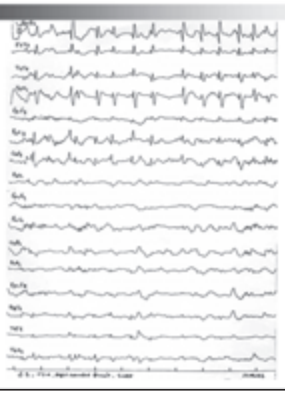
SLK – Quadro Clínico

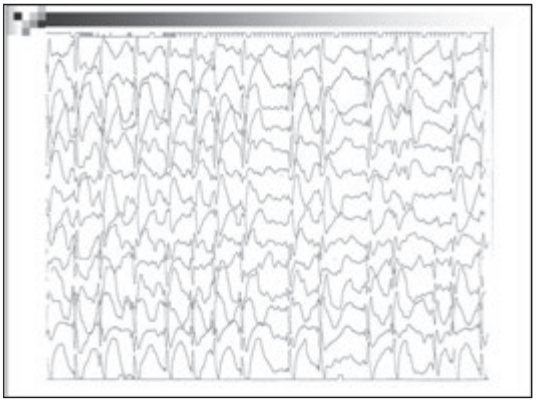
- IC: 4 e 7 anos (1,5 a 13 anos)
- Sexo: masculino
- Linguagem
  - Afasia global
  - Agnosia auditiva verbal
  - Instalação abrupta ou insidiosa
  - Diag. diferencial: surdez ou autismo
- Epilepsia
  - Crises podem ser parciais ou generalizadas
  - Freqüência variável
- Distúrbios de comportamento são comuns

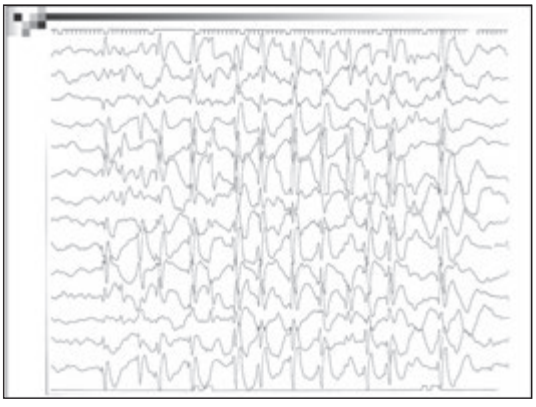
CMS

SLK - EEG

- Vigília
  - Atividade de base preservada
  - Descargas epileptiformes: generalizadas, focais ou multifocais, porém predominam em regiões temporais e à E
- Sono
  - Ativação e difusão
  - > 85%: EMES
  - Sono REM: desaparecimento ou fragmentação da atividade paroxística

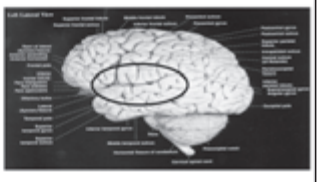






SLK – Etiologia x Fisiopatologia

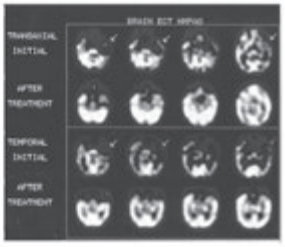
- Desconhecida
- Neuroimagem: normal
- Ablação funcional das áreas de linguagem



Deonna et al. 1989; Holmes et al. 1991

SLK – Exames Complementares

- EEG
- Neuroimagem estrutural
- Neuroimagem funcional
  - SPECT
  - PET



Guerreiro et al. 1996

SLK - Tratamento

- Clínico
  - Drogas antiepilépticas
    - Benzodiazepínicos, VPA
    - Outras: CBZ, VGB, Levetiracetam, Sulthiame
  - Corticoterapia e Imunoglobulina
  - Dieta cetogênica
- Cirúrgico
  - TSM
  - Estimulação vagal

Lerman et al, 1991; Sawhney et al, 1995; Marescaux et al, 1990; Landau, 1992; Hirsch et al, 2006; Gallagher et al, 2006; Lagae, 2009; Kramer et al, 2009

Evolução

- Epilepsia e EEG: evolução favorável
- Disfunção neuropsicológica geralmente é permanente
  - Prognóstico reservado está relacionado com início precoce e fase ativa prolongada

Brain & Development 31 (2009) 39–43

Original article

Landau–Kleffner syndrome: Long-term follow-up

Marcos H.C. Duran, Catarina A. Guimarães, Lívia L. Medeiros, Marilisa M. Guerreiro *

Department of Neurology, FCM, State University of Campinas (Unicamp), P.O. Box 6111, 13083-970 Campinas, SP, Brazil

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Abstract

Purpose: Landau–Kleffner syndrome (LKS) is a rare entity characterized by epilepsy and aphasia. It occurs in previously normal children, usually between three and seven years of age. The long-term outcome of LKS is not completely clear. The aim of this study is to verify the long-term follow-up of a group of patients with LKS, focusing on clinical and electroencephalographic (EEG) aspects, and quality of life. Methods: This was a transversal study. Between November 2006 and April 2007 seven patients with previous diagnosis of LKS were interviewed. They had had a follow-up of from 3 to 16 years after their disease onset. They were all males between the ages of eight and 27 years old. All patients had normal MRI. Parents and/or patients were interviewed by one of the authors using a structured questionnaire. The Vineland Adaptive Behavior Scales, the Conner's Rating Scale – Revised, and Short-Form Health Survey (SF-36) were used. Each patient had a prolonged routinary EEG recording. All patients had normal MRI. Results: The present investigation revealed that two patients still have seizures several years after epilepsy onset. One patient had total and three others had partial remission of language disturbance, while three patients still have aphasia and verbal auditory agnosia. With respect to quality of life, only one of our patients has a normal life at present. The remaining six patients with some sort of limitation consider the aphasia/agnosia to be the main difficulty in their lives. Five patients have normal EEGs. Conclusions: The long-term follow-up of patients with LKS shows that epilepsy and EEG abnormalities do not always disappear. Language disturbances tend to persist in most patients. The age of onset of language dysfunction does not seem to correlate with the prognosis for recovery of language function. Patients with LKS have an overall poor quality of life, mostly due to language difficulties.

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Keywords: Landau–Kleffner Syndrome; Epilepsy; Childhood; Aphasia; Agnosia; Follow-up

Evolução

- 7 pacientes
- Seguimento: 3 a 16 anos
- Sexo masculino: 8 e 27 anos
- Métodos:
  - Entrevista
  - Escala Vineland
  - Escala de Conner
  - EEG

Duran et al. Brain Dev 2009

Evolução

- Resultados:
  - Epilepsia: 2 pac com crises refratárias
  - Linguagem:
    - 1 remissão completa da SLK
    - 3 remissão parcial
    - 3 com afasia + agnosia auditiva
  - Qualidade de vida:
    - 1 vida normal
    - 6 com limitações
  - EEG: 5 normais

Duran et al. Brain Dev 2009

Evolução

- Conclusões:
  - Epilepsia e EEG nem sempre normalizam
  - A idade de início não se correlacionou com melhor prognóstico da linguagem
  - Qualidade de vida comprometida, devido principalmente às dificuldades na área da linguagem

Duran et al. Brain Dev 2009

CSWS

CSWS = POCS

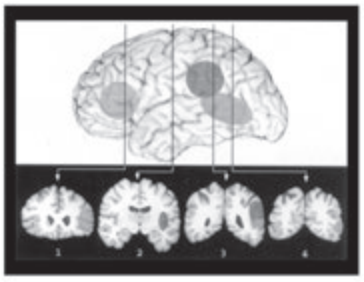
- Início na primeira década: 4-5 anos
- Distúrbio EEG paroxístico grave com complexos espícula-onda > 85% do traçado de sono
- Epilepsia: manifestação inicial em 80%
- Deterioração cognitiva e comportamental com ou sem alterações prévias do desenvolvimento neuropsicológico
- Ausência de patologia cerebral que justifique o quadro

SLK x POCS

- Dois pontos no espectro das encefalopatias epilépticas funcionais da infância
- Distúrbio epileptiforme paroxístico grave que altera a sinaptogênese de forma permanente
  - SLK: atividade paroxística interfere principalmente com a função do córtex temporoparietal (linguagem)
  - EMES: atividade paroxística interfere principalmente com a função do córtex frontal (cognição e comportamento)

Smith & Hoeppner, 2003

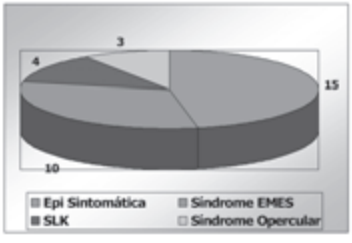
SLK x POCS



Comparação entre SLK e POCS

Variável	SLK	EMES
Sexo	68% M	63% M
Antecedente	0	36% PC
IC	5-7	5-7
Sintoma	Linguagem	Comportamento
Crises	Variadas	Variadas
Neuroimagem	13% anl	33% anl
85% CEOL	< 50%	80%
Descargas Focais	Têmporo Parietal	Frontal
Freqüência CEOL	2 Hz	2 Hz

EMES
(padrão eletrencefalográfico)



Veggiotti et al, 1999

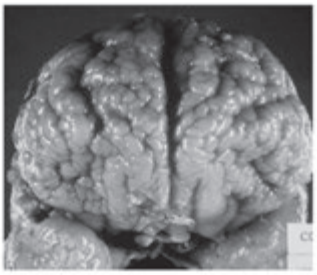
Epilepsia Sintomática

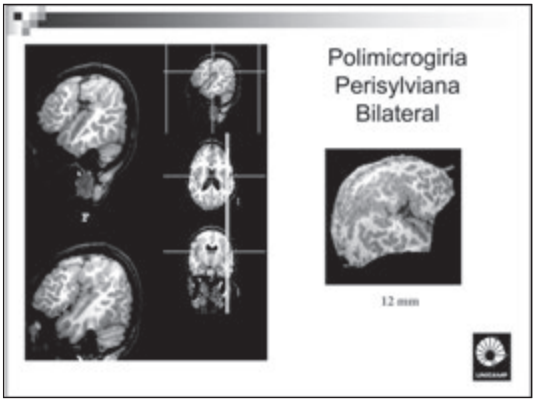
Anormalidades estruturais associadas com EMES

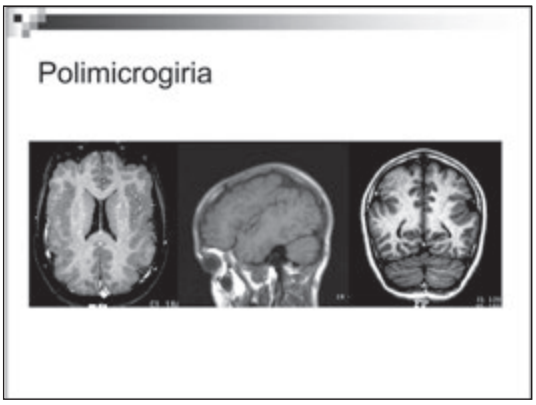
Etiologia	Van Hirtum, 2006 (33)	Buzatu, 2009 (18)	Tas, 2009 (44)	Liukkonen 2010 (17)
Vascular perinatal	21%	78%	61%	70%
MDC	24%	22%	25%	23%
Mieliniza ção anl	15%		9%	
Atrofia difusa	15%			
Túberes	6%			
Tumores	3%		5%	

Síndrome Opercular ou Síndrome Perisylviana

PMG







S. Perisylviana - Resumo

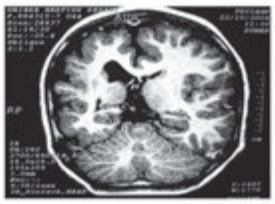
- A SP se caracteriza por manifestações clínicas decorrentes de lesões na região perisylviana que podem ser adquiridas ou congênitas
  - Na forma congênita, associa-se freqüentemente a PMG
  - A tríade clínica clássica caracteriza-se por epilepsia, déficits cognitivos e sinais pseudobulbares

Síndrome Perisylviana ou Opercular Quadro Clínico

- Manifestações pseudobulbares
  - Dificuldade para sugar e deglutir
  - Disfagia (dificuldade para alimentar-se)
  - Engasgo fácil
  - Sialorréia (às vezes por toda a vida)
  - Disartria
  - Distúrbios de linguagem
  - Pé torto
- Epilepsia
- Déficits cognitivos variáveis

Kuzniecky et al, 1993; 1994a,b
Guerreiro et al, 2000-2002

Polimicrogiria Assimétrica



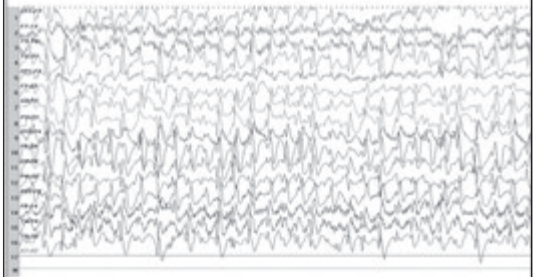
Ressonância Magnética T1 coronal sem contraste. Polimicrogiria hemisférica direita.

PMG e EMES

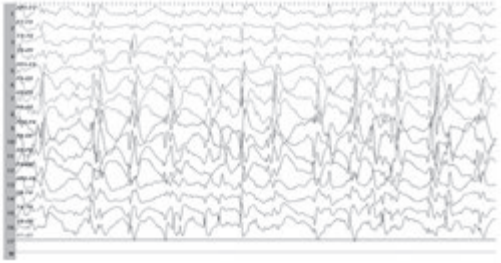
- Laminação cortical horizontal é preservada
- Danos principais na camada V (neurônios piramidais)
- Neurônios gama aminobutíricos poupados
- Desequilíbrio excitatório / inibitório
- Atividade excitatória do córtex anômalo
- Atividade inibitória exacerbada
- Espraia pela laminação horizontal preservada
- Torna bilateral e síncrono

Guerrini et al, 1998

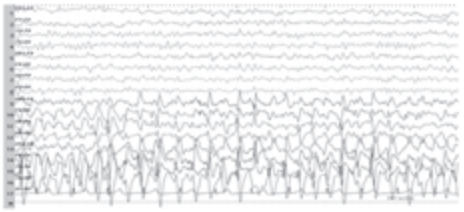
EME



EME



Atividade epileptiforme contínua focal

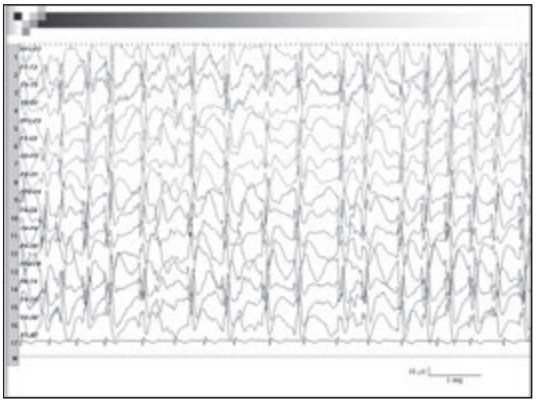


Registro eletroencefalográfico do paciente 24. Paciente em vigília. Complexos espícula e polispícula onda lenta contínuos na região fronto-centro-temporal direita. Filtro: 70 Hz, Constante de tempo :0,3s, Sensibilidade: 10mv/mm.

Evolução Atípica

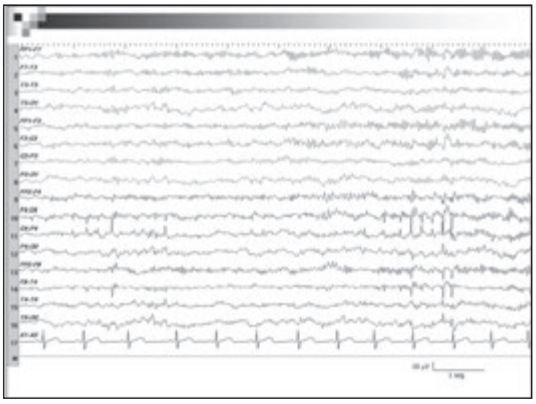
GP

- 8a: CPS (repuxamento da rima labial) - controlado
- 11/05: dificuldade escolar + déficit de atenção + várias crises epilépticas
- 03/06:
  - RM: normal
  - EEG = EMES



GP

- Tratamento: clonazepam
- 04/06: voltou à escola
- 05/06: descargas rolândicas



Evolução Atípica

- Agravamento importante das crises epilépticas
- Deterioração cognitivo comportamental acentuada com queda da performance escolar
- EEG
  - EMES

Fejerman & Caraballo, 2007

Evolução Atípica

- Deterioração acentuada:
  - Cognição e performance escolar
  - Comportamento
  - Linguagem (SLK)
- Evolução:
  - Cognição e comportamento: recuperação completa
  - Linguagem (SLK)

Fejerman & Caraballo, 2007

Evolução Atípica

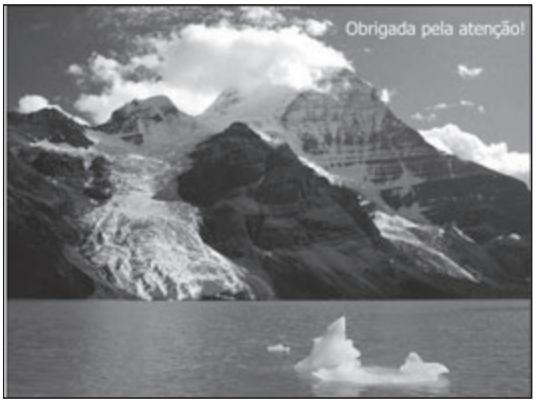
- Fisiopatologia
  - Bissincronia secundária ou Sincronia Bilateral Secundária
  - SBS refere-se às descargas bilaterais e síncronas decorrentes de foco cortical unilateral
    - EMES pode decorrer de insultos focais ao SNC

Fejerman & Caraballo, 2007

Evolução Atípica

- 6m – 2a após o início do quadro
- Evolução em surtos: maioria
- Crises mais frequentes: mioclonias e quedas
- Recuperação completa até 12-14a
- EEG:
  - Vigília: Atividade focal e generalizada
  - Sono: EMES

Aicardi & Chevrie, 1982; Aicardi, 2000; Fejerman et al, 2000; Hahn, 2000; Hahn et al, 2001; Hassa et al, 2001; Saltik et al, 2005



Helen Cross (England)

TREATMENT OF LENNOX-GASTAUT SYNDROME

Luiz Mello (Brazil)

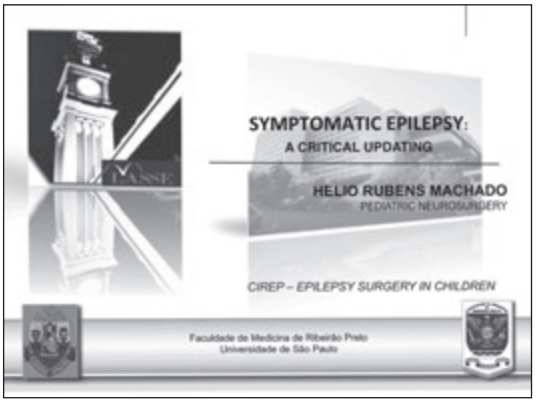
EXPERIMENTAL MODELS EVIDENCE ON ANTI-EPILEPTIC AND ANTI-EPILEPTOGENIC COMPOUNDS AND STRATEGIES

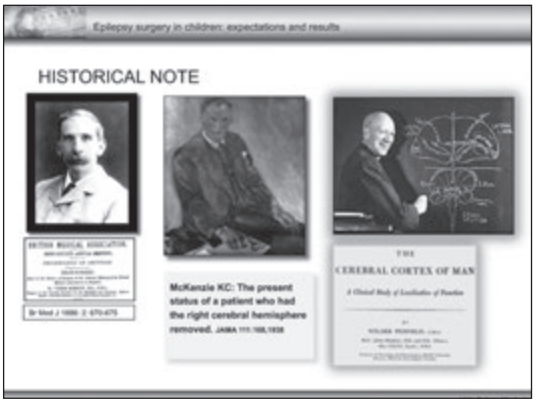
Philippe Ryvlin (France)

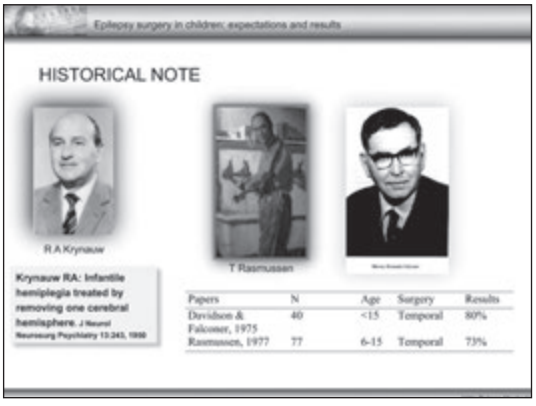
DRUG-DRUG INTERACTION IN THE TREATMENT OF SYMPTOMATIC EPILEPSY

Helio Rubens Machado (Brasil)

SURGERY IN CHILDREN







TREATMENT GOAL

- Eliminate seizures quickly
- Optimize cognitive development
- Improve behavior and quality of life

Original Research

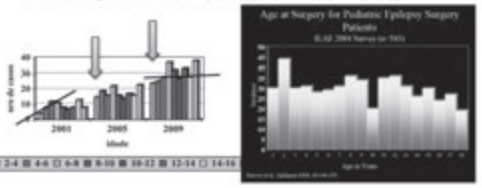
Proposed Criteria for Referral and Evaluation of Children for Epilepsy Surgery: Recommendations of the Subcommission for Pediatric Epilepsy Surgery

*J. Helen Cross, †Prasanna Jayakar, ‡Doug Nordli, §Olivier Delalande, ¶Michael Duchowny, ||Heinz G. Wieser, ||Renzo Guerrini, and §Gary W. Mathern

*On behalf of the International League Against Epilepsy †Subcommission for Pediatric Epilepsy Surgery, and the Commissions of †Neurosurgery and ‡Paediatrics

- Rationale for pediatric epilepsy surgical services
- Typical surgical syndromes
- Pediatric epilepsy unit
- Outcome assessment for pediatric surgical patients

- Rationale for pediatric epilepsy surgical services
  - Effect on brain development
    - Early surgical intervention (avoid epileptic encephalopathy)



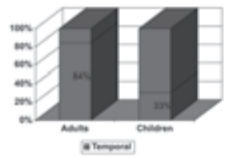
Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

- Rationale for pediatric epilepsy surgical services
  - Effect on brain development
    - Early surgical intervention (avoid epileptic encephalopathy)
  - Heterogeneity of pediatric epilepsy
    - Clinical presentation
    - Medical intractability

Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

Epidemiology

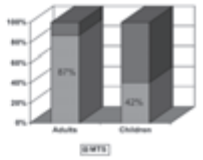
- Adults x children



CIREP – Ribeirão Preto

779 patients, 2005

- MTS – adults x children



Medical intractability in children

Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

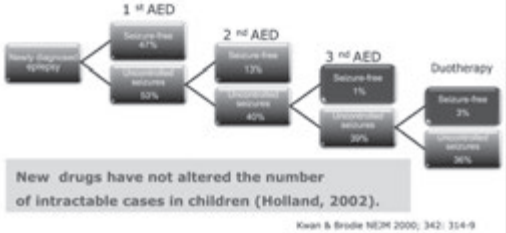
SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*†Patrick Kwan, ‡Alexis Arzimanoglou, §Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§Jacqueline French

It is proposed as a testable hypothesis that drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Treatment outcome – new onset



New drugs have not altered the number of intractable cases in children (Holland, 2002).

Kwan & Brodie NEJM 2000; 342: 314-9

- Rationale for pediatric epilepsy surgical services
  - Effect on brain development
    - Early surgical intervention (avoid epileptic encephalopathy)
  - Heterogeneity of pediatric epilepsy
    - Clinical presentation
    - Medical intractability
  - Functional plasticity
    - Positive x Negative
  - In favor – plasticity of the developing brain
    - Brain growth and maturation ~ 90% until 5 yo
    - Brain synaptogenesis, neuronal connections, dendritic maturation ~ 7 yo

Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

- Rationale for pediatric epilepsy surgical services
  - Effect on brain development
    - Early surgical intervention (avoid epileptic encephalopathy)
  - Heterogeneity of pediatric epilepsy
    - Clinical presentation
    - Medical intractability
  - Functional plasticity
    - Positive x Negative
  - Psychosocial factors
    - Cognition, behavior, QOL...

Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

- Typical surgical syndromes
  - Catastrophic epilepsy
  - Clinical characteristics of the symptomatic etiologies

Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

Catastrophic epilepsy

Seizures 666,9 / mês
Status epilepticus 40,7%

Refractory epilepsy

Progressive neurologic deficit

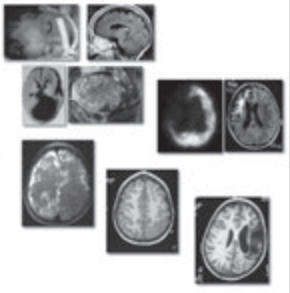
spastic hemiplegia

Developmental delay

Behavior deterioration

Catastrophic epilepsy

- Sturge Weber syndrome
- Hemimegalencephaly
- Rasmussen encephalitis
- Tuberous Sclerosis complex
- Cortical dysplasia
- Porencephaly



Epilepsy surgery in children: selection criteria

- Clinical characteristics
  - Symptomatic etiologies

1996 to 2011sept

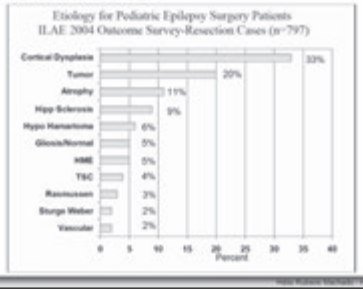
Children 378
Surgeries 401

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

Pathology	
Cortical Dysplasia	124
Tumor	53
Gliosis	55
Mesial temporal sclerosis	50
Rasmussen encephalitis	25
Porencephaly	22
Tuberous sclerosis	18
Difuse atrophy	16
MR normal	15
Sturge-Weber	9
AVM	3
(other 11) Total	401

Epilepsy surgery in children: selection criteria

- Clinical characteristics
  - Symptomatic etiologies



Cirurgia da epilepsia na infância

- Typical surgical syndromes
  - Catastrophic epilepsy
- Pediatric epilepsy unit
  - Referral
  - Presurgical evaluation

Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

Epilepsy surgery in children: expectations and results

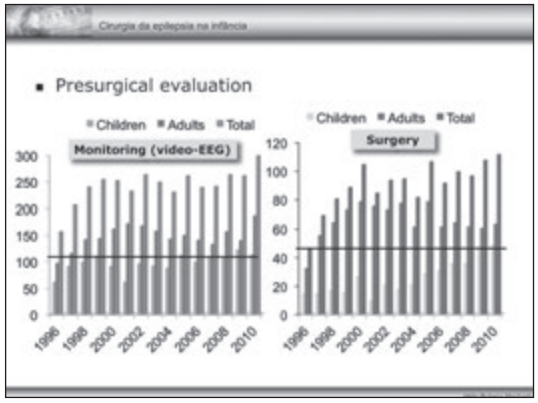
Patient management

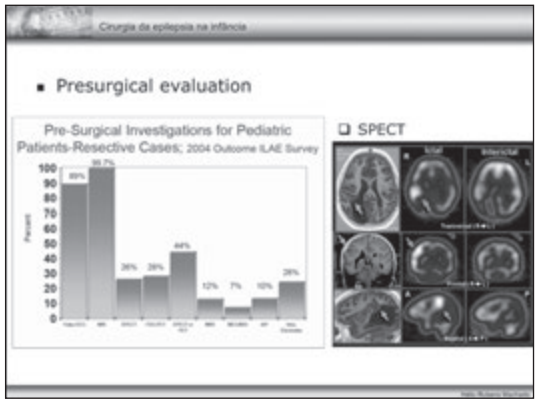
SURGERY
intraoperative ECoG

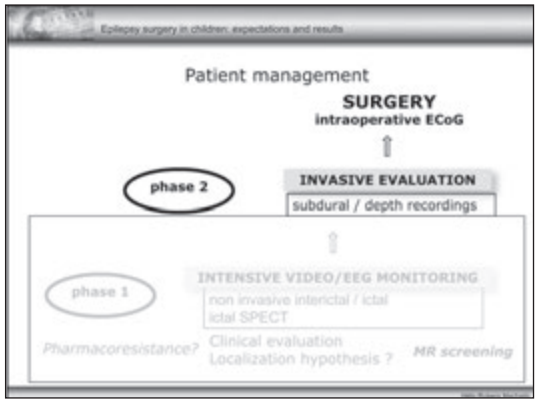
phase 2 — **INVASIVE EVALUATION**
subdural / depth recordings

phase 1 — **INTENSIVE VIDEO/EEG MONITORING**
non invasive interictal / ictal
ictal SPECT

Pharmacoresistance? Clinical evaluation
Localization hypothesis ? ***MR screening***


Cirurgia da epilepsia na infância
Presurgical evaluation
Children Adults Total
Monitoring (video-EEG)
Children Adults Total
Surgery


Cirurgia da epilepsia na infância
Presurgical evaluation
Pre-Surgical Investigations for Pediatric Patients-Resective Cases; 2004 Outcome ILAE Survey
SPECT


Epilepsy surgery in children: expectations and results
Patient management
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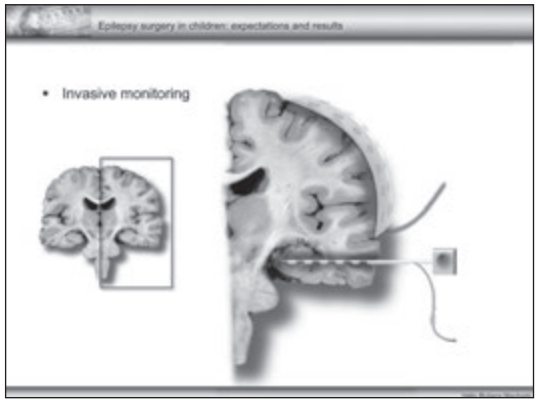

Epilepsy surgery in children: expectations and results
Invasive monitoring

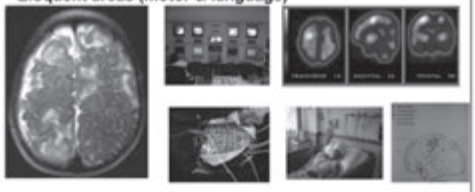
Epilepsy surgery in children: expectations and results

• 1996 to april 2008

Pathology		ECoG - Acute	Chronic
Cortical dysplasia	65	49 (75%)	11(16%)
Tumor	38	20 (52%)	-
Mesial temporal sclerosis	38	8 (21%)	2 (5%)
Rasmussen encephalitis	21	5 (23%)	-
Tuberous sclerosis	11	9 (81%)	5 (45%)
Porencephaly	10	4 (40%)	-
Gliosis	37	19 (51%)	5 (13%)
MR normal	9	1	1
Sturge-Weber	6	4	2
Diffuse atrophy	5	1	-
Arterio-venous malformation	3	2	-
(unknown 1)	Total 244	122 (50%)	26 (11 %)

Epilepsy surgery in children: expectations and results

- Epileptic zone can be identified?
- Eloquent areas (motor & language)



Epilepsy surgery in children

SURGERY

1996 to 2011sept

Children 378
Surgeries 401

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

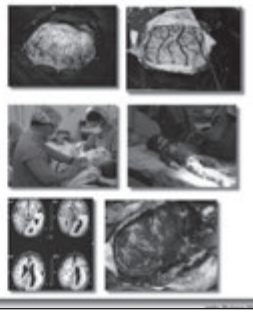
Surgical technique	
Temporal Lobectomy	100
Hemispherotomy	93
Lesionectomy	77
VNS	34
Posterior(par-occipital) cortex	26
Frontal Lobectomy	24
Callosotomy	16
Focal Corticectomy	14
Occipital Lobectomy	12
Multilobar Resection	5
(reoperation 22)	
Total	401

Epilepsy surgery in children: expectations and results

Complexity of pediatric surgery

- Early surgey = major risk

Focal resection	200 – 500 ml
Hemispherectomy	1500 ml
Hemispherotomy	500 ml

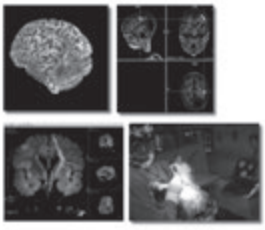


Epilepsy surgery in children: selection criteria

- Ideal situation
  - Precise and comprehensive definition of epileptogenic zone by combination of invasive and non-invasive investigations
  - EZ and eloquent zones separate and distinct
  - Complete resection renders seizure free
- Reality
  - Investigations often non-concordant
  - EZ may incorporate eloquent areas

Cirurgia da epilepsia na infância

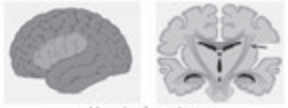
- Which technologies?
  - Neuroimaging
    - 3T, DTI, spectroscopy, fMRI, spect, MEG
  - Surgical tools
    - Neuronavigation
    - Endoscopic techniques, ultrasonic aspirator, brain sonography



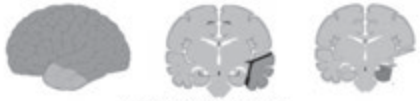
Epilepsy surgery in children: expectations and results

Complexity of pediatric surgery

- Age at surgery
- Pre-op mental retardation
- Early surgey = major risk
- Surgical technique



Hemispherotomy



Temporal lobe surgery

Epilepsy surgery in children

- Neurosurgery – microsurgery
  - Unequivocal trend toward microsurgery or minimally invasive approaches
  - Role of the surgical microscope – one of the major advances of contemporary neurosurgery
    - Allows better identification of anatomical planes
    - Better exposure to deep structures with narrow corridors
    - Epilepsy surgery? Advantages:
      - Hemostasis
      - Surgical duration
      - Low Infection rate
      - Early discharge from hospital

Epilepsy surgery in children

	Results (+)	risk
Large resection	Complete resection of EZ	Deficit
Small resection	No deficit	Persistent seizures Multiple interventions

Epilepsy surgery in children: selection criteria

- Typical surgical syndromes
  - Catastrophic epilepsy
- Pediatric epilepsy unit
  - Referral
  - Presurgical evaluation
- Outcome assessment for pediatric surgical patients
  - Long-term follow up

Cross et al, 2006 : Proposed criteria for referral and evaluation of children...

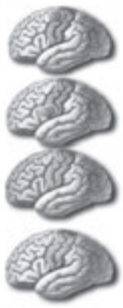
Epilepsy surgery in children: expectations and results

Rasmussen encephalitis: long-term outcome after surgery
Terra, Scorza, Machado et al., 2009

Outcome of hemispheric surgeries for refractory epilepsy in pediatric patients
Terra, Sakamoto, Machado et al., 2007

Temporal lobe epilepsy surgery in children and adolescents: Clinical characteristics and post-surgical outcome
Terra, Sakamoto, Machado et al., 2005

Epilepsy surgery in children: expectations and results



Rolandic Epilepsy
48 cases

Tailored resections for intractable rolandic cortex epilepsy in children: a single-center experience with 48 consecutive cases

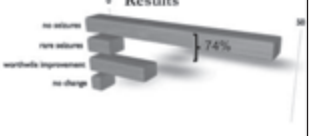
Results: 1 & 3 y f.u.

Cortical Dysplasia

Surgery (2008)

Lobectomy	
Frontal	18
Temporal	19
Parietal	3
Occipital	10
Multilobar	8
Hemispherotomy	16
Total	**74**

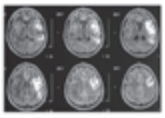
Results



New classification – preliminary results

Cortical Dysplasia	Engel I (%)
Type I	56
Type I + others (**Type III**)	71
Type II (Taylor)	60

RASMUSSEN ENCEPHALITIS IN CHILDHOOD



Children : 22 (2008)

1. **Refractory epilepsy**
   - Focal motor seizures
   - Epilepsia partialis continua - 21
2. **Neurological deficit**
   - Hemiparesis - 20
   - Aphasia – 8
   - Intellectual impairment - 22
3. **Affected side**
   - Right – 11 / Left – 11
   - < 6 y age – R -7 / L - 7

Rasmussen encephalitis

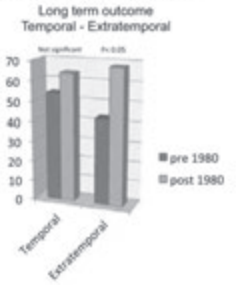
Patients:

- **Results**
  - **Motor function**
  - **Language – no change**
    - **Aphasia pre-op - 6**
    - **Normal pre-op - 2**

Pre op \ Post op	Walking	Not walking
Walking	12	2
Not walking	4	1
total	16	3

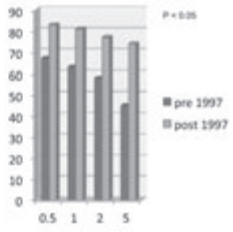
Do outcomes improve as technology improves?

Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis



Do outcomes improve as technology improves?

Improved outcomes in pediatric epilepsy surgery
The UCLA experience 1986 - 2008



Improved outcomes in pediatric epilepsy surgery
The UCLA experience, 1986–2008

CONCLUSIONS

- Surgical treatment of epilepsy in children is effective and can offer good results concerning outcome.
- More studies are necessary to evaluate the effect of surgery and of new technologies in cognition and outcome.
- New technologies can be extremely helpful for the surgeon allowing more accurate targets and reducing the risk of post operatory deficits.

Thank you

CIREP – CENTER FOR EPILEPSY SURGERY

Faculdade de Medicina de Ribeirão Preto
Universidade de São Paulo

Manuel Campos (Chile)

SURGERY IN ADULTS

"Treatment of symptomatic epilepsy"

Dr.med. Manuel Campos
Epilepsy Center. Clínica Las Condes. Santiago, Chile
Chairman. Latin America Commission ILAE

CLC

Introduction

CLC

EPILEPSY CLASSIFICATION

population-based studies of unprovoked seizures and epilepsy in children and adults

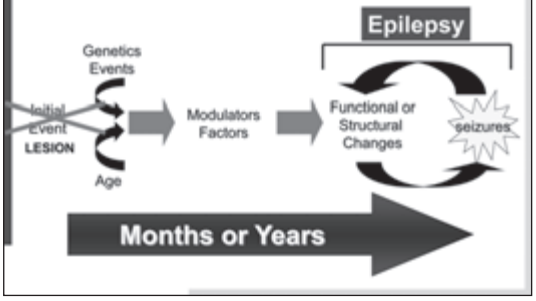
-33 to 42% are classified as symptomatic.

-21 to 53% cryptogenic (lesion or functional disorder is suspected but unproven).

-14 to 37% idiopathic (presumed to be genetically mediated).

-Olafsson E, et al. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol 2005;4(10):627–34 – Loiseau P, et al. One-year mortality in Bordeaux cohort: the value of syndrome classification. Epilepsia 2005;46(S11):11–14

Events in Epileptogenesis



Epilepsies: Etiologies

IMPOSIBLES TO PREVENT:	POSSIBLE TO PREVENT:
- Hippocampal Sclerosis	- Head Injury
- Tumors	- Birth anoxia
- Cortical Dysplasia	- Infections
- Cavernous Angioma	-¿Stroke?
- Genetics changes	- Others.
- Others.	

Problems

"Treatment of symptomatic epilepsy"

First Problem

Syndromes versus Seizures

Epileptics Syndromes (ILAE 01')

1. Crisis Neonatales benignas familiares
2. Encefalopatía mioclónica temprana
3. Síndrome de Ohtahara
4. Crisis parciales migratorias del lactante *
5. Síndrome de West
6. Epilepsia mioclónica benigna del lactante
7. Crisis benignas del lactante (no familiares)
8. Síndrome de Dravet (antigua epilepsia mioclónica severa)
9. Síndrome HH (hemiconvulsión-hemiplejia)
10. Status mioclónico en encefalopatías no progresivas
11. Epilepsia benigna de la infancia con paroxismos centrotemporales
12. Epilepsia benigna occipital temprana (tipo Panayiotopoulos)
13. Epilepsia benigna occipital tardía (tipo Gastaut)
14. Epilepsia con ausencias mioclónicas
15. Epilepsia con crisis mioclónicas astáticas
16. Síndrome de Lennox-Gastaut
17. Síndrome de Landau-Kleffner
18. Epilepsia con punta onda continua durante el sueño
19. Epilepsia ausencias infantiles
20. Epilepsias mioclónicas progresivas
21. Epilepsias generalizadas idiopáticas con fenotipos variables
22. Epilepsia ausencias juveniles
23. Epilepsia mioclónica juvenil
24. Epilepsia con sólo crisis generalizadas tónico-clónicas
25. Epilepsias reflejas
26. Epilepsia occipital fotosensible idiopática
27. Otras epilepsias sensibles a estímulos visuales
28. Epilepsia primaria de la lectura
29. Epilepsia del sobresalto
30. Epilepsia frontal nocturna autosómica dominante
31. Epilepsias familiares del lóbulo temporal
32. Epilepsias generalizadas con crisis febriles plus *
33. Epilepsia familiar focal con focos variables
34. Epilepsias focales sintomáticas (o probablemente sintomáticas)
35. Epilepsias límbicas
36. Epilepsia temporal medial con esclerosis del hipocampo
37. Epilepsia temporal medial con etiología específica

Otros tipos definidos por la localización y la etiología

38. Epilepsias neocorticales
39. Síndrome de Rasmussen
40. Otros tipos definidos por la localización y la etiología
41. Condiciones que cursan con crisis epilépticas pero que no conllevan un diagnóstico de epilepsia
    - Crisis neonatales benignas
    - Crisis febriles
    - Crisis reflejas
    - Crisis por privación de alcohol
    - Crisis inducidas por drogas o sustancias químicas
    - Crisis postraumáticas precoces
    - Crisis aisladas o en racimo
    - Crisis repetidas ocasionalmente (oligoepilepsia)

Epilepsy: Seizures Type

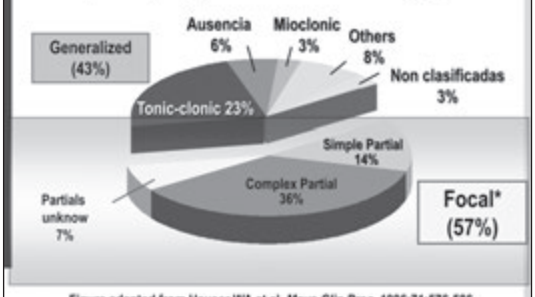


Figure adapted from Hauser WA et al. *Mayo Clin Proc.* 1996;71:576-586.

EPILEPSIES- DEFINITION

1- Epilepsy is a syndrome: a group of symptoms and sings, which have different etiologies (diseases).

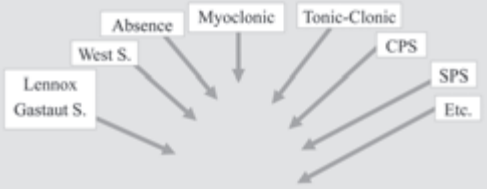
2- There is not "Epilepsy", there are "Epilepsies", with different seizures types and syndromes each one with different treatment and outcomes.

EPILEPSIES- DEFINITION

1- Epilepsy is a syndrome: a group of symptoms and sings, which have different etiologies (diseases).

2- There is not "Epilepsy", there are "Epilepsies". Diverse syndromes, each one with different treatment and outcomes.

WE CAN NOT PUT ALL EPILEPSIES IN THE SAME BAG



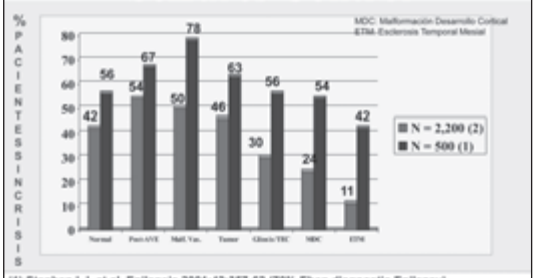
"Treatment of symptomatic epilepsy"

Second Problem

Type of Study for certificate the etiology (Lesion)

- Molecular Biologic
- Ultra-microscopic
- Histopatologic Findings
- MRI
- CT

71% of Patients with Focal Epilepsy have a lesion on MRI
(Semah, et al. Neurology 1998;51:1256-62)

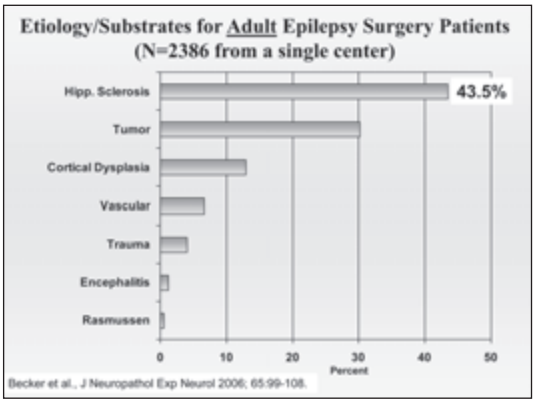


(1) Stephen L.J, et al. Epilepsia 2001;42:357-62 (70% Eben diagnostic Epilepsy)
(2) Semah F, et al. Neurology 1998;51:1256-62 (8% Eben diagnostic Epilepsy)

Primary generalized seizure types

- Generalized tonic-clonic
- Myoclonic
- Atonic
- Tonic
- Absence

Usually Normal MRI findings



Main Lesions on Epilepsy Surgery

ADULTS

Temporo Mesial Sclerosis (Hippocampal Sclerosis)

Human herpes virus 6B: A possible role in Epilepsy?

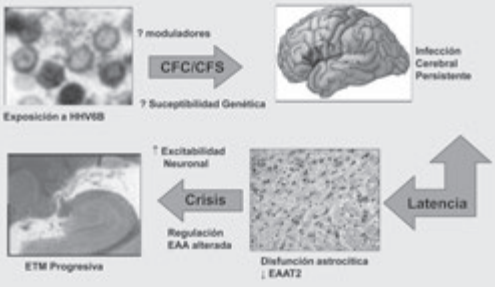
William H. Theodore et al. Epilepsia, 2001

- Double-stranded DNA virus (~ 160 Kb)
- A and B variants (75-95% homology)
- Infection in early childhood
  - ~80% by age two
  - Most mildly symptomatic, but unrecognized?
- 90% of adults sero +
- primary CNS invasion

HHV6B en Resecciones por Epilepsia

	HHV6B +	HHV6B -
ETM (23)	14	9
No-ETM (14) Tumor, AVM, cavernoma, hemimegalencefalia, MDC	0	14
Historia de crisis Febriles (9) (Todas en grupo de ETM)	5	4
Sin historia de crisis Febriles (27) (uno HHV6B + desconocido)	8	19

Rol Potential de HHV6B en ETM



Theodore WH et al. Human herpes virus 6B: A possible role in epilepsy? Epilepsia. 2008

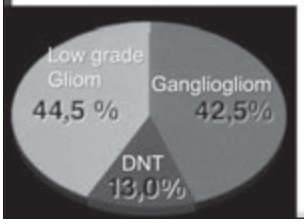
Tumors

TUMORS

- Low grade Glioms
- Ganglioglioms
- Disembrioplastic Neuroepithelial Tumor (DNT)

Surgical treatment of Neoplasm associated with medically intractable Epilepsy

Neurosurgery, 1996



TUMORS

N = 146

Trauma

Cavernous Angiom (Cavernom)

Cortical Dysplasias (CD)

Nueva Clasificación

- **Tipo I:** dislaminación radial o tangencial.
- **Tipo II:** neuronas dismórficas, balonadas.
- **Tipo III:** DCF asociada a:
  - Esclerosis Hipocampal
  - Tumores (MDC)
  - Malf. vasculares
  - TEC, lesiones isquémicas, encefalitis, etc., precoces (DCF adquiridas)

Summary (CD)

Pre-surgical Evaluation

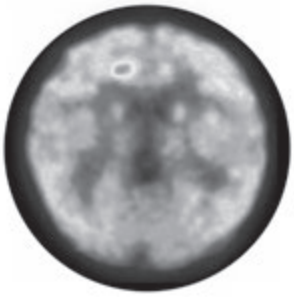
No single test 100% accurate. Multimodality evaluation

Localization and identification of CD in the presurgical evaluation:

Interictal Scalp EEG:	50%	Same mild & severe CD
Ictal Scalp EEG:	65%	Same mild & severe CD
Community MRI:	45%	Less for mild CD
Epilepsy MRI:	66%	Less for mild CD
FDG-PET:	80%	
Ictal-SPECT:	55%	

PET "Ictal"

PET Axial



RESULTS

Results in Temporal Lobe Epilepsy (TLE): Lesional versus no-Lesional

(Included All Ages)

Temporal Epilepsy (n° of Studies)	Non - Lesion N° Total Patients	Seizures Free %	95% CI
Overall (n=20)	398	45	40-49
Using MRI (n=12)	226	51	45-57
Using Histology (N=8)	172	36	29-43

Tellez et al. Surgical Outcomes in Lesional and Non-Lesional Epilepsy: A Systematic review with Meta-Analysis. Epilepsy Research, 2010

Results in Temporal Lobe Epilepsy (TLE): Lesional versus no-Lesional

(Included All Ages)

Temporal Epilepsy (n° of Studies)	Non - Lesion N° Total Patients	Seizures Free %	95% CI	Lesion N° Total Patients	Seizures Free %	95% CI
Overall (n=20)	398	45	24 %	69		66-70
Using MRI (n=12)	226	51	45-57	5[illegible]	75	71-89
Using Histology (N=8)	172	36	29 %	65		63-68

Tellez et al. Surgical Outcomes in Lesional and Non-Lesional Epilepsy: A Systematic review with Meta-Analysis. Epilepsy Research, 2010

Results in Extratemporal Epilepsy: Lesional versus no-Lesional

(included all Ages)

Extra-temporal (n° of Studies)	Non Lesion N° Total Patients	Seizures Free %	95% CI
Overall (n=13)	156	34	27-41
Using MRI (n=9)	124	35	27-42
Using Histology (N=4)	35	32	18-47

Tellez et al. Surgical Outcomes in Lesional and Non-Lesional Epilepsy: A Systematic review with Meta-Analysis. Epilepsy Research (2010)

Results in Extratemporal Epilepsy: Lesional versus no-Lesional

(included all Ages)

Extra-temporal (n° of Studies)	Non Lesion N° Total Patients	Seizures Free %	95% CI	Lesion N° Total Patients	Seizures Free %	95% CI
Overall (n=13)	156	34	32 %	66		61-70
Using MRI (n=9)	124	35	27-42	2[illegible]5	60	54-66
Using Histology (N=4)	35	32	42 %	74		67-82

Tellez et al. Surgical Outcomes in Lesional and Non-Lesional Epilepsy: A Systematic review with Meta-Analysis. Epilepsy Research (2010)

Conclusions

- Focal Epilepsies usually (≥ 70%) are associated with a structural lesion on MRI.
- Generalized Epilepsies have frequently non visible alterations on MRI.

Conclusions

- Lesional focal epilepsies are usually pharmaco resistent.
- A normal MRI is not synonym of non-lesion, because in cortical dysplasias the PET is most effective in detection.

Conclusions

- The type of lesion is different in between children and adults.
- The lesion have a direct relationship with the seizures control after the surgery.

Conclusions

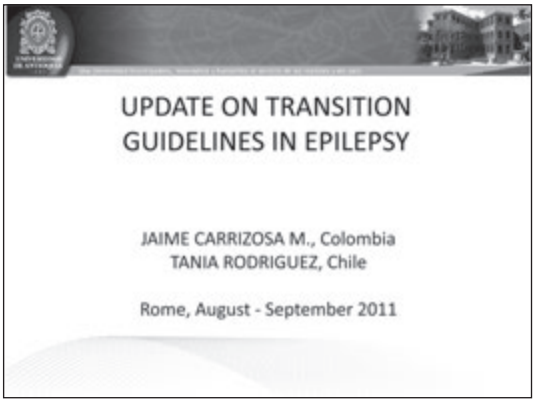
- Patients with refractory epilepsy and focal lesion (as Cavernom or Tumor) located in no eloquent area, with a concordant EEG, can go to the surgery, without other studies.

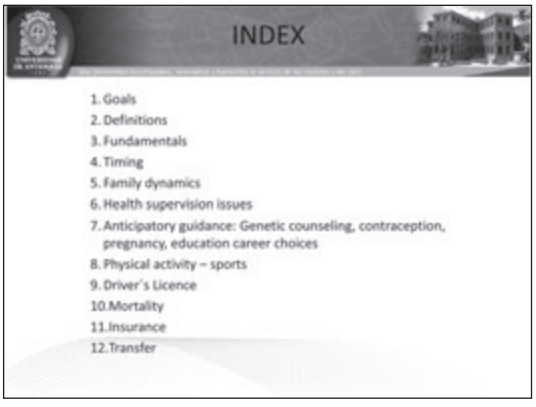
Conclusions

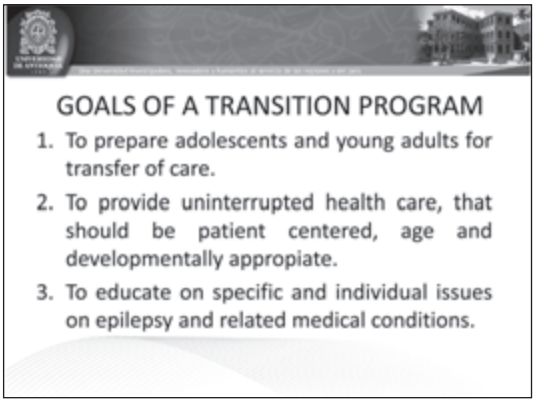
- May be in the future an early surgery, in patients with lesional epilepsy (cavernom or tumor) could prevent refractory epilepsy.

Jaime Carrizosa Moog (Colombia)

RECOMMENDATIONS FOR EPILEPSY IN THE TRANSITION TEEN-ADULT PERIOD







GOALS OF A TRANSITION PROGRAM

4. To promote communication, decision making, self care and self advocacy skills.
5. To foster personal and medical independence, sense of control over health, healthcare decisions and psychosocial environment.
6. To optimize the quality of life, life expectancy and future productivity.

DEFINITIONS

Medical transition:

The process of moving from a pediatric medical system to an adult one.

Transfer:

Time at which responsibility of patient care is passed to the adult provider.

FUNDAMENTALS OF A TRANSITION PROGRAM

"Transition is a purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions as they move from a child/familiy centered to an adult/patient centered health care system" Society of Adolescent Medicine

- Coordination by a primary care provider/team, tertiary care center or a subspeciality practice

- Education to adult providers in chronic conditions previously limited to the pediatric population

- Ongoing coordinated communication between patients, families, and pediatric and adult healthcare providers to facilitate transition and transfer.

- Acces to health care financing.

Timing of Transition

The transitional process depends on the patient´s medical and developmental status and should be individualized.

Starting time: Early and mid adolescence (?)

Steps:

- Discussion and education about diagnosis, medication and social limitations
- Promote self care skills
- Foster healthy behaviours and discuss risks of emotional lability (depression),smoking, alcohol, "recreational" drugs and unsafe sex

Timing of Transition

-Advice on birth control, pregnancy, genetics and long term outcome

- Consider future expectations for education, employment and independent living

- In patients with cognitive disability the timing of transition will be altered as appropriate (?)

EPILEPSY - FAMILY DYNAMICS

It is possible that the quality of the parent – adolescent relationship, and not the disease severity, holds the key to succesful transition, with a perceived parental acceptance having a more positive effect on adolescent psychological well being.

- Impact of a chronic illness as related to epilepsy.
- Medical monitoring, medication adjustments, hospitalizations and absences from school can affect self image and self esteem, "feeling different".
- Cultural and familiy perception on the diagnosis and treatment of epilepsy.
- Higher risk of internalizing (anxiety, depression), externalizing (aggresion, hyperactivity) behaviour problems.

EPILEPSY - FAMILY DYNAMICS

- Overprotection and dependency on parents.
- Fear of forming close relationships because of shame and not having the "self control" over the unpredictable seizure.
- Perceived and directed stigma.
- Higher risk of learning disorders and neuropsychological problems.
- Whether or not to discolse their epilepsy.

HEALTH SUPERVISION ISSUES

Role of primary care physcian/team - child neurologist:

-Accesible, comprehensive medical record with pertinent information concerning: diagnosis, medication schedule(s), neuroimaging, electrophysiological, neuropsycological studies, comorbidity, seizure follow up.

- Written transition plan that includes adult care destination.

HEALTH SUPERVISION ISSUES

•Periodic evaluation of: medication adherence, drug interactions, seizure control, adverse effects, plasma concentration, liver function, blood tests, EEG.

•Health-social maintenance needs: weight/height/BMI, nutritional counseling, vaccinations, contraception and sexuality issues, assesment of tobacco, alcohol and drug use, emotional status, academic achievment, sleep requirements, sports, social activity.

ANTICIPATORY GUIDANCE – GENETIC COUNSELING

•As the adolescent approaches the reproductive years, the cause of the epilepsy and inheritance patterns should be addressed accordind to his maturity status.

•These investigations can potentially define the risk to the adolescent/adult´s offspring.

•Targeted family history and tree construction; genetic evaluation to define a syndromic versus a non syndromic disorder; cytogenetic and/or molecular testing if indicated.

ANTICIPATORY GUIDANCE – SEXUALITY, PREGNANCY AND REPRODUCTIVE ISSUES

Contraception:

-Oral contraceptives
-Intrauterine device
-Male condom
-Emergency contraception
-Permanent sterilization

Drug interaction between oral contraceptives and AED.(?)

ANTICIPATORY GUIDANCE – SEXUALITY, PREGNANCY AND REPRODUCTIVE ISSUES

Pregnancy:

•Adolescent pregnancy is considered high risk from psychological, medical and sociological perspectives.

•Pregnancy interrupts normal develpomental tasks by forcing teens to assume adult responsibilities.

•They frequently fail to seek early prenatal care and are often noncompliant with medical recommendations.

Pregnancy:

- Higher risk of anemia, pregnancy induced hypertension, preterm births and low birth weight infants.

- Additional maternal and fetal risk posed by seizures.

- Risk of teratogenesis.

- Risk of STD exposure.

- Acces to care, health coverage and ambivalence about informing her pregnancy.

Pregnancy:

- Pregnancy termination, emotional impact.

-Continue pregnancy: pregnancy and delivery plan, focus on seizure control, medication schedule and monitoring, teratogenisis prevention/ammelioration (?)

- Keeping the baby or placing the baby into adoptive services.

ANTICIPATORY GUIDANCE – EDUCATION AND CAREER CHOICES

Academic achievement, learning disabilities, behavioural problems, inattention/hyperactivity and other psychological issues must be taken into account when planning for transition, because they all can significantly impact an adolescent´s ability to learn and assume responsibility for their health care.

Education and employment are crucial to financial security and psychological well being and therefore represent another important concern for these adolescents.

The risk for unemployment for adults with epilepsy can be expected and may be related to misunderstanding, lack of knowledge and stigma on epilepsy by employers.

EDUCATION AND CAREER CHOICES

Challenges for PWE entering the workforce: discrimination, changes in functional physical and mental capacity, unpredictability of seizures, medication side effects.

Career and education plans should be discussed during adolescence to allow for assesment of the patient´s mental, physical and social abilities.

This assesment should include the patient, family, educators, career advicers and the healthcre provider.

The adolescent should know the legal rights protecting him at workplace.

EDUCATION AND CAREER CHOICES

Patients and parents should be educated about any possible restriction that might affect ability to work (overnight work, military service or cereer, pilot etc).

For patients who are handicapped physically or mentally, vocational education, training and work should be encouraged.

PHYSICAL ACTIVITY - SPORTS

Physical activity should be encouraged; a sedentary lifestyle can contribute to other comorbid conditions such as obesity, coronary artery disease, hypertension, diabetes mellitus, dyslipidemia and osteoporosis.

There is some experimental and clinical evidence that physical and active alertness reduces seizure frequency and stabilizes mood.

Experimental studies have shown that physical activity reduces the risk of SUDEP.

PHYSICAL ACTIVITY - SPORTS

Safe types or low risk exercise and recreational activities should be recommended.

Measure the risk of injury according to seizure control, type of activity and protection elements (scuba diving, horse riding, motorcycling, rappeling, swimming etc.)

DRIVER´S LICENCE

Legislation on driver´s licence for PWE is widespead, ranging from no explicit legal to almost a total restriction to drive.

Seizure control for two or more years is "generally" accepted to get a driver´s licence.

What if driving is considered a fundamental part of the job? What about public transportation – bus driving?

MORTALITY

Mortality rates for PWE are higher than for the general population caused mainly by suicide, SUDEP, drowning and other accidents.

Psychiatric symptoms of depression/anxierty, suicidal ideation and other behavioural problems should be checked routinously and effectively treated.

A good treatment adherence, physical activity and omega 3 supplementation have demonstrated SUDEP reduction rates in experimental models.

INSURANCE – HEALTH/LIFE

Some countries have a coverage for children and adolescents with epilepsy (National Epilepsy Programs); most do not have a coverage at all and it depends on the familiy income.

Poverty and the presence of a disability influence negatively healthcare coverage of young adults.

Adolescents and young adults are living the "wonder inmortal years" and do not necessarily measure de risks of a chronic disease; so they do not seek a health or life insurance.

INSURANCE – HEALTH/LIFE

Healthcare providers should address the issue of insurability before patients with epilepsy leave their parent´s policy or lose their elegibility for children´s services.

Getting a job is onother opportunity to have a health insurance in many parts of the world.

TRANSFER

•Transfer of care from the pediatric to adult healthcare system occurs at the successful completion of a thoughtful transition process.

•Transition and transfer occur on a predictable manner.

•Transition and transfer should be considered as a rule or as a natural process that everyone goes through.

•Flexibility has to be considered according psychosocial and developmental characteristics of the individual patient.

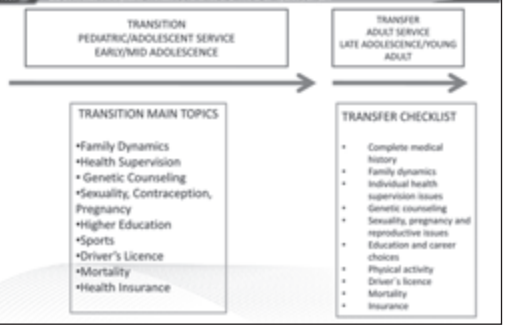
TRANSFER

Coordination between pediatric and adult services or health care proffesionals.

Transfer Checklist:

1. Complete medical history
2. Family dynamics
3. Individual health supervision issues
4. Genetic counseling
5. Sexuality, pregnancy and reproductive issues
6. Education and career choices
7. Physical activity
8. Driver´s licence
9. Mortality
10. Insurance

TRANSITION AND TRANSFER PROCESS



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PRESENTATION AND DISCUSSION OF RESEARCH PROJECTS PREPARED BY THE STUDENTS