5ª. ESCOLA LATINO-AMERICANA DE VERÃO DE EPILEPSIA
5ª. ESCUELA LATINO-AMERICANA DE VERANO DE EPILEPSIA
5th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 20 Fev. - 1 Mar 2011
Centro de Convenções Santa Mônica

COORDENAÇÃO GERAL: Prof. Dr. Esper A. Cavalheiro

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

PRESIDENTE DA LIGA BRASILEIRA DE EPILEPSIA (LBE):
Prof. Dr. Veriano Alexandre – HCFMUSP Ribeirão Preto

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

GERENTE EXECUTIVO DA ACADEMIA LATINO-AMERICANA DE EPILEPSIA (ALADE):
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Epilepsia, Comportamento, e Cognição

A definição de epilepsia se estende muito além da ocorrência de crises epilépticas espontâneas e engloba um espectro de manifestações comportamentais, psiquiátricas e cognitivas. Os dados científicos dos fatores responsáveis por estas associações vão se acumulando e incluem a compreensão da participação das lesões estruturais, dos fármacos antiepilépticos e da hiperexcitabilidade elétrica na eclosão dos distúrbios cognitivos em crianças, adultos e idosos e das encefalopatias epilépticas do lactente, muitas vezes irreversíveis, bem como dos distúrbios comportamentais e psiquiátricos, os quais, não infrequentemente antecedem o início das crises clínicas. A V LASSE-2011 com a participação de eminentes neurocientistas nacionais e internacionais, básicos e clínicos, enfatiza a estruturação da cognição humana e sua desintegração pelo processo epiléptico. A compreensão destes mecanismos alicerça o desenvolvimento de formas de prevenção.

Programa – 20.02.2011

08:00 – 09:00	Welcome address
09:00 – 10:00	The new ILAE proposal for classification of seizures and syndromes – Peter Wolf (DK)
10:00 – 10:30	Coffee break
10:30 – 11:30	Neonatal seizures - Regina M. F. Fernandes (Brazil)
11:30 – 12:30	Seizures during infancy – Vera Cristina Terra (Brazil)
12:30 – 14:00	Lunch
14:00 – 15:00	Seizures during adolescence – Katia Lin (Brazil)
15:00 – 16:00	Seizures in the adulthood – Luis Otávio Caboclo (Brazil)
16:00 – 16:30	Coffee break
16:30 – 17:30	Seizures in the elderly – Veriano Alexandre Junior (Brazil)
17:30 – 18:30	Towards a new classification of focal cortical dysplasia – Roberto Spreafico (Italy)
18:30 – 20:00	Dinner
20:30 – 21:30	Mind in Antiquity – F. Mario Fales (Italy)

THE NEW ILAE PROPOSAL FOR CLASSIFICATION OF SEIZURES AND SYNDROMES
PETER WOLF (DK)

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

LASSE V, Guarulhos February 20 – March 1, 2010

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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 comments of several experts in the same issue of *Epilepsia*, pp 713-724

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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 (**παθος**) 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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Otto Ludwig Binswanger (1899, 1913): Die Epilepsie

Epilepsy is one of the three "great diffused neuroses", i.e. disorders of the CNS without gross pathology.

Book entirely dedicated to idiopathic epilepsy

Ætiopathogenesis largely discussed. Are the anatomical findings, such as Ammon's horn sclerosis, cause or consequence of epilepsy?

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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, and in 1886 operated upon this analysis.

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

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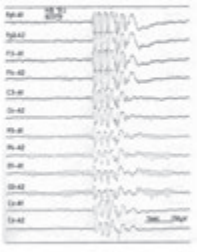
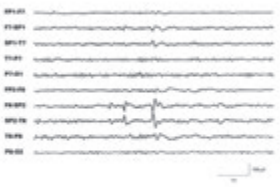
The dichotomy focal ./. generalized is based upon the EEG





It is ~ 70 yrs old

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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

Why?

- Ictal EEG in BECTS, topographic mapping (Jung et al 2003): rolandic spikes originate from sulcal or gyral cortices on either side of the central sulcus, propagation from central to mid-temporal locations across the central sulcus by intracortical spreading
- Primary Reading Epilepsy: fMRI study of orofacial reflex myocloni triggered by reading

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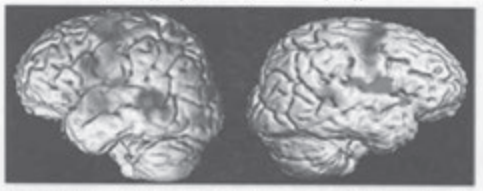
Primary Reading Epilepsy: the findings

FULL-LENGTH ORIGINAL RESEARCH

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

*Afraim Salek-Haddadi, †Thomas Mayer, *Khalid Hamandi, *Mark Symms, ‡Oliver Josephs, *Dominique Fluegel, §Friedrich Woermann, *Mark P. Richardson, ‖Uta Noppeney, ¶Peter Wolf, and *Matthias J. Koepp



Reading-induced szs **Language activations** **Motor mapping mouth/jaw**

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"Reflex szs occur in RE when a critical mass of neurons are activated through a provoking stimulus within cortico-reticular and cortico-cortical circuitry subserving normal funtions." (Salek-Haddadi et al. Epilepsia 2009; 50:256-264)

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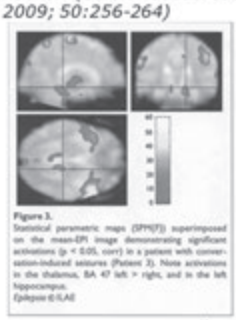

Figure 3.
Statistical parametric maps (SPM{T}) superimposed on the mean-EPI image demonstrating significant activations ($p < 0.05$, corr) in a patient with conversation-induced seizures (Patient 3). Note activations in the thalamus, BA 47 left > right, and in the left hippocampus.
Epilepsia © ILAE

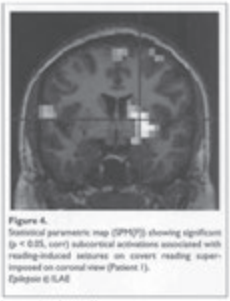

Figure 4.
Statistical parametric map (SPM{T}) showing significant ($p < 0.05$, corr) subcortical activations associated with reading-induced seizures on covert reading superimposed on coronal view (Patient 1).
Epilepsia © ILAE

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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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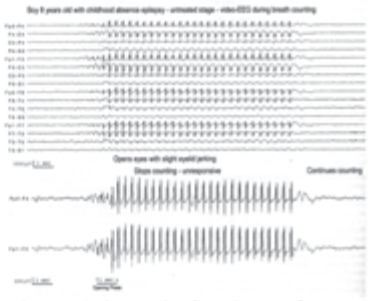
Generalised SW discharges typically are symmetric, synchronous and widespread -

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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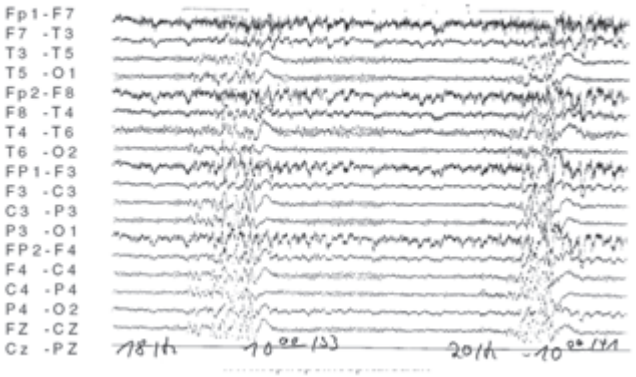

"pseudofocal" discharge

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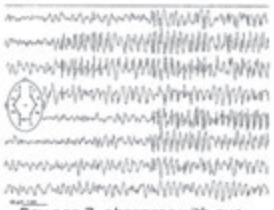
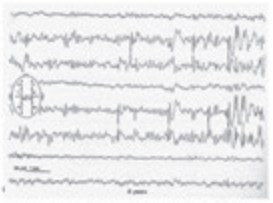


Boy age 7, absences with eye deviation to left. Benign course.



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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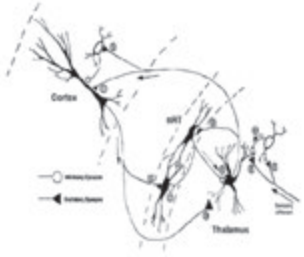

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Thalamic changes in IGE:$H_2{}^{15}O$-PET

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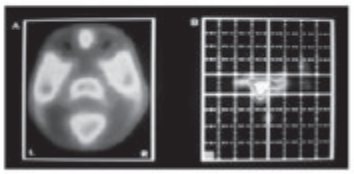
- Absences: global ~15% rCBF increase
  Thalamus: additional +4 - 8%



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: Quantitative MRT

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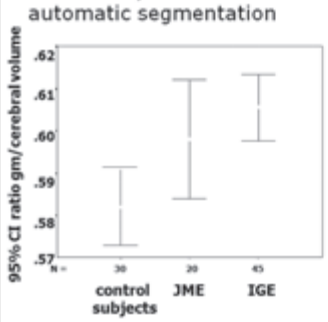
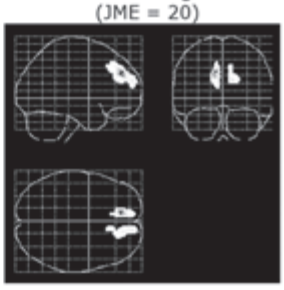
Volumetry with semi-automatic segmentation



Woermann FG et al. Brain 1998

SPM based comparison with semi-automatic segmentation (JME = 20)



Woermann FG et al. Brain 1999

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"Frontal" changes in JME: EEG - triggered fMRI

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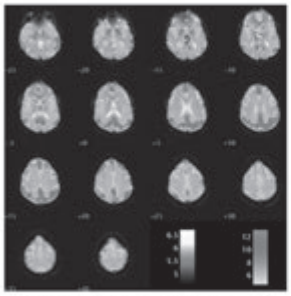
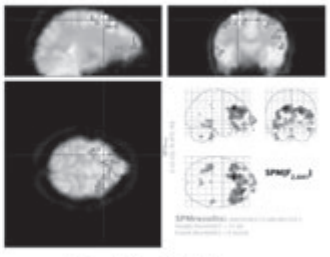


Frontal de-activations

(Salek-Haddadi et al., Ann Neurol 2003;53:663-7)



Frontal activations: 2 / 10 investigations

Hamandi K et al.

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

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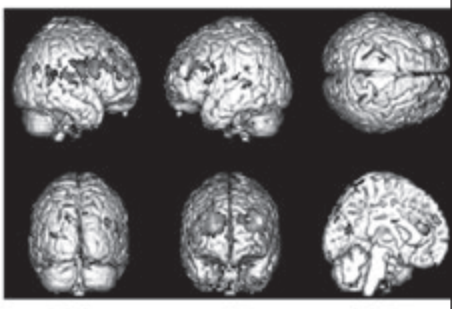
JME:
Global ⇑ of FMZ binding ($GABA_A$ receptors), especially in dorso-lateral pre-frontal cortex -

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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TV-induced seizures: photoparoxysmal EEG response

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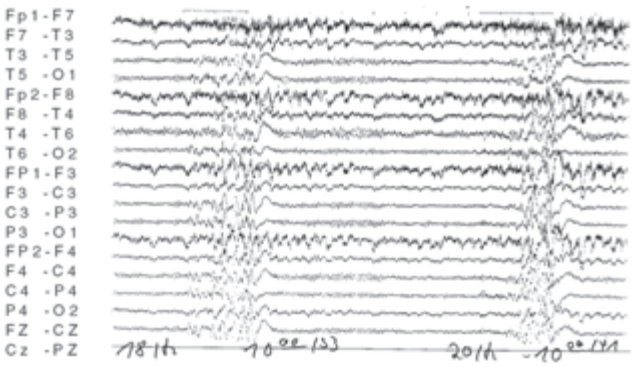

Reflex epilepsies indicate ictogenic mechanisms

(Bickford and colleagues 1953)

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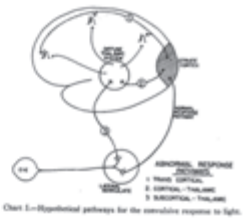
Pathophysiology: three possible pathways of convulsive effects of ILS:

1. Transcortical
2. Cortical-thalamic (eye → striate cortex → diffuse thalamic system → motor cortex)
3. Subcortical (eye → lateral geniculate body → thalamus → motor cortex

Very little discussed

Tools for study of these only recently available



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Thalamus, FS + absence: fMRI

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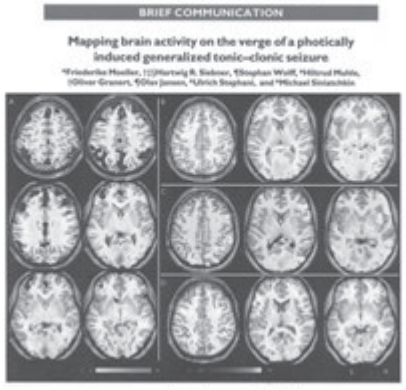

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Conclusion

These findings support Bickford's 3rd hypothesis (involvement of lateral geniculate body in photosensitive seizures) but

- It's only one case
- The seizure is an absence, not a myoclonic sz
- The process is more complex than that

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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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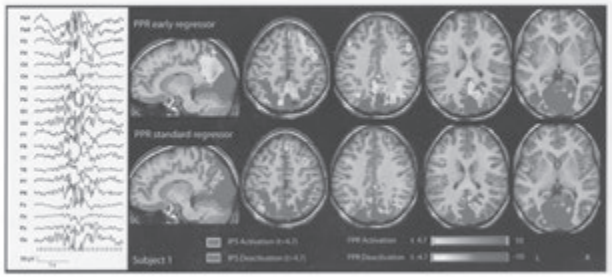
10 yr old girl with IGE and 2 generalized tonic seizures, photosensitive, no spontaneous SW



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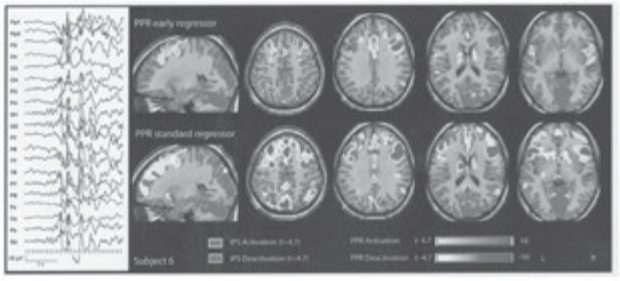
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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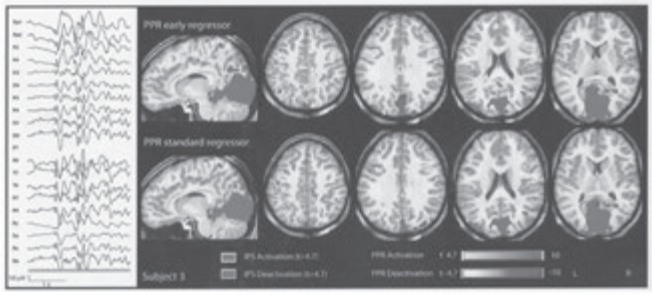
15 yr old girl with CEA, seizure free with VPA. No spontaneous SW. Only case with thalamic activation at PPR



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Authors' conclusion

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- "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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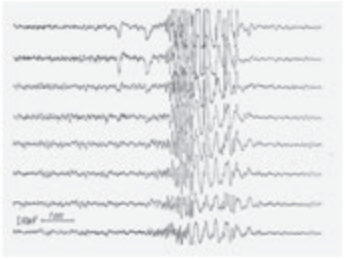
Other reflex epileptic traits in IGE:
- eye closure sensitivity



in JME, from Janz & Christian, 1957

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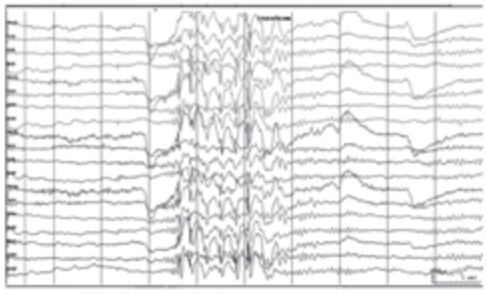
Eyelid myoclonias following spontaneous eye closure
(courtesy of Mirian Guaranha, São Paolo)



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Eye closure sensitivity

- SW within 2 sec after eye closure
- Regional accent of SW: variable
- In IGE 5 – 10 % (?) of patients
- Particularly related to eylid myocloni
- Pathophysiology: short reflex loop = proprioception of eyelid movement ⇒ eyelid myocloni
- Occipital involvement?
- No functional studies but EEG presently available

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

- 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

- 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
- No functional studies presently available

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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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Absence seizures: Individual patterns revealed by EEG-fMRI

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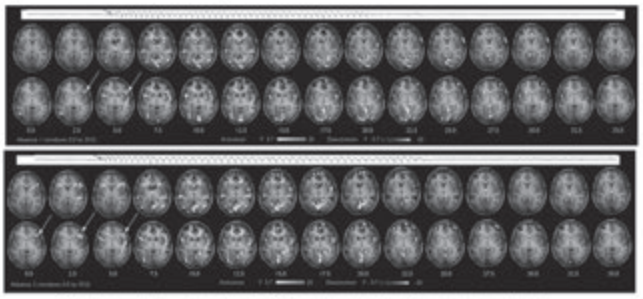

Sliding window analysis of 2 absences in the same patient

From: Moeller F et al. Epilepsia 2010

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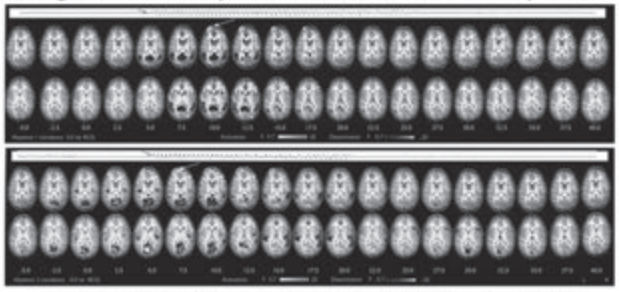
Sliding window analysis of 2 absences in other patient



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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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 +?)
- 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).

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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)

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Commission Report 2010

EPILEPSIHOSPITALET FILADELFIA

"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."

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Commission Report 2010

EPILEPSIHOSPITALET FILADELFIA

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Commission Report 2010

EPILEPSIHOSPITALET FILADELFIA

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No change of terms proposed
Falls short of the progress made

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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

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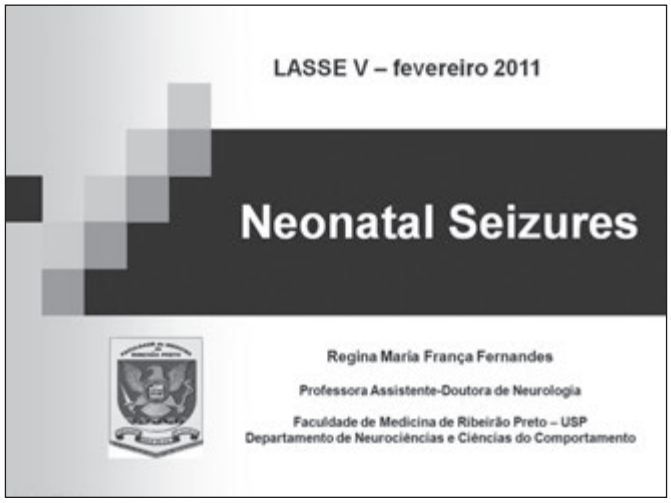
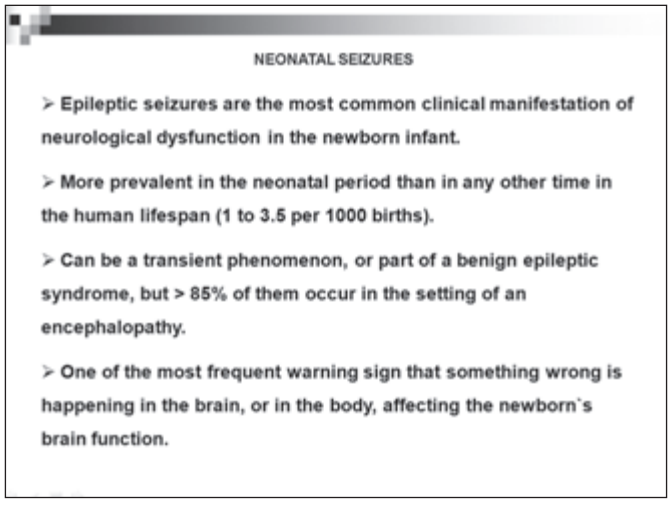
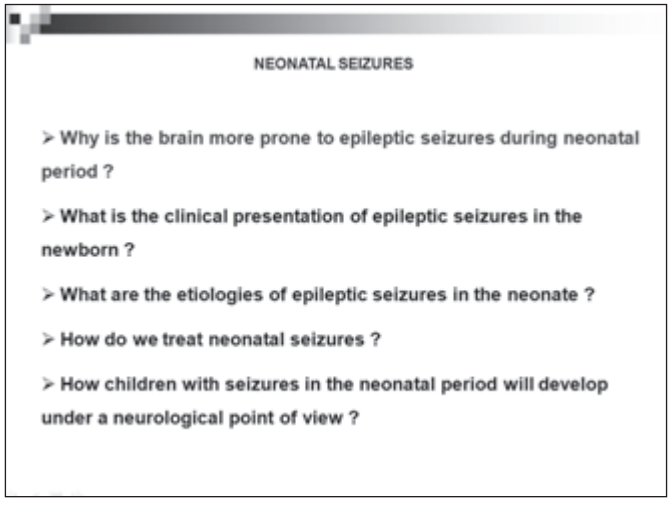
Neonatal seizures
Regina M. F. Fernandes (Brazil)

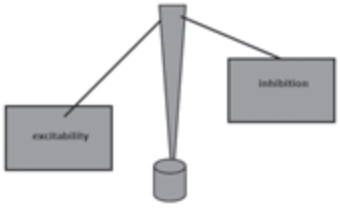






Neonatal Epileptic Seizures

- Particular mechanisms of excitability, different from other age ranges



Neurobiological Predisposition to Epileptic Seizures in the Newborn

- Glutamate (major excitatory neurotransmitter in CNS) is overexpressed during the neonatal period;
  - NMDA receptors more abundant in the variety NR2B subunit ⇒ longer current decay times and increased excitation
  - AMPA receptors with higher proportion lacking the GluR2 subunit ⇒ increased excitation and neuronal firing from enhanced Ca^{2+} at the receptor

Lawrence R, Inder T. Neonatal Status Epilepticus. *Seminars in Pediatric Neurology* 2010; 17: 163-168

Neurobiological Predisposition to Epileptic Seizures in the Newborn

- GABA (major inhibitory neurotransmitter in CNS) show alteration in expression and distribution in the newborn brain
  - Alfa 4 and Alfa 2 subunits overexpressed in comparison to Alfa 1, which is seen more in adult brain (explains the observed resistance to Benzodiazepines in the treatment of neonatal seizures

Lawrence R, Inder T. Neonatal Status Epilepticus. *Seminars in Pediatric Neurology* 2010; 17: 163-168

Neurobiological Predisposition to Epileptic Seizures in the Newborn

➢ In adult brain ⟹ low concentration of Cl^- ions inside the neurons, due to a net efflux of Cl^- out of the cell, through the KCC2 Cl^- transporter

- Substances binding to this GABA receptor lead Cl^- to flow down this gradient and into the neuron leading to hyperpolarization
- In mature brain, GABA agonists have inhibitory effect
- In immature brain this chloride gradient is reversed (low concentration of KCC2 Cl^- transporter and overexpression of NKCC1, which pumps chloride into the cell). The Cl^- gradient is reversed with a higher percentage of Cl^- ions inside the neuron

Lawrence R, Inder T. Neonatal Status Epilepticus. *Seminars in Pediatric Neurology* 2010; 17: 163-168

Neurobiological Predisposition to Epileptic Seizures in the Newborn

➢ The same GABA agonist that produced hyperpolarization in the mature neuron will instead lead to a net flux of Cl^- out of the cell. This critical difference in Cl^- distribution and GABA binding will result in a paradoxical depolarization of the immature neuron

- may be the basis for the failure of medications such as Phenobarbital and Benzodiazepines (GABA agonists) to control seizure activity in neonates

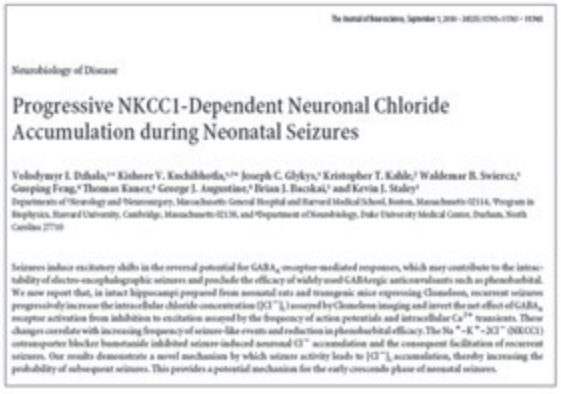
Lawrence R, Inder T. Neonatal Status Epilepticus. *Seminars in Pediatric Neurology* 2010; 17: 163-168

Neurobiological Predisposition to Epileptic Seizures in the Newborn

➢ Cl^- gradient matures in a caudal to rostral direction during development

- Mature inhibition of motor neurons within spinal cord and brainstem from GABAergic anticonvulsant compounds, with continnuous depolarization of cortical neurons ⟹ electromechanical dissociation (cessation of motor symptoms of the seizures with persistence of the electrographic seizures) with drugs such as Phenobarbital and Midazolam

Lawrence R, Inder T. Neonatal Status Epilepticus. *Seminars in Pediatric Neurology* 2010; 17: 163-168



The Journal of Neuroscience, September 1, 2010 • 30(35):11745–11761 • 11745

Neurobiology of Disease

Progressive NKCC1-Dependent Neuronal Chloride Accumulation during Neonatal Seizures

Volodymyr I. Dzhala,[1,2] Kishore V. Kuchibhotla,[1,2] Joseph C. Glykys,[1] Kristopher T. Kahle,[3] Waldemar B. Swiercz,[1] Guoping Feng,[4] Thomas Kuner,[5] George J. Augustine,[5] Brian J. Bacskai,[2] and Kevin J. Staley[1]
[1]Departments of [2]Neurology and [3]Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, [4]Program in Biophysics, Harvard University, Cambridge, Massachusetts 02138, and [5]Department of Neurobiology, Duke University Medical Center, Durham, North Carolina 27710

Seizures induce excitatory shifts in the reversal potential for $GABA_A$ receptor-mediated responses, which may contribute to the intractability of electroencephalographic seizures and preclude the efficacy of widely used GABAergic anticonvulsants such as phenobarbital. We now report that, in intact hippocampi prepared from neonatal rats and transgenic mice expressing Clomeleon, recurrent seizures progressively increase the intracellular chloride concentration ($[Cl^-]_i$) assayed by Clomeleon imaging and invert the net effect of $GABA_A$ receptor activation from inhibition to excitation assayed by the frequency of action potentials and intracellular Ca^{2+} transients. These changes correlate with increasing frequency of seizure-like events and reduction in phenobarbital efficacy. The Na^+-K^+-$2Cl^-$ (NKCC1) cotransporter blocker bumetanide inhibited seizure-induced neuronal Cl^- accumulation and the consequent facilitation of recurrent seizures. Our results demonstrate a novel mechanism by which seizure activity leads to $[Cl^-]_i$ accumulation, thereby increasing the probability of subsequent seizures. This provides a potential mechanism for the early crescendo phase of neonatal seizures.

- Why is the brain more prone to epileptic seizures during neonatal period ?
- What is the clinical presentation of epileptic seizures in the newborn ?
- What are the etiologies of epileptic seizures in the neonate ?
- How do we treat neonatal seizures ?
- How children with seizures in the neonatal period will develop under a neurological point of view ?

Epileptogenesis in the immature brain

- Sinaptogenesis first developed in limbic and mesio-temporal structures ⟹ predominance of limbic semiology in neonatal seizures
- Deficient myelinization ⟹ seizure spreading = inconstant, incomplete, not organized according to Penfield humunculus ⟹ GTC seizures virtually absent in the neonate.

Neonatal Epileptic Seizures

Clinical Semiology

- Motor automatisms
- Autonomic manifestations
- Positive motor phenomena (clonic, tonic, myoclonic)

Neonatal Epileptic Seizures

Semiological Classification according to Volpe

- Subtle
- Clonic
  - Focal, multifocal
- Tonic
  - Focal, generalized
- Myoclonic
  - Focal, multifocal
  - Generalized

Volpe J, 1995. In: Neurology of the Newborn, Saunders, 3rd Edition

Neonatal Epileptic Seizures

Semiological Classification according to Volpi

Subtle Seizures

- ❑ Motor automatisms (pedaling, roaming, swiming, posturing, succing, tongue thrusting...)
- ❑ Ocular manifestations: eye opening or fixation, blinking, eye deviation, nistagmus
- ❑ Autonomic manifestations: apnea, paleness, cyanosis, brushing, arterial hypertension, bradicardia, taquicardia
- ❑ Outros: hiccups

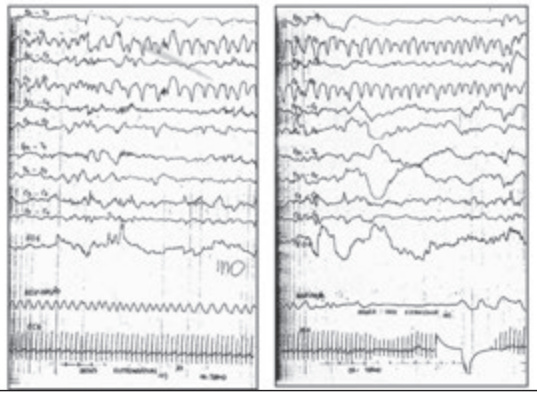
Neonatal Epileptic Seizures – clinical semiology

Electroclinical classification of Neonatal Epileptic Seizures
Mizrhai & Kellaway, 1987

- Clinical seizures with consistent electrocortical correlation (electroclinical)
- Clinical seizures without consistent electrocortical correlation
- Electrographic seizures (electromechanical dissociation)
- Infantile spasms

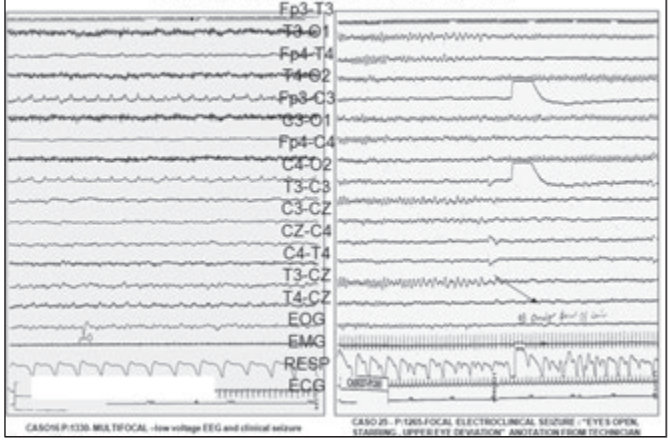
Neonatal Epileptic Seizures

Seizures with consistent electrocortical correlate



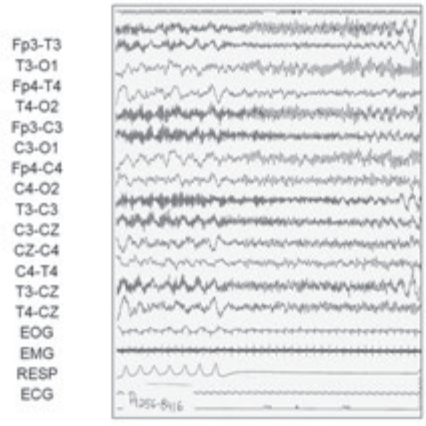
Neonatal Epileptic Seizures

Seizures with consistent electrocortical correlate



Neonatal Epileptic Seizures

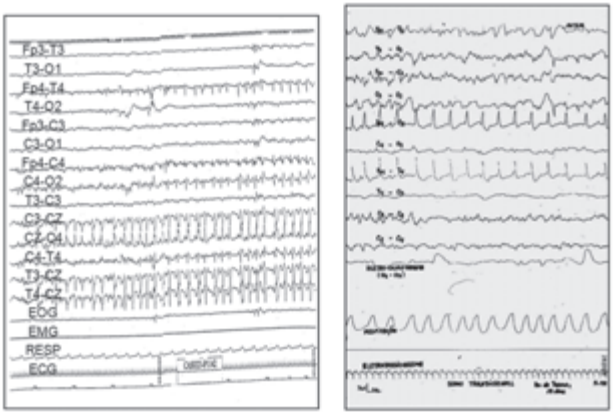
Seizures with consistent electrocortical correlate



CASE 25 P.1256 APNEA SEIZURE – MASTERS THESIS from Fabiana Penedo Leme – FMRP- USP - 2005

Neonatal Epileptic Seizures

Electrographic Seizures



Neonatal Epileptic Seizures – clinical semiology

Seizure	Electrographic Correlation	
	Common	Uncomum
▪ SUBTLE	+	
▪ CLONIC		
□ Focal	+	
□ Multifocal	+	
▪ TONIC		
□ Focal	+	
□ Generalized		+
▪ MYOCLONIC		
□ Focal, Multifocal		+
□ Generalized	+	

Volpe J, 1995. In: Neurology of the Newborn, Saunders, 3rd Edition

Neonatal Epileptic Seizures

Electrographic Seizures

- The most frequent pattern observed in newborns (50% to 80% of all documented seizures in tertiary services)
- More common after loading with Phenobarbital and/or Phenitoin, in severe cases or with complexes etiologies

Neonatal Epileptic Seizures

PROPORTION OF DE ELECTROGRAPHIC AND ELECTROCLINICAL NEONATAL SEIZURES – DATA FROM THE LITERATURE

REFERENCE	Nº OF CHILDREN	% Seizures Without Clin Signs	% Cases Treated with drugs
•Mizrahi & Kellaway, 1987	32 children	34%	36%
•Clancy et al, 1988	393 children (85% > 36 wks)	79%	83%
•Scher et al, 1993	30 children (> 37 wks)	57%	84% of the whole group
	22 children (< 30 wks)	27%	
	24 children (31-37 wks)	33%	

Neonatal Status Epilepticus

50% or more of the EEG registering time composed by ictal activity

Hang, 1995;

Lawrence R & Inder T – Neonatal Status Epilepticus. Seminar in Pediatr Neurol 2010; 17: 163-168.

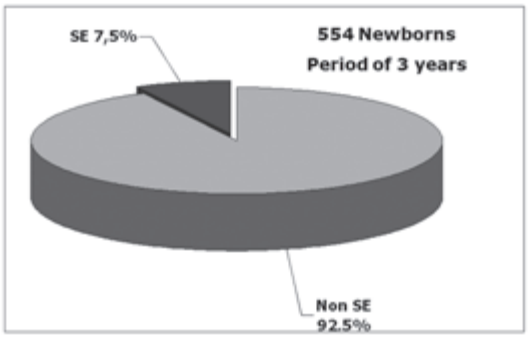
30 minutos ou metade do tempo de traçado com atividade ictal


ARTICLE IN PRESS

Original article

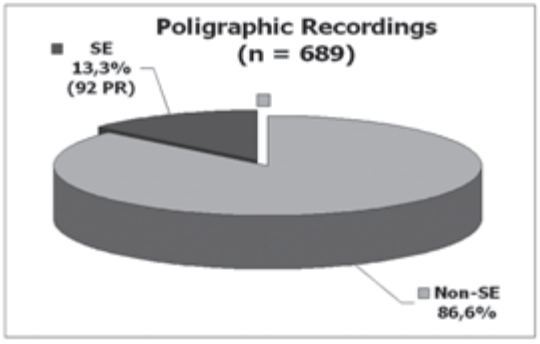
Underlying neurologic disorders and recurrence rates of status epilepticus in childhood

Status Epilepticus in Newborns submitted to Poligraphic EEG at FMRP-USP



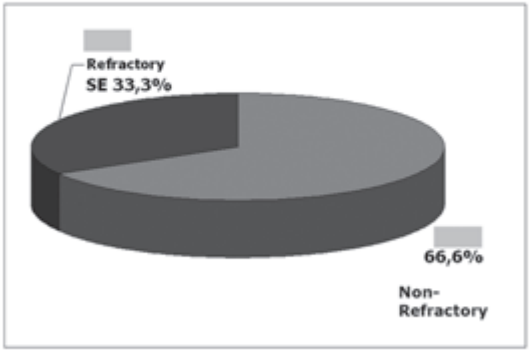
Masters Thesis from Dr Fabiana Penedo Lense, 2005, FMRP-USP

Status Epilepticus in Newborns submitted to Poligraphic EEG at FMRP-USP



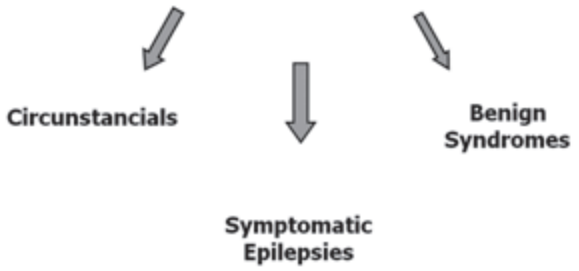
Masters Thesis from Dr Fabiana Penedo Lense, 2005, FMRP-USP

Status Epilepticus in Newborns submitted to Poligraphic EEG at FMRP-USP



Masters Thesis from Dr Fabiana Penedo Lense, 2005, FMRP-USP

Neonatal Epileptic Seizures



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ETIOLOGY

- Hipoxic-Ischemic Encephalopathy
- Congenital Infections
- Complications from Prematurity
- CNS Malformation
- Encephalopathies secondary to Systemic Disturbances
- CNS Infections (bacterian or virus – E. Coli, Lysteria, Strepto B, Herpes)
- Metabolic Diseases
- Genetic Syndromes
- Miscelaneous

Neonatal Epileptic Seizures

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants

Hasan Tekgul, Kimberlee Gauvreau, Janet Soul, Lauren Murphy, Richard Robertson, Jane Stewart, Joseph Volpe, Blaise Bourgeois and Adré J. du Plessis

Pediatrics 2006;117;1270-1280
DOI: 10.1542/peds.2005-1178

Neonatal Epileptic Seizures

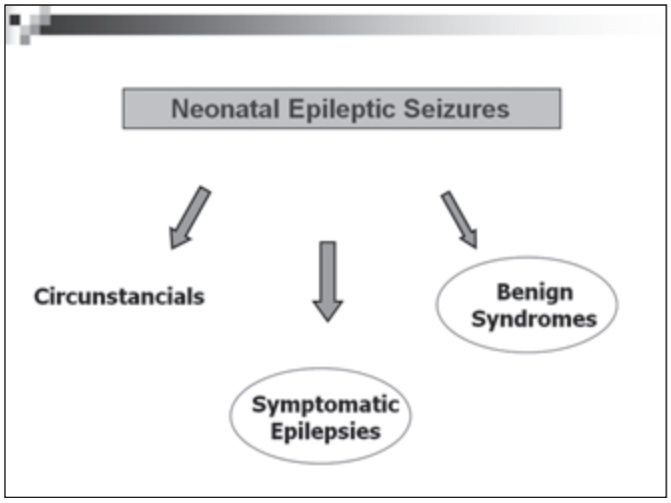
TABLE 1 Etiologic Distribution of Clinical Neonatal Seizures (*n* = 89)

	n (%)
Global cerebral HI	36 (40)
Intrapartum cerebral HI	23
Antepartum cerebral HI	10
Postnatal cerebral HI	3
Focal cerebral HI	16 (18)
Arterial infarct	13
Venous infarct	3
Intracranial hemorrhage	15 (17)
Extraparenchymal hemorrhage	11
Intraparenchymal hemorrhage	2
Combined intraparenchymal hemorrhage/extraparenchymal hemorrhage	2
Cerebral dysgenesis	4 (5)
Cortical dysplasia + agenesis of corpus callosum	2
Congenital hydrocephalus	2
Transient metabolic disturbance	3 (3)
Hypoglycemia	2
Hypocalcemia + hypomagnesemia	1
Infection	3 (3)
Bacterial meningitis	1
Herpes simplex encephalitis	1
Enterovirus encephalitis	1
Inborn error of metabolism	1 (1)
Pyridoxine dependency	1
Etiology unknown	11 (12)

Neonatal Epileptic Seizures

Ethiologies	Number of Babies
• Hipoxic-Ischemic Encephalopathy	11
• Periventricular Haemorrhage	7
• Genetic Syndroms	7
• CNS Malformations	5
• Inborn Errors of Metabolism	4
• Meningites	2
• Kernicterus	1
• TORCH	1
• Miscelaneous	4
• TOTAL	42

Masters Thesis from Dr Fabiana Penedo Lemo, 2005, FMRP-USP: Status Epilepticus in Neonatal Period



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Brain & Development xxx (2010) xxx–xxx
BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology
www.elsevier.com/locate/braindev

Review article

Epilepsies and epileptic syndromes starting in the neonatal period

Hitoshi Yamamoto [a,*], Akihisa Okumura [b], Miho Fukuda [a]

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Epileptic Syndromes Starting in the Neonatal Period

- Idiopathic Neonatal Epileptic Syndromes
  - ✓Benign Familial Neonatal Seizures
  - ✓Benign Idiopathic (non-familial) Neonatal Seizures
- Symptomatic Neonatal Epileptic Syndromes
  - ✓Ohtahara Syndrome
  - ✓Early Myoclonic Encephalopathy
  - ✓Migrating Partial Seizures in Infancy

Benign Neonatal Convulsions – Familial and Non-Familial

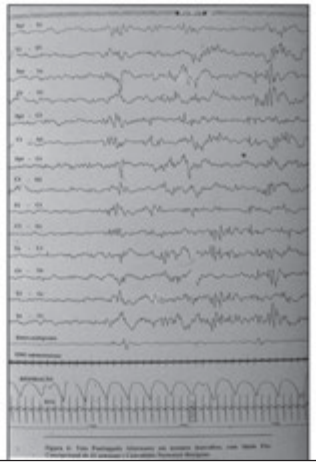
- Erratic focal clonic Szs / Apnea Szs / Subtle Szs (eye fixation, oral automatisms) / Focal Tonic Szs
- First manifestation : more frequently around the 3rd day of life in term babies
- May last up until the third or fifth month of age
- Usually, lots of Szs / day
- Child keep in good clinical condition and normal neurologic exam in between Szs
- No evidence of brain injury or other clinical disturbance
- EEG : normal or mildly to moderately abnormal / teta pointu alternant
- Canalopathy: K (KCNQ1 e KCNQ2)
- Remission after the first months of life / normal outcome

Benign Non-Familial Neonatal Convulsions

TETA POINTU ALTERNANT

HCFMRP-USP

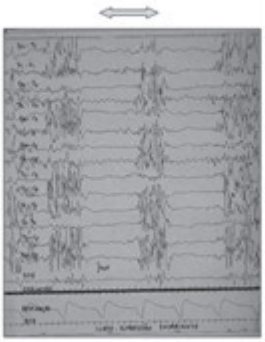
42 week of Conceptional Age



Epileptic Neonatal Encephalopathies with Burst-Suppression Pattern

Ohtahara Syndrome

- Tonic Spasms
- Abnormal findings in MRI
  - Hemimegalencephaly
  - Dentato-olivar
  - Displasia
  - Schizencephaly
  - Etc...



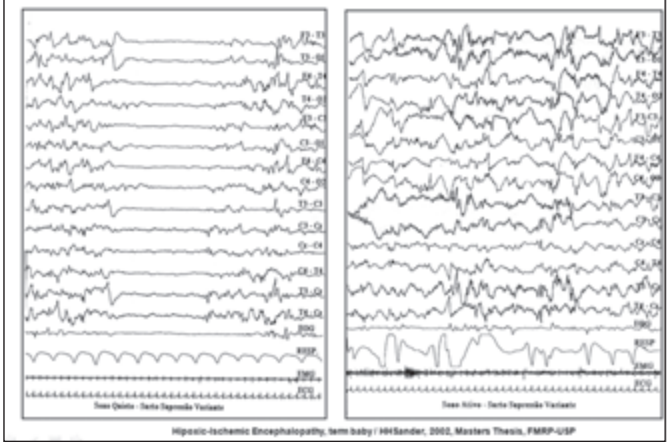
Early Myoclonic Encephalopathy

Mostly related to metabolic disorders

- Erractic or Massive Myoclonia
- MRI normal at the beggining
  - Non-Ketotic Hiperglicinemia
  - Menkes Disease
  - Piridoxin Dependency
  - Phosphate Piridoxal Dependency
  - De Vivo Syndrome
  - Etc...

Start in the neonatal period or first 3 months of life / Invariant Burst-suppression pattern on EEG

Reactive Burst-Suppression



Hipoxic-Ischemic Encephalopathy, term baby / HHSander, 2002, Masters Thesis, FMRP-USP

Differences between Burst-Suppression Pattern in Ohtahara, EME and other clinical conditions related to descontinuous burst-suppression pattern

ARTICLE IN PRESS

Table 1
Variation of suppression-burst EEG pattern seen in various conditions.

	OS	EME	SSPE	Barbiturate coma	NS
EEG features	Seen in both during sleep and awake states	Enhances in sleep sate	Mostly seen in awake state	Seen in sleep state	Seen in both during sleep and awake states
	The burst phase is similar to hypsarrhythmia	Short burst phase with longer suppression phase	Short paroxysmal phase with longer suppression phase	Mostly suppression phase	Short paroxysmal phase with longer suppression phase
	Disappears within the first two or three months	Remains longer than OS	Appears in the specific period	During anesthetic state	Disappears within the first one month

OS: Ohtahara syndrome; EME: early myoclonic encephalopathy; SSPE: subacute sclerosing panencephalitis; NS: neonatal seizures with serious brain damage.

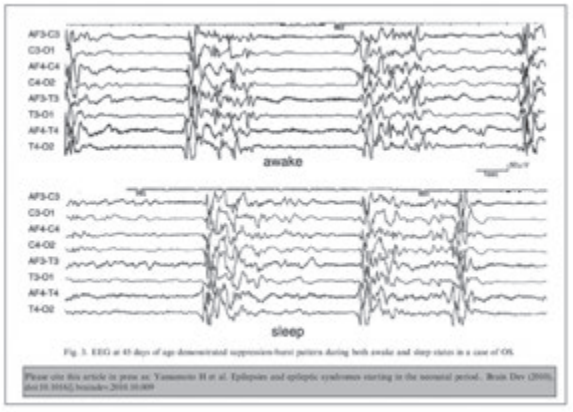


Fig. 3. EEG at 45 days of age demonstrated suppression-burst pattern during both awake and sleep states in a case of OS.

Please cite this article in press as: Yamamoto H et al. Epilepsies and epileptic syndromes starting in the neonatal period. Brain Dev (2010), doi:10.1016/j.braindev.2010.10.009

Burst-suppression pattern in Ohtahara Syndrome

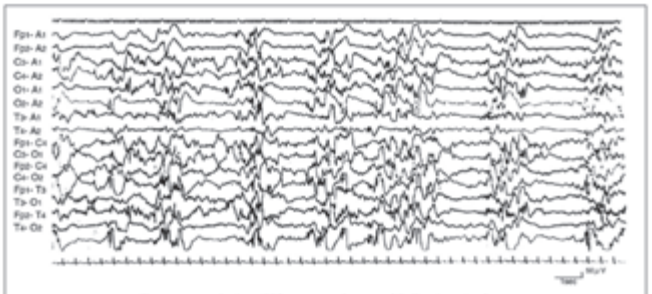


Fig. 4. A suppression-burst EEG pattern seen in a case of EME at 5 months of age.

Please cite this article in press as: Yamamoto H et al. Epilepsies and epileptic syndromes starting in the neonatal period.. Brain Dev (2010), doi:10.1016/j.braindev.2010.10.009

Burst-suppression pattern in Early Myoclonic Encephalopathy

LETTERS

nature genetics

De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy

Hirotomo Saitsu[1], Mitsuhiro Kato[2], Takeshi Mizuguchi[1], Keisuke Hamada[1], Hiroshi Osaka[3], Jun Tohyama[4], Katsuhiro Uruno[5], Satoko Kumada[6], Kiyomi Nishiyama[6], Akira Nakamura[6], Ippei Okada[1], Yukiko Yoshimura[1], Ivo-ichi Hara[1], Tatsuro Kamada[1], Kiyoshi Hayasaka[1], Atsuo Fukuda[1], Kenshiro Ogata[1] & Norimichi Matsumoto[1]

Early infantile epileptic encephalopathy with suppression-burst (EIEE), also known as Ohtahara syndrome, is one of the most severe and earliest forms of epilepsy. Using array-based comparative genomic hybridization, we found a de novo 2.0-Mb microdeletion at 9q33.3–q34.11 in a girl with EIEE. Mutation analysis of candidate genes mapped to the deletion revealed that four unrelated individuals with EIEE had heterozygous missense mutations in the gene encoding syntaxin binding protein 1 (STXBP1). STXBP1, also known as rbMUNC18-1, is an evolutionarily conserved neuronal Sec1/Munc18 (SM) protein that is essential in synaptic vesicle release in several species[1–3]. Circular dichroism melting experiments revealed that a mutant form of the protein was significantly thermolabile compared to wild type. Furthermore, binding of the mutant protein to syntaxin was impaired. These findings suggest that haploinsufficiency of STXBP1 causes EIEE.

syndrome has been suggested. Consistent with this idea, specific mutations of the ARX (aristaless related homeobox) gene at Xp22.13 have been recently found in male subjects with EIEE and West syndrome[4,5]. In most cryptogenic EIEE cases, however, the genetic cause remains to be elucidated.

Microarray technologies detect genomic copy number alterations, which may be related to disease phenotypes, at a submicroscopic level[6,7]. In a BAC array-based comparative genomic hybridization (aCGH) analysis containing 6,239 clones with 0.7-Mb resolution for genome-wide analysis[8] of individuals with normal constitution, we found a microdeletion at 9q33.3–q34.11 in a girl with EIEE (subject 1) (Fig. 1a). The deletion was 2.0 Mb in size and was confirmed by fluorescent in situ hybridization (FISH) analysis on the subject's chromosomes (Fig. 1b), whereas no deletion was found in her parents (data not shown).

More than forty genes mapped within the deletion (Fig. 1b). Among them, the gene encoding syntaxin binding protein 1

Distinction between the 2 syndromes

Etiological questions — **Therapeutic questions**

Diagnostic Difficulties

- **Differentiation between Myoclonias and Spasms may be difficult at this age range**
- **Burst-suppression could be a precocious variant of fragmented Hipsarrhythmia**
- **Not all patients fulfill completely the criteria for one or the other syndrome**

Epileptic syndromes in infancy and childhood
Rima Nabbout[a,b] and Olivier Dulac[a,b]

Current Opinion in Neurology 2008, 21:161–166

NEONATAL SEIZURES

- Why is the brain more prone to epileptic seizures during neonatal period ?
- What is the clinical presentation of epileptic seizures in the newborn ?
- What are the etiologies of epileptic seizures in the neonate ?
- How do we treat neonatal seizures ?
- How children with seizures in the neonatal period will develop under a neurological point of view ?

NEONATAL SEIZURES

TREATMENT

- Based upon the etiology of the encephalopathy or the disturbances cause the seizures
- Use of antiepileptic drugs
- Specific treatment of metabolic disorders of diseases

NEONATAL SEIZURES

Treatment with Antiepileptic Drugs

- Phenobarbital
- Phenitoína
- Benzodiazepines (lorazepan, diazepan, midazolan)
- Vigabatrin
- Valproic Acid
- Carbamazepine
- Lamotrigine
- Topiramate

NEONATAL SEIZURES

Treatment

PHENOBARBITAL

- Usual loading dose (LD) : 20 mg/Kg - IV
- Maximal LD suggested : 40 mg/Kg - IV

PHENITOIN

- Usual loading dose (LD) : 20 mg/Kg - IV
- Maximal LD suggested : 30 mg/Kg - IV

NEONATAL SEIZURES

Treatment

DIAZEPAN

- Used to be the first choice drug in many countries
- DOSE : 0,3 mg/Kg; can be repeted if necessary
- DESADVANTAGENS:
  - cardio-circulatory depression, mainly if associated to Phenobarbital
  - not a good maintenance drug
  - can inhibit the glucose transporter to CNS

Obs.: Lorazepan - 0,5 mg/Kg – available in the USA

NEONATAL SEIZURES

- Specific treatments for neonatal epilepsies due to some metabolic diseases

- Piridoxina Dependency
- Phosphate Piridoxal Dependency
- Neonatal Convulsions Sensitive to Folinic Acid
- Biotinidase dependency
- Deficiency of Serine Synthesis
- De Vivo Disease

NEONATAL SEIZURES

PROCEED WITH THE TREATMENT AFTER FB E DPH FAILURE TO CONTROL CLINICAL AND/OR EEG SEIZURES?

Perform PIRIDOXINE test first!

NEONATAL SEIZURES

Treatment with new AED

- **LAMOTRIGINE**
  - **INICIAL DOSE OF 12,5 mg/dia, once (4 dias), increasing until Sz control (BID)**
    - **Barr et al., *Pediatric Neurology* 1999; 20: 161-163**
- **TOPIRAMATE**
  - **Ho Cha et al., *Epilepsy Research*, 2002; 51: 217-232**

NEONATAL SEIZURES

Efficacy of Lamotrigine in Refractory Neonatal Seizures

Peter A. Barr, MB, BS*, Vera E. Buettiker, MD*, and Jayne H. Antony, MD†

A newborn infant with seizures of unknown etiology that were refractory to treatment with phenobarbitone, phenytoin, midazolam, clonazepam, and vigabatrin is reported. The introduction of the new antiepileptic drug lamotrigine was followed by rapid and sustained control of the seizures.

Barr PA, Buettiker VE, Antony JH. Efficacy of lamotrigine in refractory neonatal seizures. Pediatr Neurol 1999;20:161-163.

Case Report

NEONATAL SEIZURES

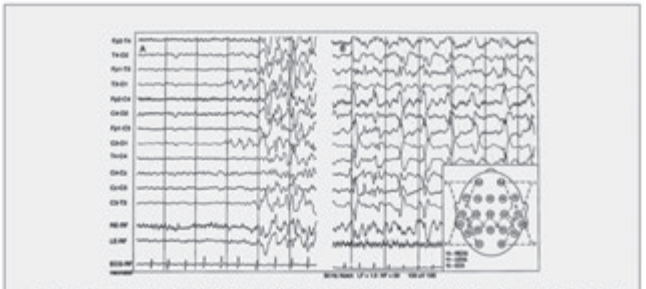


Figure 1. (A) Interictal EEG recording when the infant was 4 days of age illustrating a relatively low-voltage background interrupted by higher-voltage bursts of activity lasting 2-3 seconds. (B) Ictal EEG recording 25 minutes later demonstrating generalized repetitive discharges associated with lip smacking, irregular limb jerking, and adduction movements of the legs.

NEONATAL SEIZURES

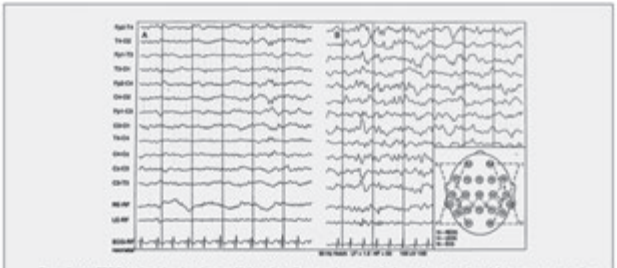


Figure 2. (A) EEG Recording when the infant was 10 days of age illustrating low-voltage background activity with no definite asymmetry or epileptic activity. (B) EEG Recording after treatment with lamotrigine when the infant was 21 days of age demonstrating improvement in the background activity.

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NEONATAL SEIZURES

ELSEVIER

Epilepsy Research 51 (2002) 217–232

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Effect of topiramate following recurrent and prolonged seizures during early development

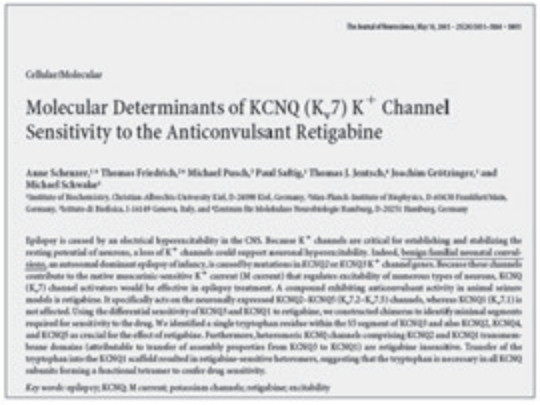
Byung Ho Cha [a,b], Diosely C. Silveira [a], Xianzeng Liu [a], Yingchun Hu [a], Gregory L. Holmes [a,*]

[a] *Clinical Neurophysiology Laboratory, Department of Neurology, Center for Research in Pediatric Epilepsy, Harvard Medical School, Children's Hospital Boston, Hunnewell 2, 300 Longwood Avenue, Boston, MA 02115, USA*

[b] *Department of Pediatrics, Wonju Christian Hospital, Wonju College of Medicine, Yonsei University, Wonju, South Korea*

Received 2 April 2002; received in revised form 4 July 2002; accepted 8 July 2002

NEONATAL SEIZURES



Cellular/Molecular

Molecular Determinants of KCNQ (K_v7) K^+ Channel Sensitivity to the Anticonvulsant Retigabine

Anne Schenzer,[1,2] Thomas Friedrich,[2,3] Michael Pusch,[3] Paul Saftig,[1] Thomas J. Jentsch,[4] Joachim Grötzinger,[1] and Michael Schwake[1]

[1]Institute of Biochemistry, Christian Albrechts-University Kiel, D-24098 Kiel, Germany, [2]Max-Planck-Institute of Biophysics, D-60438 Frankfurt/Main, Germany, [3]Istituto di Biofisica, I-16149 Genova, Italy, and [4]Zentrum für Molekulare Neurobiologie Hamburg, D-20251 Hamburg, Germany

Epilepsy is caused by an electrical hyperexcitability in the CNS. Because K^+ channels are critical for establishing and stabilizing the resting potential of neurons, a loss of K^+ channels could support neuronal hyperexcitability. Indeed, benign familial neonatal convulsions, an autosomal dominant epilepsy of infancy, is caused by mutations in KCNQ2 or KCNQ3 K^+ channel genes. Because these channels contribute to the native muscarinic-sensitive K^+ current (M current) that regulates excitability of numerous types of neurons, KCNQ (K_v7) channel activators would be effective in epilepsy treatment. A compound exhibiting anticonvulsant activity in animal seizure models is retigabine. It specifically acts on the neuronally expressed KCNQ2–KCNQ5 ($K_v7.2$–$K_v7.5$) channels, whereas KCNQ1 ($K_v7.1$) is not affected. Using the differential sensitivity of KCNQ3 and KCNQ1 to retigabine, we constructed chimeras to identify minimal segments required for sensitivity to the drug. We identified a single tryptophan residue within the S5 segment of KCNQ3 and also KCNQ2, KCNQ4, and KCNQ5 as crucial for the effect of retigabine. Furthermore, heteromeric KCNQ channels comprising KCNQ2 and KCNQ3 transmembrane domains (attributable to transfer of assembly properties from KCNQ3 to KCNQ1) are retigabine insensitive. Transfer of the tryptophan into the KCNQ1 scaffold resulted in retigabine-sensitive heteromers, suggesting that the tryptophan is necessary in all KCNQ subunits forming a functional tetramer to confer drug sensitivity.

Key words: epilepsy; KCNQ; M current; potassium channels; retigabine; excitability

Crises Epilépticas Neonatais

TREATMENT OF NEONATAL SEIZURES RESISTENT TO FIRST LINE DRUGS (Phenobarbital and/or Phenitoin) or STATUS

MIDAZOLAN and THIOPENTAL / PENTOBARBITAL

- **Drugs usually well tolerated by neonates**
- **Risk / benefit should be evaluated with neonatologists**

NEONATAL SEIZURES

- **Why is the brain more prone to epileptic seizures during neonatal period ?**
- **What is the clinical presentation of epileptic seizures in the newborn ?**
- **What are the etiologies of epileptic seizures in the neonate ?**
- **How do we treat neonatal seizures ?**
- **How children with seizures in the neonatal period will develop under a neurological point of view ?**

ARTICLE

The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants

Hasan Tekgul, MD[a,b], Kimberlee Gauvreau, ScD[c], Janet Soul, MD, CM, FRCPC[a], Lauren Murphy, PhD[a], Richard Robertson, MD[a], Jane Stewart, MD[a], Joseph Volpe, MD[a], Blaise Bourgeois, MD[a], Adre J. du Plessis, MBChB, MPH[a]

[a]Neurology, [b]Pediatrics, [c]Psychiatry, and [d]Radiology, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts, [e]Department of Neurology, Ege University Hospital, Izmir, Turkey

The authors have indicated they have no financial relationships relevant to this article to disclose.

CONCLUSIONS. Mortality associated with neonatal seizures has declined although long-term neurodevelopmental morbidity remains unchanged. Seizure etiology and background EEG patterns remain powerful prognostic factors. Diagnostic advances have changed the etiologic distribution for neonatal seizures and improved accuracy of outcome prediction. Global cerebral hypoxia-ischemia, the most common etiology, is responsible for the large majority of infants with poor long-term outcome.

Review

Effects of seizures on developmental processes in the immature brain

Yehezkel Ben-Ari, Gregory L Holmes

Infants and children are at a high risk for seizures compared with adults. Although most seizures in children are benign and result in no long-term consequences, increasing experimental animal data strongly suggest that frequent or prolonged seizures in the developing brain result in long-lasting sequelae. Such seizures may intervene with developmental programmes and lead to inadequate construction of cortical networks rather than induction of neuronal cell loss. As a consequence, the deleterious actions of seizures are strongly age dependent: seizures have different effects on immature or migrating neurons endowed with few synapses and more developed neurons that express hundreds of functional synapses. This differential effect is even more important in human beings and subhuman primates who have an extended brain development period. Seizures also beget seizures during maturation and result in a replay of development programmes, which suggests that epileptogenesis recapitulates ontogenesis. Therefore, to understand seizures and their consequences in the developing brain, it is essential to determine how neuronal activity modulates the main steps of cortical formation. In this Review, we present basic developmental principles obtained from animal studies and examine the long-lasting consequences of epilepsy.

Lancet Neurol 2006; 5: 1056–63
Institute of Neurobiology of the Mediterranean (INMED), INSERM and Université de la Méditerranée, France (Y Ben-Ari PhD), and Neuroscience Center at Dartmouth, Dartmouth Medical School, Hanover, USA (G L Holmes MD)
Correspondence to: Dr Y Ben-Ari, Institute of Neurobiology of the Mediterranean Yaa, Campus Scientifique de Luminy, 163,

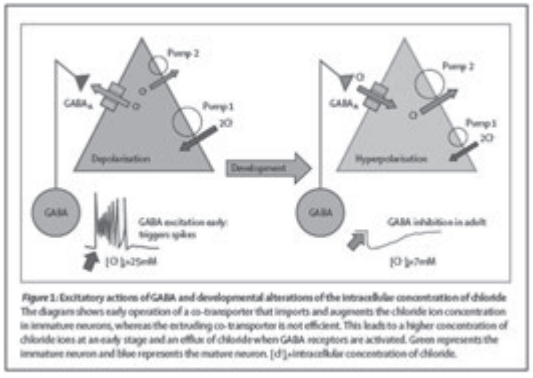


Figure 1: Excitatory actions of GABA and developmental alterations of the intracellular concentration of chloride
The diagram shows early operation of a co-transporter that imports and augments the chloride ion concentration in immature neurons, whereas the extruding co-transporter is not efficient. This leads to a higher concentration of chloride ions at an early stage and an efflux of chloride when GABA receptors are activated. Green represents the immature neuron and blue represents the mature neuron. [Cl$^-$]$_i$=intracellular concentration of chloride.

Ben-Ari Y & Holmes GL. Effects of seizures on developmental process in immature brain. *Lancet Neurol* 2006; 5: 1056-63

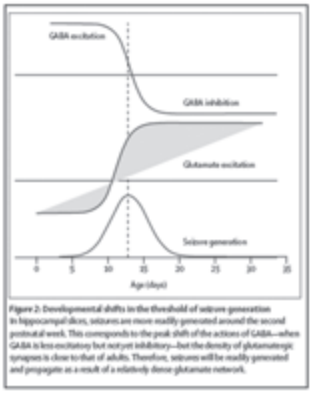


Figure 2: Developmental shifts in the threshold of seizure generation
In hippocampal slices, seizures are more readily generated around the second postnatal week. This corresponds to the peak shift of the actions of GABA—when GABA is less excitatory but not yet inhibitory—but the density of glutamatergic synapses is close to that of adults. Therefore, seizures will be readily generated and propagate as a result of a relatively dense glutamate network.

Ben-Ari Y & Holmes GL. Effects of seizures on developmental process in immature brain. *Lancet Neurol* 2006; 5: 1056-63

- Adverse effects of frequent or prolonged seizures at an early stage are primarily due to their interference with developmental programmes rather than cell loss, because developing networks are quite resistant to brain damage

Ben-Ari Y & Holmes GL. Effects of seizures on developmental process in immature brain. *Lancet Neurol* 2006; 5: 1056-63

Lancet Neurol 2006; 5: 1056-63

Severity of recurrent seizures will be time dependent

⟹ seizures or brief episodes of hyperactivity, that occur when most neurons are migrating with receptors still without functional synapses, will exert different effects than seizures occurring when neurons have many synapses and a primitive netowork driven pattern.

⟹ changes in expression or operation of functional receptors and synapses lower threshold for further seizures

⟹ possible interruption of the constriction of cortical networks, displaced cells and migration disorders

THE JOURNAL OF PEDIATRICS • www.jpeds.com Vol. 157, No. 5

The Need for More Research on Seizures in Preterm Infants

In this month's issue of *The Journal*, Davis et al within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network investigate the risk factors for clinical seizures and long-term outcomes after seizures in a large cohort of extremely low birth weight

long-term and detailed follow up of these infants are strengths of the study. The investigators demonstrate that abnormal movements, those that are clinically diagnosed and classified as seizures, are independently associated with neonatal illness, death, and neurodevelopmental impairment in ELBW infants. Thus, for the neonatal clinician, it appears that motor manifestations and behaviors that are classified as seizures in ELBW infants are associated with adverse outcome, irrespective of electrophysiological confirmation.

This study also confirms that seizures are probably more common among preterm infants than generally considered. Population-based studies have shown that preterm infants have at least 5- to 10-fold higher risk for neonatal seizures

in almost half of the infants both clinical and subclinical seizures were present.[3] Subtle seizure manifestations, for example, changes in heart rate or blood pressure, are also common and may easily be overlooked in very preterm infants.

On the other hand, nonspecific muscle twitches, limb ex-

stresses the need for further investigations of seizures in preterm infants including evaluation of antiepileptic treatment in these infants. ■

Lena Hellström-Westas, MD, PhD
Professor of Perinatal Medicine
Department of Women's and Children's Health
Uppsala University
Uppsala, Sweden

Reprint requests: Dr Lena Hellström-Westas, Department of Women's and Children's Health, Uppsala University, SE-751 85 Uppsala, Sweden. E-mail: lena.westas@kbh.uu.se.

Thank you !

SEIZURES DURING INFANCY
VERA CRISTINA TERRA (BRAZIL)

SEIZURES DURING INFANCY

CIREP

Vera Cristina Terra

Médica Assistente

Centro Cirurgia de Epilepsia de Ribeirão Preto

HISTÓRIA NATURAL DA EPILEPSIA

- **Recorrência de uma crise única em 2 anos:**

32%: epilepsias idiopáticas.

57%: epilepsias sintomáticas. *(Berg & Shinnar, 1991)*

- **Fatores de risco após o início da epilepsia**

Número de crises nos primeiros 6 meses.

Resposta à primeira DAE.

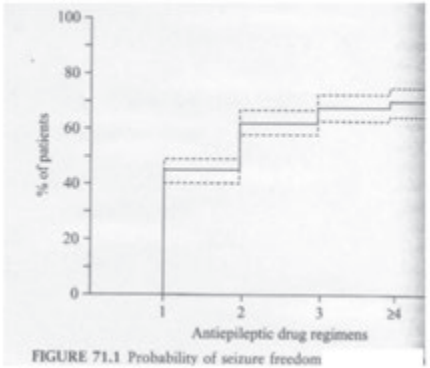
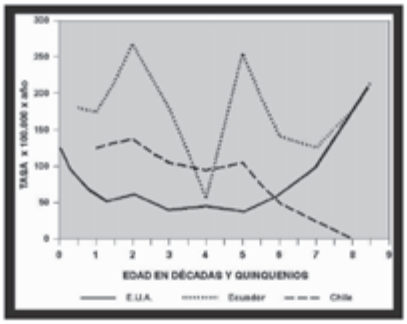


FIGURE 71.1 Probability of seizure freedom

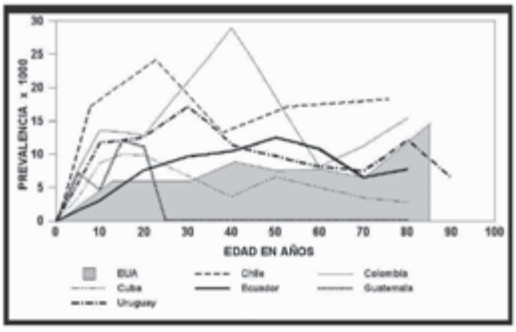
SEIZURES DURING INFANCY

EPIDEMIOLOGIA



SEIZURES DURING INFANCY

EPIDEMIOLOGIA



SEIZURES DURING INFANCY

SEMIOLOGIA

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

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.

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

Table 3. Electroclinical syndromes and other epilepsies

Electroclinical syndromes arranged by age at onset[a]
- Neonatal period
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders

SEIZURES DURING INFANCY

Table 3. Electroclinical syndromes and other epilepsies

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

SEIZURES DURING INFANCY

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 myoclonus epilepsies (PME)
  - Autosomal dominant epilepsy with auditory features (ADEAF)
  - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies

SEIZURES DURING INFANCY

Table 3. Electroclinical syndromes and other epilepsies

- Distinctive constellations
  - Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
  - Rasmussen syndrome
  - Gelastic seizures with hypothalamic hamartoma
  - Hemiconvulsion–hemiplegia–epilepsy
  - Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)

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

Table 3. Electroclinical syndromes and other epilepsies

- Epilepsies of unknown cause
- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
  - Benign neonatal seizures (BNS)
  - Febrile seizures (FS)

SEIZURES DURING INFANCY

SÍNDROMES EPILÉPTICAS NOS PRIMEIROS ANOS DE VIDA

SEIZURES DURING INFANCY

Síndrome de West

- Incidência de 1/2000 a 1/4000 nascimentos
- Início das crises entre 3 e 7 meses
- 93% dos casos antes dos 2 anos de idade
- Crises do tipo espasmos
- Outros tipos de crises podem ocorrer
- Presença de retardo mental
- Padrão de Hipsarritima ao EEG

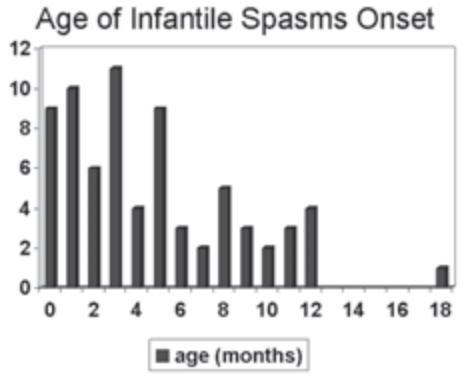
SEIZURES DURING INFANCY

Síndrome de West

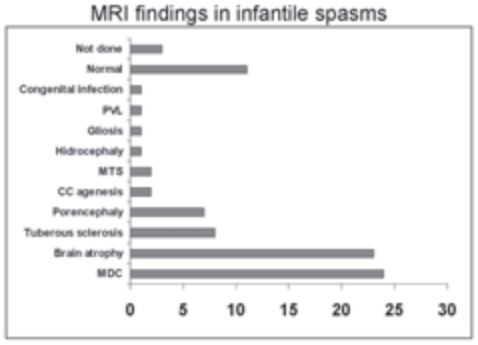
Prognóstico

- Sintomática x Idiopática
- Recuperação espontânea: 6 a 15% dos casos
- Aos 5 anos 72 a 99% dos casos sem espasmos
- Alterações focais ao EEG em 75% dos casos
- Epilepsia generalizada na evolução: 42 a 90%
- Síndrome de Lennox-Gastaut: 40 a 60%

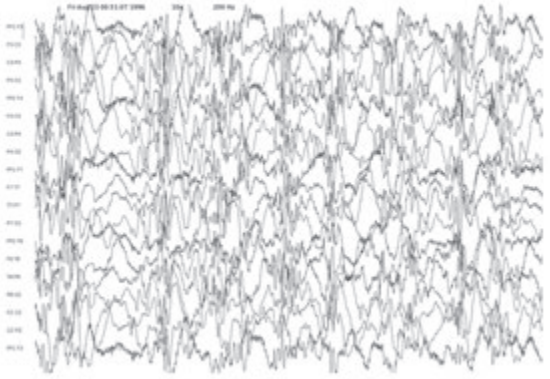
SEIZURES DURING INFANCY



SEIZURES DURING INFANCY



SEIZURES DURING INFANCY



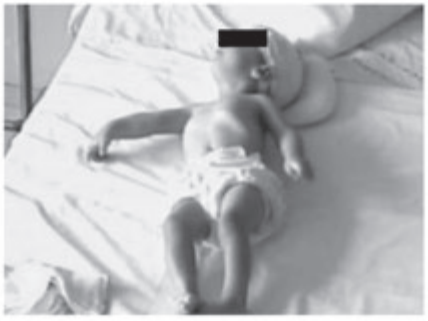
SEIZURES DURING INFANCY

Síndrome de West

Tratamento

- Ácido valpróico
- Benzodiazepínicos
- ACTH
- Vigabatrina
- Topiramato
- Imunoglobulina
- Piridoxina
- Dieta cetogênica
- Cirurgia

SEIZURES DURING INFANCY



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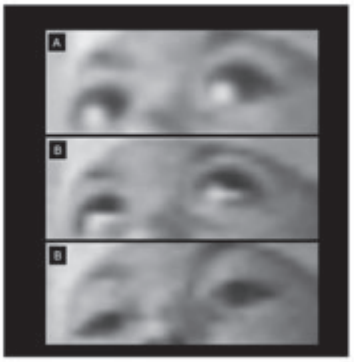


SEIZURES DURING INFANCY

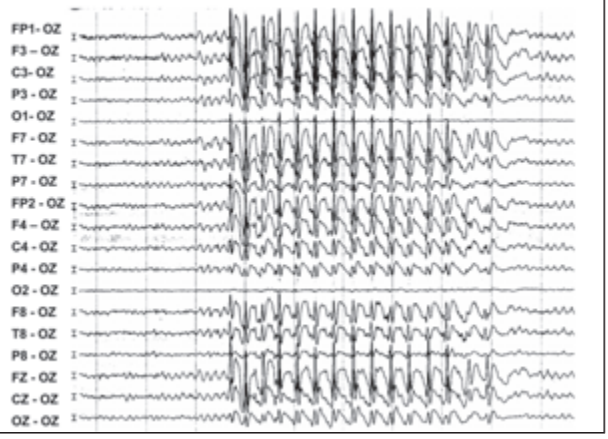
EPILEPSIAS IDIOPÁTICAS

(GENÉTICAS)

SEIZURES DURING INFANCY

AUSÊNCIA INFANTIL

SEIZURES DURING INFANCY



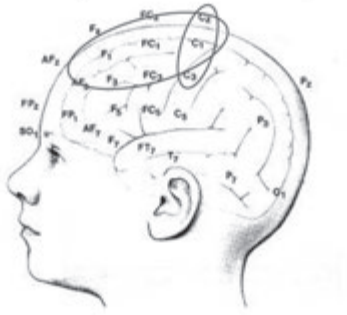
SEIZURES DURING INFANCY

EPILEPSIA BENIGNA DA INFÂNCIA

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

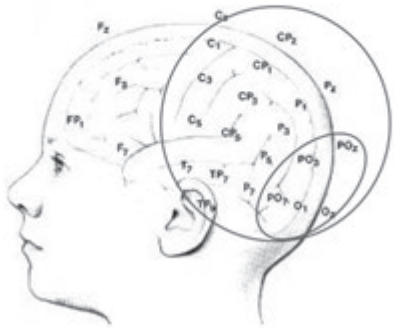
SEIZURES DURING INFANCY

EBI com pontas centro-temporais.



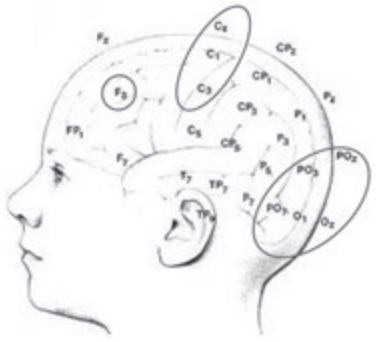
SEIZURES DURING INFANCY

Síndrome de Panayiotopoulos.



SEIZURES DURING INFANCY

EBI com pontas occipitais tipo Gastaut.



SEIZURES DURING INFANCY

Table 4. Comparison of recommendations for the treatment of paediatric epilepsy.

Seizure type or epilepsy syndrome	U.S. pediatric expert consensus survey[28]	European pediatric expert consensus survey[6]	ILAE[1]	SIGN[4]	NICE[5]	French study[7]	FDA approved[8]
Partial-onset	OXC, CBZ	OXC, CBZ	A: OXC; 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 males)	PB, PHT, CBZ, OXC, TPM
BECT	OXC, CBZ	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	ESM, 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

European Journal of Neurology 2006, **13**: 1143–1145 doi:10.1111/j.1468-1331.2006.01494.x

SHORT COMMUNICATION

Oxcarbazepine and atypical evolution of benign idiopathic focal epilepsy of childhood

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[a]*Department of Pediatrics, Pediatric Neurology Section, University of Siena, Siena, Italy;* [b]*Department of Neurosciences, Pediatric Neurology Unit, Tor Vergata University of Rome, Rome, Italy; and* [c]*Department of Neurosciences, University of Siena, Siena, Italy*

Patients that have benign epilepsy with centrotemporal spikes (BECTS) may occasionally experience an atypical development in their course when treated with drugs such as carbamazepine.

with centrotemporal spikes, drug-induced seizure, oxcarbazepine

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manifested atypical absences, neuropsychological disturbances, and generalized spike-and-wave discharges in their electroencephalograms (EEGs) that became continuous during sleep. The third patient showed, during OXC therapy, more frequent partial motor seizures which ended with ictal vomiting and post-ictal obnubilation. EEGs recorded during sleep showed discontinuous paroxysmal activity in the right centro-temporal area. Symptoms were reversed following discontinuation of the OXC therapy. Although electroclinical findings were consistent with a BECTS diagnosis, all patients had some atypical features. Our observations show that BECTS patients, in particular those presenting with atypical findings, might be at risk for developing paradoxical reactions to OXC therapy. We suggest that OXC should be included in the list of drugs that may cause electroclinical deterioration in these patients.

SEIZURES DURING INFANCY

EPILEPSIA BENIGNA DA INFÂNCIA

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

SEIZURES DURING INFANCY

EPILEPSIA BENIGNA DA INFÂNCIA

- **Prognóstico – Síndrome de Panayiotopoulos:**
  - 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

EPILEPSIA BENIGNA DA INFÂNCIA

- **Prognóstico – EBI com pontas occipitais tipo Gastaut:**
  - 40 - 50% dos casos mantém CPS e CTCG raras.
  - Evolução atípica rara.

SEIZURES DURING INFANCY

EPILEPSIAS SINTOMÁTICAS (ESTRUTURAL / METABÓLICA)

SEIZURES DURING INFANCY

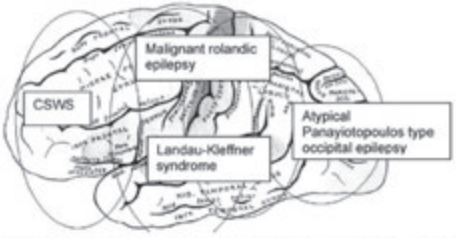
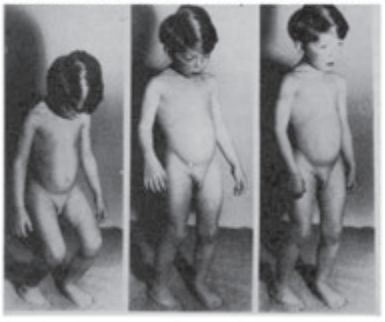


Figure 1 Epileptic encephalopathies or malignant epilepsies with electrical status epilepticus during sleep. Pathophysiology is quite the same, but symptoms are defined by the driver focus: prefrontal and frontal area in continuous spike-waves syndrome (CSWS), central region in malignant rolandic epilepsy, 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 MIOCLONO-ASTÁTICA



SEIZURES DURING INFANCY

EPILEPSIA MIOCLONO-ASTÁTICA

SEIZURES DURING INFANCY

SÍNDROME DE LENNOX-GASTAUT

- Início entre 1 e 8 anos
- História familiar em 3 a 27% dos casos
- Crises generalizadas e focais
- Sintomática x Idiopática
- Retardo mental
- Síndrome de West prévia: 30 a 40%
- Tratamento

SEIZURES DURING INFANCY

SÍNDROME DE LENNOX-GASTAUT

Prognóstico

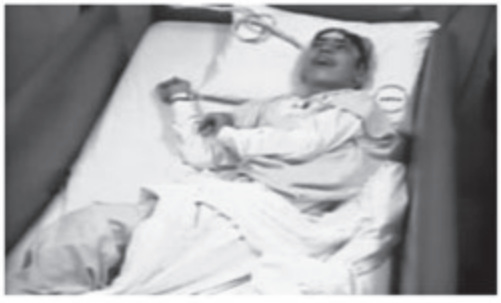
- Raro controle total das crises
- Dependência da família
- Crises diárias
- Retardo mental mais severo quanto mais precoce
- Estado de mal-epiléptico agrava a evolução

SEIZURES DURING INFANCY

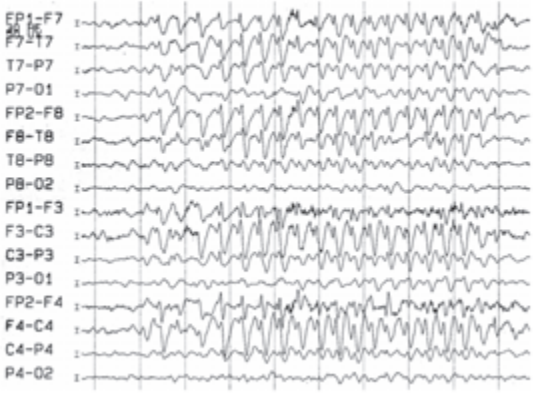
SÍNDROME DE LENNOX-GASTAUT

SEIZURES DURING INFANCY

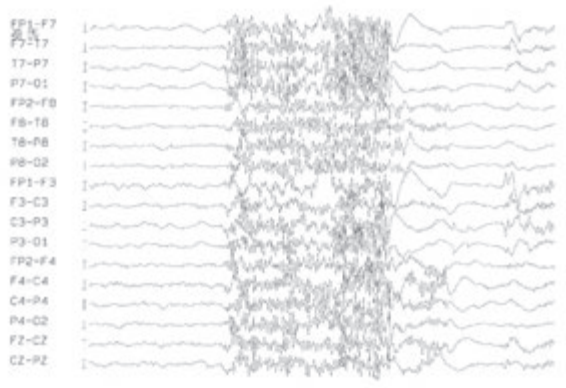
SÍNDROME DE LENNOX-GASTAUT



SEIZURES DURING INFANCY



SEIZURES DURING INFANCY



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

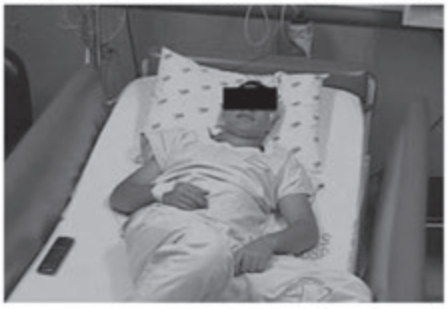
EPILEPSIA LOBO FRONTAL

SEIZURES DURING INFANCY

EPILEPSIA LOBO TEMPORAL NÃO DOMINANTE

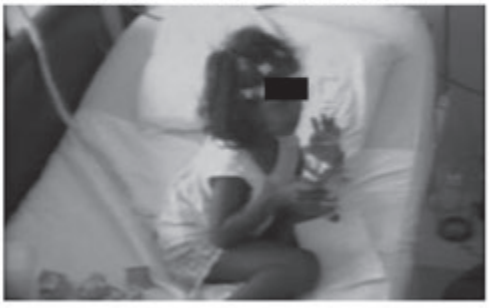
SEIZURES DURING INFANCY

EPILEPSIA LOBO TEMPORAL DOMINANTE



SEIZURES DURING INFANCY

EPILEPSIA LOBO PARIETAL

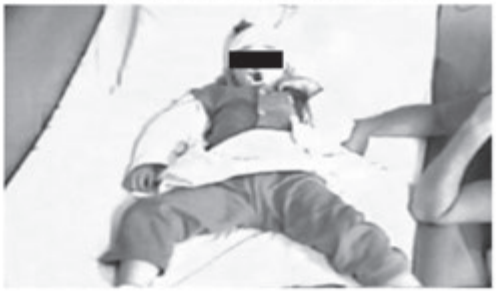


SEIZURES DURING INFANCY

EPILEPSIA LOBO OCCIPITAL

SEIZURES DURING INFANCY

ENCEFALITE DE RASMUSSEN



SEIZURES DURING INFANCY

HAMARTOMA HIPOTALÂMICO

SEIZURES DURING INFANCY

INVESTIGAÇÃO CLÍNICA

Bruna SL

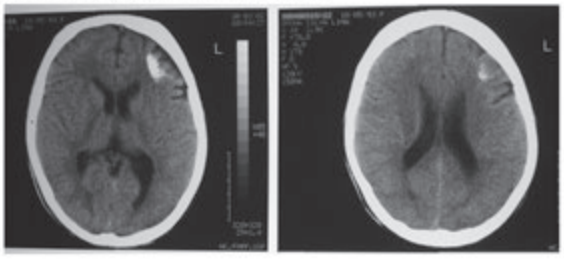
• Exame físico:

- Retardo mental moderado.
- Ausência de estigmas cutâneos.
- Involução cognitiva progressiva.
- Clinicamente em estado de mal de ausência atípica.

SEIZURES DURING INFANCY

INVESTIGAÇÃO CLÍNICA

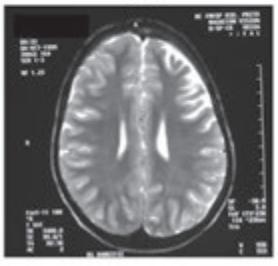
Bruna SL: Exames de investigação.



SEIZURES DURING INFANCY

INVESTIGAÇÃO CLÍNICA

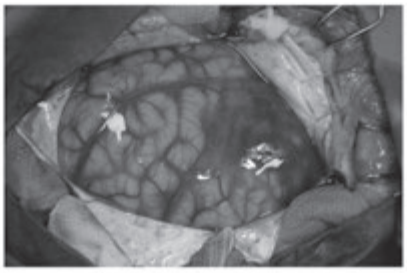
Bruna SL: Exames de investigação.



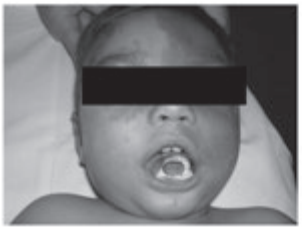
SEIZURES DURING INFANCY

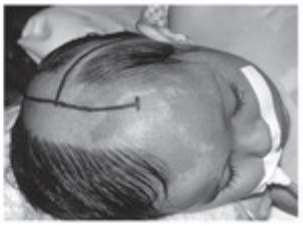
INVESTIGAÇÃO CLÍNICA

Bruna SL: Intra-operatório.



SEIZURES DURING INFANCY





SEIZURES DURING INFANCY

ESCLEROSE TUBEROSA

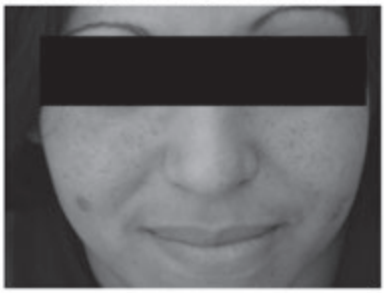
Critérios diagnósticos para Esclerose Tuberosa segundo o consenso da conferência do complexo esclerose tuberosa de 1998 (dois critérios maiores ou um critério maior e dois menores).

Critérios maiores	Critérios menores
Angiofibromas faciais ou placas fibrosas	Manchas múltiplas na destina
Fibroma periungueais ou ungueais não traumáticos	Pólipos hamartomatosos retais
Máculas hipomelanóticas (três ou mais)	Cistos ósseos
Placa de chagrém (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
Tíberes corticais	Hamartomas não retais
Nódulos subependimários	Placas retinianos acromáticos
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 de ET deve ser considerado para o diagnóstico.

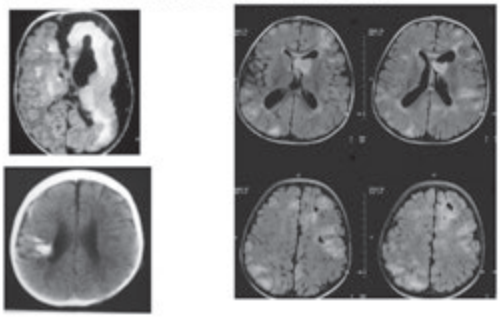
SEIZURES DURING INFANCY

ESCLEROSE TUBEROSA



SEIZURES DURING INFANCY

ESCLEROSE TUBEROSA



SEIZURES DURING INFANCY

HISTÓRIA NATURAL DA EPILEPSIA

- **Mortalidade:**

Maior risco nos primeiros 5 anos do diagnóstico e após 10 anos de diagnóstico.

Número de crises nos primeiros 6 meses.

Resposta à primeira DAE.

HISTÓRIA NATURAL DA EPILEPSIA

- **Mortalidade – causas:**

Não relacionadas: neoplasias fora do SNC, isquemia cardíaca, pneumonia, etc..

Relacionadas à doença de base: tumores cerebrais, doença cerebro-vascular, encefalites, abscessos cerebrais, doenças metabólicas.

HISTÓRIA NATURAL DA EPILEPSIA

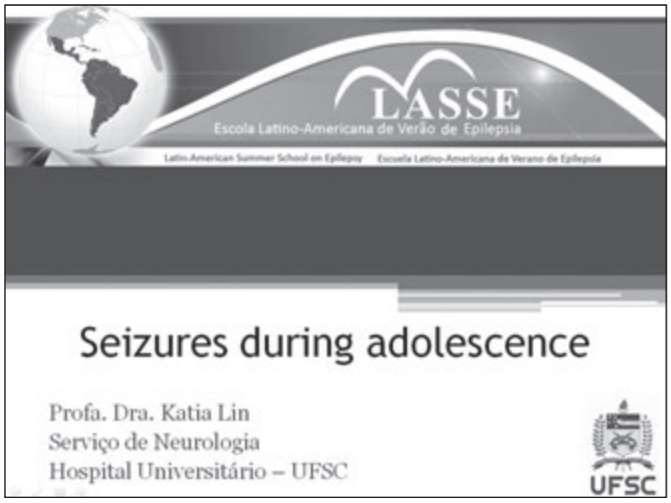
- **Mortalidade – causas:**

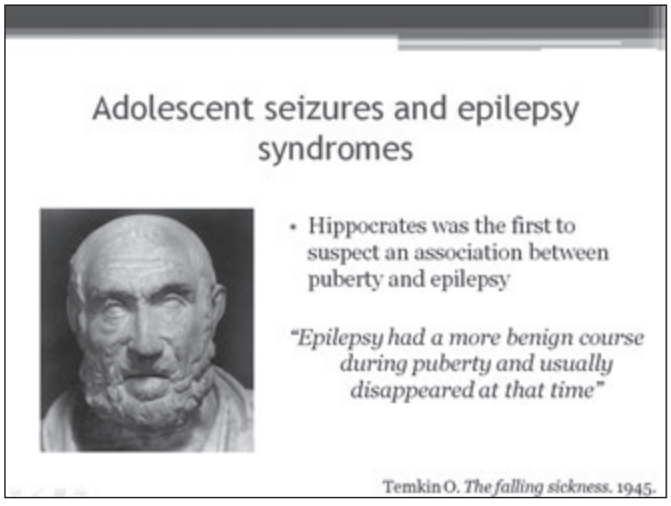
Relacionadas à epilepsia: suicídio, efeitos adversos das DAE, reações idiossindráticas das DAE, relacionadas às crises (traumas, queimaduras, afogamento), estado de mal epiléptico, asfixia, aspiração, pneumonia após uma crise, SUDEP.

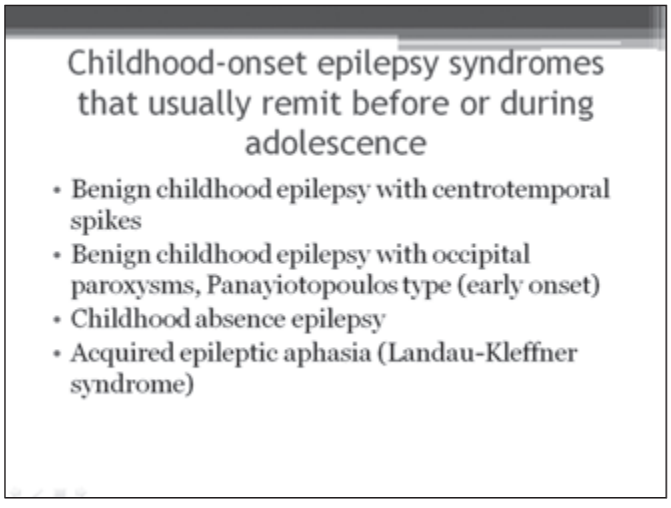
Epilepsy is more than seizures. An ongoing epileptogenic process can irreversibly damage the brain, especially maturing brain, even if seizures are controlled or missing, and causes persistent cognitive changes and finally global intellectual deficits.

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

Seizures during adolescence
Katia Lin (Brazil)







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 seizure plus
- Childhood absence epilepsy
- Epilepsy with myoclonic absences (Tassinari syndrome)
- Eyelid myoclonia with absences (Jeavons syndrome)
- Myoclonic astatic epilepsy of early childhood (Doose syndrome)

Epilepsy syndromes with onset in adolescence

- Reading epilepsy
- Photosensitive epilepsies
- Juvenile Absence Epilepsy
- Juvenile Myoclonic Epilepsy
- Epilepsy with GTCS Alone
- Progressive myoclonic epilepsies
- Mesial temporal lobe epilepsy
- Nonepileptic seizures

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

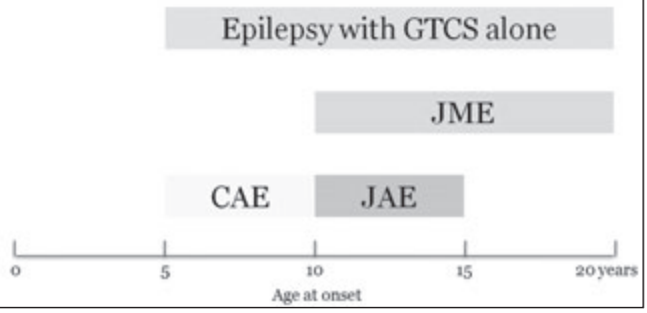
- Adolescence – Adult
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic–clonic seizures alone (EGTCSA)
  - Progressive myoclonus epilepsies (PME)
  - Autosomal dominant epilepsy with auditory features (ADEAF)
  - Other familial temporal lobe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

Berg, et al. Epilepsia, 2010.

Idiopathic 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 Generalized Epilepsies

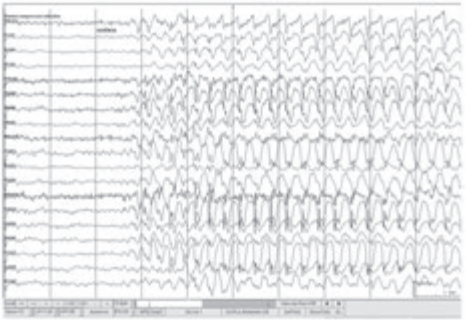


Juvenile Absence Epilepsy

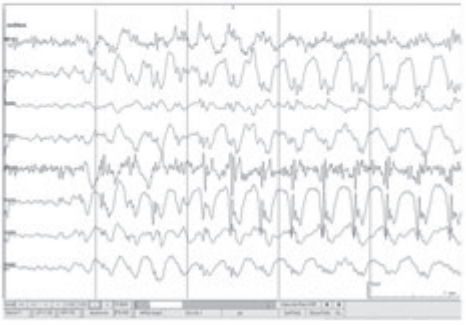
- Onset: 9-13 years (also older)
- No gender preference
- Similarity to the absence sz seen in Childhood Absence Epilepsy
  - Less frequent and milder
  - Longer duration
- Infrequent GTCS (morning) in most patients
- Mild myoclonic jerks (1/5 subjects)
- Intermediate syndrome between CAE and JME

Juvenile Absence Epilepsy

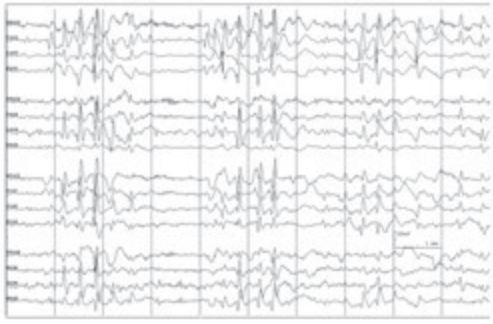
EEG background: normal. Interictal and ictal: bursts of generalized spike- or polyspike-wave discharges (fragmented or not) with slightly faster repetition rate (3-4 Hz).



Maximally over frontal head regions.
Can be precipitated by hyperventilation, sleep deprivation, and infrequently by photic stimulation.



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



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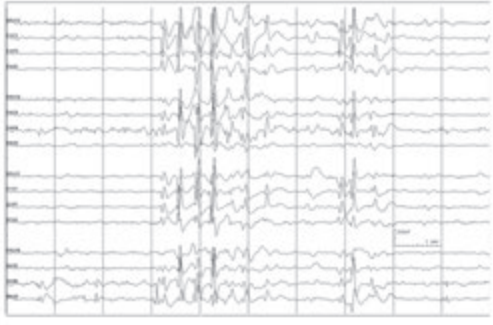
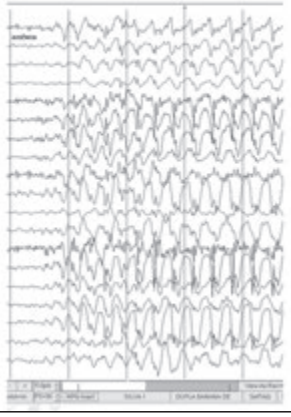
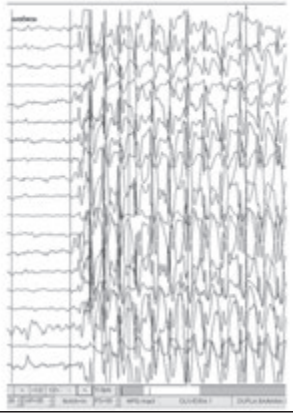
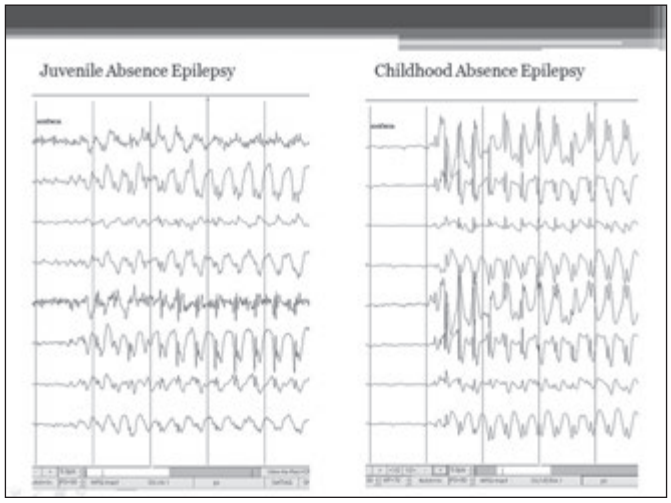


Juvenile Absence Epilepsy



Childhood Absence Epilepsy





Juvenile Absence Epilepsy

- Genetics
  - Strong genetic component
  - Chromosome linkage to chromosomes 5, 8, 18 and 21
- Prognosis
  - Sz control in most patients
  - Treatment indefinitely
  - Absence severity usually decreases with time

Juvenile Myoclonic Epilepsy

- Janz's syndrome

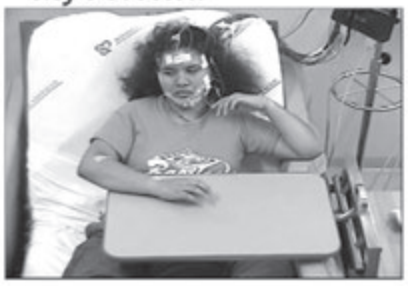
Prof. Dieter Janz
Impulsiv-Petit mal (1957)

Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-386.

Juvenile Myoclonic Epilepsy

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

Myoclonia



Essential to diagnosis.

Early morning – sudden drop of objects.

Neck, shoulder, **arms**, legs – extensor.

No alteration of consciousness.

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

Ebner, et al. Epilepsia 2001; 42:1212-1218.

Generalized clonic-tonic-clonic seizures

90-95% of subjects

Preceded by myoclonia crescendo into a clonic-tonic-clonic pattern

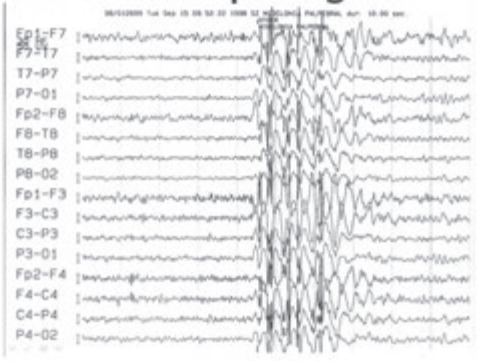
Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-386.

Absences

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

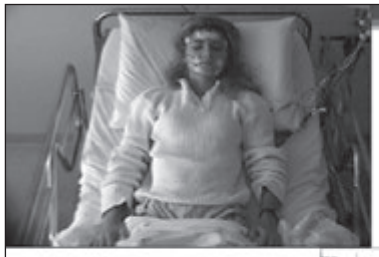
Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-386.

The electroencephalogram



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

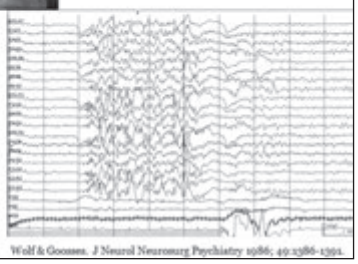
Janz & Christian. Dtsch Z Nervenheilk 1957; 176:346-386.



The photosensitivity

Sz and discharges precipitated by photic stimuli

30% of patients, female predominance



Wolf & Goosses. J Neurol Neurosurg Psychiatry 1986; 49:1386-1391.

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
  - Lifelong treatment

Epilepsy with GTCS Alone

- GTCS at various times of the day
- 6 years – middle age (peak age of onset 16-17)
- Slightly more prominent in men
- Sleep deprivation and alcohol increase sz
- EEG
  - Normal background
  - Generalized irregular and fast spike- and polyspike-wave complexes at 3-4 Hz

Progressive Myoclonic Epilepsies

- Rare – 1% of all epilepsy cases in childhood and adolescence
- Myoclonus syndrome (massive, fragmentary and multifocal)
  - Often precipitated by posture, action or external stimuli (light, sound or touch)
- GTCS
- Progressive neurological deterioration resulting in dementia
- Neurologic syndrome with cerebellar manifestations
- Specific genetic etiologies

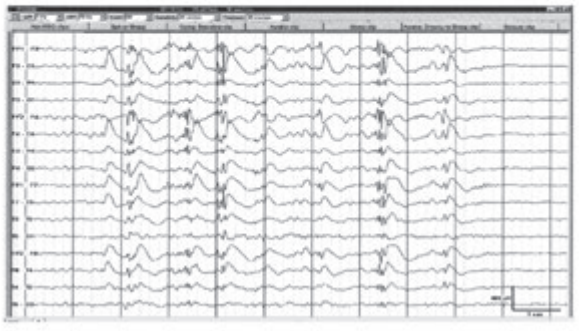
Definite diagnosis of specific types of PME

- Unverricht-Lundborg disease
  - CSTB gene mutation
- Lafora disease
  - Lafora bodies in skin biopsy or EPM2A mutation
- Myoclonic epilepsy with ragged red fibres
  - Ragged red fibres in muscle biopsy or MTTK mutation
- Neuronal ceroid lipofuscinosis
  - Typical intracellular inclusions or mutation in TPP1, CLN3, CLN5
- Sialidoses
  - Neuraminidase deficiency in leucocytes or fibroblasts
- Dentatorubral-pallidoluysian atrophy
  - Abnormal CAG repeats

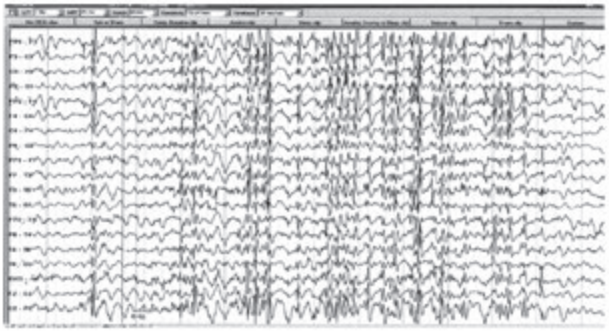
Progressive Myoclonic Epilepsies

- EEG
  - Slowing of the background rhythm
  - Generalized epileptiform discharges
  - Photosensitivity

Progressive myoclonic epilepsy with generalized, irregular polyspike or spike and slow-wave complexes seen in sleep.

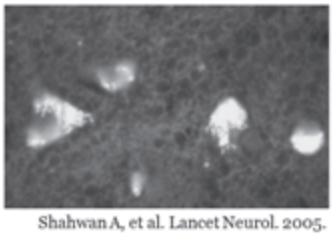


Adolescent with Lafora body disease. EEG during photic stimulation at 6 Hz shows marked photosensitivity and subsequent myoclonic jerks.



Neuronal ceroid lipofuscinoses (NCLs)

- 8 forms identified on the basis of clinicopathologic, biochemical and genetic testing
- 2 have onset during or near adolescence:
  - Batten disease
  - Kufs disease



Section of cortex examined under fluorescent light to show yellow intracytoplasmic autofluorescent accumulation of abnormal amounts of lipopigments in lysosomes

Shahwan A, et al. Lancet Neurol. 2005.

Juvenile Neuronal Ceroid Lipofuscinosis

- Type 3 – Juvenile NCL – Batten disease
- Begins between 5-8 years of age
- Typical early signs:
  - Progressive vision loss, seizures, ataxia or clumsiness, mental deterioration
- Less rapid progression
  - Death in the late teens or early 20s, although some may live into their 30s

Beretning om et mærkeligt Sygdoms-tilfælde hos fire Søskende i Nærheden af Røraas.

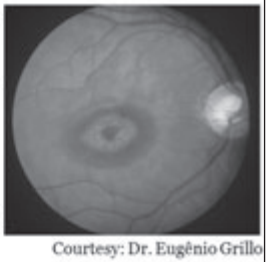
(Af C. Stengel, Læge ved Røraas Kobberverk).

Disse høist mærkværdige Sygdomstilfælde, der have viist sig her i Egnen, har jeg for en Deel været Øievidne til, og, da de vist nok baade i physiologisk og pathologisk Henseende kunde have megen Interesse, har jeg, saavidt Omstændighederne tillode det, efter Evne søgt at fremstille de Phænomener, der yttrede sig, i den Orden, de fulgte.

Fig. 3. The first page of Dr. Otto Christian Stengel's original clinical description of juvenile NCL in the first volume of the first Norwegian medical journal "Eyr" in 1826.

Bruno, 12 years old

- First seen at 8 years old
  - Sporadic sz, learning impairment
- Slow cognitive deterioration
- Progressive vision loss
- Continuous hand myoclonia
- Sporadic GTCS
- Video-EEG
- MRI



Macular degeneration

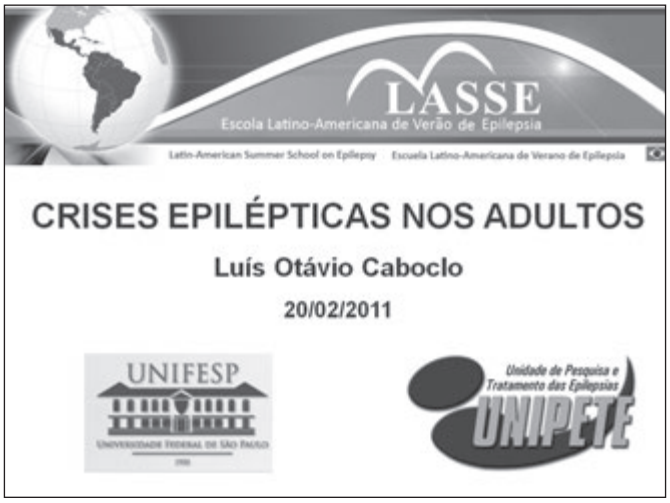
Courtesy: Dr. Eugênio Grillo

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.


Thank you!
Obrigada!
Gracias!
Profa. Dra. Katia Lin
linkatia@uol.com.br

Seizures in the adulthood
Luis Otávio Caboclo (Brazil)



- ✓ Introdução
- ✓ Diagnósticos diferenciais
- ✓ Classificação das crises
- ✓ Semiologia das crises epilépticas em adultos

Semiologia das crises epilépticas

- ✓relato do paciente
- ✓relato de observadores (familiares)
- ✓vídeo-EEG

Semiologia das crises epilépticas

I. Diagnóstico de epilepsia

II. Classificação das crises

III. Avaliação pré-cirúrgica

Diagnóstico diferencial de epilepsia

✓Crise psicogênica não epiléptica

✓Síncope

✓Crise epiléptica

Crise psicogênica não epiléptica

- pode ocorrer isoladamente ou associada a crises epilépticas
- fenômeno inconsciente
- distúrbio psiquiátrico pode não ser evidente
- fatores de risco: epilepsia, depressão
- fatores desencadeantes

VÍDEO

Diagnóstico diferencial de epilepsia

✓Crise psicogênica não epiléptica

✓Síncope

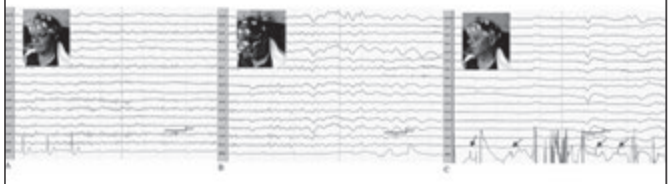
✓Crise epiléptica

Síncope

- perda transitória da consciência, com perda do tônus postural
- seguida de recuperação espontânea, sem confusão pós-crítica e sem seqüelas neurológicas
- 20% da população
- "síncope convulsiva"
  - ✓ 5-12% das síncopes vasovagais
  - ✓ 15% das síncopes cardiogênicas

Gastaut e Fischer-Williams. Lancet 1957

	Síncopes	Crises TCG
Ocorrência	circunstanciais	espontâneas
Duração	< 30 seg.	1- 2 min.
Evento precipitante	50%	nenhum
Queda	flácida ou rígida	rígida
Convulsões	80% breves, arrítmicas, multifocais ou generalizadas	2-3 min., rítmicos, generalizados
Olhos	abertos, desvio para cima ou para o lado transitório	abertos, desvio mantido
Alucinações	tardia	pode preceder TCG (aura odor e gosto)
Cor da face	pálida	cianótica
Hipersalivação, sialorréia	ausente	comum
Incontinência	comum	comum
Mordedura de língua	rara	comum
Tempo para recuperação	< 30 seg.	1- 2 min.



Diagnóstico diferencial de epilepsia

✓Crise psicogênica não epiléptica

✓Síncope

✓**Crise epiléptica**

Semiologia das crises epilépticas

I. Diagnóstico de epilepsia

II. Classificação das crises

III. Avaliação pré-cirúrgica

Classificação das crises epilépticas

Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised clinical and electrographic classification of epileptic seizures ⇨ ILAE 1981

Epilepsia 1981; 22: 489-501

Classificação das síndromes epilépticas

Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised classification of epilepsies and epileptic syndromes ⇨ ILAE 1989

Epilepsia 1989; 30: 389-399

ILAE – 1981

Proposal for revised clinical and electrographic classification of epileptic seizures

I. CRISES PARCIAIS
II. CRISES GENERALIZADAS
III. CRISES NÃO CLASSIFICADAS
IV. ADENDO

ILAE – 1981

Proposal for revised clinical and electrographic classification of epileptic seizures

I. CRISES PARCIAIS

A. CRISES PARCIAIS SIMPLES (sem comprometimento da consciência)

B. CRISES PARCIAIS COMPLEXAS (com comprometimento da consciência)

C. CRISES PARCIAIS EVOLUINDO PARA CRISES SECUNDARIAMENTE GENERALIZADAS

ILAE – 1981

Proposal for revised clinical and electrographic classification of epileptic seizures

II. CRISES GENERALIZADAS

A. AUSÊNCIA: típica e atípica

B. MIOCLÔNICA

C. TÔNICA

D. CLÔNICA

E. TÔNICO-CLÔNICA

F. ATÔNICA

ILAE – 1989

Proposal for revised classification of epilepsies and epileptic syndromes

1. EPILEPSIAS E SÍNDROMES PARCIAIS
(localization-related)

1.2 Sintomáticas

Temporal

Frontal

Parietal

Occipital

ILAE – 1989

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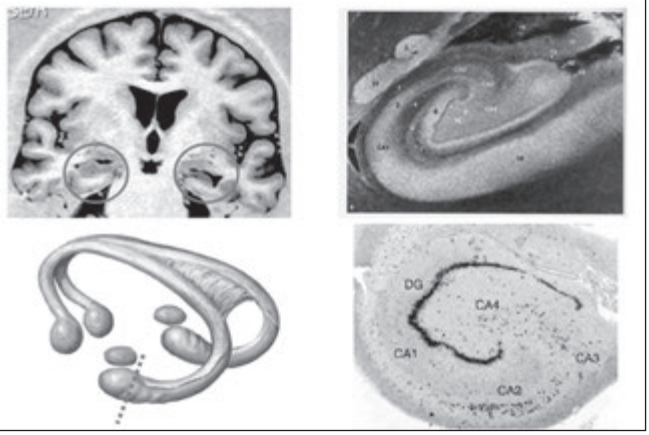
1. EPILEPSIAS E SÍNDROMES PARCIAIS
(localization-related)

1.2 Sintomáticas

Temporal: mesial e lateral

- ✓ Epilepsia do lobo temporal: epilepsia mais comum em adultos
- ✓ Esclerose mesial temporal: substrato anátomo-patológico mais frequente

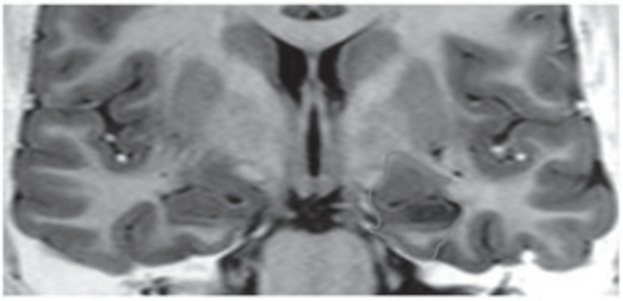


Unidade de Pesquisa e Tratamento das Epilepsias

UNIPETE

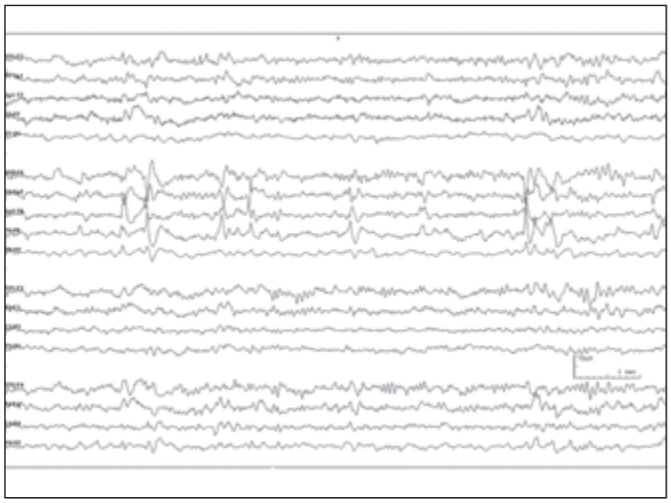
Epilepsia mesial do lobo temporal com EMT:

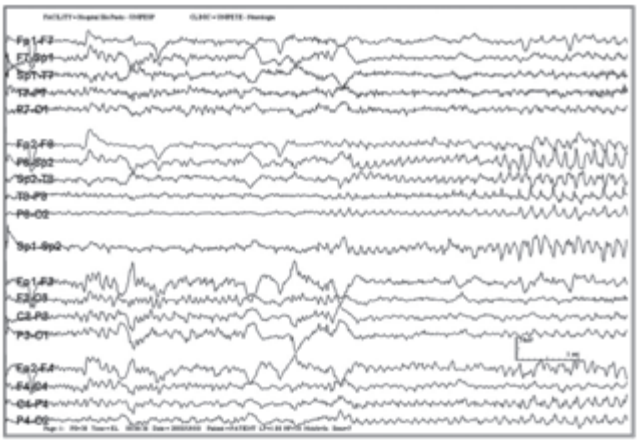
Crises originadas no hipocampo, amígdala e giro parahipocampal

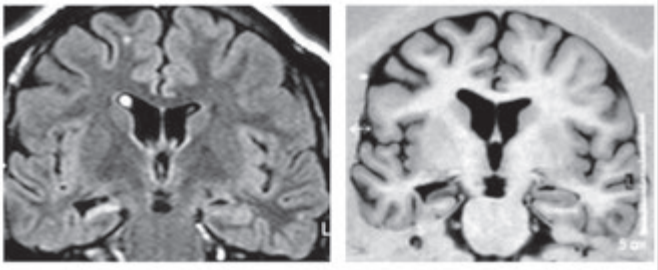


Epilepsia mesial do lobo temporal:

- EEG interictal:
  - ondas agudas temporais anteriores
  - surtos de ondas lentas temporais
- EEG ictal: ritmo teta ictal
- RM: esclerose hipocampal







Epilepsia mesial do lobo temporal:

Auras:

- sensação epigástrica ascendente (mais comum)
- fenômenos experenciais
- sintomas autonômicos-vegetativos
- olfatória/gustatória

Epilepsia mesial do lobo temporal:

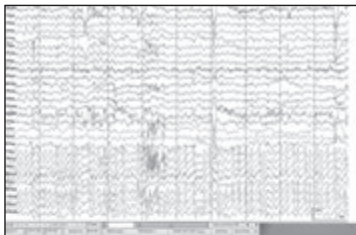
Pacientes com auras (96)	64	Parestesia	01
		Despersonalização	01
Pacientes sem auras (4)	03	Assoar o nariz	01
		Auras sem sensações viscerais	25
Tipo de aura		Medo	05
Abdominal	39	Olfatória	05
Apenas aura	13	Cefálica	03
Mais outros sintomas	26	Déjà vu	03
Medo	06	Somatosens gen	03
Cefálica	06	Indescritível	03
Calor	03	Calor	02
Gustatória	02	Gustatória	02
Olfatória	02	Urgência miccional	02
Urgência miccional	02	Intelectual (ocaso espiritual)	01
Micropsia	02	Dispnéia	01
Indescritível	02	Desorientação	01
Vertigem	01	Vertigem	01
Euforia	01	Auditiva elementar	01
Compulsões	01	Visual elementar	01

French et al., 1993

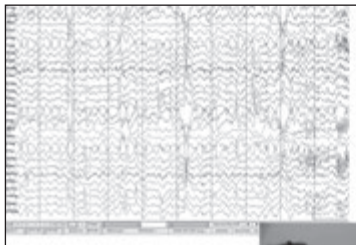
Epilepsia mesial do lobo temporal:

Crises parciais complexas:

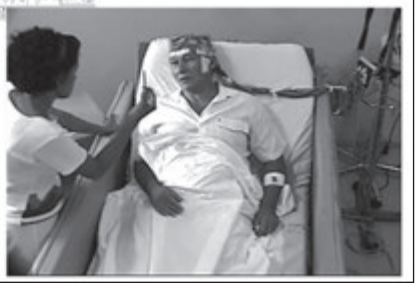
- grau variável de comprometimento da consciência
- *staring*
- automatismos
  - oroalimentares
  - manuais
  - complexos
- desvio cefálico
- postura distônica do membro superior



Crise: fala ictal



Crise: compreensão



Epilepsia mesial do lobo temporal:

Crises parciais complexas:

- **grau variável de comprometimento da consciência**
- ***staring***
- automatismos
  - oroalimentares
  - manuais
  - complexos
- desvio cefálico
- postura distônica do membro superior

Caravaggio, Medusa, 1592
Uffizi, Florença

Vídeo “STARING"

Epilepsia mesial do lobo temporal:

Crises parciais complexas:

- **grau variável de comprometimento da consciência**
- ***staring***
- **automatismos**
  - **oroalimentares**
  - **manuais**
  - **complexos**
- **desvio cefálico**
- **postura distônica do membro superior**

VÍDEO

Epilepsia mesial do lobo temporal:

Crises parciais complexas:

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  - manuais
  - complexos
- desvio cefálico
- postura distônica do membro superior

VÍDEO

Epilepsia mesial do lobo temporal:

Crises tônico-clônicas secundariamente generalizadas:

- raras (principalmente após início do tratamento)
- precedidas de versão cefálica

VÍDEO

Epilepsia mesial do lobo temporal:

Pós-ictal:

- confusão mental
- afasia: lobo temporal do hemisfério dominante

VÍDEO

ILAE – 1989

Proposal for revised classification of epilepsies and epileptic syndromes

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(localization-related)

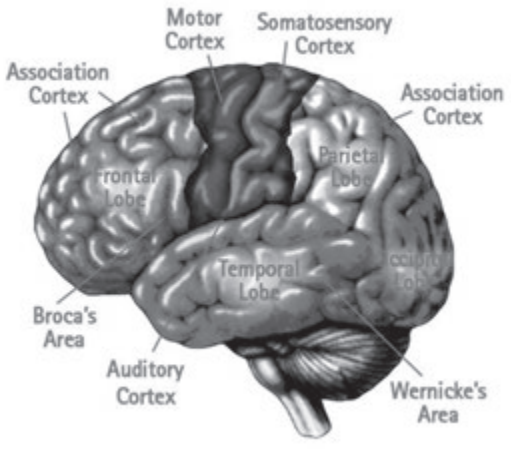
1.2 Sintomáticas

Temporal

Frontal

Parietal

Occipital



ILAE – 1989

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(localization-related)

1.2 Sintomáticas

Temporal

Frontal: **AMS, cíngulo, frontopolar, orbitofrontal, dorsolateral, opercular, córtex motor**

CRISES DO LOBO FRONTAL

- **Crises motoras clônicas focais**
- **Crises tônicas assimétricas**
- **Crises parciais complexas do lobo frontal**

Williamson et al., 1992

CRISES DO LOBO FRONTAL

Crises motoras clônicas focais

1. Área perirrolândica baixa

- ✓ **Interrupção de fala**
- ✓ **Vocalização**
- ✓ **Disfasia**
- ✓ **Movimentos tônico-clônicos da face contralateral**
- ✓ **Deglutição**

CRISES DO LOBO FRONTAL

Crises motoras clônicas focais

2. Área rolândica

- ✓ **Crises parciais motoras com ou sem marcha jacksoniana**

3. Lóbulo paracentral

- ✓ **Crises tônicas do pé ipsilateral**

Vídeo

CRISES DO LOBO FRONTAL

Crises tônicas assimétricas

Sintomas subjetivos

- ✓ **Sensações somatossensitivas de parestesias ou formigamentos**
- ✓ **Constricção ou enrijecimento**

CRISES DO LOBO FRONTAL

Crises tônicas assimétricas

Sintomas objetivos motores

- ✓ Posturas tônicas ou distônicas assimétricas dos membros superiores ou inferiores
- ✓ Postura do membro superior abduzido, fletido ou com o punho cerrado
- ✓ Movimentos do membro superior ipsilateral
- ✓ Movimentos de chutar e de caminhar
- ✓ Postura tônica-distônica do membro inferior contralateral
- ✓ Movimentos distônicos atetóides de braço, perna ou ambos

Vídeo

CRISES DO LOBO FRONTAL

Crises parciais complexas do lobo frontal

- ✓ Automatismos motores complexos, súbitos, de aparência agitada
- ✓ Vocalização (de sussuros a gritos)
- ✓ Impulsões pélvicas, movimentos negativos com a cabeça, chute, pedalada

VÍDEO

CRISES DO LOBO FRONTAL

Crises parciais complexas do lobo frontal

- ✓ **Automatismos motores complexos, súbitos, de aparência agitada**
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VÍDEO

CRISES DO LOBO FRONTAL

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VÍDEO

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Temporal

Frontal

Parietal

Occipital → EPILEPSIAS DO CÓRTEX POSTERIOR

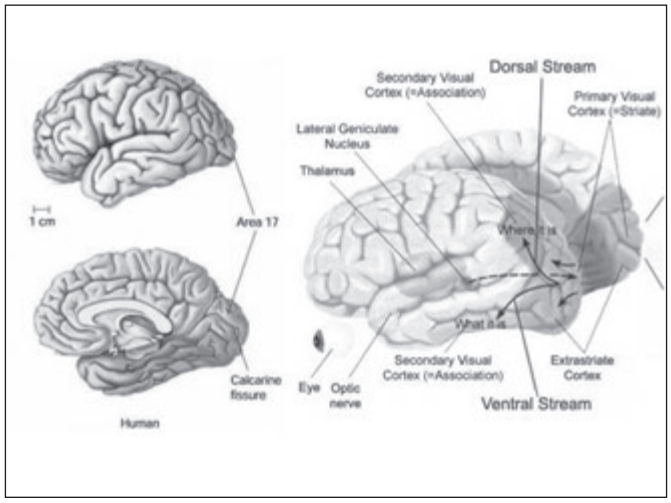
CRISES DO LOBO PARIETAL

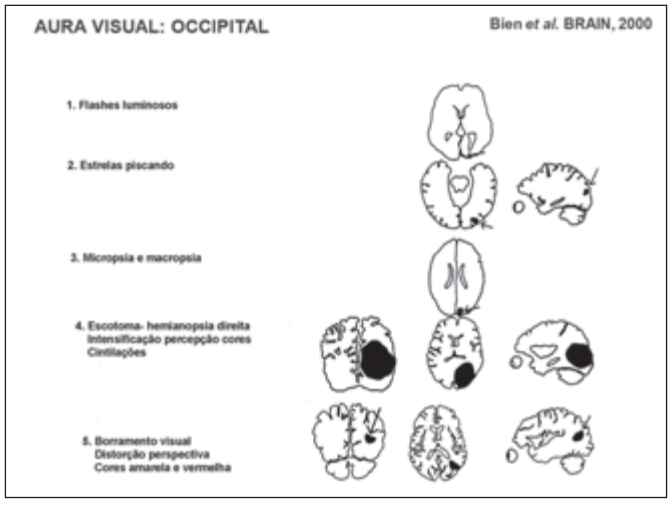
- auras > 75%
- somato-sensitivas
- dor: pode ser manifestação ictal
- imagem corporal distorcida
- alucinações visuais ou auditivas
- progressão com perda de consciência e contração motora contralateral

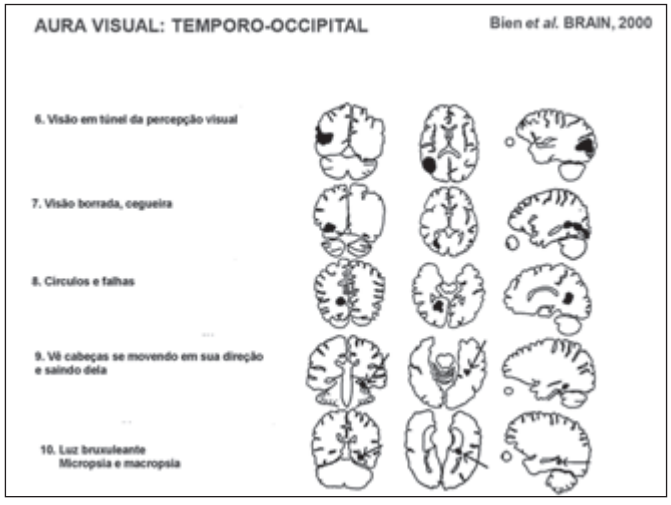
Vídeo

CRISES DO LOBO OCCIPITAL

- auras visuais: luzes piscando, cegueira ictal ocasional
- alucinações visuais complexas


1 cm
Area 17
Calcarine fissure
Human
Dorsal Stream
Secondary Visual Cortex (=Association)
Primary Visual Cortex (=Striate)
Lateral Geniculate Nucleus
Thalamus
Where it is
What it is
Secondary Visual Cortex (=Association)
Extrastriate Cortex
Eye
Optic nerve
Ventral Stream


AURA VISUAL: OCCIPITAL
Bien et al. BRAIN, 2000
1. Flashes luminosos
2. Estrelas piscando
3. Micropsia e macropsia
4. Escotoma- hemianopsia direita
Intensificação percepção cores
Cintilações
5. Borramento visual
Distorção perspectiva
Cores amarela e vermelha


AURA VISUAL: TEMPORO-OCCIPITAL
Bien et al. BRAIN, 2000
6. Visão em túnel da percepção visual
7. Visão borrada, cegueira
8. Circulos e falhas
9. Vê cabeças se movendo em sua direção e saindo dela
10. Luz bruxuleante
Micropsia e macropsia

AURA VISUAL: TEMPORAL ÂNTERO-MEDIAL

Bien *et al.* BRAIN, 2000

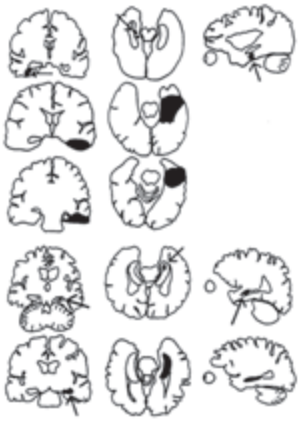
11. Fixação visual a um ponto
Sensação de que sai deste ponto

12. Vê pessoas pequenas

13. Intensificação da percepção de cores

14. Escotoma em arco-íris
Visão borrada

15. Visão em túnel
Flashes de estrelas



AURA VISUAL: TEMPORAL ÂNTERO-MEDIAL

Bien *et al.* BRAIN, 2000

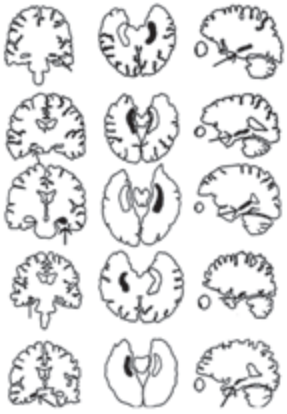
16. Entrando na cratera de um vulcão

17. Visão em túnel

18. Bola preta enorme se aproximando

19. Animais se aproximando

20. Visão borrada



TERMINOLOGIA

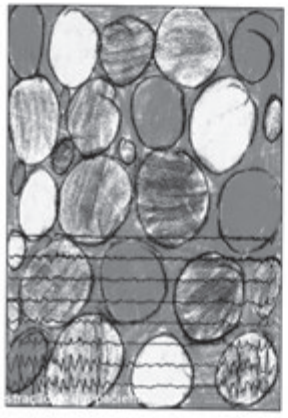
- **Alucinações visuais** são imagens de experiência subjetiva na ausência de estímulos externos
- **Alucinação visual elementar** são formas usualmente geométricas únicas, linhas ou manchas
- **Alucinações visuais complexas**: visão de objetos, faces ou cenas
- **Percepção** é a imagem mental ou o produto da percepção de qualquer objeto no espaço
- **Fosfenos** são sensações subjetivas de luz devido à estimulação não luminosa da retina. A denominação de fosfenos pode também ser usada pra definir a percepção visual da estimulação do córtex visual com estimulação elétrica, neste caso assumindo usualmente a forma de manchas ou círculos
- **Ilusões visuais** são percepções falsamente interpretadas das imagens externas reais
- **Palinopsia** é a persistência ou recorrência de imagens visuais após a remoção do estímulo que as deflagrou
- **Visão estereoscópica** é a percepção normal acurada profunda alcançada pela visão binocular
- **Visão teleoscópica** são ilusões visuais nas quais os objetos aparecem distantes ou pequenos
- **Teicopsia:** *Teico:* muralha de uma cidade + *psia:* visão

Teicopsia - espectro de fortificação

Fort Bourtange, Groningen

GSA, 18 a, enxaqueca

EPILEPSIA



ENXAQUECA

CRISES OCCIPITAIS	AURA DE ENXAQUECA
cefaléia pós-ictal: uni ou bilateral, geralmente contralateral à alucinação visual	cefaléia: unilateral, latejante, com náuseas/vômitos, foto/fonofobia
segundos, raramente 1-3 minutos, diários	4-30 minutos
círculos, formas circulares, bolas pequenas, pontos	linear – espectro de fortificação, teicoscopia; zig-zag
localização contralateral; campo temporal	localização: centro do campo visual
vermelho brilhante, amarelo, azul, verde	padrões acromáticos ou preto e branco
amaurose, cegueira branca	
dor orbital durante a fase ictal e vômito ictal	

CRISES DO LOBO OCCIPITAL

- auras visuais: luzes piscando, cegueira ictal ocasional
- alucinações visuais complexas
- piscamento, movimentos nistagmóides clônicos
- progressão para lobo temporal ou crise secundariamente generalizada

Vídeo

Semiologia das crises epilépticas

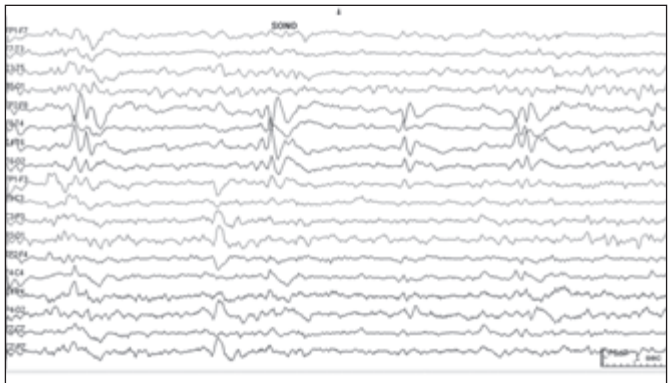
I. Diagnóstico de epilepsia

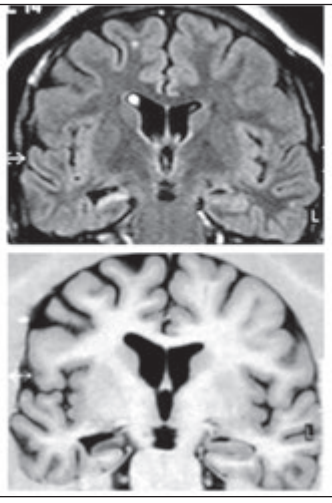
II. Classificação das crises

III. Avaliação pré-cirúrgica

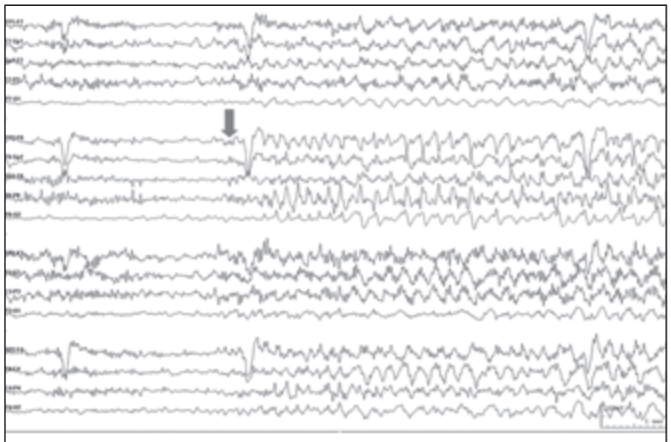
R.O.P., sexo feminino, 29 anos

- 16 anos: eclâmpsia na primeira gestação
- 24 anos: primeira crise não provocada
- aura psíquica: "o ambiente fica estranho", "angústia"
- aura epigástrica
- crises parciais complexas: parada comportamental, *staring*, automatismos bimanuais; fala ictal compreensível
- pós-ictal: confusão mental muito breve
- 1 crise/semana, a despeito do tratamento





VÍDEO



Zona de início ictal: lobo temporal direito

Semiologia das crises epilépticas

I. Diagnóstico de epilepsia

II. Classificação das crises

III. Avaliação pré-cirúrgica

OBRIGADO

Seizures in the elderly
Veriano Alexandre Junior (Brazil)

Epilepsia no Idoso

LASSE V
Guarulhos, 20 Fev 2011

Veriano Alexandre Jr

Epidemiologia

- Idoso: pessoa a partir de 65 anos
- Epidemiologia idade relacionada
- 86 novos casos/100.000 habitantes/ano
- Aumentado risco da morbidade e mortalidade

Etiologia

- Doenças vasculares cerebrais
- Doenças neurodegenerativas primárias: Alzheimer
- Tumores cerebrais primários e metastáticos
- Traumatismos crânio-encefálicos

Diagnóstico

- Características dos eventos
- Doenças associadas
- Medicamentos concomitantes
- Fatores precipitantes ou predisponentes das crises
- ECG para afastar causar cardíacas
- Exames para screening bioquímico, metabólico e infeccioso

Situações de Confusão Diagnóstica e Diagnóstico Diferencial

- Quedas
- Alterações da coordenação e do equilíbrio
- Estados confusionais e alucinações
- Alterações de memória
- Sinais neurológicos focais: transitórios, rítmicos ou estereotipados
- Parassonias REM, pernas inquietas

Diagnóstico Diferencial

Vídeo

Características Clínicas

- Predomínio das crises focais
- Chance aumentada de recorrência
- Tipo parciais complexas com ou sem generalização 2ª
- Causas estruturais são mais frequentes
- Incidência aumentada de status epilepticus

Características Clínicas cont.

- Semiologia semelhante a de pacientes jovens
- Tratamento controla crises em > 80% dos casos
- Risco de quedas e fraturas pelas crises
- Risco de complicações cárdio-respiratórias
- Consequências psicossociais das crises

Características Clínicas

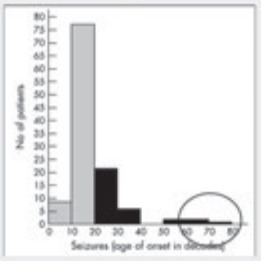
Seizure Semiology in the Elderly: A Video Analysis
Kellinghaus C et al, 2004. Epilepsia 45(3):263-267

Semiologia	Idosos	Controles
Auras	9	14
Crises Parciais Complexas	10	11
Crises Focais Motoras Simples	3	9 (p<0.05)
Crises Generalizadas Motoras	4	9
Inconsciência durante as crises	11	19

Características Clínicas

Idiopathic Generalised Epilepsy of Adult Onset: Clinical Syndromes and Genetics

Marini C, et al. J Neurol Neurosurg Psychiatry 2003; 74:192-196



Características Clínicas

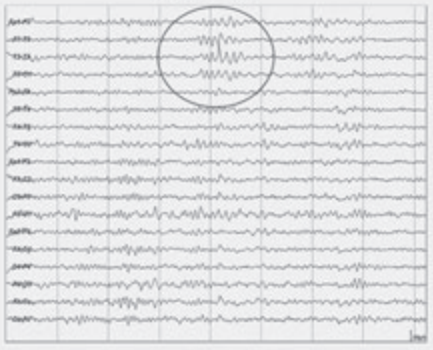
Vídeo

Eletrencefalograma

- Alterações próprias da idade
- Variações da normalidade
- Achados de significado incerto
- Anormalidades inespecíficas
- Paroxismos epileptiformes
- Atividade ictal

Eletrencefalograma

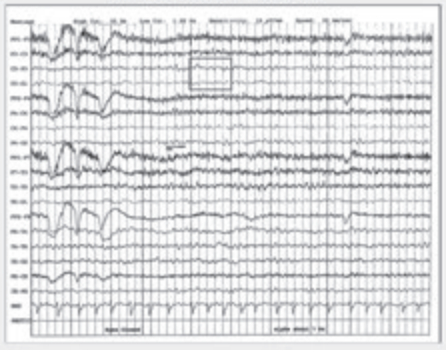
Wicket Spikes



Epileptiform Normal Variants on EEG. Benbadis S. Emedicine.medscape.com

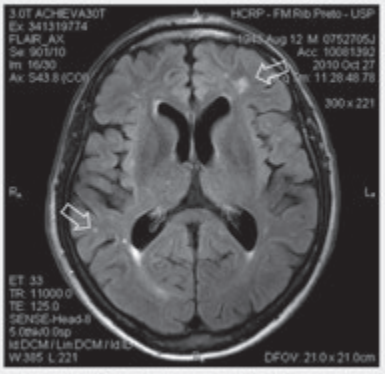
Eletrencefalograma

Lentificação do ritmo posterior



EEG in dementia and encephalopathy. Neiman ES. Emedicine.medscape.com

Neuroimagem



Focos de desmielinização ou gliose na substância branca subcortical

Mudanças Fisiológicas no Idoso que Afetam a Disposição das DAEs

- Absorção reduzida ➞ Biodisponibilidade reduzida
- Proteína sérica reduzida ➞ Elevação da fração livre
- Reduzido metabolismo hepático (DAEs indutoras) + Reduzido clearance renal + Aumento relativo da gordura corporal com ➞ volume de distribuição aumentado Meia-Vida aumentada
- Mudanças farmacodinâmicas ➞ Sensibilidade EAs

O idoso geralmente tem uma faixa terapêutica mais estreita, ou seja, a máxima concentração tolerada das DAEs é mais próxima da concentração mínima terapêutica. Isto tem implicações práticas no ajuste das dosagens.

CLINICALLY RELEVANT DRUG INTERACTIONS WITH ANTIEPILEPTIC DRUGS

Emilio Perucca
British Journal of Clinical Pharmacology 2005 61(3):246-255

Table 2
Drugs which have been found to increase the serum concentration of antiepileptic drugs, presumably by inhibiting their metabolism

Affected drug		Interfering drug
Carbamazepine	*Antiepileptic drugs:*	Felbamate[1], valproic acid[1], valpromide[1]
	Antidepressants:	Fluoxetine, fluvoxamine, nefazodone, trazodone, viloxazine
	Antimicrobials:	Clarithromycin, erythromycin, fluconazole, isoniazid, ketoconazole, metronidazole, ritonavir, troleandomycin
	Miscellaneous:	Cimetidine, danazol, dextropropoxyphene, diltiazem, risperidone, quetiapine[2], ticlopidine, verapamil
Ethosuximide	*Antimicrobials:*	Isoniazid
Lamotrigine	*Antiepileptic drugs:*	Valproic acid
	Antidepressants:	Sertraline
Phenobarbital	*Antiepileptic drugs:*	Felbamate, phenytoin, sulthiame, valproic acid
	Antimicrobials:	Chloramphenicol
	Miscellaneous:	Dextropropoxyphene
Phenytoin	*Antiepileptic drugs:*	Felbamate, oxcarbazepine, sulthiame, valproic acid[3]
	Antidepressants:	Fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine
	Antimicrobials:	Chloramphenicol, fluconazole, isoniazid, miconazole, sulfaphenazole
	Antineoplastic drugs:	Doxifluridine, fluorouracil, tamoxifen, tegafur, UFT
	Miscellaneous:	Allopurinol, amiodarone, azapropazone, cimetidine, chlorpheniramine, dextropropoxyphene, diltiazem, disulfiram omeprazole, phenylbutazone, sulfinpyrazone tacrolimus, ticlopidine, tolbutamide
Valproic acid	*Antiepileptic drugs:*	Felbamate
	Antidepressants:	Sertraline
	Antimicrobials:	Isoniazid
	Miscellaneous:	Cimetidine

The list should not be regarded as exhaustive. For further information and a list of references, see Patsalos and Perucca [1, 2].
[1]These drugs increase the concentration of the active metabolite carbamazepine-10,11-epoxide, the effect being most clinically relevant with valpromide. The concentration of carbamazepine is not affected by valproic acid and valpromide, and/s it is decreased by felbamate. [2]Interaction inconsistent and limited to an increase in unbound phenytoin concentration. Total serum phenytoin concentration usually decreases due to displacement from plasma protein binding sites.

Table 3
Drugs whose serum concentration has been reported to be decreased by coadministration of enzyme-inducing antiepileptic drugs (AEDs) (carbamazepine, phenobarbital, phenytoin and primidone)

Antidepressants[1]	Amitriptyline, bupropion, citalopram, clomipramine, desipramine, desmethylclomipramine, doxepin, imipramine, mianserin, mirtazapine, nefazodone, nortriptyline, paroxetine, protriptyline
Antimicrobials	Albendazole, doxycycline, griseofulvin[2], indinavir[3], itraconazole, metronidazole, praziquantel
Antineoplastic drugs[1]	9-aminocamptotecin, busulfan, cyclophosphamide, etoposide, ifosfamide, irinotecan, methotrexate, nitrosoureas, paclitaxel, procarbazine, tamoxifen, teniposide, thiotepa, topotecan, vinca alkaloids
Antipsychotic drugs	Chlorpromazine, clozapine, haloperidol, mesoridazine (active metabolite of thioridazine), olanzapine, quetiapine, risperidone, ziprasidone
Benzodiazepines	Alprazolam, clobazam, clonazepam, desmethyldiazepam, diazepam, midazolam
Cardiovascular drugs[1]	Alprenolol, amiodarone, atorvastatin, dicoumarol, digoxin, disopyramide, felodipine, metoprolol, mexiletine, nifedipine, nimodipine, nisoldipine, propranolol, quinidine, simvastatin, verapamil[4], warfarin[5]
Immunosuppressants	Cyclosporin A[6], sirolimus, tacrolimus
Steroids	Cortisol, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, steroid oral contraceptives[7]
Miscellaneous	Fentanyl, metadone, metyrapone, misonidazole, paracetamol, pethidine, theophylline, thyroxine, vecuronium (and some other nondepolarizing neuromuscular blocking agents)

These interactions have not necessarily been shown with all enzyme inducers, and there can be differences in the enzyme-inducing and inhibiting spectrum of carbamazepine, phenobarbital, phenytoin and primidone. The list should not be regarded as exhaustive. For further information and a list of references, see Patsalos and Perucca [2] and Vecht et al. [52]. [1]Some of these drugs (for example, bupropion, procarbazine, ifosfamide, amiodarone, disopyramide) have active metabolites. Therefore, a reduced concentration of parent drug does not necessarily imply a reduced pharmacological effect. [2]Interaction reported with phenobarbital and probably due to impaired griseofulvin absorption. [3]Interaction likely to be extended to other CYP3A4 substrates such as nevirapine, efavirenz, delavirdine, ritonavir and saquinavir. [4]Interaction only relevant after oral administration of verapamil. [5]Phenytoin may cause an initial decrease in anticoagulant effect, followed by an increase in warfarin concentration. [6]There is suggestive evidence that oxcarbazepine may also decrease serum cyclosporin A levels. [7]Other AEDs which have been found to decrease the concentration of the oestrogen and/or progestogen component of oral contraceptive steroids include felbamate, lamotrigine, oxcarbazepine and, at dosages >200 mg day^{-1}, topiramate.

Partial Seizures: Elderly Available Evidence

ILAE Treatment Guidelines: Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes

Glauser T et al. Epilepsia 47(7):1094-1120, 2006

Partial Seizures: Elderly Available Evidence

- A total of 30 RCTS with elderly participants included which examined initial monotherapy for partial-onset seizures
- Division of trials
  - Class I (n=1)
  - Class II (n=1)
  - Class III (n=2)

Glauser T et al. Epilepsia 47(7):1094-1120, 2006

Partial Seizures: Elderly Recommendations

Level A: GBP, LTG
Level B: None
Level C: CBZ
Level D: TPM, VPA
Level E: Others
Level F: None

Glauser T et al. Epilepsia 47(7):1094-1120, 2006

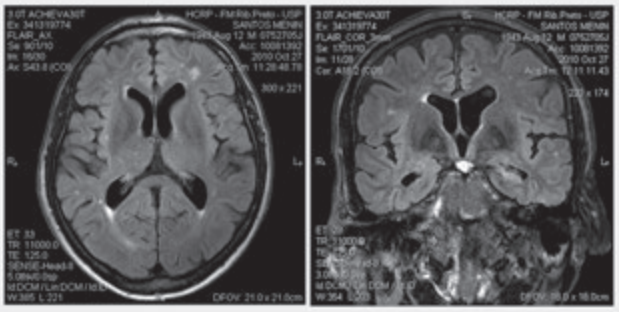
Epilepsia no Idoso – CASO CLÍNICO

LASSE V
Guarulhos, 20 Fev 2011

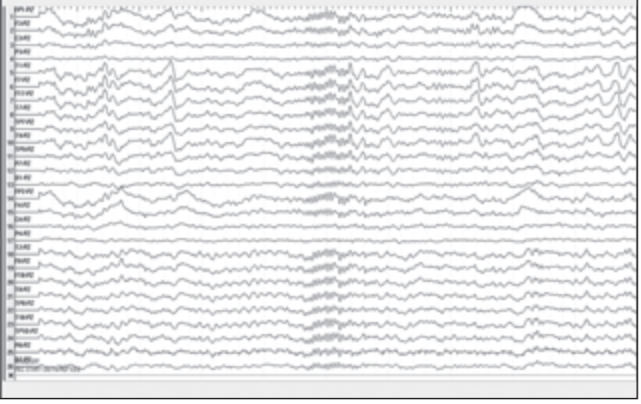
História da Doença Atual

- Procedente de Guararapes-SP, aposentado, 67 anos; casado, católico;
- Primeira crise aos 11 anos de idade, sem fatores de risco;
- Perda de consciência desde o início, automatismos típicos de crises provenientes do lobo temporal;
- Farmacorresistente à CBZ (2000 mg/dia) e TPM (500 mg/dia)

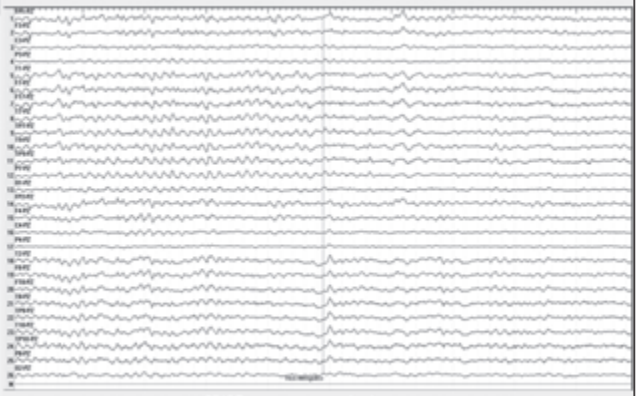
RNM



EEG interictal



EEG ictal



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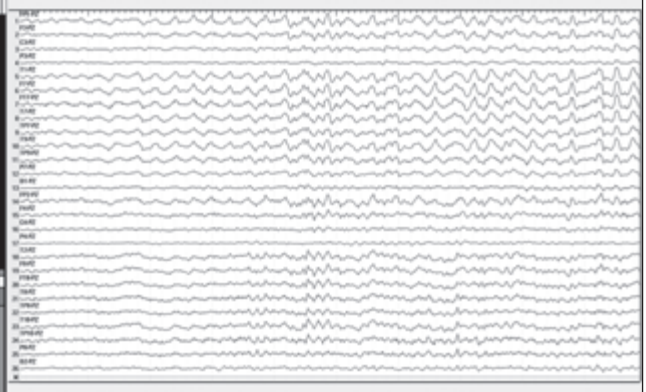
EEG ictal cont.



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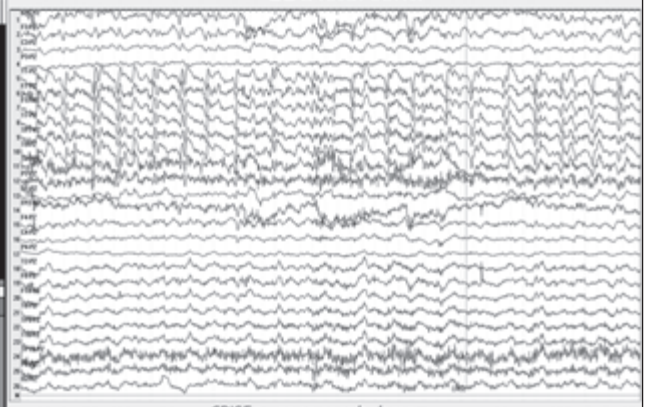

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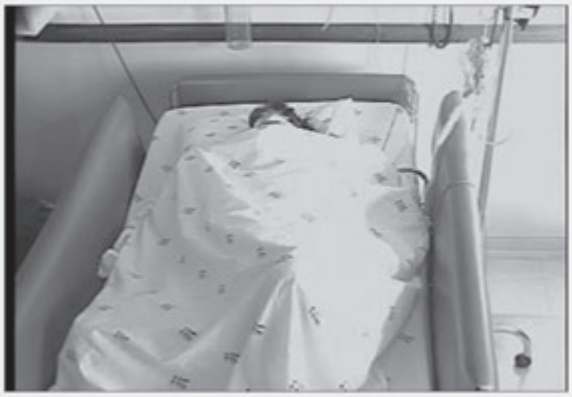
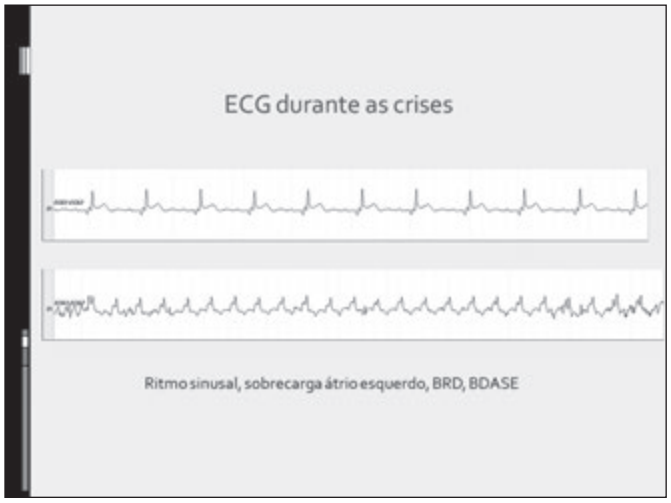
Semiologia ictal



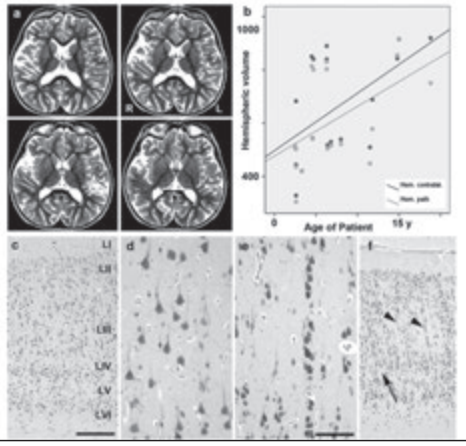

ECG durante as crises
Ritmo sinusal, sobrecarga átrio esquerdo, BRD, BDASE

TOWARDS A NEW CLASSIFICATION OF FOCAL CORTICAL DYSPLASIA
ROBERTO SPREAFICO (ITALY)

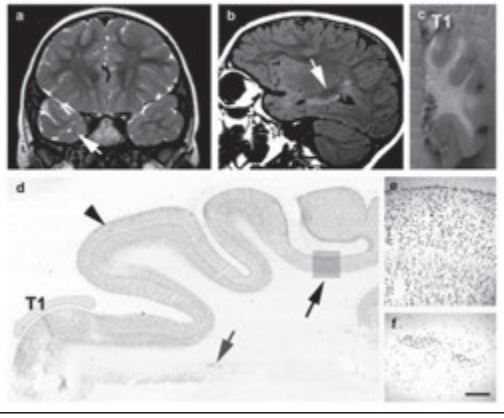
subgroups of FCD identified in two different classification schemes

Taxsi et al. [29]	Palmini et al. [25]	Dyslamination	Hyper. neuron	Dysmor. neuron	Balloon cells	WM changes
Arch. dysplasia	FCD Type IA	+	–	–	–	+/–
Cytoarch. dysplasia	FCD Type IB	+	+	–	–	+/–
Taylor's type	FCD Type IIA	++	+/–	++	–	+/–
	FCD Type IIB	++	+/–	++	++	+

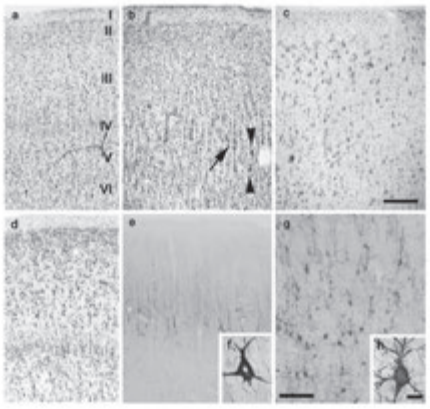
Imaging and histological findings in FCD Type IA
(isolated lesion affecting multiple lobes)



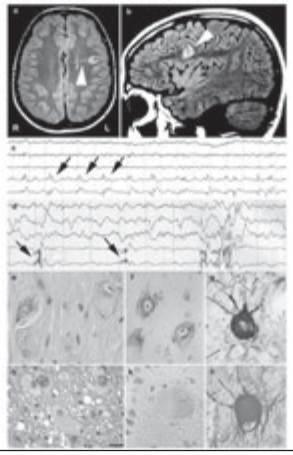
Imaging and histological findings in FCD Type IA
(associated with hippocampal sclerosis).



Histological findings in FCD Type IB (distinguishing it from FCD Type II).



Clinico-pathological findings in FCD Type IIB.



Summary of 748 patients with intractable epilepsies and histopathologically confirmed malformations of cortical development (MCD).
Data obtained from the European Epilepsy Brain Bank

MCD	Number	Age	Onset	Duration
Hemimegalencephaly	20	2.1	0	2.1
Nodular Heterotopia	16	20.8	6.7	14.5
Polymicrogyria	44	8.6	2.3	6.3
Hamartia/-toma	37	23.3	7.9	14.2
FCD Type I	99	15.6	5.5	8.9
FCD Type II	296	17.9	4.4	14.2
FCD (NOS)	159	19.9	8.3	13.3
mMCD	77	24.9	9.8	15.6
Total	748	18.1	5.7	12.5

Type I focal cortical dysplasia (FCD I): surgical outcome is related to histopathology

Laura Tassi[1], Rita Garbelli[2], Nadia Colombo[1], Manuela Bramerio[4], Giorgio Lo Russo[1], Francesco Deleo[2], Gloria Milesi[2], Roberto Spreafico[2]

Epileptic Disord. 2010; 12 (3): 1-11

FCD I: 215 pts; 5 subgroups

FCD I isolated	66 pts (31%)
FCD I + HS	76 pts (35%)
FCD I + tumors	49 pts (23%)
FCD I + other MCD	16 pts (7%)
FCD I + anoxo-ischemic lesions	8 pts (4%)

Main clinical characteristics of 215 (28%) patients with Type I FCD out of 784 operated on from 1996 to 2007

Histopathology	N° of patients (%)	Age at epilepsy onset (SD)	Duration of epilepsy (SD)	Seizure frequency (SD)	Neg. MRI (%)	SEEG (%)
FCD isolated	66 (31)	8 (10)	15 (9)	**115 (200)**	**22 (33)**	47 (71)
FCD + HS	76 (35)	8 (8)	25 (10)	10 (7)	2 (3)	11 (15)
FCD + Tumors	49 (23)	8 (6)	17 (12)	20 (29)	1 (2)	13 (27)
FCD + MCD	16 (7)	10 (7)	18 (11)	21 (19)	0	12 (75)
FCD + others	8 (4)	6 (3)	12 (7)	45 (38)	0	7 (88)
TOTAL	215	8 (8)	19 (11)	47 (120)	25 (12)	90 (42)

Lobar distribution of FCD Type I

Histopathology	Temporal (%)	Frontal (%)	Parietal (%)	Occipital (%)	Multilobar (%)
FCD isolated	15 (23)	**23 (35)**	1 (2)	1 (2)	**26 (39)**
FCD + HS	**75 (99)**	0	0	0	1 (1)
FCD + Tumors	**35 (71)**	6 (12)	1 (2)	0	7 (14)
FCD + MCD	8 (50)	1 (6)	0	0	7 (44)
FCD + Other	0	0	0	0	8 (100)
TOTAL	133 (62)	30 (14)	2 (1)	1 (1)	49 (23)

Surgical outcome in FCD I

Histopathology	Class Ia + Ic (%)	Class I (%)	Class II (%)	Class III (%)	Class IV (%)
FCD isolated	23 (35)	30 (46)	7 (11)	10 (15)	19 (29)
FCD + HS	50 (66)	62 (82)	7 (9)	3 (4)	4 (5)
FCD +Tumors	38 (78)	40 (82)	3 (6)	5 (10)	1 (2)
FCD + MCD	10 (63)	14 (88)	0	1 (6)	1 (6)
FCD + Other	2 (25)	2 (25)	2 (25)	2 (25)	2 (25)
TOTAL	123 (57)	148 (69)	19 (9)	21 (10)	27 (13)

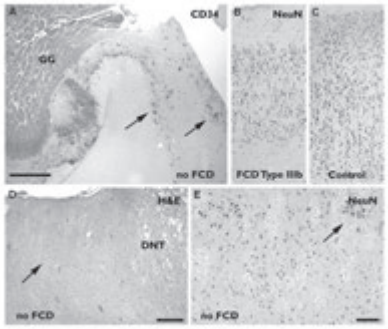
Epilepsia, **(*):1–17, 2010
doi: 10.1111/j.1528-1167.2010.02777.x

SPECIAL REPORT

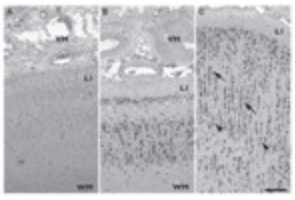
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

*[3]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, ***[3]Fernando Cendes, †††Nadia Colombo, ‡‡‡Peter Crino, §§§J. Helen Cross, ¶¶¶Olivier Delalande, ###François Dubeau, ****John Duncan, ††††Renzo Guerrini, ‡‡‡‡Philippe Kahane, §§§§Gary Mathern, ¶¶¶¶Imad Najm, ####Çiğdem Özkara, *****Charles Raybaud, †††††Alfonso Represa, ‡‡‡‡‡Steven N. Roper, §§§§§Noriko Salamon, ¶¶¶¶¶Andreas Schulze-Bonhage, #####Laura Tassi, ******Annamaria Vezzani, and ††Roberto Spreafico

Histopathologic findings in FCD (FCD IIIb) associated to ganglioglioma in A and B and to a dysembryoplastic neuroepithelial tumor (DNT) in D and E.



Histopathologic findings in FCD (Type IIIc) associated with a vascular malformation.



Histopathologic findings in FCD (Type IIId) associated with a gliomesodermal scar.

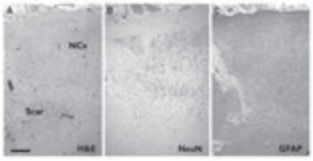


Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

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 clinically/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 variant.				

Mind in Antiquity

F. Mario Fales (Italy)

Programa – 21.02.2011

09.00 – 10:00	The universe of cortical lobes: the frontal and parietal lobes – Marina Bentivoglio (Italy)
10:00 – 11:00	The kingdom of the temporal lobe– Marina Bentivoglio (Italy)
11.00 –11.30	Coffee break
11:30 – 12:30	Memory processes and mechanisms in the mammalian brain - Richard Morris (UK)
12:45 – 14:30	Lunch
14:30 – 15:30	Role of the hippocampus in memory processing – Martin Cammarota (Brazil)
15:30 – 16:00	Coffee break
16:00 – 17:00	Effects of retrieval on memory retention - Martin Cammarota (Brazil)
17:00 – 18:00	"Cogito ergo sum" The itinerary of localization of functions in the brain– Marina Bentivoglio (Italy)
18:30 – 20:00	Dinner
20:30	Evening event

The universe of cortical lobes: the frontal and parietal lobes

Marina Bentivoglio (Italy)

The kingdom of the temporal lobe

Marina Bentivoglio (Italy)

Memory processes and mechanisms in the mammalian brain

Richard Morris (UK)

Role of the hippocampus in memory processing

Martin Cammarota (Brazil)

Effects of retrieval on memory retention

Martin Cammarota (Brazil)

"Cogito ergo sum" The itinerary of localization of functions in the brain

Marina Bentivoglio (Italy)

Programa – 22.02.2011

09:00 – 10:00	Right brain, left brain - Giuseppe Bertini (Italy)
10:00 – 11:00	Brain and gender - Marina Bentivoglio (Italy)
11:00 – 11:30	Coffee break
11:30 – 12:30	The neurobiology of memory: synaptic tagging and schemas - Richard Morris (UK)
12:30 – 14:00	Lunch
14:00 – 15:00	Neuroanatomical organization of episodic memory - Monica Munoz-Lopez (Spain)
15:00 – 16:00	System consolidation and memory persistence - Martin Cammarota (Brazil)
16:00 – 16:30	Coffee break
16:30 – 17:30	From sensation to perception: what have we learned from the study of vision – Giuseppe Bertini (Italy)
17:30 – 18:30	Formation of working groups and distribution of research topics among students
19:00 – 21:00	Dinner

Right brain, left brain
Giuseppe Bertini (Italy)

Brain and gender

Marina Bentivoglio (Italy)

THE NEUROBIOLOGY OF MEMORY: SYNAPTIC TAGGING AND SCHEMAS

RICHARD MORRIS (UK)

Neuroanatomical organization of episodic memory

Monica Munoz-Lopez (Spain)

System consolidation and memory persistence

Martin Cammarota (Brazil)

From sensation to perception: what have we learned from the study of vision

Giuseppe Bertini (Italy)

Programa – 23.02.2011

09:00 – 10:00	Practice makes perfect: nerual bases of motor and perceptual learning - Giuseppe Bertini (Italy)
10:00 – 11:00	Pondering decisions: the emerging field of neuroeconomy - learning - Giuseppe Bertini (Italy)
11:00 – 11:30	Coffee break
11:30 – 12:30	Incidence of amnesia after neonatal hypoxia/ischaemia - Monica Munoz-Lopez (Spain)
12:30 – 14:00	Lunch
14:00 – 15:00	Impact of the first seizure in the posterior psychological development – Jaime Carrizosa (Colombia)
15:00 – 16:00	Do we have reliable neurophysiologic tool to measure and understand human cognition? Alicia Bogacz (Uruguay)
16:00 – 16:30	Coffee break
16:30 – 17:30	Cognitive changes in MTLE – Carlos Guerreiro (Brazil)
19:00 – 21:00	Dinner

Practice makes perfect: nerual bases of motor and perceptual learning

Giuseppe Bertini (Italy)

Pondering decisions: the emerging field of neuroeconomy - learning

Giuseppe Bertini (Italy)

Incidence of amnesia after neonatal hypoxia/ischaemia

Monica Munoz-Lopez (Spain)

Impact of the first seizure in the posterior psychological development
Jaime Carrizosa (Colombia)

Impacto de la primera crisis en el desarrollo psicológico posterior

Jaime Carrizosa M, Md.
Profesor Universidad de Antioquia
Medellín, Colombia

DEFINICIONES

Epilepsia es un trastorno cerebral caracterizado por una predisposición a generar crisis y que produce consecuencias neurocognitivas y psicosociales.

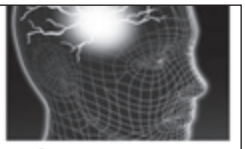
Una crisis epiléptica es un episodio transitorio de signos y síntomas debidos a una descarga anormal hipersincrónica de las neuronas.

DEFINICIONES

Crisis aguda sintomática: crisis que ocurre en espacio temporal cercano a una lesión sistémica como por ejemplo intoxicación, trauma, desequilibrio hidroelectrolítico etc.

-Tiene una clara relación temporal con el insulto
-No tiene una clara tendencia a recurrir
-No suelen desarrollar epilepsia

DEFINICIONES



Crisis única no provocada:

- No tiene un factor desencadenante
- Puede predisponer a recurrencia
- En mayores de 1 mes
- Todas las crisis que ocurren en 24 horas son una sola crisis
- 10 a 12% de las crisis únicas no provocadas son un estado epiléptico

EPIDEMIOLOGÍA

Table 1. Incidence (per 100,000 population per year) of seizures by type

				Incidence				
Author (year)	Area (country)	Population	N. cases	All	Acute symptomatic	Unprovoked	Single	Design
Loiseau et al. (1990)	Gironde (France)	1,128,164	804	71.3	29.0	42.3	18.3	Prospective
Hauser et al. (1993)	Rochester (U.S.A.)	2,003,357[a]	1,572	100.0	39.0	61.0	NA	Retrospective
Annegers et al. (1995)								
Forsgren et al. (1996)	Umea (Sweden)	101,583	218	76.0	20.0	56.0	NA	Prospective, adults
Jallon et al. (1997)	Geneva (Switzerland)	384,657	273	70.8	25.2	45.6	NA	Prospective
MacDonald et al. (2000)	London (U.K.)	100,220	NA	NA	NA	57.0	11.0	Prospective
Olafsson et al. (2005)	(Iceland)	882,151	501	NA	NA	56.0	23.5	Prospective

[a]Person-years (50-year period).
NA, not available.

Epilepsia, 49(Suppl. 1):8–12, 2008
doi: 10.1111/j.1528-1167.2008.01443.x

EPIDEMIOLOGÍA

Incidencia crisis única no provocada (Olaffson):

130,2 / 100 000 en menores de 12 meses

110,5 / 100 000 en mayores de 65 años

24,4 en hombres y 22,5 en mujeres

Table 2. Mortality of seizures in population-based studies by type

Author (year)	Area (country)	Person-years	N. cases	SMR (95% CI) All	Acute symptomatic	Unprovoked	Single	Design
Hauser et al. (1980)	Rochester (U.S.A.)	8,203	618	2.3 (1.9–2.6)	NA	2.3 (1.9–2.6)	2.3 (1.5–3.3)	Retrospective
Olafsson et al. (1998)	(Iceland)	6,308	224	1.6 (1.2–2.2)	NA	1.6 (1.2–2.2)	1.2 (0.1–4.8)	Retrospective
Loiseau et al. (1999)	Gironde (France)	804	804	9.3 (7.9–10.9)	10.3 (8.3–12.7)	4.1 (2.5–6.2)	NA	Prospective
Lindsten et al. (2000)	Vasterbotten (Sweden)	850	107	2.5 (1.2–5.2)	NA	2.5 (1.2–5.2)	NA	Prospective, adults
Beghi et al. (2005)*	(Italy)	3,098	333	2.8 (1.6–4.6)	NA	2.8 (1.6–4.6)	NA	Prospective, adults
Hesdorffer and D'Arrabo (2005)	Rochester (U.S.A.)	35.7	438	149.1 (119.0–184.7)		NA	NA	Retrospective

NA, not available; SMR, standardized mortality ratio; 95% CI, 95% confidence interval.
*Randomized pragmatic trial.

Mortality following a first unprovoked seizure in children: a prospective study
Shinnar, O´Dell, Berg Neurology 2005

- 407 pacientes entre 1 mes a 19 años
- Seguimiento medio de 14,2 años
- 68 (17%) etiología sintomática remota
- 339 (83%) etiología idiopática/criptogénica
- 86% sin tratamiento en la primera crisis
- En el año 2004: 45% con recaída
- 9 pacientes fallecieron

CAUSAS DE MUERTE

- Uno por herida de arma de fuego
- Uno por meningitis
- Uno por enfermedad neurodegenerativa
- Hemorragia subaracnoidea posradiación
- Neumonía en niño con parálisis cerebral

- Epilepsia idiopática con tratamiento, sin adecuado control por adherencia inadecuada
- Uno con epilepsia refractaria con tratamiento
- Dos tratados por disgenesia desde la primera crisis

CONCLUSIÓN

El tratamiento de la primera crisis, no tiene ningún impacto en la mortalidad.

Original Article

Patients' preferences towards antiepileptic drug therapy following first attack of seizure

V. Chandramoulesswaran, M. Dhanaraj, R. Rangaraj, A. Vengatesan*
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Neurology India | December 2006 | Vol 54 | Issue 4

Epilepsia, 49(Suppl. 1):35–39, 2008
doi: 10.1111/j.1528-1167.2008.01448.x

SUPPLEMENT - MANAGEMENT OF A FIRST SEIZURE

The socioeconomic, cultural, and emotional implications of starting or withholding treatment in a patient with a first seizure

*Dominic C. Heaney, *Gail S. Bell, and *†Josemir W. Sander

Table 2: Factors influencing preferences of AED Therapy (n=73)

Factors	Preferred group (n=39) (%)	Deferred group (n=34) (%)	Odds ratio (95% CI)*	*P*-value*
Sex				
Male	33 (85)	21 (62)	3.4 (1.0-12.1)	0.03
Female	6 (15)	13 (38)		
Education				
Primary	15 (39)	5 (15)	3.6 (1.1-13.5)	0.04
Middle school and above	24 (61)	29 (85)		
Occupation				
House-life	4 (10)	11 (32)	4.2 (1.1-17.9)	0.01
Student	7 (18)	8 (24)	0.7 (0.2- 2.5)	0.56
Manual laborer	28 (72)	15 (44)	4.1 (1.4-12.3)	0.003
Decider to take AED therapy				
Patients	24 (62)	13 (38)	2.6 (1.0-7.5)	0.03
Patients and relatives	15 (38)	21 (62)		

*Test of significance was pearson Chi-squared test/Yates corrected Chi-squared test, *Odds ratio with 95% confidence interval, AED - Antiepileptic drug

Table 3: Antiepileptic drug therapy preferences and reasons (n=73)

Preferred group	**(n=39)**
Fear of injury	4 (10%)
Occupational risk	14 (36%)
Do not want a recurrence at any cost	21 (54%)
(i) living alone	(2)
(ii) nonavailability of medical help at times of emergency	(4)
(iii) fear of dismissal from job	(3)
(iv) fear of seizure itself	(12)
Deferred group	**(n=34)**
Fear of adverse effects	19 (56%)
Wait for second attack	15 (44%)

Remembering the first seizure and the diagnosis of epilepsy: How much impact do they have in our lives?

Nuran Aydemir[a,*], Ali İ Tekcan[b], Çiğdem Özkara[c]

Más del 50% de las personas con epilepsia refieren como primera sensación al diagnóstico de epilepsia: temor, depresión, rabia e incertidumbre.

24% refieren sensaciones de exclusión, soledad, vergüenza.

Recibir el diagnóstico de epilepsia delimitó la frontera entre lo normal y "ser epiléptico" como un marcador central de identidad.

Epilepsy & Behavior 16 (2009) 156–160

Las crisis han sido descritas como "un corto viaje desde la demencia a la muerte", frente a "observadores aterrorizados", quienes observan "una reaparición de lo primitivo", que rompe el orden social al representar la crisis la debilidad humana, la imposibilidad de predicción, la impotencia, la ambiguedad y la incapacidad de cumplir las normas básicas culturales y sociales.

Epilepsy & Behavior

The reactions of parents who think that a child is dying in a seizure—In their own words

Frank M.C. Beug *, Antonia Nomayo [1], Felicity Pool

Los padres perciben la sensación de muerte en sus hijos cuando en la crisis:

- Cianosis
- Primera CTCG
- Duración de 10 minutos
- Paresia

Esa percepción de muerte la refieren entre 30 a 49% de los padres, y persistió incluso hasta 6 meses después de la crisis

Perceived health in children presenting with a "first seizure"

Lorie Hamiwka [a,*], Neetu Singh [a], Jodie Niosi [a], Elaine Wirrell [b]

VARIABLE	NORMA	CRISIS ÚNICA	P
Dolor corporal	81,3 ± 19,1	71,8 ± 21,2	= 0,03
Tiempo parental impacto	88,4 ± 20,9	72,7 ± 32,0	= 0,016
Tiempo parental emocional	81,3 ± 18,4	48,7 ± 29,0	< 0,001
Salud mental	79,7 ± 15,5	71,8 ± 17,6	= 0,03
Comportamiento general	70,8 ± 18,9	60,7 ± 22,5	= 0,002
Actividades familiares	91,1 ± 18,7	72,1 ± 26,3	< 0,001
Sicosocial general	51,1 ± 9,6	42,4 ± 11,7	< 0,001
Percepción niños Salud General	3,5 ± 1,0	3,00 ± 0.9	= 0,017

Epilepsy & Behavior 13 (2008) 485–488

El compromiso en la cohesión familiar y el dolor corporal se deben a la adaptación el evento de la crisis.

Los cambios emocionales y de comportamiento pueden iniciar precozmente o antes de la primera crisis.

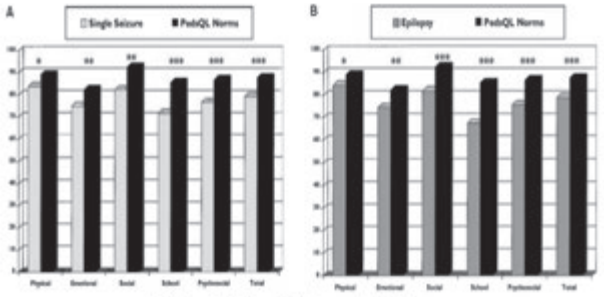
Los padres experimentan un mayor compromiso sicosocial y físico de sus hijos, que ellos mismos. Lo anterior se explica por un ajuste parental a la crisis como supervisión más cercana, restricción de actividades, cambios emocionales y comportamentales de los padres por preocupación y pena.

Even a single seizure negatively impacts pediatric health-related quality of life

*Avani C. Modi, *Andrea S. King, †Sally R. Monahan, *Julie E. Koumoutsos, †Diego A. Morita, and †Tracy A. Glauser

*Division of Behavioral Medicine and Clinical Psychology, Center for the Promotion of Adherence and Self Management, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.; and †Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.

CALIDAD DE VIDA EN CRISIS ÚNICA Y EPILEPSIA EN NIÑOS



(**A**) Pediatric Quality of Life Inventory (PedsQL) scores for children with single seizure and normative data. (**B**) PedsQL scores for children with epilepsy and normative data. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Epilepsia, 43(12):1-7, 2002
Lippincott Williams & Wilkins, Inc., Philadelphia
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Clinical Research

The Impact of a Single Seizure on Health Status and Health Care Utilization

Barbara A. Dworetzky, *Daniel B. Hoch, †Anita K. Wagner, ‡Eileen Salmanson, §Christopher W. Shanahan, and ‡Edward B. Bromfield

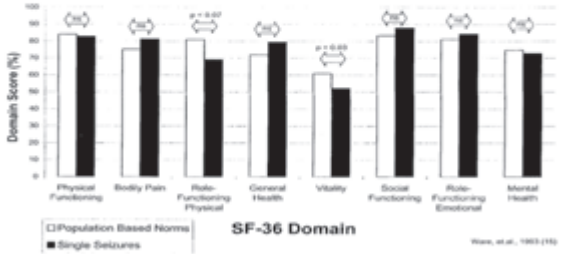


FIG. 1. SF-36 score comparison: single seizure (SS) versus population-based norms. SS (n = 36, average age, 41; SD, 17.0). Population-based norms (n = 2,474, average age, 43.6 yr; SD, 17.4) (Ware et al., 1993).

TABLE 5. *Number of patients by group with less than four, and or more visits to health providers*

Visits to health provider for condition within 1 year	SS (n = 30)	WC (n = 29)	HT (n = 24)
<4 visits [n (%)]	9 (30)	23 (79)	14 (58)
≥4 [n (%)]	21 (70)	6 (11)	10 (42)

χ^2. $p = 0.001$.
SS, single seizure; WC, well-controlled epilepsy; HT, hypertension.

17% tenían al año un temor moderado a extremo frente a una recurrencia.

38% informaban al año que la crisis aún tenía un moderado a extremo impacto en la calidad de vida, a pesar de gozar de buena salud en un 88%.

El motivo de consulta de las citas fue la crisis inicial y no la revisión de exámenes.

Behaviour problems in children with new-onset epilepsy D. W. DUNN*, J. K. AUSTIN†, & G. A. HUSTER* *Seizure* 1997; **6**: 283–287

Empleo del CBCL al inicio y a los 4 meses de la primera crisis

Table 3. Paired *t*-test time 1 vs. time 2

	Time 1		Time 2		
	M	sd	*M*	sd	*P*
Total problems	53.52	9.83	49.19	10.95	0.004
Internalizing	54.67	9.18	50.48	10.99	0.004
Externalizing	51.81	10.30	47.67	9.57	0.002
Social	54.29	8.29	54.88	9.00	ns
Thought	55.21	6.61	54.14	6.25	ns
Attention	55.55	7.73	54.31	6.82	ns

Total group, $N = 42$.

24% tenían problemas comportamentales desde el inicio

Table 4. Independent *t*-test by time testing for differences between epilepsy and one-seizure group

	Time 1				Time 2			
	Epilepsy		One seizure		Epilepsy		One seizure	
	M	sd	*M*	sd	*M*	sd	*M*	sd
Total Problems*	55.47	9.17	48.67	10.14	49.50	11.48	48.42	9.94
Internalizing	55.60	9.38	52.33	8.62	50.47	11.19	50.50	10.98
Externalizing†	54.07	9.16	46.17	11.21	48.37	10.34	45.92	7.74
Social	54.97	8.92	52.58	6.50	54.93	9.20	54.75	8.85
Thought	55.73	6.74	53.92	6.39	54.53	6.70	53.17	5.86
Attention	55.60	8.11	55.42	7.08	53.93	7.09	55.25	6.27

* At time 1 $P = 0.058$.
† At time 2 $P = 0.044$.

Behavior Problems in Children Before First Recognized Seizures

Joan K. Austin, Jaroslaw Harezlak, David W. Dunn, Gertrude A. Huster, Douglas F. Rose and Walter T. Ambrosius

Pediatrics 2001;107:115-122
DOI: 10.1542/peds.107.1.115

TABLE 4. *t* Test Results Comparing Differences in Behavior Problems Between Children With Seizures and Their Healthy Siblings

	Children (n = 224)		Siblings (n = 135)		*t* Test *P* Value
	M	SD	M	SD	
Total problems	55.9	9.9	52.4	11.2	.003
Internalizing	53.4	10.0	50.1	10.6	.004
Externalizing	53.8	10.6	53.2	10.9	.65
Aggressive behavior	56.9	9.1	56.2	8.5	.50
Anxious/depressed	55.9	7.7	54.8	7.9	.20
Attention problems	58.5	9.1	54.9	7.1	.0001
Delinquent behavior	55.1	6.7	55.8	7.5	.37
Social problems	56.8	8.4	55.1	8.2	.07
Thought problems	55.1	7.7	52.7	5.9	.002
Withdrawn	55.6	7.5	54.6	7.4	.26
Somatic complaints	54.9	6.0	52.6	5.0	.0001

TABLE 5. *t* Test Results Comparing Differences in Behavior Problems Between Children With Seizures and Their Healthy Siblings by Previous Unrecognized Seizure Status

	No Previous Seizures					Previous Seizures				
	Children (n = 148)		Siblings (n = 89)		*t* Test *P* Value	Children (n = 76)		Siblings (n = 46)		*t* Test *P* Value
	M	SD	M	SD		M	SD	M	SD	
Total problems	54.8	9.7	51.8	11.1	.03	57.9	10.2	53.6	11.4	.03
Internalizing	52.3	9.8	49.9	10.9	.08	55.5	10.3	50.5	10.1	.01
Externalizing	53.2	10.5	52.7	10.5	.69	54.9	10.8	54.4	11.7	.82
Aggressive behavior	56.4	8.8	55.7	7.6	.55	57.7	9.5	57.1	10.1	.73
Anxious/depressed	54.9	6.9	54.8	8.0	.91	57.8	8.7	54.8	7.8	.06
Attention problems	57.0	8.0	54.9	7.2	.04	61.3	10.4	55.0	6.8	.0004
Delinquent behavior	54.8	6.8	55.3	7.1	.61	55.7	6.4	56.8	8.2	.41
Social problems	56.5	7.7	54.4	7.5	.04	57.3	9.5	56.6	9.4	.68
Thought problems	54.3	7.0	53.0	5.9	.13	56.6	8.8	52.2	5.7	.003
Withdrawn	55.1	7.1	55.0	7.6	.90	56.5	8.1	54.0	6.9	.09
Somatic complaints	54.9	6.2	52.4	4.6	.001	55.0	5.8	52.9	5.7	.06

Hasta 34% de los niños pueden tener problemas comportamentales al documentarse la crisis única.

Los problemas internalizantes, de atención, de pensamiento y de quejas somáticas se encuentran con mayor frecuencia en este grupo de personas.

Es posible que las alteraciones se deban a descargas electroencefalográficas o a alteraciones cognitivas transitorias.

Recurrent Seizures and Behavior Problems in Children with First Recognized Seizures: A Prospective Study

*Joan K. Austin, †David W. Dunn, ‡Helena M. Caffrey, ‡Susan M. Perkins, ‡Jaroslaw Harezlak, and ‡Douglas F. Rose

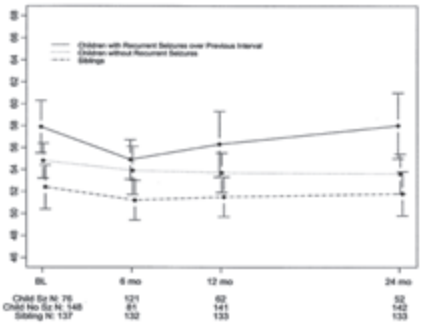
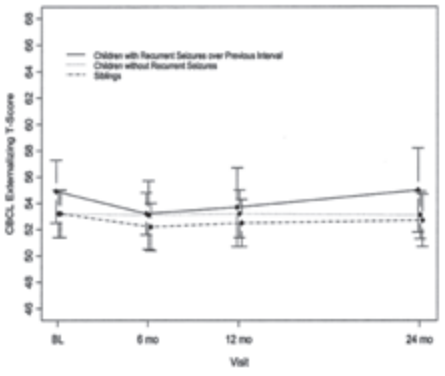


FIG 1. CBCL Total Behavior Problems Cross-Sectional Means ± 1 SE.

Epilepsia, Vol. 43, No. 12, 2002

FIG 3. CBCL Externalizing Behavior Problems Cross-Sectional Means ± 1 SE.



Los problemas comportamentales, que en total estuvieron presentes 42% de los afectados, mantienen la diferencia estadísticamente significativa a través del tiempo entre el grupo de crisis única, el grupo con recaída y sus hermanos.

Los datos son muy similares en el estudio de los problemas internalizantes, pero no hubo diferencias para los problemas externalizantes

Los problemas externalizantes se correlacionaban con una edad menor al presentarse la primera crisis y un nivel básico de educación de los padres.

A prospective study of teachers' ratings of behavior problems in children with new-onset seizures

David W. Dunn,[a,*] Joan K. Austin,[b] Helena M. Caffrey,[c] and Susan M. Perkins[c]

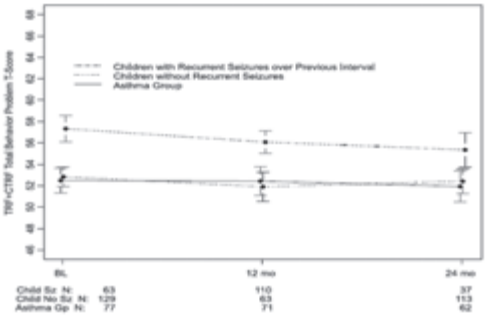


Fig. 1. TRF+C-TRF Total Behavior Problems: cross-sectional means ± SE.

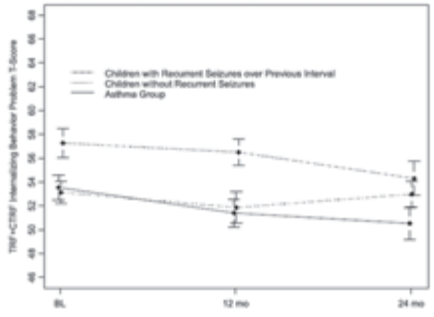


Fig. 2. TRF+C-TRF Internalizing Behavior Problems: cross-sectional means ± SE.

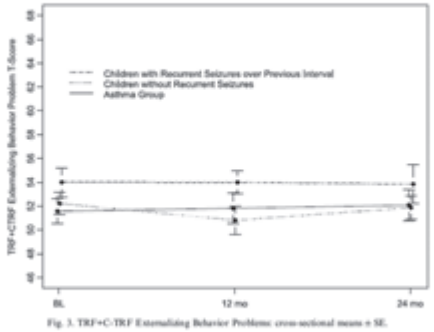


Fig. 3. TRF+C-TRF Externalizing Behavior Problems: cross-sectional means ± SE.

- Los problemas comportamentales fueron más frecuentes en los niños en tratamiento con FAE.

- El número de crisis padecido en el último año fue el predictor más fuerte de problemas comportamentales.

- Los problemas internalizantes se asociaron a edades mayores en este grupo de escolares.

Temperament, family environment, and behavior problems in children with new-onset seizures

Katherine T. Baum [a,b], Anna W. Byars [a,b], Ton J. deGrauw [a,b], Cynthia S. Johnson [c], Susan M. Perkins [c], David W. Dunn [c], John E. Bates [d], Joan K. Austin [a,*]

El temperamento es un patrón característico de la reactividad y autoregulación de origen biológico.

Las características de temperamento aparecen precozmente, son pilares de la personalidad relativamente estables, pero pueden mostrar un cambio con el desarrrollo.

El temperamento puede incidir en la capacidad de adaptación a problemas de salud como la epilepsia y producir problemas de comportamiento.

Las habilidades adaptativas de la familia pueden modificar las características del temperamento e incidir en los problemas de comportamiento.

Epilepsy & Behavior 10 (2007) 319–327

Hipótesis: Los niños con un temperamento precoz negativo tienen menos problemas comportamentales si crecen en familias con habilidades adaptativas, que si estuvieran en familias sin esas capacidades.

Cuestionario retrospectivo de características infantiles (RICQ), Subescalas: Niño difícil (emocionalidad negativa), Inadaptable (estrés a lo nuevo), Resistencia al control (inmanejable).

Profesores diligencian cuestionario sobre comportamiento de los dos meses previos a la crisis inicial, determinando problemas internalizantes (retraimiento, síntomas somáticos, ansiedad/depresión) y externalizantes (agresividad, delincuencia).

Destreza familiar: estima familiar y comunicación

Table 3
Correlations between early temperament and child behavior problems

Early temperament	Child behavior problems					
	Total		Internalizing		Externalizing	
	r	*P* value	*r*	*P* value	*r*	*P* value
Difficultness	0.20	0.0006	0.26	<0.0001	0.14	0.0183
Unadaptability	0.19	0.0016	0.23	<0.0001	0.11	0.0753
Resistance to Control	0.19	0.0011	0.18	0.0022	0.13	0.0335

Los niños con temperamento difícil tuvieron a futuro problemas comportamentales en total, internalizantes y externalizantes.

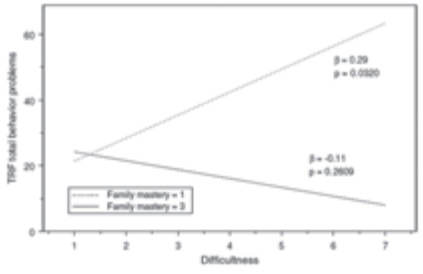


Fig. 2. Moderating effect of family mastery on the association between early Difficultness and Total Behavior Problems.

Existe un efecto moderador de la destreza familiar entre el temperamento difícil y los problemas internalizantes.

DESTREZA FAMILIAR	β ESTANDARIZADO PARA LA ASOCIACIÓN ENTRE TEMPERAMENTO DIFICIL Y PROBLEMAS INTERNALIZANTES
1	0,53 P=0,0006
3	-0,13 P=0,2418

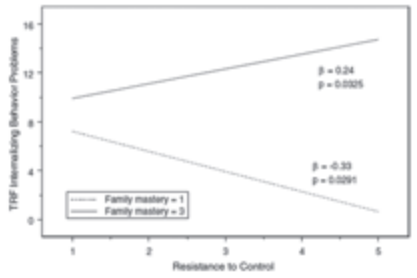


Fig. 3. Effect of family mastery on the association between early Resistance to Control and Internalizing Behavior Problems.

Neuropsychological status at seizure onset in children

Risk factors for early cognitive deficits

P.S. Fastenau, PhD
C.S. Johnson, MA
S.M. Perkins, PhD
A.W. Byars, PhD
T.J. deGrauw, MD, PhD
J.K. Austin, DNS
D.W. Dunn, MD

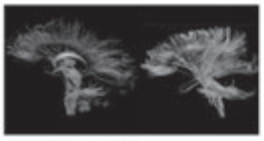
Neurology® 2009;73:526-534

Table 2 Descriptive statistics for neuropsychological and academic achievement test scores by seizure group

	Seizure group, n = 282		Sibling control group, n = 147		Seizure vs sibling d*
	Mean	SD	Mean	SD	
Language factor	0.0	0.8	0.2	0.6	−0.23†
CELF-3 Concepts & Directions†	9.7	3.2	10.2	3.3	−0.16‡
CELF-3 Word Classes†§	10.1	3.1	10.2	3.2	−0.04
CELF-3 Formulated Sentences†	9.4	2.7	9.6	2.9	−0.08
CELF-3 Recalling Sentences†§	10.3	3.3	10.4	3.1	−0.04
CTOPP Phonological Awareness Index†	95.9	14.3	98.7	12.4	−0.20
CTOPP Phonological Memory Index†	94.5	13.5	97.3	13.1	−0.21¶
Processing speed factor	0.1	0.8	0.2	0.7	−0.22#
WISC-III Coding†	9.8	3.5	10.4	3.5	−0.16
WISC-III Symbol Search†	11.5	3.8	12.5	3.4	−0.25#
CTOPP Rapid Naming Index†	98.5	15.6	100.0	15.1	−0.09
CPT-II Hit Response Time**§	47.4	11.3	49.1	10.7	−0.15
Attention/executive/construction factor	0.0	0.8	0.3	0.7	−0.36**
CPT-II Hit % Omissions**§	45.0	14.1	46.6	13.1	−0.11
CPT-II Hit Response Time Standard Error**	44.0	11.0	46.8	11.2	−0.26#
WCST % Total Errors**	49.7	11.7	53.1	11.2	−0.29†
WRAML Design Copy, % correct	89.4	14.8	93.5	10.7	−0.29†
Verbal memory and learning factor	0.0	0.8	0.2	0.7	−0.23†
WRAML Story Memory*	9.9	3.2	10.4	3.2	−0.16‡
WRAML Verbal Learning†	10.9	3.3	11.4	3.4	−0.14‡
WRAML Design Memory†§	8.4	2.7	9.2	3.0	−0.29†
Academic achievement					
W.J-R Letter-Word Identification†	105.3	16.0	104.0	14.0	0.08
W.J-R Calculation†	102.8	17.4	103.5	16.3	−0.04
W.J-R Dictation†	96.5	14.1	95.9	12.6	0.07

Table 3 Odds ratios for neuropsychological deficit in at least one neuropsychological domain, by clinical risk factor

	% of Risk group with NP deficit*	Compared to siblings		Compared to seizure children without the risk factor	
		OR	95% CI*	OR	95% CI*
Any seizure	27.4	1.70	1.08 - 2.67	--	--
Use of any AED†	33.6	2.27	1.35 - 3.84	1.91‡	1.11 - 3.30
Valproic acid†	30.8	2.00†	0.89 - 4.48	1.68‡†	0.76 - 3.73
Oxcarbazepine†	27.5	1.71†	0.77 - 3.77	1.44‡†	0.64 - 3.23
Carbamazepine†	21.4	1.23†	0.47 - 3.21	1.03‡†	0.38 - 2.79
Multiple seizures by baseline interview†	30.4	1.96	1.46 - 3.31	1.57‡§	0.87 - 2.83
Symptomatic/cryptogenic syndrome	32.3	2.15	1.29 - 3.56	1.79†	1.03 - 3.12
Generalized idiopathic absence	31.6	2.00†	0.94 - 4.26	1.29‡¶	0.61 - 2.71
Generalized idiopathic tonic-clonic	17.1	0.93†	0.37 - 2.32	0.51‡¶	0.21 - 1.20
Generalized symptomatic/cryptogenic	28.6	1.80†	0.33 - 9.93	1.08‡¶	0.21 - 5.68
Localization-related idiopathic	17.0	0.92†	0.40 - 2.10	0.49‡¶	0.23 - 1.06
Localization-related cryptogenic	31.8	2.10	1.24 - 3.53	1.47‡¶	0.85 - 2.52
Localization-related symptomatic	37.5	2.70†	0.91 - 8.04	1.67‡¶	0.58 - 4.76
Epileptiform activity on initial EEG	29.7	1.90	1.15 - 3.12	1.41‡¶	0.80 - 2.49
Multiple risk factors#	40.0	3.00	1.12 - 8.35	2.89‡#	0.71 - 11.78



Epilepsia, 48(6):1067–1074, 2007
Blackwell Publishing, Inc.

The Association of MRI Findings and Neuropsychological Functioning after the First Recognized Seizure

*Anna W. Byars, *Ton J. deGrauw, †Cynthia S. Johnson, ‡Philip S. Fastenau, †Susan M. Perkins, §John C. Egelhoff, ¶Andrew Kalnin, ||David W. Dunn, and $Joan K. Austin

34/249 niños con crisis única y RNM tenían hallazgos anormales.

VARIABLES NEUROPSICOLÓGICAS ENTRE RNM NORMAL Y ANORMAL	P
Cociente Intelectual	= 0,011
Lenguaje	= 0,034
Velocidad de procesamiento	= 0,015
Habilidad ejecutiva construccional	= 0,006
Memoria verbal y aprendizaje	= 0,010

CONCLUSIONES

Entre 20 a 40% de las personas con crisis únicas pueden tener manifestaciones sicológicas y comportamentales que están presentes desde esa primera crisis o incluso antes de la misma.

Esas manifestaciones dependen de variables propias de la persona como por ejemplo su temperamento y etiología de la epilepsia; y de circunstancias externas como su entorno familiar.

El conocimiento de esta realidad y de sus variables específicas, permite que el médico intervenga precozmente y evite un mayor compromiso de su paciente.

Si bien existen indicios de que una fisiopatología común puede ser la causal de la crisis epiléptica como de los cambios psicológicos, su relación y dinamismo no se han podido aclarar suficientemente.

De la misma forma quedan abiertas las oportunidades para explorar: ¿cuáles son las herramientas terapéuticas más efectivas en estas circunstancias? ¿logrará el control de la epilepsia revertir los problemas comportamentales? ¿podrá un mejor control del comportamiento o de las alteraciones sicológicas, mejorar la epilepsia?

Do we have reliable neurophysiologic tool to measure and understand human cognition?

Alicia Bogacz (Uruguay)

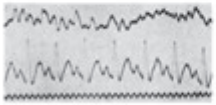
COGNICIÓN Y MÚSICA

¿Existen las herramientas adecuadas para su evaluación y comprensión?

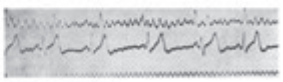
- El deseo de conocer los mecanismos que permiten el reconocimiento del mundo , y su posterior transformación, así como los mecanismos creativos han sido desde siempre objeto de la filosofía y de las neurociencias.
- Clásicamente se utilizó la correlación entre la lesión cerebral y su asociación con déficit funcionales en pacientes para analizar la representación funcional en el cerebro.
- La neurofisiología desde los primeros registros de EEG realizados por Hans Berger en 1929, psiquiatra que intenta tener una herramienta objetiva para entender los procesos psíquicos .

HANS BERGER (1925)

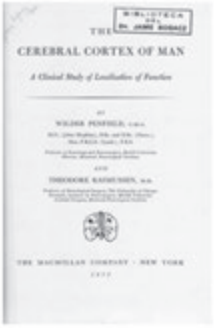
PRIMER EQUIPO DE REGISTRO



MUJER , 38 AÑOS

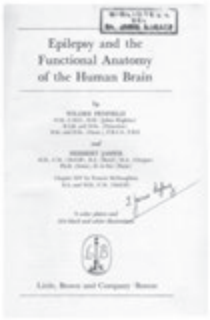


NIÑA , 15 AÑOS


CEREBRAL CORTEX OF MAN

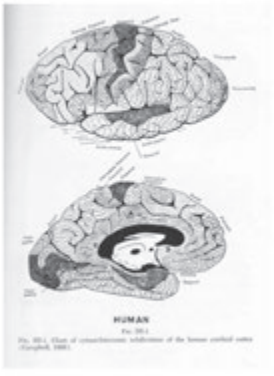
A Clinical Study of Localization of Function

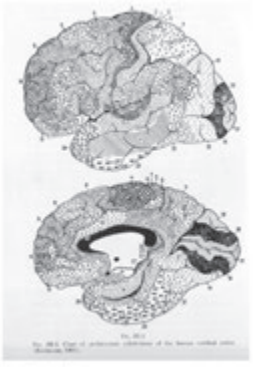
THE MACMILLAN COMPANY · NEW YORK

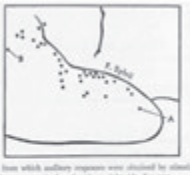

Epilepsy and the Functional Anatomy of the Human Brain

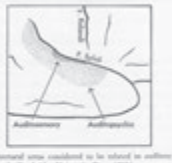
Little, Brown and Company · Boston

- Penfield y Rasmusen en "The cerebral Cortex of Man" (1950) y luego Penfield y Jasper en "Epilepsy and the Funcional Anatomy of the Human Brain" (1954) utilizaron la estimulación directa de la corteza humana estudiar la correlación anatómica con la función .


HUMAN



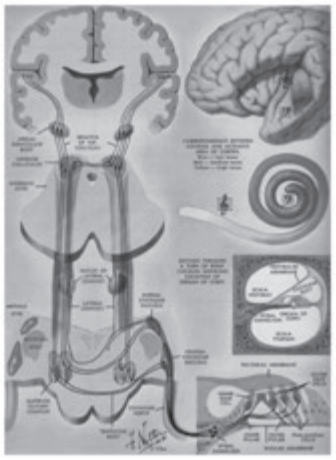




Observaron dos tipos de fenómenos auditivos:

- Simples como timbres, murmullos (humming) (booming), zumbidos (buzzing), chillidos (chirping)
- Alucinaciones psíquicas como voces o música.

VÍA AUDITIVA



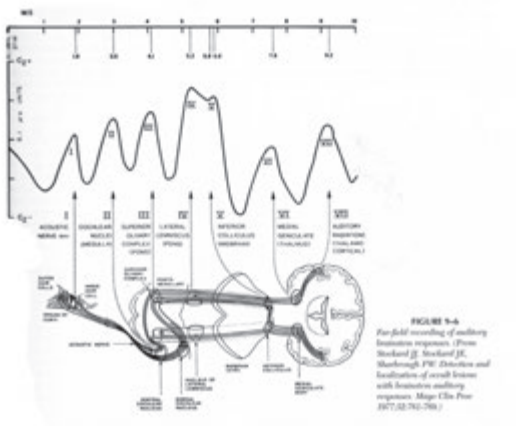


FIGURE 9-6
Far-field recording of auditory brainstem responses. (From Stockard JJ, Stockard JE, Sharbrough FW. Detection and localization of occult lesions with brainstem auditory responses. Mayo Clin Proc 1977;52:761-766.)

- La corteza auditiva primaria localizada en las áreas 41, 42 de Broca o gyrus de Heschl.
- Es muy difícil registrar su actividad con electrodos de superficie, dada su localización en la profundidad de la cisura Silviana.
- Chatrian *y col. (1960) fueron los primeros en registrar respuestas evocadas a clicks, con electrodos profundos.*
- Celesia y Puletti (1969) corroboraron estos resultados en el hombre y encontraron respuestas a la estimulación auditiva en el gyrus temporal transverso de Heschl, parte posterior del gyrus temporal superior y el borde superior de la cisura de Silvio

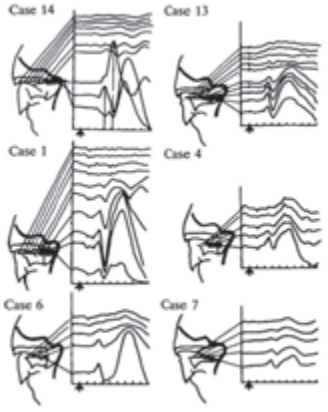
Brain (1991), 114, 139-153

LOCALIZATION OF THE PRIMARY AUDITORY AREA IN MAN

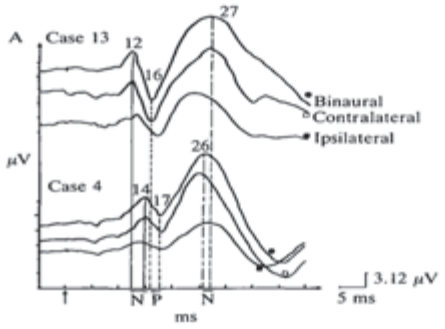
by C. LIEGEOIS-CHAUVEL, A. MUSOLINO and P. CHAUVEL
(From INSERM U 97 and Service de Neurochirurgie, Hopital Ste Anne, Paris, France)

SUMMARY
The localization of the primary auditory cortex in man was studied by direct recordings in 150 different sites in the superior transverse gyrus, especially in Heschl's gyrus and the planum temporale.
The distribution of the primary evoked responses (N13/P17/N26) was studied in 15 epileptic patients who were candidates for surgical treatment.
Precise topography of recording sites was determined stereotactically.
Our results provide evidence for considering only a restricted portion of Heschl's gyrus (its posteromedial part) as the primary auditory area.

- Click stimulation was employed, its brief duration permitting precise measurement of evoked response latency.
- Early auditory evoked potentials could be recorded only from a limited area, localized in the posterior part of Heschl's gyrus.
- Amplitudes of the evoked responses were higher when stimuli were delivered to the contralateral than to the ipsilateral ear. They were maximal when the stimulation was binaural.
- These data are in agreement with previous studies in both man (Celesia, 1976)
and animals (Rosenzweig, 1951) which suggested that each hemisphere receives input from both ears but that the contralateral ear is clearly better represented.
- By direct stimulation of Heschl's gyrus in man: in our patients as well as in the cases reported by Penfield and Perot (1963), it elicited simple auditory hallucinations most frequently referred to the contralateral side.



- Early AEP voltage distributions recorded from different sites of the right Heschl's gyrus electrode in 6 patients
- *The schematic position of the electrode exploring Heschl's gyrus is represented on the left.*
- Crossed areas show the responsive area. Each trace, on the right, corresponds to the monopolar recording of each lead of one electrode referenced to an extracephalic site.
- *Amplitude*(6.25 /»V/div) and time (5 ms/div) calibration at lower right.
- Arrows correspond to the auditory stimulation



Effect of monaural (ipsilateral and contralateral ear) and binaural stimulation on early EAPs in 2 cases

POTENCIALES COGNITIVOS - Specific event-related brain potentials - (ERPs)

- Nuevas técnicas en el análisis de las señales han beneficiado tanto al EEG como a la Magnetoencefalografía (MEG).
- Los ERPs se detectan por el análisis de las señales del EEG o MEG y estan asociados con diferentes tipos de desviaciones del estímulo.
- Dependiendo de el lugar de registro, su polaridad, latencia y las condiciones de estimulación pueden ser llamados: early right anterior negativity (ERAN), mismatch negativity (MMN) y P300.
- Diferentes estímulos, tiempo de análisis, modificación de distintos parámetros, permite el análisis de diferentes estructuras cognitivas.

- Los mecanismos de la audición son menos comprendidos que los de la visión.
- La música al igual que el lenguaje, son actividades esencialmente humanas y por lo tanto deben ser estudiados en humanos.
- Actualmente es posible realizar estudios que nos permitan dilucidar áreas cerebrales, circuitos, que llevan a cabo el reconocimiento sonoro, la altura, su ritmo, armonía, etc.
- Es importante recordar que la habilidad "musical" es testeada en protocolos experimentales, que solamente analizan un aspecto específico y limitado de la música.
Por ejemplo, la altura (pitch) se refiere a una percepción más que a una estructura de estímulo particular y percibimos una altura tanto este asociada a un tono puro o a un estímulo armónico, como un instrumento musical o voz

AUDITORY STIMULUS INTENSITY and P300

Anders M. Fjell et al., 2003

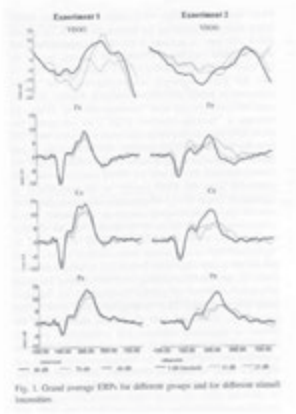
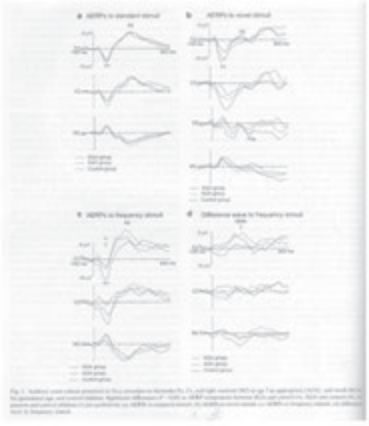


Fig. 1. Grand average ERPs for different groups and for different stimuli intensities

Auditory ERPs in preterm children at 5 years of age

Kaija Mikkola et al., 2007



Clinical Neurophysiology 120 (2009) 453–463

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Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Invited review

The mismatch negativity: A review of underlying mechanisms

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Wellcome Trust Centre for Neuroimaging, University College London, UK

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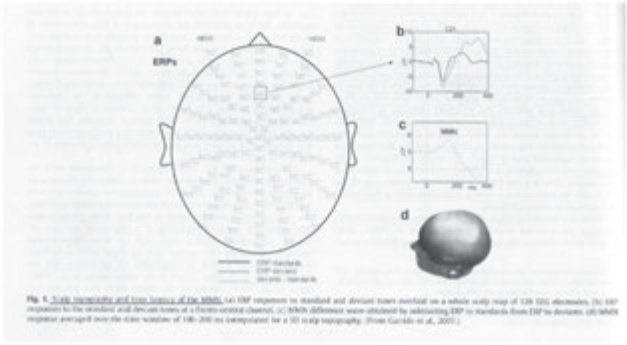
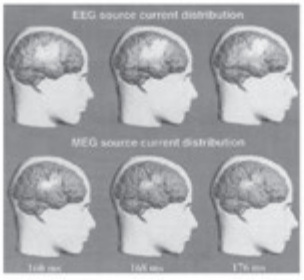
Mechanistic models
Cortical networks
Predictive coding

ABSTRACT

The mismatch negativity (MMN) is a brain response to violations of a rule, established by a sequence of sensory stimuli (typically in the auditory domain) (Näätänen R. Attention and brain function. Hillsdale, NJ: Lawrence Erlbaum; 1992). The MMN reflects the brain's ability to perform automatic comparisons between consecutive stimuli and provides an electrophysiological index of sensory learning and perceptual accuracy. Although the MMN has been studied extensively, the neurophysiological mechanisms underlying the MMN are not well understood. Several hypotheses have been put forward to explain the generation of the MMN; amongst these accounts, the "adaptation hypothesis" and the "model adjustment hypothesis" have received the most attention. This paper presents a review of studies that focus on neuronal mechanisms underlying the MMN generation, discusses the two major explanatory hypotheses, and proposes predictive coding as a general framework that attempts to unify both.



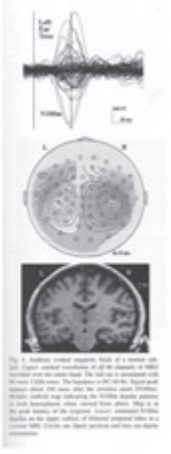


- **MMN generators estimated from EEG and MEG data**. The centre of gravity changes from temporalt o frontal areas over time. Frontal sources were detected with EEG, due to their radial orientation they might not be detected by MEG. These sources were determined with minimum norm estimates (MNE). (Adapted from Rinne et al.,2000)

AUDITORY EVOKED MAGNETIC FIELDS N100

Left ear stimulated

Nobukazu Nakasato et al., 1996



AUDITORY EVOKED MAGNETIC RESPONSES
P30 ,P50

Right ear stimulated

Toshiaki Onitsuka et al., 2003

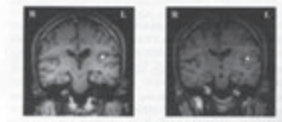


Fig. 2. The locations of the P30m and the P50m sources of one subject projected onto the appropriate coronal MRI sections. The circle signifies the P30m source in the left panel. The triangle signifies the P50m source in the right panel. The right panel is 5 mm anterior to the left one.

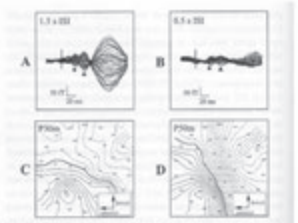


Fig. 1. Auditory evoked magnetic responses and the isomagnetic contour maps from one subject. (A) Waveforms in 1.5 s ISI condition. (B) Waveforms in 0.5 s ISI condition. In A and B, each waveform was obtained by the superimposition of all 37 channels. The circles indicate the P30m peaks, and the triangles signify the P50m peaks. Short vertical lines signify the onset of the stimulus. (C) The P30m isomagnetic contour map corresponded to the P30m peak in A. (D) The P50m isomagnetic contour maps corresponded to the P50m peak in A. In C and D, the solid lines represent the sources of magnetic fields while the dotted lines show the sinks of the magnetic fields (1 step = 2 fT). The polarities of the P30m and the P50m components are the same.

- Aunque la neurofisiología permite una mejor resolusión temporal, el PET y fRMN, complementan los estudios neurofisiológicos tienen una mejor resolución espacial, el co-registro de los ERPs con de MEG y RNM , permite una mayor definición topográfica.
- A pesar de que los métodos disponibles para el análisis de la música se han refinado considerablemente, persisten ciertas limitaciones en cuanto a la resolución de tiempo y espacio que deben ser tomadas en cuenta.
- Las técnicas de promediación necesarias para extraer los ERPs de los registros de superficie limitan la información contenida en la respuesta registrada.
- Otro aspecto crítico de la apreciación musical es el ánalisis de los estímulos que se perciben simultáneamente para formar acordes, estructuras armonicas y melodías.

The Promises of Change-Related Brain Potentials in Cognitive Neuroscience of Music

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ABSTRACT: Even when simultaneously performing a task unrelated to sounds, the human auditory cortex can precisely model the invariances of the acoustic environment. Data acquired in a mismatch negativity (MMN) paradigm have shown that temporally and spectrally complex sounds as well as their relations are automatically represented in the human auditory cortex. Furthermore, MMN data indicate that these neural sound representations are spatially distinct from phonetic and musical sounds within and between the cerebral hemispheres. Most MMN studies were conducted in pitch dimension, but temporal aspects of sound processing are also under increasing experimentation. To some extent, musical expertise is also reflected in sound representation accuracy as indexed by the MMN paradigm.

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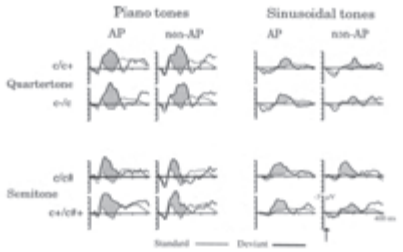

FIGURE 1. Event-related potential (ERP) recordings of absolute-pitch (AP) processors and non-absolute-pitch processors to piano and sinusoidal tones in conditions with different pitch changes, as indicated on the *left*. During the recordings, subjects concentrated on reading a book of their own choice. The *thin line* represents ERPs to standard stimuli; the *thick line*, ERPs to deviant stimuli. *Shadowing* indicates the presence of mismatch negativity (MMN) and the *arrow* the onset of the sound. Altogether, four pitch differences were employed between standard ($P = 0.9$) and deviant ($P = 0.1$) stimuli: 262/269 Hz (C/C+), 254–262 /Iz (C–/C), 262–277 Hz (C/C#), and 269–285 Hz (C+/C#+). These differences were equal to quarter tone and semitone intervals on the Western musical scale (262 Hz = C4). The combinations included all possibilities with regard to tone positions either belonging or not belonging to the scale (standard on/off the scale, deviant on/off the scale). The subjects's performance in the pitch-naming task was tested after the EEG recordings. Subjects were asked to name the pitch and octave of 50 tape-recorded synthesized piano tones (range: C2–E6). The AP subjects correctly named, on average, 82% and the non-AP subjects 9% of these test sounds.[37]

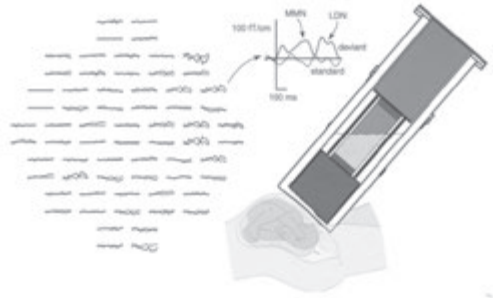

FIGURE 2. Magnetoencephalographic (MEG) recording of a healthy human fetus is performed by placing the instrument tightly against the mother's abdomen so that the surface of the instrument is 4–7 cm from the brain of the fetus (*right*). The 99-channel magnetometer of the BioMag Laboratory, Helsinki University Central Hospital, records data from 35 positions with one magnetometer and two gradiometers in each location. Responses from the gradiometer channels to standard (*black*) tones of 500 Hz and deviant (*gray line*) tones of 550 Hz are shown on the *left*. The *rightmost* channels have recorded the data above the brains of the fetus. One channel is enlarged, showing possible correlates of the fetal mismatch negativity (MMN) and the late discriminative negativity (LDN) responses.

Functional Imaging of Pitch Analysis

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ABSTRACT: This work addresses the brain basis for the analysis of pitch and pitch patterns required for normal musical perception. Recent functional imaging experiments are consistent with a hierarchical scheme for the analysis of pitch. Mechanisms in the ascending auditory pathway to the primary auditory cortex allow the representation of the spectral and temporal features of individual notes required for the perception of their pitch. Converging experiments where pitch strength is manipulated in different ways suggest that there may be a "pitch center" in the lateral part of Heschl's gyrus, adjacent to the primary auditory area. The suggestion is that there is a representation in this area that correlates with the perception of pitch rather than a simple mapping of physical stimulus characteristics. The analysis of patterns of pitch such as melodies, as opposed to the pitch of individual notes, involves much more distributed processing in the superior temporal lobes and frontal lobes. Involvement of the frontal lobe in pitch pattern analysis may in part reflect whether subjects analyze the pitch patterns in order to carry out an output task.

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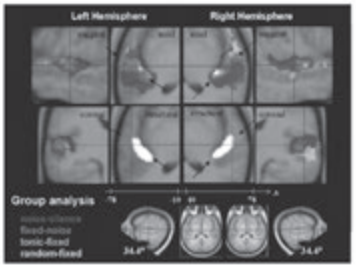

FIGURE 1. fMRI activation for contrasts between noise stimuli with different temporal regularity and pitch strength and with different pitch patterns. Group data for nine subjects. The contrasts are rendered onto the average structural image of the group. *Blue:* activation in response to noise bursts (vs silence). *Red:* differential activation in response to notes with fixed pitch (vs noise bursts). *Green:* differential activation in response to tonic melodies (vs fixed pitch). *Cyan:* differential activation in response to random melodies. The white area shows the mean position of Heschl's gyrus for the group. *Arrows* show the midline of Heschl's gyrus separately in each hemisphere. The position and orientation of the sections are illustrated in the bottom panels of the figure. The "axial" section is tilted by 0.6 radians (or 34.4 degrees) relative to the horizontal plane to show the entire surface of the temporal lobe in one plane. The other sections are sagittal and coronal with respect to the surface of the temporal lobe. The sagittal sections show front to the left for the left hemisphere and front to the right for the right hemisphere, that is, they are being viewed from outside the brain volume. Reproduced from Ref. 8 with permission.

Ann N Y Acad Sci. 2003 Nov;999:144-51.

Neuropsychological studies of musical timbre.

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Abstract

Musical timbre is a multidimensional property of sound that allows one to distinguish musical instruments. In this paper, studies that explore the cerebral substrate underlying the processing of musical timbre are discussed. Perceptual asymmetries measured in normal participants, deficits of musical timbre perception obtained in brain-damaged patients, as well as results obtained with various neuroimaging methods are reviewed. The findings obtained in all of these studies generally support the predominant involvement of right temporal lobe areas, and more specifically of its anterior part, in processing spectral and temporal envelopes of musical timbre. However, controversies still exist about the contribution of the left temporal lobe in timbre perception. The necessity of comparing data obtained with different perceptual paradigms (same-different discrimination and similarity judgment) and various types of stimuli (single tones and melodies) was emphasized by reporting lesion studies carried out in patients with unilateral temporal lobe lesions. The few neuroimaging studies published in this domain provided additional and complementary findings. Unlike lesion studies that allow us to infer the cerebral structures that are essential for timbre perception, the latter investigations implicate a more distributed neural network in timbre processing that extends along the superior temporal gyrus to include not only anterior but also posterior temporal regions and possibly frontal areas as well.

Neural Basis of Rhythmic Timing Networks in the Human Brain

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ABSTRACT: The study of rhythmicity provides insights into the understanding of temporal coding of music and temporal information processing in the human brain. Auditory rhythms rapidly entrain motor responses into stable steady synchronization states below and above conscious perception thresholds. Studying the neural dynamics of entrainment by measuring brain wave responses (MEG) we found nonlinear scaling of M100 amplitudes generated in primary auditory cortex relative to changes in the period of the rhythmic interval during subliminal and supraliminal tempo modulations. In recent brain imaging studies we have described the neural networks involved in motor synchronization to auditory rhythm. Activated regions include primary sensorimotor and cingulate areas, bilateral opercular premotor areas, bilateral SIA, ventral prefrontal cortex, and, subcortically, anterior insula, putamen, and thalamus. Within the cerebellum, vermal regions and anterior hemispheres ipsilateral to the movement became significantly activated. Tracking temporal modulations additionally activated predominantly right prefrontal, anterior cingulate, and intraparietal regions as well as posterior cerebellar hemispheres. Furthermore, strong evidence exists for the substantial benefits of rhythmic stimuli in rehabilitation training with motor disorders.

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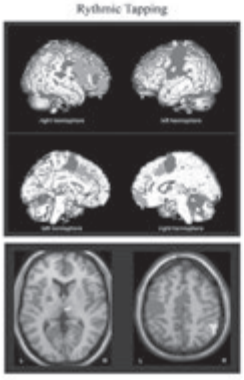

FIGURE 1. Neural maps for three conditions of rhythmic tracking: isochronous synchronization vs listening to rhythmic stimulus (*left*); finger tapping to a rhythmic stimulus whose periods are cosine wave modulated at 20% of the base interval (*grey*) vs isochronous tapping, tracking a rhythm stimulus with randomized period durations (*right*) vs isochronous tapping. Significant group differences are given at $P < 0.005$, $N = 9$. Activations (in MNI space) up to 10 mm below the surface of the brain are projected onto medial and lateral surfaces. Same activations are shown horizontally at the thalamus and basal ganglia level ($z = 6$) and at the level of the anterior cingulate, primary sensorimotor area, and inferior parietal lobe close to the intraparietal sulcus ($z = 48$).

Toward the Neural Basis of Processing Structure in Music

Comparative Results of Different Neurophysiological Investigation Methods

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ABSTRACT: In major-minor tonal music, chord functions are arranged according to certain regularities. The dominant-tonic progression, known as an authentic cadence, is often used as a marker of the end of a harmonic progression and has been considered a basic syntactic structure of major-minor tonal music by several music theorists and music psychologists. We review data from studies in which brain responses to an authentic cadence were compared to those elicited by music-syntactically inappropriate endings. In event-related electric brain potentials (recorded with EEG), the inappropriate endings elicit early right anterior negativity (ERAN), which is maximal around 200 ms after the presentation of an inappropriate chord. The ERAN is reminiscent of early anterior negativities elicited by syntactic incongruities during the perception of language. Magnetoencephalographic (MEG) data suggest that the ERAN is generated in the inferior frontolateral cortex, an area known to be crucially involved in the processing of (linguistic) syntax. Interestingly, the ERAN can be recorded in nonmusicians and in children, indicating that the ability to acquire (implicit) knowledge about musical regularities and to process musical information according to this knowledge is a general ability of the human brain. This ability is probably of great importance for the acquisition of language in infants and children.

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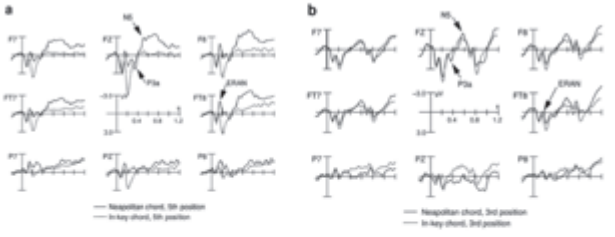

FIGURE 2. Effects of processing musical violations. **(a)** Grand-average ERPs of Neapolitan and tonic chords at the fifth position. Neapolitan chords elicited an early right anterior negativity (ERAN) and a late bilateral negativity (N5). It is suggested that the ERAN reflects the violation of a musical sound expectancy and the N5 integration processes. **(b)** Grand-average ERPs of chords at the third (0–600 ms) and fourth position (600–1200 ms). Chords at the third position were either Neapolitan chords or in-key chord functions. Both ERAN N5 elicited by the Neapolitan chords were considerably smaller than those elicited by Neapolitans at the fifth position, indicating a processing of Neapolitan chords that was dependent on regularities of musical structure. (Reprinted with permission from Koelsch *et al.*[4])

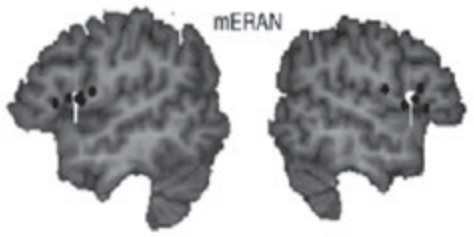

FIGURE 4. Grand-average dipole solution (white) of the mERAN (from six subjects), from left and right sagittal views. Dipole solutions for the mERAN-effect (difference signals: tonic subtracted from deviants) refer to two-dipole configurations (one dipole in each hemisphere). *Black circles* represent single subject solutions. In each hemisphere, a source was located in the frontal operculur cortex, areas known to be crucially involved in the processing of syntactic structure during language comprehension. (Adapted from Maess *et al.*[36])

Effects of Unexpected Chords and of Performer's Expression on Brain Responses and Electrodermal Activity

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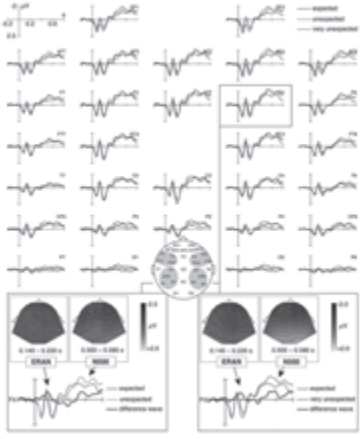
Published July 9, 2008

Abstract

Background: There is lack of neuroscientific studies investigating music processing with naturalistic stimuli, and brain responses to real music are, thus, largely unknown.

Methodology/Principal Findings: This study investigates event-related brain potentials (ERPs), skin conductance responses (SCRs) and heart rate (HR) elicited by unexpected chords of piano sonatas as they were originally arranged by composers, and as they were played by professional pianists. From the musical excerpts played by the pianists (with emotional expression), we also created versions without variations in tempo and loudness (without musical expression) to investigate effects of musical expression on ERPs and SCRs. Compared to expected chords, unexpected chords elicited an early right anterior negativity (ERAN, reflecting music-syntactic processing) and an N5 (reflecting processing of meaning information) in the ERPs, as well as clear changes in the SCRs (reflecting that unexpected chords also elicited emotional responses). The ERAN was not influenced by emotional expression, whereas N5 potentials elicited by chords in general (regardless of their chord function) differed between the expressive and the non-expressive condition.

Conclusions/Significance: These results show that the neural mechanisms of music-syntactic processing operate independently of the emotional qualities of a stimulus, justifying the use of stimuli without emotional expression to investigate the cognitive processing of musical structure. Moreover, the data indicate that musical expression affects the neural mechanisms underlying the processing of musical meaning. Our data are the first to reveal influences of musical performance on ERPs and SCRs, and to show physiological responses to unexpected chords in naturalistic music.



6. Grand-average of brain electric responses to expected, unexpected (original), and very unexpected chords (averaged across expressive and non-expressive conditions). Compared to expected chords, both unexpected and very unexpected chords elicited an ERAN and an N5. The insets in the two bottom panels show isopotential maps of the ERAN and the N5 effect (expected subtracted from [very] unexpected chords).

Prosodic and Melodic Processing in Adults and Children

Behavioral and Electrophysiologic Approaches

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ABSTRACT: The results of a series of experiments aimed at directly comparing the prosodic level of processing in language with the melodic level of processing in music are reported. The first series of experiments was conducted on adults, musicians and nonmusicians, and the second one on 7- to 9-year-old musician and nonmusician children. However, as this last study is still in progress, only preliminary results will be presented. The theoretic framework within which these experiments are taking place is described. The first problem concerns the specificity of the perceptive and cognitive computations necessary to perceive and understand language. We argue that comparing language with music can provide interesting insights into this complex issue. The second problem is linked to the relationship between different types of learning. Does early musical training influence the way in which musicians process some aspects of language as prosody? These two problems are considered and the results of the experiments are described.

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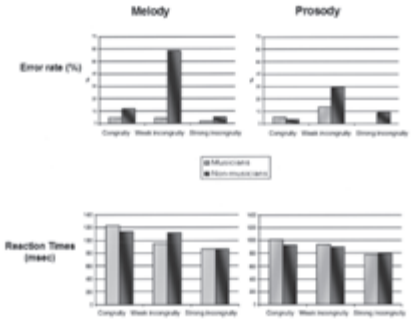

FIGURE 4. Percentage of error rates (*top panel*) and reaction times (RTs) in milliseconds (*bottom panel*) for congruous final notes or words and for weak and strong pitch violations in music and language are presented separately for musician and nonmusician adults. Clearly, the percentage of errors was highest for nonmusicians in response to weak violations in both music and language. Moreover, whereas for musicians the stronger the incongruity, the shorter the RTs, for nonmusicians no differences between congruous items and weak incongruities were found either in language or in music. Only RTs to strong incongruities were faster than those in the other two conditions.

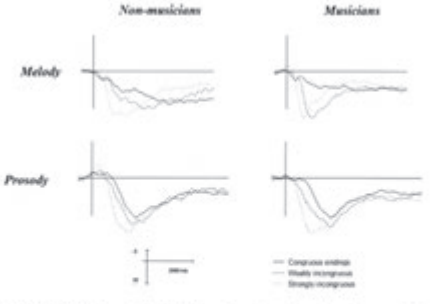

FIGURE 6. Variations in the brain electrical activity of musician and nonmusician adults, time-locked to final notes or words, elicited by congruous, weak or strong violations of pitch. Whereas the EEG was recorded from 28 electrodes, only one electrode is presented for simplicity. On this figure, as on the following ones, the amplitude (in microvolts) is plotted in the ordinate (negative up) and the time (in milliseconds) is in the abscissa.

Hum Brain Mapp. 2000 Jun;10(2):74-9.

Lateralized automatic auditory processing of phonetic versus musical information: a PET study.

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Abstract

Previous positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies show that during attentive listening, processing of phonetic information is associated with higher activity in the left auditory cortex than in the right auditory cortex while the opposite is true for musical information. The present PET study determined whether automatically activated neural mechanisms for phonetic and musical information are lateralized. To this end, subjects engaged in a visual word classification task were presented with phonetic sound sequences consisting of frequent (P = 0.8) and infrequent (P = 0.2) phonemes and with musical sound sequences consisting of frequent (P = 0.8) and infrequent (P = 0.2) chords. The phonemes and chords were matched in spectral complexity as well as in the magnitude of frequency difference between the frequent and infrequent sounds (/e/ vs. /o/; A major vs. A minor). In addition, control sequences, consisting of either frequent (/e/; A major) or infrequent sounds (/o/; A minor) were employed in separate blocks. When sound sequences consisted of intermixed frequent and infrequent sounds, automatic phonetic processing was lateralized to the left hemisphere and musical to the right hemisphere. This lateralization, however, did not occur in control blocks with one type of sound (frequent or infrequent). The data thus indicate that automatic activation of lateralized neuronal circuits requires sound comparison based on short-term sound representations

Comparing the Processing of Music and Language Meaning Using EEG and fMRI Provides Evidence for Similar and Distinct Neural Representations

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Abstract

Recent demonstrations that music is capable of conveying semantically meaningful information has raised several questions as to what the underlying mechanisms of establishing meaning in music are, and if the meaning of music is represented in comparable fashion to language meaning. This paper presents evidence showing that expressed affect is a primary pathway to music meaning and that meaning in music is represented in a very similar fashion to language meaning. In two experiments using EEG and fMRI, it was shown that single chords varying in harmonic roughness (consonance/dissonance) and thus perceived affect could prime the processing of subsequently presented affective target words, as indicated by an increased N400 and activation of the right middle temporal gyrus (MTG). Most importantly, however, when primed by affective words, single chords incongruous to the preceding affect also elicited an N400 and activated the right posterior STS, an area implicated in processing meaning of a variety of signals (e.g. prosody, voices, motion). This provides an important piece of evidence in support of music meaning being represented in a very similar but also distinct fashion to language meaning: Both elicit an N400, but activate different portions of the right temporal lobe.

Citation: Steinbeis N, Koelsch S (2008) Comparing the Processing of Music and Language Meaning Using EEG and fMRI Provides Evidence for Similar and Distinct Neural Representations. PLoS ONE 3(5): e2226. doi:10.1371/journal.pone.0002226

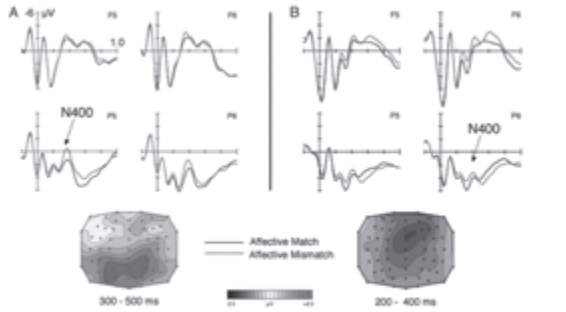

Figure 4. Reaction times on correct responses for Experiment 2. The RTs reveal a strong interaction between prime valence and target valence, whereby congruent targets are evaluated significantly faster than incongruent targets. This was the case for incongruent word targets in Experiment 2a (A) as well as incongruent chord targets in Experiment 2b (B).
doi:10.1371/journal.pone.0002226.g004

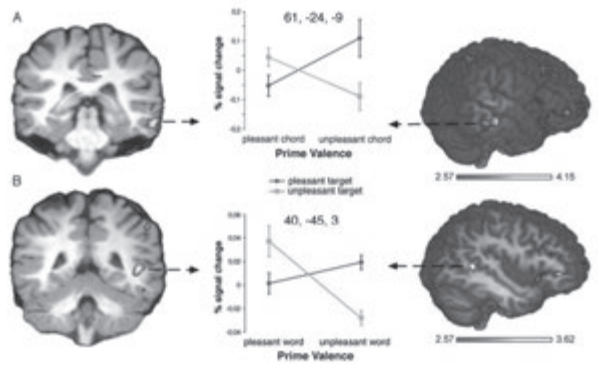

Figure 5. fMRI data in response to word targets (A) and chord targets (B) when contrasting incongruous against congruous trials. Incongruous word targets activated the right MTG (A), whereas incongruous chord targets activated the right posterior STS (B).

Musicians versus Nonmusicians

A Neurophysiological Approach

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ABSTRACT: **The ability to perceive sounds and correctly categorize them within a scale is the result of the interaction between inherited capabilities and acquired rules. If a subject listens to a melody, occasional and unexpected endings of the melody typically evoke characteristic auditory evoked responses in the latency range of 300–400 ms (P300f). Also, earlier stages of auditory information processing have been exhaustively investigated by means of mismatch negativity (MMN), a deflection that occurs in the auditory evoked response at a latency of about 200 ms, whenever a deviance is randomly inserted in a series of otherwise equal stimuli. Conceivably, perceptual deviations could also be detected against expectancies that are based on abstract rules; introspective experience suggests that such deviations may also elicit fast intuitive responses that typically initiate processes of analytical reasoning for confirmation. In music, the physical features of the stimulus are, in fact, always changing, because the melodic contour consists of a series of notes with different pitch characteristics. In such a condition, a typical mismatch negativity would not be evoked on the basis of physical deviance, but rather of criteria involving the musical contour of the stimulus. In this study, 20 healthy subjects (10 nonmusicians and 10 musicians) underwent auditory stimulation (tone, chord, chord sequence, Mozart and Bach melodies) and both electrical and magnetic recordings. Clear N1 was recorded for all paradigms, in all subjects; MMN and P300 were also recorded, and their amplitudes and latencies were significantly correlated with the musicality score and with the paradigm's difficulty.**

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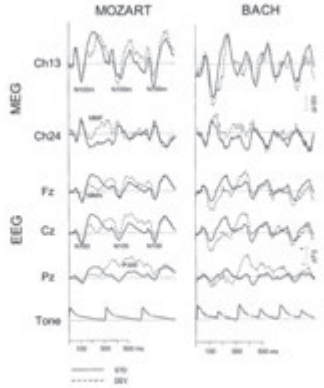

FIGURE 1. Magnetic (traces, 13 posterior and 24 anterior to the acoustical cortex) and electric (Fz, Cz, Pz) brain responses to acoustical stimulation with a simple (MOZART) and a complex (BACH) melody. Ton is rectified sound signal. Data from one subject. *Solid lines*, STD stimulus; *dashed lines*, DEV stimulus.

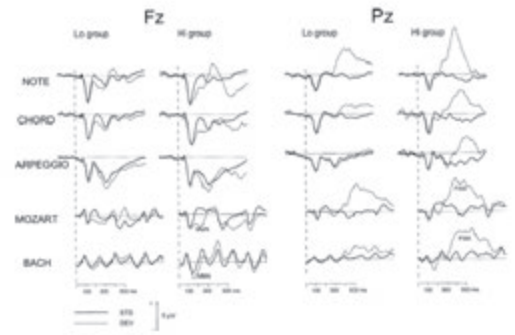

FIGURE 2. Grand averages of electric responses to stimulation with NOTE, CHORD, ARPEGGIO, MOZART, and BACH paradigms. (*Upper panel*) Electrode position Fz; (*lower panel*) Pz. Lo, group of subjects with a Bentley score of 31–36; Hi, group of subjects with a score of 42–48. *Solid lines*, STD stimulus; *dashed lines*, DEV stimulus.

Specialization of the Specialized: Electrophysiological Investigations in Professional Musicians

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[b]*Department of Neurology, Medizinische Hochschule, Hannover, Germany*

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Abstract: Several event-related brain potential (ERP) studies examining the processing of auditory stimuli by professional musicians compared with nonmusicians are reviewed. In the first study, musicians (string players) and nonmusicians attended to one of two streams of auditory stimuli characterized by a specific pitch. Musicians showed a prolonged ERP attention effect, the late portion of which was more frontally distributed than was that of the nonmusicians. In the second study, we investigated auditory spatial processing in conductors, pianists, and nonmusicians. Only the conductors showed behavioral selectivity of sound sources located in the peripheral auditory space. In addition, this group showed a negative/positive mismatch response for deviant stimuli occurring outside the focus of spatial attention. Finally, a group of drummers was compared to woodwind players and nonmusicians in a passive listening task. A real continuous drum sequence was manipulated so that some beats were anticipated by 80 ms. The drummers showed a mismatch response not only for the anticipated beats but also for the subsequent beats, suggesting a more complex representation of the temporal aspects stimulus sequences in this subject group. Together, these studies suggest qualitative differences of the neural correlates of auditory processing between musicians and nonmusicians. Moreover, these differences appear to be shaped by the specific training of a musician.

Ann. N.Y. Acad. Sci. 999: 124–130 (2003). © 2003 New York Academy of Sciences.
doi: 10.1196/annals.1284.015

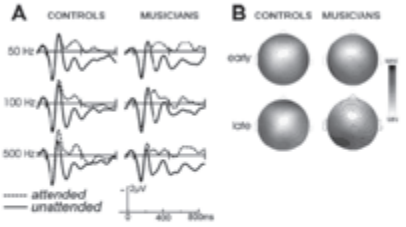

FIGURE 1. Group averages for the musicians and controls for the frontal midline site. From about 150 ms onwards, the ERPs to the attended tones are characterized by a more negative waveform in both groups. This effect is more short-lived in the control group, however. The spline-interpolated isovoltage maps show a similar distribution of the early attention effect (230–300 ms) in musicians and nonmusicians, whereas during the 500–750 ms interval a considerably more frontal distribution is observed in the musician group.

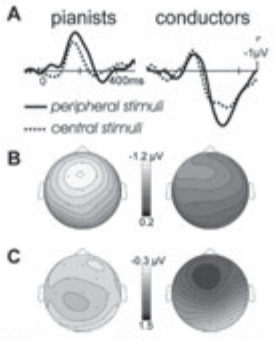

FIGURE 2. (A) Deviant minus standard difference waves for stimuli coming from the unattended directions (e.g., from the three speakers located to the right of the subject, when the centermost speaker was attended). In pianists, sizable mismatch negativity can be observed. The mismatch negativity (MMN) is somewhat smaller in conductors. However, it is followed by pronounced positivity in this group. (B) Spline-interpolated isovoltage maps illustrating the distribution of the mismatch negativity. A typical frontocentral maximum is observed. (C) Distribution of the positive peak following mismatch negativity. A distribution very similar to the MMN is observed.

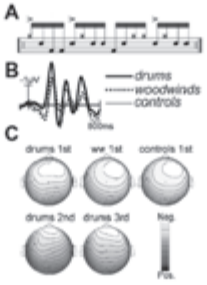

FIGURE 3. Study of the preattentive processing of temporally deviant beats in a real drum sequence. (A) Drum sequence (different notes represent the different drums of the drum set; x = hi-hat). The drum sequence was presented in loop mode. Occasionally, one of the beats was anticipated by 30 or 80 ms. (B) Deviant minus standard difference wave forms from the frontal midline electrode. In drummers, beats following the anticipated beat gave rise to a mismatch response as well. This effect was less prominent in the woodwind players and in the nonmusician controls. (C) Topographic maps show that the second and third mismatch peaks have considerably more frontal distribution than does the first mismatch response showing the typical frontocentral maximum.

Eyes Wide Shut: Amygdala Mediates Eyes-Closed Effect on Emotional Experience with Music

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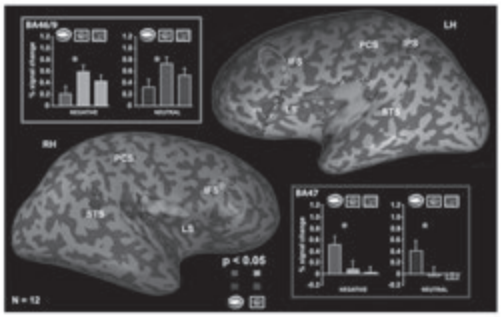
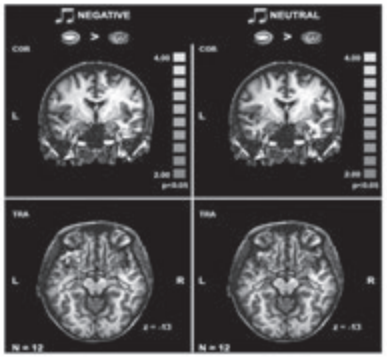
Aviv, Israel, 3 Tel Aviv University, Tel Aviv, Israel
Citation: Lerner Y, Papo D, Zhdanov A, Belozersky L, Hendler T (2009) Eyes Wide Shut: Amygdala Mediates Eyes-Closed Effect on Emotional Experience with
Music. PLoS ONE 4(7): e6230. doi:10.1371/journal.pone.0006230 Published July 15, 2009

Abstract

The perceived emotional value of stimuli and, as a consequence the subjective emotional experience with them, can be affected by context-dependent styles of processing. Therefore, the investigation of the neural correlates of emotional experience requires accounting for such a variable, a matter of an experimental challenge. Closing the eyes affects the style of attending to auditory stimuli by modifying the perceptual relationship with the environment without changing the stimulus itself. In the current study, we used fMRI to characterize the neural mediators of such modification on the experience of emotionality in music. We assumed that closed eyes position will reveal interplay between different levels of neural processing of emotions. More specifically, we focused on the amygdala as a central node of the limbic system and on its co-activation with the Locus Ceruleus (LC) and Ventral Prefrontal Cortex (VPFC); regions involved in processing of, respectively, 'low', visceral-, and 'high', cognitive-related, values of emotional stimuli. Fifteen healthy subjects listened to negative and neutral music excerpts with eyes closed or open. As expected, behavioral results showed that closing the eyes while listening to emotional music resulted in enhanced rating of emotionality, specifically of negative music. In correspondence, fMRI results showed greater activation in the amygdala when subjects listened to the emotional music with eyes closed relative to eyes open. More so, by using voxel-based correlation and a dynamic causal model analyses we demonstrated that increased amygdala activation to negative music with eyes closed led to increased activations in the LC and VPFC. This finding supports a system-based model of perceived emotionality in which the amygdala has a central role in mediating the effect of context-based processing style by recruiting neural operations involved in both visceral (i.e. 'low') and cognitive (i.e. 'high') related processes of emotions.



Differences in brain activation with eyes closed, eyes open and activation profiles of ROI. Functional averaged activation maps (N = 12, p.0.05, random effect) show the cortical activity evoked by musical clips (negative and neutral) presented with eyes closed (blue) and open
(green). The maps are superimposed on the left (LH) and right (RH) unfolded hemispheres shown in the lateral view. Quantitative analysis of the activation levels is shown for open (green patches on the maps) and closed (blue patches on the maps) eyes. While the BA 47 ('blue-framed' bars, blue circle on the map) exhibited highly preferential activation for eyes closed, the BA 46/9 ('green-framed' bars, green circle on the map) demonstrated highly preferential activation for eyes open. STS – superior temporal sulcus, IPS – intraparietal sulcus, PCS – post-central sulcus, LS –lateral sulcus, IFS – inferior frontal sulcus. Error bars, SEM. *, p.0.05



The effect of eyes closed on the amygdala. Average activation patterns (N = 12, p.0.05, random effect GLM analysis) revealed by the contrast 'eyes closed . eyes open' and superimposed on the coronal and transversal views. Significant activation was found in the amygdala/anterior hippocampus complex (orange arrows) for the negative clips (left panel) but not for the neutral ones (right panel). The color scale indicates significance level. L – left hemisphere, R – right hemisphere, COR – coronal, TRA – transversal

Exploring the Influence of Cultural Familiarity and Expertise on Neurological Responses to Music

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Ann. N.Y. Acad. Sci. 999: 113–117 (2003). © 2003 New York Academy of Sciences.
doi: 10.1196/annals.1284.013

ABSTRACT: Contemporary music education in many countries has begun to incorporate not only the dominant music of the culture, but also a variety of music from around the world. Although the desirability of such a broadened curriculum is virtually unquestioned, the specific function of these musical encounters and their potential role in children's cognitive development remain unclear. We do not know if studying a variety of world music traditions involves the acquisition of new skills or an extension and refinement of traditional skills long addressed by music teachers. Is a student's familiarity with a variety of musical traditions a manifestation of a single overarching "musicianship" or is knowledge of these various musical styles more similar to a collection of discrete skills much like learning a second language? Research on the comprehension of spoken language has disclosed a neurologically distinct response among subjects listening to their native language rather than an unfamiliar language. In a recent study comparing Western subjects' responses to music of their native culture and music of an unfamiliar culture, we found that subjects' activation did not differ on the basis of the cultural familiarity of the music, but on the basis of musical expertise. We discuss possible interpretations of these findings in relation to the concept of musical universals, cross-cultural stimulus characteristics, cross-cultural judgment tasks, and the influence of musical expertise. We conclude with suggestions for future research.

Transcultural studies of music brain processing are still limited. The available data suggest that the musical quality of a sound object is recognized by the human brain whether or not it belongs to the subject's native culture. Between-culture differences in linguistic rhythm seem to be reflected by differences in musical rhythm.

Musicogenic Seizures

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Ann. N.Y. Acad. Sci. 999: 95–102 (2003). © 2003 New York Academy of Sciences.
doi: 10.1196/annals.1284.008

ABSTRACT: **Eighty-seven reports of patients with seizures induced by listening and/or playing music and one personal observation are reviewed. Music-induced (or musicogenic) seizures are currently classified among the reflex seizures precipitated by complex stimuli. According to the available information, they are defined as focal seizures due to a discharge involving lateral and mesial temporal and orbitofrontal areas. The specific musical component responsible for seizure precipitation is still undetermined. An important role is attributed to the emotional aspect of music. The existence of this rare disorder should be borne in mind by neurologists, who should also be aware of the existing musical test batteries that may help in understanding better the nature of triggering mechanisms responsible for this unique pathological condition. The implementations of the results of ongoing investigations on brain processing of musical information will advance our understanding of the mechanisms responsible for the transition from interictal to ictal phases of epilepsy.**

Studies of the different forms of epilepsy have improved our understanding of the brain activities involved in musical perception and the mechanisms underlying seizure precipitation in terms of the analysis of musicogenic seizures and the musical defects following cerebral resections performed to treat intractable epilepsy

Dynamic Emotional and Neural Responses to Music Depend on Performance Expression and Listener Experience

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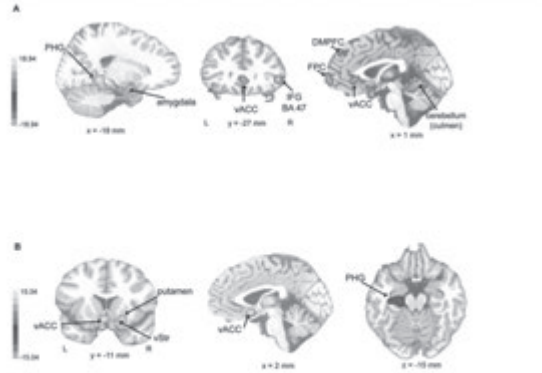
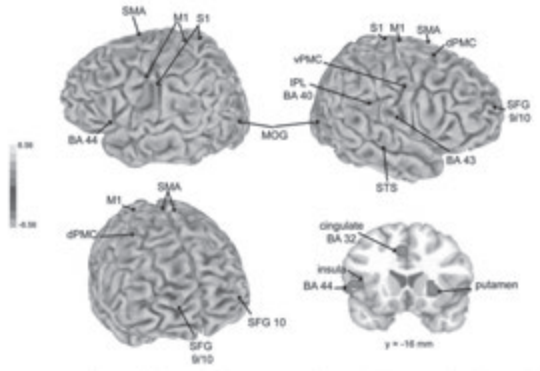
Published December 16, 2010

Abstract

Apart from its natural relevance to cognition, music provides a window into the intimate relationships between production, perception, experience, and emotion. Here, emotional responses and neural activity were observed as they evolved together with stimulus parameters over several minutes. Participants listened to a skilled music performance that included the natural fluctuations in timing and sound intensity that musicians use to evoke emotional responses. A mechanical performance of the same piece served as a control. Before and after fMRI scanning, participants reported real-time emotional responses on a 2-dimensional rating scale (arousal and valence) as they listened to each performance. During fMRI scanning, participants listened without reporting emotional responses. Limbic and paralimbic brain areas responded to the expressive dynamics of human music performance, and both emotion and reward related activations during music listening were dependent upon musical training. Moreover, dynamic changes in timing predicted ratings of emotional arousal, as well as real-time changes in neural activity. BOLD signal changes correlated with expressive timing fluctuations in cortical and subcortical motor areas consistent with pulse perception, and in a network consistent with the human mirror neuron system. These findings show that expressive music performance evokes emotion and reward related neural activations, and that music's affective impact on the brains of listeners is altered by musical training. Our observations are consistent with the idea that music performance evokes an emotional response through a form of empathy that is based, at least in part, on the perception of movement and on violations of pulse-based temporal expectancies



fMRI ANOVA results. Brain activations (F-maps) showing a significant main effect of a) performance type (F (1,24) . 7.19, corrected p ,.02), SCG = subcallosal gyrus, PHG = parahippocampal gyrus, vACC = ventral anterior cingulate, FPC = frontopolor cortex, DMPFC = dorsal medial prefrontal cortex; and b) main effect of musical experience, BG = basal ganglia, vStri = ventral striatum.
doi:10.1371/journal.pone.0013812.g004



Brain activations as a function of the tempo of the expressive performance. SFG = superior frontal gyrus, dPMC = dorsal PMC,SMA = supplementary motor area, S1 = primary somatosensory cortex, M1 = primary motor cortex, vPMC = ventral PMC, STS = superior sulcus. doi:10.1371/journal.pone.0013812.g006

Exploring the electrophysiological correlates of the default-mode network with intracerebral EEG

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1 Institut National de la Santé et de la Recherche Médicale, U821, Brain Dynamics and Cognition, Lyon, France
2 Université Claude Bernard, Lyon 1, Lyon, France
3 Neurology Department, Grenoble Hospital, Grenoble, France

While functional imaging studies allow for a precise spatial characterization of resting state networks, their neural correlates and thereby their fine-scale temporal dynamics remain elusive. A full understanding of the mechanisms at play requires input from electrophysiological studies. Here, we discuss human and non-human primate electrophysiological data that explore the neural correlates of the default-mode network. Beyond the promising findings obtained with non-invasive approaches, emerging evidence suggests that invasive recordings in humans will be crucial in order to elucidate the neural correlates of the brain's default-mode function. In particular, we contend that stereotactic-electroencephalography, which consists of implanting multiple depth electrodes for pre-surgical evaluation in drug-resistant epilepsy, is particularly suited for this endeavor. We support this view by providing rare data from depth recordings in human posterior cingulate cortex and medial prefrontal cortex that show transient neural deactivation during task-engagement.

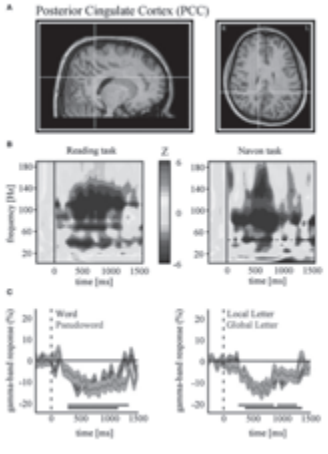


Figure 2 | Task-related gamma-band power suppressions in posterior cingulate cortex (PCC). (A) Anatomical location of the SEEG recording site in PCC of subject 1 (Talairach coordinates: *x = 10, y = −38, z = 35*). ***(B) Timefrequency*** representations of PCC activity for the reading (left panel) and Navon (right panel) tasks. Values represent task-related power modulations across time and frequency, compared with average baseline activity during fixation (Wilcoxon test). In both tasks strong decreases in PCC gamma power were found (indicated by negative *Z values*). ***(C) Time profile of percent power*** decreases (below baseline levels) at this electrode site for the conditions of each task (Left: Reading, Right: Navon). All conditions show significant gamma suppression in this region of DMN. The red/blue horizontal lines indicate statistical significance ($p < 0.05$) *based on a Wilcoxon signed rank test and* confidence intervals represent ± s.e.m.

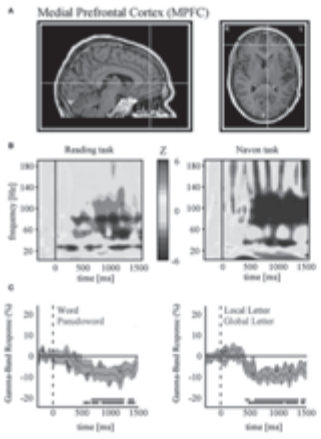


Figure 3 | Task-related gamma-band power suppressions in Medial Prefrontal Cortex (MPFC). (A) Anatomical location of the SEEG recording site in MPFC of subject 2 (Talairach coordinates: $x = -6$, $y = -46$, $z = -3$).

(B) Time-frequency representations of MPFC activity for the reading (left panel) and Navon (right panel) tasks. Strong decreases in MPFC gamma power were found in both tasks.

(C) Time profile of percent power decreases (below baseline levels) at this electrode site for the conditions of each task (Left: Reading, Right: Navon). As for PCC (**Figure 2**), **gamma activity in MPFC is** significantly suppressed for all conditions. Display conventions and methods used are identical to those of **Figure 2.**

CONCLUSIONES

- La mejor comprensión de la forma en que la música es procesada en el Sistema Nervioso Central ha dado un conocimiento nuevo sobre los mecanismos neuronales involucrados en las funciones cerebrales superiores.
- La música puede iluminar sobre distintos aspectos de las funciones cognitivas humanas complejas y su correlato neuronal.
- Los estudios en músicos y en no músicos nos pueden valiosainformación sobre la neuroplasticidad en el humano.
- De todas maneras estamos lejos de comprender los procesos creativos, emocionales y culturales del universal que llamamos MUSICA

Cognitive changes in MTLE

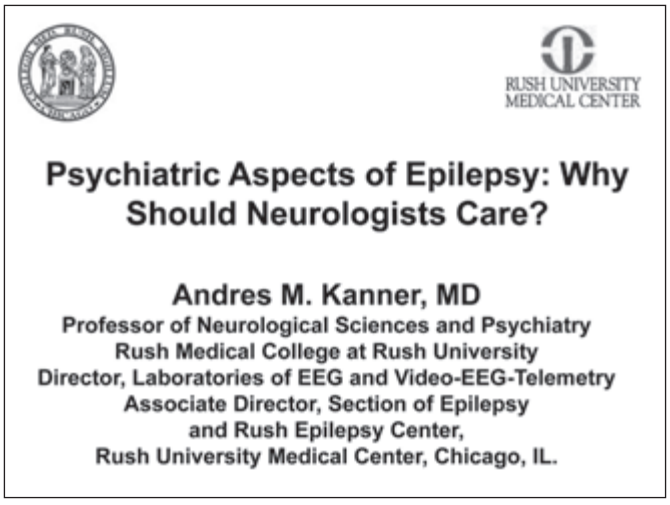
Carlos Guerreiro (Brazil)

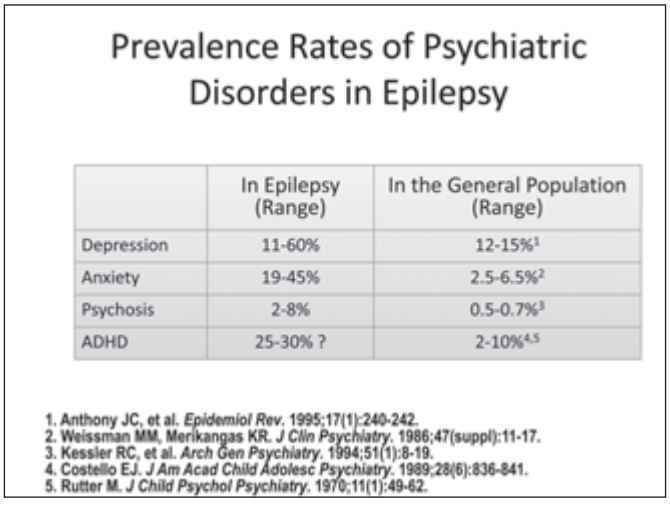
Programa – 24.02.2011

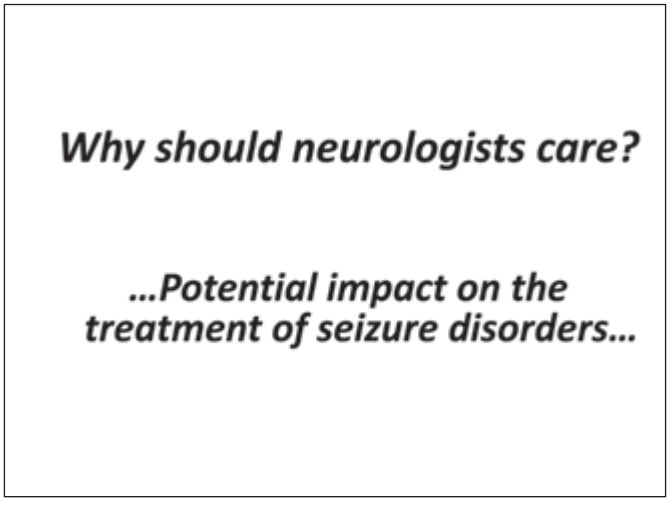
09:00 – 10:00	Psychiatric aspects of epilepsy: why neurologists should be concerned with that? Andres Kanner (USA)
10:00 – 11:00	Cognitive deficits in frontal lobe epilepsy - Silvia Kochen (Argentina)
11:00 – 11:30	Coffee break
11:30 – 12:30	Psychiatric disorders and epilepsy: Are there common pathogenic substrates? Andres Kanner (USA)
12:30 – 14:00	Lunch
14:00 – 15:00	Fast Oscillations, GABA Synchronization and Epileptiform Discharges - Massimo Avoli (Canada, Italy)
15:00 – 16:00	Cognitive aspects of benign focal epilepsies of childhood - Roberto Caraballo (Argentina)
16:00 – 16:30	Coffee break
16:30 – 17:30	Neural circuits of photosensitivity - Patricia Braga (Uruguay)
17:30 – 18:30	Dedicated to team work
19:00 – 21:00	Dinner

Psychiatric aspects of epilepsy: why neurologists should be concerned with that?

Andres Kanner (USA)







Lifetime Prevalence of Mood and Anxiety Disorders

Tellez-Zenteno, JF et al., Epilepsia, 2007; 48:2336-2344

Psychiatric Disorder	Controls (%)	Epilepsy (%)
Major Depressive Disorder	10.7 (10.2–11.2)	17.4 (10.0–24.9)
Anxiety Disorder	11.2 (10.8–11.7)	22.8 (14.8–30.9)
Mood/Anxiety Disorders	19.6 (19.0–20.2)	34.2 (25.0–43.3)
Suicidal Ideation	13.3 (12.8–13.8)	25.0 (17.4–32.5)
Any Psychiatric Disorder	20.7 (19.5–20.7)	35.5 (25.9–44.0)

Psychiatric Predictor of Pharmacologic Treatment with AEDs

- N=780
- New-onset epilepsy
- Seizure freedom at last outcome (median, 79 months [range: 24-240])
  - Psychiatric disorder at the time of diagnosis of epilepsy: OR 2.2 (*P*<.0002) against reaching seizure freedom
  - Depressive disorders accounted for the variance

Hitiris et al. Epilepsy Research. 2007.

Neurology®

Neuropsychiatric symptomatology predicts seizure recurrence in newly treated patients

S. Petrovski, BIS, BS, C.E.I. Szoeke, PhD, N.C. Jones, PhD, M.R. Salzberg, MD,L.J. Sheffield, MD, R.M. Huggins, PhD, T.J. O'Brien, MD

Objectives: To test the hypothesis that neuropsychiatric symptomatology is predictive of the successof seizure control in patients newly treated with antiepileptic drugs (AEDs).

Methods: One hundred seventy newly treated patients with epilepsy completed the A-B NeuropsychologicalAssessment Scale (ABNAS) before commencing AED therapy and were prospectively followed up for 12 months. Patients were classified as nonresponsive if they had at least 1seizure not explained by medication noncompliance or other significant provoking factors.

Results: Of the 138 patients in whom a drug response phenotype at 12 months was able to be determined, nonresponsive patients (n 45) had a higher pretreatment ABNAS score than patients whose seizures were controlled (n 93) (*p* 0.007).

Conclusions: The ABNAS provides prognostic information regarding successful seizure control in patients newly treated with AEDs.

***Neurology*® 2010;75:1015–1021**

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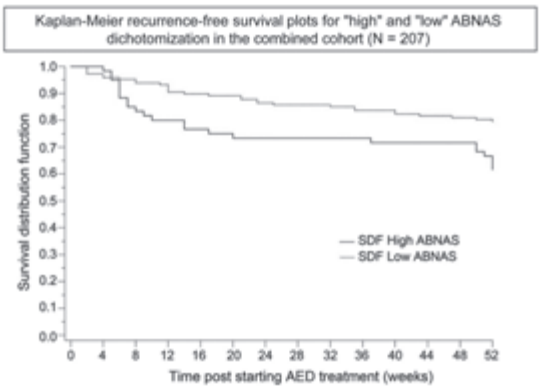
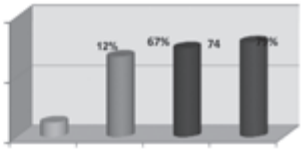


Petrovski, S. et al. Neurology 2010;75:1015-1021

Seizure Outcome After Anterior Temporal Lobectomy: Effect of LT History of Depression

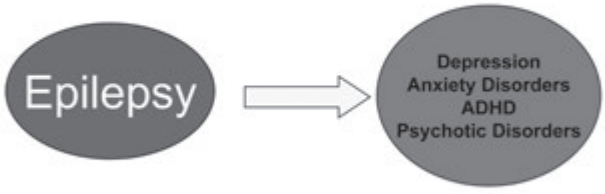
- 100 consecutive patients with anterior temporal lobectomy.
- Presurgical evaluation for lifetime psychiatric history.
- Outcome: seizure frequency at 2 years post surgery
- Mean post-op f/u: 8.3±3.1 years.



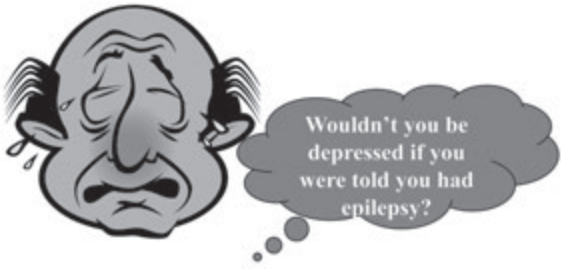
Relationship between no mood disorder history and outcome:
Class IA: OR =19.4 (95% CI=7.0-64.7)
Class IA + IB: OR=7.2 (95% CI=3.0-19.0)
Class IA, IB, IC: OR=5.1 (95% CI=1.5-2.5)

Kanner et al, Neurology 2009

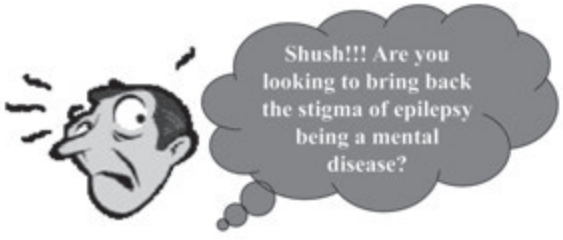
Long Held Assumptions…



A Reactive Process?



Epilepsy is not a psychiatric disorder!



I don't have time for that…

Psychiatric disorders are not covered by his insurance…

We have got news for you…

Bidirectional Relationship Between Epilepsy and Depression: Epidemiologic Evidence

Authors	Type of Study	Psychiatric History Preceding the Onset of Epilepsy/Controls
Forsgren and Nystrom, 1990	Population-based	7 times the history of depression 17 times in case of TLE
Hersdorffer et al, 2000	Population-based (Onset of epilepsy >age 55)	4 times the history of depression
Hersdorffer et al, 2006	Population-based (Iceland all ages)	5 times the history of suicidality Twice the history of major depression

Bidirectional Relationship Between Epilepsy and ADHD

Authors	Type of Study	Psychiatric History Preceding the Onset of Epilepsy/Controls
Hersdorffer et al, 2004	Population-based (All children between 3 and 16 years old)	3.7 times the history of ADD, Inattentive type

Psychiatric comorbidity in children with new onset epilepsy

Jones et al., Dev Med Child Neurol, 2007

- Children aged 8 to 18 years with recent onset epilepsy (<1 yr) of idiopathic etiology (*n*=53)
- Healthy comparison group (*n*=50)
- Structured psychiatric diagnostic interview to characterize the spectrum of lifetime-to-date history of comorbid psychiatric disorder

Psychiatric comorbidity in children with new onset epilepsy

Jones et al., Dev Med Child Neurol, 2007

- Children with epilepsy exhibited significantly higher rates of:
  - Depressive disorders (22.6 vs. 4%, p=0.01),
  - Anxiety disorders (35.8 vs 22%, p<0.05),
  - Attention-deficit-hyperactivity disorder (26.4 vs 10%, p=0.01)
- A subset of children with epilepsy (45%) exhibited DSM-IV Axis I disorders before the first recognized seizure, suggesting the potential influence of antecedent neurobiological factors that remain to be identified

The Incidence of First Provoked and Unprovoked Seizure in Pediatric Patients with and without Psychiatric Diagnoses

McAfee et al., Epilepsia, 48:6:1075-1082, 2007

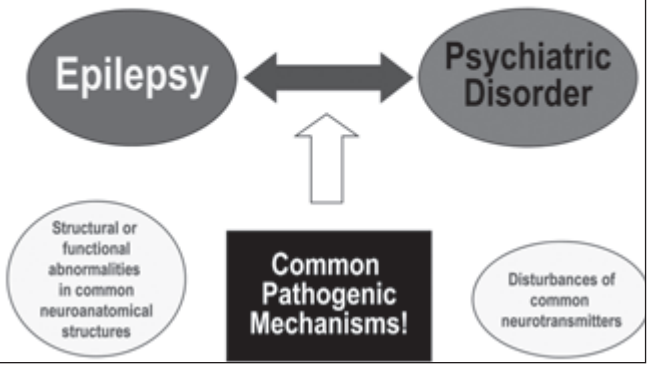
- **Retrospective cohort study of 133,440 pediatric patients (6 and 17 yrs), and without history of seizure or prior use of anticonvulsant medications, with follow-up during 2003**
- **The main outcome measure was new-onset non-febrile seizure**
- **The incidence rate of seizure among patients without psychiatric diagnoses was 149 per 100,000 patient-years (95% CI 122–180)**
- **The incidence rate of seizure among patients with psychiatric diagnoses other than ADHD was 513 per 100,000 p-y (95% CI 273–878)**

Not A New Concept: Hippocrates' Writings

"…melancholics ordinarily become epileptics, and epileptics melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy."

Lewis, 1934.

These data possibly result from a bidirectional relation between depression and epilepsy



Postictal Psychiatric Symptoms

Prevalence of postictal psychiatric disorders
Kanner et al., Neurology 2004.

- N = 100
- Sex: male, n = 38
- female, n = 62
- Age: 34.7±10.2 years
- Duration Sz. Dis. 21.5±11.3 years
- Dx: Partial seizure disorder, n =100

Results: Number of Patients with Postictal Symptoms by Category:

- N = 100
- Depression, n = 43
  - **Postictal suicidal ideation, n = 13**
  - *Active and passive suicidal ideattion, n = 5*
  - *Passive suicidal ideation only, n = 8*
- Anxiety, n = 45
- Obsessive-Compulsive, n = 10
- Psychosis, n = 7
- Neurovegetative, n = 62
- Cognitive, n = 82
- Cognitive without psychiatric, n = 14
- No Symptoms, n = 12

Results: Number of Patients with Postictal Symptoms by Category

- n = 100
- Depression, n = 43
  - *Postictal suicidal ideation, n = 13*
- Anxiety, n = 45
- Psychosis, n = 7
- Neurovegetative, n = 62
- Cognitive, n = 82
- Cognitive without psychiatric, n = 14
- No symptoms, n = 12

Depressive and anxiety disorders…

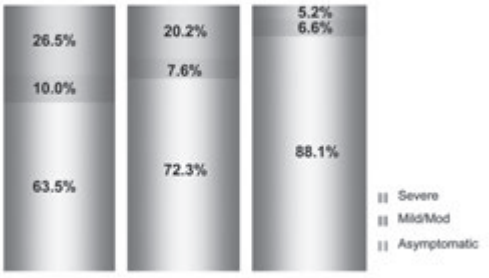
Lifetime Prevalence of Mood and Anxiety Disorders

Tellez-Zenteno, JF et al., Epilepsia, 2007; 48:2336-2344

Psychiatric Disorder	Controls (%)	Epilepsy (%)
Major Depressive Disorder	10.7 (10.2–11.2)	17.4 (10.0–24.9)
Anxiety Disorder	11.2 (10.8–11.7)	22.8 (14.8–30.9)
Mood/Anxiety Disorders	19.6 (19.0–20.2)	34.2 (25.0–43.3)
Suicidal Ideation	13.3 (12.8–13.8)	25.0 (17.4–32.5)
Any Psychiatric Disorder	20.7 (19.5–20.7)	35.5 (25.9–44.0)

Symptoms of Depression in Community-Based Patients

Identified with the CES-D

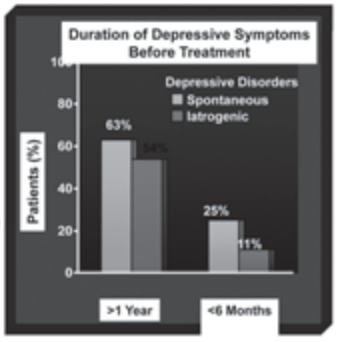


p<0.001

Ettinger, A. et. al. Neurology 2004;63:1008-1014

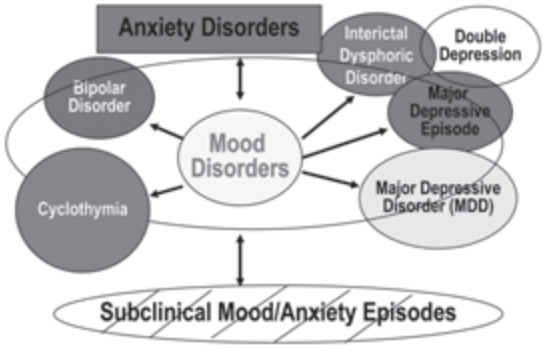
Depression in epilepsy continues to be under-recognized and undertreated

- Delay of therapy for depression[1]
  - Not related to severity of depressive disorder
- Potential reasons[2]
  - Patients minimize psychiatric symptoms
  - Symptomatology differs between nonepileptic and epileptic patients
  - Fail to inquire about psychiatric symptoms
  - Considered part of normal adaptation process of an epilepsy diagnosis
  - Risk of antidepressant therapy to lower seizure threshold

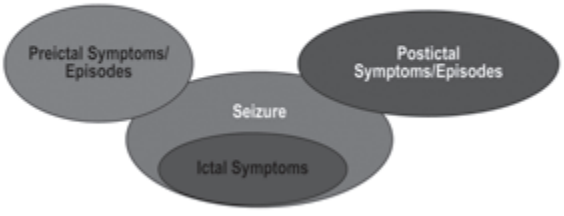


[1]Kanner AM, et al. Epilepsy Behav. 2000;1:100-105.
[2]Kanner AM, et al. Epilepsy Behav. 2000;1:37-51.

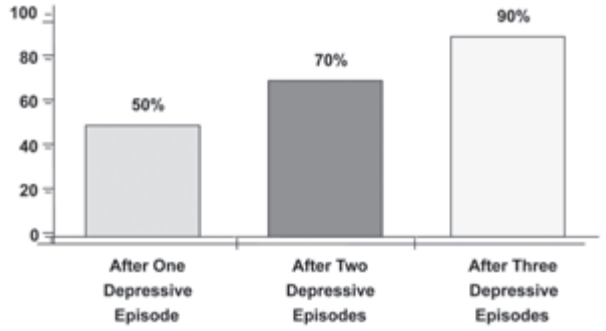
The "Pleomorphic" Expressions of Depression in Epilepsy



Depression in Epilepsy: Peri-Ictal Manifestations



Relapse and Recurrence Rates



Kupfer. Depression. 1994.
Janicak, et al. Principles and Practice of Psychopharmacotherapy. 1993.

Postictal Symptoms of Depression

Postictal Symptom	Frequency (N=100)	Duration (Range, Hours)
Poor frustration	36	24 (0.5-108)
Anhedonia	33	24 (0.1-148)
Hopelessness	25	24 (1.0-108)
Helplessness	31	24 (1.0-108)
Crying bouts	26	6 (0.1-108)
Suicidal ideation	13	24 (1.0-240)
Irritability	30	24 (0.5-108)
Guilt	23	24 (0.1-240)
Self deprecation	27	24 (1.0-120)

Any postictal symptom of depression, n=43 patients
Median number of symptoms: 5 (range: 2-9)

Kanner AM, et al. Neurology. 2004;62(5):708-713.

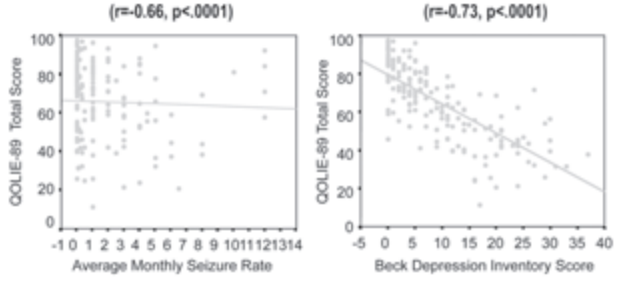
Postictal Symptoms of Anxiety

Symptoms of anxiety, total	n = 45	Median duration (range in hours)
Constant worrying	33	24 (0.5 – 108)
Panicky feelings	10	6 (0.1 – 148)
Agoraphobic symptoms	29	24 (0.5 – 296)
Due to fear of seizure recurrence	20	-
Compulsions	10	15 (0.1 – 72)
Self consciousness	26	6 (0.05 – 108)

Kanner et al., Neurology 2004

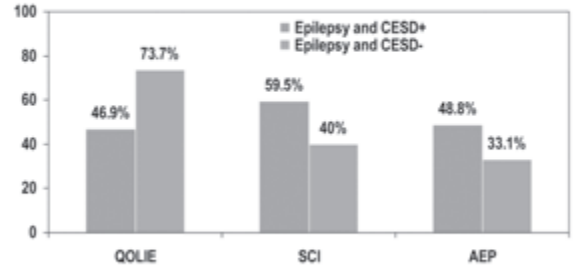
Impact on quality of life…

Correlation of Depression and HRQOL (n=194)



Gilliam F. Neurology. 2002;58(8 suppl 5):S9-20.

Depression Versus QOL, Social Concerns, and Adverse Medication Effects



Contrasting means for EPI CESD+ vs EPI CESD- subjects on total QOLIE-89, Social Concerns Index and Adverse Event Profile scales; p<.001 for all comparisons.

Cramer et al., Epilepsy & Behav, 2003

Impact of Depression and Anxiety Disorders on QOLIE

Kanner et al., Epilepsia 2010

Psychiatric Disorder	N 188	BDI-II	CES-D	QOLIE-89
None,	103	3.4±3.3	3.4±3.6	79.8±9.7
Sub-syndromic depressive episode	26	15.6±6.5	19.4±11.7	58.2±12.5
Major depressive episode only	10	22.8±9.6	21.7±13.1	51.3±17.5
Anxiety disorder	28	14.8±12.5	16.6±14.0	61.1±15.8
Major depressive/ anxiety disorder	21	28.4±10.7	31.2±13.3	45.8±16

Total QOLIE-89 Scores

Kanner et al., Epilepsia 2010

Dx. Category	Sz. Free	Persistent Szs.
Asymptomatic	82.2±9.1	76.6±9.9
Sub-syndromic	59±11.1	56.4±13.9
Syndromic	59.2±15.4	50.9±17.9

Impact on suicidal risk…

Lifetime Prevalence of Mood and Anxiety Disorders

Tellez-Zenteno, JF et al., Epilepsia, 2007; 48:2336-2344

Psychiatric Disorder	Controls (%)	Epilepsy (%)
Major Depressive Disorder	10.7 (10.2–11.2)	17.4 (10.0–24.9)
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Any Psychiatric Disorder	20.7 (19.5–20.7)	35.5 (25.9–44.0)

Epilepsy, Psychiatric Disorders and Suicide

	Rate Ratio	P value
No Epilepsy	1	
Epilepsy	2.4 (2.0-2.8)	<0.0001
Epilepsy +		<0.0001
Affective Disorder	32.0 (20.8-49.4)	<0.0001
Anxiety Disorder	11.4 (4.16-31.4)	<0.0001
Schizophrenia	12.5 (8.05-22.7)	<0.0001

Christensen et al. Lancet Neurology 6: 693–98, 2007

Suicide and Epilepsy

Table 1
Rates of suicide[a]

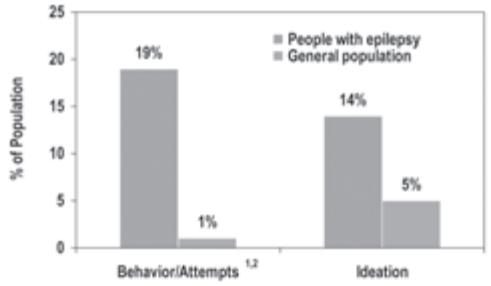
Reference	Deaths	Suicides	Deaths by suicide (%)
Blodin [21]	3	1	33
Bridge [22]	45	1	2.2
Cockerell et al. [23]	150	1	1
Currie et al. [24]	54	3	6
Dalby [25]	10	2	20
Freytag and Lindenberg [26]	294	9	3.1
Fukuchi et al. [27]	43	6	14
Hauser et al. [28]	183	3	1
Henriksen et al. [29]	104	21	20
Ivanainen and Lehtinen [30]	179	13	7.3
Krohn [31]	107	3	2.8
Lennon and Lennon [32]	118	11	9.3
Lindsay et al. [33]	9	1	11
Penning et al. [34]	171	4	2.3
Prudhomme [35]	1100	8	0.7
Rafinsson et al. [36]	224	4	1.7
Sillanpää [37]	18	1	5.6
Stapien et al. [38]	3	2	67
Taylor and Marsh [39]	37	9	24
White et al. [40]	636	21	3
Zielinski [41]	218	16	7.3
Average based on above studies			11.5
General population rate			1.1–1.2

[a] Adapted, with permission, from Robertson [6].

11.5%

Jones JE et al. Epilepsy Behav 4 (Suppl 3):S31-8, 2003

Risk of Suicidal Ideation and Attempt in People with Epilepsy



1. Boylan LS, et al. *Neurology.* 2004;62(2):258-261.
2. Jones JE, et al. *Epilepsy Behav.* 2003;4(suppl 3):S31-S38.

Suicidal Ideation in Epilepsy

- 139 outpatients from 5 centers
- Structured psychiatric interview (M.I.N.I.)
- Suicidal ideation was endorsed by 17 (12%) patients
- Suicidality was significantly increased in patients with:
  - current major depressive episode
  - current anxiety
  - current major depressive episode with anxiety

Jones et al, Epilepsy Behav. 2003;4 Suppl 3:S31-8

Bidirectional Relationship Between Epilepsy and Suicidality

Authors	Type of Study	Psychiatric History Preceding the Onset of Epilepsy/Controls
Forsgren and Nystrom, 1990	Population-based	7 times the history of depression 17 times in case of TLE
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Postictal Suicidal Ideation

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Hopelessness	25	24 (1.0-108)
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Crying bouts	26	6 (0.1-108)
Suicidal ideation	*13*	*24 (1.0-240)*
Irritability	30	24 (0.5-108)
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Self deprecation	27	24 (1.0-120)

Any postictal symptom of depression, n=43 patients
Median number of symptoms: 5 (range: 2-9)

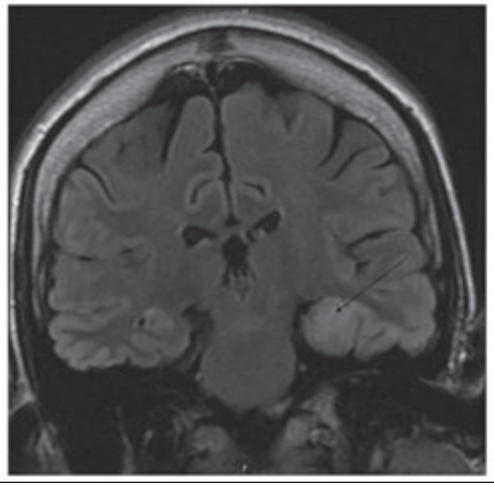
Kanner AM, et al. Neurology. 2004;62(5):708-713.

Psychiatric variables associated with postictal suicidal ideation

Psychiatric Variables	*p*
Past History of Major Depression	0.006
Previous Psychiatric Hospitalizations	<0.0001
Interictal Neurovegetative Symptoms	<0.0001

Case

- A 24 year-old left handed woman was admitted following a first secondarily GTC.
- For the previous 6 years, this patient had complained of recurrent episodes of "deja-vu", "jamais-vu" and *a "panici feeling"* after which she was noticed to "rub his fingers" repeatedly.
- Patient was unaware of the hand phenomena or any loss of awareness of his surroundings.
- Patient's primary care physician interpreted
  - ✓ the panici symptoms as anxiety disorder and
  - ✓ placed him on alprazolam (Xanax) without
  - ✓ any relief of symptoms.



Case: Work-up

- EEG study: left and left interictal antero temporal sharp waves. Focal slowing in left temporal regions.
- Video-EEG: several events beginning with a panici feeling followed by sensation of deja-vu, hand automatisms and unresponsiveness.
- Documented complex partial seizures of left antero-temporal origin.

Clinical Differentiation Between Panic Disorder and Complex Partial Seizures

	Panic Disorder	Partial Seizures
Consciousness	Usually preserved	Impaired
Agoraphobia	Common	Very rare
Duration of attack	>5 min	<120 seconds
AEDs	Occasional helpful	Very often helpful
Antidepressants	Helpful	Rarely worsen seizures
Abnormal sleep-deprived interictal EEG	Usually absent	Often present
Anticipatory anxiety	Common	Uncommon
Automatisms	Uncommon	Common

Handal NM, et al. *Psychosomatics*. 1995;36:498-501.

Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)

For the statements below, please circle the number that best describes you over the last two weeks including today.

	Always or Often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Frustrated	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
Difficulty finding pleasure	4	3	2	1
I'd be better off dead	4	3	2	1

Patient Health Questionnaire-Generalized Anxiety Disorder-7 PHQ-GAD-7

Please circle the number that best describes you over the last 2 weeks, including today

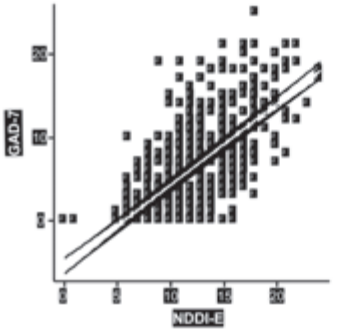
	Nearly every day	More than half the days	Several days	Not at all
Feeling nervous, anxious or on edge	3	2	1	0
Not being able to stop or control worrying	3	2	1	0
Worrying too much about different things	3	2	1	0
Trouble relaxing	3	2	1	0
Being so restless that it is hard to sit still	3	2	1	0
Being easily annoyed or irritable	3	2	1	0
Feeling afraid as if something awful might happen	3	2	1	0

Screening for Depression and Generalized Anxiety Disorder at the Rush Epilepsy Center

- N = 655 consecutive English-speaking adults.
- Age: > ≥ 18 year-old
- Gender: 54.5% women
- **NDDI-E >15: 17.9%**
- **GAD-7 >10: 20.4%**
- **Both: 10.9%**

Kanner et al, Epilepsia, 2009 Poster 2.152

Correlation between total NDDI-E and GAD-7 scores



R = 0.71
P<0.0001

Kanner et al, Epilepsia, 2009 Poster 2.152

Changes in NDDI-E, GAD-7 and NDDI-E+GAD-7 scores between 2 visits: N = 73

Remission of MDE between visit 1 and 2 N = 11/18	New onset of MDE at visit 2 N = 7	No remission of MDE between visits 1 and 2 N = 7
Remission of GAD between visit 1 and 2 N = 7/18	New onset of GAD at visit 2 N = 2	No remission of GAD between visits 1 and 2 N = 11
Remission of MDE+GAD between visit 1 and 2 N = 6/9	New onset of MDE+GAD at visit 2, N = 4	No remission of MDE+GAD between visits 1 and 2 N = 3

Psychosis of epilepsy (1)

Case: Neurologic Data:

- 45 y.o. woman with a 35 year history of epilepsy.
- CPS and 2ndGTC, 6 to 10/month.
- Bilateral hippocampal atrophy.
- Bilateral ictal foci, with 50% of seizures originating from each side.
- Graduated from a junior college.
- Worked for 12 years as clerk in post office.
- Stopped working because of increased seizure frequency in the last five years.
- Never married, lives with sister.

Case: Psychiatric Data:

- Seven year history of psychotic episodes occurring 3 to 4 days after a cluster of secondarily GTC.
- Initial insomnia

8 to 12 hours later

- Thought disorder
- Religious delusions
- Auditory hallucinations
- Marked irritability with occasional violent outbursts.
- Psychotic episodes that could last between 3 days and 4 weeks.

Case: Psychiatric Data (2):

To abort psychotic episodes…

- At first sign of insomnia after cluster of GTC family instructed to begin risperidone, @2 mg.
- Days 2 and 3: 2 mg to 4 mg/day
- Days 4 and 5: 1 mg/day for 2 days.
- In last two years, pt. presented with:
  - recurrent *interictal* episodes of pressured speech,
  - religious delusions
  - auditory hallucinations
  - agitation and occasional violent behavior resulting in a need for a brief psychiatric hospitalization.
- Symptoms improved on a regimen of 10 mg/day of olanzapine.

Postictal Psychosis: General Principles

- ❖ The postictal period can be divided into two phases:
- ➢ Immediate and delayed phases.
- ✓ The immediate postictal phase refers to the period that follows a seizure and which typically has a duration of a few minutes to two hours but may occasionally last for up to 48 and even 72 hours.
- ✓ Cognitive disturbances and headaches are typical of the immediate postictal period.

Postictal Psychosis: General Principles

- ✓ Postictal psychiatric symptoms (PPS) occur characteristically (but not exclusively) during the delayed phase, which takes place after a symptom-free period of 8 hours to 7 days duration following the seizure.
- ✓ Typically, the postictal delayed period lasts between 12 hours and 7 days but occasionally psychiatric symptoms may persist for up to 3 months.

Postictal Psychosis: General Principles

- ❖ *Postictal psychotic phenomena may be the expression of:*

1) Isolated psychotic symptoms (PS).
2) Clusters of PS mimicking a psychotic episode.
3) Postictal exacerbation in severity of interictal psychotic symptoms.

Postictal Psychotic Symptoms

- N = 100 consecutive patients with treatment resistant partial seizure disorders.
- ***Psychotic symptoms,*** ***n* = 7 Median duration**
  - Referential thinking: n = 5 15 hrs (0.1–108)
  - Auditory hallucinations n = 2 6.0 hrs (0.1–108)
  - Paranoid delusions n = 4 0.2 hrs (0.1–0.25)
  - Religious delusions n = 3 6.0 hrs (0.1–108)
  - Visual hallucinations1 n = 3 6.0 hrs (6–48)

Postictal Psychotic Episodes (PIPE)

- Account for approximately 25% of the cases of psychosis in epilepsy.
- Prevalence rates estimated to range between 6 and 10% *(Dongier 1959).*
- In patients with partial epilepsy who have undergone a VEEG, the yearly incidence of PIPE was reported to be 6.4% *(Kanner et al. 1996).*

Postictal Psychotic Episodes

(1) PIPE occur following an asymptomatic period of 12 hours to 5 days duration from the time of the seizure or cluster of seizures.

(2) Psychotic symptoms are preceded 8 to 24 hours earlier by herald symptoms consisting primarily of insomnia and/or restlessness.

(3) The onset of PIPE follows a 10-year history of a treatment-resistant seizure disorder.

Logsdail and Toone 1988; Savard et al. 1991; Devinsky et al. 1995; Umbricht et al. 1995; Kanner et al. 1996; Kanemoto et al. 1996a; Kanemoto et al. 1996b; Kanemoto et al. 1999; Kanner & Ostrovskaya 2008.

Postictal Psychotic Episodes

(4)A prompt symptom remission follows the administration of a low-dose antipsychotic medication or occasionally benzodiazepines

(5) The typical seizure type consists of secondarily GTC seizures, often in clusters.

(6) Bilateral independent ictal foci identified in a majority of patients.

Can PIPE have a localizing value of the seizure focus?

Kanner AM & Ostrovskaya A, 2008

- N = 18 patients with PIPE
- N = 36 patients with treatment resistant partial seizure disorders without PIPE
- Video-EEG monitoring study
- Bilateral independent ictal foci in 17/18 patients with PIPE vs. 5/36 controls.
- The presence of PIPE is predictive of bilateral independent ictal foci with 89% accuracy.

Can PIPE evolve into interictal psychotic episodes (IPE)?

- ❖ N = 18 consecutive adults with a partial seizure disorder and PIPE (study group)
- ❖ N = 36 patients with a partial seizure disorder but without PIPE (control group).
- ❖ These two groups were compared with respect to the likelihood of developing IPE over an 8-year follow-up period and the variables operant in the development of IPE.
- ➢ N = 7 patients with PIPE and one control patient went on to develop an IPE.
- The frequency with which patients with PIPE went on to develop IPE in our study (39%) is similar to that reported by other authors with prevalence rates ranging between 13 and 39%

Kanner & Ostrovskaya, 2008

Do PIPE occur in children?

- Very rarely!
- Typically after episode of status epilepticus.

Treatment of PIPE

- PIPE is a self-limiting condition, and is many cases can be managed by observation and nursing or carer supervision.
  - Lancman *et al* (1994a) noted that most patients returned to their pre-morbid state within one week regardless of intervention.
- With any deterioration or florid psychosis, pharmacologic intervention is required.
- Logsdail and Toone (1988) reported that over half their patients needed to be treated with antipsychotic drugs and one with lithium.
- Some patients responded well to mild sedation (with benzodiazepines or choral hydrate) given in a supportive environment.

Treatment of PIPE

- There are no studies of comparative treatments.
- Benzodiazepines may be the first choice of therapy.
- When successful, they can be administered at the time of the first herald symptom preceding the PIPE.
- Prophylactic treatment with neuroleptic medication can be considered in patients with a previous history of PIPE prior to V-EEG monitoring.
- Atypical neuroleptics are preferred.

Case

- 52 year-old male with idiopathic partial epilepsy since the age of 12 and a psychosis of epilepsy diagnosed at the age of 35.
- His seizure disorder has been controlled on lamotrigine monotherapy (450 mg/day) and he has had no psychotic episodes for five years on a regimen of haloperidol 6 mg/day.
- Two weeks prior to admission he ran out of lamotrigine and he thought that since he had been seizure-free for several years he could stay off AEDs.

Case (cont'd)

- Three weeks later he was admitted to the hospital because of a flurry of secondarily generalized tonic-clonic seizures.
- On admission to the ER, he was loaded with IV phenytoin and placed on a maintenace dose of 325 mgs/day.
- Four weeks later, he developed a recurrence of paranoid delusions, auditory hallucinations and he displayed a thought disorder consisting of losening of associations, symptoms he had not experienced for three years.

What are the mechanisms responsible for the recurrence of his psychotic symptoms?

- The induction of liver enzymes triggered by phenytoin

- Increase of haloperidol's metabolism

- A drop in haloperidol's serum concentration.

ADHD in Adults with Epilepsy

Case

- 37 year-old man, with a history of juvenile myoclonic epilepsy since the age of 21.
- Poor academic performance throughout school.
- Irritability.
- Poor frustration tolerance.
- Inability to stay in a job for more than 8 to 12 months.
- History of drug abuse.
- One brother with similar history, never evaluated or treated.

Facts and Myths:

Myths

- Children outgrow ADHD

Facts

- About 75% of children diagnosed with ADHD will continue to have symptoms through adolescence.
- About 65% of children will continue to have impairing ADHD symptoms into adulthood.

Faraone et al., 2000

Epidemiology

❖ ***Prevalence***
✓ in children (general population): 4% to 12%.
✓ *In children with epilepsy: 20 to 60%*
✓ In adults (general population): 2% to 7%.
✓ *In adults with epilepsy: ?*

➢ Male-to-female ratio (general population):
✓ pediatric: 3:1
✓ adult: 3:2

➢ Male-to-female ratio (epilepsy population): ?

DSM-IV Adult Criteria

- Three critical elements:
  - Childhood onset
  - Presence of significant symptoms
  - Impairment from these symptoms in at least two domains: school/work, social interaction, or home life

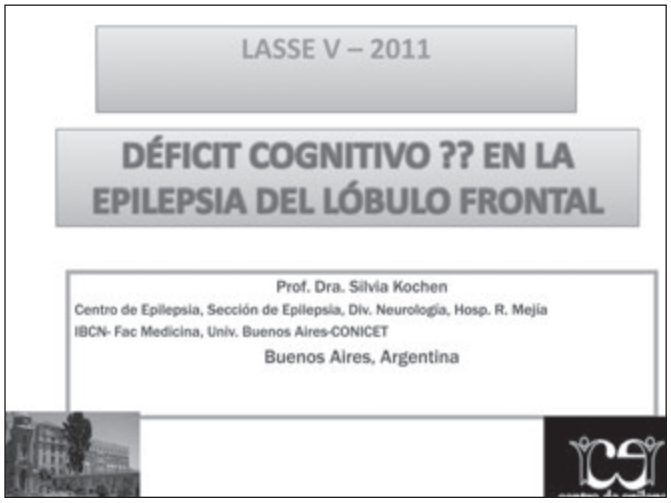
APA, 1994

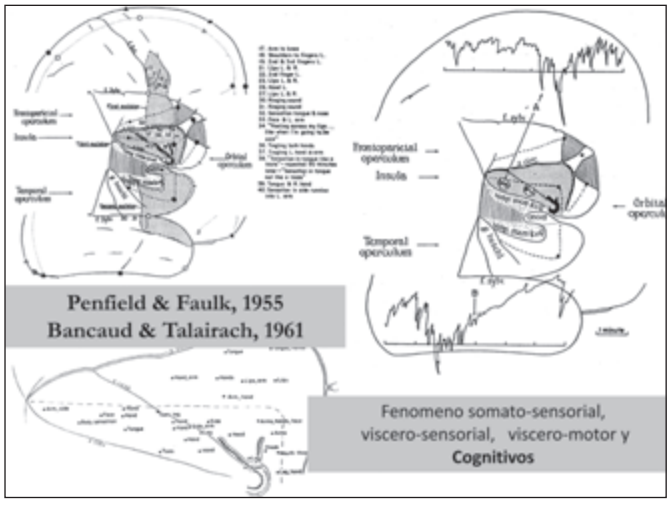
Conclusions

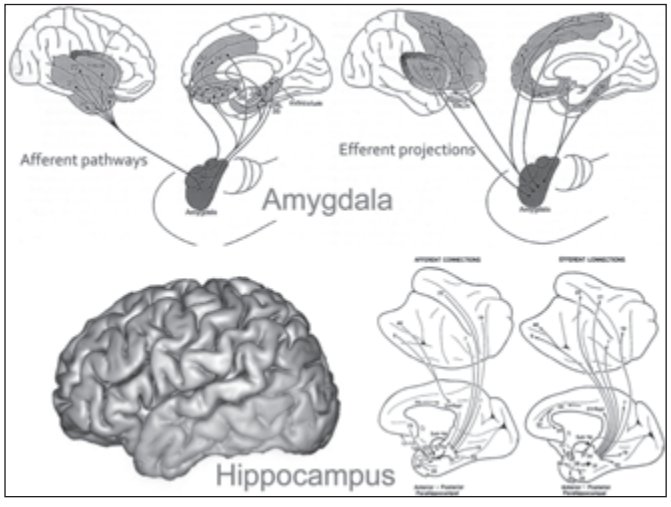
➢ **Psychiatric Disorders are frequent in people with epilepsy.**
➢ **They have a negative impact on:**
✓ **Seizure response to therapy**
✓ **Quality of life**
✓ **Adverse events to AEDs**
✓ **Increase suicidal risk**

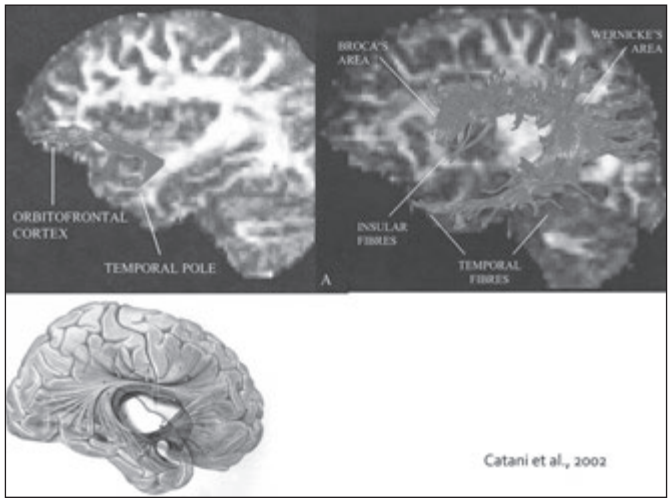
Cognitive deficits in frontal lobe epilepsy

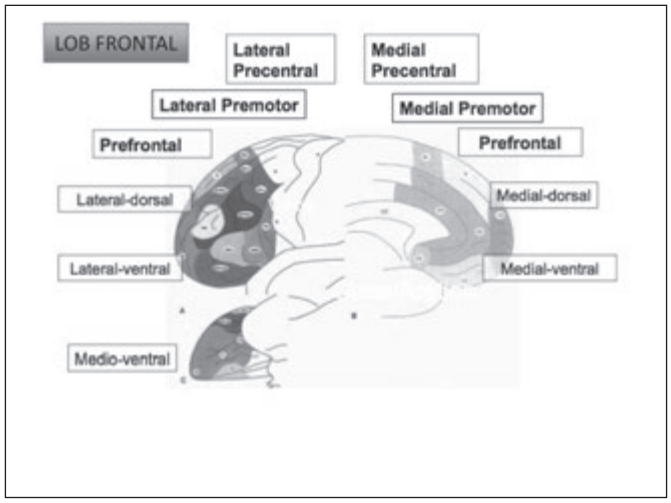
Silvia Kochen (Argentina)

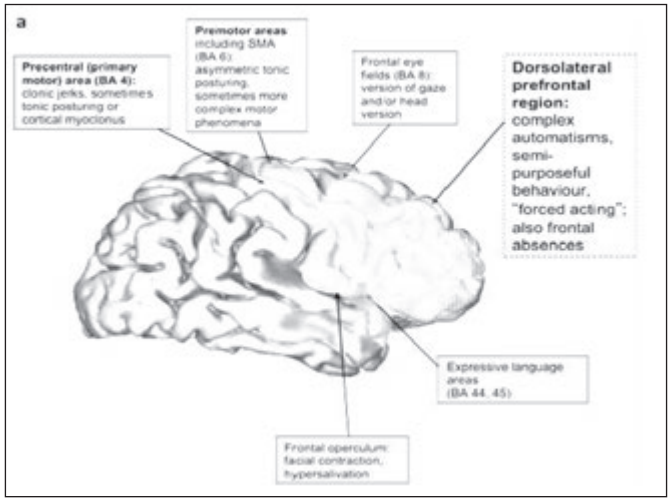


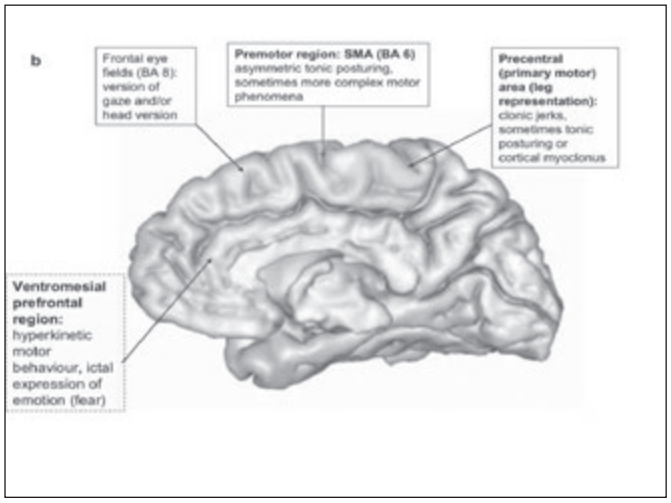


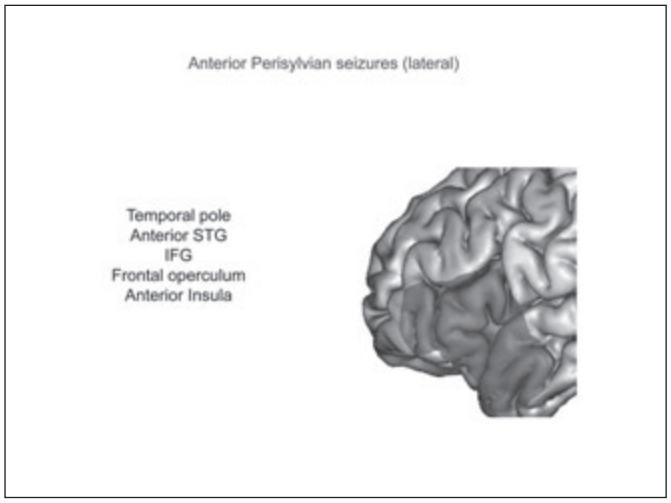


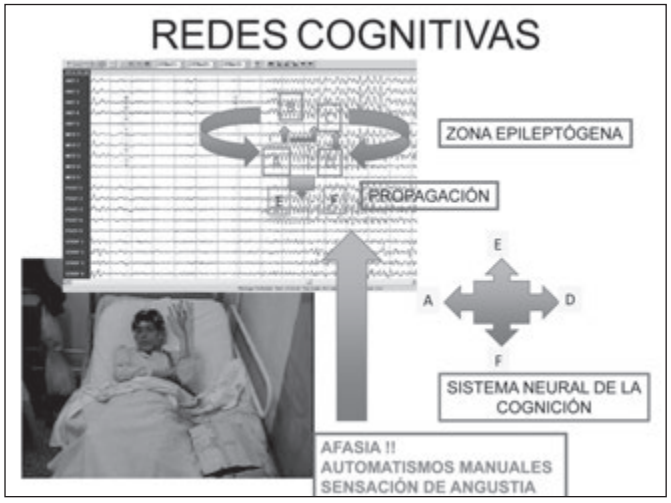

BROCA'S AREA
WERNICKE'S AREA
ORBITOFRONTAL CORTEX
TEMPORAL POLE
INSULAR FIBRES
TEMPORAL FIBRES
A
Catani et al., 2002

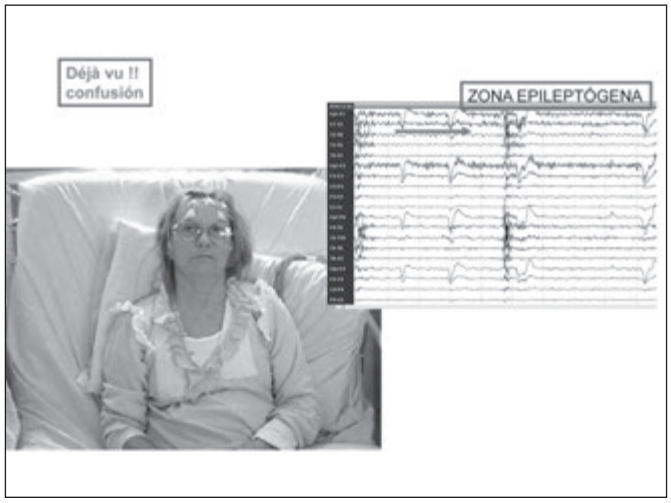

LOB FRONTAL
Lateral Precentral
Medial Precentral
Lateral Premotor
Medial Premotor
Prefrontal
Prefrontal
Lateral-dorsal
Medial-dorsal
Lateral-ventral
Medial-ventral
Medio-ventral

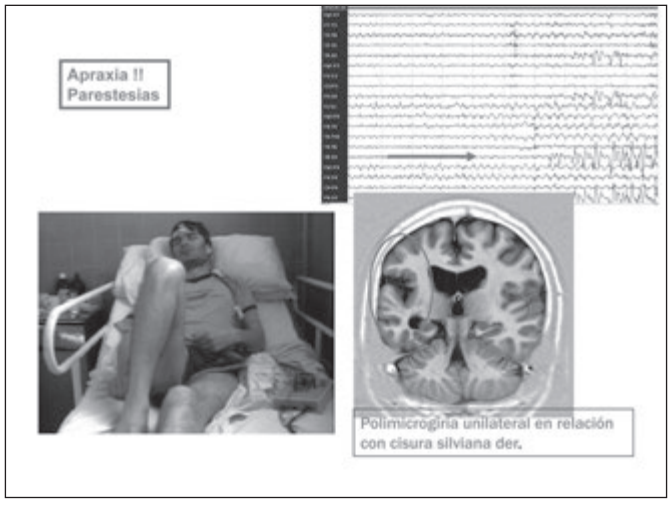

a
Premotor areas including SMA (BA 6): asymmetric tonic posturing, sometemes more complex motor phenomena
Precentral (primary motor) area (BA 4): clonic jerks, sometimes tonic posturing or cortical myoclonus
Frontal eye fields (BA 8): version of gaze and/or head version
Dorsolateral prefrontal region: complex automatisms, semi-purposeful behaviour, "forced acting"; also frontal absences
Expressive language areas (BA 44, 45)
Frontal operculum: facial contraction, hypersalivation

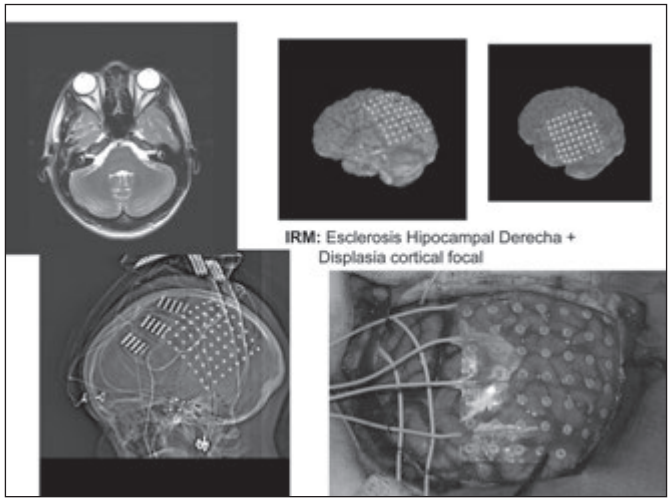

b
Frontal eye fields (BA 8): version of gaze and/or head version
Premotor region: SMA (BA 6) asymmetric tonic posturing, sometimes more complex motor phenomena
Precentral (primary motor) area (leg representation): clonic jerks, sometimes tonic posturing or cortical myoclonus
Ventromesial prefrontal region: hyperkinetic motor behaviour, ictal expression of emotion (fear)

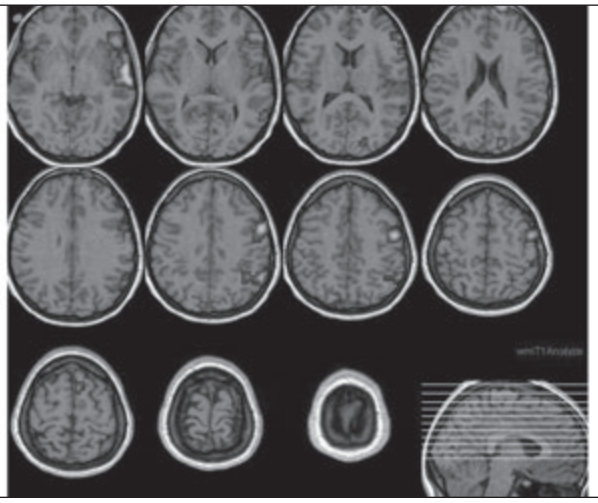

Anterior Perisylvian seizures (lateral)
Temporal pole
Anterior STG
IFG
Frontal operculum
Anterior Insula


REDES COGNITIVAS
ZONA EPILEPTÓGENA
PROPAGACIÓN
E
A
D
F
SISTEMA NEURAL DE LA COGNICIÓN
AFASIA !!
AUTOMATISMOS MANUALES
SENSACIÓN DE ANGUSTIA

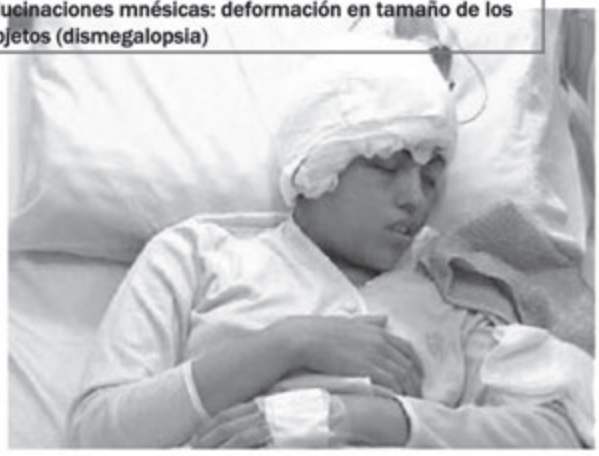

Déjà vu !!
confusión
ZONA EPILEPTÓGENA

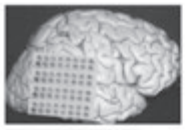

Apraxia !!
Parestesias
Polimicrogiria unilateral en relación
con cisura silviana der.

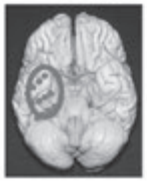

IRM: Esclerosis Hipocampal Derecha +
Displasia cortical focal



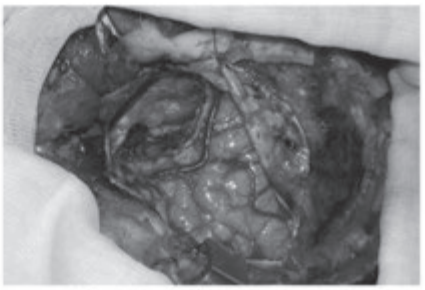
Déjà vu !!
Alucinaciones mnésicas: deformación en tamaño de los objetos (dismegalopsia)

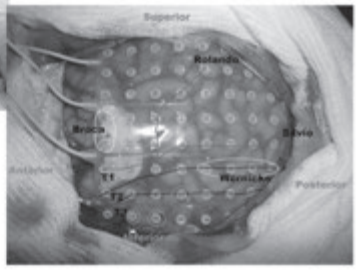






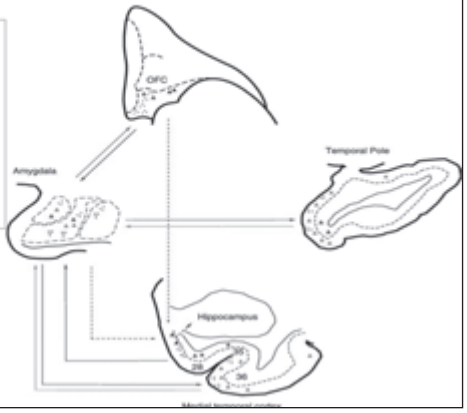
Lobectomía mesial derecha





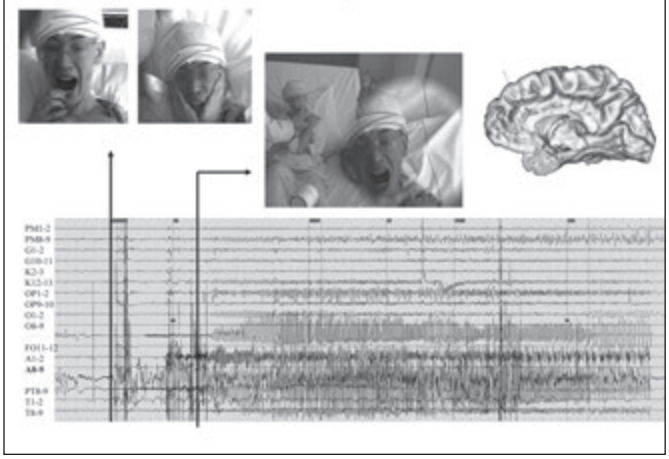
Modelo del circuito de las manifestasiones de las emociones durante la crisis

Modelo de la secuencia del procesamiento de las emociones a través de conexiones laminares especificas entre la amígdala, las áreas temporales e insulares,
y la corteza posterior orbitofrontal

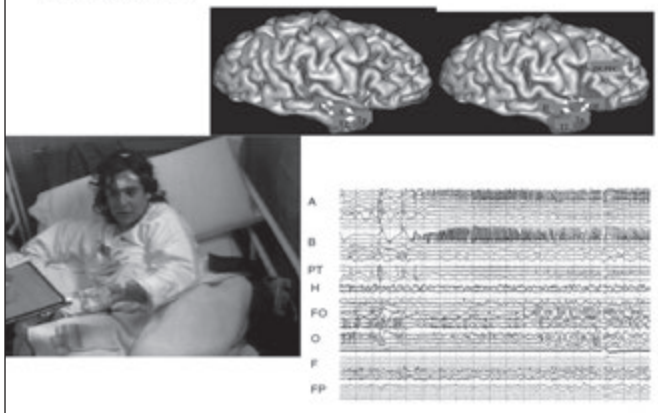


Höistad & Barbas, 2008

Region perisilviana anterior, Medial



Region perisilviana anterior: Mesio-temporal
Cx órbito frontal



EVALUACIÓN NEUROPSICOLÓGICA
DEL PACIENTE CON EPILEPSIA
Candidato a Cirugía

Protocolo de Evaluación Neuropsicológico

- Valoración global del rendimiento del paciente y en función del resultado y del tipo de cirugía a realizar, se exploran las funciones mas relevantes
- Utilización del Protocolo de Evaluación Neuropsicológico

Protocolo de Evaluación Neuropsicológico

- Inteligencia
- Dominancia Manual
- Memoria — Memoria Material Específico
- Lenguaje
- Atención
- Función Ejecutiva
- Calidad de Vida

Protocolo Evaluación NPS

- **Inteligencia:**
  Test de Inteligencia para Adultos (WAIS-III).
- **Dominancia manual**
  Cuestionario de Dominancia Manual de Edimburgo.
  Grooved Pegboard
- **Atención**
  Trial making test B (TMT B)
  Dígitos
  Test de cancelación de dígitos
  Modalidad Digito Simbolo

- **Memoria Visual (no verbal)**

  List Learning test (diseños)

  Test de la Figura Compleja de Rey

- **Memoria verbal**

  List Learning test

  (palabras)

  Rey Auditory Verbal Learning Test (RAVLT)

Protocolo de Evaluación NPS

- **Escala Wechsler de Memoria** (WMS III)
  - **Modalidad mnésica**
- **Función ejecutiva**

  Wisconsin Card Sorting Test (WCST)

  Stroop test

  Torre de Hanoi

  Fluencia verbal fonológica

Protocolo de Evaluación NPS

- **Lenguaje**
  Test de denominación por confrontación visual de Boston
  Token Test
  Vocabulario, Comprensión, Analogías(sub escalas WAIS III)

Calidad de Vida

- **Calidad de Vida**
  Cuestionario Qolie-31
  Cuestionario autoadministrado de evaluación del estado de salud relacionado con la calidad de vida

1. Preocupación sobre las crisis
2. Calidad de vida general
3. Bienestar emocional
4. Energía/Fatiga
5. Funcionamiento Cognitivo
6. Efectos de la medicación
7. Sociabilidad

Revisión Bibliográfica

- Se puede observar una tendencia que muestra a partir de los 80 del siglo pasado, que se comienza a estudiar la Epilepsia con una base científica y racional, abandonando las hipótesis que asumían a la epilepsia como causa de alteraciones cognitivas y psiquiátricas.
- A continuación algunos trabajos que resultaron aportes considerables al tema:

✓Strauss E, Loring D, Chelune G, Hunter M, Hermann B, Perrine K, Westerveld M, Trenerry M, Barr W. **Predicting cognitive impairment in epilepsy: findings from the Bozeman epilepsy consortium** J Clin Exp Neuropsychol. 1995 Dec;17(6):909-17.

- No hallaron resultados significativos de deterioro cognitivo

✓Luton LM, Burns TG, DeFilippis N. **Frontal lobe epilepsy in children and adolescents: a preliminary neuropsychological assessment of executive function.** Arch Clin Neuropsychol. 2010 Dec;25(8):762-70

- Results indicated comparable intelligence among all groups; however, the FLE cohort performed worse than controls on executive tests. The age of seizure onset differentially affected executive performance, such that early FLE onset resulted in greater executive dysfunction

✓ Risse GL. (2006).**Cognitive outcomes in patients with frontal lobe epilepsy**. Epilepsia.;47 Suppl 2:87-9.

- A typical "cognitive profile" or defining behavioral syndrome for patients with frontal lobe epilepsy (FLE) has not been described. While there have been numerous reports of impaired "executive functions" in this population, the nature and severity of these deficits is highly variable, ranging from impaired attention to difficulty with the more complex behaviors involved in planning, selecting goals, anticipating outcomes, and initiating action. Children who have undergone surgical resection of the dominant frontal lobe frequently show declines in verbal fluency, and sometimes verbal IQ, visual confrontation naming, and conceptual reasoning. Adult surgical cases have shown the most specific frontal lobe findings, including reduced word fluency with relatively small lesions of the dominant dorsolateral frontal cortex, the analogous finding of impaired nonverbal fluency with nondominant frontal lesions, and other executive deficits following large resections of prefrontal cortex bilaterally. These reports support the likelihood that it **may not be possible to identify a specific cognitive syndrome associated with FLE in the absence of a structural lesion**.

✓ McDonald CR, Delis DC, Norman MA, Tecoma ES, Iragui VJ. (2005) **Discriminating patients with frontal-lobe epilepsy and temporal-lobe epilepsy: utility of a multilevel design fluency test.** Neuropsychology. Nov;19(6):806-13.

- Patients with frontal-lobe epilepsy (FLE) or temporal-lobe epilepsy (TLE) and matched control participants were given a design fluency test that assessed nonverbal fluency and switching ability. Patients with FLE generated fewer designs in the switching condition relative to the TLE patients and controls, whereas group differences did not emerge in the basic fluency conditions. When the side of the seizure focus and the presence or absence of a structural lesion were considered in patients with FLE, only those with left-lesional FLE generated fewer designs than controls did in the switching condition. Furthermore, patients with left-lesional and nonlesional FLE produced a greater proportion of set-loss errors than did controls. These results indicate that patients with **FLE are impaired when they must simultaneously generate new designs and engage in cognitive switching; however, the pattern of impairment may depend on the side of the seizure focus and the presence of a structural lesion**.

- Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, Hermann B.Department (2009). **Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy.** Epilepsia. May;50(5):1210-9.
  - Thalamofrontal abnormalities have been identified in chronic primary generalized epilepsy, specifically in juvenile myoclonic epilepsy (JME). These regions also underlie executive functioning, although their relationship has yet to be examined in JME. This study examined the relationship between thalamic and frontal volumes and executive function in recent-onset JME compared to healthy control subjects and recent-onset benign childhood epilepsy with centrotemporal spikes (BCECTS), a syndrome not typically associated with thalamocortical or executive. Subtests from the Delis-Kaplan Executive Function System (D-KEFS) and the Behavior Rating Inventory of Executive Function (BRIEF) were used to measure executive function. Children with JME have significant executive dysfunction associated with significantly smaller thalami and more frontal CSF. Children with recent-onset BCECTS do not display the same pattern. Frontal and thalamic volumes appear to mediate the relationship between executive functioning and brain structure in JME.

- ✓ Centeno M, Thompson PJ, Koepp MJ, Helmstaedter C, Duncan JS (2010) **Memory in frontal lobe epilepsy** Epilepsy Res. 91(2-3):123-32.
  - In contrast to the well studied long-term memory dysfunction of temporal lobe epilepsy (TLE) syndromes, data on memory performance of frontal lobe epilepsy (FLE) patients are limited and controversial. Behavioural and functional neuroimaging findings suggest that different regions within the frontal lobes contribute to long-term memory functioning, offering an explanation for the variability on memory function observed on patients with frontal lobe damage. Available evidence suggests memory dysfunction is a common finding on neuropsychological evaluation of FLE patients but prevalence and underlying mechanisms remain poorly understood. Variability on memory performance reported in FLE studies suggest this deficit may be dependant on the areas involved in seizure generation and spread. Recent research findings and the application of cognitive fMRI paradigms to FLE patients holds the promise of increasing understanding further.

- Chieffo D, Lettori D, Contaldo I, Perrino F, Graziano A, Palermo C, Mittica A, Tamburrini G, Battaglia D, Di Rocco C, Guzzetta F (2010) **Surgery of children with frontal lobe lesional epilepsy: Neuropsychological study**. Brain Dev.
  - Twelve patients with lesional FLE underwent full clinical before and after surgery. Another group of lesional temporal lobe epilepsy, matched for the age at surgery and side of surgery, was likewise studied in order to compare neuropsychological patterns and to try to find out specific features in frontal lobe epilepsy evolution. All patients resulted seizure free at outcome except one belonging to Engel's class II. Before surgery general intelligence was similar in FLE as well as in TLE group. Executive functions and motor coordination were frequently affected in FLE whereas patients with TLE often presented with deficits in naming, visual memory and visuo-spatial attention. After surgery there was a frequent decline of IQ in FLE group together with a slight deterioration, especially of executive functions in some patients. Neuropsychological pre-surgical data confirms the involvement of attention and executive functions in lesional FLE. No significant neuropsychological improvement was produced by surgery that determined in some cases a slight decline of general intelligence and specific frontal abilities. Yet, generally behaviour improved and seizures were controlled.

- ✓ Hermann BP, Dabbs K, Becker T, Jones JE, Myers y Gutierrez A, Wendt G, Koehn MA, Sheth R, Seidenber (2010).**Brain development in children with new onset epilepsy: a prospective controlled cohort investigation.** Epilepsia. Oct;51(10):2038-46.
  - Prospective neurodevelopmental changes in brain structure in children with new and recent-onset epilepsy compared to healthy. Prospective changes in total cerebral and lobar gray and white matter volumes were compared within and between. Significant ($p < 0.0001$) reduction in total cerebral gray matter, due primarily to significant ($p < 0.001$) reductions in frontal and parietal gray matter. Prospective white matter volume changes differed between groups. The epilepsy group exhibited nonsignificant white matter volume change in the total cerebrum ($p = 0.51$) as well as across all lobes (all p's > 0.06). The group by white matter volume change interactions were significant for total cerebrum ($p = 0.04$) and frontal lobe ($p = 0.04$). Children with new and recent-onset epilepsy exhibit an altered pattern of brain development characterized by delayed age-appropriate increase in white matter volume. These findings may affect cognitive development through reduced brain connectivity and may also be related to the impairments in executive function commonly reported in this population.

- ✓ Kanemura H, Hata S, Aoyagi K, Sugita K (2010) **Serial changes of prefrontal lobe growth in the patients with benign childhood epilepsy with centrotemporal spikes presenting with cognitive impairments/behavioral problems.** Brain Dev.
  - Studied serial changes in frontal and prefrontal lobe volumes using three-dimensional magnetic resonance imaging in BCECTS with or without cognitive impairments and behavioral problems and evaluated correlations between prefrontal lobe growth and active seizure period. Serial changes in regional cerebral volumes were measured in two patients with cognitive impairments and behavioral problems (BCECTS(+)) and five patients without neuropsychiatric deficits (BCECTS(-)). Eleven normal subjects (4-13years old) served as controls. Volumes of the frontal and prefrontal lobes were determined using a workstation, and the prefrontal-to-frontal lobe volume ratio was calculated. Frontal and prefrontal lobe volumes revealed growth disturbance in BCECTS(+) compared with BCECTS(-) and control subjects. In addition, prefrontal-to-frontal lobe volume ratio increased serially in BCECTS(-) similarly to controls, but was stagnant or decreased in BCECTS(+). Prefrontal growth also revealed more rapid recovery in a BCECTS(+) patient with shorter active seizure period. These findings suggest that longer active seizure period as frequent spike-waves coupled with the occurrence of frequent seizures may be associated with prefrontal lobe growth disturbance, which relates to neuropsychological problems.

- ✓ Blackmon K, Barr WB, Kuzniecky R, Dubois J, Carlson C, Quinn BT, Blumberg M, Halgren E, Hagler DJ, Mikhly M, Devinsky O, McDonald CR, Dale AM, Thesen T (2010) **Phonetically irregular word pronunciation and cortical thickness in the adult brain.** Neuroimage;51(4):1453-8.
  - Accurate pronunciation of phonetically irregular words (exception words) requires prior exposure to unique relationships between orthographic and phonemic features. Whether such word knowledge is accompanied by structural variation in areas associated with orthographic-to-phonemic transformations has not been investigated. We used high-resolution MRI to determine whether performance on a visual word-reading test composed of phonetically irregular words, the Wechsler Test of Adult Reading (WTAR), is associated with regional variations in cortical structure. A sample of 60 right-handed, neurologically intact individuals were administered the WTAR and underwent 3T volumetric MRI. Using quantitative, surface-based image analysis, cortical thickness was estimated at each vertex on the cortical mantle and correlated with WTAR scores while controlling for age. Higher scores on the WTAR were associated with thicker cortex in bilateral anterior superior temporal gyrus, bilateral angular gyrus/posterior superior temporal gyrus, and left hemisphere intraparietal sulcus. Higher scores were also associated with thinner cortex in left hemisphere posterior fusiform gyrus and central sulcus, bilateral inferior frontal gyrus, and right hemisphere lingual gyrus and supramarginal gyrus. These results suggest that the ability to correctly pronounce phonetically irregular words is associated with structural variations in cortical areas that are commonly activated in functional neuroimaging studies of word reading, including areas associated with grapheme-to-phonemic conversion.

Persistencia de la memoria luego de la hipocampectomía

La persistencia de la memoria, Salvador Daly, 1931

MUCHAS GRACIAS

Prof Dra Silvia Kochen
Dra Patricia Saidón
~~Dr Damián Consalvo~~
Dra Estela Centurión
Dr Walter Silva
Dra Brenda Giagante
Dra Silvia Oddo
Dra Cristina Papayannis
Dr Marcelo Kauffman
Dra Carolina Lomlomdjian
Dr Gustavo Seifer
Dra Constanza Salera
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Neurocirujano: Dr Eduardo Seoane
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rm NEUROLOGIA

centro de epilepsia

Psychiatric disorders and epilepsy: Are there common pathogenic substrates?

Andres Kanner (USA)

RUSH UNIVERSITY MEDICAL CENTER

Common Pathogenic Mechanisms Operant in Psychiatric Disorders and Epilepsy: Do they Explain their High Comorbidity Rates?

Andres M. Kanner, MD
Professor of Neurological Sciences and Psychiatry
Rush Medical College at Rush University
Director, Laboratories of EEG and Video-EEG-Telemetry
Associate Director, Section of Epilepsy
and Rush Epilepsy Center,
Rush University Medical Center, Chicago, IL.

Lifetime Prevalence

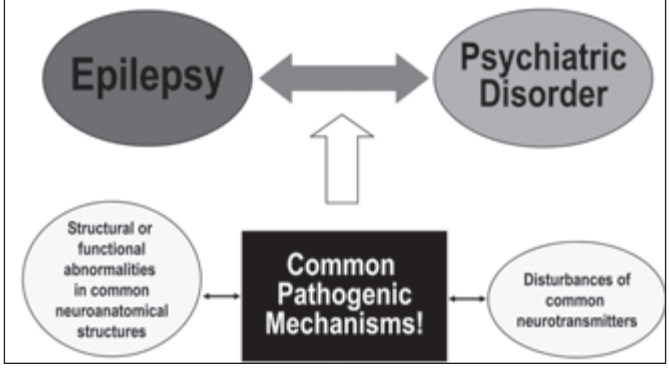
Tellez-Zenteno, JF et al., Epilepsia, 2007; 48:2336-2344

Psychiatric Disorder	Controls (%)	Epilepsy (%)
Major Depressive Disorder	10.7 (10.2–11.2)	17.4 (10.0–24.9)
Anxiety Disorder	11.2 (10.8–11.7)	22.8 (14.8–30.9)
Mood/Anxiety Disorders	19.6 (19.0–20.2)	34.2 (25.0–43.3)
Suicidal Ideation	13.3 (12.8–13.8)	25.0 (17.4–32.5)
Any Psychiatric Disorder	20.7 (19.5–20.7)	35.5 (25.9–44.0)

Bidirectional Relationship Between Epilepsy and Depression: Epidemiologic Evidence

Authors	Type of Study	Psychiatric History Preceding the Onset of Epilepsy/Controls
Forsgren and Nystrom, 1990	Population-based	7 times the history of depression 17 times in case of TLE
Hersdorffer et al, 2000	Population-based (Onset of epilepsy >age 55)	4 times the history of depression
Hersdorffer et al, 2006	Population-based (Iceland all ages)	5 times the history of suicidality Twice the history of major depression

These data possibly result from a bidirectional relation between depression and epilepsy



Outline

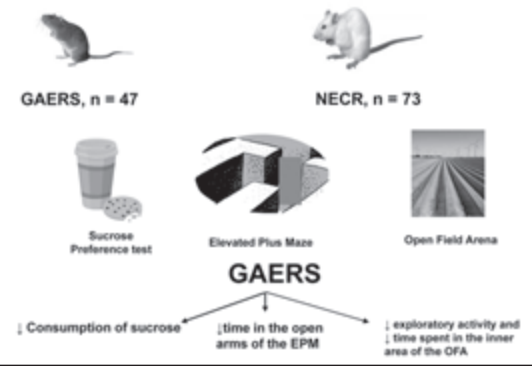
1) Can data from animal models and humans demonstrate the existence of common pathogenic mechanisms operant in epilepsy and depression?
2) Are these pathogenic mechanisms mediated by:
   - Serotonin?
   - Norepinephrine?
   - Hypothalamic-pituitary-adrenal hyperactivity?
   - Glutamate?
   - GABA?
   - Autoimmune processes?

Comorbid epileptic and psychiatric disorders in animal models….

Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy:

Before the onset of seizures

Joanes et al, Exp Neurol. 2008.



Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy:

After the onset of seizures

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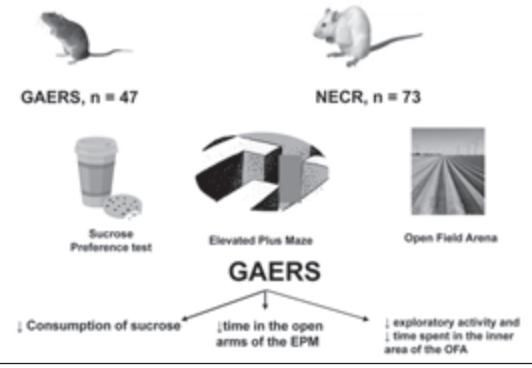


Morphometric abnormalities and hyperanxiety in genetically epileptic rats: a model of psychiatric comorbidity

Boulleret et al, Neuroimage 2009.

- Adult female GAERS (n=12) and Non-Epileptic Controls (NEC; n=11).
- GAERS had:
  - increased volume of the amygdala (right: p=0.003; left p<0.001)
  - *Hippocampal volume loss in:*
    - the medial hippocampal surface immediately caudal to the hippocampal commissure,
    - the lateral hippocampal surface over the mid-portion of the septotemporal axis.

GEPR: An animal model for predisposition for depression-like symptoms and epileptic seizures

Epileptic activity

- Genetically epilepsy-prone rat (3 and 9)
- *Innate noradrenergic and serotonergic deficits*
- *↓pre and postsynaptic GABA activity*
- Susceptibility to seizures evoked by auditory stimuli
- Deficit in NE transmission deficit more severe in GEPR-9
- Seizures more severe in GEPR-9

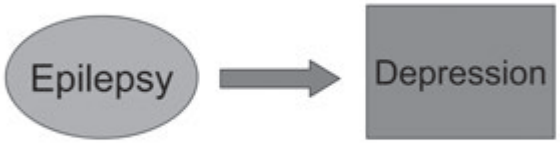
Affective-like phenomena

- *Anhedonia*: lower consumption of water with sucrose compared to controls.
- *Behavior despair* tested by the forced swim test: >50% time in despair behavior beginning with 3rd swimming episode (not seen in controls during same time).
- Diurnal abnormalities in motor behavior.

Jobe PC, et al. *Crit Rev Neurobiol.* 1999;13(4):317-356.
Dailey JW, et al. *Life Sci.* 1996;58(4):259-266.

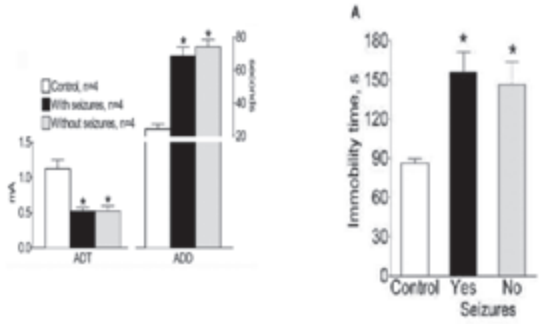
Jobe & Weber, 2005.

Can such bidirectional relation be demonstrated in animal models?

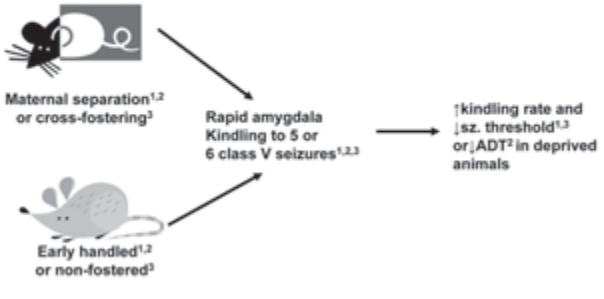


Symptoms of depression following the development of seizure activity in animal models of epilepsy and depression

Mazarati et al, Neurobiol Dis 2009, 34:457–461.

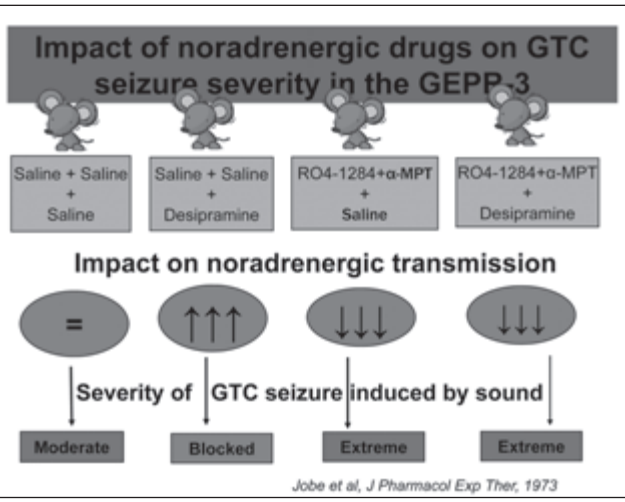


Effects of early life stress in rodent models of epilepsy/ epileptogenesis



[1]Saltzberg et al, Epilepsia 2007; 48: 2079-2085
[2]Jones et al, Behav Brain Res, 2009; 203:81-87
[3]Gilby et al, Behav Neurosci, 2009;123:337-346

Norepinephrine as a common pathogenic mechanism of depression and epilepsy



Serotonin as a common pathogenic mechanism of depression and epilepsy

Impact of SSRIs on epileptic seizures: animal models

Author	Model	Drug	Results
Daily et al, 1992	GEPR	Fluoxetine	Dose dependent reduction in sound-induced seizures
Yan et al, 1992	GEPR	Sertraline	Dose dependent reduction in sound-induced seizures
Prendeville et al, 1993	Rat	Fluoxetine before intra-cerebral application of $GABA_A$ antagosnist	Dose dependent protection from clonic seizures

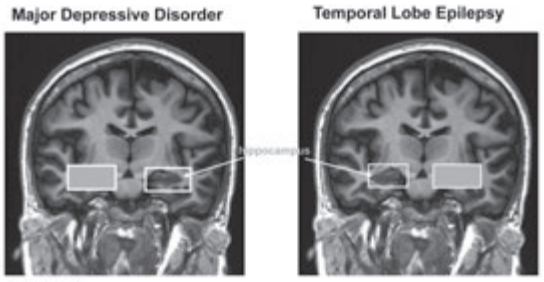
Anticonvulsant action of hippocampal serotonin is mediated by 5-HT_{1A} receptors.

Clinckers R, et al. Journal of Neurochemistry, 2004

- **The anticonvulsant effects of intrahippocampally applied 5-HT concentrations were evaluated against pilocarpine-induced seizures in conscious rats.**
- **5-HT perfusions protected the rats from limbic seizures as long as extracellular 5-HT concentrations ranged 80–350% increments relative to baseline levels.**
- **Co-perfusion with the selective 5-HT_{1A} blocker WAY-100635 clearly abolished all anticonvulsant effects.**

- **High extracellular 5-HT (> 900% increases) concentrations worsened seizure outcome.**
- **The latter proconvulsive effects were associated with significant increases in extracellular glutamate.**

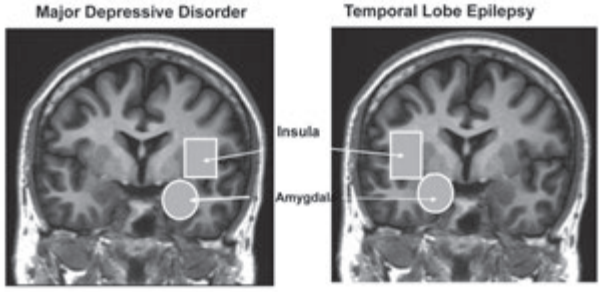
Decreased $5HT_{1A}$ Receptor Binding in Patients with Primary Depression and Temporal Lobe Epilepsy



*A decrease in postsynaptic 5-HT1A receptor availability may be a trait marker of recurrent depression[1]

*Independent of hippocampal atrophy[2]

1. Drevets et al., 1999. 2. Sargent et al., 2000. 3. Bhagwagar Z, et al. 2004. 4. Savic I, et al. Neurology. 2004;62(8):1343-1351. 5. Toczek MT, et al. Neurology. 2003;60(5):749-756.



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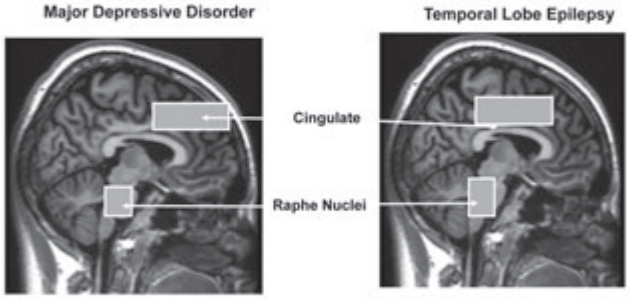

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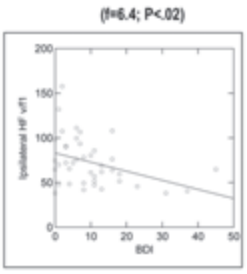
5-HT Binding in PET Studies of Patients with TLE with and Without Depression

- N=37 patients with TLE and MDD
- N=9 healthy controls
- PET with 18FCWAY

- Significant relation between increasing severity of depression and decreasing ipsilateral hippocampal Vd

- Non-significant trends present for contralateral hippocampus, and midbrain raphe (.05<p<.10) but not any other structure



Theodore WH, et al. Epilepsia. 2006;47(3):499-503.

Are SSRIs and SNRIs protective of epileptic seizures?

- **Assessment of seizure incidence between patients randomized to SSRIs, SNRIs and placebo in regulatory studies.**
- **Antidepressant treatments associated with lower seizure incidence relative to placebo for all SSRIs and SNRIs**
- **Standardized seizure ratio: 0.48, 95%C.I. 0.36-0.61.**

Alper et al., Biol Psychiatry, 2007

Effect of antidepressant drugs in seizures in humans?

Author	N	Type of Epilepsy	Drug	Result
Favale, 1995	17	Partial, refractory	fluoxetine	6 pts. Seizure free
Favale, 2003	11	Partial, refractory	citalopram	n = 9, >50% sz. reduction
Speccio, 2004	45	Partial, refractory	citalopram	N = 39 >50% sz. reduction
Fromm, 1972	16	Absence, myoclonic	imipramine	N = 10, sz. reduction
Hurst, 1986	15	various	imipramine	N = 4 sz free, >80% in 8 pts.

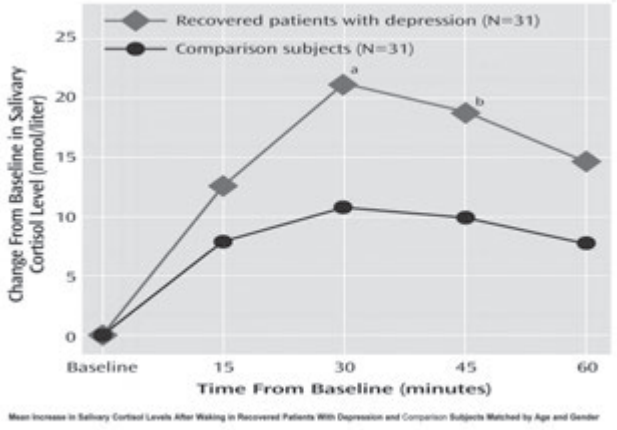
Impact of ↑HPA

Brit. J. Psychiat. (1982), **140**, 292-304

The Dexamethasone Suppression Test for Melancholia

BERNARD J. CARROLL

Summary: Melancholia is thought by many investigators to have a biological basis, and biological research, particularly on abnormalities of the neuroendocrine system and of the sleep electroencephalogram, is now beginning to yield results which can help in the differential diagnosis of depressive illness. This review will focus on the most widely studied neuroendocrine disturbance: disinhibition of the hypothalamus-pituitary-adrenal cortex (HPA) system as revealed by the dexamethasone suppression test (DST).



Mean Increase in Salivary Cortisol Levels After Waking in Recovered Patients With Depression and Comparison Subjects Matched by Age and Gender

↑HPA in patients with epilepsy

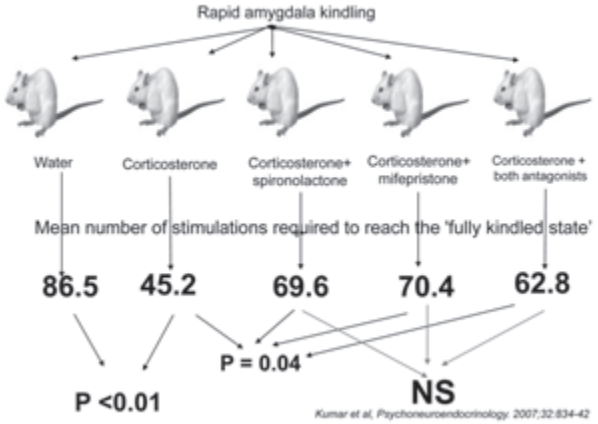
Zobel A, Eur Arch Psychiatry Clin Neurosci 2004;254(5):303-11.

- n = 16 patients with TLE
- n = 16 patients with MDD
- N = 16 healthy controls.

- Lack of inhibitory control of the HPA system in patients with epilepsy and major depression.

↑HPA in animal models of epilepsy…

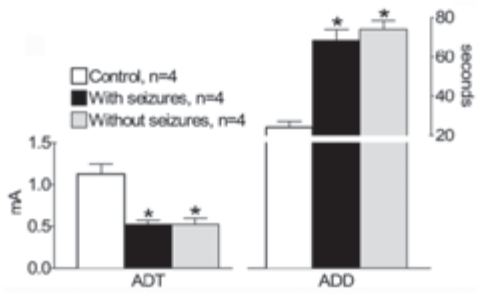
The impact of corticosterone on the kindling process

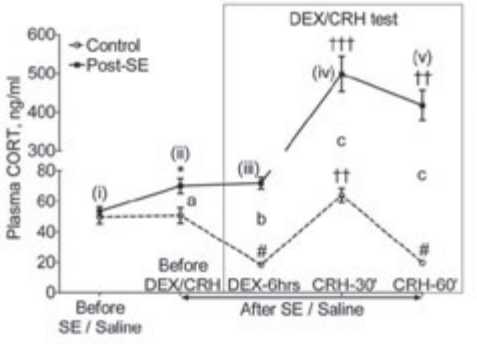


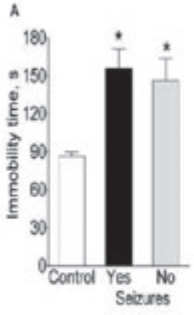
Kumar et al, Psychoneuroendocrinology. 2007;32:834-42

Elevated plasma corticosterone level and depressive behavior in experimental temporal lobe epilepsy

Mazarati et al, Neurobiol Dis 2009.







Regulation of $5HT_{1A}$, glucocorticoid, and mineralocorticoid receptor in rat hippocampus.

Lopez et al, Biol Psychiatry 1998

Chronically stressed rats

Unstressed rats

↑↑↑ Basal plasma corticosterone

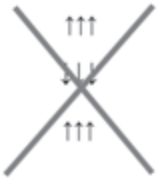
↓↓↓ $5HT_{1A}$ mRNA and binding in hippocampi

↑↑↑ MR/GR mRNA ratio in hippocampi

Pretreatment with desipramine or imipramine

Chronically stressed rats

Unstressed rats



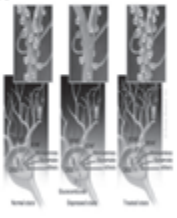
↑↑↑ Basal plasma corticosterone

↓↓↓ $5HT_{1A}$ mRNA and binding in hippocampi

↑↑↑ MR/GR mRNA ratio in hippocampi

Temporal Lobe Damage Related to High Corticosteroid Exposure

- **In experimental studies with rats and monkeys:**
  - **Damage of hippocampal neurons**, particularly CA3 pyramidal neurons mediated by reduction of dendritic branching and loss of dendritic spines that are included **in glutamatergic** synaptic inputs.
  - Decreased levels of brain-derived neurotrophic factor (BDNF) **reversed by long-term administration of antidepressants**
  - Interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus
  - ***Structural changes in:***
    - The dentate gyrus
    - Pyramidal cell layer of hippocampus
    - Amygdala
    - Temporal neocortex

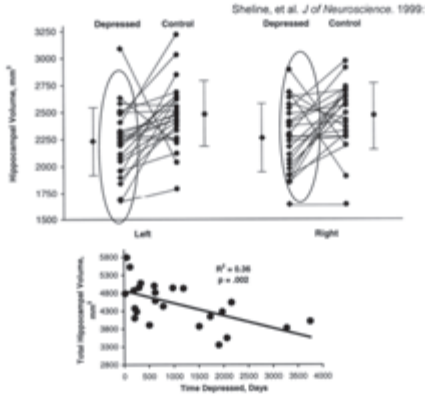


1. Holsboer F. J Affect Disord. 2001;62(1-2):77-91. Holsboer F. Curr Opin Investig Drugs. 2003;4(1):46-50. Sapolsky RM. Arch Gen Psychiatry. 2000;57(10):925-935. Shirayama Y, et al. J Neurosci. 2002;22(8):3251-3261. Nibuya M, et al. J Neurosci. 1995;15(11):7539-7547.

Impact of HPA hyperactivity in humans: Structural and functional abnormalities of temporal and frontal lobes in primary mood disorders???

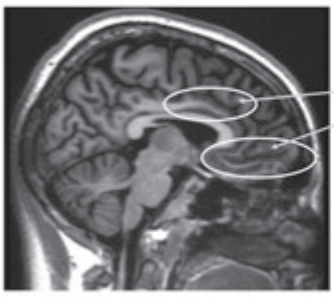
Depression But Not Age Predicts Hippocampal Volume Loss in Recurrent Depression

Sheline, et al. *J of Neuroscience*. 1999:19:5034-5043.



10% to 20%

Structural changes in frontal lobe



Atrophy of:

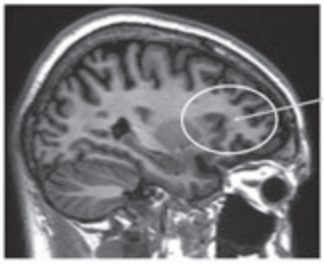
Cyngulate

Orbito-frontal cortex

The magnitude of prefrontal volume changes related to severity of the depression.

Bremner, et al. 2002; Coffey, et al. 1993.

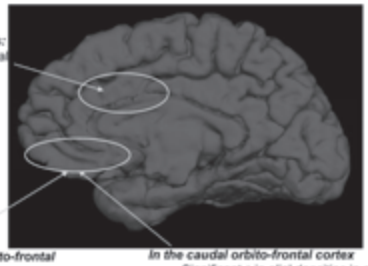
Structural changes in frontal lobe



- ↓ white matter volume
- ↑ number of white matter hyperintensities in frontal lobes' white matter seen on T2 weighted images

Neuropathological abnormalities in primary major depressive disorders

In cingulate gyrus:
- Significant ↓ in glia
- ↓neuronal size



In the rostral orbito-frontal region:
-↓Cortical thickness
-↓Neuronal sizes
-↓Neuronal densities in layers II, III, and IV

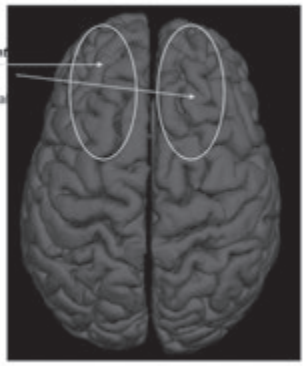
In the caudal orbito-frontal cortex
Significant ↓ in glial densities in cortical layers V and VI associated with decreases in neuronal sizes

Rajkowska, et al. Biol Psych 1999
Cotter et al. Arch Gen Psych, 2001
Lucassen et al. Am J Pathol, 2001
Bowley et al. Biol Psych 2001

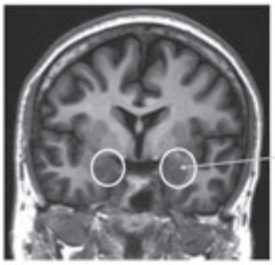
Neuropathological abnormalities in primary major depressive disorders

In the dorsolateral prefront cortex:

A ↓in neuronal and glia density and size in all cortical layers.



Neuropathological abnormalities in primary major depressive disorders



in amygdala
↓in glial cell density

Glutamate in Depression

↓ glial cells in:
prefrontal cortex
-subgenual
-cingulate
-dorsolateral

Toxic accumulation of extracellular glutamate

↑↑↑ cortisol

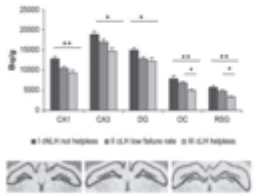
Hyperactive Hypothalamic Pituitary Adrenal Axis

↑extracellular glutamate in:
1) Prefrontal cortex
2) Nucleus accumbens
3) Hippocampus
4) Amygdala

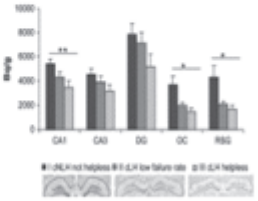
Rajkowska et al, Biol Psychiatry, 1999, 2001
Cotter et al, Arch Gen Psychiatry 2001

Reduced expression of glutamate transporters vGluT1, EAAT2 and EAAT4 in learned helpless rats, an animal model of depression
Zink et al, Neuropharmacology 2009

Semiquantitative *in situ*-hybridizations of vGluT1 and EAAT2 in three cohorts of rats. Helpless animals derived from the cLH strain (III) are compared to littermates with low failure rates (II) and not helpless animals of the cNLH-strain (I).



vGluT1



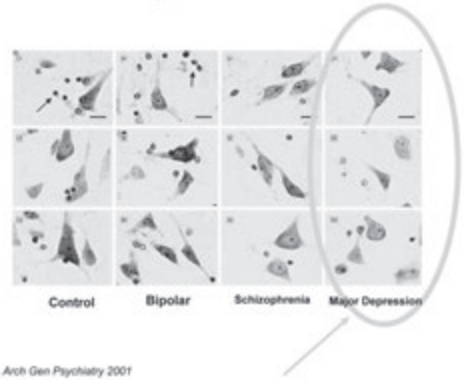
EAAT2

Antidepressant effect of Modulators of Neurotransmission: Animal Models

NMDA Antagonists	Forced swim test (rats, mice)	Tail suspension test (mice)	Chronic mild stress (rats)
MK-801	+	+	+
AP-7	+	-	
ACPC	+	+	+
CGP 37849	+		+
CGP 40116			+
CGP 39551	+		
Epirodil	+	-	
Memantine	+		

Trulas et al, Eur J Pharmacol, 1990; Del Rio & Frenchilla, 2005

Glia and neurons in layer 6 of the anterior cingulate cortex



Cotter et al, Arch Gen Psychiatry 2001

Increased cortical glutamate in depressed patients

Kugara & Sancora, CNS Spectrums 2005

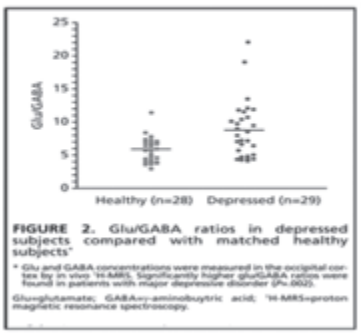


FIGURE 2. Glu/GABA ratios in depressed subjects compared with matched healthy subjects*

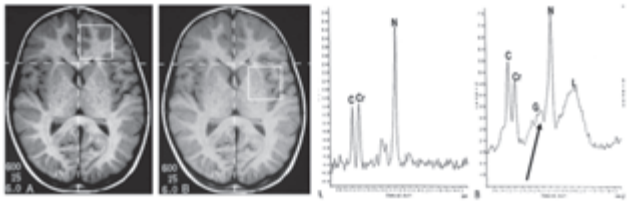
* Glu and GABA concentrations were measured in the occipital cortex by in vivo ^{1}H-MRS. Significantly higher glu/GABA ratios were found in patients with major depressive disorder ($P=.002$).

Glu=glutamate; GABA=γ-aminobutyric acid; ^{1}H-MRS=proton magnetic resonance spectroscopy.

Proton MR Spectroscopy in Children with Bipolar Affective Disorder: Preliminary Observations

Castillo et al, AJNR, 2000

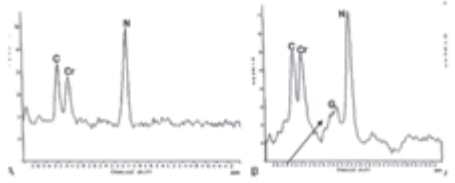
N = 10 children with Bipolar Affective Disorder (age 6 to 12)
N = 10 controls



A, Proton spectra from the left frontal lobe in a control subject show normal metabolites. *C*, choline; *Cr*, creatine; *N*, NAA.
B, Proton spectra from the left frontal lobe in a patient with BPAD show prominent resonances between 2.1 and 2.5 ppm, corresponding to Glu/Gln (*G*). The resonances between 0.8 and 1.8 ppm correspond to lipids (*L*). *C*, choline; *Cr*, creatine; *N*, NAA.

MR spectra from the temporal lobes.

Castillo et al, AJNR, 2000



A, Proton spectra from the left temporal lobe in a control subject show normal metabolites.
B, Proton spectra from the left temporal lobe in a patient with BPAD show prominent Glu/Gln (*G*) but no lipids. *C*, choline; *Cr*, creatine; *N*, NAA.

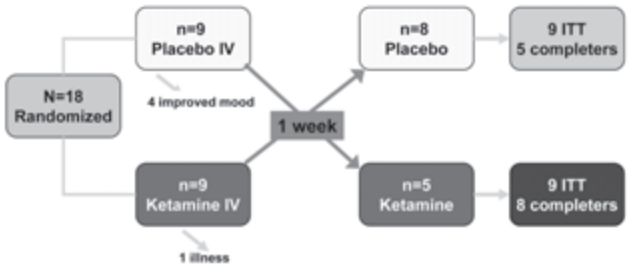
Brain Metabolic Alterations in Medication-Free Patients With Bipolar Disorder

Dager et al, Arch Gen Psychiatry, 2004

- N = 32 medication-free outpatients with BDI or BDII, predominantly in a depressed or mixed-mood state.
- N = 26 age- and sex-matched healthy controls.

➢ Patients with BD exhibited elevated gray matter glutamate, glutamine, and GABA (Glx) levels (P = .007).

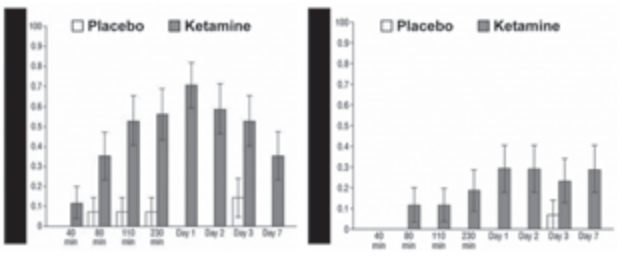
Double-blind placebo controlled study of (NMDA antagonist) in refractory Major Depressive Disorder



Infusions 1 week apart (ketamine 0.5 mg/kg)
Zarate. et al. Arch Gen Psychiatry 2006;63:856-864.

Ketamine (NMDA antagonist) effective in treatment-resistant depression

HAM-D responders (≥50% improvement) **HAM-D remitters (HAM-D ≤7)**



- **Crossover study of 18 patients**
- **Infusions 1 week apart (ketamine 0.5 mg/kg)**
- **Hamilton Depression (HAM-D) scale rated from 40 minutes to 7 days post-dose**

Zarate et al. Arch Gen Psychiatry. 2006;63(8):856-64.

Autoimmune Processes and Cytokines…

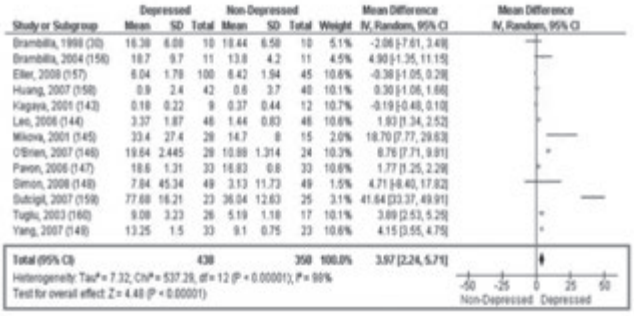
A meta-analysis of cytokines in Major Depressive Episode

- Major depression is accompanied by immune dysregulation and activation of the inflammatory response system
- 24 studies involving un-stimulated measurements of cytokines in patients meeting DSM criteria for major depression vs. controls included

Cytokine	# of studies	Depression vs. control
Tumor necrosis factor (TNF)-α	**13**	**P<0.001**
Interleukin (IL)-1β	**9**	**NS**
IL-6	**16**	**P<0.001**
IL-4	**5**	**NS**
IL-2	**5**	**NS**
IL-8	**4**	**NS**
IL-10	**6**	**NS**
Interferon (IFN)-γ	**4**	**NS**

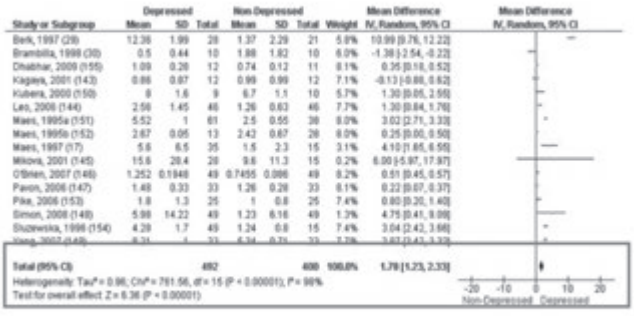
Dowlati et al. Biol Psychiatry. 2010;67(5):446-57.

Tumor necrosis factor-α.



Dowlati et al. Biol Psychiatry. 2010;67(5):446-57.

Interleukin-6



Dowlati et al. Biol Psychiatry. 2010;67(5):446-57.

GABA disturbances?

Decreased GABA in Bipolar Disorders

- Study of the GABA–synthesizing enzyme, glutamic acid decarboxylase (GAD) and its two isoforms, GAD65 and GAD67 in brains of bipolar patients.
- Decrease of the density of GAD65 and GAD67 mRNA–positive neurons by 45% and 43%, respectively in the hippocampus.
- Decrease of the density of the GAD65 in the cingulate and prefrontal cortices.

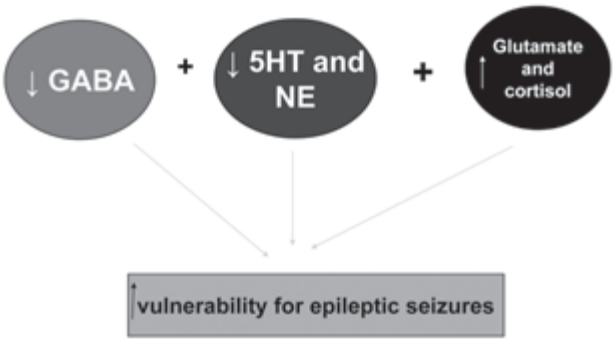
Heckers et al., 2002

Decreased GABA in Major Depression

- Normalization of GABA concentrations with the SSRI citalopram.

Sanacora et al., 2002

The perfect storm?



Hypothesis: cause of pharmacoresistant epilepsy to AEDs

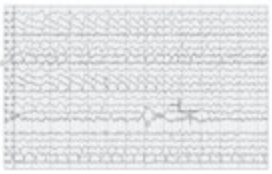
Bidirectional Relationship Between Epilepsy and ADHD ?

Authors	Type of Study	Psychiatric History Preceding the Onset of Epilepsy/Controls
Hersdorffer et al, 2004	Population-based (All children between 3 and 16 years old)	3.7 times the history of ADD, Inattentive type

Photo-Metrazol test in ADHD

Laufer MW et al, J Pediatr, 1957

- n = 32 with ADHD
- n = 18 controls
- Photo-Metrazol test
- Induced threshold dose: ≤ 5 mg/kg (abnormal)



Groups	N	+	%
Hyperkinetic	32	19	59%
Non-hyperkinetic	18	1	5%

Dual effect of Dopamine on Cortical Excitability

Starr et al, Science 1996

Anticonvulsant action of hippocampal dopamine and serotonin is independently mediated by D and 5-HT receptors.

Clinckers et al, J Neurochem. 2004.

- The anticonvulsant effects of intra-hippocampally applied DA concentrations were evaluated against pilocarpine-induced seizures in conscious rats.
- DA perfusions protected the rats from limbic seizures as long as extracellular DA concentrations ranged between 70-400% increases compared with the baseline levels.

Anticonvulsant action of hippocampal dopamine and serotonin is independently mediated by D and 5-HT receptors.

Clinckers et al, J Neurochem. 2004.

- Co-perfusion with the selective D(2) blocker remoxipride abolished all anticonvulsant effects.
- High extracellular DA (> 1000% increases) concentrations worsened seizure outcome.
- The pro-convulsive effects of high DA concentrations were associated *with significant increases in extracellular glutamate.*

Molecular Genetics of ADHD

- Studies of children with ADHD show abnormalities in:
  - D4 dopamine receptor gene on chromosome 11
    - DRD4 7-repeat allele implicated in novelty seeking
    - Location of most D4 receptors - frontal lobes

- **D4 receptors function as an inhibitory modulator of glutamate activity in the frontal cortex.**
- **The DRD4 allele that codes for subsensitive D4 receptors (i.e., the 7R allele) may increase the seizure threshold.**

Faraone et al., 2000

Dopamine D4 receptor-deficient mice display cortical hyperexcitability

Rubinstein et al, J Neurosci 2001

Evaluation of the role of DA in the initiation of motor activity and the integration of goal directed behaviors

Wildtype **D4 knockout**

1) ↑ excitability in frontal cortex.
2) + Bicuculline ⟶ seizures.
3) Lower immunolabaling of glutamate in frontal cortex pyramidal neurons.

Conclusions

- **Depression and epilepsy share common pathogenic mechanisms involving several neurotransmitters.**
- **These common pathogenic mechanisms may explain the bidirectional relation between the two conditions.**

…SO…

- *… if there is a bidirectional relation between depression and epilepsy…*

- *…can neurologists and psychiatrists please establish a bidirectional relation?*

Fast Oscillations, GABA Synchronization and Epileptiform Discharges -
Massimo Avoli (Canada, Italy)

Fast Oscillations, GABA Synchronization and Epileptiform Discharges

Massimo Avoli, MD, PhD

Montreal Neurological Institute, McGill University, Montreal, Que., Canada &
Sapienza Università di Roma, Rome, Italy

EEG oscillations from the 1930s to our times

Oscillations are known to be a basic feature of brain function since the discovery of the EEG in the 1930s by Berger, Jasper (Fig. 1A), Gibbs, etc...

These pioneer studies have shown alpha waves in normal individuals (Fig. 1B) and epileptiform spike-wave in epileptic patients (Fig. 1C).

See specific refs in bibliography #1.

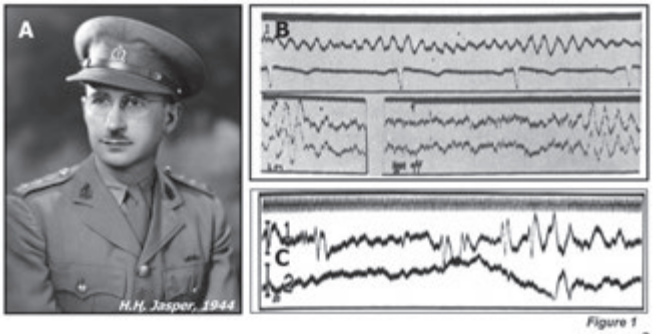


Figure 1

2

Studies performed in the 1990s have established that faster EEG oscillations in the beta-gamma (20 – 80 Hz) range and in higher frequency ranges (> 80 Hz, also termed *ripples*) can be recorded from normal individuals and from behaving rodents (Fig. 2).

Evidence indicates that these high frequency oscillations (HFOs) are implicated in higher brain processes such as attention, sensorimotor integration, consciousness, learning and memory.

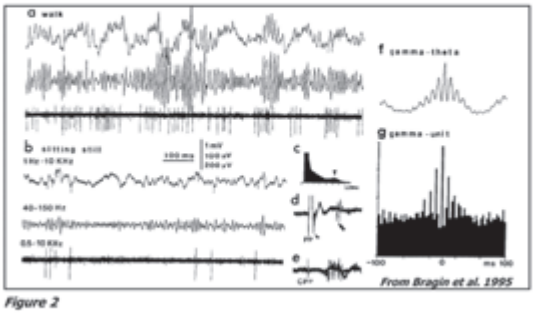


Figure 2

Therefore, it has been suggested that these oscillatory rhythms represent the basic neuronal processing state of the brain. See specific refs in bibliography #2

3

Gamma oscillations are supported by GABAergic synchronization

Cortical inhibitory networks have been proposed to play a critical role in the generation of faster activities that include oscillations in the low (i.e, beta-gamma oscillations at 20-80 Hz) and high frequency range (> 80 Hz, so called *ripples*) *in vivo* (see specific refs in bibliography #2).

Fast oscillations have also been reproduced in limbic and extra-limbic structures maintained *in vitro*. Experimental procedures capable of inducing fast oscillations include electrical tetanic stimulation, as well as application of the muscarinic agonist carbachol, high-K^+ solutions, kainic acid, or metabotropic glutamate receptor agonists

As shown in Fig. 3, findings obtained by several groups of investigators support the view that these oscillatory activities reflect the synchronization of inhibitory GABAergic networks with or without the contribution of excitatory ionotropic glutamatergic transmission.

Indeed, networks of fast-spiking interneurons co-expressing GABA and parvalbumine have been shown to promote synchronization via perisomatic interneuron-interneuron interaction in the hippocampus, in the entorhinal cortex, and in the neocortex. In addition, non-synaptic interactions through gap junctions may represent an additional mechanism for interneurons synchronization during gamma oscillations.

Hence, different populations of interconnected interneurons as well as their connections to principal (glutamatergic) cells may play a key role in gamma synchronization. See specific refs in bibliography #3.

4

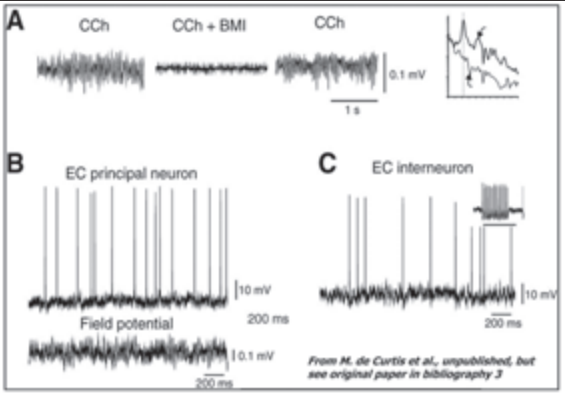


Figure 3 - Carbachol-induced gamma oscillations in the entorhinal cortex of the isolated guinea pig brain preparation. A. Field recordings demonstrate that the oscillations are blocked by bicuculline. B and C Intracellular recordings performed in a principal neuron (stellate cell in B) and a putative interneuron (in C) during these oscillations. The simultaneous field recording is shown in B. In C, typical fast firing of interneurons is shown in the inset.

5

GABA is an inhibitory neurotransmitter but also as a synchronizing factor

The amino acid GABA, originally identified as *factor I* by Florey and MacLennan in 1955, is the main inhibitory neurotransmitter in the adult forebrain.

GABA, once released from interneuron terminals, activates pre- and postsynaptic GABA receptors. GABA receptors are divided into ionotropic (type A) and metabotropic (type B) receptors, type C receptors being practically confined to the retina in the adult central nervous system.

$GABA_A$ receptor activation opens channels permeable to Cl^- and to a lesser extent to HCO_3^-. With a reversal potential that is negative to or around the resting potential, GABA release induces a post-synaptic potential that is fast and inhibitory (fast IPSP), tending to Hyperpolarize post-synaptic cells, Thus suppressing action potential firing as shown in Fig. 4.

See specific refs in bibliography #4

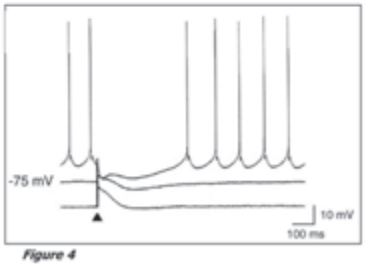


Figure 4

6

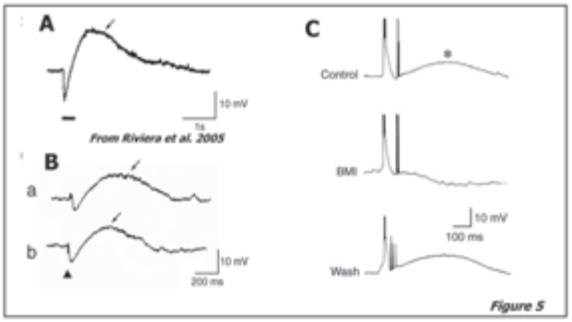


Figure 5 - GABA$_A$ receptor-mediated depolarizations in principal cells of the limbic system. Note in A and B that an early hyperpolarization followed by a long-lasting depolarization (arrows) are recorded both following brief trains of extracellular stimuli (A) or when brain slices are superfused with medium containing the K$^+$channel blocker 4-aminopyridine (4AP) (B); in both experiments glutamatergic transmission was abolished with specific receptor antagonists. In C, the long-lasting depolarization is blocked by local application of the GABA$_A$ receptor antagonist bicuculline methiodide (BMI) to the CA1 stratum radiatum. See specific refs in bibliography #4

7

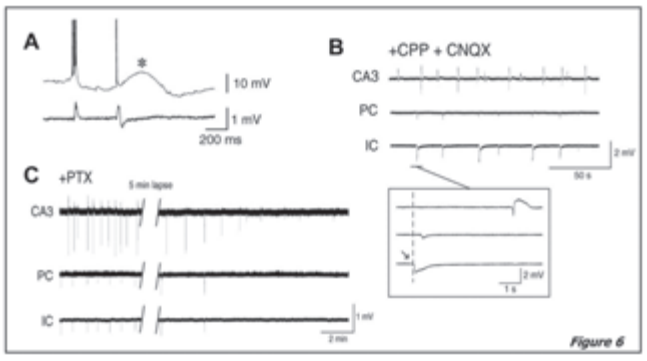


Figure 6 - GABA$_A$ receptor-mediated depolarizations are mirrored by slow field oscillations (also defined as interictal discharges) that persist during blockade of glutamatergic transmission. A: Intracellular slow and field recordings from a hippocampal slice during 4AP application. B & C: Simultaneous field recordings from hippocampus (CA3), perirhinal (PC) and insular cortices (IC) during 4AP+ glutamatergic antagonists (CPP+CNQX) and after addition of the GABA$_A$ receptor antagonist picrotoxin (PTX); note that slow, glutamatergic independent interictal discharges persist in B but disappear following GABA$_A$ receptor antagonism in C. See specific refs in bibliography #4.

8

GABA$_A$ receptor-mediated mechanisms support and presumably initiate prolonged epileptiform synchrony (i.e., seizure-like discharges)

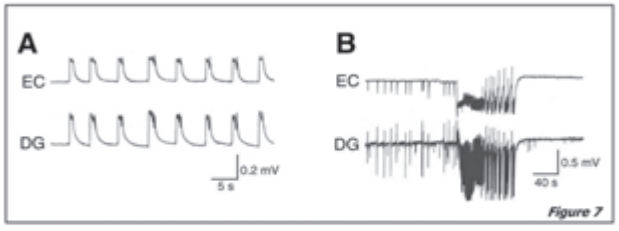


Figure 7 - Seizure-like discharges are not observed *in vitro* during GABA$_A$ receptor antagonism. A and B panels illustrate the synchronous field discharges recorded in an *in vitro* brain slice preparation from the entorhinal cortex (EC) and the dentate gyrus (DG) during application of the GABA$_A$ receptor antagonist picrotoxin (50 μM) (A) or 4AP (50 μM) (B). Note that only short-lasting interictal discharges occur in the presence of picrotoxin while during 4AP both interictal and istal events are generated.

9

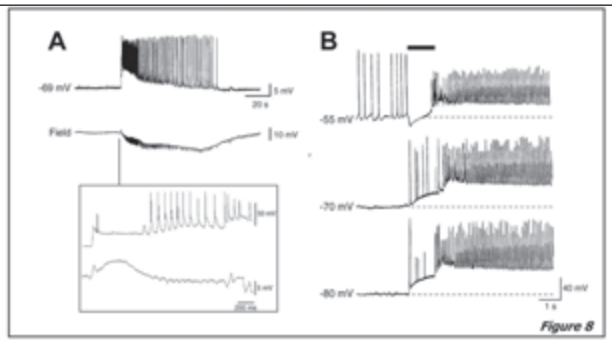


Figure 8

Figure 8 **- Intracellular characteristics of ictal-like discharges induced by 4AP in rodent brain slices. A: Ictal event recorded from an amygdala neuron; note in the expanded trace that the discharge onset consists of a slow depolarization. B: Changes induced by intracellular injection of steady current in a rat entorhinal cortex neuron; note that when the neuron is depolarized (-55 mV trace) the amplitude of the sustained ictal depolarization decreases while the initial slow depolarization becomes hyperpolarizing as compared with the recording obtained at resting membrane potential (-70 mV). The time occupied by this initial hyperpolarization is indicated by the continuous line on the top. Note also that during steady hyperpolarization (-80 mV trace) both initial and sustained depolarizations increase in amplitude.**

10

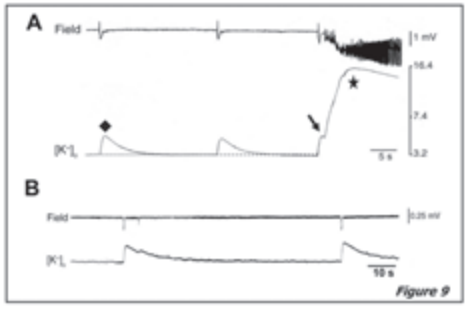


Figure 9

Figure 9 **- A: Field and $[K^+]_o$ recordings obtained from a rat entorhinal cortex slice during bath application of. Note that distinctive, transient increases in $[K^+]_o$ (up to around 4.5 mM) are associated with the slow interictal discharges (diamond) and appear to precede the ictal discharge onset (arrow); note also that during the sustained ictal event these increases in $[K^+]_o$ reach values in excess of 12 mM. B: Phamcologically isolated GABA-mediated potentials continue to be associated with transient increases in $[K^+]_o$.**

11

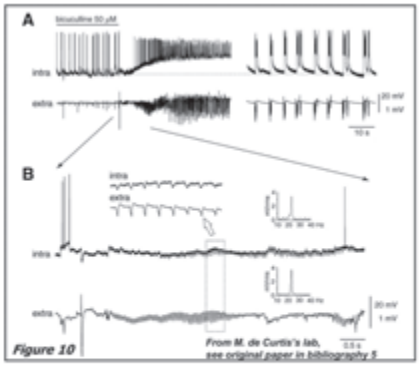


Figure 10

From M. de Curtis's lab, see original paper in bibliography 5

Figure 10 **- Further evidence for the participation of GABA transmission in seizure-like activity induced in the isolated guinea pig brain by a brief arterial perfusion of bicuculline. This procedure induced both interictal and ictal discharges that were recorded in this experiment from the entorhinal cortex. Note in the enlarged panel in B that seizure onset is characterized by fast activity at 20-30 Hz that consist of IPSPs in coincidence with field oscillations. See specific refs in bibliography #5.**

12

High frequency oscillations (HFOs) and epileptic disorders

HFOs are believed to play important roles in pathologic brain function as well. In particular, growing evidence indicates that HFOs at 250-600 Hz also termed *fast ripples* occur in the epileptic tissue only. However, it is yet to be established whether oscillation frequency alone distinguishes normal from pathological HFOs. Accordingly, there is considerable overlap in spectral frequency between normal and epileptogenic oscillatory

HFOs are mainly related to interictal spikes and are state-dependent since they occur more frequently during slow-wave sleep. Higher HFO rates are significantly correlated with higher seizure frequency in epileptic patients, and appear to be more specific markers than interictal spikes in identifying the seizure onset zone, independently of the underlying pathology.

Fast ripples are thought to reflect pathological activity and seizure onset zones in several epileptic disorders including temporal lobe epilepsy as well as in animal models such as the pilocarpine rodent model. The spatial distribution of HFOs in the epileptogenic zone depends on the type of epileptic discharge, as widespread interictal spikes propagating across multiple cortical regions are often related to HFOs that can be recorded on multiple channels

Unlike ripples, *fast ripples* are thought to be independent from inhibitory transmission and to reflect the synchronous activity of principal neurons (see Fig. 11).

See specific refs in bibliography #6.

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Figure 11 - Activity recorded *in vivo* from the dentate gyrus in a pilocarpine-treated epileptic mouse. A: Example of two single population spikes (diamonds) and HFOs (bracket). (A1) Raw data recorded with 0.1–5.0 kHz frequency band. (A2) The same data filtered with frequency band 200–500 Hz. (A3) Discharges of the granular cell (labeled in B) recorded by a glass microelectrode with the tip located 200 µm from the tungsten microelectrode, which recorded the field potentials in A1. (A4) Color-coded power spectrogram of the HFOs. B: The recorded granular cell labeled by neurobiotin at the end of the experiment. C: Evoked field potential in response to perforant path stimulation. Note that the population EPSP onset (arrow) is followed by two population spikes (diamonds). D: Perievent histogram of the granular cell discharges during 232 spontaneous population spikes (red).

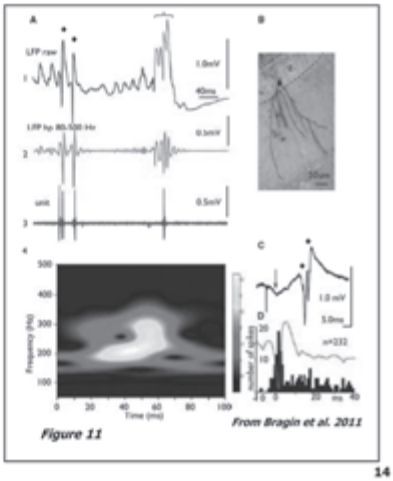

Figure 11

From Bragin et al. 2011

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HFOs (ripples and fast ripples) and pilocarpine-induced epileptogenesis

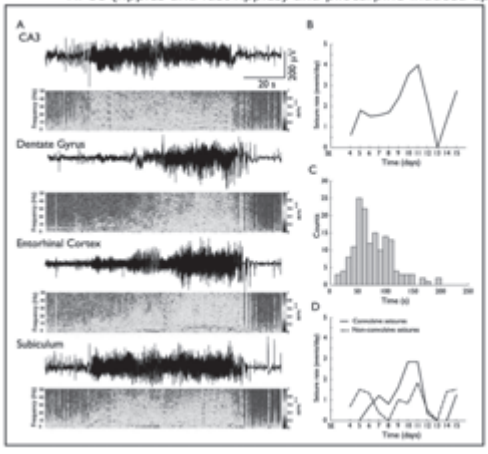
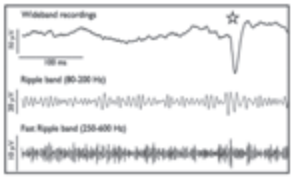


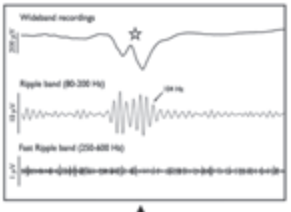
Figure 12 - In this and following figures data derive from pilocarpine-treated epileptic rats A. Representative seizure recorded from multiple sites. B. Average seizure rate. For all rats (n= 7) across the entire recording period (4 to 15 days after SE); note that seizures occur in clusters, with higher rates between days 9 and 12 after SE. C. Distribution histogram of seizure duration. D. Average rate of occurrence of convulsive and non-convulsive seizures.

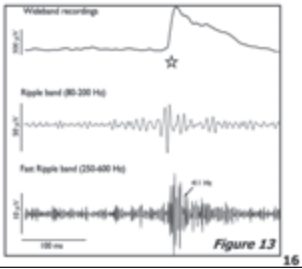
15

Do interictal spikes (associated or not with either ripples or fast ripples) correlate with seizures in pilocarpine-induced epileptogenesis?

Local field potentials from pilocarpine-treated epileptic rats (in all three panels, recordings were obtained from the entorhinal cortex) demonstrate that interictal spikes (stars) can occur without concomitant HFOs







In association with ripples (80-200 Hz)

Or with fast-ripples (250-600 Hz)

Figure 13

16

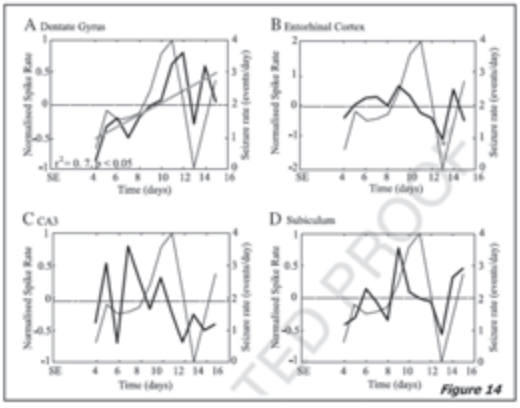


Figure 14

Figure 14 **- A to D panels shown the average rates of interictal spikes without HFOs. Note that the DG was the only region to show a significant increase of spike rates over time (blue line). A significant decrease of interictal spike rates was observed in the EC (B) on the 13th day (*).**

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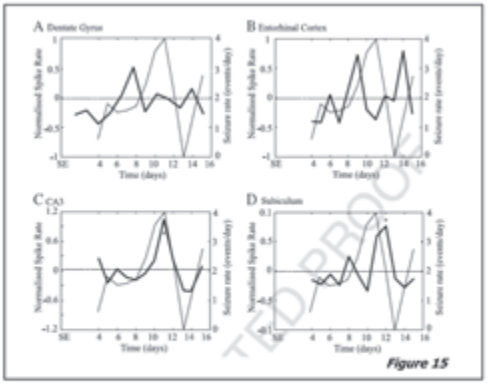

Figure 15

Figure 15 **- A to D panels shown the average rates of interictal spikes that co-occurred with fast ripples. A significant increase of interictal spike rates was observed on the 11th day in CA3 (C) and on the 12th day in the subiculum (D). Moreover, interictal spikes co-occurring with ripples did not show any specific relation to seizure occurrence (not shown).**

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Cognitive aspects of benign focal epilepsies of childhood

Roberto Caraballo (Argentina)

Neural circuits of photosensitivity
Patricia Braga (Uruguay)

Circuitos Neurales de la Fotosensibilidad

Dra. Patricia Braga
LASSE V- 2011

Future needs :
Photosensitivity, visually sensitive seizures and epilepsies
Dorothée G.A. Kasteleijn-Nolst Trenité Epilepsy Research 70S (2006)

I. Large-scale multinational epidemiological studies in the general population
-incidence and prevalence of FS, sensitivity and specificity of photic, pattern and TV stimulation in the laboratory, impact of longer duration of stimulation, occurrence of a PPR in non-affected persons and to follow-up

II. Epidemiological studies in neurological and epilepsy patients in general:
-distribution among epilepsy syndromes and ethnic groups, compare follow-up

III. Epidemiological studies in visually sensitive patients:
-prognosis, pure FS epilepsy, video game seizures; value of asymmetric findings; visual priming; role of sex.

IV. Double-blind placebo-controlled trials to determine the efficacy of all AEDs and non-drug preventive measures in visual sensitive patients.

V. Imaging, functional and genetic studies to unravel the pathophysiology.
- fMRI studies and MEG studies, genetic studies

P.Braga - LASSE V - 2011

Importancia y abordaje del tema

1. Comprensión del funcionamiento cerebral
   A. CODIFICACIÓN EN LA VÍA VISUAL
   B. CODIFICACIÓN EN LA INTEGRACIÓN SENSORIAL
2. Posibilidades de modulación exógena
3. Modelo de estudio de ictogénesis

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1.A Comprensión del funcionamiento cerebral: codificación en la vía visual

- **FOTOSENSIBILIDAD: respuesta anormal del EEG a luz o patrones de estimulación, consistente en una RFP.**
- **Con o sin manifestación clínica: crisis**
- **Rango de frecuencias**

Frecuencia temporal de estimulación visual

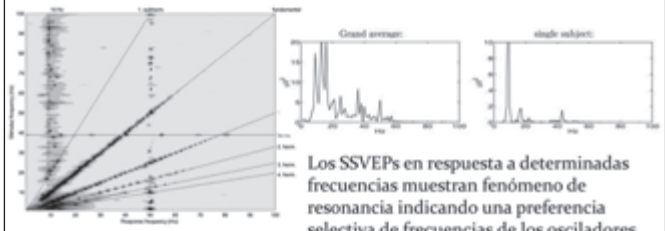
	Método de estudio	Estimulación fótica	Medida de efecto	Respuesta
Fox et al, 1984	**PET**	**Frecuencia** (1-60 Hz)	Pico FSCr en córtex occipital mesial	Respuesta máxima entre **7.8 y 15.5 Hz**
Herrmann et al, 2001	**EEG**	Frecuencia (1-100 Hz)	Frecuencias evocadas preferidas	Respuesta a frecuencia igual a estim. y subarmónicas
	SS-VEP		Fenómeno de resonancia en osciladores neurales	**10, 20, 40 y 80 Hz**
Singh et al, 2003 Emir et al, 2008	**BOLD-fMRI + EEG** **BOLD-fMRI**	Frecuencia (2-12Hz) (1-44Hz)	Cambio BOLD en córtex occipital	Pico de respuesta a **8 Hz** (y armónicos)

Stimulus rate dependence of regional cerebral blood flow in human striate cortex demonstrated by positron emission tomography.
Fox PT, 1984.

- Objetivo : determinar la relación entre el índice de repetición de un estímulo visual simple y el FSCr en el cerebro humano (voluntarios sanos).
- Entre 0 y 61Hz, el **FSCr en el córtex estriado varió como función de la frecuencia temporal** del estímulo fótico, formando una curva de respuesta unimodal con un **máximo entre 7.8 y 15.5 Hz**.
- La localización anatómica de la región con pico de respuesta vascular fueron los lóbulos occipitales a nivel mesial, a lo largo de la cisura calcarina (córtex visual primario) para todos los sujetos estudiados
- Ninguna otra área cerebral mostró un cambio consistente.

Human EEG responses to 1-100Hz flicker - Herrmann C. 2001

- Estudio en 10 individuos sanos.
- Muestra **frecuencias evocadas preferidas frente a distintas frecuencias de estimulación fótica.**



El sistema responde sobre todo con frecuencia igual a la de la estimulación y con frecuencias subarmónicas a la estimulación.

Los SSVEPs en respuesta a determinadas frecuencias muestran fenómeno de resonancia indicando una preferencia selectiva de frecuencias de los osciladores neurales. **Fenómenos de resonancia ocurrieron a frecuencias de 10, 20, 40 y 80 Hz.**

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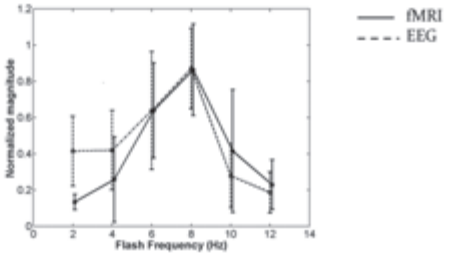
Correlation Between BOLD-fMRI and EEG Signal Changes in Response to Visual Stimulus Frequency in Humans - Singh M - 2003



- Estudio en 8 sujetos sanos con estimulación flash 2-12 Hz.
- **Ambas modalidades muestran un cambio de señal similar con la frecuencia de estimulación, con un pico en ambos casos a 8Hz.**
- Picos a similar frecuencia se encontraron en estudios con PET y fMRI BOLD, para paradigma con damero.

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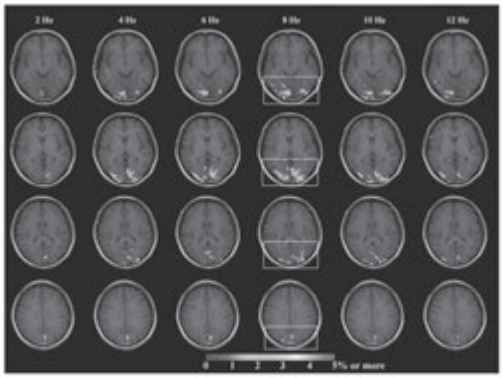

Cambio en el nivel de señal BOLD con la frecuencia de estimulación, con un pico de respuesta a 8Hz, en un individuo.

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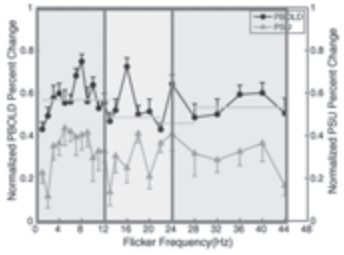
Changes in BOLD transients with visual stimuli across 1–44Hz
Uzay E. Emir – 2008

- fMRI en cada ELI a diferentes frecuencias de 1 a 44Hz, en sujetos sanos
- El **pico global para la respuesta BOLD fue a 8Hz**, con picos secundarios a 16 y 24 Hz, y un pico más amplio de 36-40Hz.
- 3 **bandas de diferentes perfiles de respuesta** según correlaciones entre positive BOLD signal and post-stimulus undershoot (PSU).
- el aumento en la actividad excitatoria amplifica tanto PBOLD como PSU
- el aumento en la actividad inhibitoria evoca un descenso en la señal PBOLD sin alterar PSU



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Esta activación de la corteza occipital diferencial a distintas frecuencias de estimulación:

- ¿es característico del cerebro humano normal, sin patología...o al menos sin epilepsia?
- ¿está presente-ausente-alterada en pacientes fotosensibles?

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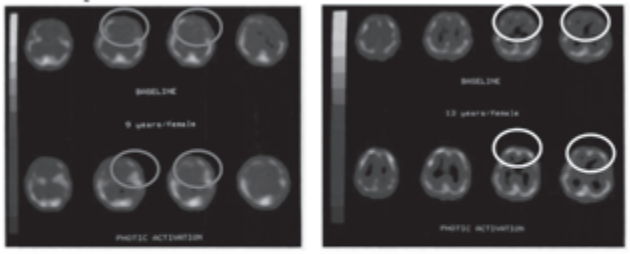
Brain SPECT evaluation of patients with pure photosensitive epilepsy – L.O. Kapucu 1996



SPECT INTERICTAL vs ICTAL (crisis inducidas porTV)
SPECT INTERICTAL: HIPOPERFUSIÓN FRONTAL en 6/7 pacientes + 1 normal
SPECT ICTAL: HIPERPERFUSIÓN FRONTAL en 7/7
Patrón de alteraciones del FSCr FRONTAL relativamente consistente, sugiriendo que los lóbulos frontales están involucrados en las crisis asociadas a FS en estos pacientes.

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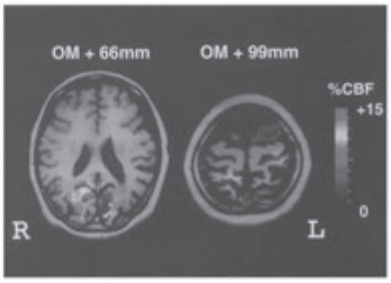
Central pathway of photic reflex myoclonus. Kanouchi T et al. 1997

H2o-PET co-registro con MRI (1Hz flash vs reposo) en un paciente con mioclonus fótico reflejo del MSD (sin clínica durante PET)

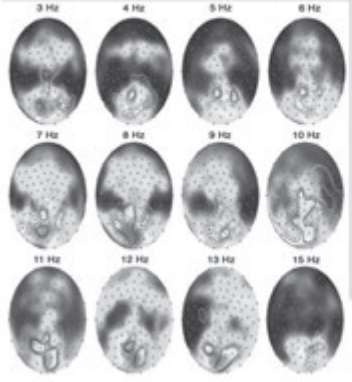


- Datos anatómicos en primates muestran que proyecciones del área visual terminan en el área premotora y precentral.

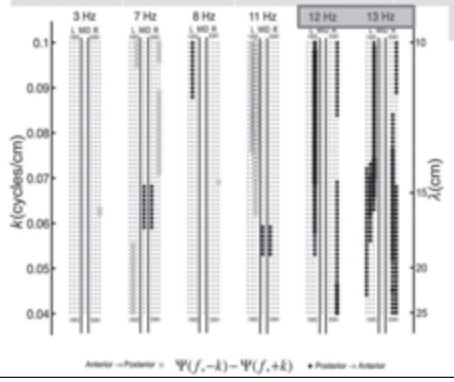
Esta activación selectiva de regiones frontales en relación con la estimulación visual "epileptogénica":

- ¿es específica de los individuos fotosensibles?
- ¿es el posible sustrato de la respuesta anormal a este estímulo?

	Método de estudio	Estimulación fótica	Medida de efecto	Respuesta
Srinivasan R et al. 2006	SSVEPs 110 electrodos	patrones de puntos al azar a frecuencias 3-30 Hz	Distribución SSVEP	-en bandas α baja y Δ se observan respuestas frontales bilaterales -a frecuencias de 12-13 Hz se evidencia sólo en electrodo frontal derecho -los canales occipitales muestran SSVEP robustos a todas las frecuencias de estimulación inferiores a 20Hz

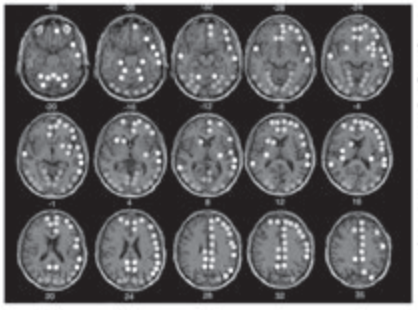


	Método de estudio	Estimulación fótica	Medida de efecto	Respuesta
Srinivasan R et al. 2006	SSVEPs 110 electrodos	patrones de puntos al azar a frecuencias 3-30 Hz.	Dinámica de SSVEP	12-13Hz: ondas propagándose de electrodos occipitales a pre-frontales



- ✓SSVEPs son sensibles a la frecuencia de estimulación
- ✓cambios en 1Hz pueden modular la respuesta en los canales frontales

	Método de estudio	Estimulación fótica	Medida de efecto	Respuesta
Mentis et al, 1997	PET $H_2{}^{15}O$	Estímulo monocular alternante con frecuencias de 1,4,7,14Hz	FSCr : magnitud y distribución	Pico 7 Hz en córtex estriado Pico 4 Hz en cíngulo ant izq



- Respuestas bifásicas: Aumento en el córtex estriado hasta un pico en 7Hz
  Aumento en cíngulo anterior izquierdo (pico 4 Hz)
- Respuetas monotónicas:
  - Aumento en áreas posteriores
  - Descenso en áreas anteriores y cíngulo derecho

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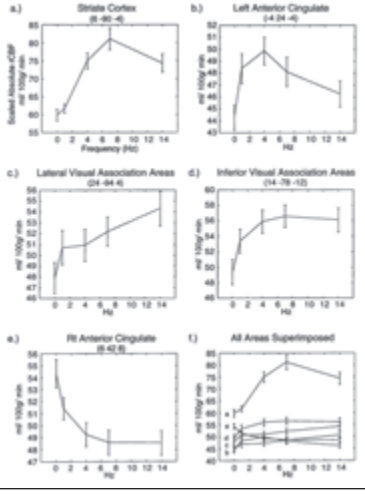
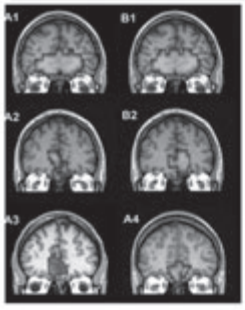


Frequency Variation of a Pattern-Flash Visual Stimulus during PET
Differentially Activates Brain from Striate through Frontal Cortex. M. J. Mentis - 1997

P.Braga - LASSE V - 2011

	Método de estudio	Estimulación fótica	Medida de efecto	Respuesta
Srinivasan R - 2007	fMRI	Damero reversible con frecuencia 3-14Hz	Patrones de activación	cluster: corteza frontal mesial, activación preferencial en el rango 3.5-5Hz



Los resultados de estos estudios apoyan la hipótesis de que la conectividad del cerebro humano es frecuencia-dependiente.

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Estímulo visual: otros factores

- el estímulo luminoso no es un evento único de características estáticas, homogéneas, sino que es un fenómeno que incluye numerosas variables, además de la frecuencia temporal de estimulación
- un individuo puede ser "fotosensible" a determinadas características del estímulo y no a otras
- sensibilidad del examen estandarizado de la fotosensibilidad

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- **Simples** (destello): intensidad, color-longitud de onda-, duración, distancia de la fuente
- **Más complejos**: patrones de repetición regulares o irregulares, frecuencia temporal, frecuencia espacial; homogéneos o heterogéneos en sus distintas cualidades simples y en diferentes combinaciones
- Conceptos vinculados a la percepción visual como el **contexto** visuo-espacial, la uni o plurimodalidad del estímulo, la atención, el reconocimiento o la novedad del mismo, entre otros.

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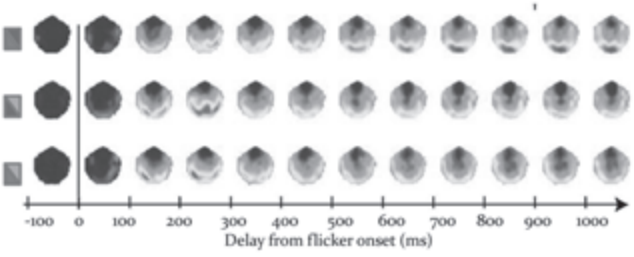
Estímulo visual complejo: video-juegos

- Pacientes sensibles a patrones pero no a la ELI
- Video-juegos: factores dependientes del hardware (frecuencia scan) o del software (color, contraste, luminancia, patrones geométricos).
- Mayor seguridad con frecuencias de scan de 100Hz en la pantalla de TV en comparación con frecuencias más bajas.
- Potencial del estímulo cromático combinado
- Pokemon – secuencia con pantallas flash alternativamente en rojo y azul, cambiando a 12.5/seg por aprox. 4seg.
- Factores adicionales: estrés, atención, toma de decisiones

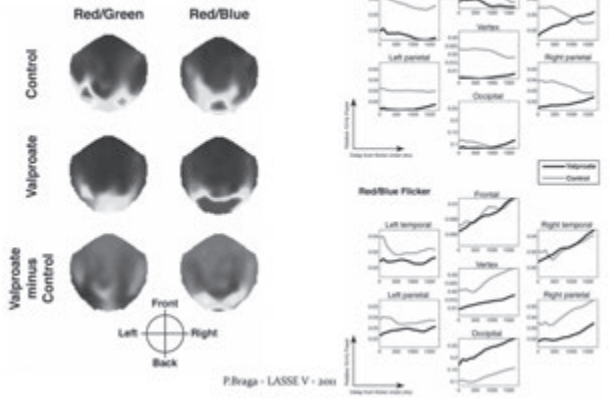
Procesamiento cromático

Watanabe K – 2002

- sujetos sanos- evaluación de respuesta MEG a flickers cromáticos a 10 Hz.
- Activación parieto-occipital bilateral precoz, y en polo occipital más tardía
- La correlación negativa lleva al planteo de que **la actividad PO temprana directa o indirectamente podría suprimir el desarrollo de la actividad tardía en el córtex visual (mecanismo defensivo).**

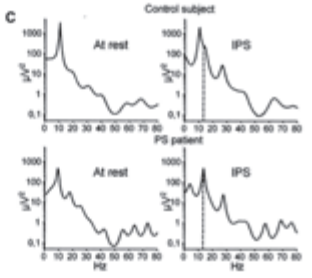


Effect of Sodium Valproate on Neuromagnetic Responses to Chromatic Flicker: Implication for Photosensitivity. Watanabe K et al, 2004.



Photosensitive epilepsy: spectral and coherence analysis of EEG using 14 Hz intermittent photic stimulation.
E Visani et al, 2010

Fig 1.
- Pico alfa occipital en reposo
- En IPS:
  - Pico en frecuencia alfa conservado en controles
  - Picos prominentes a 14 Hz y armónicos en pacientes
- Actividad alfa dominante como protector de sincronía gamma y PPR



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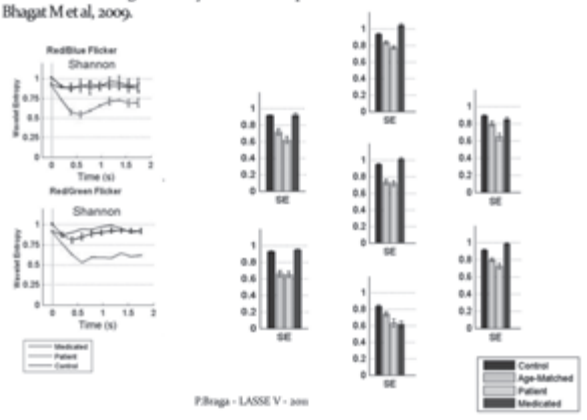
Investigating Neuromagnetic Brain Responses against Chromatic Flickering Stimuli by Wavelet Entropies
Bhagat M et al, 2009.



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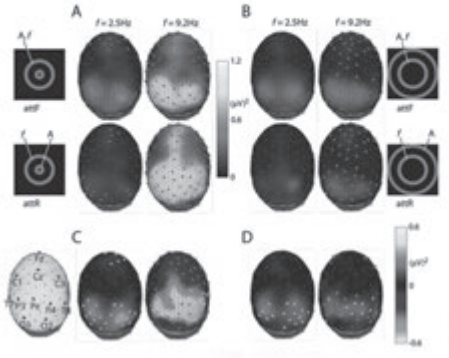
Frecuencia temporal y atención

- El poder de los PEV-SS aumenta con la atención en el estímulo intermitente
- Frecuencias de estimulación específicas (9.2Hz) modulan el poder y la distribución de la respuesta evocada: **selección de otras vías de activación**

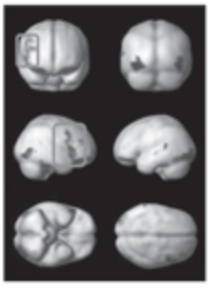


Jian Ding et al, 2006

Regularidad temporal del estímulo visual

- **Zeki S et al- 2008 - Objetivo:** evaluar si el cerebro tiene sistemas para registrar secuencias de estímulos visuales en términos de su relación temporal de regularidad e irregularidad.

Letters
Luminance
Numbers
Colour



- confluencia de regiones selectivas para la irregularidad de diferentes sub-modalidades visuales, en corteza pre-frontal dorso-lateral.

El efecto principal de la percepción de un patrón irregular fue la activación de una región en el córtex frontal dorso-lateral.

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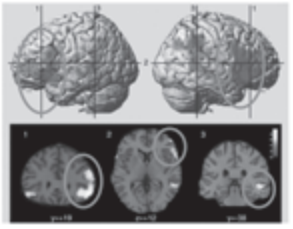
- **Similar topografía a la región frontal dorso-lateral que se activa con irregularidades de estímulo auditivo**
- secuencias musicales inesperadas , que violan la sintaxis musical, evocan una respuesta eléctrica cerebral: ERAN
- ERAN sería similar a ELAN - respuesta evocada por alteración de la sintaxis del lenguaje.
- Formarían parte de un sistema peri-silviano de información procesando las irregularidades del input auditivo.



MEG localiza principal generador neural de ERAN en córtex frontal lateral-inferior (pars opercularis inferior).

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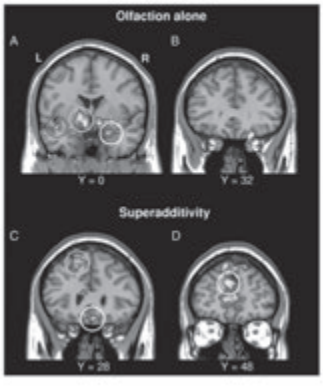
1.B Comprensión del funcionamiento cerebral: integración multisensorial

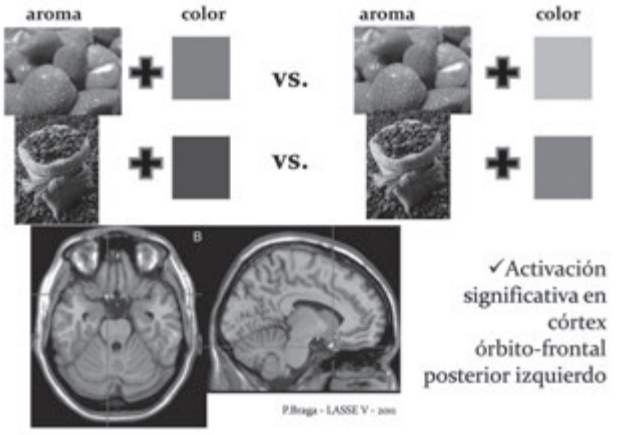
Color of Scents: Chromatic Stimuli Modulate Odor Responses in the Human Brain - O´sterbauerR, 2005.

1. Estímulo olfatorio
(A)Respuesta bilateral en córtex piriforme, amígdala, estriado ventral, ínsula izquierda, y (B) órbito-frontal derecho.

2. Estímulo olfatorio y visual simultáneos
(C) Respuesta aditiva en córtex órbito-frontal medial derecho, SFG y (D) cíngulo anterior.



✓ Concordancia del estímulo olfatorio y visual



✓Activación significativa en córtex órbito-frontal posterior izquierdo

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Codificación neurofisiológica en la integración multisensorial

- En experimentación animal se vio que descargas de puntas en frecuencia gamma 30-80 Hz, s/t aprox. 40Hz, se asocian a las funciones de fusión de información referente a características individuales de un estímulo complejo, o sincronización de información procesada por diferentes grupos neuronales específicos para una información contextual o global (Gestalt).
- Experimentos en humanos mostraron que oscilaciones gamma inducidas están presentes en el EEG cuando dos partes de una barra en movimiento se perciben como un objeto coherente.

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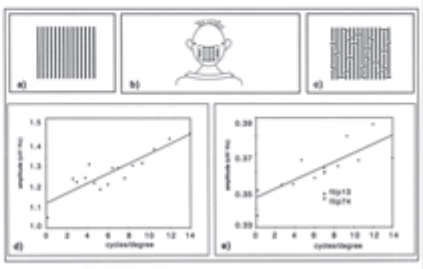
Different frequencies for different scales of cortical integration: from local gamma to long range alpha-theta synchronization. Von Stein A et al-2000.

- Análisis espectral del EEG frente a estímulos visuales de frecuencia creciente. Estudio de coherencia.
- Aumento de la amplitud del componente gamma en el EEG lineal con el aumento de barras en el estímulo visual.
- El poder gamma disminuyó frente al estímulo de igual frecuencia con elementos "incoherentes".
- Estos resultados sugieren que la sincronización cortical en el rango de frecuencias gamma puede ser medida en el EEG en humanos y refleja un criterio Gestáltico de coherencia visual.

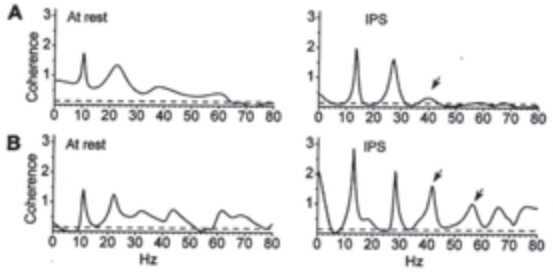


Fotosensibilidad y banda gamma

- pacientes con **epilepsia fotosensible idiopática** evaluados con **MEG** durante ELI a 10, 15 y 20 Hz, en comparación con controles.
- **Aumento del poder en la banda gamma (30-120Hz) en períodos previos a una ELI con RFP vs períodos previos a ELI sin RFP**
- **distribución espacial-**
  - ELI sin RFP - mayores valores en regiones occipitales.
  - **ELI con RFP - valores mayores más allá de las regiones occipitales**, distribuidas sobre todo en las regiones parietales, centrales y temporales.
- **tipo de crisis -**
  - paciente con **mioclonias**: aumento esp. **frontal y central**
  - paciente con **ausencias**: aumento dominante en sensores **parietales**
  - ➢ **La dinámica de la actividad en frecuencias gamma puede ser predictor de RFP y crisis FS.**

Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception? - J. Parra; S. N. Kalitzin; J. Iriarte; W. Blanes; D. N. Velis; F. H. Lopes da Silva. 2003.

Visani E et al, 2010



- Fig 2 – Espectro de coherencia según bandas de frecuencia. A-Controles. B- Pacientes fotosensibles

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2- Modulación exógena

- La fotosensibilidad, marcadora de una respuesta anómala a un factor exógeno o ambiental, proporciona un modelo para intentar interferir con la ictogénesis mediante la modulación perceptual
  - Prevención de exposición: evitar la exposición a estímulos visuales de determinadas características físicas. Tradicionalmente la exposición a determinadas frecuencias de estimulación luminosa intermitente, como luces de discotecas o la reglamentación para los clips televisivos
  - Modificación "preventiva" de la percepción, como puede ocurrir con la sensibilidad a colores

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Fotosensibilidad: modulación por cambio en la percepción cromática

Usefulness of Blue Sunglasses in Photosensitive Epilepsy –
Takahashi T, Tsukahara Y. 1992 –

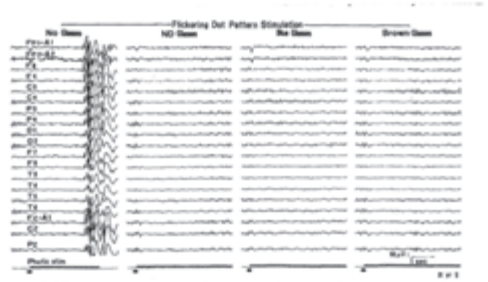

FIG. 2. EEG changes in response to 15-Hz flickering dot pattern stimulation with and without sunglasses on patient 5. Without sunglasses a generalized photoparoxysmal response (PPR) with a latency of 2 s appeared; with sunglasses of neutral density (ND), blue, and brown, no PPRs were activated.

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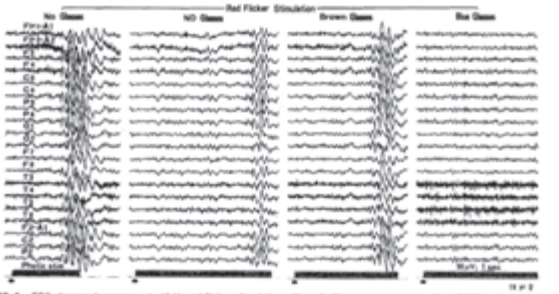

FIG. 3. EEG changes in response to 15-Hz red flicker stimulation with and without sunglasses in patient 3. Without sunglasses and with neutral density (ND) and brown sunglasses, generalized photoparoxysmal responses (PPRs) were induced with latencies of 1.5, 3.8, and 2.8 s, respectively; there was no activation of PPRs with blue sunglasses.

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Suppressive Efficacy by a Commercially Available Blue Lens on PPR in 610 Photosensitive Epilepsy Patients

**Giuseppe Capovilla, †Antonio Gambardella, ‡Guido Rubboli, *Francesca Beccaria, *Alessandra Montagnini, §Umberto Aguglia, Maria Paola Canevini, ¶Susanna Casellato, **Tiziana Granata, ††Francesco Paladin, ‡‡Antonino Romeo, §§Giuseppe Strano, Paolo Tinuper, ¶¶Pierangelo Veggiotti, **Giuliano Avanzini, and ‡Carlo Alberto Tassinari*

	Disappearance	Reduction	Persistence
Whole group, n (%)	463 **(75.9)**	109 (17.9)	38 (6.2)
Sex			
Male	157 (74.8)	39 (18.6)	14 (6.6)
Female	306 (76.5)	70 (17.5)	24 (6)
Age at evaluation			
<14 yr	308 (77.7)	66 (16.7)	22 (5.6)
≥14 yr	155 (72.5)	43 (20.1)	16 (7.4)
Therapy			
Yes	288 (75.6)	73 (19.1)	20 (5.3)
No	175 (76.4)	36 (15.8)	18 (7.8)
Type of epilepsy			
Generalized	312 (75.3)	80 (19.3)	22 (5.4)
Focal	103 (83.1)	15 (12.1)	6 (4.8)
EE	34 (68.0)	8 (16.0)	8 (16)
Unclassified	14 (63.7)	6 (27.3)	2 (9.0)

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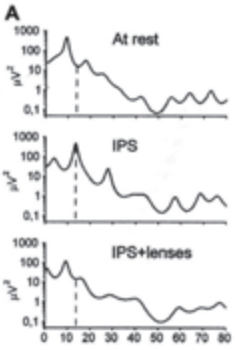
Photosensitive epilepsy: Spectral and coherence analyses of EEG using 14 Hz intermittent photic stimulation

Visani E, Varotto G, Binelli S, Fratello L, Francheschetti S, Avanzini G, Panzica F
Clin Neurophysiol 2010

- **Basal**: aumento de la coherencia en la banda gamma en pacientes con epilepsia fotosensible
- **ELI:** actividad gamma con aumento adicional en pacientes fotosensibles
- **ELI + Lentes azules Z1:** perfiles de espectro y coherencia retornaron a los basales.



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3. Ictogénesis en crisis reflejas: de un estímulo "normal" a una respuesta "patológica"

✓ **HIPEREXCITABILIDAD CORTICAL FOCAL**

El primer planteo para asociar un estímulo sensorial con una respuesta exagerada de neuronas corticales, capaces de generar crisis epilépticas, sería la existencia de un foco epileptógeno o grupo neuronal hiper-excitable en la corteza sensorial primaria o de asociación, en este caso, visual, cuya activación fisiológica en el proceso de percepción determina una respuesta exagerada, hiper-sincrónica, patológica.

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A FAVOR -Trabajo de Clementi –

- inducción de convulsiones por fotoestimulación en perros previamente tratados con estricnina en el córtex visual.
- La estricnización de otras zonas corticales con función de integración sensitiva también era capaz de producir lesiones irritativas con potencial epileptógeno si se aplicaba el estímulo sensorial pertinente.

EN CONTRA –

- Las crisis reflejas no son habitualmente crisis parciales simples sensoriales, sea visuales, auditivas, somatosensitivas
- Si bien el córtex sensorial primario debe estar involucrado de una u otra forma, estos hechos nos llevan de la mano a la necesidad de comprender mejor la fisiología de las redes neuronales involucradas en la percepción y sus códigos de interrelación.

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✓ **ALTERACIÓN ESTRUCTURAL DE VÍAS**

Síntomas derivados de activación apareada de cierta área ("sincinesias"). No necesariamente mecanismo epiléptico.

✓ **ALTERACIÓN FUNCIONAL DE VÍAS**

cambio **cualitativo** en los **patrones de activación de determinados grupos neuronales**, o de selección de determinadas vías de propagación, desencadenado por un estímulo sensorial o algunas características del mismo

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- **Vías normales pero activadas con codificación alterada?**

Ej: vía occípito-frontal activada a diferente frecuencia en pacientes fotosensibles?

- **Codificación alterada del estímulo o alteración del contexto cerebral en que se presenta?**

Rol de la plurimodalidad del input aferente.

Aumento en la actividad en la banda gamma, que refleja procesamiento multimodal, favorecería crisis

Disminución de la actividad sincronizada a una frecuencia de banda o mantenimiento de estado de entropía elevada basal, con rol protector (valproato)

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Fotosensibilidad y placer

- Manifestación clínica de fotosensibilidad
  - CTCG, Mioclonias
  - Ausencias, Versivas, Mioclonicas palpebrales
  - Crisis parciales simples: visuales, vegetativas; Crisis parciales complejas
  - **Equivalentes ictales: sensación de placer**
- Sensaciones de placer, e incluso de orgasmo ictal han sido descritas en diferentes tipos de crisis y epilepsias, particularmente en distintas crisis reflejas.

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- En pacientes con crisis musicogénicas se ha planteado el rol del componente emocional asociado a la secuencia musical epileptogénica
- Estudio comparando áreas activadas en música con y sin impacto emocional, mostró que éste se asoció a:
  - ✓**Activación en ínsula y córtex órbito-frontal**, entre otros
  - ✓**Disminución de actividad en la amígdala**, al intensificarse la respuesta emocional positiva.
  - ✓Este patrón es similar al observado en otros estudios de euforia o emoción placentera.
- El sentimiento placentero desencadenado por escuchar música parece depender del **mismo sustrato neural asociado con la recompensa biológica a eventos ambientales biológicamente significativos**, como la alimentación y reproducción sexual.

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¿Existe un compromiso de redes hedónicas en las crisis reflejas y en la fotosensibilidad?

- ❑Fenómeno de autoinducción de crisis frecuente
- ❑Rol del placer en la perpetuación de crisis:
  - ✓Círculo vicioso por alteración-hiperexcitabilidad propia de circuitos de recompensa biológica
  - ✓Círculo vicioso por alteración-facilitación del reclutamiento de los circuitos de recompensa biológica en descargas iniciadas a distancia
  - ✓Rol homeostático – "reset" del sistema

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¿Qué es Fotosensibilidad en Epilepsia?

➢cambio **cualitativo** en los **patrones de activación de determinados grupos neuronales**, desencadenado por un **estímulo luminoso** o algunas características del mismo, y que ocurre en pacientes predispuestos, probablemente por un aumento en la excitabilidad de toda o parte de la red involucrada

➢asociación cronobiológica implica factores ontogénicos de especialización cerebral y formación de redes, involucra la plasticidad cerebral e implica el compromiso de una delicada sincronía témporo-espacial de mecanismos excitatorios e inhibitorios.

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Programa – 25.02.2011

09:00 – 10:00	AEDs and psychiatric commorbidities in epilepsy - Andres Kanner (USA)
10:00 – 11:00	Behavioral and psychological changes in JME – Bettina Schmitz (Germany)
11:00 – 11:30	Coffee break
11:30 – 12:30	Penelope Syndrome: ESES, Encephalopathy with Status Epilepticus during sleep – Carlo Alberto Tassinari (Italy)
12:30 – 14:00	Lunch
14:00 – 15:00	MRI abnormalities associated with depression in MTLE - Fernando Cendes (Brazil)
15:00 – 16:00	Cognitive consequences of neonatal seizures – Magda Lahorgue Nunes (Brazil)
16:00 – 16:30	Coffee break
16:30 – 17:30	The patients' perception about epilepsy and what they do about it - Peter Wolf (Denmark)
17:30 – 18:30	Cognitive decline in pediatric epilepsies – Solomon Moshe (USA)
18:30 – 20:00	Dinner
20:30 – 21:30	ALADE lecture - Epilepsy: the importance of learning to classify for learning to treat – Carlos Medina-Malo (Colombia)

AEDs and psychiatric commorbidities in epilepsy
Andres Kanner (USA)

RUSH UNIVERSITY MEDICAL CENTER

Antiepileptic Drugs and Psychiatric Comorbidities in Epilepsy

Andres M Kanner, MD
Professor of Neurological Sciences and Psychiatry, Rush Medical College

Director, Laboratory of EEG and Video-EEG-Telemetry,
Associate Director, *Rush Epilepsy Center, Rush University Medical Center, Chicago, IL.*

AED usage

- Epilepsy
- Migraine
- Pain
- Psychiatry

- Mechanism of Action
  - Channels
  - Network systems

Prevalence of Psychiatric Disorders in Epilepsy

	In epilepsy (range)	In the general population (range)
Depression	11%–60%	2%–4%[1]
Anxiety	19%–45%	2.5%–6.5%[2]
Psychosis	2%–8%	0.5%–0.7%[3]
ADHD	25%–30%?	2%–10%[4,5]

ADHD=attention-deficit hyperactivity disorder.
[1]Anthony JC, et al. *Epidemiol Rev.* 1995;17:240-242; [2]Weissman MM, et al. *J Clin Psychopharmacol.* 1986;47(suppl 6):11-17; [3]Kessler RC, et al. *Arch Gen Psych.* 1994;51:8-19; [4]Costello EJ. *J Am Acad Child Adolesc Psychiatry.* 1989;28:836-841; [5]Rutter M, et al. In: *Clinics in Developmental Medicine.* Vol 35/36. Philadelphia, Pa: Lippincott Williams & Wilkins; 1970.

Outline

1) Positive Psychotropic Properties of AEDs:
   Do they prevent comorbic psychitaric comorbidities in epilepsy?
2) Negative Psychotropic Properties of AEDs: Do they cause psychiatric disorders?
3) Do AEDs increase the suicidal risk of patients with epilepsy?
4) Do psychiatric comorbidities have an impact on the tolerance and efficacy of AEDs?

AEDs in Affective Disorders

- Pathogenic Mechanism
  - Do affective disorders and epilepsy share common pathogenic mechanisms?
- Neurotransmitters
  - What are the common neurotransmitters involved in affective disorders and epilepsy?
- AED → Mechanism
  - Is the therapeutic effect of AEDs in affective disorders an expression of their effect on such mechanisms?

Neurotransmitters Involved in the Pathogenesis of These 2 Disorders

EPILEPSY	AFFECTIVE DISORDERS
• GABA	• Serotonin
• Glutamate	• Norepinephrine
• Serotonin	• Dopamine
• Norepinephrine	• Glutamate
• Dopamine	• GABA

GABA=gamma-aminobutyric acid.

Serotonergic and Noradrenergic Deficits in Epilepsy and Depression (1)

- GEPR-3 and GEPR-9
- Seizures more severe in GEPR-9
- Susceptibility to seizures evoked by auditory stimuli
- Exhibit susceptibility to electrical limbic kindling (more pronounced in GEPR-9)
- *Innate noradrenergic and serotonergic deficits*

GEPR=genetically epilepsy-prone rat.
Dailey JW, et al. *Biochem Pharmacol*. 1996;52:1323-1329.

Serotonergic and Noradrenergic Deficits in Epilepsy and Depression (2)

- Deficit in NE transmission more severe in GEPR-9
- Deficit in 5HT transmission comparable among the 2 strains
- Increase in *serotonergic and noradrenergic* transmission protects GEPR against audiogenic seizures
- Decrease in *serotonergic and noradrenergic* transmission worsens seizure frequency and severity in both GEPR strains

NE=norepinephrine.
5HT=5-hydroxytryptamine.

Serotonergic and Noradrenergic Deficits in Epilepsy and Depression (3): Neurotransmitter Changes in Other Animal Models of Epilepsy

- Similar effects have been reproduced in the kindling process of nongenetically prone
  - Rats
  - Cats
  - Rabbits
  - Rhesus monkeys

Jobe PC, et al. 2001.

Impact of AEDs on Neurotransmitters (1)

- Carbamazepine releases 5HT from hippocampal slices
- In GEPR and rats, carbamazepine releases 5HT
- 5HT depletion greatly reduces the anticonvulsant effect against GTC seizure in these animal models of epilepsy

GTC=generalized tonic-clonic.
Dailey JW, et al. *Epilepsia*. 1998;39:1054-1063.

Impact of AEDs on Neurotransmitters (2)

- Lamotrigine causes concentration-dependent inhibition of NE and 5HT in rat brain synaptosomes (and human platelets)[1]
- Valproic acid causes dose-related increments in 5HT in the extracellular fluid of the hippocampus of rats[2]
- Zonisamide causes dose-related increments in 5HT in the extracellular fluid of the hippocampus of rats[3]

[1]Southam E, et al. *Eur J Pharmacol*. 1998;358:19-24.
[2]Biggs CS, et al. *J Neurochem*. 1992;59:1702-1708.
[3]Okada M, et al. *Epilepsy Res*. 1992;13:113-119.

Impact of 5HT and NE Secretion on VNS Antiepileptic Efficacy

- Experimentally induced deletion of 5HT and NE neurons sharply decreases or prevents VNS-induced anticonvulsant effects against electroshock or pentylenetetrazol-induced seizures in rats[1]
- Damage to locus coeruleus prevents antiepileptic effect of VNS in rats[2]

VNS=vagal nerve stimulation.
[1]Browning, et al. 1997.
[2]Krahl SE, et al. *Epilepsia*. 1998;39:709-714.

AEDs in Affective Disorders

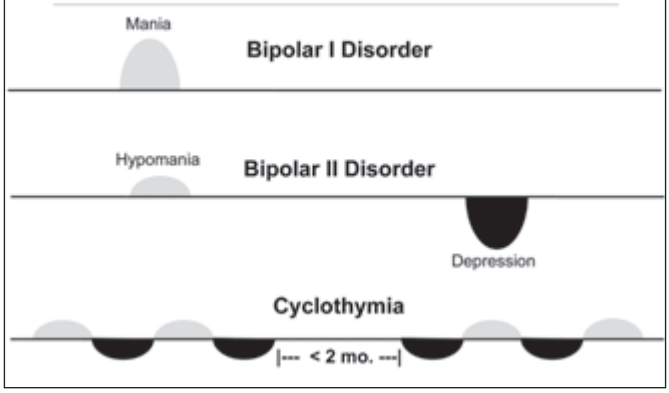
- Carbamazepine
- Valproic acid
- Clonazepam
- Gabapentin
- Lamotrigine
- Topiramate
- Oxcarbazepine
- Pregabalin*

*Currently under FDA review.

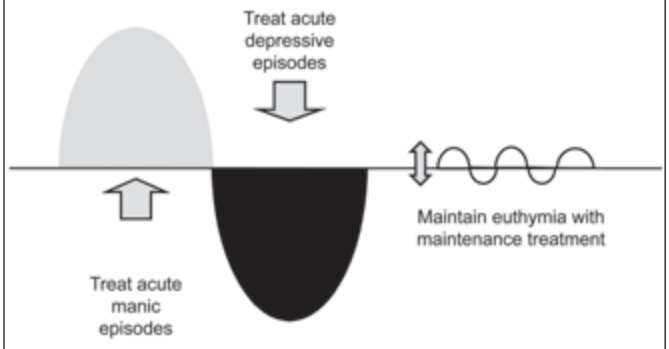
AEDs in Psychiatry

- To date, FDA-approved for psychiatric disorders
  - **Valproate**
    - **acute mania**
  - **Lamotrigine**
    - **Maintenance treatment - prevention of mood episodes in bipolar I disorder.**
  - **Gabapentin**
    - **Treatment of Social Phobia**
- However, AEDs are often used to treat certain target symptoms and as adjunctive treatments for major psychiatric illnesses

The Spectrum of Bipolar Disorders



Treatment of Bipolar Disorders



FDA-Approved Treatments for Bipolar Disorder

Acute Mania	Maintenance
• Lithium	• Lithium
• ***Valproate***	• ***Lamotrigine***
• Olanzapine	
• Chlorpromazine	

Carbamazepine in Affective Disorders

Acute Mania

- Gold standard: lithium
- 19 double-blind, controlled studies with mixed results.
- 1 double-blind placebo- controlled study demonstrating antimanic efficacy.

Acute Depression

- One small double-blind, placebo-controlled cross-over study of 9 patients with bipolar depression demonstrated efficacy.

Prophylactic treatment

- 14 controlled or partially controlled studies showing prophylactic effect against manic and depressive recurrences
- Carbamazepine is more effective in lithium non-responders.

Post RM, et al. *Psychopharmacology.* 1996;128:115-129
Bellanger JC, Post RM. *Commun Psychopharmol. 1978; 2:159-175*
Bellanger JC, Post RM. Am J Psychiatry. 1980; 137:782-790.

Valproic Acid in Affective Disorders

Acute treatment of mania

- Four randomized placebo-controlled studies demonstrating efficacy in 48 to 53% of patients.
- Superior to lithium for mixed mania and rapid cycling

Prophylactic treatment

- Positive prophylactic efficacy for manic and depressive episodes demonstrated in one placebo-controlled study and two double-blind studies using lithium as comparator drug.

Antidepressant treatment

- One double-blind-placebo controlled study (unpublished) failed to show significant differences between VPA and placebo.

Bowden CL. *Bipolar Disord*. 2003;5:189-202.

Gabapentin in Affective Disorders

- Mood-stabilizing efficacy suggested in "open" studies[1]
- Double-blind vs placebo: no advantage[2]
- Consensus: gabapentin considered effective as "add-on" to other mood-stabilizing agents[1]

[1]Carta MG, et al. *J Affect Disord*. 2003;75:83-91.
[2]Pande AC, et al. *Bipolar Disorder*. 2000;2:249-255.

Lamotrigine in Affective Disorders

Antimanic treatment

- No efficacy demonstrated in three controlled studies.

Antidepressant treatment

- Three controlled studies demonstrated antidepressant efficacy in depression of patients with bipolar I and rapid cycling bipolar disease.
- These studies revealed a dose-dependent antidepressant response in bipolar depression.

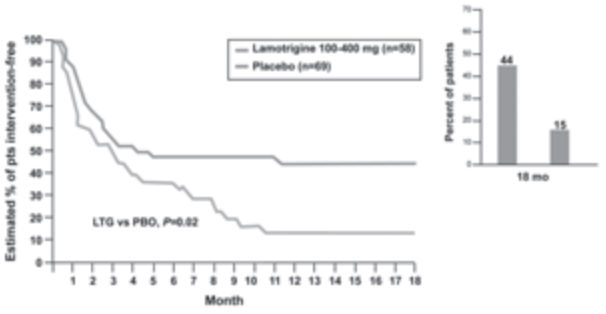
Prophylactic treatment

- Mood-stabilizing properties suggested in one open and two double-blind, controlled trials.

Calabrese JR, et al. J Clin Psychiatry, 2000; 61:841-860.

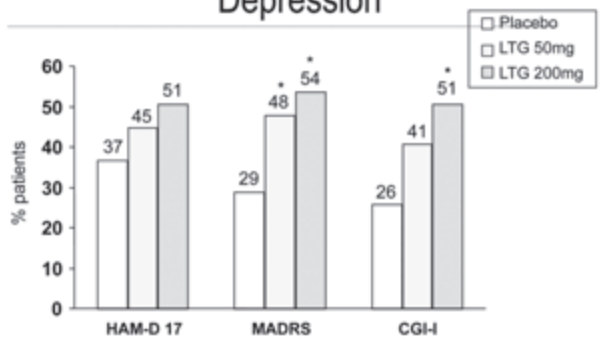
Lamotrigine Delayed Time to Intervention or Mood Episodes

Currently or Recently Manic/Hypomanic Patients



[1] Bowden et al. *Arch Gen Psychiatry.* 2003;60:392-400.

Lamotrigine in Acute Bipolar Depression



*$p<0.05$ *vs* placebo

Calabrese et al. *J Clin Psychiatry* 1999;60:79-88.

No controlled data for:

- Oxcarbazepine
- Topiramate
- Zonisamide
- Tiagabine
- Levetiracetam

AEDs in Bipolar Disorders: Conclusions

- Incomplete response to lithium
- Poor lithium tolerance
- Rapid cycling
- Negative family history
- Organic mood disorders

Anxiety Disorders: Clonazepam

- Evidence of antimanic efficacy in controlled studies
- Adverse Profile:
  - Dependence
  - Ataxia
  - Cognitive

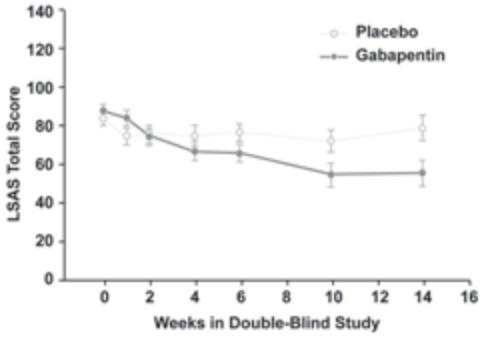
Curtin F, Schulz P. *J Affect Disord*. 2004;78:201-208.

AEDs in Social Phobia

- GBP
  - Gabapentin found to be effective in animal models of anxiety disorder[2]
  - Gabapentin shown to be effective in a double-blind study of 69 patients[1]

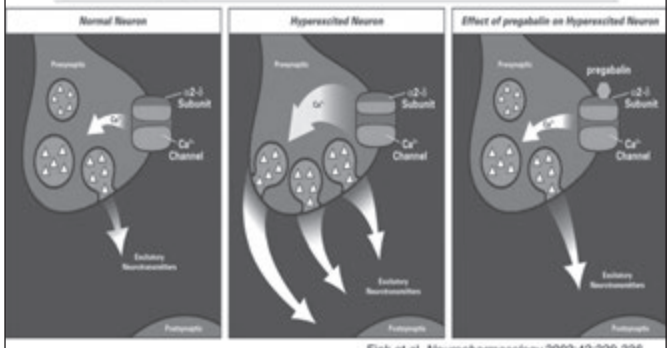
[1]Pande AC, et al. *J Clin Psychopharm*. 1999;19:341-348.
[2]de-Paris F, et al. *Behav Pharmacol*. 2000;11:169-173.

Gabapentin in Social Phobia
Liebowitz Social Anxiety Scale (LSAS)



Pande et al. *J Clin Psychopharmacol* 1999;19:341-8

Pregabalin Binds to the $\alpha 2\delta$ Subunit of Voltage-gated Ca^{2+} Channels in the Brain

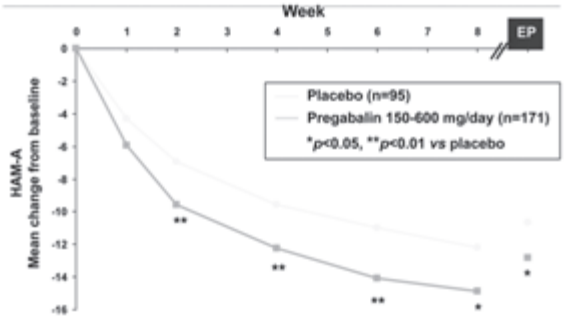


Fink et al. *Neuropharmacology* 2002;42:229-236
Data on file, Pfizer Inc

Pregabalin binds to the $\alpha 2\delta$ Subunit of Calcium Channels in the Nervous System

- Pregabalin reduces neurotransmitters release:
  - Substance P
  - Glutamate
  - Noradrenaline

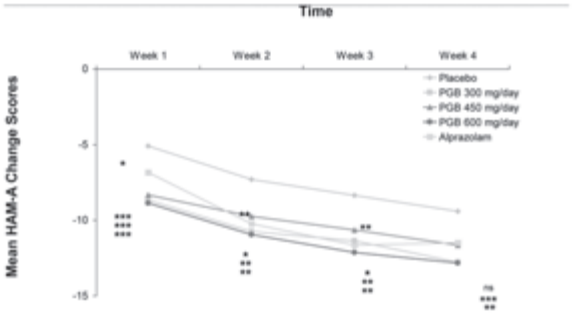
Pregabalin in Elderly Patients with GAD



Mean HAM-A baseline score = 26.5

Data on file, Pfizer Inc

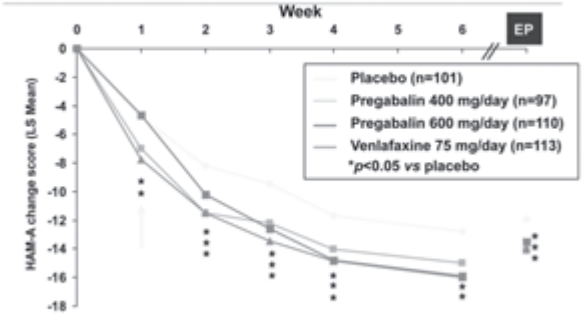
Pregabalin vs. alprazolam in GAD



*P<0.05; **P<0.01; ***P<0.001
PGB = pregabalin
HAM-A = Hamilton Rating Scale for Anxiety

Rickels et al. *APA*. 2002.

Pregabalin *vs* Venlafaxine in GAD
Onset of Anxiolytic Efficacy



Mean HAM-A baseline score ~ 26.5

Kasper et al. APA 2002

AEDs in Panic Disorders

- VPA
  - efficacy demonstrated in double-blind study[1]
  - can block lactate-induced panic attacks[2]
- GBP
  - Gabapentin effectiveness suggested in open trials
- CBZ
  - not effective
- LTG
  - Lamotrigine caused panic attacks in 9/90 patients[3]

[1]Lum M, et al. *Biol Psychiatry.* 1990;27:164A-165A.
[2]Keck PE, et al. *Biol Psychiatry.* 1993;33:542-546.
[3]Kanner and Frey. Unpublished.

Negative Psychotropic Properties of AEDs

- Dose-related (all AEDs)
- May result from discontinuation of AEDs with positive psychotropic drugs in vulnerable patients
- May result from pharmacokinetic interactions with psychotropic drugs in vulnerable patients

AEDs With Highest Risk of Negative Psychotropic Effects

- Phenobarbital
- Primidone
- Benzodiazepines
- Vigabatrin
- Tiagabine
- Topiramate
- Ethosuximide
- Levetiracetam

Standard AEDs With Negative Psychotropic Effects

AED	Affective disorder	Behavior disorder	Anxiety disorder	Psychosis
Phenobarbital/Primidone	+	+	+	+
Clonazepam		+		
Ethosuximide	+	+	+	+
Phenytoin		+[r]		
Carbamazepine		+[r]		
Valproic acid		+		

New AEDs With Negative Psychotropic Effects

AED	Affective disorder	Anxiety disorder	Behavior disorder	Psychosis
Felbamate	+		+[MR]	
Gabapentin			+[MR]	
Lamotrigine		+[PANIC]		+[R]
Vigabatrin	+	+	+	+
Tiagabine	+		+	+
Topiramate	+		+	+
Oxcarbazepine				
Levetiracetam	+		+	+
Zonisamide	+		+	

AEDs With Positive and Negative Psychotropic Effects (PE)

AED	Positive PE	Negative PE
Carbamazepine	+	+
Clonazepam	+	+[r]
Valproic acid	+	+
Gabapentin	+	+[MR]
Lamotrigine	+	+
Topiramate	+	+

Do AEDs cause suicidal ideation and behavior?

Lifetime Prevalence

Tellez-Zenteno, JF et al., Epilepsia, 2007; 48:2336-2344

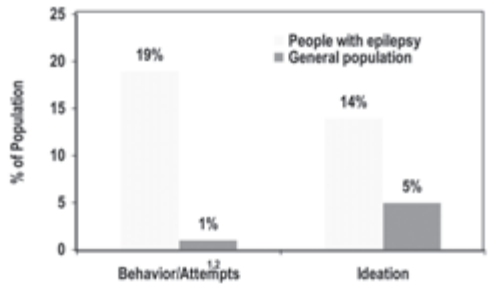
Psychiatric Disorder	Controls (%)	Epilepsy (%)
Major Depressive Disorder	10.7 (10.2–11.2)	17.4 (10.0–24.9)
Anxiety Disorder	11.2 (10.8–11.7)	22.8 (14.8–30.9)
Mood/Anxiety Disorders	19.6 (19.0–20.2)	34.2 (25.0–43.3)
Suicidal Ideation	13.3 (12.8–13.8)	25.0 (17.4–32.5)
Any Psychiatric Disorder	20.7 (19.5–20.7)	35.5 (25.9–44.0)

Epilepsy, Psychiatric Disorders and Suicide

	Rate Ratio	P value
No Epilepsy	1	
Epilepsy	2.4 (2.0-2.8)	<0.0001
Epilepsy +		<0.0001
Affective Disorder	32.0 (20.8-49.4)	<0.0001
Anxiety Disorder	11.4 (4.16-31.4)	<0.0001
Schizophrenia	12.5 (8.05-22.7)	<0.0001

Christensen et al. Lancet Neurology 6: 693–98, 2007

Risk of Suicidal Ideation and Attempt in People with Epilepsy



1. Boylan LS, et al. *Neurology.* 2004;62(2):258-261.
2. Jones JE, et al. *Epilepsy Behav.* 2003;4(suppl 3):S31-S38.

Suicidal Ideation in Epilepsy

- 139 outpatients from 5 centers
- Structured psychiatric interview (M.I.N.I.)
- Suicidal ideation was endorsed by 17 (12%) patients
- Suicidality was significantly increased in patients with:
  - current major depressive episode
  - current anxiety
  - current major depressive episode with anxiety

Jones et al, Epilepsy Behav. 2003;4 Suppl 3:S31-8

Bidirectional Relationship Between Epilepsy and Suicidality

Authors	Type of Study	Psychiatric History Preceding the Onset of Epilepsy/Controls
Forsgren and Nystrom, 1990	Population-based	7 times the history of depression 17 times in case of TLE
Hersdorffer et al, 2000	Population-based (Onset of epilepsy >age 55)	4 times the history of depression
Hersdorffer et al, 2006	**Population-based (Iceland all ages)**	**5 times the history of suicidality Twice the history of major depression**

Postictal Suicidal Ideation

Postictal Symptom	Frequency (N=100)	Duration (Range, Hours)
Poor frustration	36	24 (0.5-108)
Anhedonia	33	24 (0.1-148)
Hopelessness	25	24 (1.0-108)
Helplessness	31	24 (1.0-108)
Crying bouts	26	6 (0.1-108)
Suicidal ideation	*13*	*24 (1.0-240)*
Irritability	30	24 (0.5-108)
Guilt	23	24 (0.1-240)
Self deprecation	27	24 (1.0-120)

Any postictal symptom of depression, n=43 patients
Median number of symptoms: 5 (range: 2-9)

Kanner AM, et al. Neurology. 2004;62(5):708-713.

Psychiatric variables associated with postictal suicidal ideation

Psychiatric Variables	*p*
Past History of Major Depression	0.006
Previous Psychiatric Hospitalizations	<0.0001
Interictal Neurovegetative Symptoms	<0.0001

Review of the Literature...

?

Psychiatric Risk Factors for Psychiatric Adverse Events

Author	AED	N	% PAE	Risk factors
Brent et al.	PB	40	44	Family history of Major Depression
Mula et al.	LEV	517	10%	Past psychiatric history
Mula et al.	TPM	431	24%	Past Psychiatric History Family Psychiatric History

What Risks to Look For?

1. Past and current personal and familial psychiatric history of:
   - Depression
   - Anxiety
   - Suicidality
2. Postictal suicidal ideation/ behavior

FDA Alert of suicidality associated with AEDs:

Overall finding

- 80% *increased* risk for suicidality for AED vs placebo (OR=1.80; 95% CI=1.24-2.66)
- 2.1 more suicidality events per 1,000 people exposed to AEDs (95% CI=0.7-4.2)
  - 4.3/1,000 in the drug treated group
  - 2.2/1,000 in the placebo group

FDA conclusion

- "The increased risk of suicidality was:
  - Generally consistent for the 11 AEDs
  - Consistently increased risk across indications"

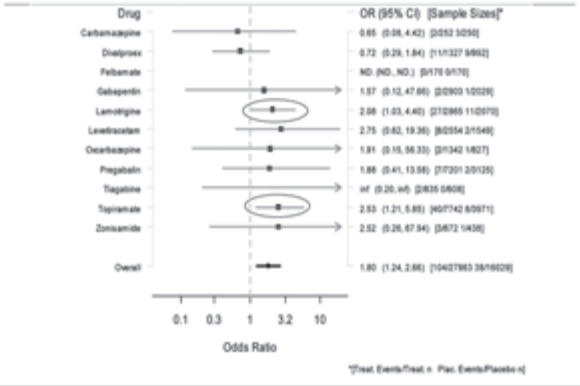
Concerns of Professional Societies (AES, EF, ANA)

- Data reviewed by two independent investigators with expertise in research methodology in Epilepsy and Statistics
  - Dale Hesdorffer, PhD. and Anne Berg, PhD.
- Critical review of the FDA data raised significant concerns over the results and conclusions of the meta-analysis.

(1) Problems with methods of suicidality data collection

- Collected from *spontaneous* reports of adverse events
- Data *not elicited in a systematic or standardized* manner.
- More treatment arms on "active drug" than placebo which can lead to reporting bias
  - a flaw in measuring outcome that results in outcomes for one group being measured more accurately and completely than another (e.g. a treatment versus a control group).
  - *This problem acknowledged by FDA*

(2) The finding was not seen for all drugs



(3) Findings were inconsistent by indication and Region

Indication

- Epilepsy OR=3.53 – adjunctive therapy in 92% of trials
- Psychiatric OR=1.51 – adjunctive therapy in 14% of trials
- Other OR=1.87 – adjunctive therapy in 15% of trials

Region

- North America OR=1.38
- Non-No. America OR=4.53

Conclusions from Review of Data (Suicidality Symposium AES meeting, 2008)

1. ***Do AEDs increase the suicidal risk of patients with AEDs?***
   - *Some* AEDs probably do in certain populations at risk.

2. ***Should the suicidality risk associated with AEDs be investigated?***
   - Absolutely! In prospective studies in which:
     - suicidality data are obtained *in all patients* with the same instruments
     - other psychiatric relevant variables are identified *in all patients* in a systematic manner.

BDI-II Suicidal Ideation

0. I don't have any thoughts of killing myself
1. I have thoughts of Killing myself, but I would not carry them out.
2. I would like to kill myself
3. I would kill myself if I had the chance.

If options 2 or 3 chosen, ask:

"What has kept you from hurting yourself?

Quick screen of suicidal risk: Item 9 from BDI-II

N = 188

0. **I don't have any thoughts of killing myself: n = 164 (87.3%)**
1. **I have thoughts of killing myself, but I would not carry them out: n = 22 (7.2%)**
2. **I would like to kill myself: n = 1 (0.5%).**
3. **I would kill myself if I had the chance: n = 1 (0.5%).**

Suicidality Module M.I.N.I*.

n = 655

1.	Did you ever make a suicide attempt?	YES	NO	7.3%
In the past month did you:				
2.	Think you would be better off dead or wish you were dead?	YES	NO	6.2%
3.	Want to harm yourself?	YES	NO	3%
4.	Think about suicide?	YES	NO	5.4%
5.	Have a suicide plan?	YES	NO	1.5%
6.	Attempt suicide?	YES	NO	0.5%

*Sheehan et al, J Clin Psychiatry 1998

Kanner et al, Epilepsia 2009. Poster 2.152

Suicidal Risk based on MINI in an outpatient population of patients with epilepsy

YES in 1, or 2, or 3 = LOW RISK
YES in 4 or 1 + 3 = MODERATE RISK
YES in 5 or 6 or 1+4 = HIGH RISK

- Low risk: 9.2%
- Moderate risk: 3.6%
- High risk: 2.4%

Kanner et al, Epilepsia 2009. Poster 2.152

Association between severity of suicidal risk and the presence of suspected diagnosis of MDE, GAD and MDE+GAD

Association* between suicidal risk and:

- NDDI-E > 15:
  - $x^2 = 75.6$, df = 3, p<0.0001
- GAD-7 > 10
  - $X^2 = 77$, df = 3, p<0.0001
- NDDI-E > 15 + GAD-7 > 10
  - $X^2 = 69.3$, df = 3, p<0.0001

*Kruskal Wallis Test

Kanner et al, Epilepsia 2009. Poster 2.152

Lyrica Suicide Lawsuit

Lyrica linked to Increased Risk of Suicide & Suicidal Behavior

- Contact an Attorney
- FDA Alert
- Lyrica (Pregabalin)
- Suicidal Ideation

- **Lyrica May Cause Suicide or Suicidal Thoughts (Suicidal Ideation)**
- **Did your loved one commit or attempt to commit Suicide while taking Lyrica (Pregabalin)?**

- **Attorneys are standing by to speak with you NOW!**
  - Submit the following form to be contacted regarding a suicide which may be attributable to taking Lyrica.
  - First Name: *
  - Last Name: *
  - Address:
  - City:
  - Zip code: *
  - Email: *
  - Home number: *
  - Cell number:
  - Preferred time to call:
  - Did your loved one commit suicide or attempt suicide? *
  - Comments or Questions:
- **1-877-619-4111**

- **Call NOW to speak with an attorney regarding Lyrica and suicidal ideation. This is a TOLL-FREE call.**

From Google.com

Do depressive and anxiety disorders worsen non- psychiatric adverse events?

Adverse Events Profile

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

	Always	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

Baker G et al, Epilepsia 1994.

Impact of Psychiatric Disorders on Perception of AED-Related Adverse Events

Psychiatric Dx.	N 188
Asymptomatic	103
Sub-syndromic depressive episode	26
Major depressive episode	10
Anxiety Disorders	28
MDE + Anxiety Disorders	21
p	

Impact of Psychiatric Disorders on Perception of AED-Related Adverse Events

Psychiatric Dx.	N 188	AEP Score: all items
Asymptomatic	103	32.2 (±7.6)
Sub-syndromic depressive episode	26	45.1 (±9.6)
Major depressive episode	10	49.6 (±9.3)
Anxiety Disorders	28	45.5 (±10.8)
MDE + Anxiety Disorders	21	52.8 (±9.2)
p		F = 38.3, <0.0001

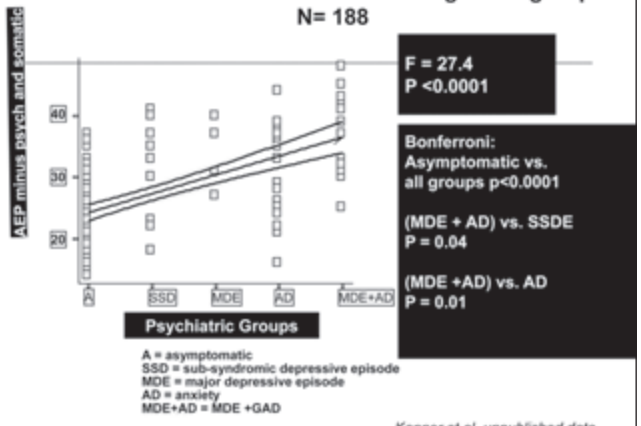
Impact of Psychiatric Disorders on Perception of AED-Related Adverse Events

Psychiatric Dx.	N 188	AEP Score: all items	AEP Score: No psychiatric items
Asymptomatic	103	32.2 (±7.6)	26.3 (±6.5)
Sub-syndromic depressive episode	26	45.1 (±9.6)	35.4 (±7.6)
Major depressive episode	10	49.6 (±9.3)	39.0 (±7.4)
Anxiety Disorders	28	45.5 (±10.8)	35.1 (±8.3)
MDE + Anxiety Disorders	21	52.8 (±9.2)	40.2 (±6.6)
p		F = 38.3, <0.0001	F = 28.7, <0.0001

Impact of Psychiatric Disorders on Perception of AED-Related Adverse Events

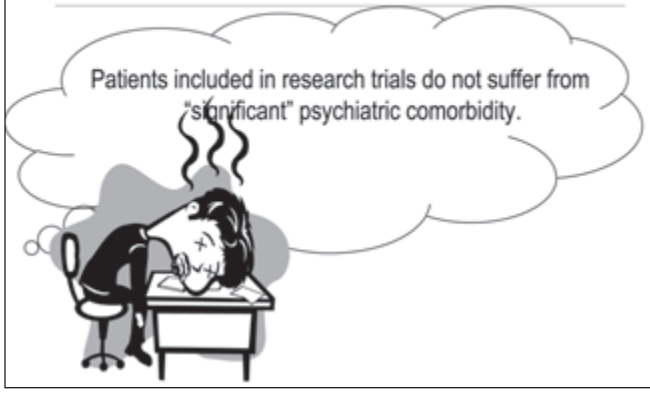
Psychiatric Dx.	N 188	AEP Score: all items	AEP Score: No psychiatric items	AEP score: No psychiatric or somatic items
Asymptomatic	103	32.2 (±7.6)	26.3 (±6.5)	24.1 (±6.0)
Sub-syndromic depressive episode	26	45.1 (±9.6)	35.4 (±7.6)	32.3 (±6.7)
Major depressive episode	10	49.6 (±9.3)	39.0 (±7.4)	35.8 (±7.3)
Anxiety Disorders	28	45.5 (±10.8)	35.1 (±8.3)	32.7 (±8.3)
MDE + Anxiety Disorders	21	52.8 (±9.2)	40.2 (±6.6)	36.8 (±6.8)
p		F = 38.3, <0.0001	F = 28.7, <0.0001	F = 27.1, <0.0001

Relation between AEP score and diagnostic groups
N= 188



Kanner et al, unpublished data

…the longest-held myth in AED research trials…



Conclusions

- AEDs play an important role in the treatment of some psychiatric disorders.
- Their efficacy in preventing psychiatric comorbidities in epilepsy is yet to be established in controlled studies.
- There is no evidence that all AEDs cause increased risk of suicidal ideation and behavior at this time.
- Some AEDs can increase the suicidality risk in patients at risk for psychiatric disorder.

Behavioral and psychological changes in JME

Bettina Schmitz (Germany)

Juvenile Myoclonic Epilepsy

Behavioral and psychological changes

Bettina Schmitz

Berlin
Germany

Personality traits in JME: Immature and „Frontal“?

- weakness of rational self control
- neglect of physical needs
- don't avoid seizure provoking behaviour
- don't learn from bad experiences
- tend to deny problems and conflicts
- impressionable, open, distractible
- weakness of endurance, continuity
- immature, child-like attitude (Janz and Christian 1957)
- „adult child" (Tellenbach 1965)
- „perpetual adolescents" (Pellock 1999)

Psychiatric comorbidity in JME

Author	n	Method	Prevalence
Lund 1976	33	Clinical interview	36%
Perini 1996	18	SADS [1]	22%
Gelisse 2001	170	Retrospective	27%
Trinka 2006	43	SCID [2]	35%

1 Schedule for Affective Disorders and Schizophrenia
2 Structured Clinical Interviews for DSM IV diagnoses

Psychiatric comorbidity in JME

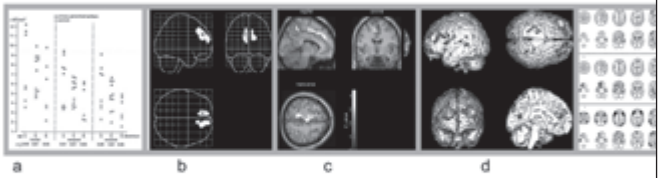
Author	n	Personality disorders
Lund 1976	33	36% (character neurosis)
Perini 1996	18	0 %
Gelisse 2001	170	11%
Trinka 2006	43	23%

1 Schedule for Affective Disorders and Schizophrenia
2 Structured Clinical Interviews for DSMIV diagnoses

„Frontal“ neuropsychological problems in JME

Gershengorn et al.	1992
Swartz et al.	1994
Devinsky et al.	1997
Malagold et al.	1997
Sofia et al.	1997
Hättig et al.	2000
Yu Ge et al.	2003
Sonmez et al	2004

Frontal lobe problems in JME pathological and imaging studies
mesial and dorsolateral cortex



a. Neuropathology	Meencke and Janz *Epilepsia* 1995[a]
b. Volumetric MRT	Woermann et al. *Brain* 1998 / 1999[b,c] Kim et al. *Neuroimage* 2007
c. MR-spectroscopy	Savic et al. *Epilepsia* 2000
d. Flumazenil-PET	Koepp and Duncan. In: Schmitz and Sander 2000[d]
e. FDG-PET-activation study	Swartz et al. *Neurology* 1996[e]

6 elements task

Shallice und Burgess 1991, modificated by Kliegel et al. 2000

6 tasks in three groups

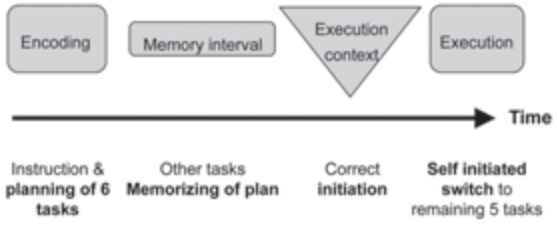
	Tasks	Elements
Group 1	Word finding	A B
Group 2	Calculations	A B
Group 3	Naming pictures	A B

Rules

1. Each task has to be done
2. Time limitation 6 minutes
3. Never complete A and B of one group after another

JME: prospective memory

6-Elements-Task: Shallice und Burgess 1991, modificated by Kliegel et al. 2000



Instruction & **planning of 6 tasks**

Other tasks **Memorizing of plan**

Correct **initiation**

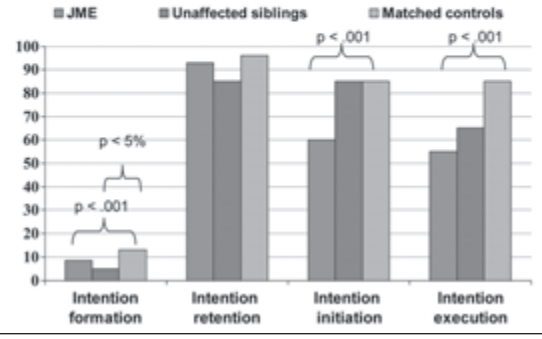
Self initiated switch to remaining 5 tasks

Prospective memory

is impaired in unaffected siblings of JME probands

Wandschneider et al. Neurology 2010

28 Patients with JME, 14 unaffected siblings, 28 controls



Professional choice in JME versus TLE

Pung et al. Epilepsia 2006

20 JME / 20 TLE Patienten
controlled for age, sex, education, duration of epilepsy

Profession	JME	TLE
Communicative	14	6
Non-communicative	5	14

$p < 0.05$

„Are you a morning- or evening type?“

20 JME and 20 TLE Patients

	JME	TLE
Morning type	7	**14**
Evening type	13	**6**

Pung et al. Epilepsia 2006

„At which time of the day do you feel on top?“

20 JME and 20 TLE Patients

	JME	TLE
before 10am	1	**16**
after 10am	19	**4**

Pung et al. Epilepsia 2006

JME
Factors associated with psychiatric comorbidity

- Anxiety
  - Lack of seizure control
  - Total number of GTCS
- Impaired self control
  - Duration of epilepsy
- Personality disorders
  - ??????????????

Martinovic Seizure 2001, de Aurujo Filho Epilepsy and Behaviour 2007

JME
Risk factors for treatment resistence

- Psychiatric comorbidity
- Non compliance
- 3 seizure types
- EEG-asymmetry
- Weak circadian dependence
- Low intelligence
- Postictal confusion
- Delayed diagnosis
- Auras

Dasheiff et al. Seizure 1993, Genton et al. Epilepsia 1999, Fernando-Dongas et al. Seizure 2000, Trinka et al. 2001

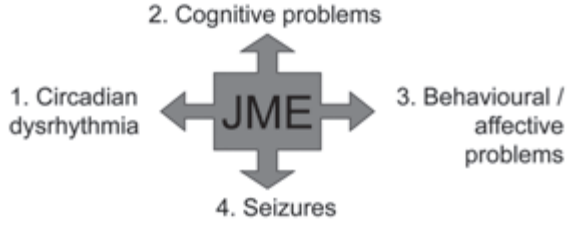
Psychotherapy in JME
22 patients uncontrolled with AED (out of 55)

Psychotherapy lead to seizure freedom in 50% of pharmaco- and counselling-resistant patients

Martinovic Seizure 2001

JME: Neuropsychology and Psychiatry

The Janz-syndrome is a genetically determined neuropsychiatric disorder of brain maturation causing age related frontocortical-subcortical network dysfunction manifesting with



JME
Genetics, pathology, behaviour and prognosis

Behavioural problems in JME
Conclusions

Less frequent than in TLE
Underrecognised
Genetically determined
Consequence of „frontal“ cognitive deficits
Associated with poor prognosis

Behavioural problems in JME
Open questions

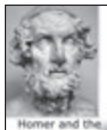
Drug effects
Age dependancy
Predictor or consequence of poor prognosis
Syndrome specificity for JME or IGE
Psychotherapeutic options

Penelope Syndrome: ESES, Encephalopathy with Status Epilepticus during sleep

Carlo Alberto Tassinari (Italy)

Penelope syndrome: ESES, Encephalopathy with Status Epilepticus during Sleep

Carlo Alberto Tassinari, Gaetano Cantalupo, Guido Rubboli



Homer and the Odyssey

Penelope syndrome

Carlo Alberto Tassinari et al.

Penelope and the Suitors (1912)- John William Waterhouse

Penelope-Odysseus-Trojan War-Weaving a shroud for Odysseus' father, Laertes

Tassinari et al. Epilepsia 2009;50(Suppl 7):4-8

Cognition and Paroxysmal EEG Activities: From a Single Spike to Electrical Status Epilepticus during Sleep

Carlo Alberto Tassinari, Guido Rubboli

Epilepsia 2006;47 (Suppl 2): 40-43

Mechanisms Leading to Cognitive Deterioration

- Focal discharges originating from a given cortical area may specifically impair cognitive functions mediated by that particular cortical area, suggesting that even a single epileptic spike (or the following slow wave) can lead, with a precise neuroanatomic specificity, to a transitory disruption of cortical processes

Aarts et al., 1984; Shewmon & Erwin, 1988 a, b, c; Binnie, 1993; Seri et al., 1988

Mechanisms Leading to Cognitive Deterioration

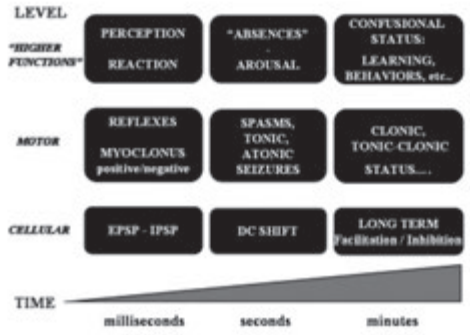
- In benign epilepsy with centrotemporal spikes (BECTS), there is a relationship between disturbances of higher cortical functions and morphology and location of interictal EEG paroxysms, particularly when abundant spike–wave activity persists during sleep

Dalla Bernardina & Beghini, 1976; Baglietto et al., 2001; Massa et al., 2001;Metz-Lutz & Filippini, 2006; Stepphani & Carlsson, 2006

Mechanisms Leading to Cognitive Deterioration

- In children with idiopathic partial epilepsy, chronic cognitive dysfunctions selectively correlate with the location of interictal focal abnormalities

Wolff et al., 2006



- Epileptic EEG paroxysms can interfere with cognitive processes producing transitory effects, such as those related to a single spike, as well as long-lasting effects, such as in electrical status epilepticus during slow-wave sleep (ESES)
- Focal spike-related disruption of cortical functions can produce transitory cognitive impairment, with neuroanatomical specificity between the site of the epileptic focus and the impaired cognitive tasks

- Continuous and diffuse spike and wave during sleep was labeled as a "status epilepticus" [reminiscent of the electroencephalography (EEG) pattern of petit mal status], but without clinical correlates since it occurs during sleep—hence the terms "subclinical" and "electrical"

Patry G, Lyagoubi S, Tassinari CA. (1971) Subclinical electrical status epilepticus induced by sleep in children. Arch Neurol 24:242–252.

- None of the six reported cases in that report could be classified as "acquired epileptic aphasia": cases 2 and 3 "never acquired speech"; cases 1 and 5 were mentally and physically retarded; case 4 did not have speech problems; and case 6 was normal up to 11 years, at which time "aphasic seizures" and "an alarming school regression" occurred. No reference was made in this article to the "acquired epileptic aphasia" described 14 years earlier by Landau and Kleffner

Landau W, Kleffner FR. (1957) Syndrome of acquired aphasia with convulsive disorder in children. Neurology 7:523–530.

- In 1977, with Roger and Dravet, we reported additional cases and proposed that the "status epilepticus during sleep" or SES was responsible for the psychotic behavior and "mental deterioration"; the condition was then qualified as an "encephalopathy" with SES or ESES

Tassinari CA, Dravet C, Roger J (1977) ESES: encephalopathy related to electrical status epilepticus during slow sleep. In Proceedings of the 9th Congress International Federation of EEG and Clinical Neurophysiology, Elsevier Science, Amsterdam, pp. 529–530.

- Kellerman was the first to make, in 1978, a specific connection between "recurrent" aphasia and "subclinical bioelectric status epilepticus during sleep"

Kellerman K. (1978) Recurrent aphasia with subclinical bioelectric status epilepticus during sleep. Eur J Pediatr 128:207–212.

- From a broader perspective, SES may be responsible not only for acquired aphasia, but also (and often concomitantly) for other dysfunctions, such as severe behavioral disturbances, and motor impairment (i.e., apraxia, and negative myoclonus). SES can occur:

  - in children with organic brain lesions such as migrational disorders, hydrocephalus (Veggiotti P et al., 1998; Caraballo et al., 1999, 2008)
  - thalamic lesions (Guzzetta et al., 2005; Kelemen et al., 2006)
  - as well as in children with an epilepsy of benign evolution—whether idiopathic or cryptogenic (Dalla Bernardina et al., 1989)

- Rare familial cases of ESES (Beaumanoir et al., 1995; Praline et al., 2006)
- Recent report of two families characterized by coexistent BECTS and cryptogenic epilepsy with ESES in first-degree relatives suggest a possible genetic basis (De Tiège et al., 2006)

PROGNOSIS

- Prognosis cannot be inferred by the EEG data. This complexity is related to the large number of neuropsychological disorders reported, such as:

  - Attention deficit, decreased IQ, language disorders, disturbances in spatial and temporal orientation, and memory impairment (Roulet –Perez et al., 1993)
  - Motor disorders (Neville et al., 1998)
  - Extensive metabolic abnormalities (De Tiège et al., 2008)

- Patients with the Landau-Kleffner syndrome (LKS) consistently show the pattern of SES, persisting for several months or years
- In these patients, there is a parallel evolution of SES and language disturbances; indeed, when there is progressive language recovery, SES tends to disappear (or it is already over)

Fifty Years of Landau-Kleffner Syndrome. Alden-Biesen, Belgium, from 2–4 November 2007

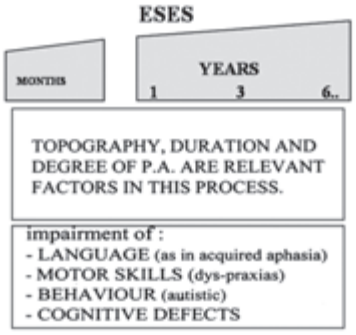
Van Bogaert P, Paquier PE. Epilepsia 2009;50(Suppl 7):1-2

Landau-Kleffner Syndrome

William L. Landau

Frank R. Kleffner

Duration of ESES and topography of interictal paroxysmal activity (PA) play a major role in influencing the degree and type of cognitive dysfunction



Encephalopathy with status epilepticus during slow sleep: "The Penelope syndrome"

Carlo A. Tassinari, Gaetano Cantalupo, Loreto Rios-Pohl, Elvio Della Giustina, Guido Rubboli

Epilepsia 2009;50 (Suppl 7):4-8

Mechanisms Leading to Cognitive Deterioration

- The relationships, in terms of physiopathological mechanisms between ESES and the peculiar patterns of neuropsychological and/or motor derangement, have not yet been fully elucidated
- Several findings indicate that the duration of ESES and the localization of interictal foci play a relevant role in influencing the degree and type of cognitive dysfunction. This hypothesis implies that epileptic EEG paroxysms may interfere with physiologic functions, and possibly, with neuroplasticity processes involved in higher cortical functions—such as learning and memory—occurring during sleep
- Indeed, recent studies support a role of sleep in neuroplastic remodeling of neural networks mediating cognitive performances and behavior, particularly in children. In fact, learning and memory consolidation can take place over extended periods, from hours to days, and sleep has been demonstrated to play a fundamental role in these processes both in humans and in animals

Stickgold et al., 2002; Benington & Frank, 2003; Wlaker & Stickgold, 2004; Shank & Margoliash, 2009

Mechanisms Leading to Cognitive Deterioration

- From the electrophysiologic point of view, EEG activity associated with most of normal sleep is characterized by slow wave activity (SWA), which is in turn relates to slow oscillations of membrane potentials of cortical neurons

Steriade, 2000; Steriade & Amzica, 2003

Mechanisms Leading to Cognitive Deterioration

- The slow (<1 Hz) oscillations of SWA correspond to "up" and "down" states of individual neurons. Several experimental data have shown similarities in cortical network dynamics between the "up" states of the sleep slow oscillations and the "activated" state during wakefulness
- These data may provide the theoretical support for behavioral experiments that have shown that the slow-oscillation "up" states are necessary for the replay and possible consolidation of previously learned tasks or experiences

Destexhe et al., 1999; Bazhenov et al., 2002; Destexhe et al., 2007

Mechanisms Leading to Cognitive Deterioration

- EEG SWA fluctuations are homeostaticaly regulated, showing a decrement during wakefulness and returning to baseline during sleep

Borbelli & Ackermann, 2000

Mechanisms Leading to Cognitive Deterioration

- Particularly interesting are the results obtained by Tononi's group that suggested that a learning task involving a specific brain region may influence, locally, sleep homeostasis (Huber et al., 2004);
- in fact, they observed the occurrence of a circumscribed change of EEG SWA (i.e, a local increment of SWA) during sleep, in a cortical region involved in the performance of a learning task, following the performance of that task. This local increment of SWA resulted in a significant improvement in the task performance when it was repeated after sleep, in contrast to task performance in subjects who did not sleep in between the two tests. Conversely, prolonged immobilization of an arm causes a local decrement of EEG SWA during sleep in the corresponding arm cortical area (Huber et al., 2006);
- These data have been interpreted as indicating that the electrophysiologic marker of sleep homeostasis, SWA, can be selectively modulated in circumscribed cortical areas, suggesting, therefore, a local regulation of sleep (Huber et al., 2004);
- In addition, a local SWA increment following a learning task is presumably associated with plastic changes occurring in the cortical regions involved in learning processes. These data, therefore, may demonstrate a correlation between local SWA homeostasis during sleep and learning/cognitive performances related to the cortical areas in which SWA homeostasis was modulated.

Mechanisms Leading to Cognitive Deterioration

- Maintenance of SWA homeostasis probably reflects local synaptic modifications underlying a cellular need for sleep

Tononi & Cirelli, 2003

Mechanisms Leading to Cognitive Deterioration

- Taking into account these data, ESES might be considered as a model of the clinical effects of a localized disruption of EEG activity during sleep caused by long-lasting sleep-related focal epileptic activity
- Following the data provided by Tononi's group, we hypothesize that prolonged focal epileptic activity during sleep (as it occurs in ESES) interferes with local SWA at the site of the epileptic focus, impairing neural processes and, possibly, the local plastic changes associated with learning and other cognitive functions

Tassinari & Rubboli, 2006

MRI abnormalities associated with depression in MTLE
Fernando Cendes (Brazil)

MRI abnormalities associated with depression in MTLE

Fernando Cendes
Departamento de Neurologia
FCM - UNICAMP

Controversies in Epilepsy and Behavior
When did neurologists and psychiatrists stop talking to each other?
Andres M. Kanner

- Patients with epilepsy have a significantly higher prevalence of psychiatric comorbid disorders involving depression, anxiety, psychotic, and attention deficit disorders.
- Accordingly, one would expect that psychiatrists would be actively involved in the evaluation and management of these patients.

Epilepsy & Behavior
Volume 4, Issue 6

IDENTIFICAÇÃO E CARACTERIZAÇÃO DAS VARIÁVEIS BIO-PSICO-SOCIAIS NA EPILEPSIA DE LOBO TEMPORAL

Tese de Doutorado

Priscila Camile Barioni Salgado

Orientação: Prof. Dr. Fernando Cendes

Universidade Estadual de Campinas / UNICAMP

APOIO CAPES

AVALIAÇÃO DO RESULTADO CIRÚRGICO:

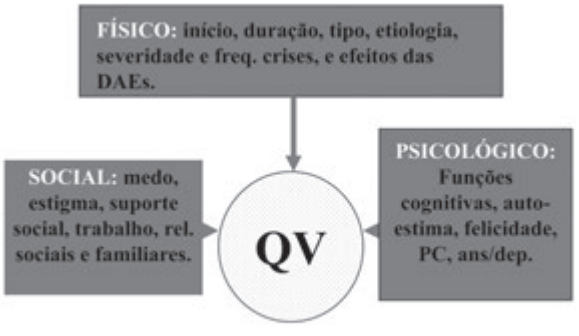
- Redução ou remissão total de crises?
- Expectativas pré-operatórias?
- Ajustamento pré-operatório?
- Ansiedade e depressão antes e depois da cirurgia?
- Idade?
- Tempo de adaptação?

QUALIDADE DE VIDA - HRQOL

"... é a diferença entre as expectativas das pessoas e suas experiências atuais."

(CALMAN, 1984)

MODELOS DE QV



HERMANN & WHITMAN (1986)

BAKER et al (1993)

PERCEPÇÃO DE CONTROLE DE CRISES

Quando o sujeito percebe que não tem o controle de suas próprias respostas, seu senso de auto-determinação é prejudicado, o que o torna menos capaz de aprender sobre si mesmo através de suas próprias experiências.

INCIDÊNCIA DE ANSIEDADE E DEPRESSÃO NA ELTM

ANSIEDADE: 11 a 44 %

DEPRESSÃO: 29 a 55%

ANSIEDADE

Componentes psicológicos/fisiológicos

Propulsora de desempenho

DEPRESSÃO

- **Tristeza**
- **Irritação**
- **Perda de interesse**
- **Mudança súbita de apetite e peso**
- **Insônia ou hipersonia**
- **Sentimento de inutilidade ou culpa**
- **Pensamentos de morte recorrentes**

ETIOLOGIA

PSICOLÓGICA:

TEORIA DO DESAMPARO APRENDIDO: déficits motivacionais, cognitivos e emocionais.

O desamparo é APRENDIDO!

Desamparo em uma situação	Generalização do desamparo	Frustração	Desamparo

(SELIGMAN, 1977)

ETIOLOGIA

BIOLÓGICA:

ELTM (lesão focal no sistema límbico), alterações eletrofisiológicas nestas áreas, lateralidade da lesão, DAEs, duração da epilepsia, tipo de crise

Depression in Epilepsy: A Neurobiologic Perspective
Andres M. Kanner, M.D.

AMERICAN EPILEPSY SOCIETY

EPILEPSY CURRENTS
Reviews and Critical Analysis

- *Depression is the most frequent psychiatric comorbidity in patients with epilepsy.*
- *Patients with depression are at higher risk of developing epilepsy than are controls.*
- *Such bidirectional relations raise the question of whether both disorders share common pathogenic mechanisms, presenting with common neurotransmitter abnormalities and involvement of the same neuroanatomic structures.*

OBJETIVO GERAL

1. Criar dois instrumentos de medida que avaliem as expectativas de mudança de vida de pacientes que se submetem à cirurgia de epilepsia (Instrumento 1) e a real mudança de estilo de vida e ajustamento psicossocial destes pacientes após o procedimento cirúrgico (Instrumento 2).

OBJETIVO GERAL

2. Identificar as variáveis psicossociais (QV, ansiedade e depressão) que estão inter-relacionadas com ELTM e sua relação com características clínicas (tipo e freqüência de crises, duração da epilepsia) e de neuroimagem (volumetria hipocampal).

EXPECTATIVAS PRÉ-OPERATÓRIAS E MUDANÇA DE ESTILO DE VIDA APÓS O TRATAMENTO CIRÚRGICO: DOIS QUESTIONÁRIOS DESENVOLVIDOS PARA SE ENTENDER O PROCESSO DE AJUSTAMENTO PSICOSSOCIAL APÓS A CIRURGIA DE EPILEPSIA

SUJEITOS

- **72 pacientes esperando a cirurgia (PREOP)**
- **36 pacientes operados e avaliados 6 e 12 meses após a cirurgia (POSOP 1 e POSOP 2)**

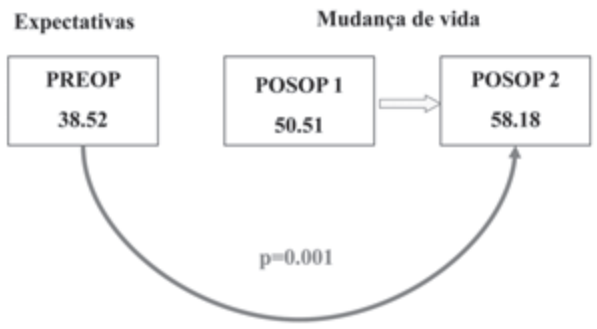
RESULTADOS

CARACTERÍSTICAS CLÍNICAS E DEMOGRÁFICAS DOS SUJEITOS

	PREOP	POSOP1	POSOP2
IDADE	15 a 52 (M=35)	18 a 50 (M=34)	18 a 50 (M=34)
ESCOLARIDADE	Fundamental	Fundamental	Fundamental
TRABALHO	67% sem trabalho	74% sem trabalho	71% sem trabalho
ESTADO CIVIL	70% solteiro	74% solteiro	65% solteiro
DURAÇÃO DA EPILEPSIA	2 a 48 (M=25)	6 a 50 (M=24)	6 a 50 (M=25)
FREQ DE CRISES (p=0.003)	1 a 30 (M=9.62)	0 a 30 (M=2.96)	0 a 30 (M=3.71)
PERCEPÇÃO DE CONTROLE (p<0.0001)	37% SIM	94% SIM	97% SIM

RESULTADOS

ESCORES DOS QUESTIONÁRIOS



RESULTADOS

PROPRIEDADES PSICOMÉTRICAS DOS QUESTIONÁRIOS

	CONSISTÊNCIA INTERNA	TESTE-RETESTE	QUESTÃO-OURO
PREOP	0.855	0.79	p<0.001
POSOP	0.833	0.92	p<0.001

DISCUSSÃO

- **Trabalho é o aspecto mais afetado pela epilepsia.**
- **Não há aumento significativo da empregabilidade após a cirurgia.**
- **Pacientes passam a observar que a EPILEPSIA NÃO É A CAUSA deste problema social.**
- **Pacientes SENTEM-SE capazes de trabalhar, embora não tenham oportunidade de emprego ou acreditem que não há mais mercado para eles.**

DISCUSSÃO

EXPECTATIVAS MAIS COMUNS:

- **Ser feliz**
- **Ser menos preocupado**
- **Usar menos DAEs**
- **Trabalhar**

EXPECTATIVAS PRÉ-OPERATÓRIAS E MUDANÇA DE ESTILO DE VIDA APÓS O TRATAMENTO CIRÚRGICO PARA EPILEPSIA DE LOBO TEMPORAL

RESULTADOS

- **A presença de ansiedade e depressão no POSOP não foi associada à ocorrência destes distúrbios no PREOP.**

DISCUSSÃO

DEPRESSÃO demorou mais para melhorar: dificuldade de adaptação e ajustamento após longo período com um padrão de comportamento definido.

ANSIEDADE e QV tiveram leve piora com o tempo: efeito da sensação de cura miraculosa.

CONCLUSÃO

- **O tratamento cirúrgico melhora a QV, ansiedade, depressão e freqüência de crises em pacientes com ELT.**
- **Importância do registro da avaliação psicossocial dos pacientes antes e depois do tratamento cirúrgico.**

AVALIAÇÃO DE ANSIEDADE E DEPRESSÃO NA EPILEPSIA DE LOBO TEMPORAL MEDIAL

MÉTODO

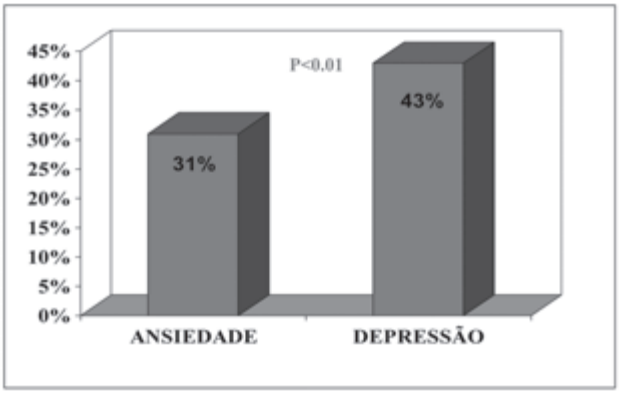
SUJEITOS:

67 pacientes com ELTM e exame de RM com volumetria dos hipocampos.

INSTRUMENTOS:

- STAI II
- BECK

RESULTADOS



RESULTADOS

	Direita	Esquerda	Bilateral	p-valor
Duração	30.05	27.31	32	0.5
Freqüência	6.21	9.15	3	0.3
Depressão	35.71%	46.66%	55.55%	0.2
Ansiedade	28.57%	33.33%	33.33%	0.6

CONCLUSÃO

O impacto da epilepsia se estende além da experiência de crises e envolve a avaliação do paciente de sua realidade.

Ansiedade e depressão são conseqüências da forma como os pacientes lidam com suas vidas.

DISCUSSÃO

Neste estudo, a incidência de ansiedade e depressão foi menor do que em estudos prévios, devido ao controle de crises da maioria dos sujeitos e ao maior número de sujeitos com percepção de controle da epilepsia.

CONCLUSÃO

Ansiedade e depressão ocorrem na epilepsia a partir da associação de aspectos psicológicos (PC e QV) e clínicos (freqüência e controle de crises).

CONCLUSÕES FINAIS

1. **A maioria dos pacientes se beneficia com o tratamento cirúrgico para ELTM, independente da eliminação total das crises epilépticas.**

2. **As maiores razões pelas quais os pacientes se submetem à cirurgia são: ser feliz, poder trabalhar, ser menos preocupado, e diminuir a quantidade de medicação.**

CONCLUSÕES FINAIS

3. **Os aspectos que foram representativos de maiores mudanças na vida dos pacientes após a cirurgia foram: ser capaz de cuidar da casa e da família, ser aceito pela família, sentir-se normal e menos discriminado.**

4. **Trabalho é o aspecto mais afetado pela epilepsia.**

CONCLUSÕES FINAIS

5. **Após um ano de cirurgia, os pacientes estão mais ajustados do ponto de vista psicossocial do que após seis meses.**

6. **Após a cirurgia de epilepsia, há melhora significativa da QV, ansiedade e depressão, e conseqüente satisfação com as mudanças obtidas após o tratamento.**

CONCLUSÕES FINAIS

7. **Ansiedade e depressão são distúrbios de humor que ocorrem concomitantemente na ELTM.**

8. **Não há associação entre ansiedade, depressão e lateralização do volume hipocampal.**

CONCLUSÕES FINAIS

9. **Ansiedade, depressão e QV não estão associadas aos dados pessoais dos pacientes (idade, sexo, estado civil, nível de escolaridade, emprego).**

10. **Depressão e QV não estão associadas aos dados clínicos da ELTM (tipo e freqüência de crise, duração da epilepsia, volumetria hipocampal).**

CONCLUSÕES FINAIS

11. **O único aspecto clínico da epilepsia que está associado à ansiedade é a freqüência de crises.**
12. **A percepção de controle da epilepsia acontece a partir do controle real ou da redução da freqüência de crises, e esta relacionada à QV.**
13. **Ansiedade e depressão estão negativamente associadas à QV e à percepção de controle da epilepsia.**

Epilepsy & Behavior 19 (2010) 422–427

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Neuroimaging changes in mesial temporal lobe epilepsy are magnified in the presence of depression

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ABSTRACT

Objective: The aim of this study was to investigate differences in gray matter volume between patients with mesial temporal lobe epilepsy (MTLE) with and without depression using voxel-based morphometry.
Method: We included 48 adults with refractory MTLE (31 women, 39.18 ± 8.4 years) and 98 healthy controls (79 women, 37.11 ± 8.8 years). For the psychiatric evaluation, the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Axis I, was used for the diagnosis of depression, and the Beck Depression Inventory, for the determination of symptom intensity. All patients underwent an MRI scan. Patients were separated into two groups: those with MTLE with depression (*n* = 24) and those with MTLE without depression (*n* = 24). We performed voxel-based morphometric analysis, comparing patients with controls using the *t* test.
Results: The number of areas of gray matter volume loss was higher in patients with MTLE with depression than in those with MTLE without depression.
Conclusions: The evidence of more widespread gray matter volume loss in patients with MTLE and depression calls our attention to the importance of timely recognition and treatment of depression in patients with MTLE and also to the bidirectional relationship between the two disorders and their frequent co-occurrence.

Table 1
Characteristics of the study participants.

	Healthy controls (*n* = 98)	MTLE (*n* = 48)	MTLE without major depression (*n* = 24)	MTLE with major depression[a] (*n* = 24)	Right MTLE (*n* = 22)	Right MTLE with major depression (*n* = 9)	Left MTLE (*n* = 26)	Left MTLE with major depression (*n* = 15)
Age	37.11 (8.8)	39.18 (8.4)	38.7 (7.7)	39.66 (9.1)	38.7 (7.2)	40.2 (6.6)	39.5 (9.3)	39.3 (10.4)
Sex								
Female	75	31	17	13	15	3	16	11
Male	21	17	7	11	7	5	10	5
BDI score	–	14 (13)	4 (3.7)	24 (11.1)	8.8 (9.6)	18.6 (10.1)	18.3 (13.8)	26.6 (10.9)
Epilepsy onset	–	9.7 (7.8)	10.7 (8.4)	8.7 (6.8)	9 (8.7)	11.9 (7)	10.3 (8.4)	7.4 (6.8)
Epilepsy duration[b]	–	27.8 (10.4)	25.8 (10.9)	26.7 (9.8)	28.2 (11.2)	28.2 (11.4)	27.5 (9.8)	30.5 (9.2)
Seizure frequency[c]	–	8.8 (8.6)	10.4 (9.7)	7.2 (7.2)	8.7 (8.7)	8.2 (6.5)	8.9 (8.7)	7.8 (7.7)

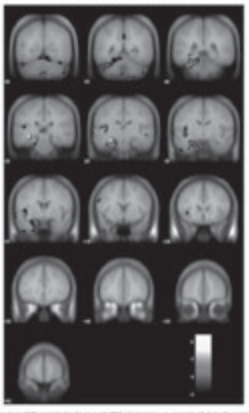
Note. Data are means (SD).
[a] According to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Axis I (SCID-I).
[b] Epilepsy duration was defined as years since first seizure.
[c] Seizure frequency was defined as number of seizures per month.

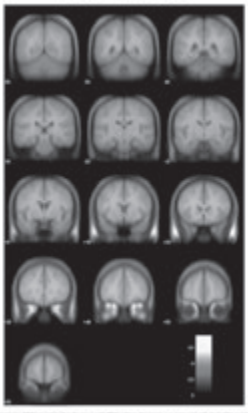
Table 2
Decrease in GMV in patients with MTLE with depression relative to the healthy controls matched for age and gender.

Region	Laterality	Voxel cluster size	*t*	*P* (FDR-corrected)
Hippocampus, parahippocampal gyrus, uncus	Bilateral	132432	7.50	<0.001
Thalamus	Left	32332	7.20	<0.001
Inferior and superior temporal gyrus	Bilateral	1145	4.65	<0.001
Inferior and middle frontal gyrus	Bilateral	8462	4.54	<0.001
Middle occipital gyrus, cuneus, fusiform gyrus	Left	239	2.97	0.016
Caudate body	Right	107	2.81	0.023
Postcentral gyrus	Left	52	2.62	0.033

Table 3
Decrease in GMV in patients with MTLE without depression relative to the healthy controls matched for age and gender.

Region	Laterality	Voxel cluster size	*t*	*P* (FDR-corrected)
Hippocampus, parahippocampal gyrus	Left	1296	5.37	0.005
Thalamus	Left	215	4.05	0.028
Inferior and middle frontal gyrus	Right	473	4.63	0.008
Caudate body	Left	34	3.84	0.004





Widespread damage in MTLE and Depression

- This more widespread extension of gray matter loss was also observed in our study, despite the fact that we selected patients with unilateral hippocampal atrophy for this study.
- This finding provides evidence that volumetric abnormalities among patients with chronic unilateral MTLE and depression extend beyond the affected ipsilateral areas.

Cognitive consequences of neonatal seizures

Magda Lahorgue Nunes (Brazil)

Cognitive consequences of neonatal seizures

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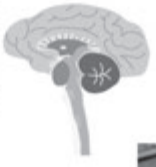
A translational approach



Clinical background

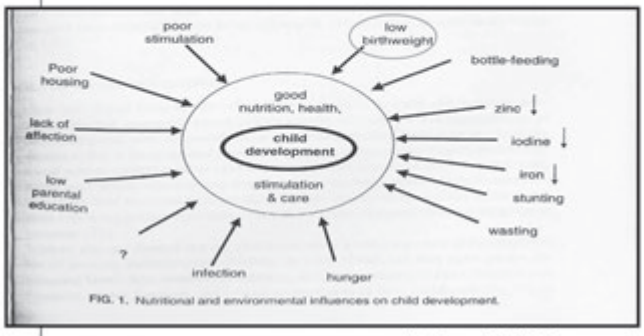


FIG. 1. Nutritional and environmental influences on child development.

Mc Gregor & Ani,2002

Clinical background

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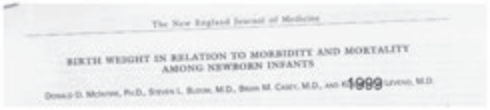
TABLE 1 Exposures before birth

Exposures	Short-term influence on	Putative long-term or permanent influence on
Socioeconomic status	Fetal growth and development	Adult cardiovascular disease and its risk factors
Maternal birth and current weight	Fetal growth and development	Adult cardiovascular disease and its risk factors
Maternal nutrition	Fetal growth and development	Adult cardiovascular disease and its risk factors
		Bone health
		Development/cognition
Maternal smoking	Fetal growth and development	Respiratory function
	Respiratory function	Adult cardiovascular disease and its risk factors
		Bone health
		Development/cognition
Maternal hypercholesterolemia	Fatty streaks in wall of aorta	Atherosclerotic changes
Maternal blood pressure	Fetal growth and development	Blood pressure
Gestational diabetes	Fetal growth and development	Later obesity and risk factors for adult cardiovascular disease
		Development/cognition

Short-term influences are not necessarily in the causal pathway between the exposure and putative long-term or permanent influence.

Morley & Dwyer, 2002

Clinical background: low birth weight



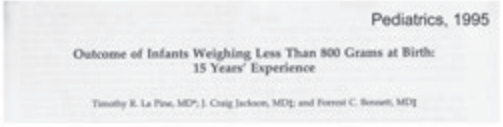
The New England Journal of Medicine

BIRTH WEIGHT IN RELATION TO MORBIDITY AND MORTALITY AMONG NEWBORN INFANTS

Donald D. McIntire, Ph.D., Steven L. Bloom, M.D., Brian M. Casey, M.D., and Kenneth J. Leveno, M.D.

1999

Mortality and morbidity are increased among term infants whose birth weight are at or below the 3rd percentile (122.754 singleton deliveries at a hospital in Dallas from 1988-1996)



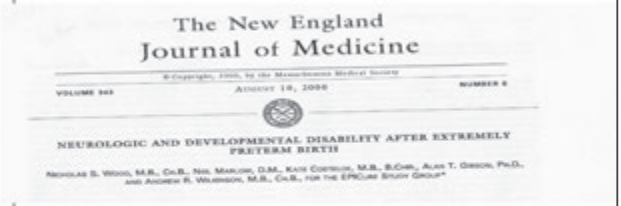
Pediatrics, 1995

Outcome of Infants Weighing Less Than 800 Grams at Birth: 15 Years' Experience

Timothy R. La Pine, MD*; J. Craig Jackson, MD‡; and Forrest C. Bennett, MD‡

Major neurosensory impairment observed in 22%

Clinical background: prematurity



The New England Journal of Medicine

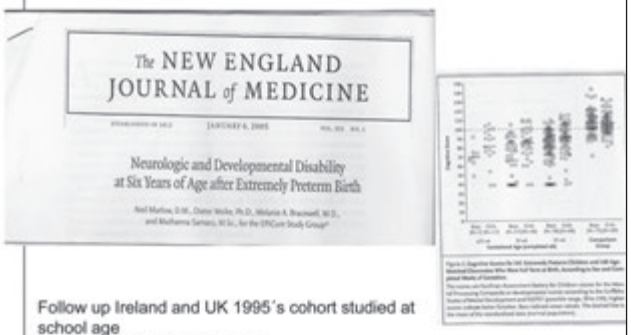
VOLUME 341 AUGUST 19, 1999 NUMBER 8

NEUROLOGIC AND DEVELOPMENTAL DISABILITY AFTER EXTREMELY PRETERM BIRTH

Nicholas S. Wood, M.B., Ch.B., Neil Marlow, D.M., Kate Costeloe, M.B., B.Chir., Alan T. Gibson, Ph.D., and Andrew R. Wilkinson, M.B., Ch.B., for the EPICure Study Group*

- Population study, Ireland and UK
- All children born <24 weeks GA in 1995
- Mean FU 30 months (n=283) : 49% had disability and among them 46% were severely disabled

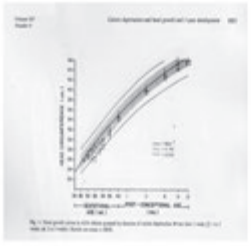
Clinical background: prematurity

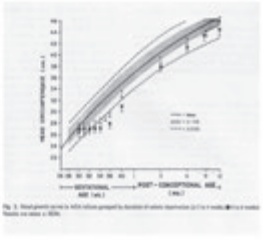

The NEW ENGLAND JOURNAL of MEDICINE

Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth

Follow up Ireland and UK 1995´s cohort studied at school age
41% with cognitive impairment
22% severe neurological disabilities

Clinical background: prematurity and caloric deprivation





Longer caloric deprivation on AGA preterm newborns correlated to suboptimal head growth and developmental delay at age 1year

Georgieff et al, 1985

Prematurity and low birth weight

Common outcomes:

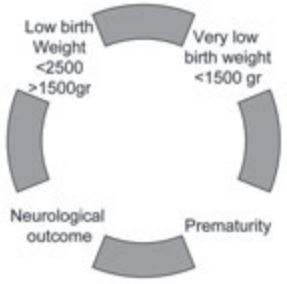
- Developmental delay
- Cognitive impairment
- Learning disorders
- Behavioral disorders
- Increased risk of epilepsy
- Cerebral palsy

Table 1 Birth prevalence of cerebral palsy among babies of different gestational ages

Gestational age (weeks)	Prevalence per 1000 live births	Birthweight (g)	Prevalence per 1000 live births
< 28	79.8	< 1000	82
28–31	40.4	1000–1499	54
32–36	6.7	1500–2500	6.7
> 36	1.11	> 2500	1.2

Original table data from Himmelmann et al (17).

Human model: high risk for sz preterm and low birth weight newborn



The developing brain: paradigms

- The developing brain is more susceptible for sz.
- The developing brain is less vulnerable to cell loss after sz.
- Although NS do not result in cell loss , it does not mean that sz do not cause any morphologic damage.
- The vulnerability might be explained due to disruption of highly demanded developmental processes like synaptogenesis, pruning, neuronal migration and differentiation.

Holmes GL, Clin Perinatol 2009; Galanopoulou & Moshé, Epilepsia 2009

Consequences of Neonatal Seizures in the Rat: Morphological and Behavioral Effects

Holmes GL et al. Annals of Neurology, 44:1-13,1998

- **When studied as adults, rats with recurrent flurothyl seizures had a significantly lower seizure threshold to PTZ than controls. Rats with recurrent seizures had greater numbers of dentate granule cells and more newly formed granule cells than the controls.**
- **Rats with recurrent seizures also had sprouting of mossy fibers in CA3 and supragranular region.**
- **Recurrent brief seizures during the neonatal period have long term detrimental effects on behavior, seizure susceptibility, and brain development.**

Animal model: malnourished rats submitted to seizures

- **Extrauterine malnutrition:** Limitation feeding by separating part of the litter from the lactating rat for increasing periods of time. The deprivation period starts on P2 for two hours and increase daily in two hours for a maximum of 12 hours. During separation, pups are maintained in heated cages.
- **Intrauterine malnutrition:** In this paradigm, the dams had a 50% reduction of the received ration from pregnancy until the pups' birth.
- **Seizures:** brief seizures and SE, agent: flurothyl

Effects of undernourishment

- Rats postneonatal undernourished form birth to P20, in adulthood were more susceptible to electrically induced sz in hippocampus (Taber et al.1979)
- Prenatal protein malnutrition retard the appearance of full motor convulsive sz with perforant path kindling even after nutritional rehabilitation (Bronzino et al. 1990)
- Prenatal protein malnutrition significant reduces the synaptic component of long term potentiating (LTP) , in adult rats (Austin et al. 1986)
- Adult rats previously malnourished during the suckling period had increased velocity of spreading depression (Rocha de Melo & Guedes, 1997)
- Pre natal protein malnutrition leads to behavior alterations and altered home orientation in P11 rats (Galler et al., 1994)

Research article

Effects of intra-uterine and early extra-uterine malnutrition on seizure threshold and hippocampal morphometry of pup rats

Mariana Lorenzet Florian, Magda Lahorgue Nunes

We evaluate the influence of different malnutrition paradigms (intra-uterine × extra-uterine) in body and brain weight, in seizure threshold and in hippocampus morphometry, in developing rats. Intra-uterine malnutrition model consisted in reduction by half of the ration offered to pregnant female; extra-uterine malnutrition consisted of progressive limitation of lactation, from P2 to P15. Seizure induction was accomplished by exposure to flurothyl, at P15. At the same day animals were sacrificed. Morphometric analysis was based on hippocampal pyramidal and granular cells estimate number, through volume calculation and cellular density. Extra-uterine malnutrition significantly reduced pups body and brain weight, seizure threshold and neuronal number in CA4 region only. Intra-uterine malnutrition reduced neuronal number in CA2, CA4 and DG regions regarding well-nourished and extra-uterine malnourished animals. In CA3, CA4 and dentate gyrus, a significant cell increase was observed in groups exposed to seizures, regarding similar control groups.

Nutritional Neuroscience 2010 Vol 13 No 5 1

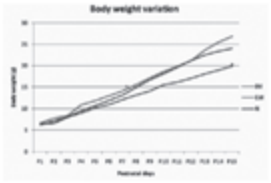


Table 1 Comparison of the cerebral weight among groups

Group	Brain weight (g)		
	Maximum	Minimum	Mean ± SD
IM	1.3	1.1	1.17 ± 0.075
EM	1.2	0.9	1.03 ± 0.091*
N	1.3	1.0	1.16 ± 0.106

Table 2 Variation of brain weight at P15 according to seizure paradigm

Group	Brain weight (g)		
	Maximum	Minimum	Mean ± SD
IM	1.3	1.1	1.17 ± 0.075
IMS	1.2	1.0	1.08 ± 0.106
EM	1.2	0.9	1.03 ± 0.091*
EMS	1.3	1.0	1.15 ± 0.104*
N	1.3	1.0	1.16 ± 0.106
NS	1.3	1.1	1.21 ± 0.781

Table 3: Variation of seizure threshold between groups.

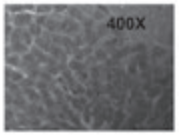
Group	Threshold in minutes (mean ± SD)
IMS	5.795 ± 1.627
EMS	2.916 ± 0.489*
NS	6.170 ± 0.918

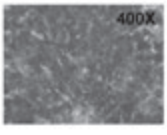
Florian & Nunes 2010

Table 4 Variation of cell counting according to the nutritional paradigm in each hippocampal region.

Region	IM Min - max (mean ± SD)	EM Min - max (mean ± SD)	N Min - max (mean ± SD)
CA1	10249–22762 (14615 ± 3996.9)	11371–31060 (20265 ± 6093.1)	16295–23160 (19491 ± 2311.8)
CA2	674–3011 (1370.2 ± 737.9*)	1325–7703 (3930.0 ± 2467.7)	2214–4856 (3594.6 ± 895.7*)
CA3	7266–19671 (13658 ± 3226.4)	9198–35762 (17574 ± 8370.4)	7934–25553 (14558 ± 6791.3)
CA4	1229–3418 (2591.8 ± 795.7*)	1597–4597 (2936.1 ± 1019.9**)	2694–7572 (4755.5 ± 1510.4***)
DG	20034–31123 (24902 ± 3908.7*)	22245–44569 (32462 ± 7137.7***)	19221 - 29978 (23991 ± 4027.0**)







cell size
P< 0.001

Nunes & Florian, 2010

Table 5 Cell counting (minimum, maximum, mean and SD (standard deviation)) in different regions according to seizure paradigm.

Group		Region					
		IMS	EMS	NS	IM	EM	N
CA1	Max	13650	13081	16920	10249	11371	16295
	Min	2577	2914	20562	22762	31060	23160
	Mean	19562	19320	22329	14615	20265	19491
	SD	± 3962.9	± 4156.7	± 3632.8	± 3996.9	± 6093.1	± 2311.8
CA2	Max	705	2039	2531	674	1325	3214
	Min	4101	5989	5130	3011	7703	4856
	Mean	2368.1	3472.0	3682.8	1370.2	3930.0	3594.6
	SD	± 1151.5	± 1969.1	± 856.4	± 737.9	± 2467.7	± 895.7
CA3	Max	3402	8044	12940	7266	9198	7934
	Min	20670	21639	31268	19671	35762	25553
	Mean	14810	14540	22067	13658	17574	14558
	SD	± 4003.5	± 4325.0	± 5816.0*	± 3226.4	± 8370.4	± 6791.3*
CA4	Max	1982	5099	1957	25034	1597	2694
	Min	3772	7624	6536	31123	4597	7572
	Mean	2677	5384	4120	24902	2936.1	4755.5
	SD	± 734.9	± 1616.9*	± 1246.0	± 3908.7	± 1019.9*	± 1510.4
DG	Max	23962	19854	25196	20034	22245	19221
	Min	32621	36838	45547	31123	44569	29678
	Mean	29322	26467	34717	24902	32462	23991
	SD	± 3142.2	± 7545.2	± 7571.8*	± 3908.7	± 7137.7	± 4027.0*

Asterisk(*) indicates statistically significant difference.SD, standard deviation.
Groups: intra-uterine malnutrition with seizure (IMS), extra-uterine malnutrition with seizure (EMS), nourished with seizure (NS), intra-uterine malnutrition without seizure (IM), extra-uterine malnutrition without seizure (EM), and nourished control (N).

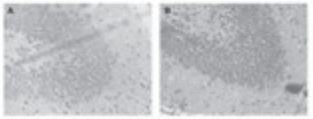
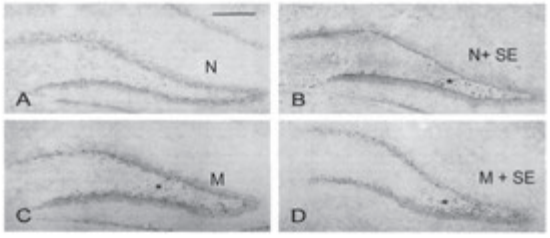


Figure 5 (A) Representative photomicrograph of the dentate gyrus of a rat of the nourished control (N) group. (B) Representative photomicrograph of the dentate gyrus of a rat of the adequate nutrition with seizure group (NS), showing the visible difference in the cellular quantity.

Malnutrition Increases Dentate Granule Cell Proliferation in Immature Rats After Status Epilepticus



Brain and Body Weight Evolution

/eight (g) /group	BW P2	BW P15	BW P30	BW P60	BRW P15	BRW P30	BRW/BW P15 (%)	BRW/BW P30(%)
Nourish	6.867 (± 0.64)	29.124 (± 6.14)	81.557 (± 11.03)	255.367 (± 35.37)	1.400 (± 0)	1.423 (± 0.03)	4.6% (± 0.71)	1.7% (±0.302)
alnourish	6.665 (± 0.46)	19.549[a] (4.66)	66.367[b] (± 14.40)	203.533 (33.48)	1.275[c] (± 0.05)	1.478 (± 0.01)	6.3%[d] (±0.129)	2.2%[e] (±0.631)

Values expressed as average± sd, BW= body weight, BRW= brain weight a) p=<0.0001, b) p=0.0017, c) p=0.029, d) p=<0.0001, e) p=0.0349.

(Nunes ML et al. J Pediatr 2002)

Malnutrition and seizure threshold

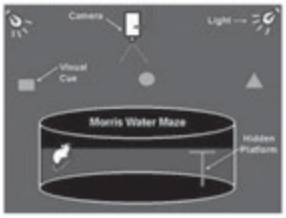
Nunes ML et al. J Pediatr (Rio J) 2002

Table 1: Seizure thresholds (time in seconds ± standard deviation) on P15 and P30 according t nutritional status and sex

Type of seizure/age	Controls	Malnourished rats	Males	Females
Clonic / P15	567±152	495±187 ↓	538±174	538±163
Tonic / P15	614+168	537+151 ↓	535±113	635±179
Clonic / P30	521±70	536±152 ↑	554±152	501±72
Tonic / P30	660±149	746±110 ↑	729±127	691±41

Obs.: differences between groups were not statistically significant (P> 0.05).

Morris water maze: test hippocampal-dependent spatial memory



Centro da Memória- IPB-PUCRS

Enriched environment

Neurolab –IPB - PUCRS

Sz threshold : recurrent brief x SE

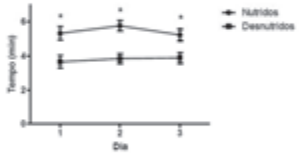


Figura 16 Comparação do limiar convulsivo em P8, P9 e P10.

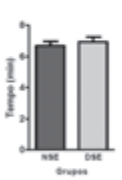


Figura 17 Comparação do limiar convulsivo em P16

Model : recurrent brief sz at P8,P9 and P10, SE at P16, enriched environment P30-P60

Porto al, 2010 (unpublished data)

Multiple trials, animals raised in enriched environment better performance

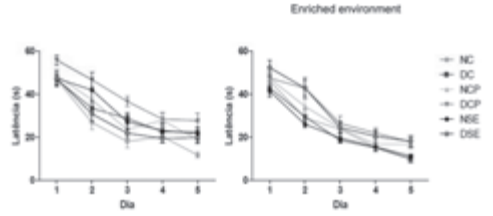


Figura 18 Curvas de aprendizado.

Porto al, 2010 (unpublished data)

Time spent in target quadrant

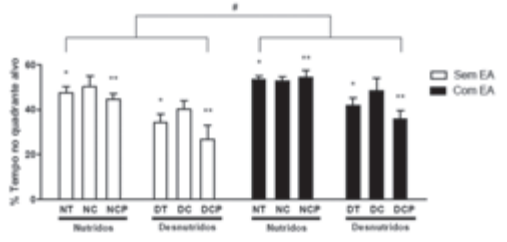


Figura 19 Teste de prova (I)

As médias da porcentagem de tempo despendido no quadrante alvo foram maiores nos animais submetidos ao enriquecimento ambiental (EA).

Porto al, 2010 (unpublished data)

Summary of Experimental Evidences

- The effects of sz and SE in developing rats appears to be age-dependent
- Brief recurrent sz during early development results in cognitive impairment , mossy fiber sprouting in CA3, reduced neurogenesis, alterations in the expression and distribution of glutamate and GABA receptors, enhanced excitability
- Enriched environment improves spatial memory

Neonatal Follow up Outpatient Clinic

HOSPITAL SÃO LUCAS DA PUCRS

Other consultants: Ophthalmology, Speech Disorders, Physical Therapist
Activities include Medical students, Interns, Residents and PhD students

Neonatal Follow up Outpatient Clinic

Groups of interest

- Preterm newborns (GA <37 weeks)
- Low birth weight (<2500 grams)
- Neonatal seizures
- Mechanical ventilatory support

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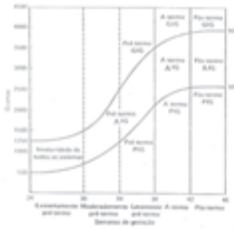
Classification of birth weight



SGA = small for gestational age
AGA = adequate for gestational age
LGA = large for gestational age

(Battaglia & Lubchenco, 1967)

- Below 2500 grams: low birth weight
- Below 1500 grams: very low birth weight
- Below 1000 grams: extremely low birth weight

(Sweet, 1990; Wong, 1999)

Screening

- Denver II (0-6 years)
- Bayley (until age 3 years)
- Connors (from 3 years on)
- WPPSI (4-6 years)
- WISC e neuropsychological assessment (>6 y)
- Clinical Neurological Examination

Birth cohort 1999

HOSPITAL SÃO LUCAS DA PUCRS

- Initial cohort - 222 preterm neonates (GA <37 weeks), born between January 1st and December 31st , 1999.

⇩

- 25 deceases in the neonatal period
- During 1999-2000, around 60-70% were regularly followed at ages 3,6,9,12 months.

Arq Neuropsiquiatr 2006;64(4):926-931

CLINICAL ASSESSMENT OF LANGUAGE DEVELOPMENT IN CHILDREN AT AGE 3 YEARS THAT WERE BORN PRETERM

Carolina Rizzotto Schirmer[1], Mirna Wetters Portuguez[2], Magda Lahorgue Nunes[3]

ABSTRACT - *Objective:* To evaluate the influence of gestational age and birth weight on language development and neurodevelopmental outcome at age 3 years in children born preterm. *Method:* Cross sectional study including 69 children followed in our developmental outpatient clinic. Patients were consecutively included at the time of the 3 years of age appointment and stratified for birth weight (<1500 grams and between 1500-2500 grams). All patients were assessed for receptive and expressive language , Denver II and Bayley II tests and clinical neurological examination. For analysis patients were divided in two groups n o rmal language acquisition (NLA) and delay in language acquisition (DLA). *Results:* NLA children had higher scores on mental and psychomotor (p=<0.01, p=0.012) indexes of Bayley II. Newborns with less than 1500 grams had lower scores on all Bayley scale at age 36 months (p=0.002, p=0.007 and p<0.001). Multivariate analysis suggests an association between gestational age (p=0.032), abnormal behavior (p=0.001) and delay in language acquisition. Denver test at 12 and 24 months of age was a good predictor for delayed receptive and expressive language at three years of age (p=<0.01 and p=<0.01). *Conclusion:* Children born prematurely with low birth weight had an increased risk of language acquisition delay, and those had also lower cognitive and behavior scores when compared to NLA.

KEY WORDS: prematurity, low birth weight, language acquisition, developmental delay, Bayley infant scale, Denver test.

CLINICAL ASSESSMENT OF LANGUAGE DEVELOPMENT IN CHILDREN AT AGE 3 YEARS THAT WERE BORN PRETERM

Table 1. Clinical characteristics between the groups with and without language alteration at 36 months of age.

Characteristics	NLA n=34	DLA n=35	p
Gestational age (weeks)	33.18±2.58	32.03±2.80	0.081
Birthweight (grams)	1622.79±472.49	1483±475.09	0.228
Sex			
Male	15 (44.1)	7 (48.6)	0.811
Female	19 (55.9)	18 (51.4)	–
Neonatal neurological disorder	12 (35.3)	11 (31.4)	0.802
Without neonatal neurological disorder	22 (64.7)	24 (68.6)	–
Bayley score (36 months)			
Mental score	103.15±14.68	88.11±110.86	**<0.01**
Psychomotor score	105.29±13.01	96.03±16.55	**0.012**
Alteration behaviour scale – Bayley test (36 months)	7 (20.6)	23 (65.7)	**<0.01**
Abnormal Denver test II (36 months)	2 (5.9)	11 (31.4)	**0.012**
Normal Denver test II (36 months)	32 (94.1)	24 (68.6)	–

NLA, normal language acquisition; DLA, delay in language acquisition (DLA). Data are presented as mean (±) standard deviation or percentage (), chi-square test.

In the group studied, 23 children had neonatal neurdogical disorders such as perinatal asphyxia (9), intraventricular hemorrhage grade I (6), congenital infection (4), seizures (3) and bacterial meningitis (1).

CLINICAL ASSESSMENT OF LANGUAGE DEVELOPMENT IN CHILDREN AT AGE 3 YEARS THAT WERE BORN PRETERM

Table 5. Multivariate analysis: association between gestational age, Denver test (12 and 24 months) and abnormal behavior and language alteration at 36 months of age.

Variable	OR (IC 95%)[1]	p-value[2]	OR (IC 95%)[1]	p-value[2]	OR (IC 95%)[1]	p-value[2]
Gestacional age						
<32.5 wk	1		1		1	
>32.5 wk	3.91 (0.77-19.81)	0.100	2.84 (0.70-11.58)	0.144	3.47 (1.11-10.85)	0.032*
Denver 12						
Normal	1		1		–	–
Abnormal	1.85 (0.25-13.39)	0.543	3.64 (0.83-16.00)	0.088	–	–
Denver 24						
Normal	1		–	–	–	–
Abnormal	3.85 (0.58-25.68)	0.164	–	–	–	–
Bayley-behavioral scale						
Normal	1		1		1	
Abnormal	14.04 (2.78-70.97)	0,001*	9.73 (2.34-40.55)	0.002*	8.47 (2.66-27.00)	0.000*

Statistical significance, [1]Odds ratio adjusted, [2]Weld test.

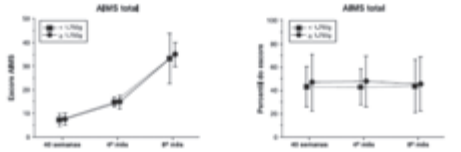
Jornal de Pediatria

ARTIGO ORIGINAL

Evaluation of motor performance of preterm newborns during the first months of life using the Alberta Infant Motor Scale (AIMS)

Avaliação do desempenho motor de prematuros nos primeiros meses de vida na Escala Motora Infantil de Alberta (AIMS)

Silvia Maneschy[1], Magda Lahorgue Nunes[2]



44 newborns, 14 with birth weight <1750 grams and 30 with ≥ 1750 grams

J Pediatr (Rio J). 2008;84(1):53-59

0021-7557/08/84-01/
Jornal de Pediatria

ORIGINAL ARTICLE

Cognitive and behavioral status of low birth weight preterm children raised in a developing country at preschool age

Júlia L. do Espírito Santo,[1] Mirna W. Portuguez,[2] Magda L. Nunes[2]

Table 1 - Results from WPPSI subtests

Subtests	Mean ± SD	Minimum score	Maximum score	% of children with abnormal results
Information	8.99±3.05	1	15	10.0
Vocabulary	8.29±2.23	2	15	7.5
Arithmetic	8.06±4.02	1	18	32.5
Similarities	10.46±2.56	2	15	5.0
Comprehension	7.96±2.69	1	18	17.5
Animal pegs	7.79±3.14	1	17	27.5
Picture completion	10.33±2.96	3	18	6.3
Mazes	7.90±2.65	2	16	16.3
Geometric design	8.04±3.02	1	19	16.3
Block design	8.20±2.59	1	14	13.8

SD = standard deviation; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

Table 2 - Comparison between WPPSI total IQ and Mental and Motor Bayley Development Scales (previously done), neurological examination, Denver Test, and neonatal problems

Items	Total IQ: Inferior, n (%)	Total IQ: Average/Superior, n (%)	p
Bayley mental			< 0.001*
Normal	4 (15.4)	22 (84.6)	
Questionable	3 (16.7)	15 (83.3)	
Below	6 (100.0)	0 (00.0)	
Bayley motor			0.015*
Normal	6 (16.2)	31 (83.8)	
Questionable	4 (44.4)	5 (55.6)	
Below	3 (75.0)	1 (25.0)	
Neurological exam			0.007*
Normal	12 (17.1)	58 (82.9)	
Abnormal	6 (60.0)	4 (40.0)	
Denver test			< 0.001*
Normal	8 (13.3)	52 (86.7)	
Questionable	3 (30.0)	7 (70.0)	
Abnormal	7 (70.0)	3 (30.0)	
Neonatal disorders			1.000†
Yes	18 (23.4)	59 (76.6)	
No	0 (0.0)	3 (100.0)	

WPPSI = Wechsler Preschool and Primary Scale of Intelligence.
* Chi-square.
† Fischer's test.

Table 3 - Scores obtained in the Conners' Parent Rating Scale-Revised and percentage of children with abnormal results for each variable

Variable	Mean ±SD	Variation of scores	% of abnormal results
Oppositional behavior	62.40±12.63	39-90	36.3
Cognitive deficits /inattention	65.39±14.04	44-90	43.8
Hyperactivity	64.08±12.68	41-90	43.8
Anxious-shy	58.08±12.28	38-90	27.5
Perfectionism	59.15±9.58	41-85	25
Social problems	61.71±14.85	44-90	31.3
Psychosomatic	62.14±14.89	42-90	41.3
ADHD index	61.93±13.36	40-90	33.8
Restless-impulsive	62.38±12.84	39-90	35.0
Emotional-ability	55.74±11.92	39-83	21.3
Conners' global index	60.89±11.63	38-90	31.3
DSM-IV inattention	61.90±13.63	41-90	36.3
DSM-IV hyperactive-impulsive	66.28±12.71	43-90	48.6
DSM-IV ADHD total	65.44±12.84	41-90	41.3

ADHD = attention deficit/hyperactive disorder; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; SD = standard deviation.

Summary : outpatient follow up clinic

1999-2006 cohort
Preterm (GA<37 wks)
Low birth weight (<2500gr)

↓

406 patients followed
8% post neonatal epilepsy
26% developmental delay
Neonatal sz and IVH were risk factors for both outcomes

Factors that affect cognition in epilepsy

- Premorbid and non seizure related
  - acquired cerebral lesions
  - hereditary background
  - psychosocial influences
- Sz related
  - Etiology
  - Age at sz onset
  - Type, frequency and duration of sz
  - Structural damage caused by repetitive or prolonged sz
  - Ictal and interictal physiological dysfunction
  - Duration of epilepsy
- Treatment related
  - DAEs
  - Sequelae of epilepsy surgery

Meador, Neurology 2002

Pediatr Neurol 2004;30:271-277.

Risk Factors for Developing Epilepsy After Neonatal Seizures

Luis Fernando Garcias Da Silva, MD, Magda Lahorgue Nunes, MD, PhD, and Jaderson Costa Da Costa, MD, PhD

Time of follow-up (months)	PNE (n)	Incidence (%)
12	28	22
24	33	26
36	36	28.3
48	38	30

6528 neonates admitted between 1987 and 1997/ 158 with sz
Incidence of neonatal seizures in the population 24.2:1000
Mortality after sz 15% (early 4/158 and late 20/158)
34.6% preterm, 56% male

Table 1. Relationship between etiologic factors associated with neonatal seizures and incidence of postnatal epilepsy in premature and term newborns

Etiology	Newborns With Seizures (n = 127)		Postnatal Epilepsy (n = 43)		Significance (P)	
	Premature	Term	Premature	Term	Premature	Term
Perinatal asphyxia	15	28	4	14	0.85	0.19
Hemorrhage						
IVH	7	0	2	0	1.0	—
Cryptogenic	2	7	1	3	1.0	0.29
Traumatic	0	1	0	1	—	0.38
CNS infection						
Congenital	1	0	1	0	0.25	—
<Expand>C	4	11	1	8	1.0	0.04*
CNS dysgenesis	2	2	1	1	0.44	1.0
Benign neonatal seizures	0	1	0	0	—	1.0
Withdrawal syndrome	0	4	0	0	—	0.29
Metabolic disorders						
Electrolytic imbalance	16	21	1	2	0.73	0.48
Persistent hypoglycemia	1	0	1	0	1.0	—
IEM	0	4	0	2	—	0.38

* Statistically significant result.

Abbreviations:
CNS = Central nervous system
IEM = Inborn error of metabolism
IVH = Intraventricular hemorrhage

Da Silva et al, 2004

Table 2. Relationship between clinical and neurophysiologic aspects associated with neonatal seizures and postnatal epilepsy

Variables	Result	Number of Newborns	Postnatal Epilepsy (n)	Significance (P)
Time of seizures	Early	106	38	0.130
	Late	21	4	
Maintenance of AED therapy*	Yes	92	38	0.002**
	No	35	4	
Neurologic exam	Normal	32	2	0.003**
	Abnormal	95	39	
Polysomnography	Normal	17	1	0.025**
	Abnormal	83	36	

* Newborns on chronic AED therapy.
** Statistically significant results.

Abbreviation:
AED = Antiepileptic drug

Da Silva et al, 2004

Table 3. Etiology of seizures during neonatal period and its relationship with the epileptic syndrome developed

Type of Epilepsy	n	Etiology and No. of Patients	
Focal symptomatic epilepsy	10	Asphyxia	4
		Acquired CNS infection	4
		Electrolytic imbalance (Ca^{++})	1
		Cryptogenic hemorrhage	1
West syndrome	12	Asphyxia	6
		Congenital CNS infection	1
		CNS dysgenesis	2
		IVH	1
		Persistent hypoglycemia	1
		Electrolytic imbalance (Ca^{++}, Na^{+})	1
Early infantile epileptic encephalopathy	3	Inborn error of metabolism	1
		IVH	1
		Acquired CNS infection	1
Early myoclonic encephalopathy	2	Asphyxia	1
		Inborn error of metabolism	1
Other generalized symptomatic epilepsies	3	Asphyxia	
		Acquired CNS infection	1
		Cryptogenic hemorrhage	2
		Traumatic hemorrhage	1
Lennox-Gastaut syndrome	1	Cryptogenic hemorrhage	1
Partial cryptogenic epilepsy	1	Electrolytic imbalance (Na^{+})	1
Syndromes not determined as focal or generalized	9	Asphyxia	6
		Acquired CNS infection	3

Abbreviations:
CNS = Central nervous system
IVH = Intraventricular hemorrhage

Table 4. Outcome and comorbidity in newborns with and without postneonatal epilepsy

Outcome and Comorbidity	Postneonatal Epilepsy (n = 45)	Without Postneonatal Epilepsy (n = 84)	Significance (χ^2) and RR (95% CI)
Normal development	25%	62%	
Cerebral palsy	14%	8%	$P < 0.01$ RR 3.7 (1.45–8.30)
Cognitive deficits	11.6%	4.7%	$P = 0.01$ RR 3.77 (1.43–8.72)
CP + CD	51.6%	27.3%	$P < 0.01$ RR 3.39 (1.74–6.42)

Abbreviations:
CD = Cognitive deficits
CI = Confidence interval
RR = Relative risk

Da Silva et al, 2004

Arq Neuropsiquiatr. 2008;66(2-A):168-174

NEUROLOGICAL OUTCOME OF NEWBORNS WITH NEONATAL SEIZURES

A cohort study in a tertiary university hospital

Magda Lahorgue Nunes[I], Maurer Pereira Martins[I], Bianca Menke Bavaresco[I], Ricardo C. Weinberg[II], Jailson Costa da Costa[II]

Abstract – Objective: To describe the neurological outcome of newborns with seizures. Method: Cohort study with newborns prospectively followed. Perinatal characteristics and etiological screening were related to outcome in a regression model. Results: During the study 3689 newborns were admitted and 2.7% were diagnosed as having seizures. Hypoxic ischemic encephalopathy (51%) was the etiology more frequently associated to seizures and also to postneonatal epilepsy (55%). In the follow-up 25 died during the acute neonatal illness and 9 during the first years of life. 19 were diagnosed as having post-neonatal epilepsy, 70 had developmental delay and 13 an association among this two comorbidities. A significant association between abnormal postnatal EEG and neuroimaging to developmental delay (p=0.04, p=0.026) was observed. The group of newborns that had seizures presented an increased risk of developing epilepsy compared to newborns from the same cohort without seizures (18.1/100 vs. 1.6/100, p<0.001). Conclusion: In this study neonatal seizures predominated in term newborns with perinatal asphyxia an elevated perinatal mortality and post neonatal morbidity was observed. The follow- up showed an increased risk for developing postnatal epilepsy and developmental delay.

- 3689 admitted (january 1999 - decemeber 2003) , 101 NS (2.7%),
- Perinatal mortality whole unit 8%, in neonates with sz 25%
- 57% male, 28.6 % preterm, 71% AGA
- Outcomes (36 months of follow up, n=64): Postneonatal death 8.9%, Postneonatal epilepsy : 30%, developmental delay 54.6%,

Table IA. Risk factors for developmental delay

Variables		Yes n (%)	No n (%)	RR (CI 95)	p
Discharge with AED	Yes	24 (58.5)	19 (44.2)	1.3 (0.7–2.3)	0.33
	No	9 (42.9)	12 (57.1)		
Neonatal EEG	Altered	25 (53.2)	22 (46.8)	1.5 (0.9–2.5)	0.30
	Normal	3 (30)	7 (70)		
Postneonatal EEG	Altered	15 (71.4)	6 (28.6)	2.8 (1.4–5.7)	0.001
	Normal	4 (19)	17 (81)		
Birth weight (grams)	<2500g	13 (80)	3 (20)	1.9 (1.3–2.9)	0.01
	≥2500g	20 (41.7)	28 (58.3)		
Neonatal neuroimaging	Altered	22 (66.7)	11 (33.3)	1.9 (1.1–3.3)	0.01
	Normal	11 (35.5)	20 (64.5)		
Postneonatal neuroimaging	Altered	18 (81.8)	4 (18.2)	3.5 (1.4–8.8)	<0.001
	Normal	15 (35.7)	27 (64.3)		
Prematurity (GA<37wks)	Yes	11 (84.6)	2 (15.4)	1.9 (1.3–2.9)	0.008
	No	22 (43.1)	29 (56.9)		
Repeated seizure	Yes	24 (53.3)	21 (46.7)	1.0 (0.5–2.1)	0.94
	No	6 (54.5)	5 (45.5)		
Sex	Male	15 (40.6)	19 (59.4)	0.6 (0.4–1.1)	0.80
	Female	20 (62.5)	12 (37.5)		
Type of delivery	Vaginal	17 (58.6)	12 (41.4)	0.9 (0.5–1.9)	0.98
	Cesarean	14 (58.3)	10 (41.7)		

RR, relative risk; CI, confidence interval; AED, antiepileptic drug; EEG, electroencephalogram; GA, gestational age (Pearson Chi-Square and Fisher's Exact Test with 95% Confidence Interval).

Nunes et al. 2008

Table 24. Risk factors for postnatal epilepsy

Variables		Yes n (%)	No n (%)	RR (CI 95)	p
Discharge with AED	Yes	16 (37.2)	27(62.8)	1.9 (0.7–5.1)	0.14
	No	4 (19)	17 (81)		
Neonatal EEG	Altered	16 (34)	31 (66)	1.4 (1.0–1.8)	0.25
	Normal	1 (10)	9 (90)		
Postneonatal EEG	Altered	15 (71.4)	6 (28.6)	2.7 (1.3–5.5)	**0.002**
	Normal	5 (23.8)	16 (76.2)		
Birth weight (grams)	<2500g	9 (60)	6 (40)	2.9 (1.4–5.7)	**0.008**
	≥2500g	10 (20.8)	38 (79.2)		
Neonatal neuroimaging	Altered	10 (30.3)	23(69.7)	1.1 (0.5–2.2)	0.86
	Normal	10 (32.3)	21 (67.7)		
Postneonatal neuroimaging	Altered	11 (50)	11 (50)	1.6 (1.0–2.5)	0.02
	Normal	9 (21.4)	33 (78.6)		
Prematurity	Yes	6 (46.2)	7 (53.8)	1.7 (0.8–3.5)	0.19
	No	14 (27.5)	37 (72.5)		
Repeated seizure	Yes	14 (31.1)	31 (68.9)	1.1 (0.5–2.5)	0.81
	No	3 (27.3)	8 (72.7)		
Sex	Male	10 (31.3)	22 (68.8)	1 (0.7–1.4)	1
	Female	10 (31.3)	22 (68.8)		
Type of delivery	Vaginal	7 (24.1)	22 (75.9)	1.2 (0.8–1.8)	0.29
	Cesarean	9 (37.5)	15 (62.5)		

RR, relative risk; CI, confidence interval; AED, antiepileptic drug; EEG, electroencephalogram; GA, gestational age (Pearson Chi-Square and Fisher's Exact Test with 95% Confidence Interval).

Nunes et al. 2008

Conclusions

- The etiology of sz is the primary determinant of outcome
- Lack of effective treatments and possible deleterious effects of DAEs in the developing brain may influence outcome
- Electrographic sz without clinical manifestations might result in brain damage
- Death, postneonatal epilepsy, behavioral problems and mental retardation are common outcomes for neonates with seizures
- Morbidity and mortality : increased risk in preterm and low birth weight newborns

Thanks to

Malnutrition Team in Brazil

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THE PATIENTS' PERCEPTION ABOUT EPILEPSY AND WHAT THEY DO ABOUT IT

PETER WOLF (DENMARK)

EPILEPSIHOSPITALET
FILADELFIA

The patients' perception of epilepsy and what they do about it
Peter Wolf (Denmark)

LASSE V, Guarulhos February 20 – March 1, 2010

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Two aspects

1. Perception of the seizures
2. Perception of epilepsy as a disease

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Perception of seizures
Different situations to be considered

1. Some patients have only seizures with subjective symptoms (e.g. isolated auras, myoclonic szs)
2. Many have seizures with both subjective symptoms and objective signs
3. Others have seizures with only objective signs

Difference fundamental for self-perception!

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1) Subjective symptoms only (isolated auras)

Isolated auras as the only or first manifested seizure type

- Patients are often not aware that their symptoms have anything to do with epilepsy or that they are pathological at all.
- These patients typically talk for the first time about their experiences to a doctor when eventually they get a first GTC seizure, typically evolving out of the aura
- May have had auras since many years
- Can be very shocking experience
- Literary examples: Margiad Evans; Kirillov in Dostoyevsky's "Devils"

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Isolated auras as remaining seizure type

- In some pts with focal epilepsies AED therapy controls all other seizure types but not the isolated auras
- Tendency to neglect or dissimulate these. Pts may even not be aware of their significance if auras earlier always evolved into a major seizure.
- May have understood aura as a "warning" *before* the seizure and not *part of* the seizure.
- Needs to be explained
- They need to be specifically asked about these
- Neglected isolated auras may be a reason for relapse at discontinuation of AEDs with "seizure free" pts

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Patients' concerns

- Depending on the aura type pts may be unwilling to talk about these: afraid that they may be thought crazy.
- Especially true for hallucinations
- Some pts afraid themselves of becoming crazy
- Need to be assured that these are not symptoms of psychosis
- Rarely auras experienced as pleasurable, fascinating: pts keep them secret as a private treasure

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2) Szs with both subjective symptoms and objective signs

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- Pts whose seizures start with subjective symptoms (auras) can learn to make use of them
- 2/3 of patients with epilepsies have experience with spontaneous attempts to arrest szs
  Paulson GW, Inhibition of seizures. Dis Nerv Syst 1963; 24: 657-664
- Own data from Bethel (Reker 1988, in German):
  - Questionnaire, 45 in-patients with ep on reference day
    - 30 have szs with auras (27) or only subjective symptoms (3): 2/3.
    - 27 (90%) have attempted seizure arrest
    - 23 (85%) sometimes or often successful
    - Spontaneous strategies: relaxation (8), concentration (5), shift of attention (5), sensory countermeasures (5)

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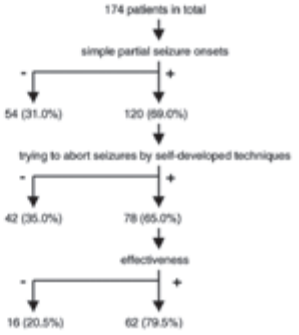
Lee SA, No YJ. Seizure 2005; 14:100-105

Simple focal sz onsets present in 120 of 174 patients, of whom 78 tried to abort szs by self-developed techniques. 62 patients reported self-inhibition methods as effective in stopping szs.

Pts exist who successfully treat themselves this way, and we never see them



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Seizure arrest as a therapeutic strategy:

Patients can be trained to develop their experiences or ideas into a successful intervention

- *Gowers WR. Epilepsy and other convulsive diseases. Churchill, London 1881*
- *Efron R. Brain 1956; 79: 267-281*
- *Efron R. Brain 1957; 80: 251-262*
- *Wolf P. Epileptic Seizures and Syndromes. Libbey, London 1994, 667-673*
- *Wolf P, Okujava N 1999; 8: 45-53*

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Other uses of auras: to hide

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Edward Lear (1812-1888)





Other reactions to auras

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- Move out of potentially dangerous situation
- Lie down etc
- Alert helpers
- Enjoy aura experiences
- Write about them
- Reflect on them

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Margiad Evans (1908-1958, 1.GTCS 11.5.1950)

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"The old idea of demoniac possession, I am sure, arose not from the onlookers of sufferers in fits but from the sufferers themselves. Because in the violent attacks one feels as though the body has been entered by a terrific alien power; and that that power is trying, after entrance, to push its way out again."

(A Ray of Darkness, p. 154)

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3) Szs without subjective experiences

1. With indirect indications of having had a seizure
   - Tongue bite
   - Enuresis
   - Bruises
   - "Hangover"
   - Finding oneself in an unexpected place
   - People's behaviour
2. Without any indications
   - Complete unawareness of seizures (GTC, CP, absences)

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Consequences of unawareness for self-perception?

"Learned helplessness"

- Definition: "The perception that one's behaviour cannot produce a desired outcome" *(Chovaz et al, Seizure 1994; 3:171-176).*
- Rosenbaum M & Palmon N. Helplessness and resourcefulness in coping with epilepsy. J Consult Clin Psychol 1984; 52:244-253
- Hermann BP et al. Learned helplessness, attribution style, and depression in epilepsy. Epilepsia 1996;37:680-686
- Established relation to depression, severity of epilepsy, to perception of locus of control, not to seizure type or awareness. No recent research?

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Consequences for self-perception

Locus of control

2 dimensions: general LOC and health-related LOC

Pts with epilepsy have externalized LOC perceptions for both dimensions

Gehlert S. Epilepsia 1994; 35: 81-88

Krakow et al. Seizure 1999; 8:111-115

Spector S, Cull C, Goldstein LH. Epilepsia 2001; 42:556-564

Gramstad A et al. Epilepsy Research 2001; 46: 53-61

Asadi-Pooya AA et al. Epilepsy & Behavior 2007; 11:347-350 (HR LOC)

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LOC: only rudimentary investigation of influence of seizure type

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TABLE 2. *Demographic information for high and low controllers*

	High controllers (n = 58)	Low controllers (n = 21)	Significance
Gender			
Males	27 (46.6%)	4 (19.0%)	$\chi^2 = 4.8$, 1 df, $p = 0.027$
Females	31 (53.4%)	17 (81.0%)	
Age (yr) [Mean (SD)]	34.5 (10.3)	40.2 (12.6)	$t = -2.06$, 77 df, $p = 0.043$
Age at onset of epilepsy (yr) [Mean (SD)]	10.6 (6.8)	14.1 (12.7)	NS
Duration of epilepsy (yr) [Mean (SD)]	24.2 (11.2)	25.6 (11.6)	NS
Participants with warnings of seizures (%)	42.1%	30.0%	NS
Seizures per month			
Mean (SD)	17.2 (23.8)	15.9 (22.8)	NS
Median	9.0	10.0	
Seizure types			
Complex partial seizures	31 (55%)	17 (81%)	$\chi^2 = 4.26$, 1 df, $p = 0.039$
Simple partial seizures	7 (12%)	0 (0%)	NS
Secondary generalized seizures	19 (33%)	6 (29%)	NS
Primary generalized seizures	15 (26%)	2 (10%)	NS

From: Spector et al, Epilepsia 2001. Many pts had >1 seizure type!

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Locus of control: hypothesis

- Learned helplessness and externalized locus of control depend upon
  - the retention or loss of awareness (consciousness) during a seizure
  - the patients having a perception of their own seizures or not

Nice research project

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Perception of a single (first) seizure

- In the literature on 1st epileptic seizures no attention paid to patients' perceptions.
- Includes author's own work in Engel & Pedley's "Comprehensive Textbook" (1st ed, 1997) on 104 own patients with 1st szs: no record of patients' perceptions
- Shocking experience for many, e.g. life-threatening
- Loss of control, of the natural matter of course
- Worries about recurrence, prognosis
- Some people have a social stereotype of "epileptics" which now challenges their image of their own personality
- Reactions of significant others, doctors, third parties
- Consequences for job, driver's license, insurances
- Weekend seminars in Bethel

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Margiad Evans (1908-1958, 1.GTCS 11.5.1950)

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"A Ray of Darkness" (1952), autobiographical account of her epilepsy

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Margiad Evans' first GTCS, alone by night in cottage, working on a poem

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"The night was quiet and dark – I went to the door and looked out once or twice. … I made tea, looked up at the clock – a strange chance – saw that it was ten minutes past eleven. The next thing I was still looking up at the clock and the hands stood at five and twenty minutes past midnight. I had fallen through Time, Continuity and Being.

I discovered I was lying on the floor on my back, my head against the rungs of a rocking-chair and my body, full length, crowded between the steel fender and the little table at which I had been writing.The lamp … was burning steadily on the table; … I had made up a large fire to work by and this was burning hotly in the open fireplace with wood and coal ablaze.

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Margiad Evans' first GTCS (cont.)

Much later on I realized how dangerously I had been placed, unconscious, certainly in convulsions, in a locked cottage alone with my dog at midnight and a quarter of a mile from the village.

The space in which I was lying was perhaps a yard wide. My sleeve was charred by an ember, but this was all. Had some special agent of preservation laid me down between lamp and fire it could not have been more dexterously done. …

Slowly mind and body began to try to come together and to work out a scheme for movement. It was the most difficult feat I have ever attempted, for *nothing* physical or mental was in unison, nor were they ready to fuse and to act for one body."

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Margiad Evans' first GTCS (cont.)

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Margiad Evans (1908-1958)

"The old idea of demoniac possession, I am sure, arose not from the onlookers of sufferers in fits but from the sufferers themselves. Because in the violent attacks one feels as though the body has been entered by a terrific alien power; and that that power is trying, after entrance, to push its way out again."

(A Ray of Darkness, p. 154)

In addition, the book includes highly interesting descriptions of the isolated auras she had long before the 1st seizure, and how she used them in her literary writings.

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Monika Maron (*1941)

Atheist background, then scandal: a critique of communist system

- Novel *Animal triste (1996)*
- Protagonist an atheist
- Natural scientist
- Experiences an unlimited, all-encompassing and eventually mortal love affair
- Heralded by a singular seizure event

Based on personal experience of an isolated seizure

Monika Maron 1996

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She is walking on a certain street in Berlin when

"A sudden mysterious numbness in the tongue soon spread to the rest of my senses. What happened during the next twenty minutes, I only know from the report of a young woman."

(Description of a generalized TC seizure)

"For several weeks I had at times the impression that something in my head didn't function as it did before the spell – reversed sides, as if someone had switched the poles around. For example, I remembered people's first names after their last names, or I wrote twenty-three when I meant to write thirty-two."

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Monika Maron, Animal triste (1996)

The narrator is perfectly aware that such symptoms have a logical explanation,but …

she becomes "obsessed with the idea that an alien force had simply switched me off for fifteen minutes … and … slightly altered the way my brain functions. I didn't really believe that, but it corresponded well with the state in which this inexplicable incident had left me."

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Perception of epilepsy as a disease

Potentially useful perceptions about the disease even if pts are unaware of the single seizures

- Repetition patterns
  - only in sleep (warn people)
  - only soon after awaking (wait 1 hr before leaving house)
  - never > 1 sz a day (safe to go out after sz; provoke sz)
  - clusters: prevention after 1. sz
  - cyclic patterns (e.g. catamenial epilepsy)

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Perception of epilepsy as a disease

An incapacitating condition

- Health dimension
- Personal dimension
- Social dimension

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Health dimension

- Seizures
- AED as symbol of illness ⇒ compliance
- Typical attitude passive
- Even if pts may realise that certain actions, lifestyle etc may facilitate or provoke seizures, they don't necessarily draw their own conclusions
- For many this becomes easier when doctor invites them to do so ⇒ lifestyle hygiene (sleep, alcohol, stress)
- Most patients willing to take active role in their treatment , if invited, and can see results
- Remember what many do about auras

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Acute drug administration (ADA)

Indications

1. Prevention of generalized tonic-clonic seizures (GTCS) after minor seizures (absence, myoclonic, simple focal or aura)
2. Prevention of seizures in patients with perceived risk of seizures or triggering factors.
3. Prevention of clusters of seizures

Choice of drug depends on available time

Usually oral Clobazam 10 – 20 mg

If rapid action desired: rectal diazepam, buccal midazolam, nasal lorazepam

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ADA: 24 own patients with uncontrolled szs

- Free of all szs 5
- Free of disabling szs 1 } 44%
- > 50% reduction 4
- Minor reduction / no change 11
- Undetermined 3

- Compliance:
  - Always correct use of ADA 10
  - Mostly correct use 7
  - Sporadic / not used at all 7

Patient satisfaction very high because they are given a means of efficient self-control

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Wolf P: Acute administration of benzodiazepines as part of treatment strategies for epilepsy. CNS Neuroscience & Therapeutics 2010 (online)

"Conclusions: ADA is an elegant and often successful but underused treatment option for selected patient groups where it can make the difference between becoming seizure free or not. Depending on the individual case it can be applied as monotherapy or in combination with a basis AED."

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Wolf P. Acute drug administration in epilepsy: A review. CNS Neuroscience & Therapeutics 2010 (online)

"The drugs most commonly used for ADA are the benzodiazepines diazepam (oral or rectal), clobazam and buccal or nasal midazolam and lorazepam. …

The best evidence for the efficacy of ADA exists in febrile and nonfebrile childhood seizures, whereas the evidence in catamenial epilepsy is weak. Prevention of clusters is a well-proven principle but its application has been little studied. Prevention of imminent seizures predicted by well-established triggers, defined risk factors, or premonitory minor seizure activity seems to be at the same time the most intelligent and the least investigated application of ADA and would deserve to be better studied."

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Handicaps, personal dimension

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- Mobility (e.g. sports, travel, intercontinental flights, driving)
- Independent living (job, responsibilities)
  - PWE are underemployed
- *Clarke et al. Work beliefs and work status in epilepsy. Epilepsy & Behavior 2006; 9:119-125*
- PWE *not* working believe significantly more frequently that
- need to work to be normal, have not enough education
- families fear work injuries fam don't want them work
- work = risk for injuries szs would affect performance
- they would hurt others if have a sz at work
- not having job only barrier to independence

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Personal dimension

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Family (to marry, to take care of children)

Batzel & Dodrill (USA 1984): 61% of men but 45% of women never marry; relation of low scores in MMPI + cognitive tests, independence, and getting married

Dansky et al (1980, Canada) marriage rate of PWE

(population in italics)

1941	men	33% *(57%)*	women	33% *(60%)*
1979	men	37% *(64%)*	women	62% *(74%)*

Conclusion: several factors at work; some changed between 1941 and 1979 only for women

For men concern to make a living and feed a family

For women concern to take responsibility for being alone with kids: what happens in case of seizure? ⇒ individual solutions

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Social dimension

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The two perennial social handicaps with epilepsy:

Stigma and discrimination

- What do patients do about it?
- Exceptional patients stand publicly out as role models
  - e.g. US Congress man Tony Coelho
  - ski jump champion Jan Boklöv
  - Some patients fight stigma in their own ambience by being open about their condition; usually beneficial
  - Self-help groups: social refuges

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Patients as role models

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Marion Clignet, born 1964, World Championships and Olympic medals in road race cycling in spite of epilepsy.

One of the most prominent spokespersons for epilepsy

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Social dimension: the internet

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- Internet information fora: virtual social refuges
  - Many facebook entries
  - Many discussion groups
  - Some established and run by IBE Chapters etc
  - Others spontaneous
  - May lead up to alternative approaches
  - Challenge to the health system

Chinese Sharp-Pei

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Conclusions

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- Many patients have perceptions about their seizures and their epileptic condition from which they may derive important conclusions and decisions
- May be adequate and reasonable but are not always
- Important source for externalised control perceptions
- Always worth knowing and discussing with the patient
- Help pts with finding appropriate reactions to aspects that can become part of successful therapy and rehabilitation

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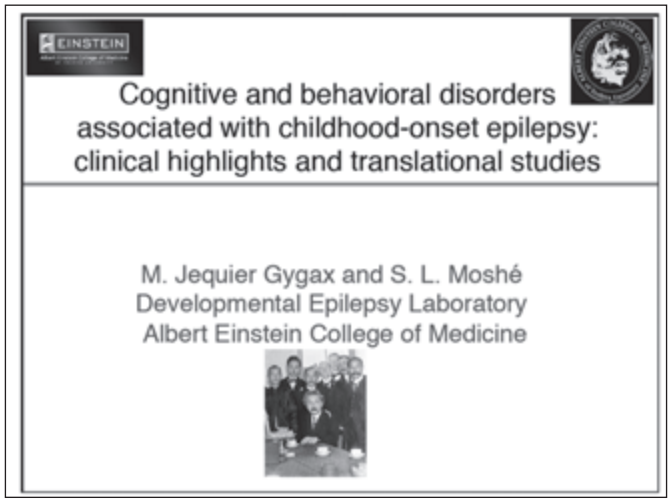
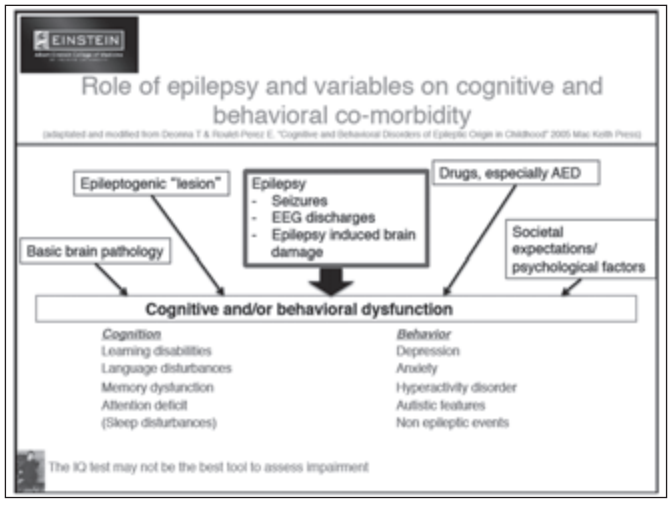
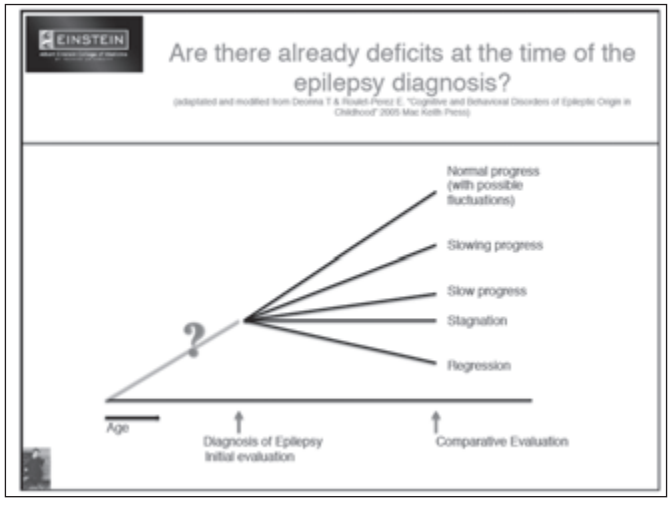
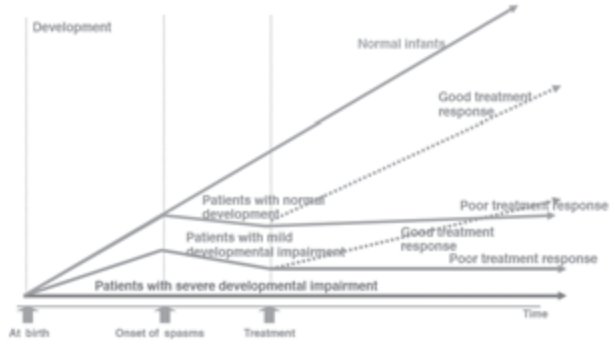
Cognitive decline in pediatric epilepsies
Solomon Moshe (USA)







Treatment response and outcome



Cognition, Behavior and Childhood-Onset Epilepsy: **Keypoints**

- In infants and children, the emergence of seizures may unmask cognitive deficits
- Under certain conditions, interictal discharges, seizures and status epilepticus may induce or augment the deficits
- Children with newly diagnosed epilepsy or new onset epilepsy frequently exhibit comorbid psychiatric or cognitive/behavioral disorders. MR, ADHD and academic difficulties are most prevalent
- Relation to autism

Challenges

- It is important to separate the impact of seizures on cognition, memory and behavior according to etiology and epilepsy syndrome
- Many patients have a form of epilepsy that does not conform to any of the recognized epilepsy syndromes
- **Some patients with cognitive dysfunction may not be identified until they develop seizures; the temporal relation between epilepsy and cognitive deficit is not clear**

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Translational Studies (animal models)
Impact of **seizures and epigenetic influences** on structure and cognition

Neonatal Seizures ⟶ Permanent alteration in glutamatergic synapses in adult (Cornejo et al. 2007)

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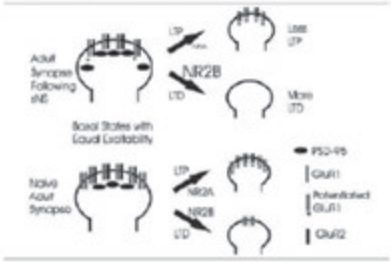
A Single Episode of Neonatal Seizures Permanently Alters Glutamatergic Synapses

Brandon J. Cornejo, BS,[1,2] Michael M. Mesches, PhD,[1,3,4] Steven Coultrap, PhD,[5] Michael D. Browning, PhD,[1,3,4] and Timothy A. Benke, PhD, MD[1,3,4,6]

Ann Neurol 2007;61:401–410



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Translational Studies (animal models)
Impact of **seizures and epigenetic influences** on structure and cognition

Neonatal Seizures ⟶ Permanent alteration in glutamatergic synapses in adult (Cornejo et al. 2007)

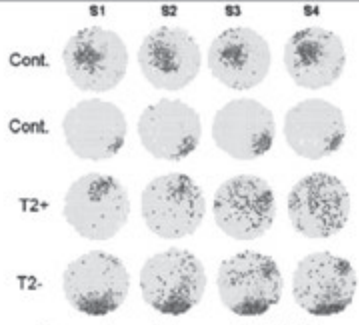
Complex Febrile Seizures ⟷ Anatomic changes, and learning and memory dysfunctions, epileptogenesis through inflammation (Dube et al. 2009, 2010)

Cognitive dysfunction after experimental febrile seizures

- Testing on adult rats with a prior history of experimental febrile seizures as pups
- Seizure-experiencing rats were found to have moderate deficits in memory and strategy shifting in the Morris water maze test.
- Abnormal firing rate and poor stability of hippocampal CA1 place cells, neurons involved in encoding and retrieval of spatial information was present
- Learning and memory functions of the high signal MRI T2-positive rats were significantly worse than those of T2-negative cohorts and of controls.

Dubé et al. 2009

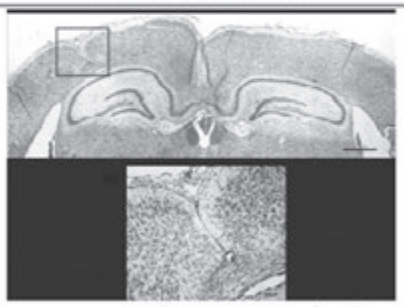
Cognitive dysfunction after experimental febrile seizures



Examples of place cell stability

Dubé et al. 2009

Atypical hyperthermic seizures in rats with focal cortical dysplasia leads to spontaneous recurrent seizures and learning and memory deficits



Scantlebury et al. 2005

Translational Studies (animal models)
Impact of **seizures and epigenetic influences** on structure and cognition

Neonatal Seizures	⟶	Permanent alteration in glutamatergic synapses in adult (Cornejo et al. 2007)
Complex Febrile Seizures	⟶	Anatomic changes and learning and memory dysfunctions, epileptogenesis through inflammation (Dube & al. 2009, 2010)
Status epilepticus	⟶	Variable results

Status epilepticus in normal developing rats

- Does not usually induce hippocampal cell loss or synaptic reorganization in the dentate gyrus till after the third postnatal week
- Does not usually increase susceptibility to provoked or spontaneous seizures but with improvements in technology EEG seizure patterns may appear with age
- In occasional models, damage has been observed:
  - Cell Loss in CA1 Hippocampal layer, spatial memory deficit (Wu et al. 2001)
  - Apoptosis and Cell death in CA1 and Gyrus dentatus (Lopez-Meraz et al. 2010)
- May affect learning and behavior but to a different (lesser?) degree
  - Spatial learning deficit and anxiety (Da Silva et al. 2005; Sayin et al. 2004)
- There are many compensatory changes

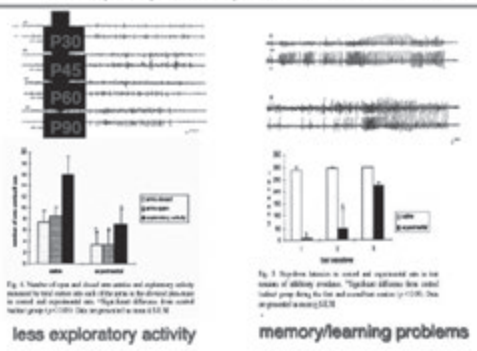
Status epilepticus or repetitive episodes of status epilepticus

Alterations are subtle and site-specific

- Hippocampus
- Substantia nigra pars reticulata

(Da Silva et al. 2005; Heida et al. 2006; Galanopoulou et al. 2006; Coppola and Moshe 2009)

Multiple pilocarpine-SE in PN7-9 rats

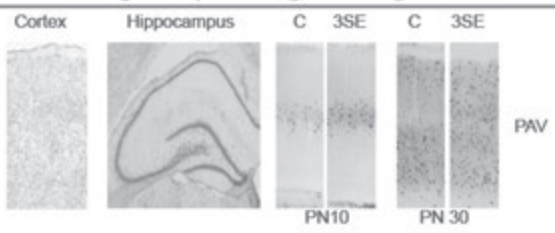


less exploratory activity

memory/learning problems

Da Silva et al. 2005

No gross pathologic changes but..



There are progressive subtle site-specific alterations of intra-cortical and hippocampal circuitry which could explain the epileptic discharges and cognitive deficits observed later in life

Da Silva et al. 2005

Exposure to 3 episodes of status epilepticus (SE) before PN6

Causes no significant acute neuronal injury

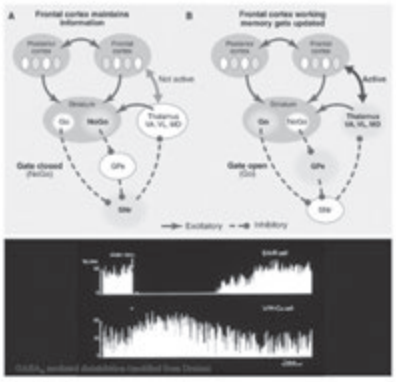
But accelerates the switch of synaptic $GABA_A$ergic responses in rat SNR in a sex specific fashion, limiting the time that calcium dependent process remain in effect

And disrupts the $GABA_A$-driven functions of the SNR including the ability to suppress seizures in adulthood
he SNR is involved in motor control and cognition

Ben Ari et al. 2002; Galanopoulou et al. 2003

EINSTEIN

Computational Model: Dynamic gating produced by disinhibitory circuits through the SNR and frontal cortex



O' Reilly et al. 2006

EINSTEIN

Translational Studies (animal models) Impact of **seizures and epigenetic influences** on structure and cognition

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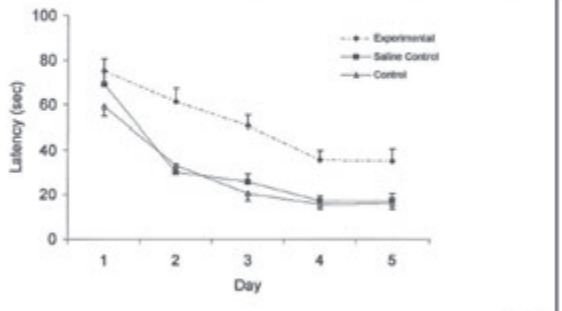
Status epilepticus	⟶	Variable results
Repetitive seizures	⟶	Decrease in CA1 neurons and mossy fiber sprouting (Holmes et al. 1999), modulation of neurogenesis depending on age (Xia-Yu et al. 2007), enhancement of neocortical excitability (Isaeva et al. 2010)

EINSTEIN

Performance of adult rats in Morris water maze following **repetitive/recurrent seizures** in infancy



Lee et al. 2001

Translational Studies (animal models)
Impact of seizures and epigenetic influences on structure and cognition

Neonatal Seizures	→	Permanent alteration in glutamatergic synapses in adult (Cornejo et al. 2007)
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Interictal spikes	→	Impairment in learning memory (Khan et al. 2010)

The impact of interictal epileptiform abnormalities

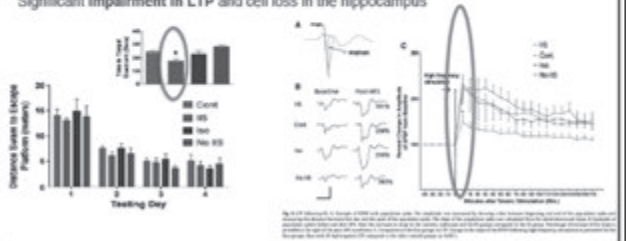
- Electrical induction of spikes in the hippocampus impairs spatial memory in rats (Holmes and Lenck Santini, 2006; Kahn et al. 2010)
- Impairment of the development of receptive fields in visual cortex (Chow et al. 1978; Ostrach et al. 1984; Prevost et al. 2010)
- The slow spike-wave discharges do not appear to contribute to the cognitive impairment in animal model of atypical absence/Lennox-Gastaut syndrome

Results are not uniform →
Syndrome or etiology dependent?

Impact of interictal spikes (ISS)

Khan OI et al. "Interictal spikes in developing rats cause long-standing cognitive deficits." Neurobiology of Disease 2010

- Inhaling flurothyl, rat pups developed repetitive ISS (10 days treatment), without seizures
- Hippocampus-dependent memory impairment (at P60 Morris Water maze and at P 68 four-trial radial arm water maze)
- Significant **Impairment in LTP** and cell loss in the hippocampus



ISS= Flurothyl induced itS; Cont=control; iso=isoflurane exposure without Flurothyl; No itS= F and isoflurane but no spikes

Translational Studies (animal models)
Impact of **seizures and epigenetic influences** on brain structure and cognition

Neonatal Seizures	→	Permanent alteration in glutamatergic synapses in adult (Cornejo et al. 2007)
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Interictal spikes	→	Impairment in learning memory (Khan et al. 2010)
Cortical Dysplasias	→	Delay in somatic and locomotor maturation (Croquelois et al. 2009)
Hypoxia-Ischemia	→	Myelination deficit and long term spatial learning and memory dysfunction (Huang et al. 2009); impaired learning capacities and exploratory behavior, impaired cognitive flexibility in mild HI model (Van der Kooij et al. 2010)

Translational studies :
epileptic syndromes and related animal models

Neonatal period		
BFNE	→	SKCNQ2 Knockout mouse (Watanabe et al. 2000)
Ohtahara Syndrome	→	Munc18-1 knockout mouse (Verhage et al. 2000)
Infancy		
West Syndrome	→	*At least 7 animal models for infantile spasms*
Dravet Syndrome	→	Heterozygous Scn1a+/- mice (Yu et al. 2006)
Lennox-Gastaut S.	→	MAM-AY rat model (Berbaresco et al. 2004)
Childhood and adolescence		
Childhood Absence Epilepsy	→	GAERS (Marescaux et al. 1992) and WAG/Rij (Coenen et al. 2003)
Atypical Absence Epilepsy	→	AY-9944 *rat* and GABAB R1afg *mouse* (Chan et al. 2006, Wu et al. 2007)

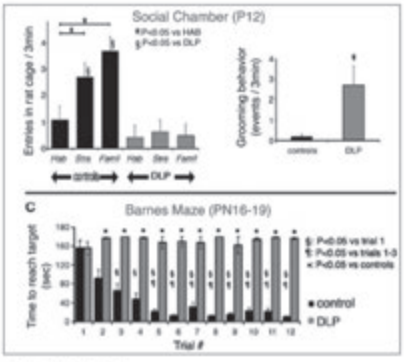
Infantile Spasms-Models

Unknown (Cryptogenic)
- TTX
- Stress related models
  - CRH (Baram and Schultz, 1995)
  - Betamethasone-NMDA (Velisek et al. 2010)

Genetic models
- Down model (Ts65Dn mouse) (Cortez et al. 2009)
- ARX mutation based models (Marsh E et al. 2009;Price MG et al. 2009)

Structural/metabolic (Symptomatic)
- Multiple-Hit Model (Scantlebury et al. 2010)

Infantile spasm model (Multiple Hit): Autistic features and learning deficits



Scantlebury, Galanopoulou, et al. 2010

AEDs may induce apoptotic neurodegeneration in developing rat brain

- Phenobabital, phenytoin, diazepam, clonazepam, valproate
- Effect more prominent between PN0-PN14

Atypical Absence/Lennox-Gastaut model

AY-9944 (AY rat) creates a model of atypical absence

$GABA_B$ R1a^{tg} mouse has atypical absence phenotype

- Both show cognitive deficit; in AY model, ETX treatment do not suppress spatial working memory deficit (RAM)
- Both show hippocampal dysfunction
- Cognitive impairment in both is $GABA_B$R-dependent
- SSWD in both appears to be independent of cognitive impairment

Cortez et al. 2001
Chan et al. 2006
Wu et al. 2007

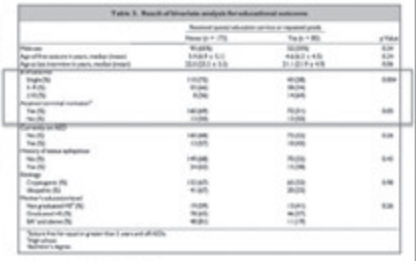
Clinical studies: Impact of seizures, SE and interictal discharges in humans

- Data derived from:
  - One *single* seizure
  - Febrile seizures
  - Recurrent seizures
  - Newly diagnosed epilepsy
  - Specific syndromes (CAE, BECTs) considered to have a more "benign" outcome
  - Epileptic "catastrophic" encephalopathies

Outcome following first **single** seizure: Less need for special educational services

Children with one first single seizure require less educational supports

They could represent a distinctive group, more similar to siblings controls



Sogawa Y et al. 2010

Long-term intellectual and behavioral outcomes of children with **febrile seizures**

381 children with febrile seizures
- 287 simple febrile seizures
- 94 complex febrile seizures

12,981 controls also born one week April 1970

Children with febrile convulsions (including complex and recurrent) performed as well as controls in terms of academic progress, IQ and behavior at age 10 years.

Verity et al. 1998

Effects of **recurrent seizures** in the developing brain

- The earlier the age of onset of seizures, the higher the likelihood of neurological sequelae
  - Between 20-40% of term infants who have seizures are subsequently handicapped compared to to almost 90% in preterm infants (Scher et al. 1993)
- In 100 patients with intractable epilepsy secondary to focal brain lesions, age at seizure onset was associated with low IQ scores
  - Children with onset of epilepsy <24 months had a FSIQ 14 points below that in patients with onset >24 months

(Vasconcellos et al. 2001)

Repetitive seizures with progressive deterioration

- Repetitive seizures with a single focus
  - Focal cortical dysplasia
- Repetitive seizures of variable topography :
  - Migrating partial seizures in infancy *(Coppola)*
  - Severe myoclonic epilepsy in infancy *(Dravet)*
  - Devastating encephalopathy in children (DESC)

Newly diagnosed epilepsy and ADHD

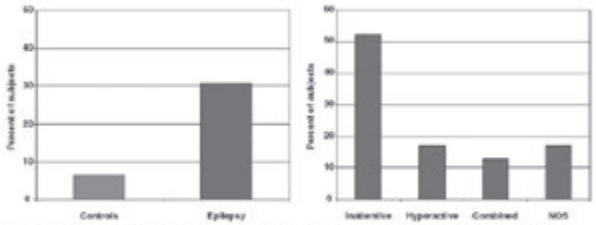


Fig 1 ADHD is significantly elevated in youth with epilepsy (left panel) and predominantly characterized by the inattentive subtype (right panel).

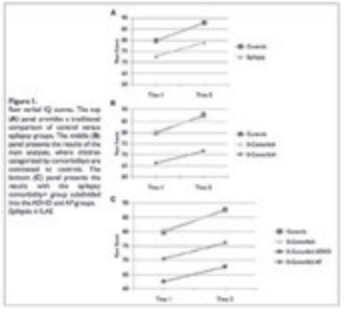
Hermann et al. 2007

Newly diagnosed epilepsy and cognitive development

The group Epilepsy and Comorbidity performed worse in all cognitive domains (intelligence, accademic achievement, language, executive function, psychomotor speed) except memory

46% of children with idiopathic epilepsy without comorbidity at onset (ADHD, AP) will have a normal cognitive outcome

Outcome: No association with other epilepsy factors (IGE vs LRE, AED, age of onset)



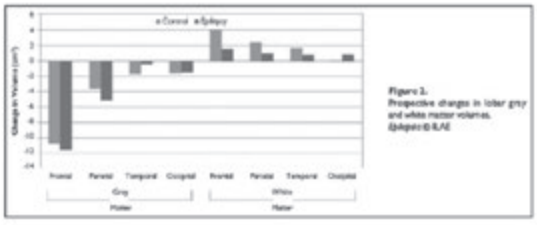
Hermann et al. 2008

Newly diagnosed epilepsy and structural changes

No changes in Gray Matter Volume

Significant growth attenuation of White Matter Volume in children with new onset epilepsy

No data on impact of comorbidities – Are structural brain developmental abnormalities underlying cognitive impairment, and which are they?



Hermann et al. 2010

Absence epilepsy: Long-Term psychosocial outcome - *sometimes a wolf in sheep's clothing*

- 65 children with typical absence epilepsy had greater difficulties than 76 children with Juvenile Rheumatoid Arthritis in academic-personal and behavioral domains ($p < 0.001$)
- Those not in remission did worst

Wirrell et al. 1997

Absence epilepsy: Outcome

- 453 children with absence epilepsy randomely assigned to treatment with VPA, ETX or LTG. VPA and ETX more effective in the treatment of CAE.
- No discontinuation differences because of adverse effect
- *Attentional dysfunction more common with VPA than with ETX*

Glauser et al. 2010

- 69 CAE children and 103 age- and gender-matched control children evaluated with psychiatric interviews, cognitive and linguistic testing
- CAE children: 25% subtle cognitive deficits, 43% linguistic difficulties, 61% psychiatric diagnosis (most ADHD) and anxiety disorders – severity related to duration of illness, seizure frequency and AED

Caplan R et al. 2008

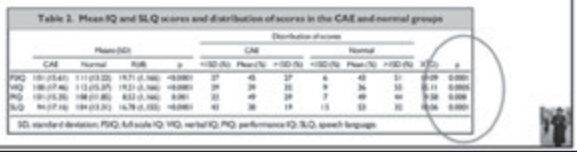


Table 2. Mean IQ and SLQ scores and distribution of scores in the CAE and normal groups

	Mean (SD)				Distribution of scores							
					CAE		Normal					
	CAE	Normal	Diff.	p	>1SD (%)	Mean (%)	>1SD (%)	>1SD (%)	Mean (%)	>1SD (%)	χ^2 (1)	p
FSIQ	101 (15.44)	111 (13.22)	10.71 (5.166)	<0.0001	37	45	27	4	43	31	9.09	0.003
VIQ	106 (17.46)	112 (15.37)	5.21 (5.166)	<0.0001	39	39	33	9	36	33	5.11	0.0035
PIQ	101 (15.35)	108 (11.85)	6.53 (5.166)	0.201	33	49	29	7	49	44	9.58	0.008
SLQ	94 (17.16)	104 (13.31)	14.78 (5.153)	<0.0001	43	38	19	15	53	31	10.06	0.001

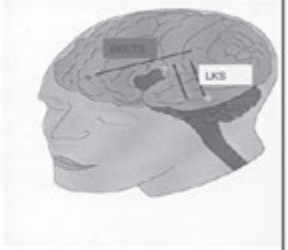
SD, standard deviation; FSIQ, full scale IQ; VIQ, verbal IQ; PIQ, performance IQ; SLQ, speech language.

Rolandic epilepsy - BECTS: Variable etiology ?

- Worsening of cognitive outcome of BECTS (role of drugs?) induced by sulthiame? (Wirrell et al. 2008, study in 6 children)
- Symptomatic: usually vascular, ± thalamic lesion; Gangliogliome (Kalman et al. 2006; Mikati et al. 2009)
- Genetic? SRPX2 – X-linked dominant –with expressive dysphasia (Michelucci et al. 2008)
- Landau-Kleffner spectrum (Deonna & Roulet-Perez 2010)

BECTS - Dipole Orientation Relationship to Cognitive and Behavioral Effects

- **Dipole orientation in BECTS and LKS**: the orientation of the dipole vertically to the planum temporale (intra-perisylvian region) appears to be associated with the findings in LKS.
- The spectrum of cognitive and behavioral differences present in BECTS versus LKS versus AER may be related to the orientation of the spike discharge.



BECTS and attention impairment

- Attention systems are impaired in children with active centrotemporal spikes (CTS) implying a more widespread functional cortical disturbance in RE than previously held
- These impairments may resolve upon EEG remission

Kavros et al. 2008

Benign childhood epilepsy with centrotemporal spikes (BECTS) : Deficit in attention, no more so "benign"

- Impairment in *selectivity* (impulsivity, focused attention, selective attention, aspects of divided attention) and in *arousal* of attention
- Attention is tested and not ADHD
- No impairment of vigilance
- *EEG centrotemporal spikes during sleep not sufficient to impair attention*

Cerminara et al. 2010

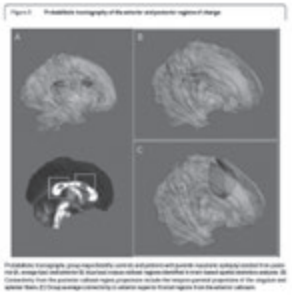
Chase spikes ?

- Improvement in behavior in children whose interictal epileptiform discharges were markedly suppressed by AED (LTG).

Pressler et al. 2005

JME : recent DATA

- Reduction of grey matter volume in the supplementary motor area (SMA) and posterior cingulate cortex is associated with dysfunction in verbal fluency, non verbal memory and mental flexibility.
- Fractional Anisotropy, and tractography (callosal track connecting SMA and pre-SMA) studies



O'Muircheartaigh et al. 2011

JME : recent DATA

- Patients with JME and their siblings have specific deficit in formation and intention execution of prospective memory.
  Thus, frontal dysfunction is part of genetically determined syndrome.
  (Wandschneider et al. 2010)
- JME: Reduced white matter connectivity in SMA is the structural correlate of functional frontal lobe abnormality, which is normal in FLE patients, suggesting different involved and affected networks
  (Vulliemoz et al. 2010)

Epileptic "catastrophic" Encephalopathy

"A condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function"

ILAE, Epilepsia 1989

- Early myoclonic encephalopathy
- Ohtahara syndrome
- West syndrome
- Dravet syndrome
- Myoclonic status in nonprogressive encephalopathies
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome
- Epilepsy with continuous spike-waves during slow-wave sleep (CSWS)

…Or part of different spectrum genetically determined and epigenetically influenced?

"Benign" epilepsy like BECTS to Landau-Kleffner Syndrome

"Benign" epilepsy like absence epilepsy to atypical absence epilepsy to Lennox-Gastaux Syndrome

GEFS+ to SMEI (Dravet Syndrome)

Combination of frequent seizures with « interictal » activity of SW more or less continuous, and specific psychomotor/cognitive impact

- Ohtahara syndrome and neonatal myoclonic encephalopathy with burst-suppression : motor deficits
- West syndrome with hypsarrhythmia : sensory problems/autism
- Lennox-Gastaut syndrome with frontal S&W : executive problems (sometimes difficult to distinguish from myoclonic-astatic epilepsy)

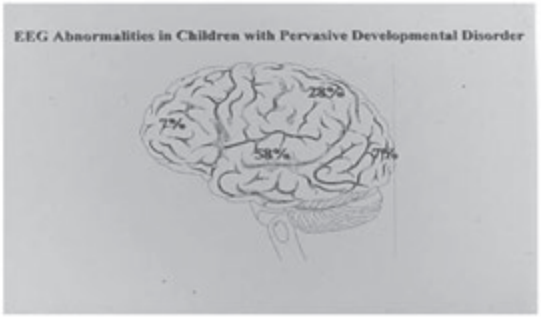
Epilepsy in Autism: prevalence and risk factors

- Prevalence of epilepsy in autism 5%----38.3%
- Two-Peak Distribution:
  - < 5 years; > 10 years
- Lowest rates in studies done exclusively in children
- Autism in 30% of children with epilepsy and mental retardation

- Risk Factors (??)
  - Genetics
  - Cognition
  - Motor deficit

Can epileptic syndromes lead to autism?

EEG Epileptiform discharges in children with ASD and no seizures



Epileptic EEGs and regression

- Autistic regression = 30% children with autism → 20% of these cases are associated with an epileptiform EEG
- Behavioral phenotypes of CSWS, LKS and autistic regression overlap (Tuchman 2009)
- Seizures and epileptiform EEGs significantly more likely in children with language regression as compared to children with both language and autistic regression
- **Infantile spasms** are the strong predictor of developing autism in children with tuberous sclerosis

Deonna et Roulet-Perez 2006

CONCLUSIONS

- Behavioral/Cognitive deficit/decline could be associated to epilepsy as part of a "developmental syndrome", most of them genetically determined, but still badly defined; these deficit could be influenced or not by epileptic fluctuations or control
- Epilepsy does not mean cognitive deficit and behavioral disorder
- Exact incidence of cognitive decline is difficult to ascertain
  - Comorbidities are frequent in childhood epilepsy
  - Condition may significantly affect epilepsy
  - Treatments impact comorbid conditions and may induce a decline too
- Under certain conditions, seizures and interictal discharges may induce or augment cognitive and/or behavioral deficits
  - The developmental age when the epilepsy first appears, the gender of the subject may be important

CONCLUSIONS

- Well-designed animal models should help
  - in understanding of the underlying pathological mechanisms and effect of age and gender on the outcome
  - in defining the association genotype-phenotype for the different syndrome, and their variations
  - in testing new treatment
- Some of underlying causes may be preventable
  - Early identification allows for medical and educational interventions
- Optimal treatment should be designed to benefit both epilepsy and seizure-induced cognitive decline

Disclosures

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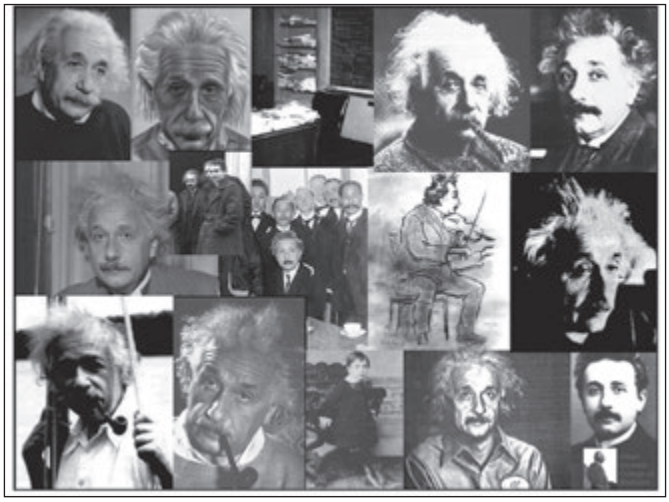
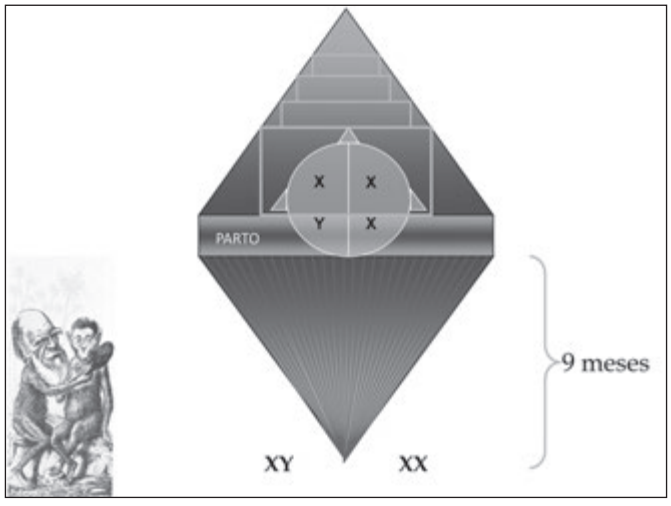
MJG: Supported by a fellowship for researcher from the Swiss National Science Foundation PBLAP3-129421

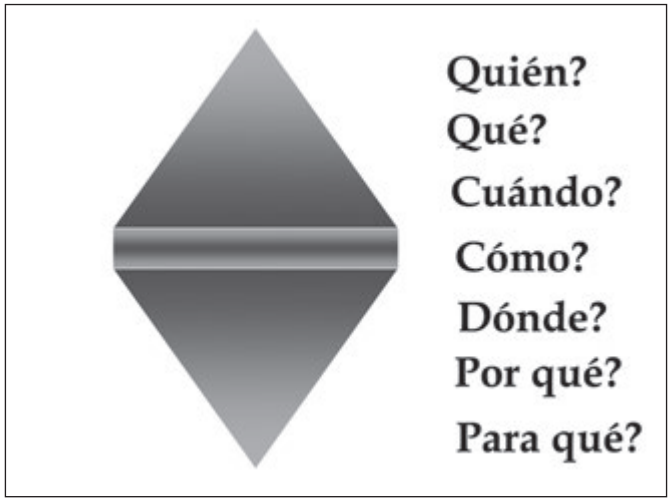
• Intellectual properties:
Patent # 60/900,487, assignee: AECOM
"A model of infantile spasms"



ALADE lecture - Epilepsy: the importance of learning to classify for learning to treat

Carlos Medina-Malo (Colombia)



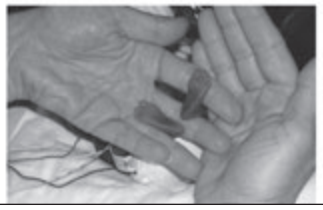


Riesgos

Síndromes

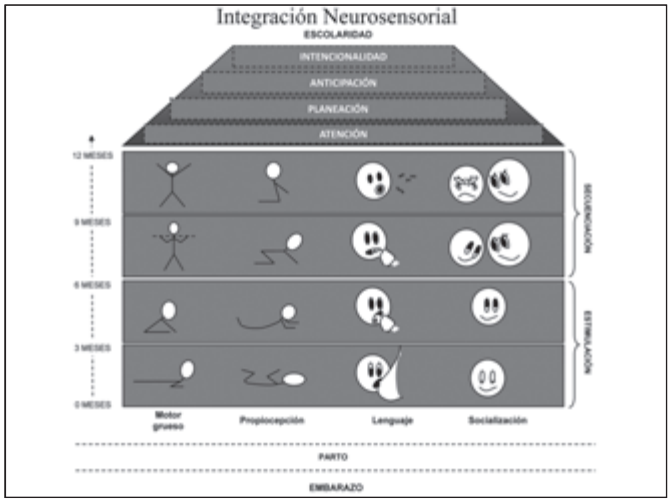
Epilépticos

Neurológicos



Neurodesarrollo

Aprendizaje



Estadística

Prevalencia 50-100 millones en el mundo

USA: 3´000.000

Colombia 800.000

Promedio de 0.65% al 2.07%

Incidencia: 31-57 x 100.000

Probabilidades

Mortalidad hasta 1970

Colombia: 24% en el primer año de vida

Mortalidad sobre el 2000

4% con 20% de morbilidad

Probabilidad de riesgo 100/20 = 5%

Contenidos

- Epilepsia
- Complejidad
- Clínica
- Clasificación
- Grupos
- Evolución
- Examen Neurológico
- Tratamiento

Contenidos

- Epilepsia
- Complejidad
- Clínica
- Clasificación
- Grupos
- Evolución
- Examen Neurológico
- Tratamiento

Epilepsia | Complejidad | Clínica | Clasificación | Grupos | Pronóstico | Examen Neurológico | Tratamiento

Epilepsia

Síndrome cerebral crónico
caracterizado por crisis recurrentes
debido a descargas hipersincrónicas de varias

Etiologías

asociado a trastornos de conciencia,
sensaciones
o movimientos (convulsiones) autolimitados,
con ocasionales hallazgos paraclínicos

Mecanismos Básicos de Epilepsia (MBE)

Susceptibilidad
Plasticidad
Células madre
Reparaciones
Génesis

MBE (subyacentes)

- Crisis en cerebros normales
- Epileptogénesis en el cerebro normal
- Crisis en un cerebro con disminución genética del umbral por su susceptibilidad en crisis
- Genéticamente disminución del umbral por epilepsia
- Plasticidad cerebral y daño epiléptico que lleva a epileptogénesis

Ejes

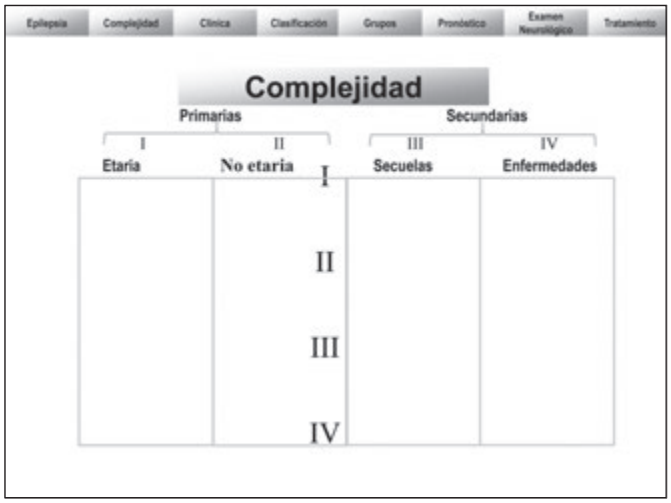
Semiología
Crisis
Síndromes
Etiología
Psicosocial

Dimensiones

Zona epileptogénica
Semiología de crisis
Etiología
Frecuencia de crisis
Información médica relacionada

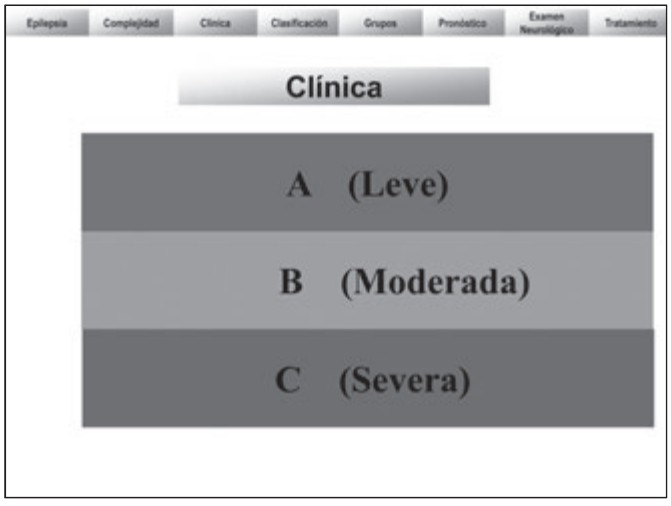
Nosológica (Epistasis)

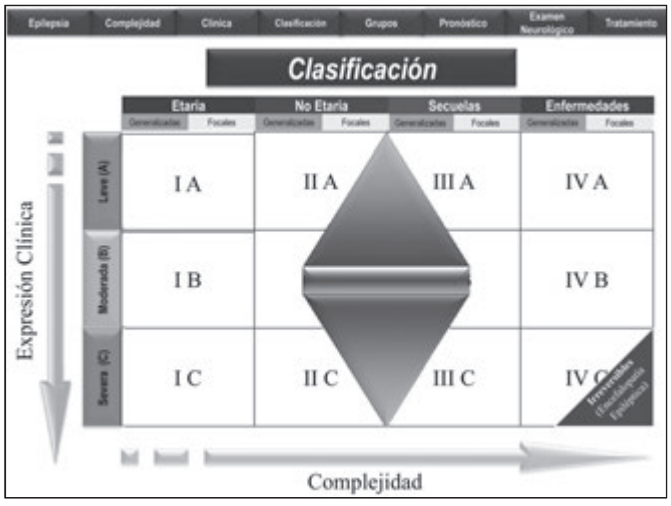
Poligénicos – Desarrollo (I)
Múltiples Genes y locus – Canalopatías (II)
Plasticidad cerebral y epileptogénesis (III)
Factores de riesgo ambiental (IV)

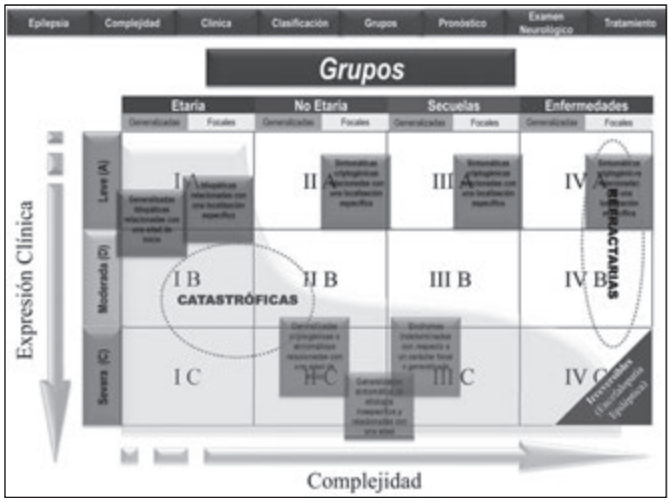


Expresión clínica
MBS

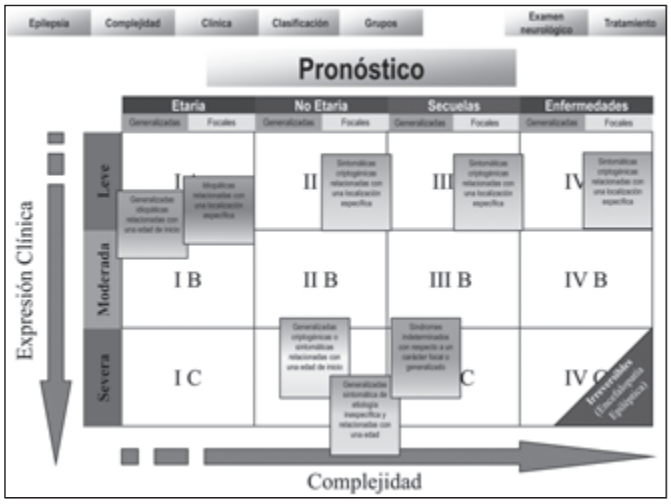
Susceptibilidad
Plasticidad
Células madre
Reparaciones
Génesis

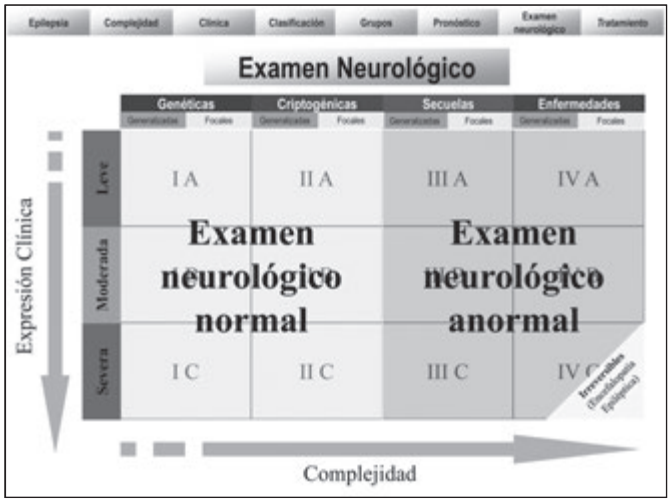




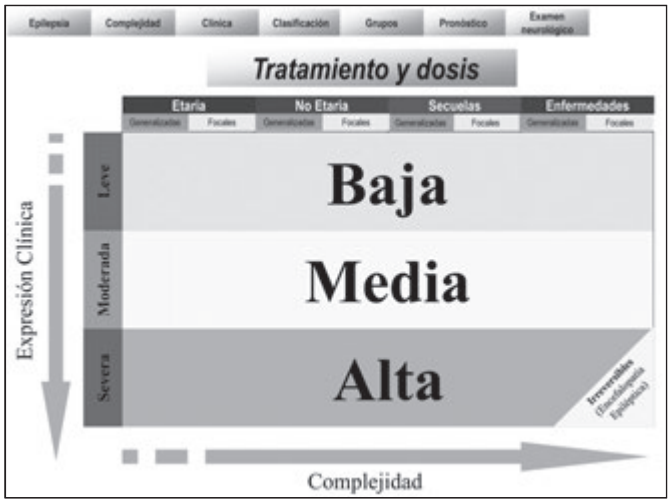

Epilepsia
Complejidad
Clínica
Clasificación
Grupos
Pronóstico
Examen Neurológico
Tratamiento
Grupos
Etaria
No Etaria
Secuelas
Enfermedades
Generalizadas
Focales
Leve (A)
Moderada (D)
Severa (C)
I A
II A
III A
IV A
I B
II B
III B
IV B
I C
II C
III C
IV C
CATASTRÓFICAS
REFRACTARIAS
Expresión Clínica
Complejidad

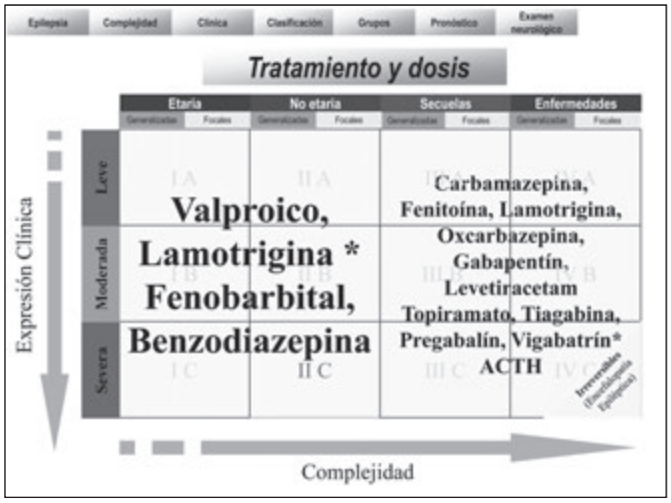

Epilepsia
Complejidad
Clínica
Clasificación
Grupos
Pronóstico
Examen neurológico
Tratamiento
Pronóstico
Bueno
Regular
Malo


Epilepsia
Complejidad
Clínica
Clasificación
Grupos
Examen neurológico
Tratamiento
Pronóstico
Etaria
No Etaria
Secuelas
Enfermedades
Generalizadas
Focales
Leve
Moderada
Severa
I B
II B
III B
IV B
I C
IV C
Expresión Clínica
Complejidad


Epilepsia
Complejidad
Clínica
Clasificación
Grupos
Pronóstico
Examen neurológico
Tratamiento
Examen Neurológico
Genéticas
Criptogénicas
Secuelas
Enfermedades
Generalizadas
Focales
Leve
Moderada
Severa
I A
II A
III A
IV A
I C
II C
III C
Examen neurológico normal
Examen neurológico anormal
Expresión Clínica
Complejidad


Epilepsia
Complejidad
Clínica
Clasificación
Grupos
Pronóstico
Examen neurológico
Tratamiento
Tratamiento y dosis
Baja
Media
Alta


Epilepsia
Complejidad
Clínica
Clasificación
Grupos
Pronóstico
Examen neurológico
Tratamiento y dosis
Etaria
No Etaria
Secuelas
Enfermedades
Generalizadas
Focales
Leve
Moderada
Severa
Baja
Media
Alta
Expresión Clínica
Complejidad



Estado temporal de crisis recurrentes	Período silente	Estado epileptogénico
Epilepsia mioclónica benigna de la infancia: crisis mioclónicas entre 4 meses-3 años	84% remite	16% desarrolla crisis TCG
Crisis neonatales familiares benignas: canalopatía KICNQ2 y KCNQ3. Crisis recurrentes del 2 día a 1 mes; rara a los 12 meses	89% remite	11% epilepsia crónica
Epilepsia de ausencias infantiles: GABRg2, GABRb3	Sindrome de ausencias >90% remite entre 12-19 años. Sindrome de ausencias infantiles con epilepsia TCG en la adolescencia	5-10% ausencias crónicas 60% epilepsia de ausencias crónicas +TCG

www.basicmechanismsepilepsiesworkshops.neurology.ucla.edu "THE EPILEPSIES AND EPILEPSY RESEARCH"

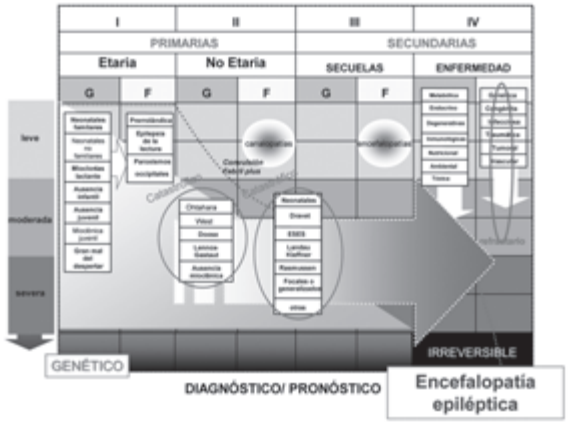
Susceptibilidad: crisis se presentan por privación de sueño, alcohol, menarquia, menstruación o fiebre	**Período silente**	**Estado epileptogénico: epilepsia permanente**
Estado epileptogénico: epilepsia permanente	8% sin crisis, ni tratamiento o desencadenantes >50% requiere tratamiento para evitar mioclonías o CTCG ligadas a desencadenantes	Crisis con o sin desencadenantes: 40% crisis permanentes aún sin desencadenantes
Crisis desencadenadas por fiebre; crisis febriles entre 3 meses-5 años Loci cromosoma 7 - SCNA1, SCNA2, SCNB1, VHS tipo 6	Crisis febriles simples Crisis febriles complejas	2% epilepsias crónicas 4-12% epilepsia crónica, incluyendo epilepsia del lóbulo temporal

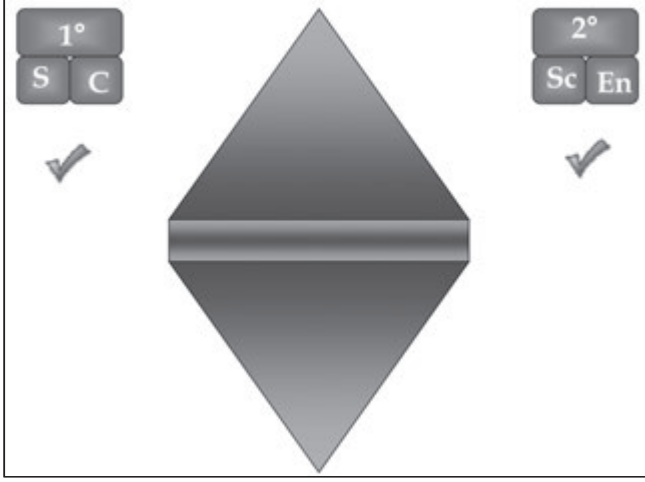
www.basicmechanismsepilepsiesworkshops.neurology.ucla.edu "THE EPILEPSIES AND EPILEPSY RESEARCH"

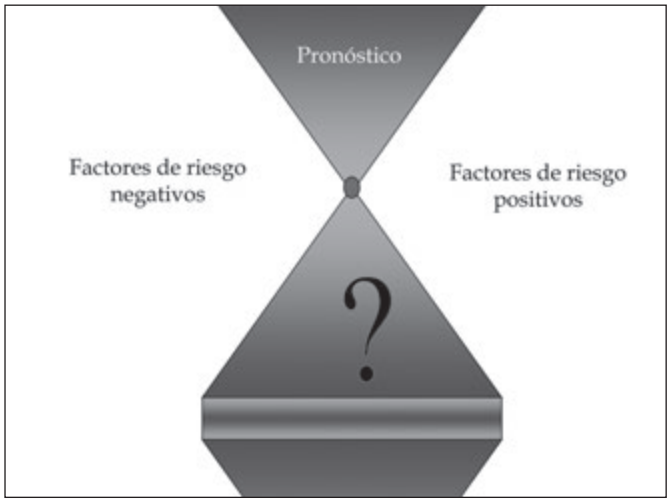
Mecanismos básicos de las epilepsias (BME)

	Cerebro normal	Cerebro con epilepsia. Mutaciones genéticas	Cerebro lesionado
Susceptibilidad (disminución del umbral a crisis) + crisis agudas	Si	Si/No	Si/No
Latencia para la epileptogenicidad; plasticidad cerebral en comunicación intercelular e intracelular; genética; epigenética	Si	No	No (sin comprobar en especímenes de lobectomía)
Epileptogenicidad (disminución del umbral a epileptogénesis)	Si	No	No (sin comprobar en especímenes de lobectomía)
Epileptogénesis/Epileptogénico (estado de epilepsia crónica con mejorías y recidivas)	No	No	No

www.basicmechanismsepilepsiesworkshops.neurology.ucla.edu "THE EPILEPSIES AND EPILEPSY RESEARCH"






Pronóstico
Factores de riesgo negativos
Factores de riesgo positivos
?

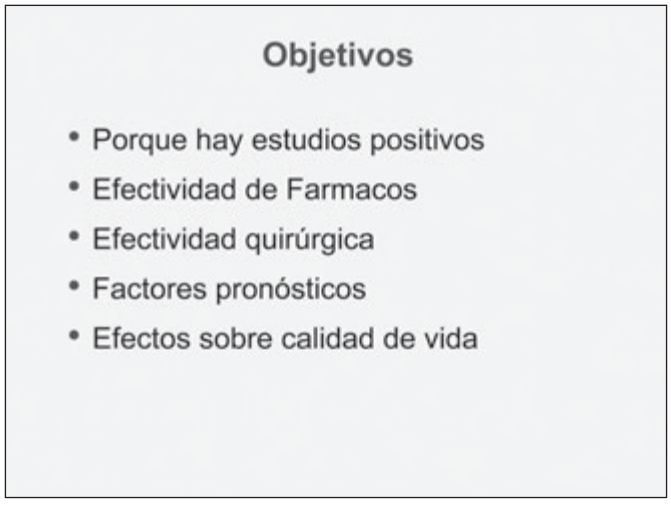

Gracias

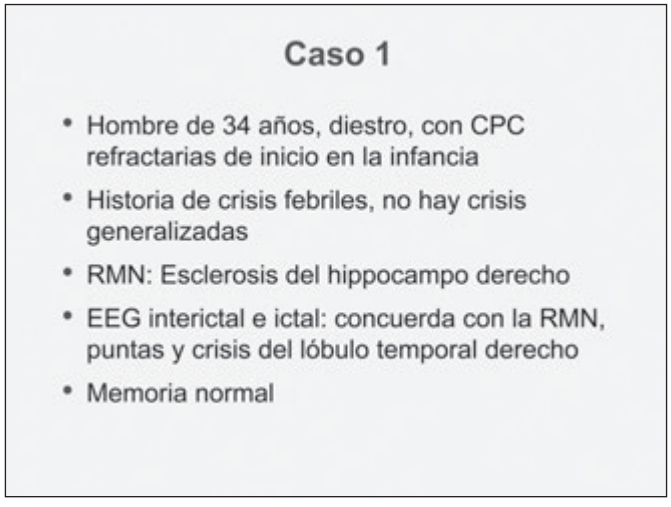
Programa – 26.02.2011

08:30 – 09:30	Progressive cognitive deficits in MTLE – Samuel Wiebe (Canadá)
09:30 – 10:30	Predictors of postoperative memory and cognitive impairment in MTLE - Fernando Cendes (Brazil)
10:30 – 11:00	Coffee break
11:00 – 12:00	Genetic testing in the epilepsies--report of the ILAE Genetics Commission – What is the relevance for diagnosis of catastrophic epilepsies? – Iscia Lopes Cendes (Brazil)
12:00 – 13:00	Memory and language in refractory epilepsy – Mirna W. Portuguez (Brazil)
13:00 – 15:00	Lunch
15:00 – 19:00	Dedicated to team work
19:00 – 21:00	Dinner

Progressive cognitive deficits in MTLE

Samuel Wiebe (Canadá)





Caso 1

- Resección anteromedial Temporal derecha
- Histopatología confirma esclerosis Hipocampal
- 12 meses: Tiene auras, pero no CPC
- Toma CBZ 800mg y Topiramato 200 mg
- EEG de seguimiento: sin puntas

Caso 2

- Mujer de 34 años.
- Eventos diarios durante 6 años
  - Desorientacion o lentitud mental prolongada (horas)
  - Fluctuaciones en memoria y atención
  - Crisis TCG frecuentes
- Hospitalización frecuente por confusión prolongada
- RMN normal
- Neuropsicología: normal excepto desinhibición leve
- Psiquiatría: Normal, no sugiere histeria

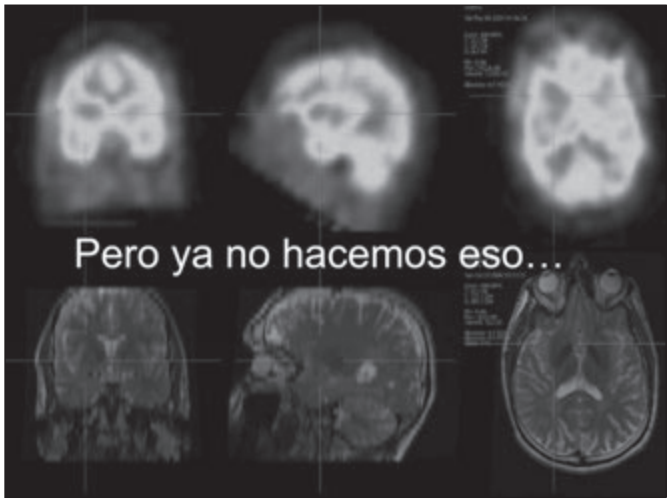
Caso 2 – seguimiento

- Tolera el procedimiento increíblemente bien
- 36 meses después: aún sin crisis
- Toma Lamotrigina 300mg, Levetiracetam 2000mg
- EEG de seguimiento: efectos postoperatorios, algunas puntas en el margen quirúrgico.

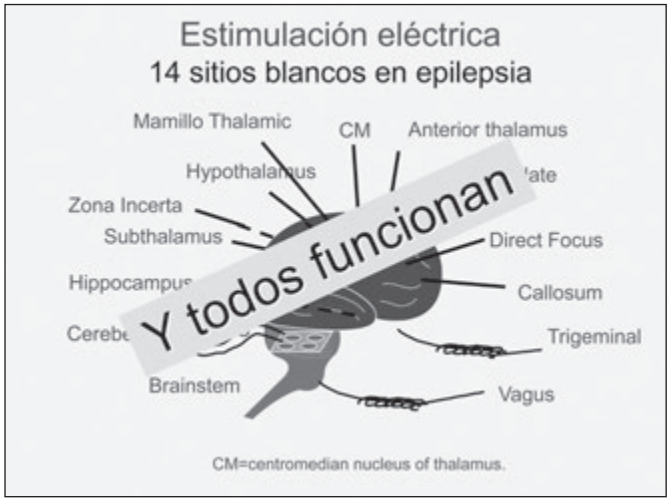
Epilepsy & other chronic convulsive diseases 1881

William Gowers

- Trepanación
- Cauterización
- Castración
- "El hipocampo tiene poco que ver con la epilepsia"
- …prefería la circuncisión


Pero ya no hacemos eso…


Lobectomía Anteromesial
Amigdalohipocampectomía
Termocoagulación
Lesionectomía
Corticectomía
Lesionectomía plus
Y todas funcionan
Reseccion Multilobar
Hemisferectomía (otomía)
Callosotomía (parcial/total)
Transecciones Subpiales
Estimulación eléctrica
Radiocirugía


Estimulación eléctrica
14 sitios blancos en epilepsia
Mamillo Thalamic
CM
Anterior thalamus
Hypothalamus
Zona Incerta
Subthalamus
Hippocampus
Cerebellum
Brainstem
Direct Focus
Callosum
Trigeminal
Vagus
Y todos funcionan
CM=centromedian nucleus of thalamus.

Porqué obtenemos buenos resultados?

1. El tratamiento funciona
2. Azar
3. Sesgo (Diferencias)
   1. Entre pacientes tratados y controles
   2. En el tipo y nivel de atención
   3. En tratamientos ancilares
   4. En el entorno clínico y científico
   5. En la medición de resultados

Necesitamos una imagen clara...

Medicina Basada en Evidencia

- Dos Principios Básicos
  - Usamos evidencia para tomar decisiones
  - Existe una jerarquía en la credibilidad de la evidencia

Tipos de Evidencias

De mejor a peor

- Aleatorio controlado (EAC)
- Controlado pero no aleatorio
- Sin controles
- Series de casos
- Anécdotas ("nuestra experiencia")

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

TABLE II. – *Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission (S=52, C=50)*

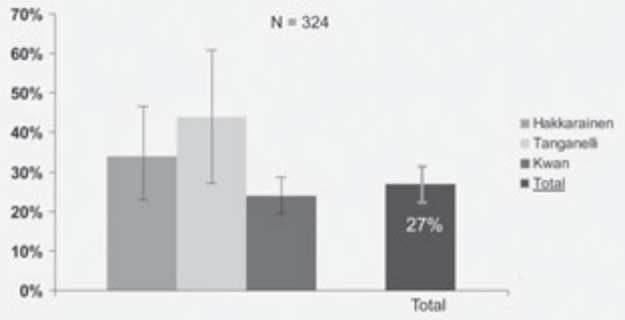
Radiological Assessment	Streptomycin Group		Control Group	
Considerable Improvement	28	51%	4	8%

NNT = 2

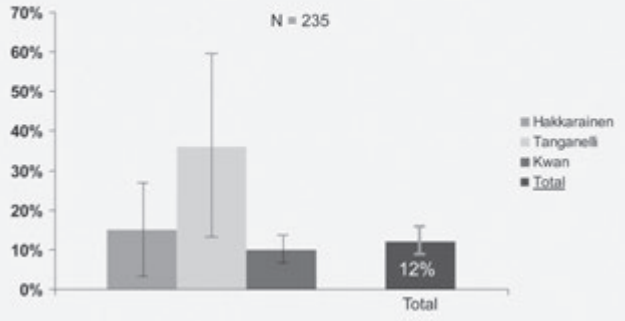
MRC Streptomycin in Tuberculosis. BMJ 1948; ii: 769-782.

Cual es el tratamiento más efectivo para la epilepsia focal?

Porcentaje Controlados
Si falla el 1° FAE



Porcentaje Controlados
Si fallan 2 FAEs



Depende del diagnóstico

2,200 patients con tratamiento médico

Semah F, et al. *Neurology*. 1998

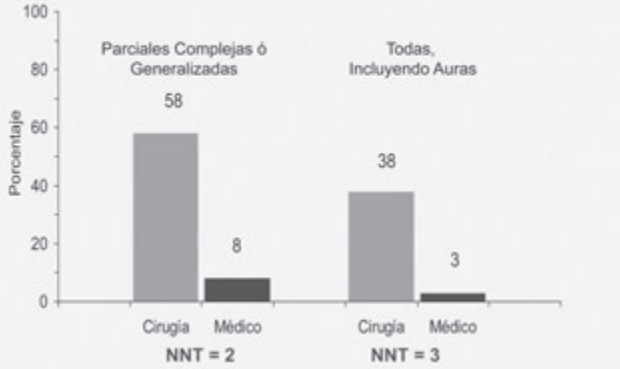
The New England
Journal of Medicine

VOLUME 345 AUGUST 2, 2001 NUMBER 5

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

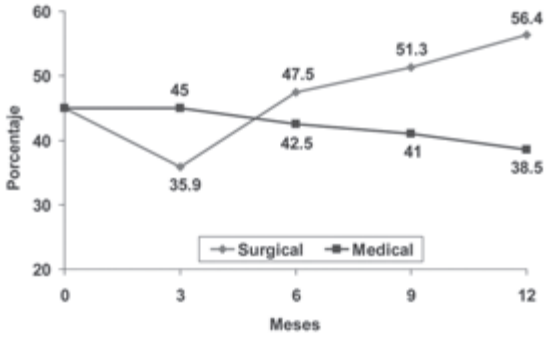
SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*

Libertad de Crisis Durante 12 Meses



Wiebe, *N Engl J Med* 2001;345:311-318

Trabajan ó Estudian

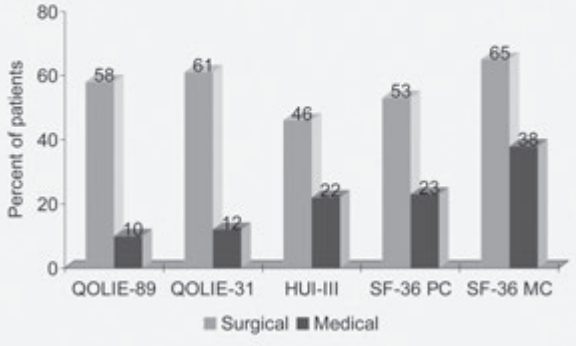


Wiebe, N Engl J Med 2001;345:311-318

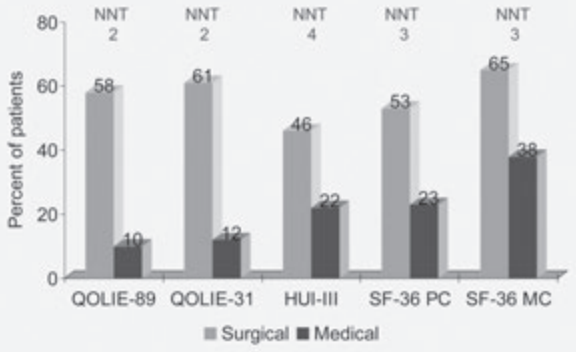
Mejoria Clínicamente Significativa

Instrumento	Cambio Significativo
QOLIE-89	10.1
QOLIE-31	11.8
SF-36 mental	4.6
SF-36 physical	3.0
HUI – III	0.15

Mejoria Clínicamente Significativa



Mejoria Clínicamente Significativa

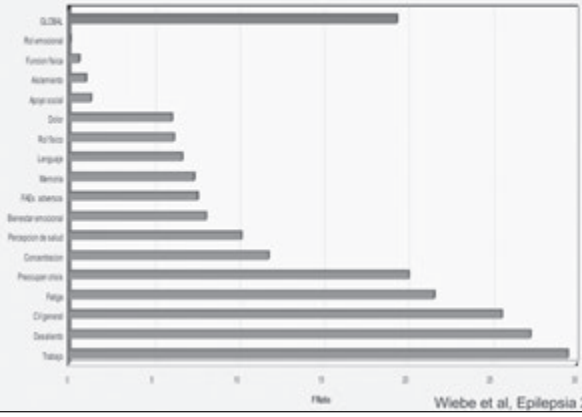


QOLIE-89

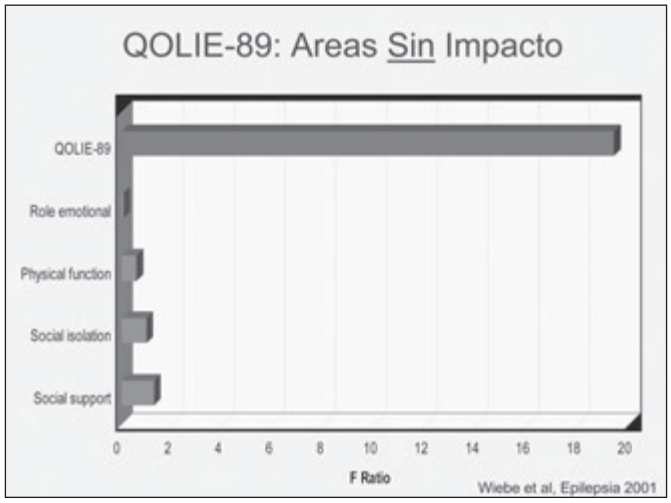
- El instrumento más usado en calidad de vida en epilepsia
- Desarrollado específicamente para epilepsia
- Mide aspectos generales de calidad de vida
  - Función física, emocional, social, dolor
- Mide aspectos específicos para epilepsia
  - Temor de crisis, efectos de medicamentos, memoria, nivel de energia
- 1 score global y 18 scores para areas especificas
  - Rango de 0 (peor) a 100 (mejor)

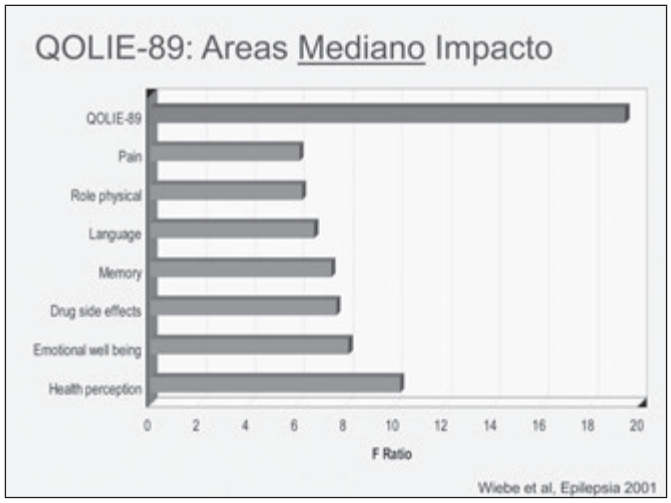
Devinsky, Epilepsia 1993

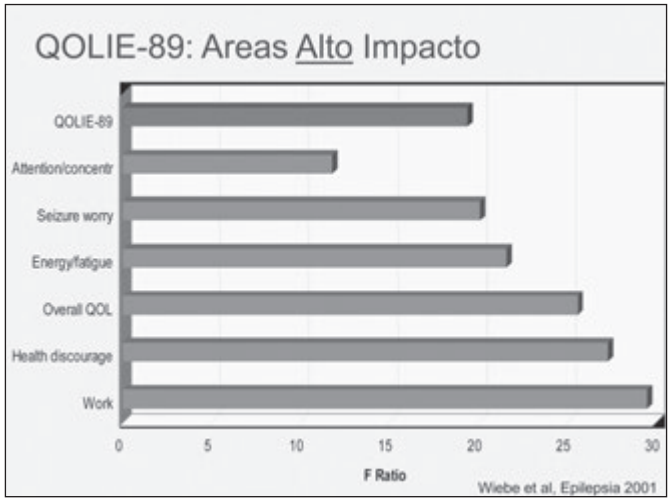
Cirugía / FAEs
Score global y areas específicas



Wiebe et al, Epilepsia 2001

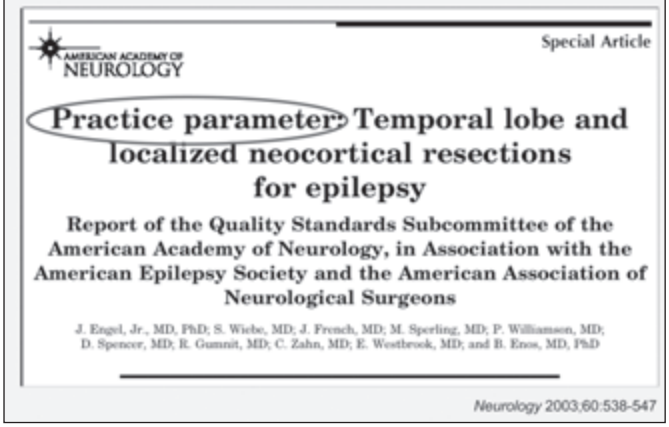

QOLIE-89: Areas Sin Impacto
QOLIE-89
Role emotional
Physical function
Social isolation
Social support
0 2 4 6 8 10 12 14 16 18 20
F Ratio
Wiebe et al, Epilepsia 2001


QOLIE-89: Areas Mediano Impacto
QOLIE-89
Pain
Role physical
Language
Memory
Drug side effects
Emotional well being
Health perception
0 2 4 6 8 10 12 14 16 18 20
F Ratio
Wiebe et al, Epilepsia 2001


QOLIE-89: Areas Alto Impacto
QOLIE-89
Attention/concentr
Seizure worry
Energy/fatigue
Overall QOL
Health discourage
Work
0 5 10 15 20 25 30
F Ratio
Wiebe et al, Epilepsia 2001

Conclusiones: Calidad de Vida

- La cirugía produce mejoría Global y específica
- La mejoría
  - Inicia temprano (en 3 primeros meses)
  - Se sostiene a largo plazo
  - Es clinicamente significativa
    - Diferencia absoluta en porcentaje de pacientes 30% to 50%
    - NNT de 2 a 3



Special Article

AMERICAN ACADEMY OF NEUROLOGY

Practice parameter: Temporal lobe and localized neocortical resections for epilepsy

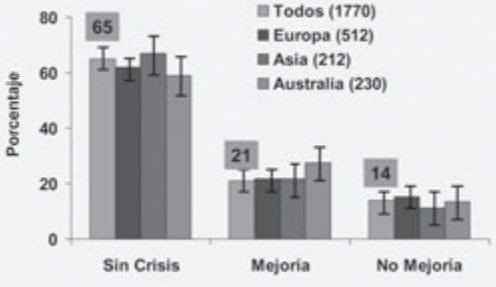
Report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons

J. Engel, Jr., MD, PhD; S. Wiebe, MD; J. French, MD; M. Sperling, MD; P. Williamson, MD; D. Spencer, MD; R. Gumnit, MD; C. Zahn, MD; E. Westbrook, MD; and B. Enos, MD, PhD

Neurology 2003;60:538-547

Cirugía Anteromesial Temporal

seguimiento < 5 años, 1,770 pacientes



Engel J Jr, et al. *Neurology*. 2003.

La cirugía resectiva es el tratamiento más efectivo para la epilepsia focal

Cirugia Temprana?

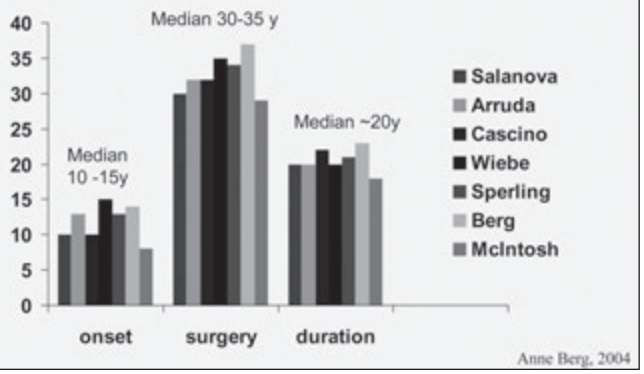
The Rationale

- Increased psychosocial problems
- Increased cognitive decline
- Increased mortality

The Assumptions

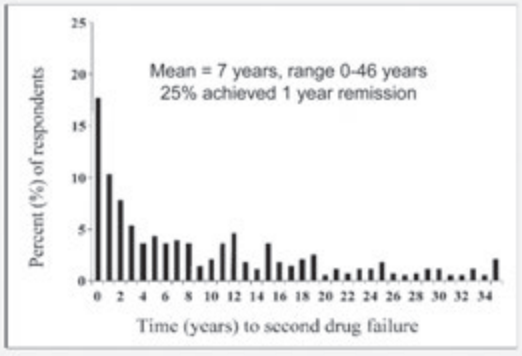
- Surgery is done too late
- "Intractable" patients can be identified early
- "Early" surgery is better than "late" surgery

Age at Onset & Age at Surgery



Anne Berg, 2004

Time to "intractability"



Berg, Neurology 2003

Surgical Candidates

StudyPatients		% Sz Free on AEDs	
Wiebe	TLE	8%	All Sz
Semah	TLE	10%	All Sz
Vickrey	All	5%	All Sz
		11%	Auras or Sz free

Is it Really ~10% ? Two Examples

- Luciano
  - N=155, chronic epilepsy, mean prior AED=6
  - 28% seizure free with another AED
- Callaghan
  - N=246, failed 2 AEDs
  - 14% seizure free with another AED

Callaghan, Ann Neurol 2007; Luciano, Ann Neurol 2007

Predictors of Intractability?

- ≥5 AEDs
- Longer course of epilepsy or earlier onset
- History of status epilepticus
- Mental retardation

Callaghan, Ann Neurol 2007; Luciano, Ann Neurol 2007

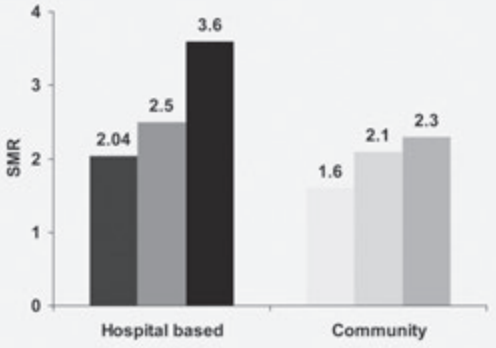
Interpreting Response to AEDs

- Good initial control
  - No guarantee of long-term seizure freedom
- Poor initial control
  - No guarantee of life-long intractability
- Patients can become intractable at any time… and then respond

Why are there differences?

- No prospective incidence cohorts
- Heterogeneous
  - Patients
  - Management
  - Outcome assessment
  - Definitions
- Insufficient numbers and follow-up

Mortality in Six Large Series



Hitiris, E&B 2007

Memory Decline with Epilepsy

- 25% to 40% have cognitive decline
- Averted with successful surgery
  - Practice effects?
  - Regression to the mean?
  - AED effects?
  - Other confounders (eg, extent & chronicity)?

Helmstaedter 2003, Hermann 2006

Risks of Surgery

- Morbidity 2%
- Mortality <1%
- Memory 40%

Do earlier benefits outweight earlier surgical risks?

Minimum Criteria for Valid Studies

- "Inception" Cohort
  - All patients captured at similar (early) point in time
- Outcomes defined a priori
- Comparison groups defined a priori
- Assessment blinded or masked
- Sufficiently Long Follow-Up for majority
- All important prognostic variables analysed

Pero…
Tiene efecto duradero?

doi:10.1093/brain/awh449 Brain (2005), 128, 1188–1198

Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis

José F. Téllez-Zenteno,[1,3] Raj Dhar[1] and Samuel Wiebe[2]

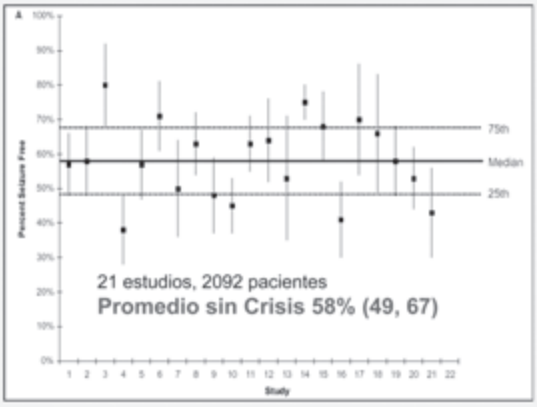
[1]Department of Clinical Neurological Sciences, London Health Sciences Centre, London, Ontario, [2]Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada and [3]Department of Neurology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Correspondence to: Dr Samuel Wiebe, Division of Neurology, Foothills Medical Centre, 1403-29 St N.W., Calgary, Alberta, Canada T2N 2T9
E-mail: swiebe@ucalgary.ca

1,500 Citas → 142 (9%) Potencial → 76 (54%) Incluidos

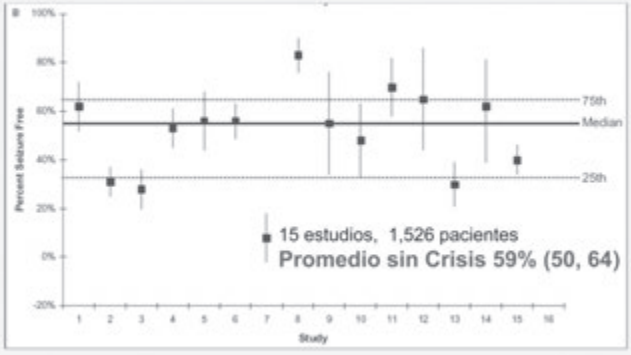
>5 años seguimiento, >20 pacientes, despues de 1990

Lóbulo Temporal



Tellez & Wiebe, Brain 2005

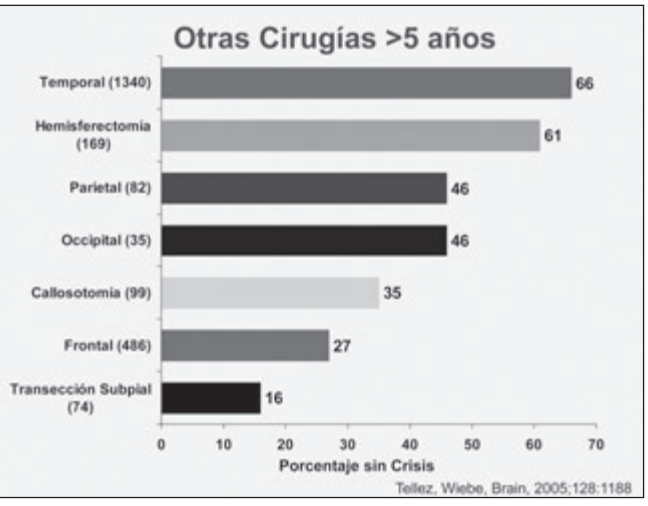
Temporal y Extratemporal



Tellez, Wiebe, Brain, 2005;128:1188-98

Sí Tiene efecto duradero

…pero no es igual para todas las cirugías



…Tampoco es igual para todos los pacientes

A corto plazo (>1 año)

ELSEVIER

Epilepsy Research 62 (2004) 75–87

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Predictors of epilepsy surgery outcome: a meta-analysis

C. Tonini[a,b], E. Beghi[a,c,*], A.T. Berg[d], G. Boglium[a,c], L. Giordano[a], R.W. Newton[e], A. Tetto[a,f], E. Vitelli[a,g], D. Vitezic[h], S. Wiebe[i]

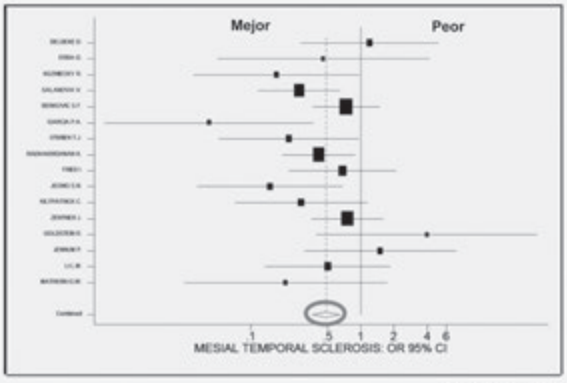
Estudios con >30 pacientes, 1984 a 2001

1,051 Citas → 383 Potencial → 47 Incluidos

3,511 pacientes

Mejor Resultado: Esclerosis TM

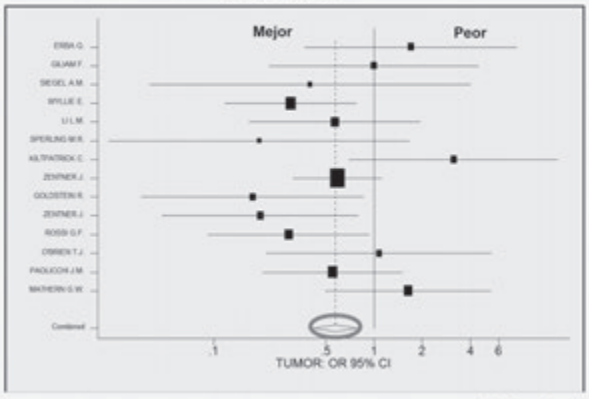
16 estudios



Tonini, Beghi, et al. 2004

Mejor Resultado: Neoplasias

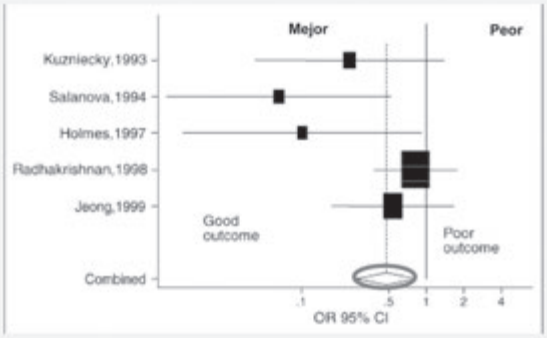
14 estudios



Tonini, Beghi, et al. 2004

Mejor Resultado: Crisis Febriles

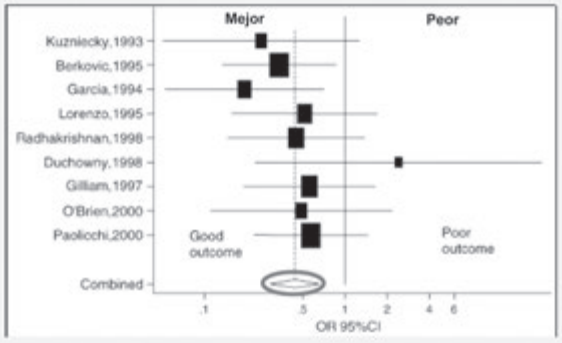
5 estudios



Tonini, Beghi, et al. 2004

Mejor Resultado: Lesión en RMN

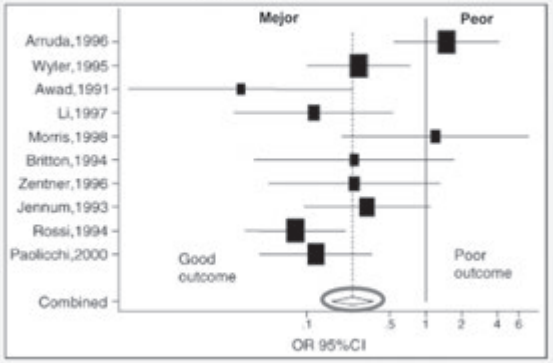
9 estudios



Tonini, Beghi, et al. 2004

Mejor Resultado: Resección Completa

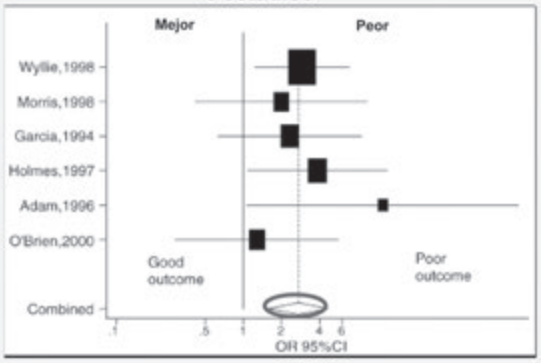
10 estudios



Tonini, Beghi, et al. 2004

Peor Resultado: EEG Intracraneal

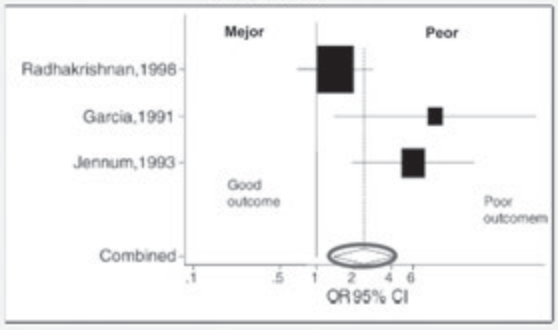
6 estudios



Tonini, Beghi, et al. 2004

Peor Resultado: Puntas EEG Postop

3 estudios

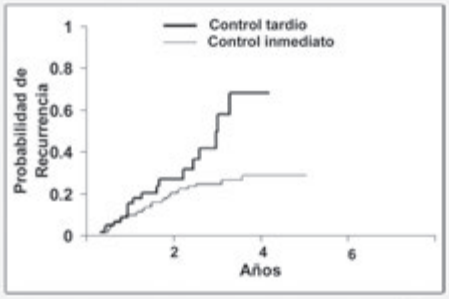


Tonini, Beghi, et al. 2004

Además, el primer año es crucial

Recurrencia: control temprano o tardío

- Cirugía temporal medial en 297 pacientes
- El pronóstico es dos veces mejor si hay control inmediato



Spencer, Neurology 2005

Los primeros días son cruciales

- 307 pacientes con cirugía temporal

McIntosh, Ann Neurol 2005

El Paciente Ideal: Largo Plazo

8 características

- 5 Clinicas
  - Cirugía temporal no-dominante
  - Historia de crisis febriles, pero nó TCG
  - Un sólo foco epileptógeno resecable
  - Lesión en RMN
  - No requiere monitoreo intracraneal
- 1 Quirúrgica
  - Resección completa
- 2 post-operatorias
  - Sin puntas en el EEG de seguimiento
  - Sin crisis en el primer año

Es curativa la cirugía ó sólo disminuye la resistencia a FAEs?

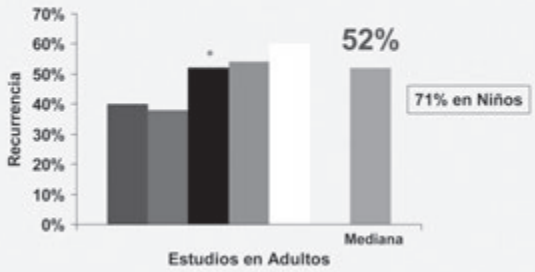
Revision Sistemática: Corto plazo

- Criterios de Inclusion de estudios
  - Cirugía resectiva
  - Descontinuacion de FAEs "pre-planeada"
  - Seguimiento ≥ 6 meses
  - ≥ 5 pacientes con reduccion de FAEs
  - Distingue entre descontinuacion y disminucion de FAEs

Schmidt, Epilepsia 2004

Cuantos Pacientes sin Crisis Descontinúan FAEs?

Años de Seguimiento = 3 (1-6)

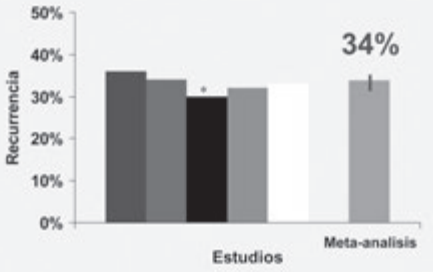


*Disminución solamente

Schmidt, Epilepsia 2004

Recurrencia post-descontinuación

Años de Seguimiento = 3 (1-6)

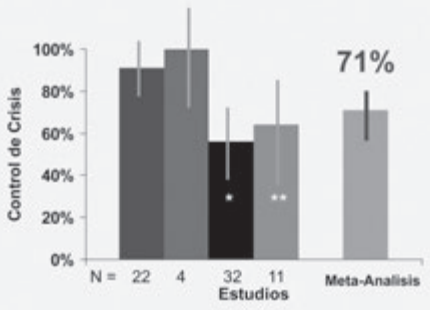


*Disminución solamente

Schmidt, Epilepsia 2004

Pacientes Controlados al Reiniciar FAEs

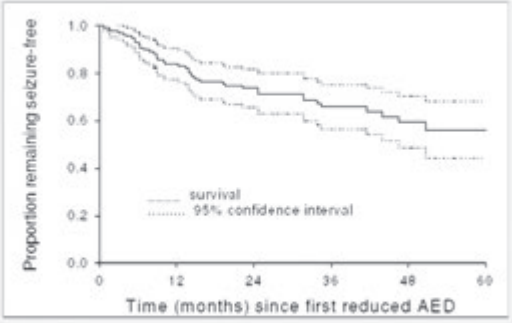
Años de Seguimiento = 3 (1-6)



* Incluye disminucion ** Niños

Schmidt, Epilepsia 2004

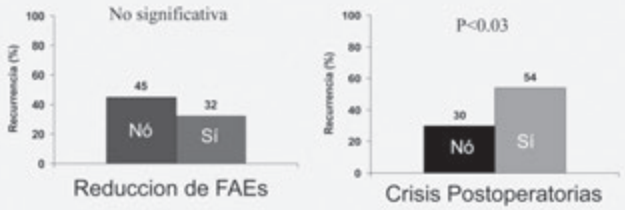
Remisión a corto plazo (N=396)



Porcentaje con remision sostenida despues de reducir FAEs (iniciada si ≥1 ano sin crisis)

Berg, Epilepsia 2006

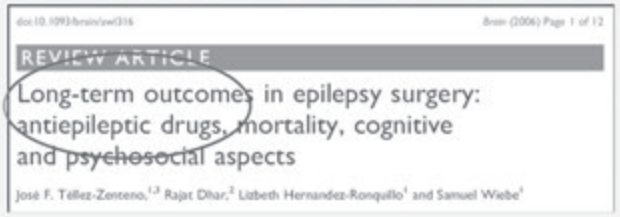
Cohorte Multicéntrica (N=396)



Unico factor pronostico → Remisión inmediata

Berg, Epilepsia 2006

Que Sucede a Largo Plazo?

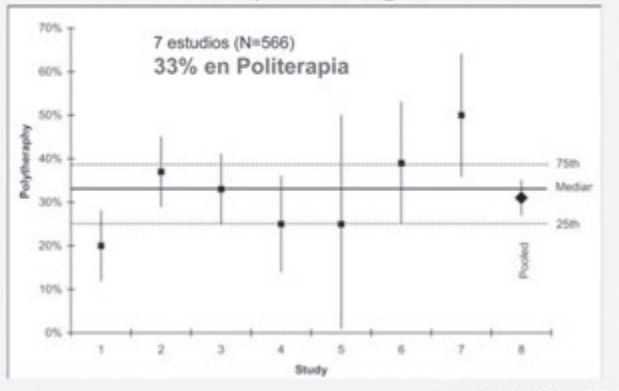


1794 Citas → 154 Potencial → 35 (22%) Incluídos

7 años de seguimiento medio

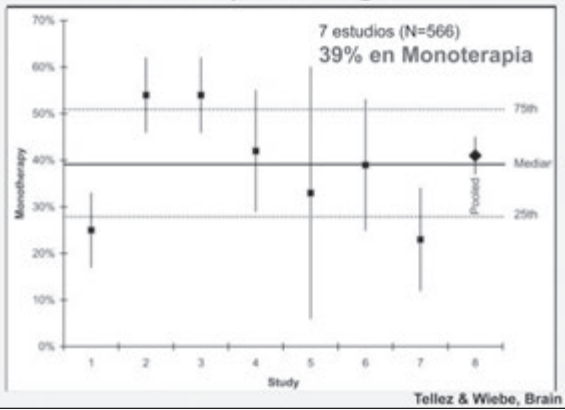
Tellez & Wiebe, Brain 2006

Politerapia
Todo Tipo de Cirugías



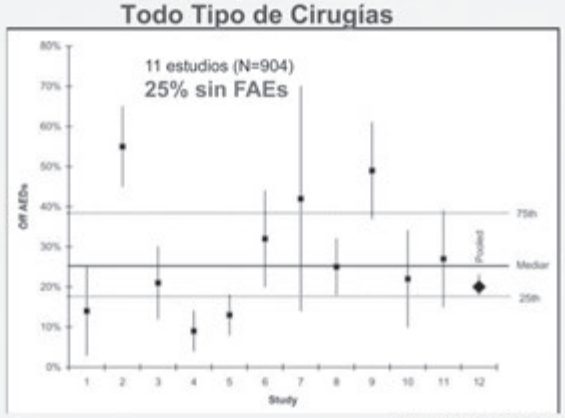
Tellez & Wiebe, Brain 2006

Monoterapia
Todo Tipo de Cirugías



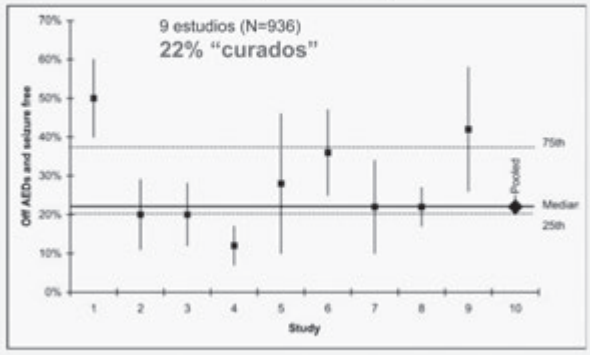
Tellez & Wiebe, Brain 2006

Porcentaje Sin FAEs
Todo Tipo de Cirugías



Tellez & Wiebe, Brain 2006

Porcentaje Sin FAEs y Sin Crisis
Todo Tipo de Cirugías

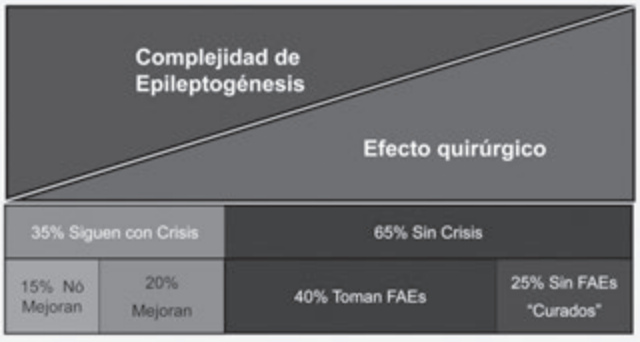


Tellez & Wiebe, Brain 2006

La cirugía cura?
ó
sólo disminuye resistencia a FAEs?

Ambas

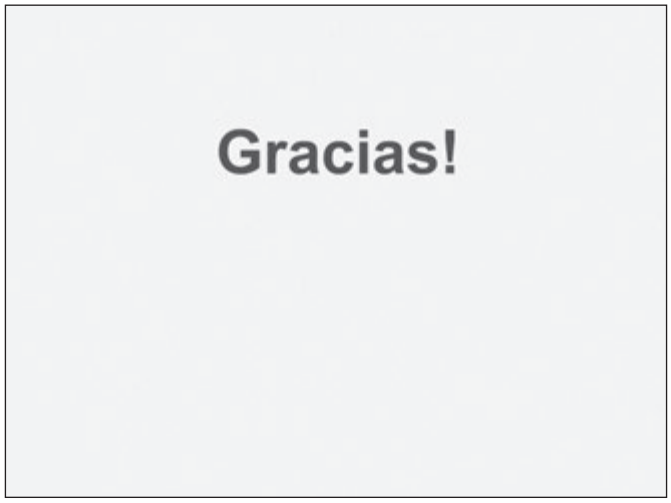
La curación quirúrgica



Tellez & Wiebe, Brain 2005 & 2007; Schmidt, Epil Res 2004; Engel, Neurology 2003

Conclusiones

- Los efectos benéficos a corto y largo plazo son similares y duraderos
  - Tienden a disminuir a muy largo plazo
  - Dependen de factores clínicos y quirúrgicos
- 50% a 60% de adultos disminuyen FAEs
- 25% los descontinúan y de éstos 30-35% recurren
- El reinicio de FAEs controla las crisis en 70%
- La espera no parece influenciar el resultado
- A largo plazo, 22% permanecen "curados"
- El control temprano es un indicador crucial


Gracias!

Predictors of postoperative memory and cognitive impairment in MTLE

Fernando Cendes (Brazil)

Genetic testing in the epilepsies-report of the ILAE Genetics Commission – What is the relevance for diagnosis of catastrophic epilepsies?

Iscia Lopes Cendes (Brazil)

Genetic testing in the epilepsies

Iscia Lopes-Cendes, M.D., Ph.D.
Professor of Medical Genetics
Faculty of Medical Sciences
University of Campinas – UNICAMP

Campinas, SP - BRAZIL

UNICAMP

Progress in Epilepsy Genetics Research

- Since 1995, more than 20 genes identified with a major influence on risk for human epilepsy syndromes
- Importance in research context:
  - Elucidation of pathogenic mechanisms
  - Development of new treatments
  - Development of methods to prevent epileptogenesis
- Importance in clinical context: **GENETIC TESTING**

Progress in Gene Identification

- Mendelian idiopathic epilepsy syndromes
- Mendelian symptomatic epilepsy syndromes
- Complex (nonMendelian) epilepsies

ILAE Genetics Commission

Members (2006-2009):

Ruth Ottman, Ph.D., USA (Chair)

Shinichi Hirose, M.D., Ph.D., JAPAN

Satish Jain, M.D., D.M., F.R.C.P., INDIA

Holger Lerche, M.D., GERMANY

Iscia Lopes-Cendes, M.D., Ph.D., BRAZIL

Jeffrey L. Noebels, M.D., Ph.D., USA

Ingrid E. Scheffer, M.B.B.S. Ph.D. F.R.A.C.P., AUSTRALIA

José Serratosa, M.D., Ph.D., SPAIN

Federico Zara, Ph.D., ITALY

- Highest priority: to develop a report on genetic testing
- Provide a framework for considering the utility of testing that can be applied to many different genes, syndromes, and clinical contexts
- Was submitted to Epilepsia

Definition of Genetic Testing

The use of molecular genetic information, either to clarify to diagnosis in people already known or suspected to be affected, or to predict onset in people at risk because of a family history

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

Potential benefits of genetic testing

- Clarify the diagnosis
- Provide information about prognosis or treatment
- Save patient and family from expensive and uncomfortable or invasive tests
- Provide an answer to patient's questions about what caused the disorder
- Help with reproductive decisions

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

What questions should be asked to evaluate whether or not a genetic test provides useful information for clinical care?

ASSESSING THE POTENTIAL VALUE OF CLINICAL GENETIC TESTS

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

Evaluation Process for Genetic Testing

ACCE components:

Analytic validity: does the test accurately identify the genotype?

Clinical validity: Does the test accurately predict whether or not a person has the disorder (or will develop it in the future)?

Clinical utility: What are the benefits and harms of introducing the test into clinical practice?

Ethical, Legal, and Social Issues

Office of Public Health Genomics, CDC, and the Foundation for Blood Research (http://www.cdc.gov/genomics/gtesting/ACCE.htm).

Components of Clinical Validity

- **Sensitivity**: What proportion of affected individuals have a positive test result?
- **Positive predictive value**: What proportion of those who test positive have the disorder?
- **Negative predictive value:** What proportion of those who test negative do not have the disorder?

Influences on Clinical Validity

- Reduced penetrance:
  - Some of those who inherit a mutation do not develop epilepsy
  - Reduces PPV for predictive test: some of those who test positive will remain unaffected
  - For many previously identified epilepsy genes, penetrance is <80%
  - EXAMPLE: Penetrance of mutations in ***LGI1*** is 67%, suggesting only about 2/3 of those who inherit a mutation will develop AD partial epilepsy with auditory features

Genotype-Phenotype Complexities

- Variable expressivity:
  - Mutations in a single gene can produce different epilepsy phenotypes in different individuals
  - Best example: GEFS+
  - A positive gene test does not allow prediction of the clinical outcome
- Genetic heterogeneity:
  - A single syndrome may be caused by mutations in different genes in different families
  - Many families do not have mutations in any previously identified genes

Locus Heterogeneity: Impact on Testing

- Many families do not have mutations in any previously identified gene
- A negative test is not informative
  - Family could have mutation in a different gene
  - Family could still have the syndrome
- In some genes, *de novo* mutations found in isolated cases
  - Rare
  - In absence of family history, test has low sensitivity
  - Positive test could have important clinical implications, so need to balance cost vs. benefit

Syndrome	Genes	% of families with mutations
ADNFLE	CHRNA4 CHRNA2 CHRNB2	~20%
ADPEAF/ ADLTE	LGI1	~50%
GEFS+	SCN1A	~10%
	SCN2A SCN1B GABRG2	<10%

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Dravet Syndrome

- ~80% of patients have a mutation in *SCN1A*
- Most are truncating, some missense
- More than 95% arise *de novo* (so neither parent is a carrier)
- In rare cases, parent is carrier, sometimes with gonadal mosaicism
- Diagnostic test has high clinical sensitivity regardless of family history

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Clinical Utility

- Is the test result likely to lead to a meaningful change in the procedures used for evaluation? (e.g., liver biopsy, repeated spinal tap or repeated neuroimaging)
- Is the test result likely to lead to a change in the optimal treatment choice or prognosis?
- Is the test result likely to have other positive or negative social or psychological effects? (e.g., relief, comfort, anxiety, depression)

	Dravet Syndrome (SCN1A)	GEFS+ (SCN1A)	ADPEAF/ADLTE (LGI1)
Clinical context	Patient with clinical features consistent with syndrome	Family history consistent with GEFS+, individual with phenotype in spectrum	Family history consistent with ADPEAF; individual with focal epilepsy with auditory symptoms
Clinical validity	Truncation mutation strongly predicts diagnosis; missense less clear	Positive test (missense mutation) confirms dx; negative test uninformative	Positive test confirms dx; negative test uninformative
Clinical utility	**HIGH** • Establishes etiology so avoids further diagnostic test procedures • Allows early optimization of AEDs • Genetic counseling implications	**LOW** • Extreme phenotypic heterogeneity • Mutation status does not predict prognosis or treatment response • Genetic counseling implications	**LOW-MEDIUM** • Usually benign course • Mutation status not likely to alter management decisions • *De novo* mutations found in rare cases • Genetic counseling implications

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Predictive Testing

- Dravet syndrome
  - Clinical context: Sibling of individual with truncation mutation
  - Clinical validity: mutation strongly predicts disease onset
  - Clinical utility: Knowledge of high risk allows preparation for more aggressive treatment at onset

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Assessing the potential value of a genetic tests

ACCE components:

- **Analytic validity: does the test accurately identify the genotype?**
- **Clinical validity: Does the test accurately predict whether or not a person has the disorder (or will develop it in the future)?**
- **Clinical utility: What are the benefits and harms of introducing the test into clinical practice?**
- **Ethical, Legal, and Social Issues**

Analytic Validity

- The analytic validity of a test refers to the laboratory component of testing
- Accuracy involves:
  - analytic sensitivity (the ability of the test to identify a positive sample correctly)
  - analytic specificity (the ability of the test to identify a negative sample correctly)
  - laboratory quality control (procedures for assuring the test results fall within specified limits)
  - and reliability (the ability of the test to produce the same results if repeated on the same sample)

Analytic Validity

- Analytic validity depends on the molecular aspects of detecting a gene variant in a DNA sample rather than on the disease
- Even when a test for a specific change within a gene is accurate, the test could still miss other important changes it is not designed to detect
- No single test currently available examines all aspects of variation within a gene

Analytic Validity

- A test result that reports "no change detected" does not exempt the gene from contributing to disease in any particular individual
- On the other hand, a negative result when looking for a specific mutation that is present in other affected family members usually provides a definitive answer

Technical Considerations

- The source of the DNA sample provided for testing:
  - If a mutation occurs during embryonic development, it may lead to an uneven distribution in different tissues, "somatic mosaicism." such as *SCN1A* mutations in Dravet syndrome.

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Technical Considerations

- Type of molecular changes to be detected:
  - Nucleotide substitutions X insertions and deletions (CNVs). Microdeletions in *SCN1A* in Dravet syndrome which are NOT detected by conventional sequence analysis

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Technical Considerations

- Therefore, to maximize the sensitivity of genetic testing, a wider array of molecular methods should be used

Molecular Methods

- Mutation scanning
- Sequencing
- Fluorescent in situ hybridization (FISH)
- Array-Comparative Genomic Hybridization (Array-CGH)
- Single nucleotide polymorphism arrays (SNP arrays)
- Multiplex ligation-dependent probe amplification (MLPA)
- Other (linkage analysis, methylation analysis, protein truncation testing (PTT), uniparental disomy (UPD) study, Southern blot analysis)

How to Test

- Current information about genetic testing for many disorders, including epilepsy, is available from the Gene Tests website (www.genetests.org), a publicly funded medical genetics information resource

Before Testing

- No genetic test should be ordered without the patient's informed consent. Since genetic information can be complex, it is important to make sure the patient understands the ramifications of testing in order to make an informed choice

Before Testing

- No genetic test should be performed without pre-test and post-test genetic counseling
- Pre-testing counseling should deal with several issues including the test limitations (e.g., the sample required, the information that will and will not be provided by the test)
- All of the information should be presented in a non-judgemental and non-coercive manner, to assist the individual to make an informed decision

Before Testing

- Post-test counseling is crucial to help the patient understand the test result and begin to digest it in the context of his or her life circumstances
- The session should convey the test results in terms that the patient understands, discuss the implications for the patient and other family members

Summary

- Genetic testing has many potential benefits
- Potential harms should also be considered
- Rapid progress in genetic research and expanding list of genes complicates decision-making
- Consideration of ACCE provides useful framework

Summary

- Technical considerations (**Analytic validity)** are an important part of the ACCE framework
- No single test currently available examines all aspects of variation within a gene
- Information about genetic testing is available at www.genetests.org
- No genetic test should be performed without pre-test and post-test genetic counseling

Memory and language in refractory epilepsy

Mirna W. Portuguez (Brazil)

Programa – 27.02.2011

09:00 – 10:00	Neuropsychological effects of seizures - Gus Baker (England)
10:00 – 11:00	Mesial temporal lobe epilepsy: clinical or surgical treatment? - Samuel Wiebe (Canada)
11:00 – 11:30	Coffee break
11:30 – 12:30	Neuropsychological consequences of intrauterine exposure to antiepileptic drugs - Gus Baker (England)
12:30 – 14:00	Lunch
14:00 - 15:00	Treatment of newly diagnosed epilepsy – Emilio Perucca (Italy)
15:00 – 16:00	Neuropsychological consequences of seizures in Childhood Absence Epilepsies – Marco Tulio Medina (Honduras)
16:00 – 16:30	Coffee break
16:30 – 17:30	Treatment of refractory epilepsy - Jacqueline French (USA)
18:30 – 20:30	Dinner

Neuropsychological effects of seizures
Gus Baker (England)

The Walton Centre NHS for Neurology and Neurosurgery NHS Trust

University of Liverpool

Natural history of cognitive functioning in people with newly diagnosed epilepsy:

The immediate impact of epilepsy

Joanne Taylor

Epilepsy: A historical perspective

- "In its slighter form there is merely defective memory…In more severe degree there is greater imperfection of intellectual power, weakened capacity for attention and often defective moral control. Mischievous restlessness and irritability in childhood may develop into vicious, even criminal tendencies in adult life"

GOWERS 1881

Limitations in investigating the Cognitive adverse effects of AED's

- Few studies adhere to basic standards of method, design, analysis, and neuropsychological evaluation

Cochrane, Marson and Baker *Epilepsia* 1998;39: 1068-97

Factors that may influence neuropsychological and psychological functioning

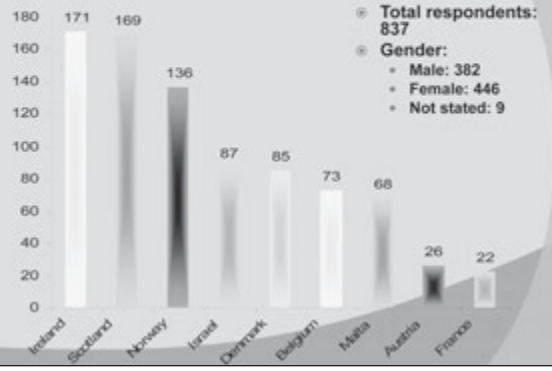
Neurobiological	Psychosocial	Medication
Age of onset	Locus of control	Monotherapy v polytherapy
Duration of disorder	Fear of seizures	CNS dose-related side effects
Seizure type and frequency	Parental overprotection	Folate deficiency
Structural brain changes	Perceived stigma	Presence/absence of barbituates
Efficiency of cerebral metabolism	Years of education	Medication induced alterations in cerebral metabolism
Alterations in neurotransmitters	Social support	

Hermann & Whitman 1996

Neuropsychology of epilepsy

- We already know that a significant number of people with epilepsy experience impairments in their cognitive functioning
- The main factors that appear to contribute to cognitive dysfunction are:
  - effects of the underlying aetiology
  - side effects of AEDs
  - effects of recurrent seizures
  - psychosocial issues
- These impairments can be seen on both objective neuropsychological tests as well as subjective self-report

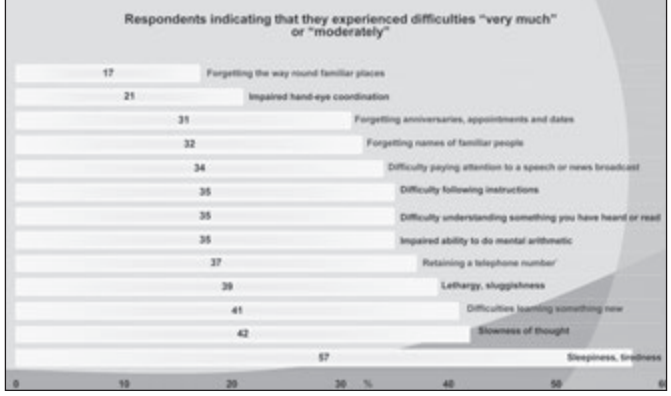
IBE Epilepsy and Cognitive Function Survey Results



- **Total respondents: 837**
- **Gender:**
  - **Male: 382**
  - **Female: 446**
  - **Not stated: 9**

Experience of cognitive impairment

n = 837



Relationship between memory and AEDs

- Total of 66% of respondents associated cognitive impairment with their epilepsy medication and / or condition
- Of these:
  - 41% stated that it was due to a combination of condition and medication
  - 16% stated that it was due to medication alone
  - 9% stated that it was due to the effects of epilepsy alone

Real life experience

"The effect of memory loss is too incidental not to be associated with regular intake of anti-epileptic medication"

"I certainly think that the tiredness I experience is due to medication and this has been apparent since taking medication. I also wonder about difficulty with names and learning new skills"

"Medication helps to prevent fits, but makes me tired, confused and slow"

Implications

- PWE already at increased risk of psychological problems and reduced QOL
- Cognitive dysfunction may also impact on day to day functioning and QOL
- 56% of adults reported cognitive impairment significantly affected ability to engage in:
  - work, education, leisure activities and had a negative impact on family and relationships

IBE, Epilepsy and Cognitive Function Survey (2004)

- Assessment at the time of diagnosis. Identify those at risk of cognitive dysfunction
- Refer for appropriate intervention and education
- AEDs may be an additional burden on cognition

Immediate impact of epilepsy

Authors	PWE	Controls	Tests	Results
Smith et al (1987)	622	75	General intellectual functioning, attention &concentration, mental flexibility, motor & manipulation, emotional/mood states	PWE < controls
Kälviäinen et al (1992)	74	39	WAIS, digit span, Corsi block, alt S, letter cancellation, object naming, verbal fluency, story recall, list learning, trails, Stroop, discrim RT, finger tapping	No diff IQ and verbal ability PWE < controls learning, delayed recall, recog & RT, letter cancellation, stroop 30% subtle memory dysfunction (<1 SD)
Äikiä et al (1995)	56	48	WAIS, story recall, list learning	No diff story recall, list learning PWE < controls delayed recall of words, % retention PWE (52%) vs controls (15%) mild and moderate impairments
Prevey et al (1998)	201	45	Motor speed & integration, memory, concentration & flexibility	PWE < controls on 17/18 measures some not reach stat significance
Pullainen et al (2000)	59	26	Ravens prog matrices, finger tapping, pegboard, digit span, visual span, trails, stroop, learning, retention	PWE< controls on 16/20 Differences between groups less evident
Äikiä et al (2001)	39	46	VIQ, verbal memory (story recall, list learning)	PWE < controls on verbal memory More PWE have mild and moderate impairments

Our current research

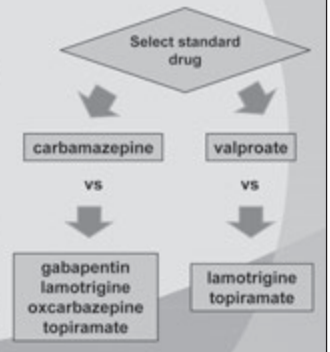
- Longitudinal study investigating the natural history of cognitive functioning in newly diagnosed untreated patients with epilepsy
- Aims
  - Impact of epilepsy at time of diagnosis
  - Cognitive profile of newly diagnosed untreated PWE compared with healthy volunteers

The SANAD Trial

A RCT OF LONGER-TERM CLINICAL OUTCOMES AND COST EFFECTIVENESS OF STANDARD AND NEW ANTIEPILEPTIC DRUGS

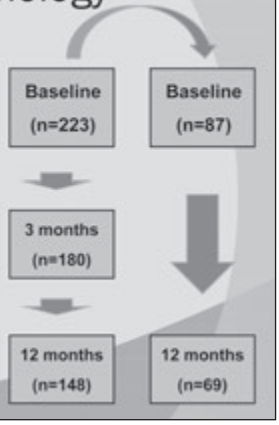
SANAD trial

- Large, prospective, multicentre, unblinded, RCT assessing the clinical and cost effectiveness of standard and new AEDs
- Marson et al (2007a,b)
- As part of SANAD, patients were randomised to one of 2 arms



SANAD Neuropsychology

- Previously untreated patients with newly diagnosed epilepsy
- 87 age and sex matched healthy volunteers
- Comparison between PWE and healthy volunteers at baseline



Neuropsychology battery

Domains	Tests
Psychomotor Speed	Finger Tapping Task Visual Reaction Time AMIPB (motor speed)
Learning & Memory	Recognition of words/figures Story Recall Rey Auditory Verbal Learning Task
Mental Flexibility	Stroop Colour-Word Tasks Verbal fluency
Information Processing	AMIPB (info processing) Binary Choice Reaction Time Computerised Visual Search Task
Mood	Profile of Mood States
Subjective report of cognitive problems	ABNAS

Knowledge of tests

- Attention and Concentration
- Memory
- Learning
- Executive tests
- Mood

Comparisons at baseline

- 68 patients had either a learning disability, previous neurological history or abnormal neuroimaging on clinical MRI so were excluded from this analysis.
- Based on 155 patients at baseline (otherwise neurologically normal) vs 87 healthy volunteers
- No differences in age and sex. Healthy volunteers higher levels of education ($p<0.001$)

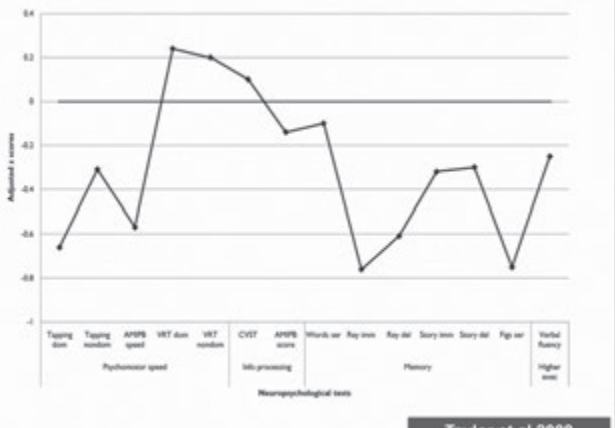
	PWE (n=155)	Controls (n=87)
Male (n, %)	79 (51.6)	45 (51.7)
Mean age, yrs (SD, range)	35.04 (14.41, 15-78)	35.14 (16.37, 15-80)
Education (n, %)		
<11	89 (57.4)	19 (21.8)
12-15	44 (28.4)	33 (37.9)
>15	22 (14.2)	35 (40.2)
Seizure type (n, %)		
Partial	109 (70.3)	-
Generalised	24 (15.5)	-
Unclassified	22 (14.2)	-

Preliminary Results I: memory

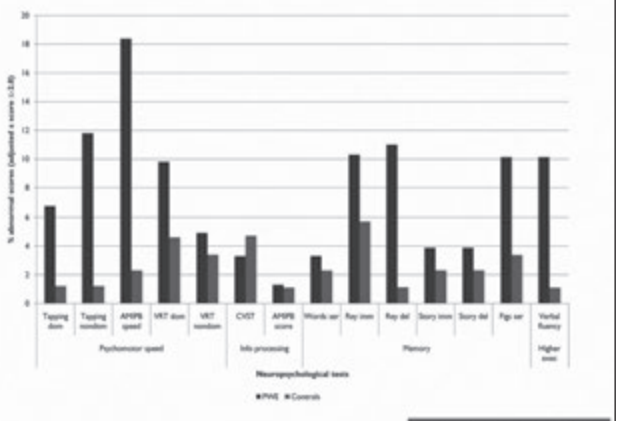
TEST	Rivermead immediate	Rivermead delayed	AVLT Trial 5	Words Serial Recognition	Words Simultaneous Recognition	Shapes Serial Recognition	Shapes Simultaneous Recognition
Control Mean	9.84	8.48	13.15	19.06	21.15	15.87	17.94
Patient Mean	8.19	6.61	10.62	14.24	14.98	12.25	13.76
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

Preliminary Results II: Neuropsychological Functioning

TEST	STROOP	WORD FLUENCY	AMIPB Info	AMIPB Speed	Visual Reaction Time Dominant	Visual Reaction Time Non Dominant	Finger Tapping Dominant	Finger Tapping Non Dominant	Binary Choice	Visual Search
Control Mean	104.9	37.5	62.1	47.1	309.1	299.8	60	52	505.8	10.3
Patient Mean	92.1	39.9	60.2	45.7	324.9	317.1	56.1	51.2	392.3	11.8
P value	<0.01	<0.01	ns	ns	ns	<0.05	<0.01	<0.05	<0.01	<0.01



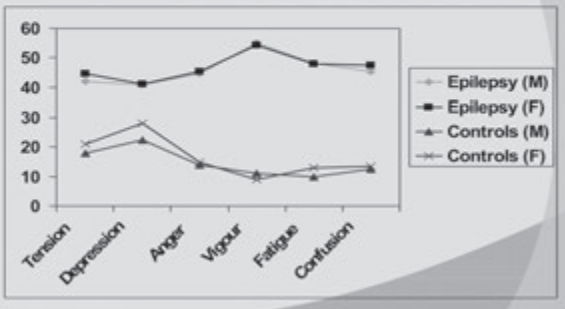
Taylor et al 2009

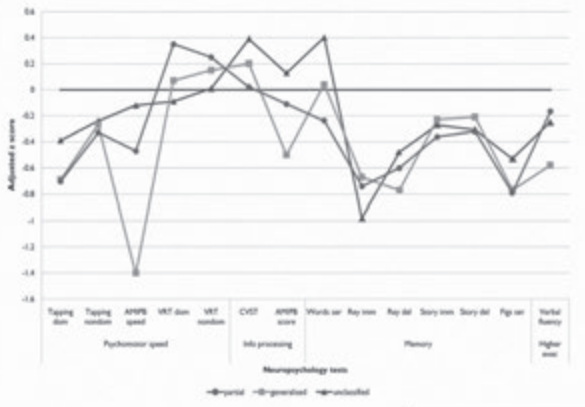


Impairment index

Prop of tests impaired	>2SD		>1.5SD	
	PWE	Controls	PWE	Controls
0	72 (46.5)	69 (79.3)	39 (25.2)	45 (51.7)
>1%	83 (53.5)	18 (20.7)	116 (74.8)	42 (48.3)
>25%	15 (9.7)	2 (2.3)	38 (24.5)	9 (10.3)
>50%	1 (0.6)	0 (0.0)	11 (7.1)	1 (1.1)

Preliminary Results III:
Profile of Mood States





Taylor et al 2009

Results

- No relationships total number of seizures before baseline or number of tonic-clonic seizures and any cognitive measures
- PWE reported more tension, confusion and less vigour but no relationships mood factors and cognitive measures

Effects of seizure activity

- Little is known about the effects of seizures
- Difficult to determine the individual effects of seizures due to methodological issues [Vingerhouts 2006, Dodrill 2004]
- Seizure frequency may have an impact when seizures are generalised tonic clonic seizures [Thompson and Duncan 2005]
- Generalised seizures greater impact than partial seizures [Aldenkamp and Bodde 2005].
- Multifactorial model is responsible for cognitive decline [Kramer et al 2006]

Results of SANAD Trial

- No differences for remission at 12 months v continued seizures for Arm A and Arm B apart from Profile of Mood Scores .

Characteristics of the impaired group

- No differences those classified as impaired vs those not impaired:
  - Gender
  - Age at assessment
  - Education
  - Epilepsy type
  - No of seizures at baseline
  - Age at first seizure
  - Mood

Summary

- Observed differences not mediated by type or frequency of seizure activity
- Epilepsy-related or mood variables not explain the differences
- Mechanisms underlying cognitive impairments remains unclear
  - Epileptogenesis
  - Psychological adjustment (Velissaris et al, 2007)

Future research

- Understand more the characteristics of those who appear to be at immediate risk of epilepsy and its treatment
- Need more studies following up newly diagnosed patients.
  - Different cognitive trajectories?
- Need to agree on a uniform standardised battery of tests
  - Academic research
  - Clinical practice

Thank you for your time and attention

Acknowledgments
SANAD group
Caroline Perischine
Patients with epilepsy and volunteers

Mesial temporal lobe epilepsy: clinical or surgical treatment?
Samuel Wiebe (Canada)

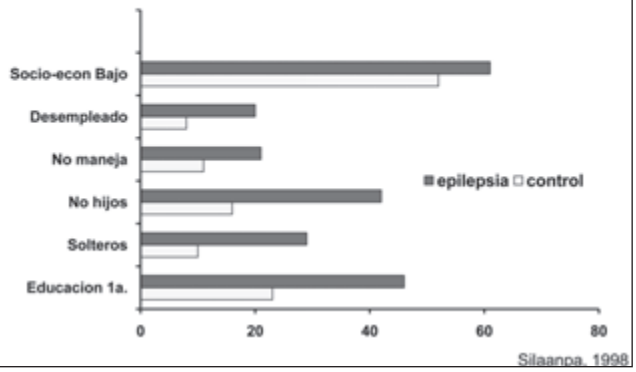
Progressive Cognitive Decline in TLE Epilepsy

Samuel Wiebe
University of Calgary
LASE V, Sao Paulo, Feb 25, 2010

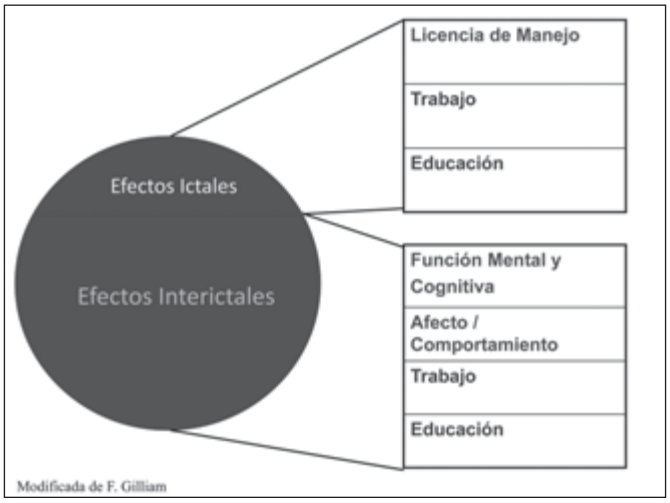
Background

Epilepsia en Remision Sin FAEs

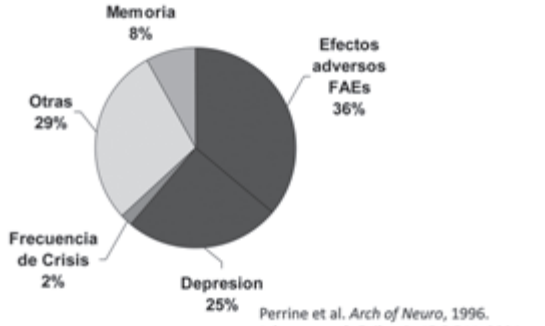
Seguimiento: 27 años, Edad = 33



Silaanpa, 1998



Modificada de F. Gilliam

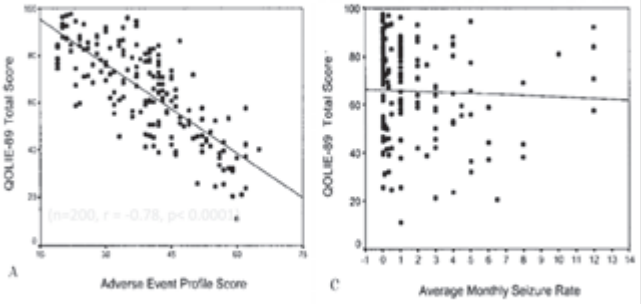


Perrine et al. *Arch of Neuro*, 1996.
Johnson et al. *Epilepsia* 45:5 544, 2004
Gilliam *Neurology* 58(Suppl 5):9-19, 2002

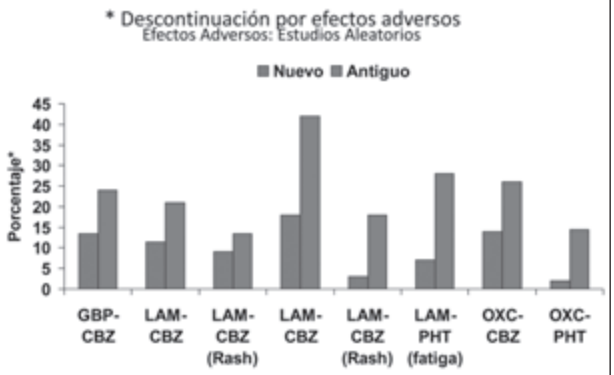
Qué es lo Importante Para los Pacientes?

Modificada de F. Gilliam

Efectos Adversos y Bienestar del Paciente



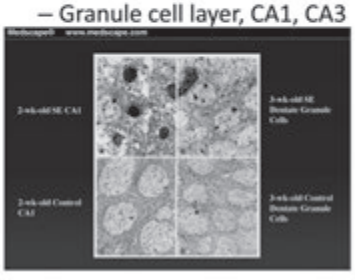
Gilliam et al. *Neurology* 2004;62:23-27



Evidence from Animal Models

Apoptotic Cell Death after Seizures

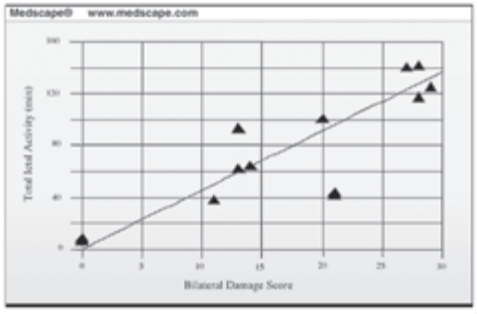
- >24 studies in animal models
  - Pilocarpine, kainic a, kindling, perforant path stim
  - Granule cell layer, CA1, CA3



Bengzon, Progr Brain Res 2002

Hippocampal cell loss & Status Epilepticus

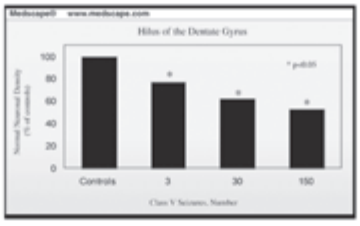
- Correlation between hippocampal cell damage following status epilepticus and duration of ictal activity (each data point = an individual animal).



Medscape 2000

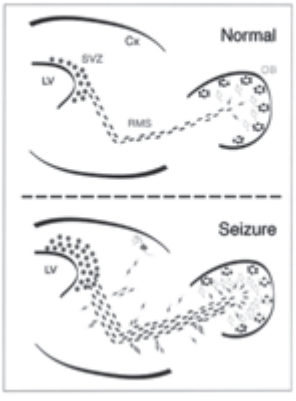
Apoptotic Cell Death after Seizures

- >24 studies in animal models
  - Pilocarpine, kainic a, kindling, perforant path stim
  - Granule cell layer, CA1, CA3



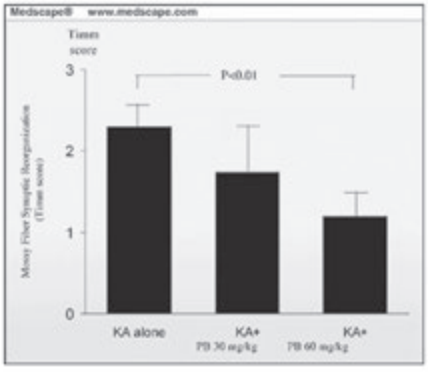
Bengzon, Progr Brain Res 2002

Seizures induce neurogenesis



Parent, Progr Brain Res 2002

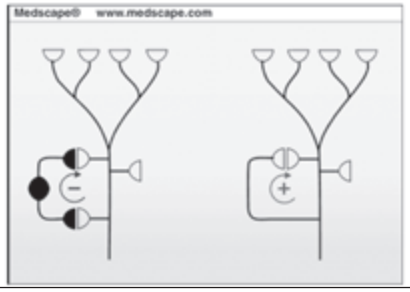
Phenobarbital and Mossy Fiber Sprouting



Medscape 2000

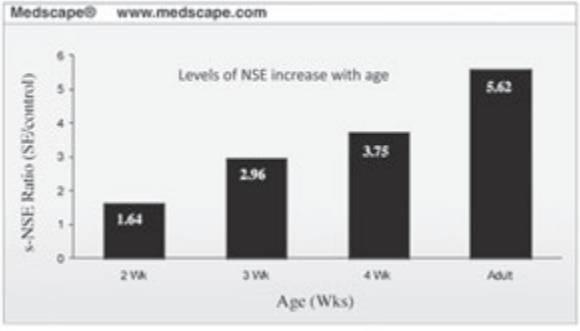
The "epileptogenic loop."

- Normal interneuron inhibitory feedback circuit (left)
- Altered when mossy fiber sprouting replaces a damaged interneuron, creating an excitatory feedback circuit (right).



Medscape, 2000

The immature brain is more resistant to neuronal damage by seizures



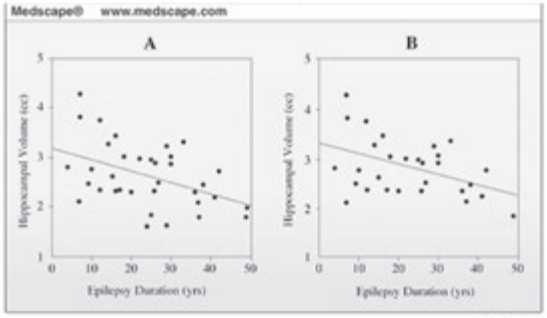
Medscape 2000

Evidence from Humans

Cell loss in Human HC, direct correlation w duration of epilepsy

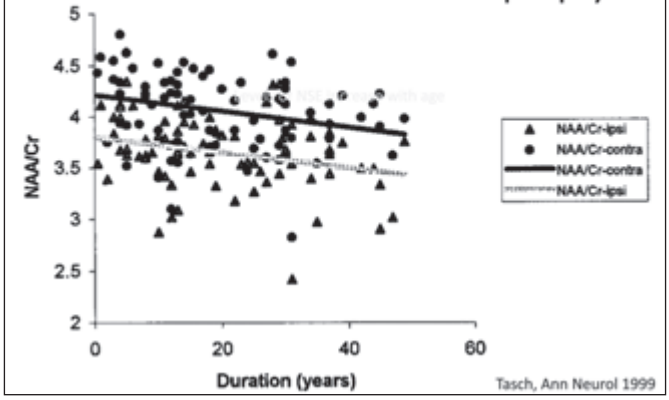
A) Patients with Temporal Lobe Epilepsy

B) Persists after Complex or prolonged febrile seizures excluded



Medscape 2000

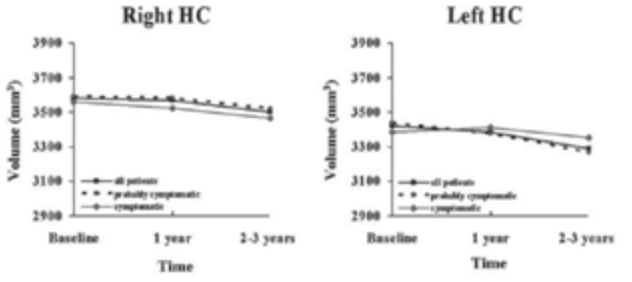
HC atrophy and Cell loss in Humans correlates with duration of epilepsy



Tasch, Ann Neurol 1999

Longitudinal HC volume loss
103 Patients with Epilepsy & 20 controls

NO Differences found



Salmenpera, Neurol 2005

HC Neuronal loss in epilepsy

Mathern, Progr Brain Res 2002

The Excitotoxic Cascade

- excessive glutamate release
- glutamate receptor overstimulation
- cellular calcium influx
- apoptosis
- NO synthase overproduction
- free radical accumulation
- neuronal reorganization
- enhanced hyperexcitability
- cell death

Medscape 2000

Progressive Epilepsy: Conflicting Evidence

Pro (Animal Evidence)

- neuronal injury after status epilepticus and single seizures
- increased seizure susceptibility in kindling models
- neuronal injury and reorganization inhibited by some AEDs

Con (Clinical Evidence)

- natural history of remission despite frequent seizures in some syndromes
- time to remission unchanged by early AED intervention
- AED prophylaxis ineffective

Medscape 2000

Behavior and Intelligence in Children

Predictores en Ninos

- 72 ninos con epilepsia, hermanos controles
- Examen anual , media 4 anos
- Predictores
  - Mayor # de FAEs y toxicidad por FAEs – Cuidado!
  - Edad inicio temprano

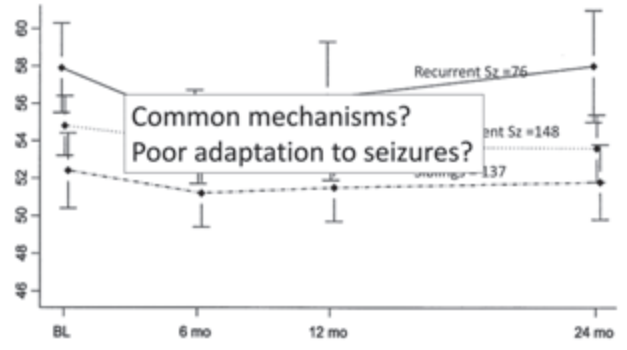
Table 4. Distribution of Epileptic Patients According to Changes in IQ Values over Time

IQ Pattern over Time[a]	No. of Patients (%) (n = 72)	IQ[b] First Testing	IQ[b] Last Testing
Decrease	8 (11.1)	108.1 ± 19.5	88.0 ± 19.5
Increase	12 (16.7)	93.7 ± 24.2	108.8 ± 23.5
Fluctuation	29 (40.3)	99.3 ± 19.0	100.8 ± 19.3
No change	23 (31.9)	100.3 ± 19.8	101.6 ± 19.8

Burgeois, Ann Neurol 1983

Progressive Behavioral Changes

Total CBCL

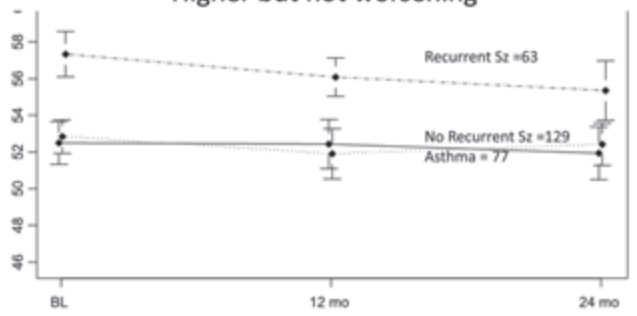


Austin, Epilepsia 2002

Progressive Behavioral Changes

Teachers ratings: TRF-CTRF

-Higher but not worsening-



Dunn, E&B, 2003

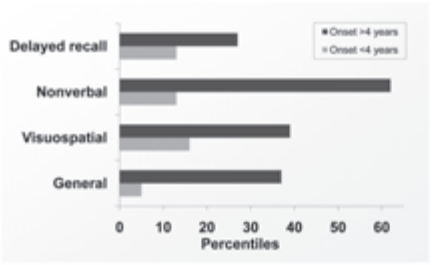
Behavioral problems in children

- Mostly Cross sectional studies
- Strongest associations
  - Number of seizures
  - Early onset and long duration of epilepsy
  - Poor seizure control
  - Multiple seizure types
- Number of seizures is strongest predictor
  - Not seen in other conditions (frequent asthma attacks)

Austin, Progr Brain Res 2002

IQ in Childhood Absence

- Lower than in Controls (25 vs. 55 percentile)
- Worse if onset younger



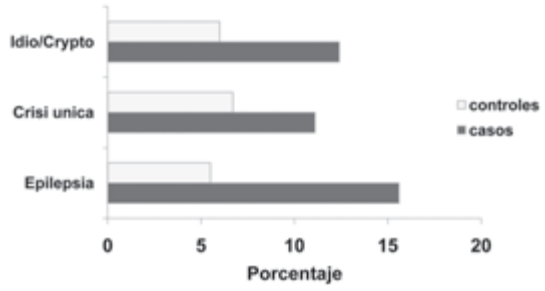
Patients n=16
Controls n=16
Mean age 9 years

Pavone P, et al. Neurology 2001;56:1047-1051

La ADHAD Precede al Inicio de Crisis

casos (N=109) controles (N=218)

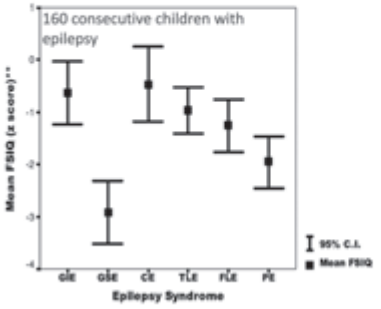
ADHD: Factor de Riesgo para Epilepsia?



Hesdorfer, 2004

IQ in Childhood Epilepsies

- Syndrome: Most important determinant of IQ

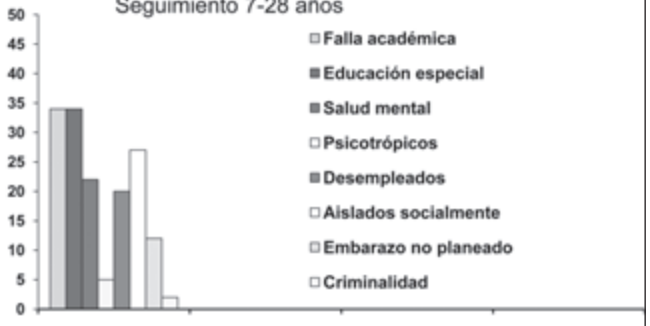


- Age of Onset responsible for 17% of decline

Nolan MA, et al. Epilepsy Res 2003;53:139-150

Desarrollo Social Subsecuente

337 Niños Neurológicamente Sanos
Seguimiento 7-28 años



Camfield, 1993

Seizures Beget Seizures

Seizures Beget Seizures

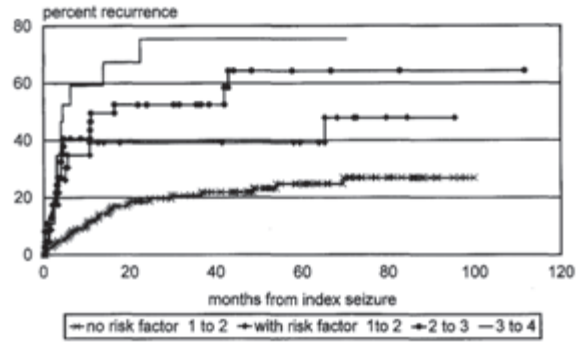
Recurrence rate ratio[a] by seizure category

Risk group	Number	Rate ratio	95% Confidence
1st idiopathic			
Family Hx$^+$/GSW$^+$	23	2.3	1.1–4.8
1st remote symptomatic	59	2.2	1.3–3.9
2nd idiopathic	37	3.7	2.1–6.5
3rd idiopathic	20	5.8	2.9–11.6
2nd and 3rd remote symptomatic	47	6.4	3.8–10.6

[a] The reference group consisted of patients with 1st idiopathic seizure, EEG negative of GSW and no family history of epilepsy ($n = 122$).

Hauser, Progr Brain Res 2002

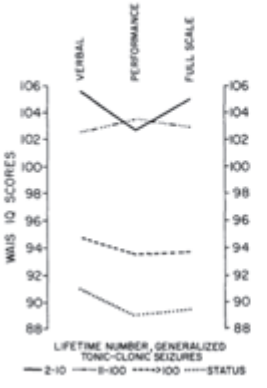
Seizures Beget Seizures



Hauser, Progr Brain Res 2002

Does Cognition deteriorate?

Seizures & Decline - Review

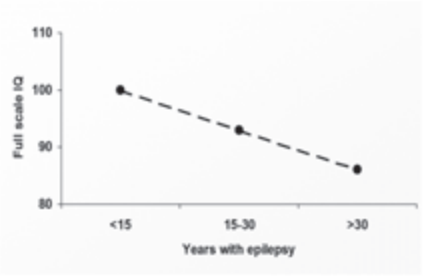


- Literature review, 16 eligible papers
- 12/16 showed mild but definite relation between seizures & decline
- Only for GTC Sz
- Effects larger in Cross sectional than in longitudinal studies

Dodrill, Progr Brain Res 2002

Duration of epilepsy = IQ decline

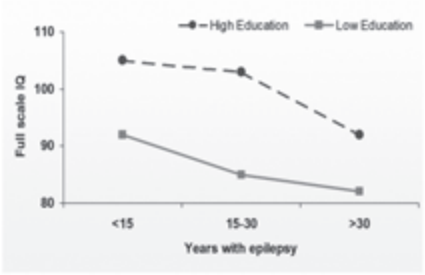
Temporal Lobe Epilepsy, N=209



Jokeit H, et al. J Neurol Neurosurg Psychiatry 1999; 67:44-5

Decline Not Explained by Education

Temporal Lobe Epilepsy, N=209



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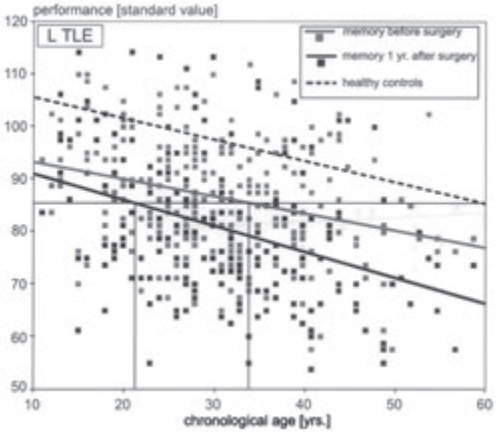
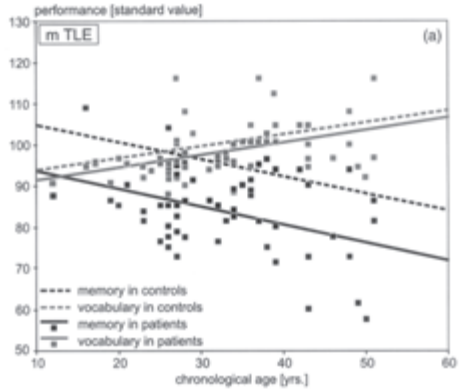
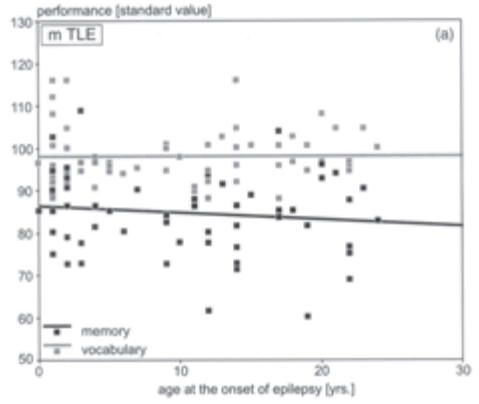


Helmstaedter, Progr Brain Res 2002



memory is impaired in TLE, in particular in TLE with mesial temporal pathology. With the exception that mesial functions appear increasingly affected by chronic non-mesial TLE, memory decline in TLE is not different from that observed in healthy control subjects. However, since patients perform poorer than controls at any age, normal senescence brings patients to mnesic disability at a younger age. Semantic memory seems unaffected by this process but early cortical lesions appear to interfere with knowledge acquisition. Longitudinal data come to a different conclusion regarding the contribution

Helmstaedter, Progr Brain Res 2002



Helmstaedter, Progr Brain Res 2002

doi:10.1093/brain/awp182 Brain 2009: 132; 2822–2830 | 2822

BRAIN
A JOURNAL OF NEUROLOGY

Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease?

C. Helmstaedter and C. E. Elger

our perspective towards patients with chronic epilepsy should change; it must shift away from viewing epilepsy as a progressively dementing disease and back towards showing how epilepsy, at its origin, interferes with brain maturation and cognitive development. In the long run, this increases the risk of premature 'dementia'. Additional efforts are thus needed to identify patients who are at risk and to counteract negative cognitive development in TLE at the very beginning.

Helmstaedter, Brain 2009

doi:10.1093/brain/awp182 Brain 2009: 132; 2822–2830 | 2822

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Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease?

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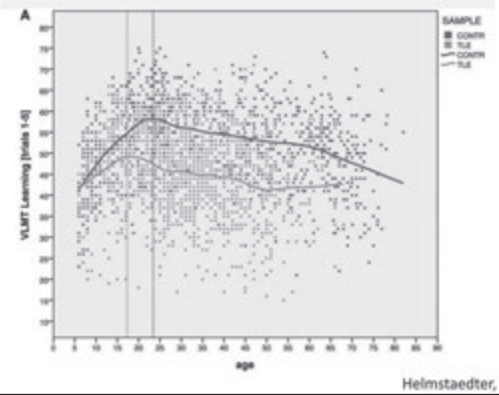
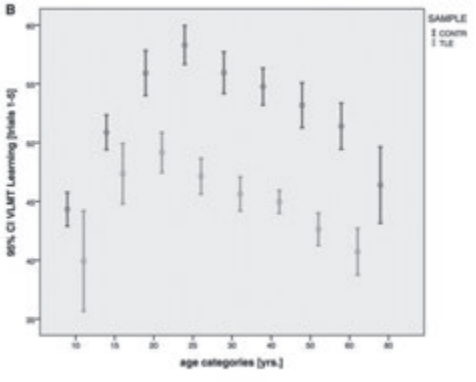
observed in chronic temporal lobe epilepsy (TLE) patients? We examined cross-sectional comparisons of age-related regressions of verbal learning and memory in 1156 patients with chronic TLE (age range 6–68 years, mean epilepsy onset 14 ± 11 years) versus 1000 healthy control subjects (age range 6–80 years) and tested the hypothesis that deviations of age regressions (i.e. slowed rise, accelerated decline) will reveal critical phases during which epilepsy interferes with cognitive development. Patients were recruited over a 20-year period at the Department of Epileptology, University of Bonn. Healthy subjects were drawn from

Helmstaedter, Brain 2009

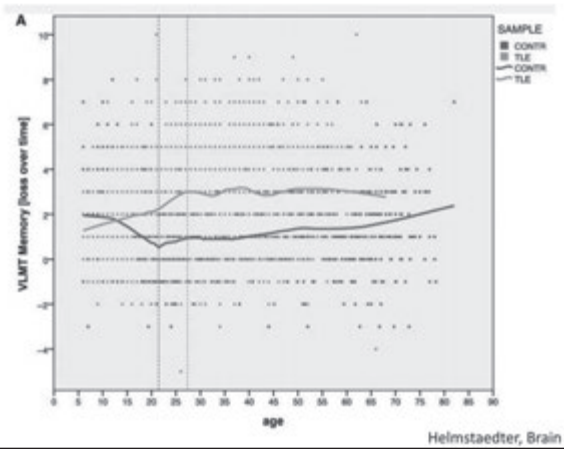
Developmental Hindrance Rather than Decline



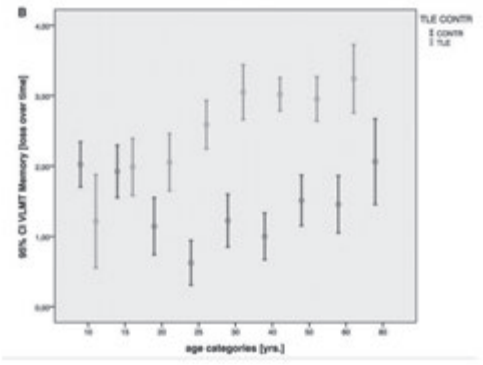
Helmstaedter, Brain 2009



Helmstaedter, Brain 2009



Helmstaedter, Brain 2009

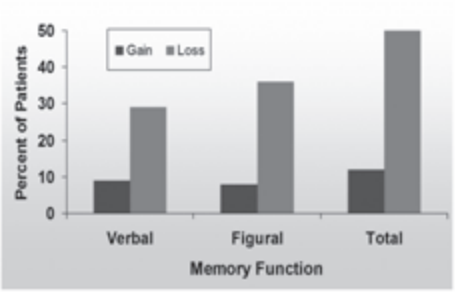


Helmstaedter, Brain 2009

Effect of surgery

Temporal Lobe Epilepsy: Cognition

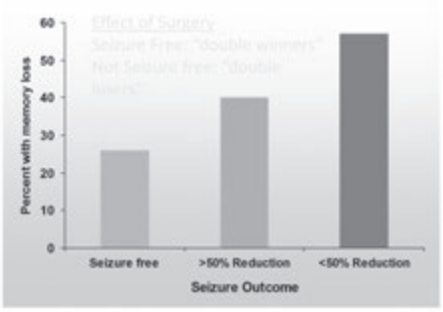
N=102, medical therapy, follow-up 2-10 years



Helmstaedter C, et al. Ann Neurol 2003;54:425-432

TLE: Effect of Seizure Outcome

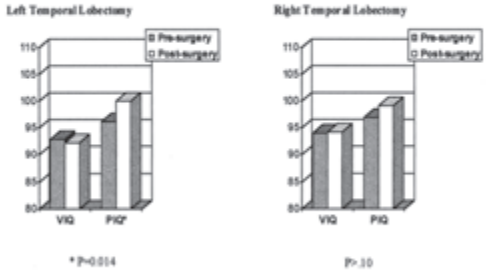
Medical 102, Surgical 147, follow-up 2-10 years



Helmstaedter C, et al. Ann Neurol 2003;54:425-432

TLE Surgery In Children

82 patients, mean age 14 years

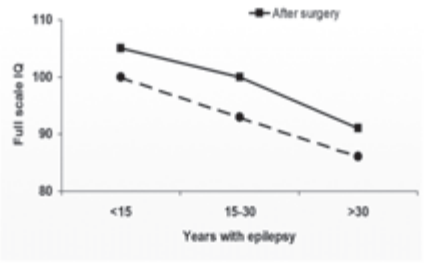


Decline more likely in older patients

Westerveld M, et al. J Neurosurg 2000; 92:24-30

Surgery Helps

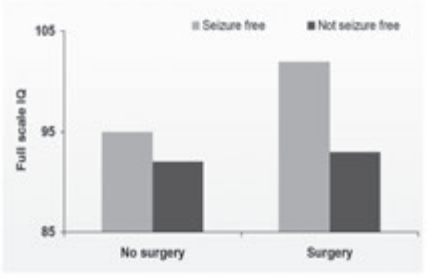
Temporal Lobe Epilepsy, N=209



Jokeit H, et al. J Neurol Neurosurg Psychiatry 1999; 67:44-5

Effect of Seizure Outcome

Temporal Lobe Epilepsy, N=209



Jokeit H, et al. J Neurol Neurosurg Psychiatry 1999; 67:44-5

Traditional Predictors

- Severity of hippocampal sclerosis
  - (Hermann et al., 1992; Sass et al., 1994)
- Hippocampal volume on pre-operative MRI
  - (Trenerry et al., 1993).
- Better Pre-operative memory performance
  - (Helmstaedter and Elger, 1996; Jokeit al., 1997).

Probability of Memory Loss
Reliable Change Index

•Amount of change that excludes chance or error with 80% certainty

• 10-point change Adult Memory and Information Processing Battery (AMIPB)

Not Significant Predictors

•Age at onset
•Hippocampal sclerosis
•Other structural lesions
•Normal MRI

Model	Whole (n=288)	Right (n=125)	Left (n=163)
Significant predictors	-High preop memory -Left side surgery -Older -Cortical dysplasia	-High preop memory -Older -Low verbal IQ	-High preop memory -Cortical dysplasia

Baxendale, Epilepsia 2006

Probability of Memory Loss
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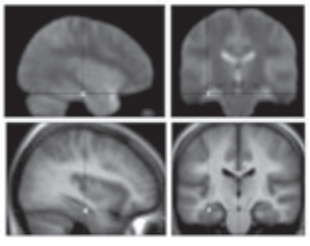
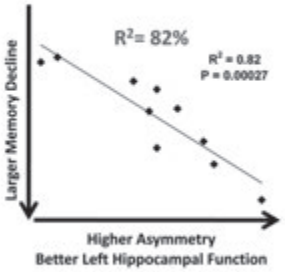
Significant predictors	-High preop memory -Left side surgery -Older -Cortical dysplasia	-High preop memory -Older -Low verbal IQ	-High preop memory -Cortical dysplasia
Hit Rate	70%	76%	61%
Sensitivity	74%	61%	78%
Specificity	68%	79%	53%

Baxendale, Epilepsia 2006

Asymmetry: Left minus Right



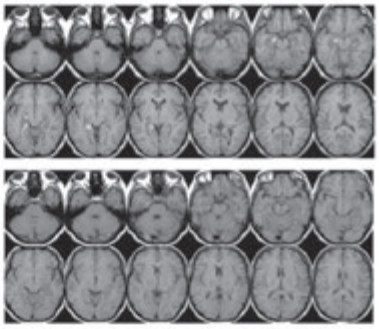


Richardson, Brain 2004

Reverse asymmetry ratio = good outcome

Left MTLE

Right MTLE

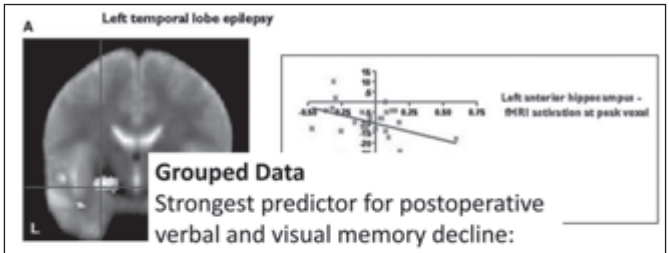


Rabin, Brain 2004

fMRI – Prediction of Memory Decline

- 72 MTLE patients (41 left), 20 controls
- Assessed verbal and visual memory
  - Words, pictures, faces in single fMRI session
- Memory function
  - Baseline & **4 months** post-op

Bonelli, Brain 2010



Grouped Data

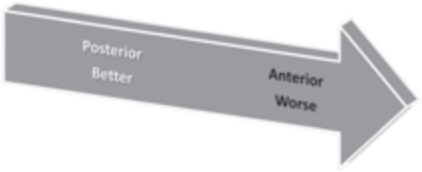
Strongest predictor for postoperative verbal and visual memory decline:

Asymmetry of activation for encoding words and faces in the ipsilateral anterior medial temporal lobe

Bonelli, Brain 2010

fMRI – Prediction of Memory Decline

- Asymmetry
  - Surgery on the temporal lobe with higher activation = higher risk of memory loss
  - Verbal or visual
- Ipsilateral hippocampal activation gradient



Bonelli, Brain 2010

However…

- Poor predictor for **individual patients**
- Positive predictive values
  - Verbal 35%
  - Visual 20%

Bonelli, Brain 2010

Prediction for Individual Patients

- Three variables predict decline
  - fMRI memory asymmetry index
  - Strong Left Language lateralization
  - High Preoperative memory (verbal or visual)

Memory decline	Sensitivity (%)	Specificity (%)	Predictive Value (%)
Verbal (Left T)	100	86	70
Visual (Right T)	50	100	100

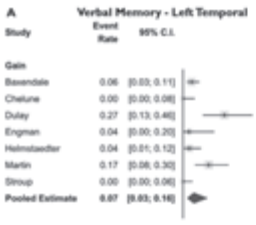
Bonelli, Brain 2010

Profile of Cognitive Outcomes
Meta-analysis

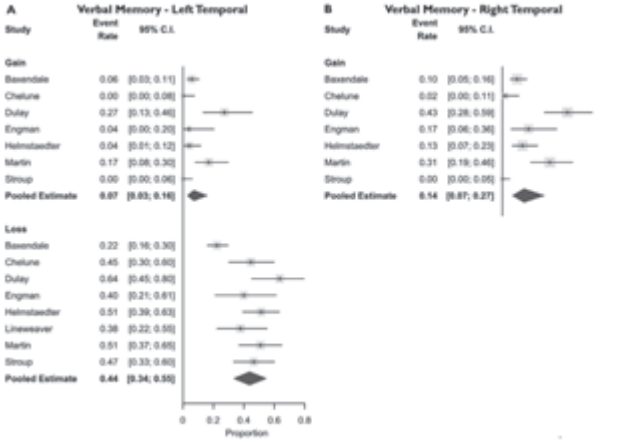
- N >20 patients
- Clearly described before-after cognitive measures
- Reporting number of patients with losses or gains
  - Reliable Change Index
  - Regression based measures
- Extensive Literature search

5,061	193	23	**22**
Epilepsy Surgery	Cognitive Outcomes	Met eligibility criteria	**Temporal Lobe**

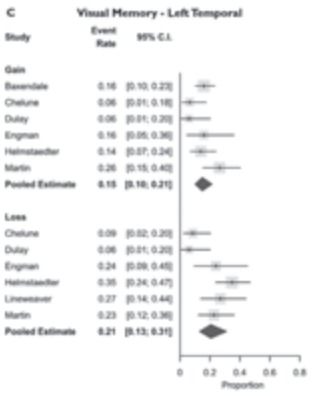
2,012 patients



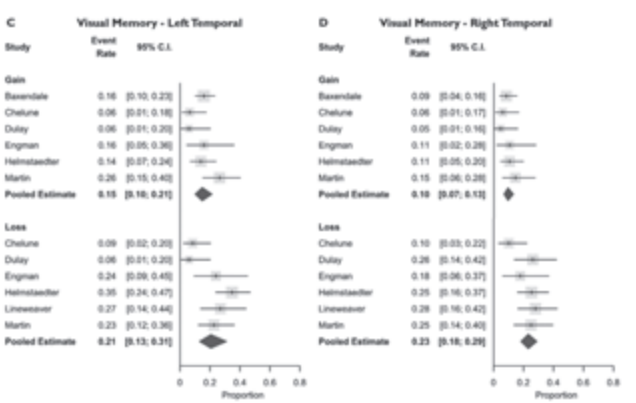
Sherman, Wiebe, etal, in Press



Sherman, Wiebe, etal, in Press



Sherman, Wiebe, etal. in Press



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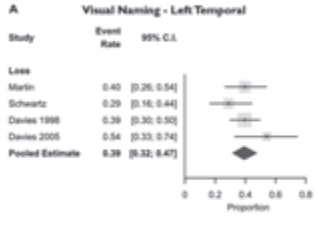

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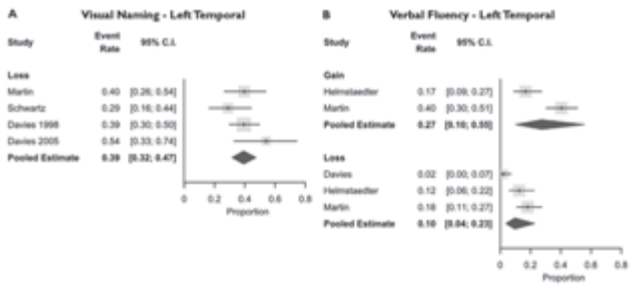


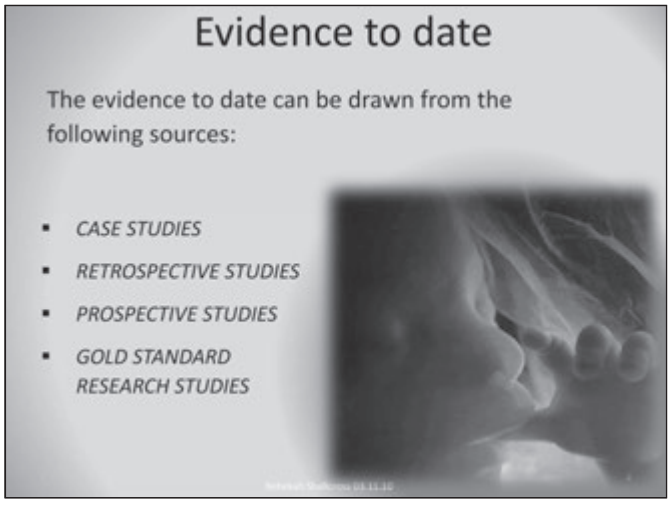
Sherman, Wiebe, etal. in Press

"The existence of forgetting has never been proved: We only know that some things don't come to mind when we want them."

Friedrich Nietzsche

Neuropsychological consequences of intrauterine exposure to antiepileptic drugs

Gus Baker (England)



AED Teratogenicity: is there published evidence of an increased risk...?

Possible Detrimental Pregnancy Outcomes

Antiepileptic Drug taken in Pregnancy	Congenital Malformations ?	Dysmorphic Features ?	Digit Effects ?	Developmental Delay ?	Behavioural Difficulties ?
Sodium Valproate (VPA)	✓	✓	✓	✓	✓
Carbamazepine (CBZ)	✓	✓	✓		
Phenytoin (PHT)	✓	✓	✓		
Lamotrigine (LTG)	✓				
Levetiracetam (LVT)					

AED: Potential Teratogenicity?

Trimethadione and Human Teratogenesis

JAMES GERMAN, ARETA KOWAL AND KATHRYN H. EHLERS
The New York Blood Center and Department of Pediatrics, Cornell University Medical College, New York City 10021

ABSTRACT A family is described in which four malformed children were born to a mother while she was taking trimethadione, an antiepileptic drug infrequently prescribed for adults. Following discontinuation of the drug, she had two normal children. This family led to a survey of all 278 epileptic women admitted to one hospital during the 23 years following the introduction of trimethadione for treatment of petit mal. Only eight women had ever taken it or its close congener paramethadione, and only three had taken it early in a pregnancy. Thus the outcomes of 14 pregnancies, during which the mothers took trimethadione or paramethadione early, have become known to the authors, those in the index family and those in three additional families ascertained through the survey. These pregnancies showed a high frequency of abnormality: eight children with developmental defects of various types, only three of whom have survived early infancy; one child with multiple hernias and juvenile, nonfamilial diabetes; and three spontaneous abortions. The survey suggests that neither epileptic women as a group nor those taking antiepileptic drugs usually prescribed for adults have an obviously increased frequency of malformed children but that epileptic women taking trimethadione or paramethadione may constitute a special subgroup whose children do have an increased frequency of birth defects. The small number of observations possible at a single institution, although suggestive, precludes a firm opinion as to the possible role as human teratogens of the oxazolidine-2,4-diones.

(1970). Teratology, 3(4), p349-361.

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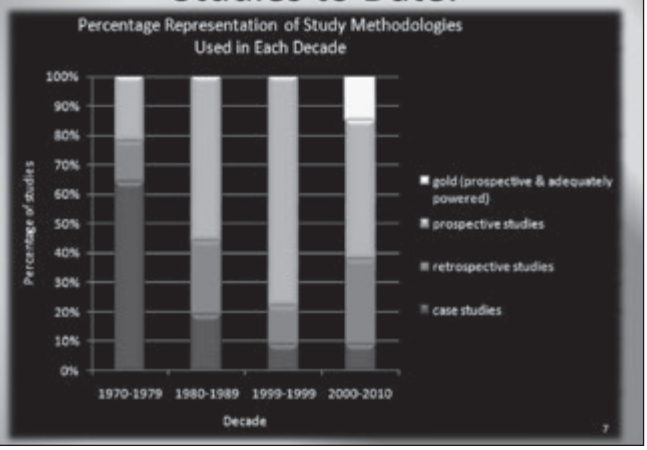
Valproic Acid and Its Metabolites: Placental Transfer, Neonatal Pharmacokinetics, Transfer *via* Mother's Milk and Clinical Status in Neonates of Epileptic Mothers[1]

H. NAU, D. RATING, S. KOCH, I. HÄUSER and H. HELGE
Institut für Toxikologie und Embryonalpharmakologie, Freie Universität Berlin (H.N., I.H.) and Kinderklinik der Freien Universität Berlin, Kaiserin-Auguste-Victoria-Haus (D.R., S.K., H.H.)

Accepted for publication August 24, 1981

- First Prospective recruitment study
- 12 cases of VPA exposure
- 4 (33%) were delayed in psychomotor development

Studies to Date:



Criticism of current and previous research

1.) Selection Bias

2.) Ill Defined Terms

3.) Inadequately Powered

4.) Absence of a Control Group

5.) Failure to account for confounding variables

6.) Inappropriate outcome measures

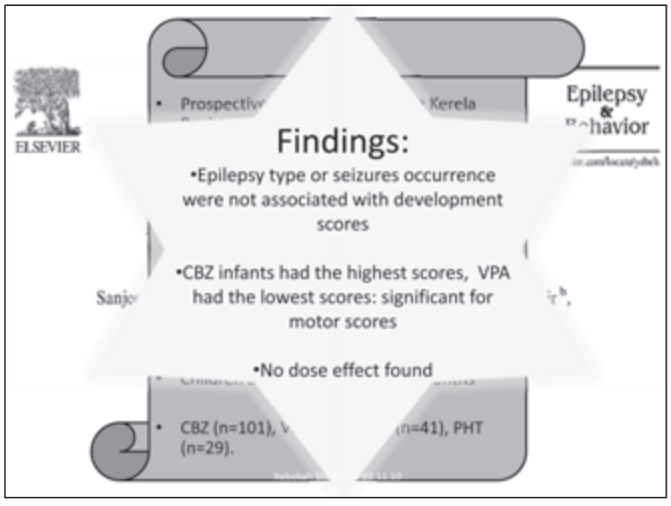
Gold Standard Research

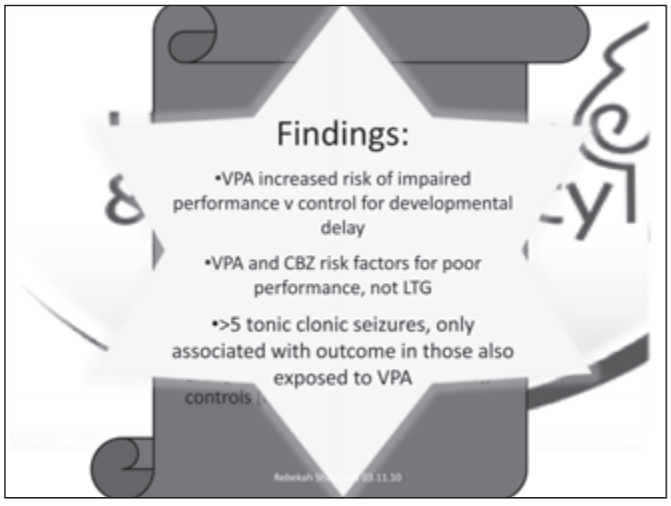
- Use of numerous neuropsychological measures
- Statistical control of confounding variables
- Recently normed standardized measures
- Follow up to at least six years of age
- Adequate numbers to each AED group
- Use of prospective control
- Blinded assessment
- Prospective Recruitment

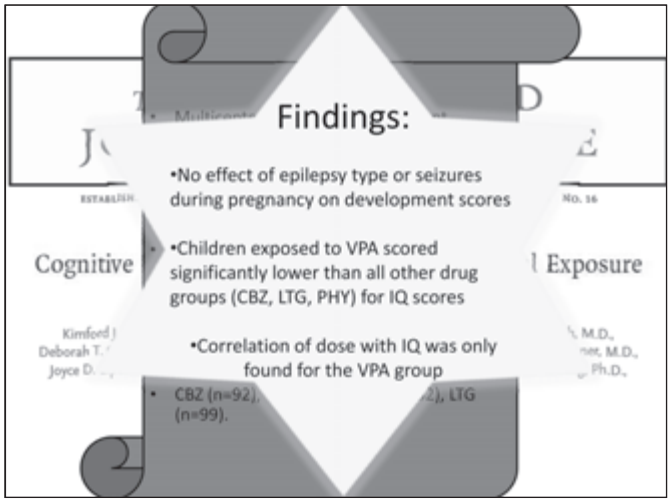
(Bromley Thesis 2009)

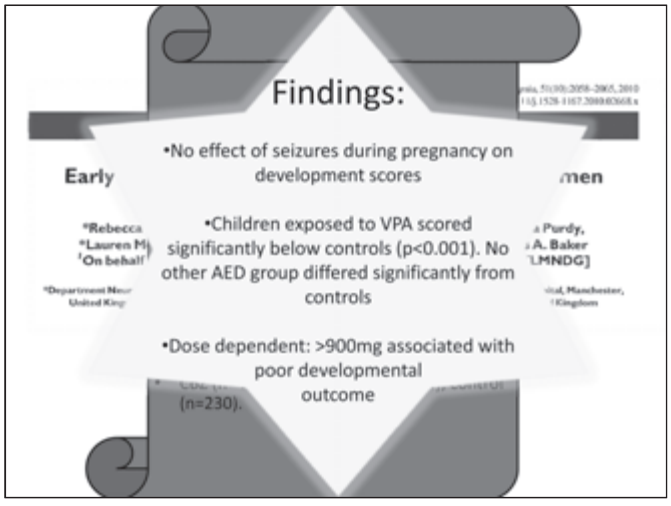
Prospective Studies to date

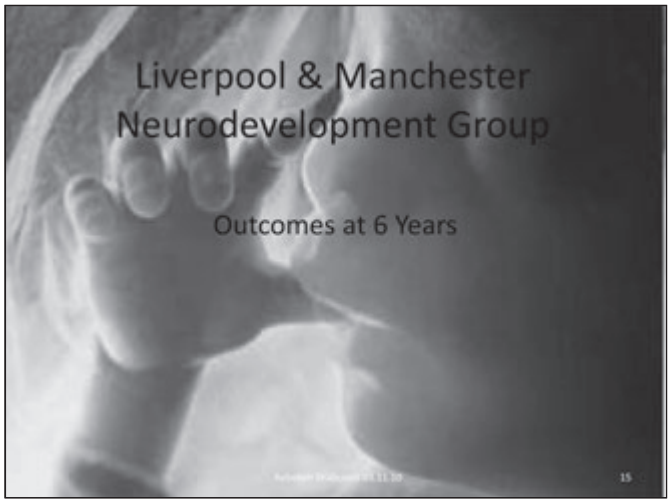
	Cummings 2008	Thomas 2008	Meador 2009	Bromley 2010	Shallcross 2010
Prospective Recruitment	✓	✓	✓	✓	✓
Standardised Measures	✓	✓	✓	✓	✓
Adequately Powered	✓	✓	✓	✓	✓
Control Group	✓	✓	No	✓	✓
Different outcomes measured	✓	✓	✓	✓	✓
Blinded assessor	✓	✓	✓	✓	No
Follow up until 6 years	No	✓	✓	✓	✓
Control of confounders	✓	✓	✓	✓	✓
Measure of maternal IQ	✓	No	✓	✓	✓






Findings:
•No effect of epilepsy type or seizures during pregnancy on development scores
•Children exposed to VPA scored significantly lower than all other drug groups (CBZ, LTG, PHY) for IQ scores
•Correlation of dose with IQ was only found for the VPA group
Cognitive
Exposure
CBZ (n=92),
(n=99).


Findings:
•No effect of seizures during pregnancy on development scores
•Children exposed to VPA scored significantly below controls (p<0.001). No other AED group differed significantly from controls
•Dose dependent: >900mg associated with poor developmental outcome
Early
(n=230).


Liverpool & Manchester Neurodevelopment Group
Outcomes at 6 Years

LMNDG Unpublished 6 Year Data

- Focus on CBZ and VPA exposed children assessed at 6 years of age:
  - 43 exposed to VPA
  - 45 exposed to CBZ
  - 177 control children
- Children assessed using a wide range of neuropsychological assessments to inform on:
  - IQ
  - Memory
  - Language
  - Attention
- Information was collected from the teachers and parents regarding speech therapy or extra educational needs

Results – IQ, Memory & Naming

Regression Analysis:
Maternal IQ
Maternal age
Maternal epilepsy type
Seizure exposure
Gestational age
Socioeconomic status
Alcohol and nicotine exposure

Exposure to CBZ

Not significant

But…….. Memory p=0.049

Exposure to VPA

FSIQ p=0.006

Memory p=0.001

Naming p=0.008

Results- Attention

Regression Analysis:
Maternal IQ
Maternal age
Maternal epilepsy type
Seizure exposure
Gestational age
Socioeconomic status
Alcohol and nicotine exposure

Exposure to VPA

Auditory attention p=0.025

Visual attention - NS

Exposure to CBZ

Auditory attention – NS

Visual attention – NS

But …….. P=0.032

Results – Real Life Implications

- **Speech and Language Therapy**
  - 47%! of children exposed to VPA- RR 6.923 (3.735-12.833)
  - 9% of children exposed to CBZ- RR 1.354 (0.463-3.958)
  - 6% of control children
- **Additional Educational Input**
  - 34% of children exposed to VPA- RR 6.750 (3.251-14.013)
  - 9% of children exposed to CBZ – RR 1.760 (0.578-5.359)
  - 5% of control children
- Not merely statistical differences!

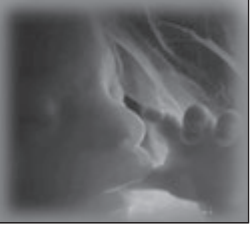
Liverpool & Manchester Neurodevelopment Group

Outcomes at 3 Years

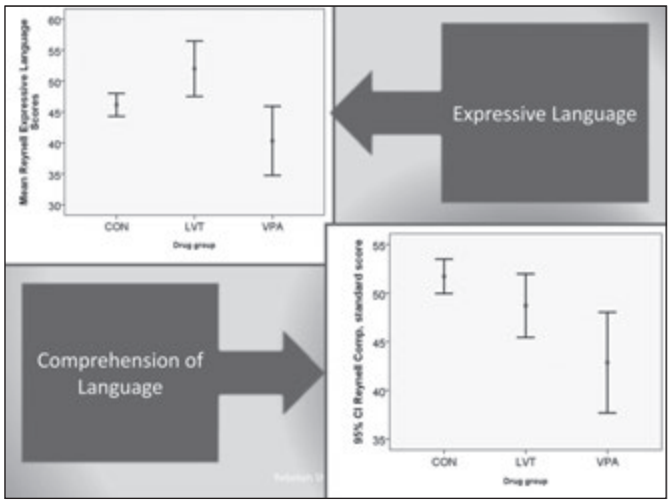
(Levetiracetam vs Sodium Valproate vs Controls)

Methods

- Children exposed to LEV (n=40), VPA (n=36) and control children (n=125). Prospectively recruited from the *UK Epilepsy and Pregnancy Register (UKEPR)* or the *Liverpool and Manchester Neurodevelopment Group (LMNDG).*
- Assessed between 3 – 4.5 years of age using the Griffiths Mental Development Scale (GMDS 2-8 years)[1] and the Reynell Scales for Language development[2].
- The Results are preliminary in nature, data collection continues.



1. 'The Abilities of Young Children: A comprehensive system of mental measurement for the first eight years of life' (1984). Ruth Griffiths. ARNOS, The Test Agency, Bucks, UK.
2. 'The Reynell Developmental Language Scales III' The University of Reading Edition. Edwards, S. Fletcher, P. Garman, M. et al., (1997). nferNelson Publishing Company LTD, London, UK.



GMD Subscale	LEV vs CON	LEV vs VPA
Locomotor	**p=1.0**	**p=0.001***
Personal & Social Skills	**p=0.74**	**p=0.016***
Hand & Eye Coordination Skills	**p=0.91**	**p=0.012***
Performance Skills (non-verbal problem solving)	p=1.0	p=1.0
Practical Reasoning	p=1.0	p=0.081

* Significant difference

Rebekah Shallcross 09.11.10 23

Limitations:

- ***preliminary results***, not controlling for confounding variables!
- Possible selection bias.
- Developmental assessment only.

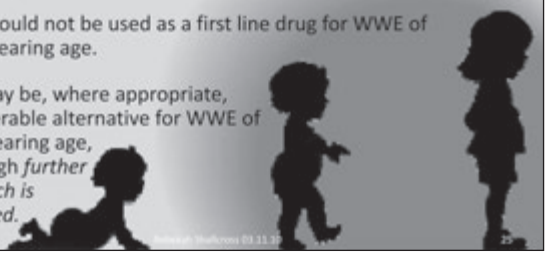
Preliminary Results:

- When compared with controls, children exposed to LEV did not differ from controls.
- When compared with children exposed to VPA, children exposed to LEV scored higher on a number of developmental assessments.

Rebekah Shallcross 09.11.10 24

Conclusions....

- Children exposed to VPA most at risk of later cognitive problems
- The possible effects of CBZ is not yet fully understood
- 'Gold Standard' research confirms findings from case and retrospective studies
- ***'Real life'*** implications for exposed children
- VPA should not be used as a first line drug for WWE of child bearing age.
- LEV may be, where appropriate, a preferable alternative for WWE of childbearing age, although *further research is required.*



Future Research of the LMNDG: Future Implications for Exposed Children?

- More subtle effects of AEDs on cognition: both VPA and others
- Conduct MR scans to investigate structural changes in the brain
- Investigate Newer AEDs
- Research based intervention studies
- Follow up to assess future impact:
  - Cost of intervention for extra education support and speech and language therapy
  - Do effects persist into adulthood?
  - Implications for prospective employment and further education
  - Future earning potential
  - Driving Abilities

...Questions?

Thank you for your time and attention...

Acknowledgements:

- Professor Gus Baker (supervisor)
- The Manchester & Liverpool Neurodevelopment Group
- The UK Pregnancy and Epilepsy Register

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Treatment of newly diagnosed epilepsy

Emilio Perucca (Italy)

Treatment of Newly Diagnosed Epilepsy

Emilio Perucca
Institute of Neurology and Clinical Pharmacology Unit, University of Pavia, Pavia, Italy

LASSE, 27 February 2011

The Primary Goals of AED Therapy

- A normal quality of life
- Complete seizure control
- Avoidance of adverse effects (including adverse drug interactions)
- Treatment of any co-morbidity
- No interference with daily routines

Key Decision Steps in the Management of Epilepsy

- To treat or not to treat?
- Which drug when starting treatment?
- Which dosing strategy?
- Which strategy when monotherapy fails?
- Which strategy after sustained seizure freedom has been achieved?

To Treat or Not to Treat? Factors to be Considered

- Risk of seizure recurrence (and the risks associated with recurrence)
- Risks of side effects of AED treatment
- The view of the patient, or parents

Definition of Epilepsy (ILAE 2005)*

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

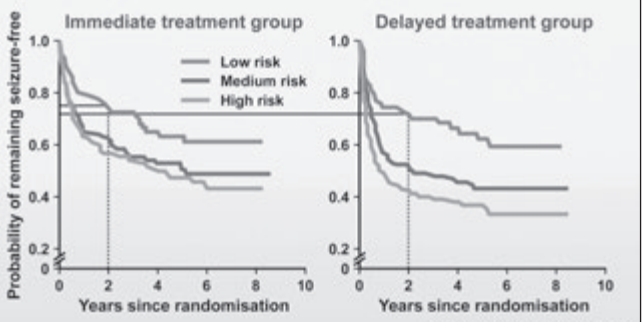
The definition of epilepsy requires the occurrence of at least one epileptic seizure.

* Fisher RH et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005: 46:470-5

Factors Associated with Increasing Risk of Recurrence of Unprovoked Seizures

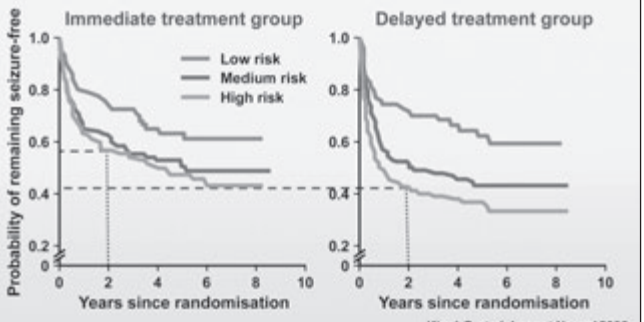
- History of more than one seizure
- Brain lesion or neurological abnormality
- Epileptiform EEG abnormalities
- History of a focal seizure
- Positive family history of seizures / epilepsy

Immediate Treatment Does Not Reduces the Probability of Recurrence in Low-risk Groups



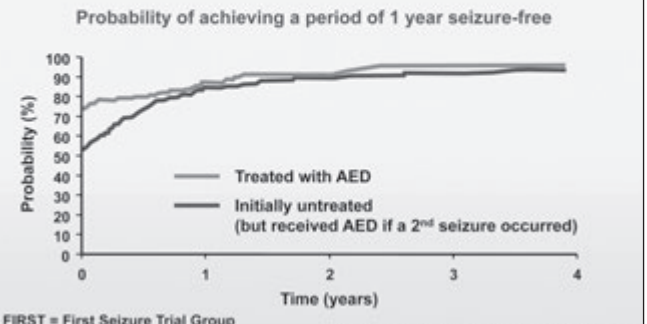
Kim LG *et al. Lancet Neurol* 2006

Immediate Treatment Reduces the Probability of Recurrence in Medium- and High-risk Groups



Kim LG *et al. Lancet Neurol* 2006

Immediate Treatment Does Not Increase Long-term Probability of Seizure Freedom



FIRST = First Seizure Trial Group

Adapted from Musicco M *et al. Neurology* 1997

Which AED for Initial Treatment?

Phenobarbital
Lacosamide
Oxcarbazepine
Phenytoin
Gabapentin
Lamotrigine
Valproic acid
Fosphenytoin
Topiramate
Carbamazepine
Rufinamide
Levetiracetam
Primidone
Stiripentol
Tiagabine
Zonisamide
Pregabalin
Felbamate
Ethosuximide
Eslicarbazepine acetate
Benzodiazepines
Vigabatrin

The "Pragmatic" Approach

- Consider the properties of each individual drug, based on available evidence
- Consider the characteristics of the epilepsy and other individual specificities
- Chose the drug whose properties provide the best match for the patient's needs

Lines of Evidence to be Considered when Chosing an Antiepileptic Drug

- Spectrum of efficacy (seizure types and syndromes)
- Efficacy
- Adverse effect profile
- Impact on co-morbidity
- Drug interactions
- Ease of use
- Other (regulatory aspects, insurance, cost)

Individual Features which Are Crucial in Tailoring AED Choice

- Person's attitudes with respect to risk of seizure recurrence and side effects
- Seizure type and syndrome
- Past history (e.g. side effects from previous AED exposures)
- Genes (including gender)
- Age
- Comorbidities and comedications

Individual Features which Are Crucial in Tailoring AED Choice

- Person's attitudes with respect to risk of seizure recurrence and side effects
- Seizure type and syndrome
- Past history (e.g. side effects from previous AED exposures)
- Genes (including gender)
- Age
- Comorbidities and comedications

Efficacy Spectrum of Available AEDs

Most seizures & syndromes	Broad spectrum but not anti-absence	Mostly for focal seizures	Absence only
Valproic acid	Phenobarbital	Carbamazepine*	Ethosuximide§
Benzodiazepines	Primidone	Phenytoin*	
Lamotrigine§		**Oxcarbazepine***	
Topiramate		**Eslicarbazepine ac.***	
Levetiracetam		**Gabapentin***	
Zonisamide		**Pregabalin***	
Rufinamide (?)		**Tiagabine***	
Felbamate (?)		Vigabatrin*	
		Lacosamide*	

*May exacerbate myoclonic and absence seizures
Vigabatrin is also effective in infantile spasms
§Lamotrigine may aggravate severe myoclonic epilepsy of infancy

Modified from Perucca, Epilepsia 2005; 46 (suppl 4):31-7

How Common Is Seizure Aggravation by CBZ? Relevance of Syndromic Classification

- Survey of 28 consecutive patients with juvenile myoclonic epilepsy (JME) who received CBZ:
  - 19 (68%) showed aggravation of seizures, especially myoclonic jerks
  - 2 developed myoclonic status
- Survey of 40 consecutive patients with benign epilepsy with centrotemporal spikes (BECT) who received CBZ:
  - Only 1 (2.5%) showed aggravation of seizures

CBZ = carbamazepine

Genton P, et al. *Neurology.* 2000;55-1106-9
Genton P. *Epilepsia.* 2001; 42:754-9.

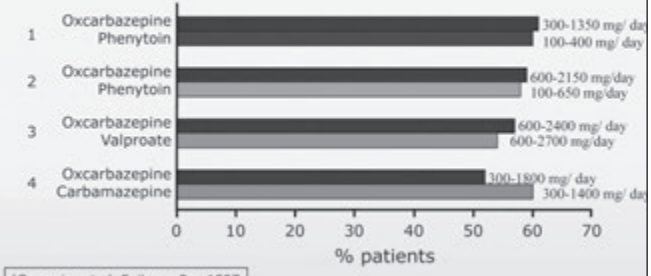
Which AED in Newly Diagnosed Epilepsy? Comparative Efficacy of New Generation AEDs

- Systematic review of RCTs in newly diagnosed epilepsy - partial and generalized tonic-clonic seizures only
  - Oxcarbazepine *vs* carbamazepine, valproate or phenytoin
  - Lamotrigine vs carbamazepine, valproate or phenytoin
  - Gabapentin vs carbamazepine
  - Topiramate versus carbamazepine or valproate
  - Levetiracetam vs carbamazepine
  - Vigabatrin vs carbamazepine
- No significant differences in efficacy outcomes between newer and older drugs (but most studies were not adequately powered)

ILAE Commission on Therapeutic Strategies. Epilepsia 2006; 47: 1094-120.
Brodie et al. Neurology 2007; 68: 402-8.

RCTs of Oxcarbazepine vs Other AEDs in Newly Diagnosed Epilepsy

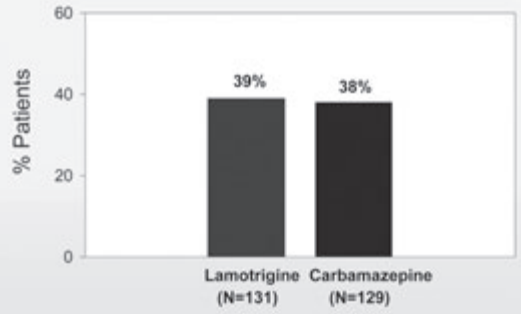
Proportion of Patients Seizure-free



[1]Guerreiro et al, Epilepsy Res 1997
[2]Bill et al, Epilepsy Res 1997
[3]Christe et al, Epilepsy Res 1997
[4]Dam et al, Epilepsy Res 1989

RCT of Lamotrigine vs Carbamazepine in Newly Diagnosed Epilepsy

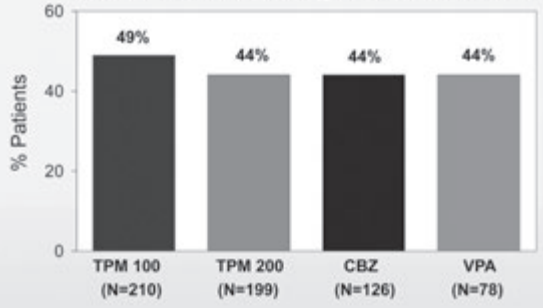
Proportion of Patients Seizure-free



Brodie et al, Lancet 1995;345:476-9

RCT of Topiramate vs Carbamazepine vs Valproate in Newly Diagnosed Epilepsy

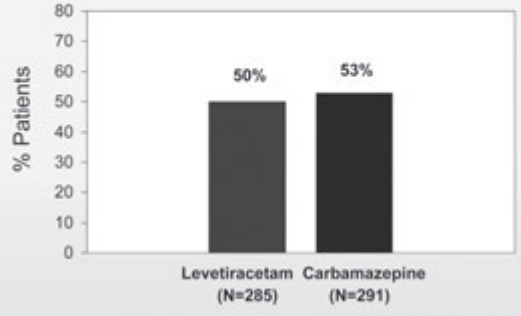
% of Patients Achieving 6-Month Remission



Privitera et al, Acta Neurol Scand 2003, 107:165-75

RCT of Levetiracetam vs Carbamazepine in Newly Diagnosed Focal Epilepsy

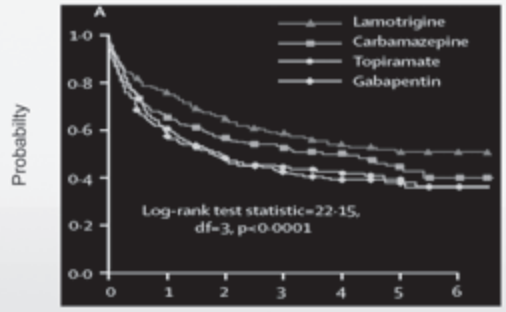
Proportion of Patients Seizure-free for 1 Year (ITT)



Brodie et al, 2007:68:402-408

RCT of Gabapentin vs Lamotrigine vs Topiramate vs Carbamazepine in Patients with Newly Diagnosed (mostly) Partial Seizures

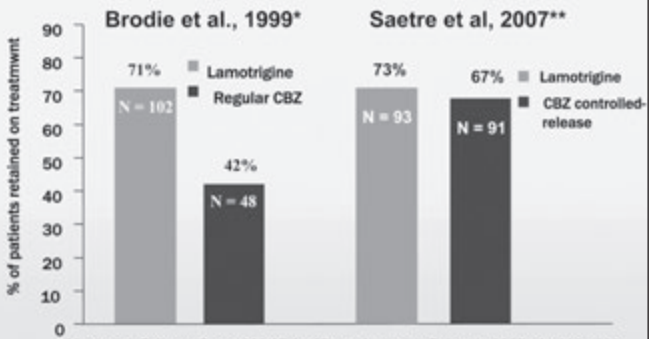
Probability of Remaining on the Allocated Treatment



Duration of follow-up (yearsi)

Marson et al. The Lancet 2007;369;1000-15/1016-29

What Difference can a Formulation Make? Treatment Retention in 2 Double-blind RCTs in Elderly People with New Onset Epilepsy

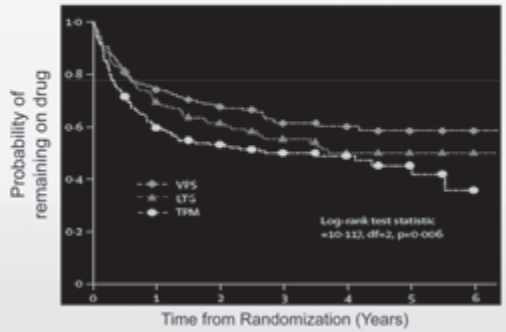


* 20 wk trial, Epilepsy Res. 1999;37:81-87 ** 40 wk trial, Epilepsia 2007;48:1292-1302

Dosing and titration schemes were identical in both trials

SANAD: Randomized Comparison of Lamotrigine vs Topiramate vs Valproate in Recently Diagnosed Generalised or Unclassified Epilepsies

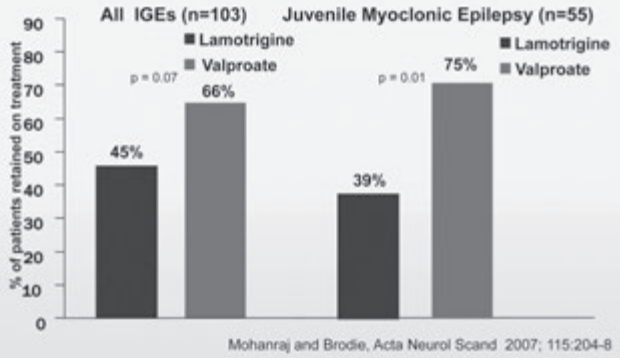
Time to Treatment Failure



Time from Randomization (Years)

Marson et al. The Lancet 2007;369;1000-15/1016-29

Valproate vs Lamotrigine in Idiopathic Generalized Epilepsies (IGEs) in Adult Age: 1-Year Remission Rates on Initial Treatment



Mohanraj and Brodie, Acta Neurol Scand 2007; 115:204-8

Individual Features which Are Crucial in Tailoring AED Choice

- Person's attitudes with respect to risk of seizure recurrence and side effects
- Seizure type and syndrome
- Past history (e.g. side effects from previous AED exposure)
- Genes (including gender)
- Age
- Comorbidities and comedications

Hypersensitivity to Carbamazepine and the HLA-B*-1502 Allele

- **44** patients with CBZ-induced Stevens-Johnson syndrome (SJS), 101 CBZ-treated controls and 93 healthy subjects
- The HLA-B*-1502 allele was present in 44/44 (100%) SJS patients vs only 3% (3/101) of CBZ-treated controls, or 9% (8/93) of healthy subjects
- The strongest association found so far between an HLA marker and a disease!
- Has led to a screening test for routine application in subjects of Chinese / South Asian origin

CBZ = carbamazepine

Chung et al, Nature 2004;428:486

Individual Features which Are Crucial in Tailoring AED Treatment

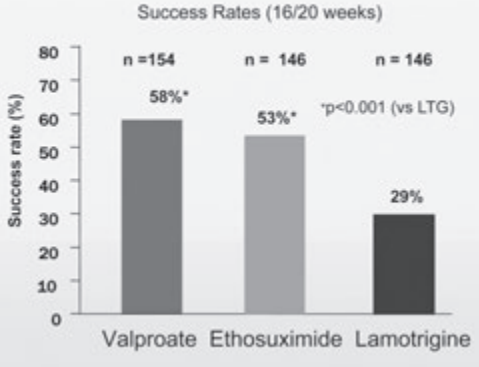
- Person's attitudes with respect to risk of seizure recurrence and side effects
- Seizure type and syndrome
- Past history (epilepsy, drugs and side effects)
- Genes (including gender)
- Age
- Comorbidities and comedications

Issues with Antiepileptic Drug Treatment in Children

Children with epilepsy are not "small adults"!

- The disease is different (many childhood epilepsies are not found in adults)
- Pharmacokinetics differ from those in adults
- Pharmacodynamic sensitivity to drugs may differ

Lamotrigine vs Ethosuximide vs Valproic Acid in Newly Diagnosed Absence Epilepsy



Glauser et al, *New Engl J Med* 2010; 362:790-9;

Increased Pharmacodynamic Sensitivity in Old Age

VA Cooperative Studies #118 & #264

Mean Plasma Concentration in Patients With Adverse Effects (μg/mL)

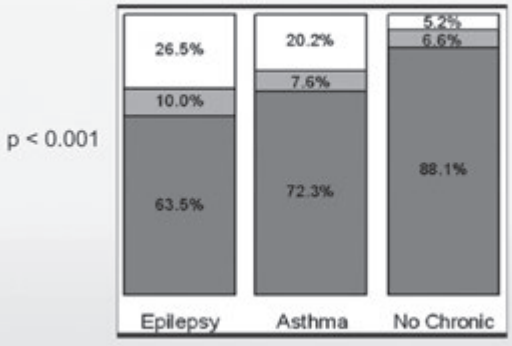
Age	CBZ	VPA
<40	7.4	79.5
40-64	5.9	83.7
≥65	3.6	66.3

Ramsay et al. *Epilepsia*. 1994;35(suppl 8):91A.

Individual Features which Are Crucial in Tailoring AED Treatment

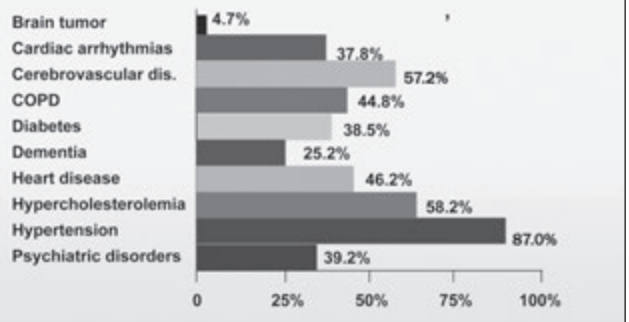
- Person's attitudes with respect to risk of seizure recurrence and side effects
- Seizure type and syndrome
- Past history (side effects from previous AED exposures)
- Genes (including gender)
- Age
- Comorbidities and comedications

Depression in Epilepsy: A Community-Based Study



Ettinger et al. Neurology 63:1008-1014, 2004

Co-morbidities among 9,682 Elderly Veterans (>65 years) with Newly Diagnosed with Epilepsy



Pugh et al, J Am Geriatr Soc 2010;58:465-71

Efficacy of AEDs on Some Major Co-morbidities

Carbamazepine	Bipolar disorder, trigeminal neuralgia
Valproate	Bipolar disorder, migraine
Primidone	Essential tremor
Gabapentin	Neuropathic pain
Oxcarbazepine	Bipolar disorder
Pregabalin	Neuropathic pain, generalized anxiety d.
Lamotrigine	Bipolar I depression
Topiramate	Migraine, binge eating disorder

Spina, Epileptic Disorders 2004;6:57-7; Zaremba, Pharmacol Rep 2006;58:1-12

Drug Interactions

AEDs as Enzyme Inducers and Inhibitors

Enzyme inducers

Potent broad spectrum inducers:	Phenytoin Carbamazepine Phenobarbital / primidone Rufinamide
Weak CYP3A4 inducers:*	Oxcarbazepine Felbamate

Enzyme inhibitors

Valproic acid (UGT, CYP2C9, epoxide-hydrolase), oxcarbazepine (CYP2C19), felbamate (CYP2C19, epoxide-hydrolase)

*Topiramate at dose >200 mg and lamotrigine (300 mg) may stimulate the metabolism of oral contraceptive steroids

Examples of Drugs whose Clearance is Enhanced by Enzyme Inducers

- Many AEDs
- Calcium antagonists
- Oral anticoagulants
- Statins
- Steroids
- Anticancer agents
- Many antimicrobials

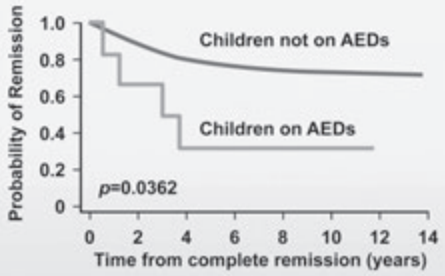
Annals of Pharmacotherapy 2000 April, Volume 34, 465-70

Carbamazepine-Indinavir Interaction Causes Antiretroviral Therapy Failure

Patricia WH Hugen, David M Burger, Kees Brinkman, Hadewych JM ter Hofstede, Rob Scuurman, Peper P Koopmans and Yechiel A. Hekster

Department of Clinical Pharmacy, University Hospital Nijmegen, Nijmegen, the Netherlands

Effect of Enzyme Inducing AEDs on Event -free Survival in Children with Leukaemia



Relling *et al., Lancet* 2000; 356:285-90

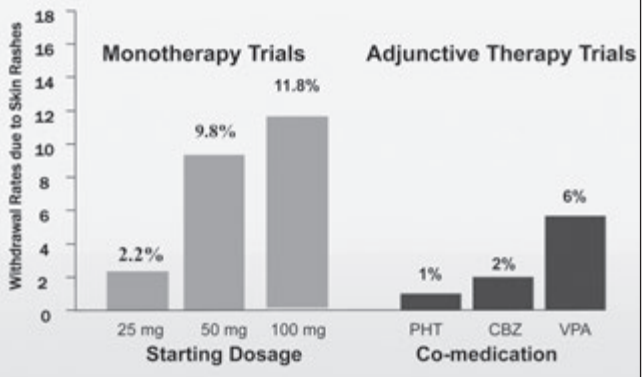
Key Decision Steps in the Management of Epilepsy

- To treat or not to treat?
- Which drug when starting treatment?
- **Which dosing strategy?**
- Which strategy when monotherapy fails?
- Which strategy after sustained seizure freedom has been achieved?

Key Decisions in Dosing Strategies

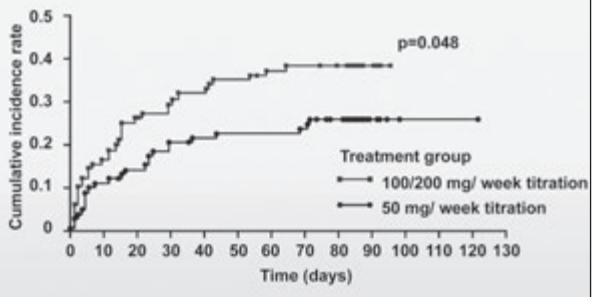
- Titration rate
- Initial target dose
- How high should dose be increased in non responders?
- What is the role for TDM?

Lamotrigine: Withdrawal Rates due to Skin Rash vs Starting Dosage and Co-Medication



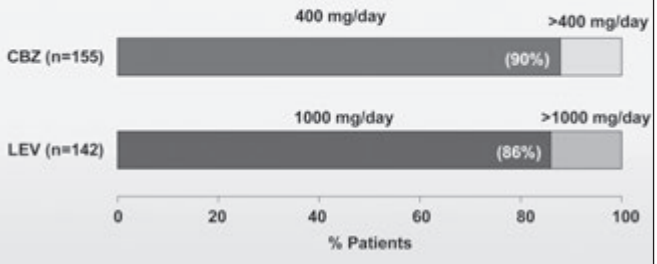
Guberman et al, Epilepsia 199:40:985-91; Messenheimer at al, Drug Safety 1998;18:281-6

Cumulative Incidence of Adverse Events Leading to TPM Dose Reduction or Discontinuation (adjunctive therapy, epilepsy)



Biton et al, Ann Pharmacother 2001;35:173-9

RCT of Levetiracetam vs CBZ-CR in Newly Diagnosed Epilepsy: Distribution of Dosages in Patients Achieving 1-Year Remission



Brodie et al. Neurology 2007; 68: 402-8

Conclusions

- Individuals differ in their clinical characteristics – seizure and epilepsy type are just one of many factors
- In addition to efficacy, the adverse effect profile is crucially important for drug selection
- Newer AEDs are not more efficacious than older agents, but some have improved tolerability, including avoidance of enzyme induction
- With so many AEDs now available, opportunities for tailoring treatment choices have never been greater

Neuropsychological consequences of seizures in Childhood Absence Epilepsies

Marco Tulio Medina (Honduras)

TREATMENT OF REFRACTORY EPILEPSY
JACQUELINE FRENCH (USA)

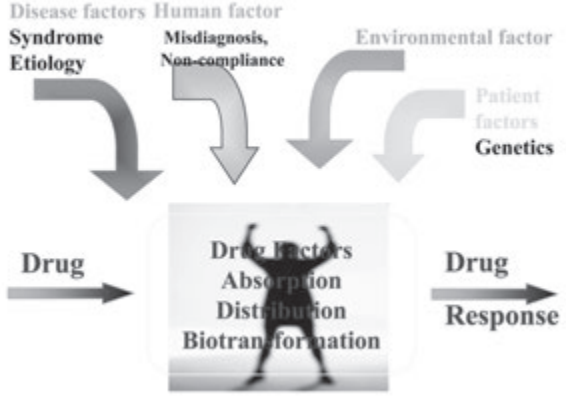
TREATMENT OF REFRACTORY EPILEPSY

Jacqueline A. French MD
Department of Neurology
NYU School of Medicine

Consequences of Treatment resistant epilepsy

- Shortened lifespan
  - SUDEP
- Bodily injury, hospitalization
  - Status epilepticus
- Neuropsychological and psychiatric impairment
  - Depression
  - Reduced quality of life
- Social disability
  - Reduced marriage rates
  - Reduced employment

Causes of Refractoriness



Definition of Intractability: Factors to Consider

- Diagnosis confirmed?
- Patient given adequate dose?
  - Serum concentrations necessary?
  - Pharmacokinetic factors ruled out?
- How many medications tried?
- How many seizures/unit time?
  - Is one breakthrough seizure intractability?
- To date, absence of a unifying definition has hampered epidemiologic studies

Definition of Treatment Resistant Epilepsy

- New ILAE consensus definition. Intent is to unify research methodology
- Three elements to definition:
  - Definition of failure of a specific AED
  - Definition of treatment success with a specific AED
  - Definition of Drug resistant epilepsy

Definition of treatment failure

- Treatment failure is defined as recurrent seizure(s) after an "informative trial" of an intervention.
- In general, this requires application of an "appropriate" intervention at adequate strength / dosage for a sufficient length of time

Definition of Treatment Response

- Treatment response is defined as freedom from seizures for a *minimum* of three times the longest pre-intervention inter-seizure interval or 12 months, whichever is *longer*.
- If a patient has been seizure-free for less than three times the pre-intervention inter-seizure interval or 12 months, seizure control should be categorized as "undetermined".

Definition of Drug Resistant Epilepsy

- *"Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."*
- *No seizure frequency requirement*

What is in a name?

- Refractory implies there is no hope for redemption
- Treatment resistant indicates difficult, but not impossible to treat

How Common is Drug Resistant Epilepsy?

Long-Term Follow-Up of
Mixed Population (N=525)*

Seizure-free
63% (n=333)

Uncontrolled
37% (n=192)

*Epilepsy Unit, Glasgow, Scotland 1984-1997
Kwan P, Brodie MJ. N Engl J Med 342:314, 2000

WHEN DOES INTRACTABILITY OCCUR?

- Immediate
- Over time
  - Acquired
  - Tolerance

OUTCOME AFTER FAILURE ON FIRST AED

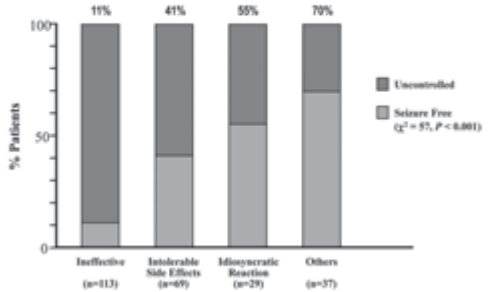


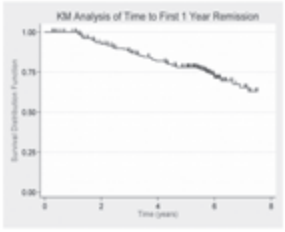
Figure on top of bar represents percentage seizure free.

Can refractory epilepsy be "cured"?

- Study at the University of Pennsylvania[1]
- 246 patient identified as having drug refractory epilepsy (≥1 sz/month, failed ≥ 2 drugs)

[1] Callaghan BC, et al, Epilepsia 2004 (abstract)

Remission

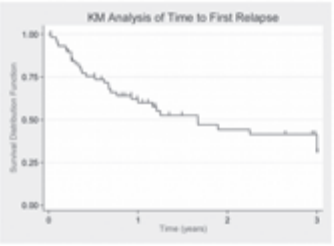


- 38 (15.5%) attained six-month seizure remission and were still free by the end of the observation period .
- 26 (10.6%) became sz free with change in AED therapy (addition of an AED or change in dose), 1 (0.4%) became seizure free with no change, and 11 (4.5%) became seizure free after surgery.

Relapse

- Statistically significant negative predictors of remission included mental retardation, symptomatic generalized epilepsy, duration of intractability, and number of antiepileptic medications failed. Only the number of anti-epileptic medications failed was statistically significant in an adjusted model.

Relapse

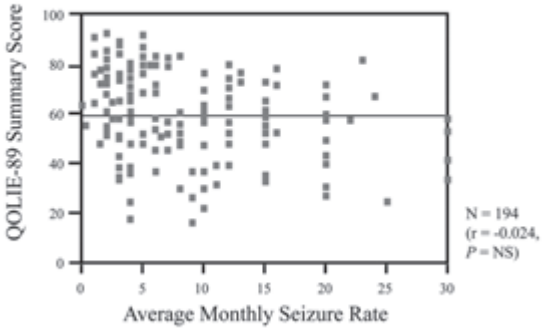


- The cumulative risk of relapse in the entire cohort who entered remission was 56% (95% confidence interval, 42-70%) by 2 years after achieving a one year remission and 71% (95% confidence interval, 55-86%) by 5 years.

What about the rest?

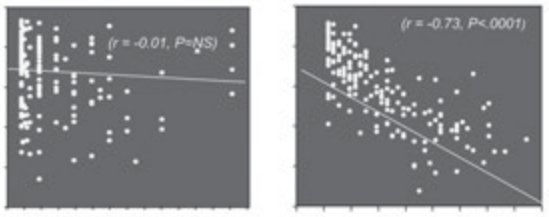
- Most patients will continue to experience seizures (at least for the short-term)
- These patients' lives can still be improved!
  - Reduction in seizures
  - Elimination of clusters
  - Treatment of depression
  - Counseling/Social Intervention

Comparison of Average Monthly Seizure Rate to HRQOL



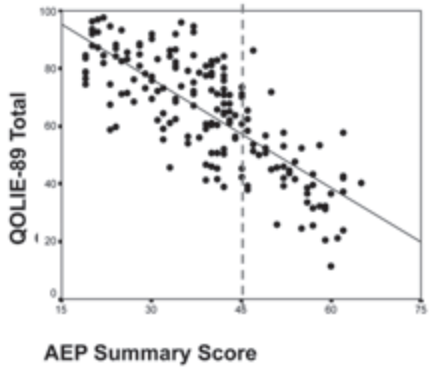
Gilliam F, et al. 2000.

HRQoL: Relationship with Seizure Control and Depression



Gilliam et al.,Neurology, 2002;23;58(Suppl 5):S9-20

Relationship of Subtle AED Toxicity to Quality of Life



N = 200
r = -0.76,
***P*<0.0001**

Gilliam, et al. Neurology 2004;62:23-27

Issues in treatment of refractory epilepsy

- Choice of therapy
  - AED
    - Selection
    - Strategy
      - "push to toxicity monotherapy
      - Combinations
    - Rescue therapy
      - Status
      - Clusters
  - Devices
  - Other
    - Psychiatric
    - Psychosocial
    - Cognitive

ANTIEPILEPTIC DRUGS: NEW AND OLD

- Phenytoin
- Carbamazepine
- Sodium Valproate
- Phenobarbital
- Primidone
- Ethosuximide
- Felbamate
- Gabapentin
- Lamotrigine
- Topiramate
- Tiagabine
- Oxcarbazepine
- Levetiracetam
- Vigabatrin
- Zonisamide
- Pregabalin
- Lacosamide

U.S. News and World Report, 14 January 2003

Can we tailor AEDs to patients?

- We can select the appropriate drug for a given syndrome
- Beyond that, at present, we cannot determine which AED will be effective for which patient
  - Cannot select by mechanism of action
- Yet, it seems that continuing to try new AEDs is important

SUDEP in adjunctive RCT's

Trials arms	Efficacious doses	Non-efficacious doses	Placebo
Patient-years	2554	174	1879
# SUDEP	2	3	12
	.08%/year		.64%/year

Ryvlin et al, AES Abstract 2009

OLD AEDs

- Efficacy established
- Long-term side effects established
- Less expensive, more available for some

NEW AEDs

- Less interactions
- No enzyme induction/inhibition
- Well tolerated
- Broader spectrum
- Less issues for women

NEW AEDS:SPECTRUM OF ACTIVITY

	PARTIAL	LENNOX-GASTAUT	JME	ABSENCE
ZNS	+	?	?+	?
GBP	+			
LTG	+	+	?	?+
OXC	+			
TPM	+	+	?+	?
LEV	+	?	?+	?+
TGB	+			
PGB	+			

DOES IT MATTER WHICH DRUG YOU START WITH? (CROSS-TOLERANCE)

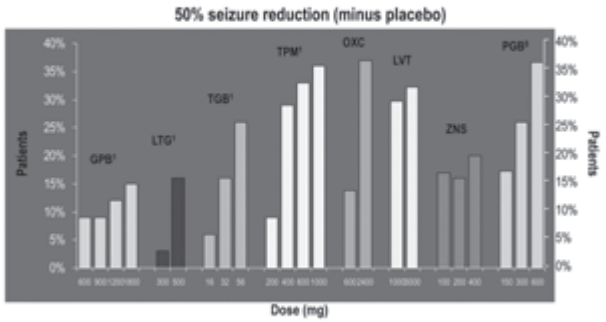
- LTG administered to kindled rats
  - Robust suppression of kindled szs, increased sz threshold
- High-dose LTG administered *prior to* each kindling stimulation
  - LTG no longer suppressed kindled seizures[1]
  - CBZ no longer suppressed kindled seizures![2]

[1]Postma et al, Epilepsia, 41:1514-1521 2000
[2] Krupp et al, Exp Nerol 162:278-289, 2000

REFRACTORY EPILEPSY: IDEAL CHARACTERISTICS

- High responder rate
- High seizure free rate
- Well tolerated as adjunctive Rx
- Ability to convert to monoRx
- No development of tolerance

Seizure Reduction With New AEDs in Controlled Clinical Trials*



*New AEDs used as adjunctive therapy in patients refractory to standard AEDs.

[1]Cramer JA, et al. *Epilepsia*. 1999;40:590-600. [2]Barcs G, et al. *Epilepsia*. 2000;41:1597-1607. [3]Cereghino JJ, et al. *Neurology*. 2000;55:236-242. [4]Faught E, et al. *Neurology*. 2001;57:1774-1779. [5]French JA, et al. *Neurology*. 2003;60:1631-1637.

*SEIZURE FREEDOM IN RANDOMIZED CONTROLLED ADD-ON TRIALS**

AED	Dose	Sz Free
Gabapentin	600-1800 mg	up to 1.1%
Lamotrigine	300-500 mg	.8%
Topiramate	200-1000 mg	5% (pooled)
Tiagabine	N/A	
Oxcarbazepine	600-2400 mg	2.2%
Levetiracetam	1000-3000 mg	up to 6.4%
Zonisamide	500 mg	1.7%
Pregabalin	50-600 mg	up to 1.1%

*Based on completer ITT, titration included, French et al, submitted

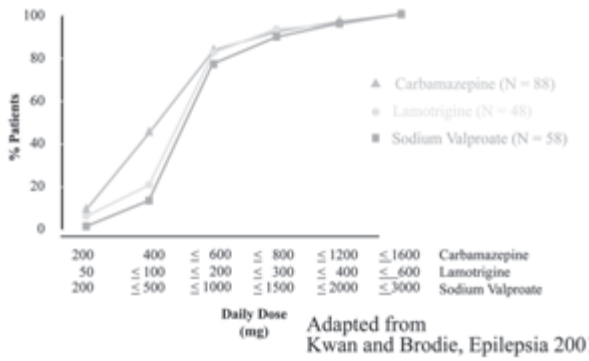
EFFICACY

- Demonstrated effects during clinical trials
  - Often with refractory population
  - Often at fixed doses
  - Highly motivated patients
  - Often polytherapy

EFFECTIVENESS

- "Tweak effect"
- Can up-titrate new drug and down-titrate background AEDs simultaneously
- Can find individual maximal effective/tolerated dose
- Can use in broader population

DAILY DOSES OF FIRST AED TAKEN BY SEIZURE-FREE PTS

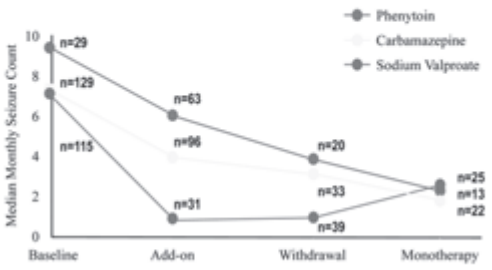


Adapted from
Kwan and Brodie, Epilepsia 2001

PUSH TO TOXICITY?

- There is still a role for slowly increasing dose to maximal tolerated
- Caution for difficult to withdraw AEDs:
  - Benzodiazepines
  - Barbiturates

"RATIONAL" POLYTHERAPY?



Brodie et al, Epilepsy Res. 1997;26:423-432.

Choices of strategy

- When a pt is not doing well, in terms of side effects OR seizures OR QOL, doctor has a choice of strategy
  - Add another drug onto current therapy
  - Switch to a different regimen

Reasons to switch vs add

- Switch
  - First AED inappropriate, or provided poor seizure control
  - Patient not tolerating first AED
  - First AED has disadvantages
  - Drug interactions expected
  - Pregnancy anticipated

- Add
  - Pt tolerating first AED
  - No anticipated drug interactions
  - Patient risk-averse, or consequences of seizure exacerbation are high
  - First AED appropriate, provided partial control

AEDs for add-on therapy

- Additional benefit or harm?
  - Pharmacodynamic plus or minus?
  - Pharmacokinetic plus or minus?

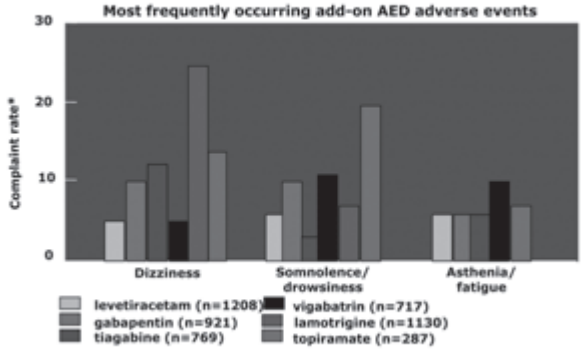
SIDE EFFECTS

- Types of Side effects:
  - Dose-related
  - Pharmacodynamic
  - Minor non dose-related
  - Major Safety
  - Long-term
  - Teratogenic

AEDS: SIDE EFFECTS

- Potential for side effects is individual and unpredictable
- Patients need a wide spectrum of AEDs to arrive at the best tolerated.

NEW AEDS: COMPLAINT RATES



Cramer et al., 1999
***Data on file, UCB*

PSYCHOLOGICAL SIDE EFFECTS: NEW AEDS (RATE MINUS PLACEBO)

# AED/ PCB	GPN 543/378	LTG 711/419	TGB 404/275	OXC 171/139	TPM 200400 113/174	LEV 769/439	ZNS 269/230
ASTHENIA			6		7	6	6
SOMNOLENCE	10	7	3	12	20	7	10
FATIGUE	6			4			2
PSYCHOMOTOR SLOWING					15		
NERVOUS			7	1	8	2	2
CONC DIFF			4	1	7		3
MEMORY DIFF					9		4
CONFUSION			2		5	2	3

After Cramer et al, 1999

IDIOSYNCRATIC AE'S: SERIOUS

	Rash	Hepatic Failure	Pancreatitis	Aplastic Anemia	Glaucoma
Carbamazepine	+	+		+	
Phenytoin	+	+		+	
Valproic Acid	+	+	+		
Phenobarbital	+	+		+	
Lamotrigine	+				
Gabapentin					
Topiramate		?			+
Tiagabine					
Oxcarbazepine	+				
Zonisamide	+				
Levetiracetam					
Pregabalin					

CNS SIDE EFFECTS: NEW AEDS (RATE MINUS PLACEBO) AS ADD-ON

# AED/ PCB	GPN 543/378	LTG 711/419	TGB 404/275	OXC 171/139	TPM 200400 113/174	LEV 769/439	ZNS 269/230
Dizziness	10	25	12	20	14	5	6
Ataxia	7	16	2	9	14	2	5
Speech / Language				2	19		3
Diplopia	4	21		16	8	1	
Headache							2

RISK OF DRUG INTERACTIONS

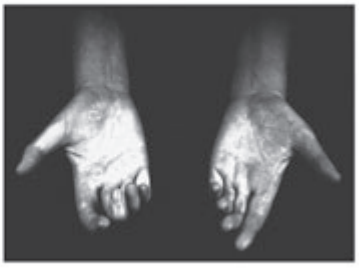
	Low bioavail ability	High pro-binding	Enzyme Ind/Inh
Carbamazepine			++
Phenytoin		++	++
Valproic Acid		++	++
Phenobarbital			++
Lamotrigine			
Gabapentin	++		
Topiramate			
Oxcarbazepine			
Levetiracetam			
Zonisamide			
Pregabalin			

NON DOSE-RELATED EFFECTS

	Na+ ↓	Weight Increase	Weight Decrease	Renal Calculi
Carbamazepine	+	+		
Phenytoin				
Valproic Acid		++		
Phenobarbital				
Lamotrigine				
Gabapentin		+		
Topiramate			+	+
Tiagabine				
Oxcarbazepine				
Zonisamide			+	+
Levetiracetam				
Pregabalin		+		

LONG-TERM SIDE EFFECTS

- No long-term side effects known for new AEDs
- Some may present over time
- Long-term comparative studies needed



LTG SIDE EFFECTS: ADJUNCTIVE VS MONOTHERAPY (REFRACTORY)

	Ltg Adjunctive (N=76)	Ltg Monotherapy (N=43)
Dizziness	20%	7%
Nausea	16%	7%
Headache	13%	7%
Dyspepsia	0%	3%
Somnolence	8%	0%
Asthenia	12%	2%
Coordination ABN	12%	2%

*Gilliam et al, Neurology 1998

ISSUES FOR WOMEN

	Interference w/ Hormonal milieu	OCP Interaction	Interference w/ Vit D/K
Carbamazepine	++	+++	++
Phenytoin	++	+++	++
Valproic Acid	++		
Phenobarbital	++	+++	++
Lamotrigine		+	
Gabapentin			
Topiramate		+	
Oxcarbazepine		+	
Levetiracetam			
Zonisamide			
Pregabalin			

Treating seizure clusters

- Seizure clustering is a common component of treatment resistant epilepsy in adults and children
- If a patient knows from prior experience that more seizures are expected, why not try to prevent them?

Prevalence of seizure clustering

- Prevalence of clustering may be up to 60% in intractable epilepsy
- In one prospective diary study, 43% of subjects experienced at least one episode of 3 sz/24 hours during a one year follow up

Acute benzodiazepine therapy

Medication	Formulation	Dose
Diazepam	Oral tablet Oral solution	Frequently prescribed as a dose of 2.5-10 mg
	Rectal gel	0.5mg/kg for ages 2-5; 0.3mg/kg for ages 6-11; 0.2mg/kg for age >=12.
Lorazepam	Oral tablet Sublingual	Frequently prescribed as a dose of 0.5-2.0 mg
Midazolam	Buccal	Not specified; studies have examined 0.5 mg/kg
	Intranasal	Not specified; studies have examined 0.2-0.3 mg/kg

CONCLUSION

- Even refractory epilepsy can be improved, or even remit
- It is crucial to continue attempts to render patients seizure free, by meds, devices, or resective surgery.

Programa – 28.02.2011

08:30 – 09:30	Impact of surgery for treatment of epilepsy on cognition - Manuel Campos (Chile)
09:30 – 10:30	Cognitive deficits resulting from the use of antiepileptic drugs – Jacqueline French (USA)
10:30 – 11:00	Coffee break
11:00 – 12:00	New technologies for pediatric epilepsy surgery: What is its impact on cognition? - Helio Rubens Machado (Brazil)
12:00 – 14:00	Lunch
15:00 – 19:00	Dedicated to team work
19:00 – 21:00	Dinner

Impact of surgery for treatment of epilepsy on cognition
Manuel Campos (Chile)

Impact of surgery for treatment of epilepsy on cognition

Dr.med. Manuel Campos
Centro Avanzado de Epilepsias. Clínica Las Condes
Chair. Comisión Latinoamericana ILAE

Factores a analizar

- Niños versus Adultos
- Lóbulo Afectado (Temporal o extra-temporal)
- Epilepsia Temporal: tiempo de evolución, lateral versus mesial, etc.

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- Niños versus Adultos
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CIRUGIA DE LA EPILEPSIA

¿Es lo mismo en niños que adultos?

?

Para el Cerebro en desarrollo:

"Eliminate seizures as soon as possible to optimize cognitive development, and improve behavior and quality of life"

Cross JH, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: Recommendations of the sub-commission pediatric epilepsy surgery. Epilepsia 2006; 47:952-959.

Encefalopatía Epiléptica

Grupo de desordenes donde el paciente presenta epilepsia refractaria y/o actividad paroxística inter-ictal en el EEG. Esto tiene riesgo de daño cognitivo progresivo y de déficits neurológicos.

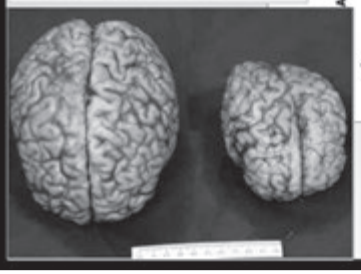
Las anormalidades epileptiformes mismas contribuyen a las alteraciones progresivas de las funciones cerebrales.

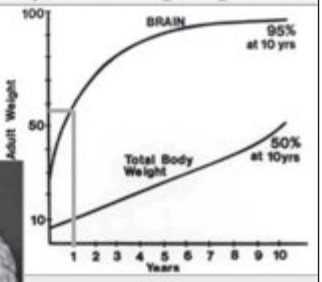
La mayoría de estas condiciones están relacionadas con la edad y afectan al cerebro inmaduro que esta en desarrollo.

¿Cuales son los riesgos de las crisis no controladas?

Cerebro en desarrollo y crisis epilépticas

- Más del 50% del volumen cerebral definitivo se alcanza al año de vida.



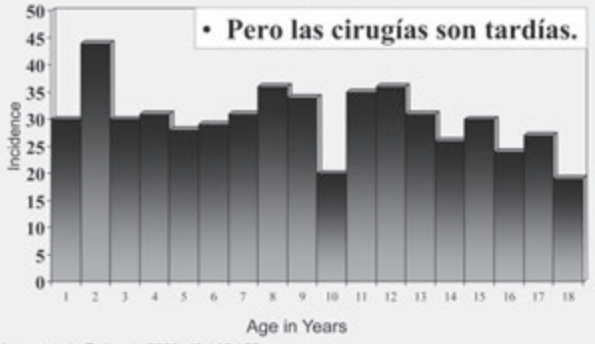


Age at Seizure Onset ILAE 2004 Pediatric Epilepsy Surgery Survey (n=543)

- Las crisis suelen iniciarse en los 2 primeros años de vida.

Harvey et al., Epilepsia 2008; 49:146-155.

Age at Surgery for Pediatric Epilepsy Surgery Patients; ILAE 2004 Survey (n=543)



Harvey et al., Epilepsia 2008; 49:146-155.

Factor "Tiempo"

- **En adultos Ud. se puede dar hasta 2 años de tiempo antes de declarar a un adulto "refractario a fármacos"**
- **pero, en niños Ud. NO puede darse más allá de un año para establecer la refractariedad, incluso hay autores, quienes plantean 6 meses**

Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings

Neurology. 2007; 69(4):389-97

- Wyllie E; Lachhwani DK; Gupta A; Chirla A; Cosmo G; Worley S; Kotagal P; Ruggieri P; Bingaman WE

Department of Neurology and Pediatrics, Cleveland Clinic Children's Hospital, Cleveland, OH 44195, USA. wylliee@ccf.org

CONCLUSIONES

- Los resultados apoyan el poder ofrecer cirugía a seleccionados *niños y adolescentes con epilepsia refractaria severa y grandes lesiones unilaterales en la RM, de tipo congénitas o adquiridas precozmente*. A pesar de abundantes descargas generalizadas o contralaterales en el EEG.
- Los resultados post-quirúrgicos fueron similares comparados a otras series de cirugías en pacientes con lesiones similares y EEG ipsilateral.

Neurology. 2007; 69(4):389-97

CIRUGIA DE LA EPILEPSIA

¿Es lo mismo en niños que adultos?

NO

¿Cuando referir un niño a un Centro de Cirugía de la Epilepsia?

Todo Niño Cross JH, et al., Epilepsia 2006; 47:952-959.

Persistencia de crisis Generalizadas o Focales, después de usar 2 o 3 FAEs o por efectos inaceptables de los FAEs. Especialmente importante si hay más de una crisis por día, aunque la RM inicial sea "negativa".

Niños bajo 2 años

Urgente referir para prevenir retraso del desarrollo y encefalopatía epiléptica, especialmente si hay crisis diarias.

Casos Especiales

Epilepsia del lóbulo, displasia cortical, tumores con crisis, esclerosis tuberosa, Sturge-Weber, Hemimegalencefália, encefalitis de Rasmussen, hamartoma hipotalámico, etc.

Factores a analizar

- Niños versus Adultos
- Lóbulo Afectado (Temporal o extra-temporal)
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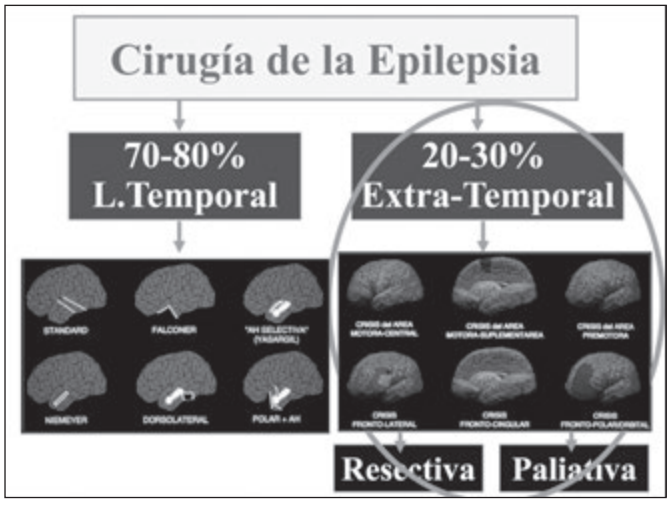

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CIRUGIA DE LA EPILEPSIA TEMORAL - RESULTADOS

- **Control de Crisis.**
- **Memoria anterograda.**
- **Calidad de Vida**

The New England Journal of Medicine

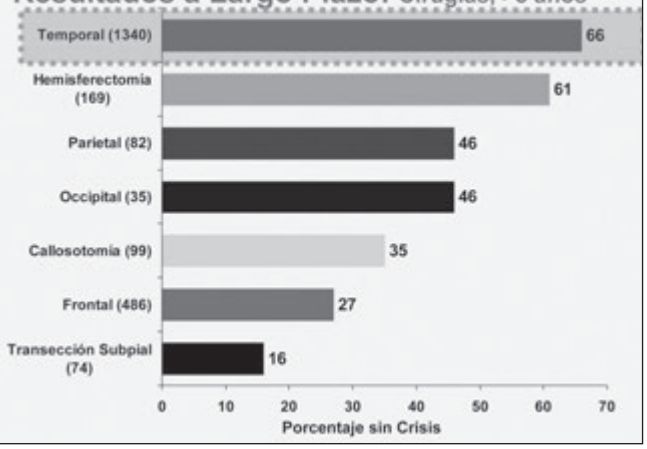
VOLUME 345 AUGUST 2, 2001 NUMBER 6

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*

N = 80

- Libres de crisis: 58% grupo quirúrgico P < 0.001
  8% grupo médico



CIRUGIA DE LA EPILEPSIA TEMORAL - RESULTADOS

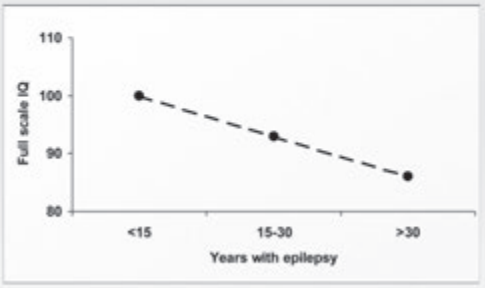
- **Control de Crisis.**
- **Memoria anterograda.**
- **Calidad de Vida**

Epilepsia Temporal Memoria Corto Plazo

- **Tiempo de evolución.**
- **Lateral versus mesial.**

Duración de Epilepsia = ¿Deterioro?

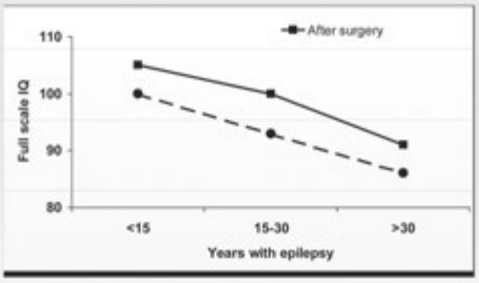
Epilepsia Lóbulo Temporal, N=209



Jokeit H, et al. JNNP, 1999; 67:44-50

¿Ayuda la Cirugía?

Epilepsia Lóbulo Temporal, N=209

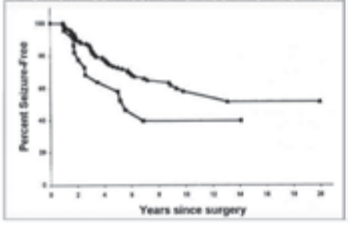


Jokeit H, et al. JNNP, 1999; 67:44-50

CONTROL DE CRISIS POST-CIRUGIA RESECTIVA EN EPILEPSIAS

Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery

Neurology 2003;61:445-450



- **N = 175**
- **56% libres de crisis a 10 años.**

Factores Pronóstico Negativos

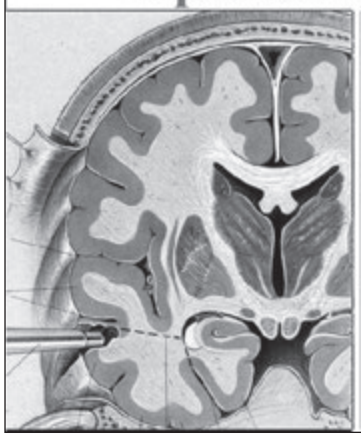
- Más de 10 años de historia de crisis.

- Histología normal del tejido resecado!

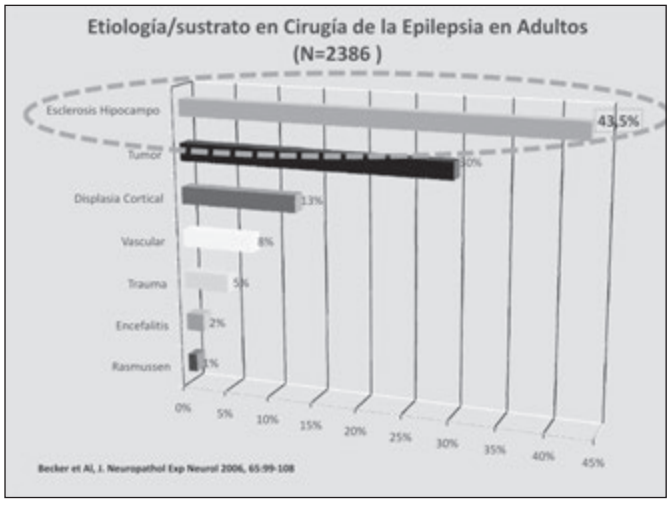
Epilepsia Temporal Memoria Corto Plazo

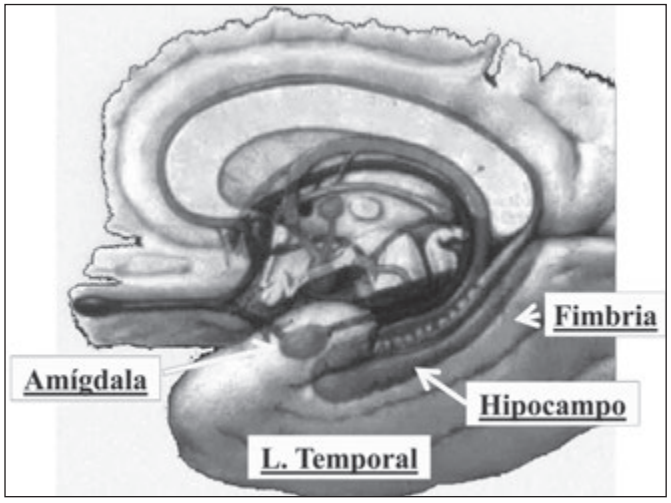
- **Tiempo de evolución.**
- **Lateral versus mesial.**

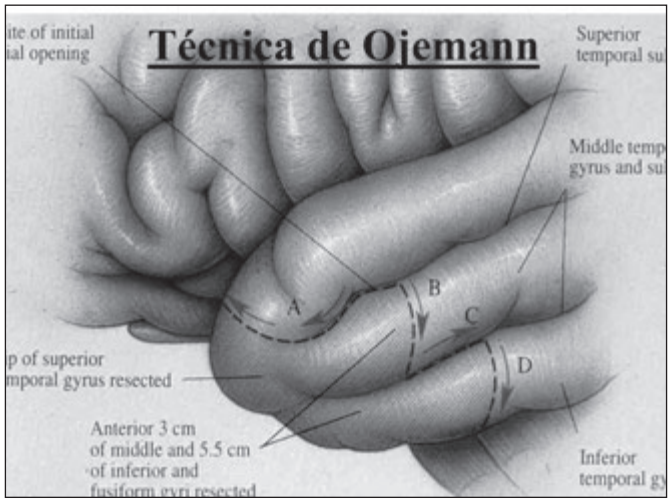
Tipos de epilepsias



- Síndrome temporal mesial.
  - ETM
  - Lesiones
  - sin lesión
- Epilepsia temporal lateral.
  - con lesión
  - sin lesión






Técnica de Ojemann
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Anterior 3 cm
of middle and 5.5 cm
of inferior and
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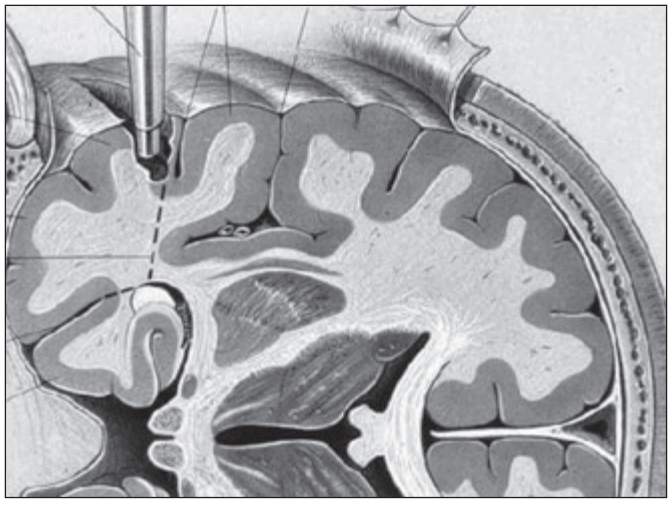
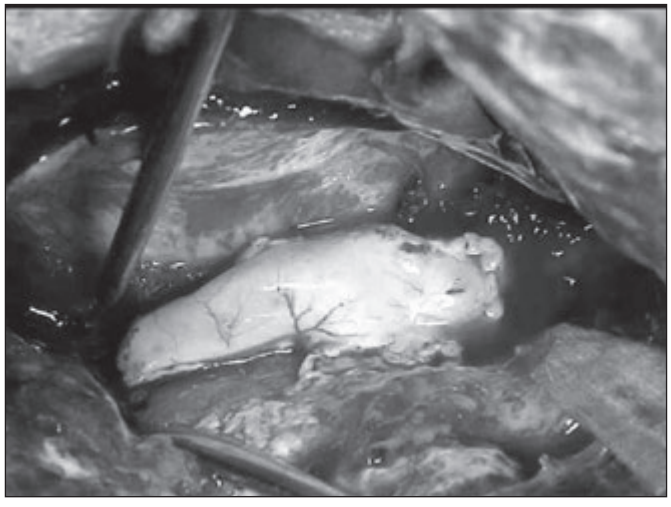
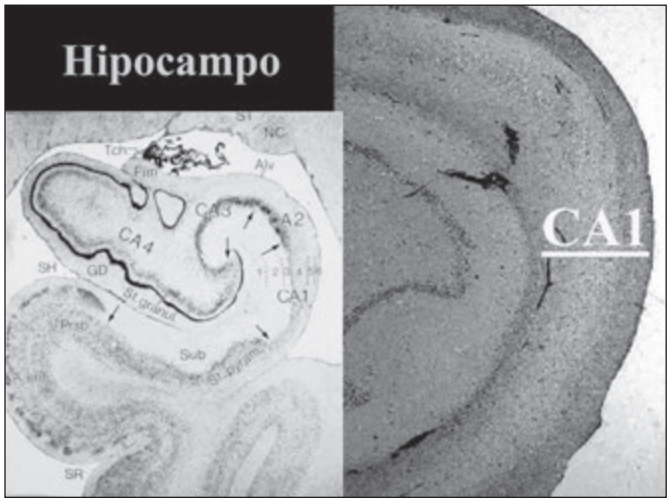
Inferior
temporal gy

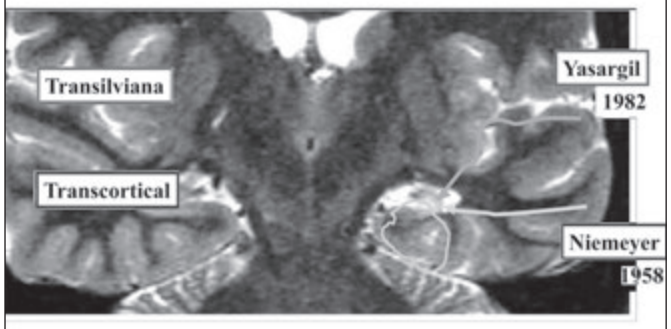




Hipocampo



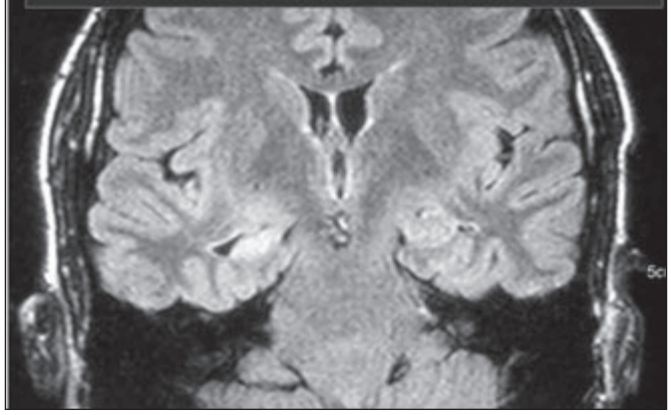
Amígdalo Hipocampectomía Selectiva (SAH)



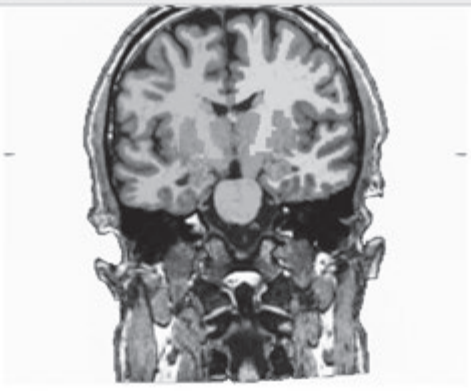
CASO CLINICO

- **Paciente portador de Epilepsia temporal mesial derecha, sin daño cognitivo en la evaluación neuropsicológica**

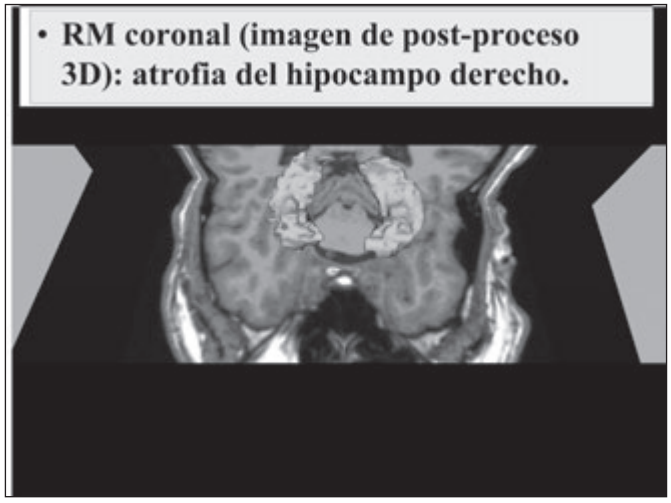
- RM coronal (FLAIR): atrofia y aumento de señal en hipocampo derecho.



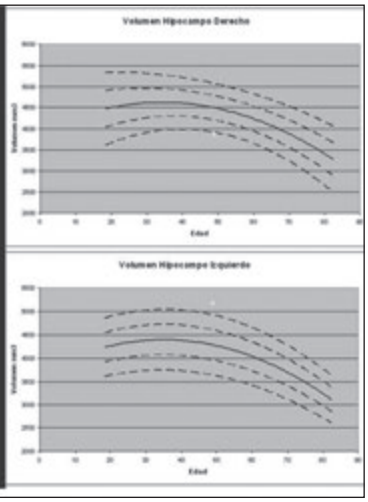
- RM coronal (imagen de post-proceso): atrofia del hipocampo derecho.



- RM coronal (imagen de post-proceso 3D): atrofia del hipocampo derecho.



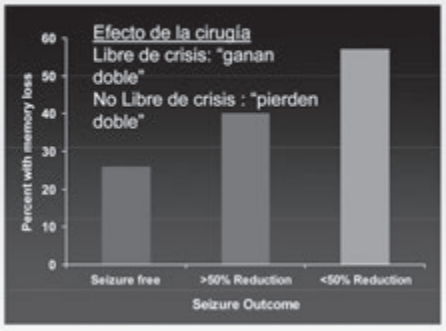
- En Epilepsia temporal medial de instalación precoz en el desarrollo, cabe la posibilidad que el hipocampo "sano" reemplace la función del hipocampo "enfermo", por neuroplasticidad.



RESULTADOS

ELT: Efecto Quirúrgico

Pacientes operados 147, follow-up 2-10 años



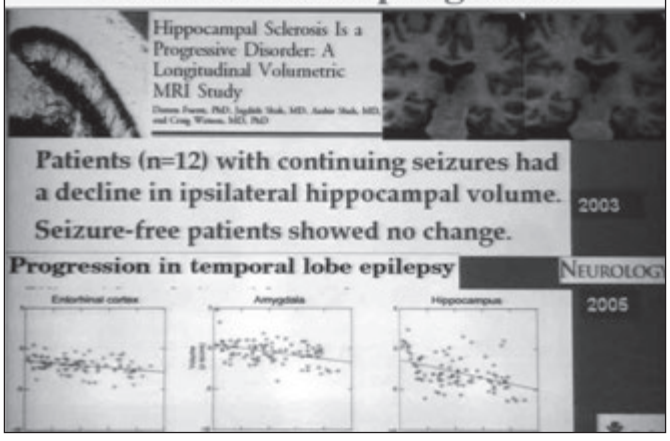
Helmstaedter C, et al. Ann Neurol 2003;54:425-432

Temporal Lobe epilepsy surgery and the quest for optimal extend of resection: a review

Johannes Schramm- Epilepsia 49:1296-1307,2008

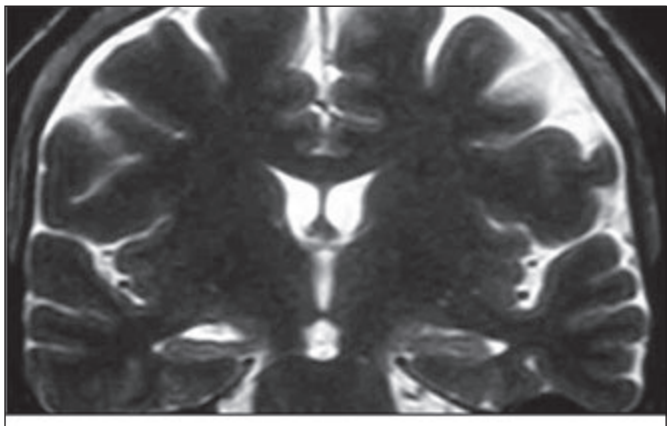
- **No hay disponible evidencia Clase I para control de crisis relacionada a tipo y extensión de la resección temporal.**
- **Pareciera que AHS tiene similar resultado que LT en el control de crisis, pero quizás mejor resultado neuropsicológico. Es incierto que sacar más se asocie a mejor "outcome".**
- **Se necesitan más estudios prospectivos.**

Daño cerebral progresivo



Casos difíciles Epilepsia temporal

- **1) Sospecha que el área de lenguaje involucre el área ictal.**
- **2) No se logra lateralizar el origen de la crisis con estudios de superficie.**
- **3) Sin lesión en la RM.**



ETM BILATERAL

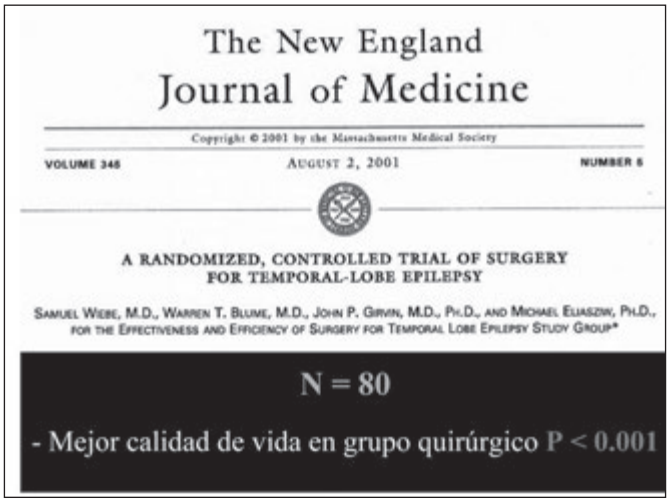
Evaluación Neuropsicológica

William Scoville (1906-1984)

La evaluación neuropsicológica inicialmente fue para lateralización y localización del foco epiléptico. En 1953, Scoville operó al paciente HM, resecando ambos hipocampos. HM sufrió una completa incapacidad para adquirir nueva memoria. Este caso índice fue tomado por Brenda Müller, para hacer rutinariamente la predicción post-operatoria de la función cognitiva.

CIRUGIA DE LA EPILEPSIA TEMORAL - RESULTADOS

- **Control de Crisis.**
- **Memoria anterograda.**
- **Calidad de Vida**



Epilepsia Refractaria: Riesgo de Vida

- La riesgo de mortalidad de una persona sana es 1.
- El de un paciente con epilepsia refractaria es 5.
- Pero vuelve a 1 si queda libre de crisis post-cirugía!!

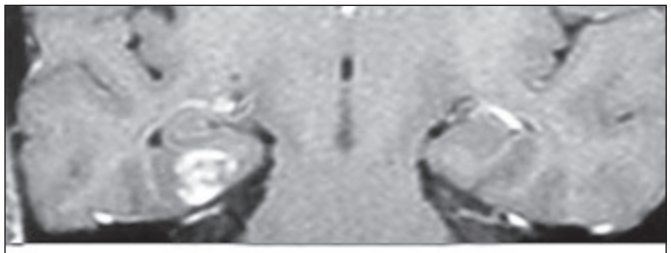
CIRUGIA DE LA EPILEPSIA ESTADO DEL ARTE

- **Pasado**
- **Presente**
- **Futuro**

CASO CLINICO

- **Paciente de 40 años con CPC desde los 35 años, las cuales se hacen refractarias último 1 año.**
- **Semiología temporal (aura abdominal, automatismos bucales).**
- **EEG: actividad inter ictal temporal anterior derecha.**

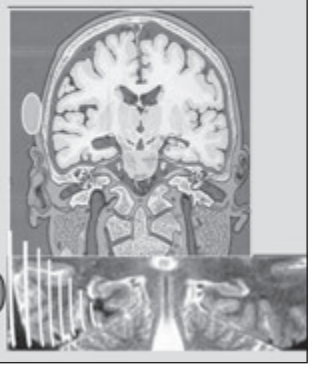
¿NECESITA MONITOREO DE VÍDEO EEG PARA PLANTEAR CIRUGIA?

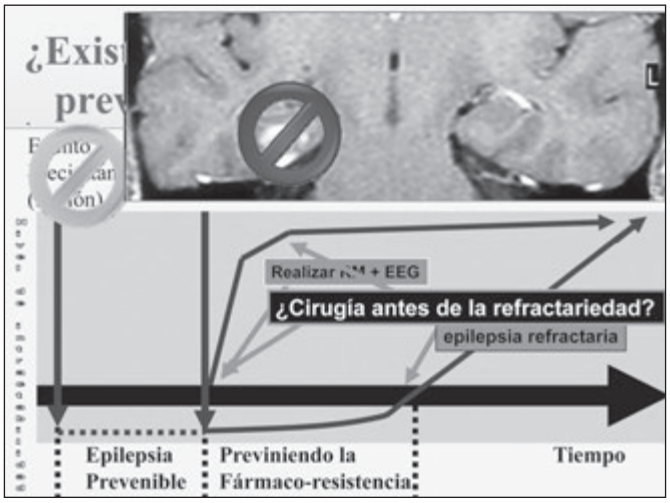


La lesión está en el Giro Parahipocampal
¿ De donde vienen las crisis?
¿ Cómo saberlo?

Practical problems when defining the epileptogenic zone

- **Surface EEG can not define precisely the actual seizure onset zone:**
  - **Surface ictal EEG is imprecise. It can not detect the initiation of seizure activity. Seizure activity must spread to involve relatively extensive cortical areas to become visible on surface electrodes. Besides, because of the distance between recording electrodes and the neurons initiating the seizure, precise source localization is impossible**





CONCLUSIONES
Niños

- La cirugía de la Epilepsia en niños debe plantearse a penas aparezca la resistencia a fármacos.
- En Síndromes especiales (Hemimegalencefalia, S. Rasmussen, etc.) la cirugía se debe plantear aún más precozmente.
- La meta no es solo controlar las crisis, sino también permitir un adecuado desarrollo del cerebro sano.

CONCLUSIONES
Adultos

- La cirugía de la Epilepsia debe plantearse a penas aparezca la resistencia a fármacos, basta con probar 2 FAEs.
- Especialmente en el caso de existir lesión en la RM.
- La meta es mejorar la calidad de vida del paciente en todo sentido (crisis, memoria y conducta).

CONCLUSIONES

- **El éxito depende de:**
  - **Un equipo de trabajo multidisciplinario.**
  - **La sensibilidad de los médicos, tanto especialistas, como no especialistas a derivar precozmente a los pacientes a estudios pre-quirúrgicos.**

Cognitive deficits resulting from the use of antiepileptic drugs
Jacqueline French (USA)

Cognitive Effects of Antiepileptic Drugs

Jacqueline A French, MD

NYU Comprehensive Epilepsy Center

New York, NY

Acknowledgement

- Dr Kimford Meador, Emory University

Introduction

- Epilepsy imposes a tremendous burden of illness
- Associated with significant cognitive and behavioral comorbidity
- Cognitive and behavioral impairment associated with AEDs poses challenge in treatment
- Older AEDs have known limitations, including unfavorable neurotoxicity profiles
- Some newer AEDs are associated with favorable side-effect profiles, including minimal effects on cognitive and behavioral function

Antiepileptic Drugs

OLDER AEDs

- 1857 - Bromides
- 1912 - Phenobarbital
- 1937 - Phenytoin
- 1944 - Trimethadione
- 1954 - Primidone
- 1960 - Ethosuximide
- 1974 - Carbamazepine
- 1975 - Clonazepam
- 1978 - Valproate

NEWER AEDs

- 1993 - Felbamate
  Gabapentin
- 1995 - Lamotrigine
- 1996 - Topiramate
- 1997 - Tiagabine
- 2000 - Levetiracetam
  Oxcarbazepine
  Zonisamide
- 2005 - Pregabalin
- 2009 – Rufinamide
  Lacosamide
  Vigabatrin

Quality-of-Life Issues for Patients With Epilepsy

Psychosocial	Cognitive
Independence	Speed of mental processing
Self-esteem	Memory
Stigma of epilepsy	Language
Need to take medication	Abstract thought
Education	Judgment and reasoning
Social activities	
Social support	
Physical role limitations	
Driving	
Embarrassment from seizure	

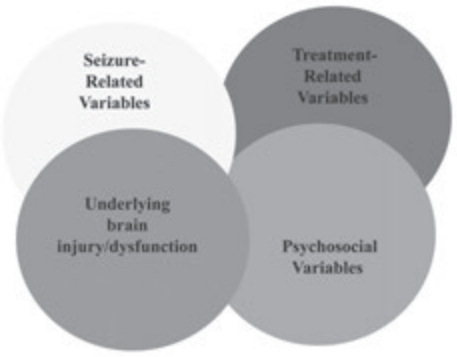
International Bureau for Epilepsy:

- 44% Difficulty learning
- 45% Felt that they were slow thinkers
- 59% Felt sleepy or tired
- 63% AED effects prevented them from achieving activities or goals

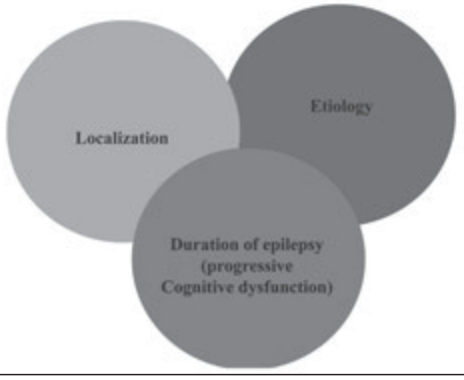
N = 425 Europeans with epilepsy

www.ibe-epilepsy.org/whatsnew_det.asp

Variables Associated With Cognitive and Behavioral Impairment



Underlying Brain Injury/Dysfunction



Issues with AED studies

- Test
  - What are relevant tests?
- Dose
  - What is relevant dose
  - What is *comparable* dose?
  - Levels?

How to study AED effects

- Normal volunteer studies
  - Advantages
    - Usually used to study cognitive effects
    - "cleanest" studies
    - Monotherapy easier
    - Can use non-drug control
  - Disadvantages
    - AED effects may not be the same in healthy and epileptic brain
    - NI volunteers may not tolerate doses used in patients

How to study AED effects

- Patient studies
  - Advantages
    - Usually used to study QOL/behavioral effects
    - Pts may have different effects due to underlying disease
  - Disadvantages
    - If not randomized, cannot rule out bias in AED selection
    - Monotherapy difficult
    - Add-on to Rx trial vs stand-alone trial

Challenges to Interpreting Comparative AED Studies in Patients

Methodological

- **Measures: choice & administration**
  - Appropriate measures administered by properly trained personnel?
- **Dosing regimen**
  - Consistent current guidelines?
  - Are comparators being dosed equivalently?
- **Subject selection bias**
  - If not randomized, why did these patients receive the different drugs in the first place?
- **Confounding factors** (eg, seizures)
  - What if one AED substantially reduces szs?
- **Generalization**
  - To what extent will results with this sample generalize to all patients?

Statistical

- **Failure to correct for multiple comparisons (Type I error)**
- **Over correct: Type II error**
- **Low power due to small sample sizes**
- **Statistical vs Clinical Significance**

Cognitive Effects of AEDs: Important variables

- **Higher Dose / ABL**
- **Polytherapy**
- **Rapid Titration**
- **Habituation**
- **AED differences**
- **Individual differences**

Cognitive Abilities Most Likely to be Affected by AEDs

- **Processing Speed** (e.g., reaction time)
- **Complex or Sustained Attention**
- **Dual Processing**
- **Verbal learning**
  - Paragraphs more sensitive than word lists, unlike the pattern seen in other disorders of memory (e.g., TBI)
- **Verbal fluency**
  - Rate at which words beginning with a specific letter or from a specific category can be generated

Cognitive Effects of Older AEDs

- Healthy Adults
- Double-blind, randomized, crossover studies
  - Cognitive/motor speed
  - Memory
  - Other cognitive measures
  - Mood and symptoms

Meador KJ, et al. *Neurology*. 1991;41:1537-1540; *Epilepsia*. 1993;34(1):153-157; *Neurology*. 1995;45:1494-1499.

Differential Cognitive Effects of Older AEDs in Healthy Adults

- 90% CBZ = PHT (others split even)
- 96% PHT = VPA (1 of 22 different)
- 32% PB<PHT and VPA

- 52% CBZ and PHT<nondrug
- 55% PB, PHT, and VPA<nondrug

Meador KJ, et al. *Neurology*. 1991;41:1537-1540; *Epilepsia*. 1993;34(1):153-157; *Neurology*. 1995;45:1494-1499.

Evidence of Differential Cognitive Effects New AED (GPN) vs Old AED (CBZ)

- Double-blind, randomized, crossover
  - 35 healthy adults
    - 5-week treatment arms
    - 31 variables
  - GBP 2,400 mg/day
  - CBZ 731 mg/day (8.3 µg/mL)
- 26% GBP>CBZ (0% CBZ>GBP)
- 48% ND>CBZ (3% CBZ>ND)
- 19% ND>GBP (3% GBP>ND)

Meador KJ, et al. *Epilepsia*. 1999;40(9):1279-1285.

Evidence of Differential Cognitive Effects New AED (LTG) vs Old AED (CBZ)

- Double-blind, randomized, crossover design
- Two nondrug baselines, two 10-week AED treatment periods, and 1 posttreatment nondrug baseline
- Only completers analysed
- Neurobehavioral battery (40 variables)
- 25 healthy adult subjects
- AED mean doses
  - LTG = 150 mg/day (±0)
  - CBZ = 696 mg/day (400-1,000 mg/day) (to standard serum level)

Meador KJ, et al. Neurology. 2001 May 8;56(9):1177-82

Cognitive Function Outcomes Significantly Favor LTG Over CBZ

— 19/40 (48%) of indicators favor LTG over CBZ [0/40 (0%)]
— Indicators for which LTG is favorable

Cognitive Items	Subjective Items
• Cognitive/Motor Speed – CRT (initiation)	• AB Neurotoxicity Scale
• Memory – MCG Paragraph Memory (#1, #2, and delayed recall)	• Cornell Dysthymia Scale
• Other Cognitive – Symbol Digit Modalities Test – Stroop (word and color)	• POMS – Vigor, fatigue, confusion, and overall score
	• QOLIE-89 – Attention, language, and memory
	• SEALS – Cognition and tiredness
	• Stanford Sleepiness Scale

Meador KJ, et al. Neurology. 2001 May 8;56(9):1177-82

Worse cognitive outcome for topiramate vs lamotrigine, gabapentin

- 17 healthy volunteers
- Randomized to 3 AEDs
- Tests of attention, psychomotor speed, language, memory, and mood at baseline (predrug), acute single-dose period, and after 2 and 4 weeks on the drug
- Compared with baseline, only topiramate group had selective, statistically significant declines on measures of attention and word fluency at acute doses, and continued to display neurocognitive effects at 2 and 4 wks.

Martin et al, *Neurology* 1999;52:321

POMS for topiramate vs lamotrigine, gabapentin

- TPM group had higher scores on the depression scale ($t[5] = 4.5$, $p < 0.01$) and the anger–hostility scale ($t[5] = 4.5$, $p < 0.01$) at week 4 compared with their baseline scores.
- The TPM group also had higher scores on the confusion scale at week 2 ($t[6] = 3.0$, $p < 0.03$) and at week 4 ($t[5] = 3.2$, $p < 0.03$) compared with their baseline scores.
- Study criticized for titration schedule

Martin et al, *Neurology* 1999;52:321

Favorable Tolerability and Cognitive Profile With Various GBP Doses in Refractory Epilepsy

- Placebo-controlled, add-on, crossover study in adult epilepsy patients (N = 27)
- 3-month treatment arms
- No significant differences on 37 neuropsychological variables
- Drowsiness higher at 2,400 mg/day

Leach JP, et al. *J Neurol Neurosurg Psychiatry.* 1997;62:372-376.

Favorable Cognitive Outcomes for TPM vs VPA

- Double-blind, randomized, parallel (17 variables)
- Add-on to CBZ in epilepsy patients

	TPM	VPA
Titration (mg/day/week)	25 mg	150 mg
Completers	24	29
Dropouts	8	4
Mean dose (mg/day)	251	1,384

- VPA>TPM on verbal memory

Titration = 12 weeks; maintenance = 8 weeks

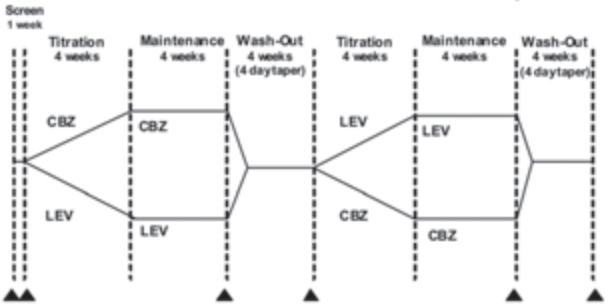
Aldenkamp AP, et al. 2000.

Favorable Effects of LTG on Mood/Cognition and QOL

- Smith, et al. 1993[1] (N = 62)
  - LTG (200-400 mg/day) vs placebo
  - Positive QOL effects on 2 of 6 (HRQOL)
- Gillham, et al. 1996[2] (N = 256)
  - LTG>CBZ on SEALS (QOL measure)
- Steiner, et al. 1999[3] (N = 181)
  - LTG 150 mg/day; PHT 300 mg/day
  - LTG>PHT on SEALS (QOL measure)

[1]Smith D, et al. *Epilepsia.* 1993;34:312-322. [2]Gillham R, et al. *Epilepsy Res.* 1996;24:47-55. [3]Steiner TJ, et al. *Epilepsia.* 1999;40(5):601-607.

Levetiracetam vs Carbamazepine



CBZ titration: 200 mg × 1 week, 200 mg BID × 1 week, then adjusted to midrange blood levels with TID dosing. LEV titration: 500 mg × 2 weeks, 500 mg BID × 2 weeks, then 1,000 mg BID.

Meador K J et al. Neurology 2007;69:2076-2084

AMERICAN ACADEMY OF NEUROLOGY

Carbamazepine vs Levetiracetam

- Significantly worse effects for CBZ on 44% (15 of 34) of the neuropsych variables tested
- Both CBZ ($p \leq 0.001$) and LEV ($p \leq 0.05$) differed from non-drug on the overall score.
- Comparing the two AEDs to non-drug across individual variables revealed significantly worse effects on 76% (26 of 34) of the variables for CBZ and 12% (4 of 34) for LEV compared to non-drug

Meador et al., Neurology 2007 69(22):2076-84.

Healthy Volunteers: Newer AEDs vs Placebo

AED	% tests with placebo better than AED
gabapentin	0 – 19%
lamotrigine	1 – 17%
levetiracetam	11%
oxcarbazepine	46%
topiramate	29 – 88%
tiagabine	0%

Kalviainen et al, *Epi Res* 1996;25:291-7. Dodrill et al, *Neurology* 1997;48:1025-31. Leach et al, *JNNP* 1997;62:372-6. Meador et al., Epilepsia 1999;40(9):1279-1285. Meador et al., Neurology 2001;56:1177-82. Salinsky et al., *Epilepsy & Behavior* 2004;5:894-902. Aldenkamp et al., Epilepsia 2000;41:1167-7. Meador et al., Neurology 2003;13;60:1483-8. Salinsky et al., Neurology 2005;64:792-8. Meador et al., Neurology 2005;64(12):2108-2115. Blum et al., Neurology 2006;67:400-406.

Healthy Volunteers: Newer AEDs vs Other AEDs

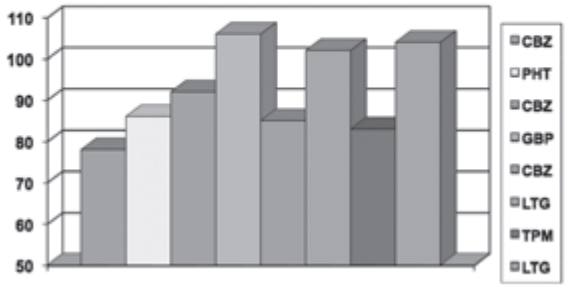
LESS impact on cognition	**MORE** impact on cognition	% tests
gabapentin	carbamazepine	26%
gabapentin	topiramate	50%
lamotrigine	carbamazepine	48%
lamotrigine	topiramate	80%
levetiracetam	carbamazepine	42%
oxcarbazepine	phenytoin	0%

Meador et al., *Epilepsia* 1999;40(9):1279-1285. Meador et al., *Neurology* 2001;56:1177-82. Salinsky et al., *Epilepsy & Behavior* 2004;5:894-902. Meador et al., *Neurology* 2003;13;60:1483-8. Salinsky et al., *Neurology* 2005;64:792-8. Meador et al., *Neurology* 2005;64(12):2108-2115.

How severe is the effect of AEDs on Memory?

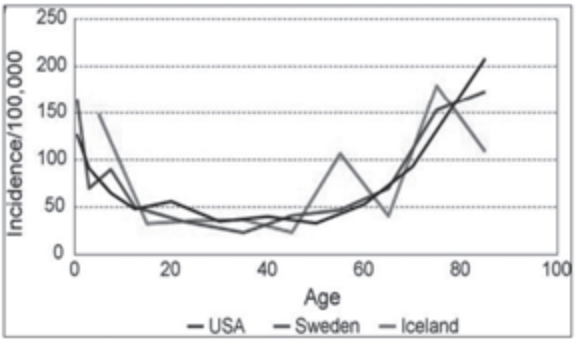
Delayed Recall % Compared to Non-Drug Average

Healthy Volunteer Studies



Meador et al, 1991, 1993, 2000, 2001, 2005

Incidence of Unprovoked Seizures in Developed Countries



Cloyd et al. *Epilepsy Res* 2006;68(Suppl 1):39-48

Cognitive Effects of AEDs in the Elderly

- **PHT = VPA**

  Craig & Tallis, Epilepsia 1994;35:381-390

- **Elderly more sensitive to cognitive effects of AEDs: CBZ, PB, PHT, PRM**

  VA Cooperative Study

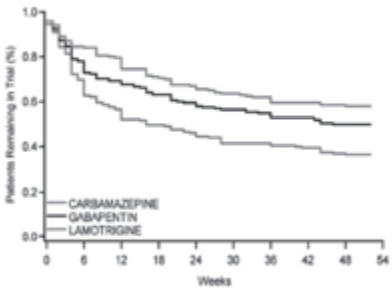
VA Coop Geriatric Epilepsy Study

N = 593

≥65 y/o

New onset epilepsy

Mean Dose (mg/d)	ABL (mcg/ml)
CBZ = 558	6.8
GBP = 1424	8.7
LTG = 152	3.5



Rowan et al, Neurology 2005;64:1868-73

Cognitive Effects of AEDs in Children

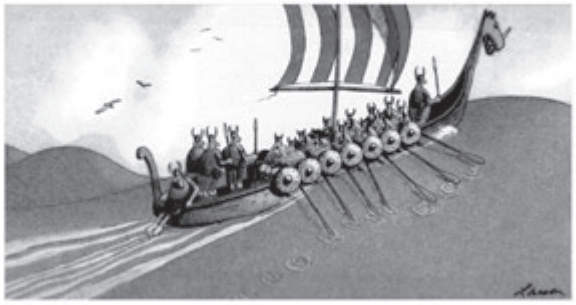
- Loring & Meador, Neurology 2004;62:872-7
- Pressler et al., Neurology 2006;66(10):1495-9.
- Donati et al, Neurology 2006;67:679-682.

Children AED Cognition Studies

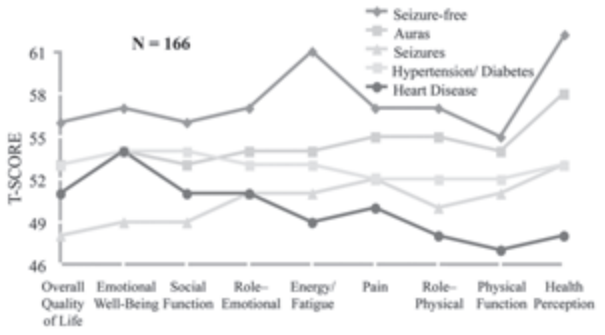
Vining et al, 1987	PB < VPA
Farwell et al, 1990	PB < Placebo
Forsythe et al, 1991	CBZ = PHT = VPA
Chen et al, 1996	PB < CBZ = VPA
Aldenkamp et al, 1998	CBZ = PHT = VPA
Pressler et al, 2006	LTG = Placebo
Donati et al, 2006	CBZ = OXC = VPA
Kang et al, 2007	TPM < CBZ

Vining et al, Pediatrics 1987;80:165-174; Farwell et al,.NEJM 1990;322:364-369; Forsythe et al, Dev Med Child Neurol 1991;33:524-534; Chen et al, Epilepsia 1996;37:81-86; Aldenkamp et al, Epilepsia 1998;39:1070-4; Pressler et al, Neurology 2006;66:1495-9; Donati et al, Neurology 2006; 67;679-682; Kang et al, Epilepsia 2007;48:1716-23

Quality of Life

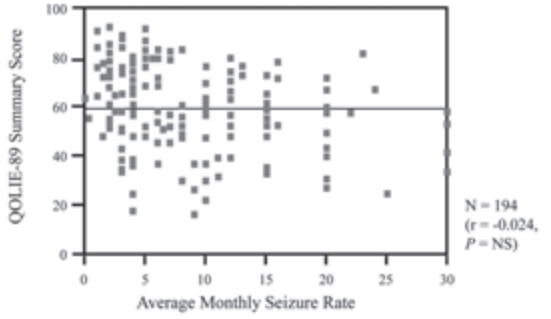


Comparison of Quality of Life: Seizures, HTN, Diabetes, & Heart Disease



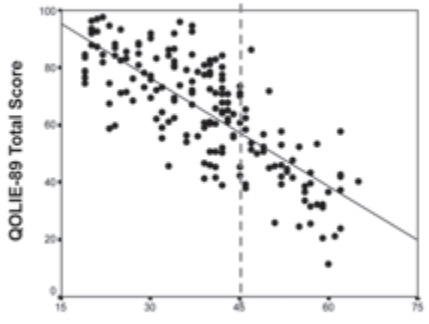
Vickrey BG. *Epilepsia*. 1994;35:597-607

Comparison of Average Monthly Seizure Rate to HRQOL



Gilliam F, et al. 2000.

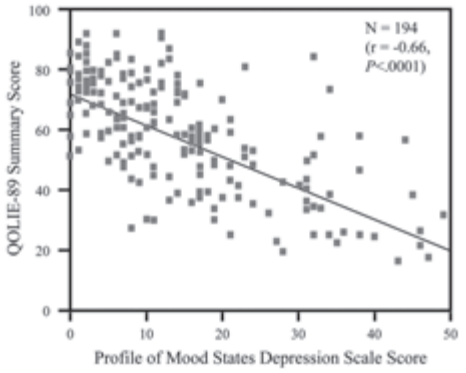
Relationship of Subtle AED Toxicity to Quality of Life



N = 200
r = -0.76,
***P*<0.0001**

Gilliam, et al. Neurology 2004;62:23-27

Relationship of POMS-D to QOL Scores



Gilliam F, et al. 2000.

Memory, Mood & Perception
Post Anterior Temporal Lobectomy

	LATL	RATL
CVLT (LDFR)	.19	.33
POMS Depression	-.48*	-.38
POMS Total	-.50*	-.50*

Correlations (r value) for pre/post-op changes in perceived memory; *p≤.05

CVLT = California Verbal Learning Test; LDFR = Long-term Delay Free Recall

Sawrie et al, Neurology 1999;53:1511-7

Mood, Quality of Life, & Neuropsychological Function

Subjective Perception	Mood	Best Objective Test	All Objective Tests
Memory	17.2%	4.3%	7.9%
Language	14.6%	4.9%	12.7%
Attention	28.7%	3.6%	9.3%
QOLIE-89 total	46.7%	5.2%	13.3%

% Variance explained by each factor

N = 257 epilepsy patients

Perrine et al, Arch Neurol 1995;52:997-1003

Lamotrigine-Topiramate

	# significant correlations	
	Lamotrigine	Topiramate
Healthy Volunteers		
21 Subjective Measures	71% (15/21)	29% (6/21)
69 Objective Measures	3% (2/69)	0% (0/69)
Patients with Epilepsy		
9 Subjective Measures	100% (9/9)	67% (6/9)
7 Objective Measures	0% (0/7)	14% (1/7)

Meador KJ et al. *Epilepsia* 2005;46(Supp 8):261;
Meador KJ et al. *Neurology* 2006;66(Supp 2):A72.

Strategies for Reducing AED Neurotoxic Effects

- Use of appropriate drug
  - Seizure type
  - AED cognitive risk factors
  - Comorbidity and neurologic status
- Monotherapy or best-tolerated combination
- Proper dosing
- Consider drug interactions with OTCs
- Monitor clinical status

Summary: Cognitive Issues in Epilepsy

- Cognitive impairment in epilepsy is multifactorial.
- **Least** cognitive effects: GBP, LEV, TGB, LTG.
- **Intermediate** effects: CBZ, PHT, OXC, VPA.
- **Most** adverse effects: PB, TPM, Benzos.
- AED susceptibility can vary across patient groups as well as across individual patients.
- Subjective and objective measures of cognitive function can dissociate.

Conclusions

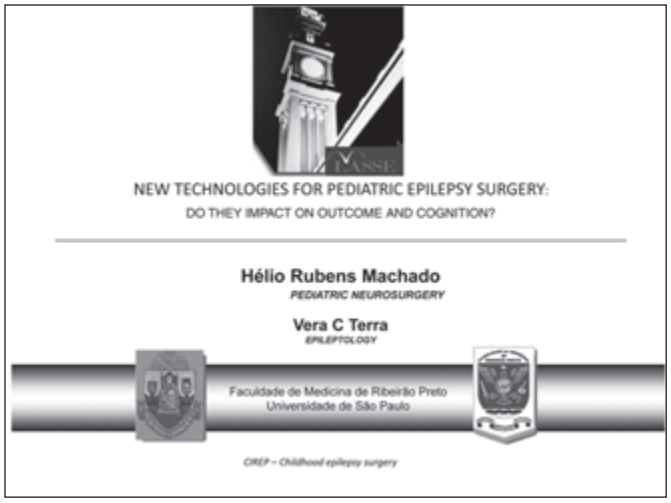
- Epilepsy has significant cognitive and behavioral comorbidity, and cognitive and behavioral issues may overshadow seizure reduction, especially when seizure freedom is incomplete
- Efficacy, safety, and cognitive and behavioral profiles should determine the choice of AEDs

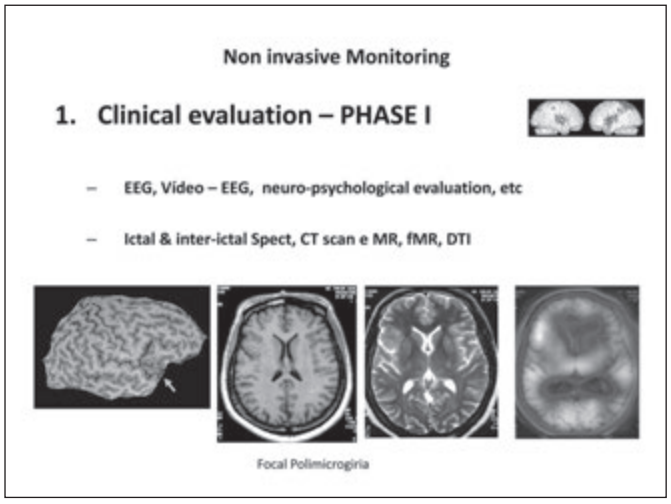
Minimizing Adverse Behavioral Effects of AEDs

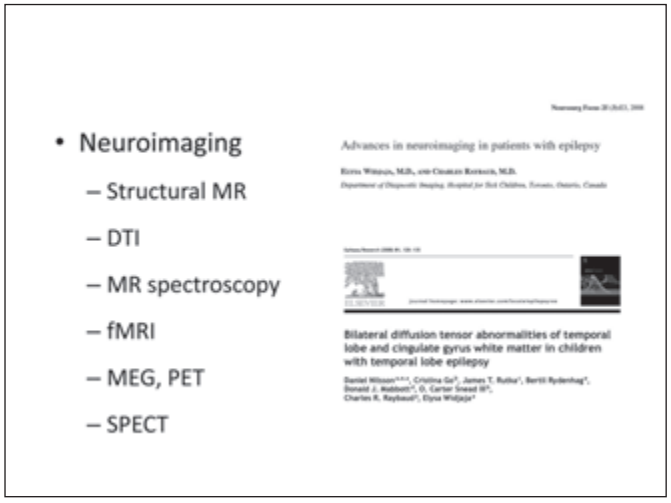
- Decrease or discontinue AEDs with negative psychotropic effects
- Add AEDs with positive psychotropic effects
- Identify potential drug interactions (eg, EIAEDs)

New technologies for pediatric epilepsy surgery: What is its impact on cognition?

Helio Rubens Machado (Brazil)







- fMRI in epilepsy surgery in children
  - Language lateralization
    - Studies in children
  - Motor area identification

  - Invasive monitoring
    - Concordant?

- 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

	Results (+)	risk
Large resection	Complete resection of EZ	Deficit
Small resection	No deficit	Persistent seizures Multiple interventions

- 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

Any choices?

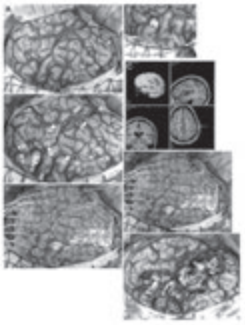
Benifla J NSG Peds 2009

Rolandic epilepsy in children – resection in eloquent cortex

22 children – HSC – Toronto

20/22 with deficits – some improveal – large resections

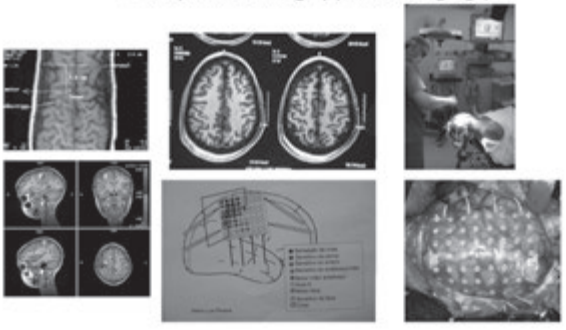
some deficits were worse than expected



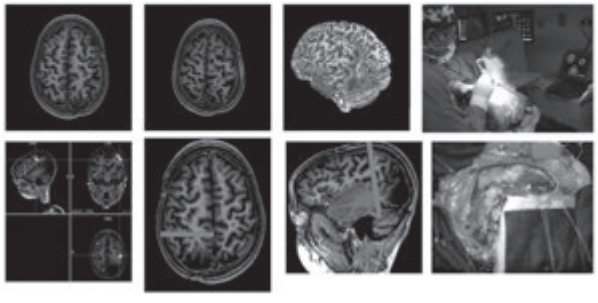
- Paradigm shift of smaller resection? – better targetting
  - EVOLUTION – progressively sophisticated non-invasive imaging to delineate epileptogenic region
    - SPECT ictal – SISCOM, MEG, PET, EEG high density, intraoperative neuronavigation

- Epilepsy surgery
  - Hemipherectomy X Hemispherotomy
  - Large resections X disconnective surgeries
  - Endoscopy – hypothalamic hamartoma
  - Neuronavigation

- Eloquent areas surgery (motor & language)



- RM 3 T ; DTI (tractography) ; fMRI
- Neuronavigation



Epilepsy surgery in children

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

1996 to 2009

Children 305
Surgeries 326

Pathology	
Cortical Dysplasia	97
Tumor	48
Gliosis	47
Mesial temporal sclerosis	46
Rasmussen encephalitis	25
Porencephaly	16
Tuberous sclerosis	13
MR normal	8
Sturge-Weber	8
Difuse atrophy	9
AVM	3
(other 6) Total	326

Helio Rubens Machado

Epilepsy surgery in children

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

1996 to 2009

Children 305
Surgeries 326

Surgical technique (305 patients)	
Temporal Lobectomy	96
Hemispherotomy	78
Lesionectomy	60
Frontal Lobectomy	21
Posterior(par-occipital) cortex	21
Calosotomy	16
Focal Corticectomy	14
Occipital Lobectomy	9
VNS	6
Multilobar Resection	5
(reoperation 20)	

Total 326

Invasive Monitoring

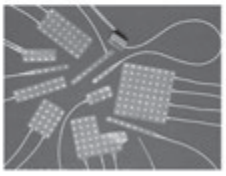
2. Invasive evaluation – PHASE II

" CORTICAL MAPPING "

CORTICAL GRIDS OR STRIPS

DIRECT CORTICAL STIMULATION

Intraoperative ECoG or chronic monitoring



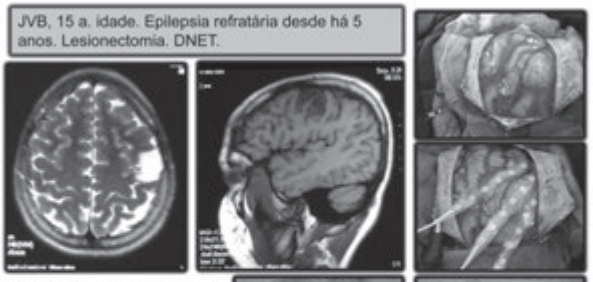
Pathology		ECoG - Acute	Chronic
Cortical dysplasia	65	49 (75%)	11(16%)
Tumor	38	20 (52%)	-
Mesial temporal sclerosis	38	8 (21%)	2 (5%)
Rasmussen encephalitis	21	5 (23%)	-
Tuberous sclerosis	11	9 (81%)	5
Porencephaly	10	4 (40%)	(45%)
Gliosis	37	19 (51%)	5
MR normal	9	1	(13%)
Sturge-Weber	6	4	2
Diffuse atrophy	5	1	-
Arterio-venous malformation	3	2	-
(unknown 1) Total	244	122 (50%)	26 (11 %)

Catastrophic epilepsy

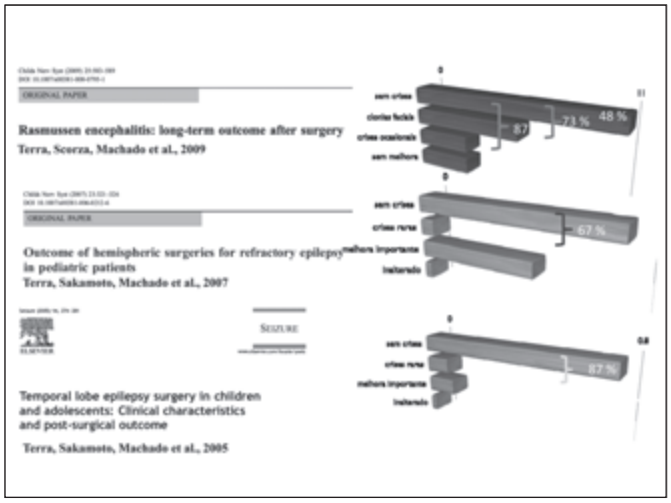
- Refractory epilepsy
- Progressive neurological deficit
  - spastic hemiplegia
- Mental retardation
- Severe behavioral problem

TUMORES E EPILEPSIA

JVB, 15 a. idade. Epilepsia refratária desde há 5 anos. Lesionectomia. DNET.



Resultados tardios	
Recidivas	não
Deficits Focais	não
Sem crises – DNET (26)	100 %
Inalterados – Glioma	3 / 12

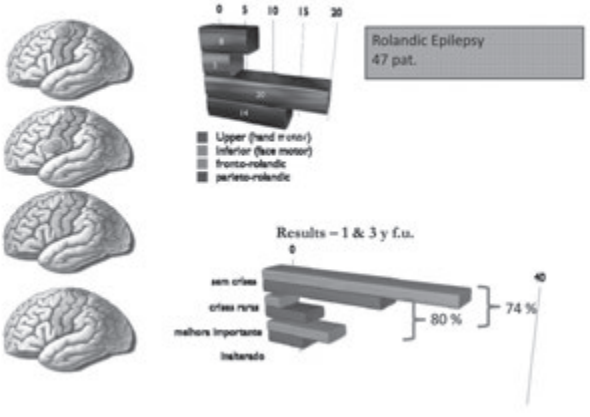


Encefalite de Rasmussen

Pacientes:

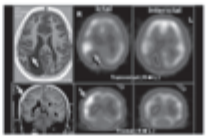
1. **Resultados**
   1. **Motor – marcha**

Pre op \ Pos op	Marcha	Não
Marcha	13	2
Não	4	3
total	17	5

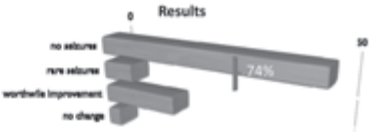


Cortical Dysplasia

Surgery (2008)	
Lobectomy	
Frontal	18
Temporal	19
Parietal	3
Occipital	10
Multilobar	8
Hemispherotomy	16
Total	**74**

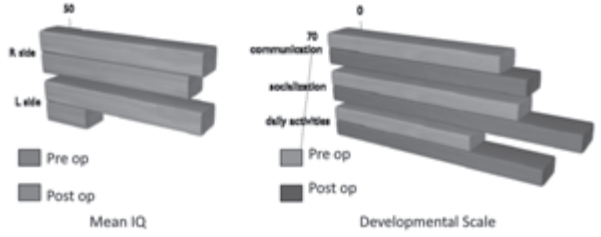


Pathology (Palmini)	
Type I A	12
Type I B	13
Type II A	29
Type II B	20



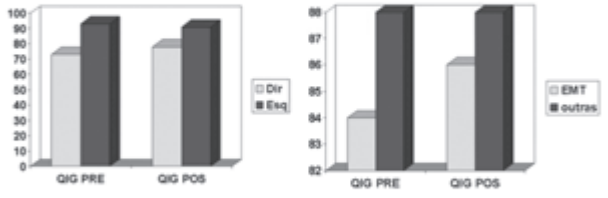
IQ/ DS performance after hemispherotomy in children with Rasmussen encephalitis

Souza-Oliveira C, Escorsi-Rosset S, Terra VC, Machado HR, Sakamoto AC, 2008



Cirurgia do lobo temporal em crianças
Prognóstico cognitivo

Souza-Oliveira C, Escorsi-Rosset S, Terra VC, Machado HR, Sakamoto AC, 2009



CONCLUSION

- Persistence of epilepsy is unnacceptable
- Resection of EZ is desirable but…
  - No correlation between extent of resection and outcome
  - Maximal resection = higher risk
- In some cases neurological deficit is acceptable if epilepsy is controlled
- Continued refinements in localization allows better effectivity and may require limited resections

Programa – 01.03.2011

9:00 – 18:00 Presentation and discussion of research projects prepared by the students