10ª. ESCOLA LATINO-AMERICANA DE VERÃO EM EPILEPSIA
10ª. ESCUELA LATINO-AMERICANA DE VERANO EN EPILEPSIA
10th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 21 DE FEVEREIRO A 1 DE MARÇO DE 2016
Centro de Convenções Santa Mônica

COORDENAÇÃO GERAL
Prof. Dr. Esper A. Cavalheiro

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EPILEPSIA NA AMÉRICA LATINA: O QUE TEMOS PELA FRENTE

A 10ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) é uma atividade da lnternational League Against Epilepsy (ILAE) e da Academia Latino-Americana de Epilepsia (ALADE) com o apoio da Liga Brasileira de Epilepsia (LBE).

Com início em 2002, as "Escolas de verão em epilepsia", organizadas pela International League Against Epilepsy (ILAE) têm se tornado uma referência como experiência didática. Como professores e alunos permanecem em contato bastante próximo por quase duas semanas consecutivas, esse tipo de Escola tem facilitado a integração entre pesquisadores e alunos permitindo uma melhor compreensão das novas descobertas para o benefício das pessoas com epilepsia. A décima edição "Escola Latino-Americana de Verão em Epilepsia (LASSE)" realizada em Guarulhos entre 21 de fevereiro e 01 de março de 2016 aborda o tema o futuro da epilepsia na América Latina além de comemorar os resultados obtidos ao longo dos dez anos da escolar.

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

A COMISSÃO ORGANIZADORA

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10TH. Latin-American Summer School on Epilepsy – LASSE X
"EPILEPSY IN LATIN-AMERICA: The future ahead"
21 February - 1 March 2016 – São Paulo, Brazil

PROGRAM

27/02 - Saturday

14:00-18:00 LASSEans' Symposium
Chairs: Jaime Carrizosa, Lili Morales, Loreto Rios, Patricia Braga
Participants:
Angelica Uscategui Daccarrett
Blanca Doris Rodriguez
Chiara del Furia
Christian Gomez Castillo
José Cláudio da Silva
Rodolfo Cesar Callejas Rojas
Selvin Reyes García

28/02 – Sunday

Whole day dedicated to group working

29/02 – Monday

01/03 – Tuesday

09:00-18:00 h - Presentation of research projects
18:00-Closure

/ /

Esper Cavalheiro (Brazil)

WELCOME AND INTRODUCTION TO LASSE

Alicia Bogacz (Uruguay)

IMPORTANCE AND IMPACT OF THE ILAE CLINICAL DEFINITION OF EPILEPSIES

DEFINICIÓN OPERACIONAL DE EPILEPSIA

Dra. Alicia Bogacz
Sección Epilepsia Instituto de Neurología
Montevideo-Uruguay LASSE 2016

DEFINICIÓN CONCEPTUAL

Epilepsy is a sudden excessive and rapid discharge of grey matter of some part of the brain, it is a local discharge.
(John Hughlinds Jackson, 1873)

- Una crisis epiléptica es la ocurrencia transitoria de signos y/o síntomas producidos por una descarga anormal, excesiva y sincrónica de la actividad neuronal cerebral.
(Fisher, R. y col, 2005)

DEFINICIÓN CONCEPTUAL

- Epilepsia se define como una condición neurológica crónica caracterizada por crisis epilépticas recurrentes.
(Hausser W.A.y col,1991) (Blume W.T. y col,2001)
- Epilepsia es un desorden cerebral caracterizado por la predisposición persistente a generar crisis epilépticas y por las consecuencias neurobiológicas, cognitivas, psicológicas y sociales de esta condición.
(Fisher, R y col., 2005)

ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

Summary

DEFINICIÓN OPERACIONAL

La epilepsia es una enfermedad cerebral y se considera que existe en cualquiera de las siguientes situaciones:

- Por lo menos dos crisis no provocadas (o reflejas) que ocurrieron con una separación de más de 24 horas.
- Una crisis no provocada (o refleja) y que la probabilidad de que ocurran más crisis sea similar al riesgo general de recurrencia luego de dos crisis no provocadas (por lo menos el 60%), ocurriendo en los siguientes 10 años.
- Diagnóstico de un síndrome epiléptico.
- La epilepsia se considera resuelta en aquellos individuos con un síndrome epiléptico edad dependiente y que hayan sobrepasado la edad aplicable al síndrome y en aquellos que han permanecido libres de crisis por 10 años y 5 años sin medicación contra las crisis. (Fisher y col, 2014)

DEFINICIÓN OPERACIONAL

Aspectos positivos	Aspectos negativos
• Crea la necesidad de investigar los riesgos de recurrencia.	• Puede crear confusión entre los pacientes de si tienen o no epilepsia.
• Se ajusta a la manera de pensar de la mayoría de los epileptólogos.	• No es claro su efecto sobre los estudios epidemiológicos.
• Puede ser usada para propósitos específicos.	• Puede afectar las reglas y reglamentaciones en relación a epilepsia.

¿ENFERMEDAD o DESORDEN?

- Epilepsia comprende muchas enfermedades y condiciones.
- Desorden se refiere a una alteración funcional que no necesariamente perdura.
- Enfermedad es una alteración funcional más duradera.
- El término desorden es poco comprendido por el público y se minimiza la naturaleza severa de la epilepsia, por lo que la ILAE y el IBE concordaron en referirse a epilepsia como enfermedad.

CRISIS PROVOCADAS versus CRISIS NO PROVOCADAS

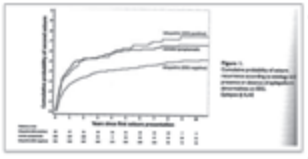
- Las **crisis provocadas** o sintomáticas agudas son aquellas en las que un factor transitorio disminuye el umbral para las crisis en un cerebro por otra parte normal. Las crisis provocadas por TEC, fiebre, privación de alcohol, no deben ser consideradas para el diagnóstico de epilepsia.
- El factor provocador es diferente a la etiología.
- En las **crisis reflejas** existe una tendencia patológica a generar crisis por estímulos comunes, que el paciente no puede evitar, por lo cual se considera que es epilepsia.
- En las **crisis no provocadas** no existe un factor reversible que disminuya el umbral de las crisis.
- Este es un término impreciso porque no se puede asegurar que no exista un factor provocador y su existencia no contradice que exista una anormalidad epiléptica duradera.

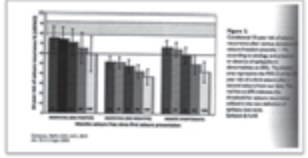
RIESGO DE RECURRENCIA

- En pacientes que han presentado una única crisis, pero tienen un alto riesgo de recurrencia de crisis, en la práctica se los trata como a una epilepsia.
- Se conoce que el riesgo en el caso de ACV, TEC, infección del SNC(Hersdorffer, 2009), o en niños con una alteración estructural y un EEG con actividad epileptógena, (Stroink, 1998), es similar a cuando se han tenido dos crisis, entre 60-90%.
- Se desconoce el riesgo de recurrencia en la mayoría de los casos individuales y el 60 % es una guía aproximada.

CRISIS ÚNICA más LESIÓN o EEG PATOLÓGICO

- No llenan los requisitos de la definición de manera definitiva.
- Los estudios disponibles muestran diferentes resultados:
  -Dutch Epilepsy Study, 1998: 71%
  - Shinar, 1990: 56%
  - Lawn, 2015: 76%
- No hay datos de cómo se combinan o suman los riesgos por lo que hay que decidir en cada caso individual.
- El riesgo de recurrencia está en relación al tiempo transcurrido, cuanto mayor el tiempo desde la crisis menor el riesgo (Lawn,2015).





- 1034 pacientes 1° crisis no provocada con un seguimiento medio de 6 años.
  -**Idiopáticos** (sin causa evidente o genética (EEG con actividad epileptógena, **positivos** y sin actividad epileptógena, **negativos**).
  -**sintomáticos** (causa conocida remota)
- 40% tuvieron un riesgo inicial = o >a 60% altamente dependiente del tiempo libre transcurrido, independiente de la etiología y otros factores de riesgo.
- **Predictores independientes** fueron: etiología conocida, crisis focales, EEG con actividad epileptógena y crisis durante el sueño.

Lawn et al; 2015. Epilepsia,56 (9):1425-1431

SINDROMES EPILÉPTICOS

- Los **síndromes epilépticos** se consideran como epilepsia.
- Epilepsia de la niñez con descargas centro-temporales o Epilepsia Rolándica.
- Síndrome de descargas continuas durante el sueño lento.
- Síndrome de Landau-Kleffner.

IMPLICANCIAS PARA EL TRATAMIENTO

- El diagnóstico y la decisión de tratar están relacionados pero son problemas diferentes.
- Debe ser individualizado en función de:
  - Los deseos del paciente.
  - Valoración entre el riesgo de una segunda crisis y los posibles efectos secundarios de la medicación.
  - Opciones disponibles.
  - Costo para los pacientes.
- Un paciente puede tener una encefalitis y ser tratado con FAE y no ser una epilepsia, otro tener crisis muy leves y/o muy esporádicas y no ser tratado aunque indiscutiblemente sea una epilepsia.

CRISIS SEPARADAS EN EL TIEMPO

- El lapso entre dos crisis es ambiguo.
- Las crisis en clusters dentro de las 24 horas tienen el mismo riesgo de recurrencia que una crisis única (Neligan, 2012).
- Algunos consideran que luego de 5 años sin crisis existe una remisión. Esta definición no especifica un límite de tiempo entre las dos crisis, por lo tanto si hay una crisis al año de vida y otra a los 80 años es epilepsia (oligoepilepsia) (Rajna, 2011).

RESOLUCIÓN DE LA EPILEPSIA

- **¿Una vez diagnósticada la epilepsia está para siempre?**
- La definición previa no dejaba lugar a la curación, aunque la persona estuviera sin crisis por décadas.
- Las crisis pueden ser superadas por una terapia exitosa, la persona puede sobrepasar la edad de su epilepsia y estar permanentemente libre de crisis.
- **¿Por qué resolución?**
- **Remisión-** implica la falta temporaria de enfermedad, pero no su ausencia.
- **Cura-** implica que el riesgo de presentar una crisis es similar al de la población no afectada, pero luego de una historia de epilepsia, esto nunca se alcanza estadísticamente.
- **Resuelta-** implica que la persona no tiene más epilepsia, pero no se garantiza que no pueda volver a tener crisis.

¿Qué intervalo de tiempo y circunstancias deben caracterizar la resolución de la epilepsia?

- No hay datos adecuados disponibles del riesgo de recurrencia luego de períodos prolongados de libertad de crisis y sin FAE.
- El riesgo de recurrencia de crisis disminuye con el tiempo y la mayoría de las recaídas son precoces.
- Las recidivas son raras luego de los 5 años y luego de 10 años sin FAE el riesgo anual de probabilidad de crisis es muy bajo (Chadwick,D, 1996).
- Se eligió definir la resolución de la epilepsia en los casos de síndromes edad dependientes que hayan sobrepasado dicha edad y en aquéllos que han estado libres de crisis por 10 años y por 5 años sin medicación.

Table 1. Prognostic predictors.

Prognostic Predictor	Authors, year
Symptomatic aetiology	Bonnett et al., 2014; Worrell et al., 2012; Sillanpää et al., 2012; Sillanpää and Schmidt, 2009a; Jallon et al., 2001; Berg et al., 2001; Ko and Hobson, 1999; Nikiu et al., 1999; Sillanpää et al., 1998; Annegers et al., 1979
Abnormal intelligence	Sillanpää et al., 2012; Worrell et al., 2012; Nikiu et al., 1999; Sillanpää, 1993; Camfield et al., 1993; Bronson and Hirtzema, 1987
Tonic or simple focal seizures	Bonnett et al., 2014; Yu et al., 2013; Jonsson and Eeg-Olofsson, 2011; Del Felice et al., 2010; Ko and Hobson, 1999; Shafer et al., 1988
Complex focal or atonic seizures	Nikiu et al., 1999; Sillanpää, 1993
Early childhood age at onset	Worrell et al., 2012; Sillanpää et al., 2012; Ko and Hobson, 1999; Sillanpää, 1993; Camfield et al., 1993
Prior neonatal seizures	Sillanpää, 1993; Camfield et al., 1993
High seizure frequency prior to treatment	Yu et al., 2013; Berg et al., 2001; Camfield et al., 1993
High seizure frequency during early treatment	MacDonald et al., 2000; Arts et al., 1999; Cockerell et al., 1997
Poor early effects of treatment	Bonnett et al., 2014; Sillanpää et al., 2012; Arts et al., 1999; Sillanpää et al., 1998; Annegers et al., 1979
Neurological dysfunction	Annegers et al., 1979
Abnormal interictal EEG	Berg et al., 2014; Yu et al., 2013; Worrell et al., 2012; Berg et al., 2001; Shafer et al., 1988
Time to first remission	Sillanpää et al., 2012; Sillanpää and Schmidt, 2009b

Beghi E et al. Epileptic Disord 2015; 17 (3): 243-53

RIESGOS DE RECIDIVA A LARGO PLAZO

- EMJ tiene un elevado riesgo de recurrencia, pero existen remisiones en el largo plazo (Senf, P., 2013).
- Lesiones estructurales como las malformaciones del desarrollo cortical tienen un elevado riesgo de crisis en el largo plazo (Rowland,NC.,2012), en otras como los cavernomas luego de operados las crisis pueden recidivar en plazos variables (Kim,W.,2011).
- Luego de cirugía del lóbulo Temporal, el 54% de las recidivas ocurren en los primeros 6 meses, mientras que sólo el 2% luego de 4 años (Goellner, E.,2013).
- Niños libres de crisis y sin medicación por 5 años tuvieron una recurrencia del 6 %. No hay datos de los que estuvieron más de 10 años libres de crisis (Berg,AT, 2011).

The course of childhood-onset epilepsy over the first two decades: A prospective, longitudinal study

*Ahona T. Berg and Karen Rychlik

Epilepsia, 56(1):49–60, 2015
doi: 10.1111/epi.12862

Ahona T. Berg is a Research Professor in the Department of Pediatrics Northwestern Feinberg School of Medicine and the Epilepsy Center of Lurie Children's Hospital in Chicago, Illinois.

Summary:

Objective: Determine frequency of remissions, relapses, and pharmacoresistance over two decades. Develop a composite measure of seizure control over that time.

Methods: Community-based cohort of children with newly diagnosed epilepsy prospectively followed for up to 21 years with frequent calls and periodic medical record review. Multiple periods of 1-, 2-, 5-, and 10-year remission with subsequent relapses were recorded. Other outcomes included pharmacoresistance (failure of two adequately used drugs), early remission and early pharmacoresistance by 2 years, and complete remission at last contact (CRLC; ≥ 2 years both seizure- and drug-free at last contact). A composite summary of seizure course was created with eight categories ranging from early sustained remission and CRLC (best) to never achieving a 1-year remission (worst).

Results: Five hundred sixteen of 613 participants were followed ≥ 10 years. An initial 1-, 2-, 5-, and 10-year remission occurred, respectively, in 90%, 85%, 69%, and 61%. Relapses followed in 43%, 41%, 39%, and 19%, respectively. Repeated remission after relapse was common. Up to seven 1-year, five 2-year and 5-year, and two 10-year remissions were recorded per participant. Pharmacoresistance at any time, early pharmacoresistance (≤ 2 years), early remission, and CRLC occurred in 118 (22.9%), 78 (15.6%), 380 (74.0%), and 311 (60.3%). Composite outcomes were early sustained remission (ESR; CRLC [N = 172, 33%]; later but then sustained remission with CRLC [N = 51, 10%]; one [N = 41, 12%] or more [N = 37, 7%] remission–relapse episodes but then CRLC); various non-CRLC outcomes (N = 179, 35%); and never achieved 1-year remission (N = 56, 5%). These patterns varied across groups defined by epilepsy type and presence of brain insults or neurodisability (p < 0.0001).

Significance: The seizure prognosis of pediatric epilepsy is highly variable. Most patients follow complex courses not easily summarized by remission status at the end of a period of follow-up. These complexities may facilitate efforts to understand the impact epilepsy has on young people entering adulthood.

KEY WORDS: Prognosis, Remission, Longitudinal study, Children, Epilepsy.

- En 613 niños seguidos desde el diagnóstico de epilepsia durante 10 años o más.
- El 81% tuvo una remisión de 5 años, pero al final del seguimiento el 60% estaba libre de crisis.
- Concluyeron que aún en un seguimiento de 20 años puede ser insuficiente para tener el pronóstico completo de las crisis a lo largo de la vida, aunque puede permitirnos mejorar nuestra comprensión del mismo y ver que sucede en la madurez.
- No obstante pueden perderse en el pronóstico los estudios basados en los diagnósticos y tratamientos contemporáneos.

(Berg y col,2015)

Información imperfecta

- La nueva definición brinda relevancia al proceso clínico del diagnóstico.
- Requiere capacidades de interpretación y diagnóstico con las cuales no siempre se cuenta, especialmente en el nivel primario de atención.
- Existe incertidumbre sobre la potencial epileptógenicidad de lesiones en la RNM.
- Sin registro con VIDEO-EEG, hay situaciones en que el diagnóstico de crisis epiléptica permanece incierto.
- En ausencia de información segura la expresión "Usted probablemente tenga epilepsia", se prefirió a usar el concepto de "epilepsia probable".

CONSECUENCIAS DE LA NUEVA DEFINICIÓN

- **Para el paciente:**
- Puede mejorar el pronóstico.
- Permitiría prevenir injurias físicas innecesarias y las consecuencias sociales de la recurrencia de crisis.
- Daría la oportunidad de intervenciones que modifican la enfermedad previniendo la progresión de la epilepsia y sus comorbilidades.

CONSECUENCIAS DE LA NUEVA DEFINICIÓN

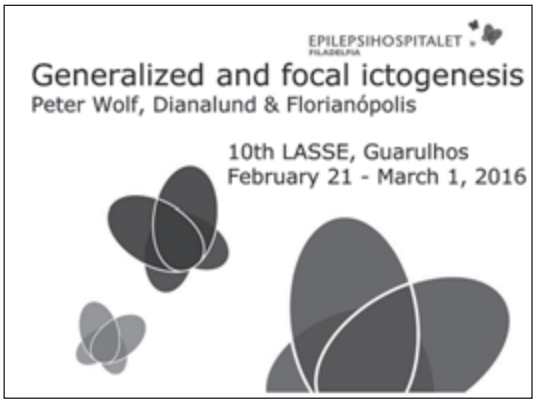
- ¿Como modificaría la prevalencia?
- Correcto diagnóstico.
- Inclusión de crisis reflejas.
- Resolución de la epilepsia.
- Consecuencias económicas y legales.

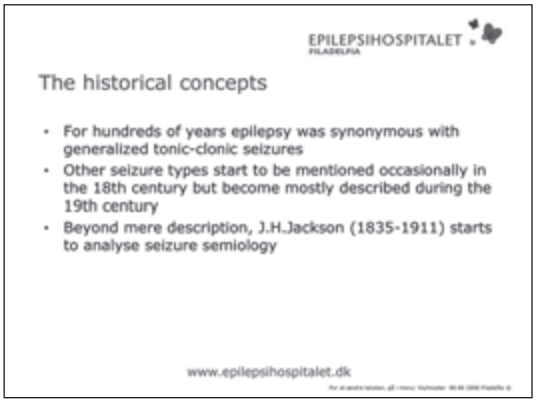
CONCLUSIONES

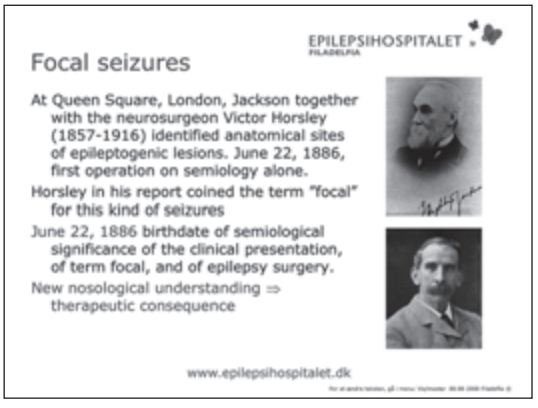
- Se incluye como epilepsia a quienes con una crisis única presenten otros factores que se asocian a un alto riesgo de recurrencia de crisis, alrededor del 60%.
- Se conoce este riesgo en pacientes que han tenido un ACV, una infección del SNC, TEC y síndromes epilépticos específicos.
- Se incluyen las crisis reflejas con el mismo valor que las no provocadas.
- La epilepsia no es necesariamente una condición para toda la vida y se considera resuelta si la persona ha estado libre de crisis por 10 años y 5 años sin FAE.
- Los estudios de riesgo de recurrencia son pocos. Se debería incentivar más estudios de recurrencia en etiologías específicas.

Peter Wolf (Denmark)

FOCAL AND GENERALIZED ICTOGENESIS







"Generalized"

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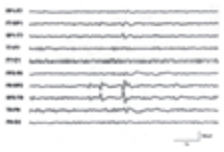
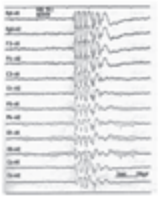
- The term generalized in its present use is defined by the EEG





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Concepts of ictogenesis: 1970 Classification

- Generalized szs: "Clinical features do not include any sign or symptom referable to an anatomical and/or functional system localized in one hemisphere. … The responsible neuronal discharge takes place, if not throughout the entire grey matter, then at least in the greater part of it and simultaneously on both sides."
- Note: the definition of generalized seizures is negative!

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The common view of generalized epilepsy

- "Generalized seizures are commonly thought to involve the entire brain homogeneously" (*McNally KA, Blumenfeld H Epilepsy & Behavior 2004; 5:3-12*)

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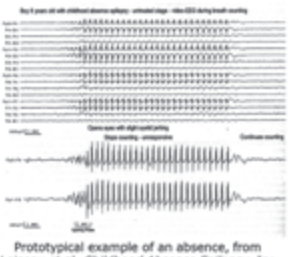
Generalised SW discharges typically are symmetric, synchronous and widespread -

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

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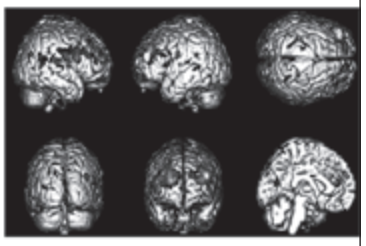
JME:
Global ⇑ of FMZ binding ($GABA_A$ receptors), especially in dorso-lateral pre-frontal cortex -

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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Morphological findings

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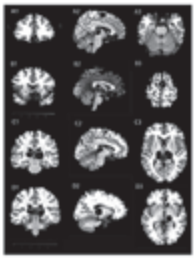
Cao et al (2013): meta-analysis of 7 studies of JME with voxel-based morphometry:

- Gray matter density increased in medial frontal and anterior cingulate gyrus, reduced in thalamus



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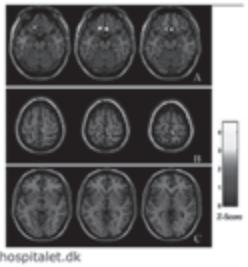
Voxel-based morphometry: JME, absence epilepsy, healthy controls: *Betting et al NeuroImage 2006; 32:498-502*

- A: JME pts vs ctrls: fronto-basal increased GMD
- B: AE pts vs ctrls: fronto-dorsal – parietal > GMD
- C: all patients with absences (JME + AE) vs ctrls: GMD increased in anterior thalamus



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"pseudofocal" discharge

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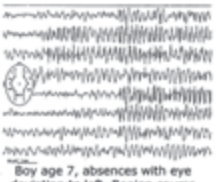
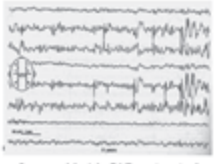


Boy age 7, absences with eye deviation to left. Benign course.



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

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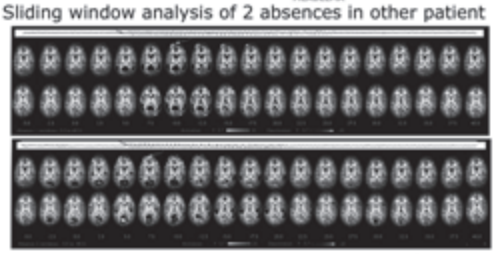
Sliding window analysis of 2 absences in other patient



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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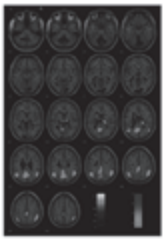
Benuzzi F et al, Epilepsia 2012; 53: 622-630: Changes of BOLD signal before and during absences: 15 Pat

<u>At onset of SW,</u> bilateral

- BOLD signal increase in
  - Thalamus
  - Cerebellum
  - anterior gyrus cinguli
- BOLD signal decrease in
  - medial prefrontal cortex
  - lateral parietal cortex
  - medial/posterior gyrus cinguli
  - Praecuneus
- (after preceding increase)



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Conclusion at present

- "Generalized" SW and absences are generated as resonance phenomena in a circuit comprising parts of the frontal, parietal and occipital cortex, default mode network (DMN) and anterior thalamus
- Triggered off from variable cortical loci (intraindividually consistent?)
- Precuneus the leading structure
- Pathological deactivation of the DMN explains absence?

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Reflex epileptic mechanisms in IGEs

- Photosensitivity
- Eye closure sensitivity
- Oro-facial reflex myocloni (with talking, reading)
- Praxis induction

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TV-induced seizures: photoparoxysmal EEG response

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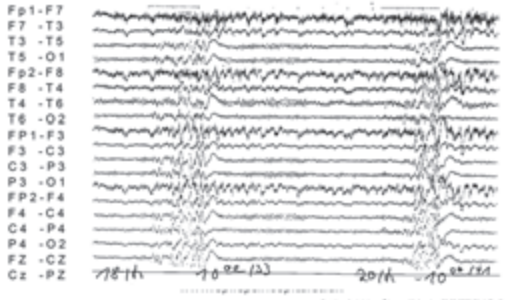

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DOI: 10.1093/brain/awg109 *Brain* (2003), **126**, 1164–1172

Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception?

J. Parra,[1] S. N. Kalitzin,[1] J. Iriarte,[2] W. Blanes,[1] D. N. Velis[1] and F. H. Lopes da Silva[1]

MEG: "Enhancement of phase synchrony in the γ band (30-120 hz), harmonically related to the frequency of stimulation, preceded those stimulation trials that evolved into PPRs, and differed significantly from that encountered in trials not followed by PPR or in control subjects":
"a pathological deviation of normally occurring synchronization of γ oscillations underlying perceptional processes mediates the epileptic transition in PSE".

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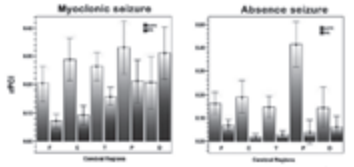
rPCI = relative phase clustering index



Red: stimulation with photoparoxysmal response (PPR)
Blue: stimulation without PPR

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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 (MEG)

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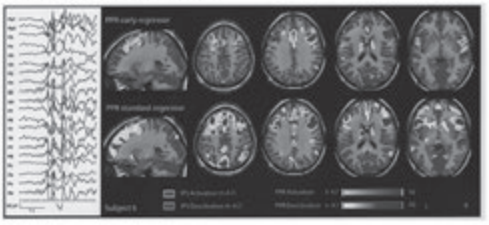
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2 years. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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Authors' conclusion

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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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Eye closure sensitivity:

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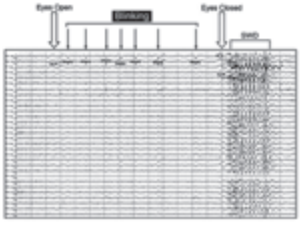
Vaudano et al Ann Neurol 2014; 76:412-27
Patients with Jeavons syndrome, all photosensitive



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Eye lid myoclonia with absence
Vaudano et al, EEG-fMRI

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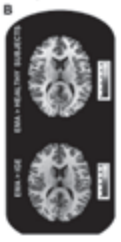
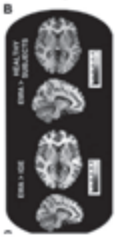
At eye closure



Following 3 sec



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Praxis induction

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- Precipitation 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 – 30% 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

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Connectivity in JME

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BRAIN

Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study

Christian Vollmar,[1,2,3] Jonathan O'Muircheartaigh,[4] Gareth J. Barker,[5] Mark R. Symms,[1,2] Pamela Thompson,[1,2] Veena Kumari,[6] John S. Duncan,[1,2] Dieter Jane,[7] Mark P. Richardson[3] and Matthias J. Koepp[1,2]

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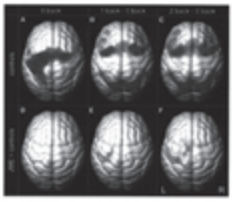
"Working memory paradigm": a spot appears in random sequence in one of 4 fields: where is it now? where was it last time? where the time before?

The more difficult the task, the more primary motor cortex and supplementary motor area become co-activated.
30 JME vs. 30 controls.
Motor response
Network working memory
JME minus controls



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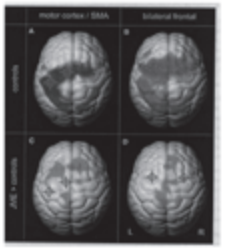
Vollmar et al. Motor system hyperconnectivity in JME: a cognitive fMRI study. Brain 2011; 134:1710-1719



Study: fMRI with an executive frontal lobe paradigm

Findings:

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

C+D: increased connectivity in JME patients

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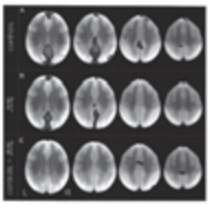
Concomitant deactivion of default mode network (frontopolar and præcuneus)

JME patients deactivate less

"An 'overload' of the task-positive cognitive network during a highly demanding task, together with impaired deactivation of the default mode network, could lead to hyperexcitability and hyper-connectivity across systems, including the motor cortex, and cause myoclonic jerks".



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Conclusion

- Pathological activity in a functional anatomical system normally serving physiological function (complex visuo-motor coordination)
- = the probable basis for praxis induction

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Conclusion on IGE: areas involved in corticothalamic and intracortical networks

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

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Epilepsia, 53(5):771–778, 2012
doi: 10.1111/j.1528-1167.2012.03462.x

CRITICAL REVIEW AND INVITED COMMENTARY

The system epilepsies: A pathophysiological hypothesis

*Giuliano Avanzini, †Paolo Manganotti, ‡Stefano Meletti, §Solomon L. Moshé, *Francesco Panzica, ¶Peter Wolf, and **Giuseppe Capovilla

*Department of Neurophysiology, IRCCS Foundation Neurological Institute "Carlo Besta," Milano, Italy; †Department of Neurological, Neuropsychological, Morphological and Movements Sciences, University of Verona, Verona, Italy; ‡Department of Neuroscience, University of Modena and Reggio Emilia, Modena, Italy; §Saul R. Korey Department of Neurology, Dominick P. Purpura Department of Neuroscience and Department of Pediatrics, Laboratory of Developmental Epilepsy, Montefiore/Einstein Epilepsy Management Center, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, U.S.A.; ¶The Danish Epilepsy Center, Dianalund, Denmark; and **Epilepsy Center, Department of Child Neuropsychiatry, C. Poma Hospital, Mantova, Italy

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The new view of IGEs: system epilepsies

- Epilepsies, usually idiopathic, where the ictogenic mechanisms use pre-existing functional anatomical networks that normally subserve physiological function.
- Well-demonstrated by reflex epileptic seizures
- *Avanzini G, Manganotti P, Meletti S. Moshé SL, Panzica F, Wolf P, Capovilla G. The system epilepsies: a patho-physiological hypothesis. EPILEPSIA 2012;53:771-778*

Examples of neurological system disorders?

Motoneuron disease – Polyneuropathies - Myasthenia gravis

System epilepsies

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Development of view of 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 tools of investigation.
- 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) and PET
- 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
  - triggered by EEG

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Focal ictogenic networks

- The networks around focal epileptic lesions are quite widespread
- It is not yet quite clear to what extent they represent excitation and to what extent, inhibition
- Inhibition contributes to synchronisation and is, thus, an important factor of ictogenesis

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fMRI group analysis of 32 TLE pts. 3,5 a.7 sec after interictal discharge

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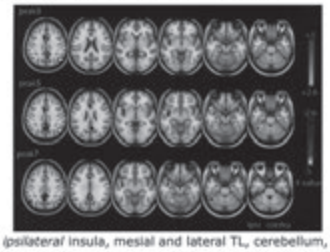

Activation: *ipsilateral* insula, mesial and lateral TL, cerebellum, *bilateral* mid-cingulate gyrus
Deactivation: *bilat.* inferior parietal lobules, posterior cingulate gyrus, precuneus, *contralat. post.* temp. cortex *Fahoum et al Epilepsia 2012*

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14 pts with frontal lobe epilepsy

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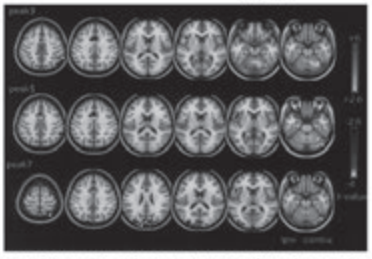

Activation: *bilateral* cingulate gyrus, *ipsilat* frontal operculum,medial thalamus, internal capsule, *contralat* cerebellum
Deactivation: *bilateral* cuneus, *contralat* inf and sup parietal lobules

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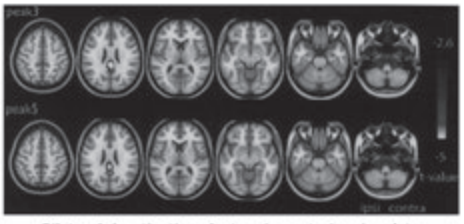
20 pts with posterior cortical epilepsies



Bilateral deactivation clusters in posterior cingulate cortex and precuneus

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Interictal connectivity in focal epilepsies

- Mesial temporal lobe epilepsy which is little prone to exogenous influences shows *decreased* connectivity with functionally related regions (prefrontal cortex, contralateral MTL, default mode network, brain stem): *Pittau et al, EPILEPSIA 2012; 53: 1013-1023 (EEG-fMRI study)*
- Opposed to *increased* functional connectivity in JME

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Pittau et al findings

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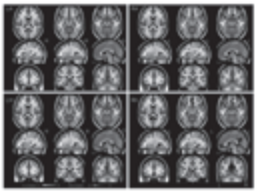
- For RA and RH, functional connectivity is significantly decreased in the brain areas of the DMN, the ventromesial limbic prefrontal regions, and the contralateral mesial temporal structures;
- For LA and LH, a significant decreased connectivity is present in DMN and contralateral hippocampus. Additional decreased connectivity is found between LA and pons and between LH and ventromesial limbic prefrontal structures.



Subtraction TLE pts fom healthy controls

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Voets et al (Montreal): study using diffusion tensor imaging

Structural substrates for resting network disruption in temporal lobe epilepsy

"Patients showed altered (typically reduced) functional connectivity between the hippocampus, anterior temporal, precentral cortices and the default mode and sensorimotor networks"

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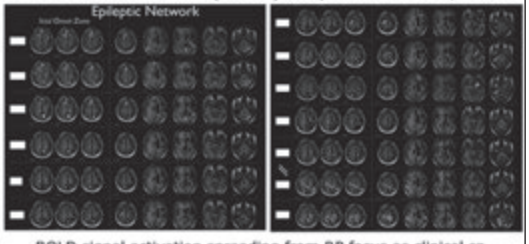
Ictal: Donaire et al (2009) sequential fMRI,rPLsz



BOLD signal activation spreading from RP focus as clinical sz spreads; concomitant contralateral BOLD signal decrease.

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Conclusion on focal lesional epilepsies

- Network disease, too
- Physiological functional anatomic networks used for seizure spread.
- Seizure generation in individual networks around the epileptic lesion
- Built upon existing pathways including long-loop connections

How are the focal ictogenic networks established?

Possibility for prospective connectivity studies after brain trauma

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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
- 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

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Ictogenesis in idiopathic LREs

Components

- Somatosensory system (contralateral spikes evoked by tapping or electrical stimulation, Manganotti et al 1998)
- Onset in sensory cortex ⇒ motor cortex? (Kellaway 2000)
- Close relation to sleep-regulating thalamic nuclei: high correlation of CT spikes with spindle avtivity (Nobili et al 1999)
- Age-dependence: functional instability of immature systems in the developing brain (Avanzini et al 2012)

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Conclusion

Ictogenesis of focal seizures in Rolandic epilepsy totally different from symptomatic focal epilepsies

Uses physiological functional anatomical networks

Idiopathic LREs are "system epilepsies" (Avanzini et al 2012)

Examples of neurological system disorders

Motoneuron disease

Polyneuropathies

Myasthenia gravis

System epilepsies

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Ictogenesis in focal and system epilepsies

Focal epilepsies

- Onset defined by focus
- Onset, often also evolution restricted to one hemisph.
- Pathogenic networks individual, fundamentally de novo, although pre-existent circuits may be recruited

System epilepsies

- Possible trigger zones variable within network
- Involvement of distributed bilateral (symmetric or asymmetric) selective cortical-subcortical networks
- Using pre-existent , syndrome-specific physiological systems

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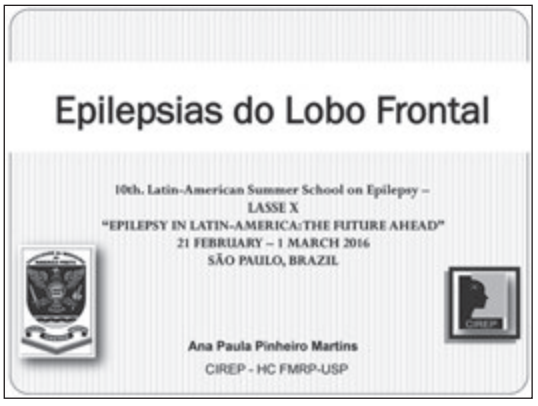
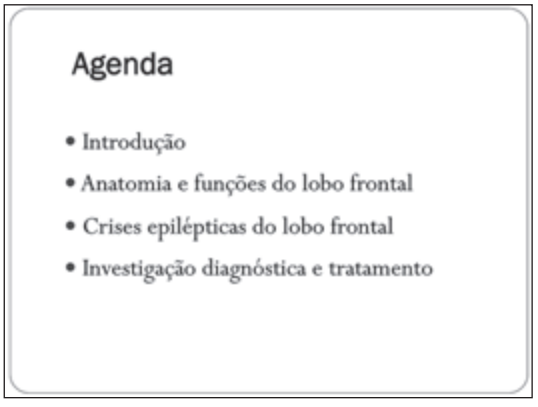
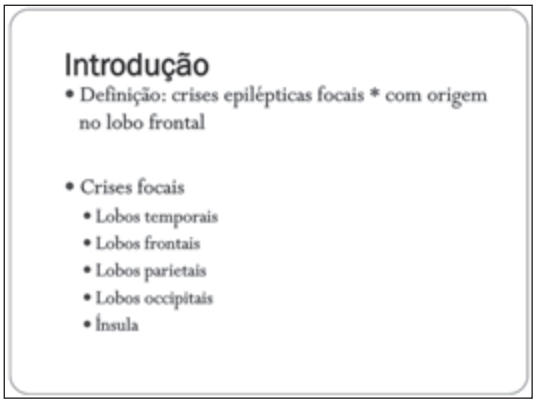
Ana Paula Martins (Brazil)

FRONTAL LOBE EPILEPSIES







Introdução

"A grande desafiadora"

- Diversidade semiológica e neurofisiológica (EEG)
  - Manifestações motoras primárias e complexas
  - Breve duração, *clusters*
  - Relação com o sono
  - Comprometimento da consciência
- Diferentes etiologias
- Baixa qualidade de vida

Introdução

- Etiologias semelhantes: temporais neocorticais, frontais e do córtex posterior (Elger et al, 2001; Dalmagro et al., 2005)
- Análise histopatológica de 110 casos (Pinheiro-Martins, 2014):
  - displasias corticais focais (48%)
  - lesões sequelares (21%)
  - neoplasias (21%)
  - esclerose tuberosa (7%)
  - malformações vasculares (3%)

Introdução

- Baixa qualidade de vida
  - Morbimortalidade
    - Generalização mais frequente
    - Traumas
    - Qualidade de sono
  - Estigma
  - Prejuízos cognitivos

Classificando crises epilépticas lobo frontal

ILAE, 1989

- (1) Córtex motor primário
- (2) Área motora suplementar
- (3) Frontopolar anterior
- (4) Orbitofrontal
- (5) Dorsolateral
- (6) Opercular
- (7) Cíngulo

Salanova et al, 1995

- (1) Motoras focais
- (2) Área motora suplementar
- (3) Psicomotoras

Mas...

... como classificar?
De onde vêm?

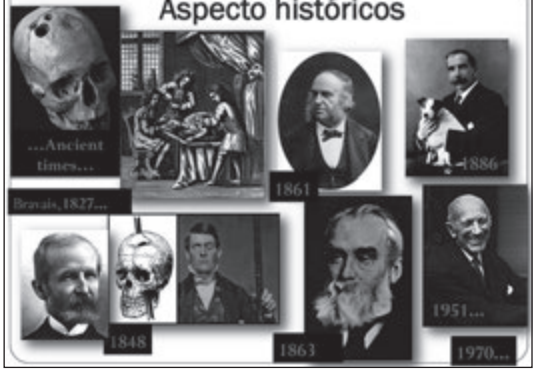
Who in the world am I?
Ah, that's the great puzzle.

- Gelásticas, dacrísticas
- Alucinações complexas
  - Visuais, no lobo frontal?
- Experiência/expressões de emoções
  - Medo? Alegria?

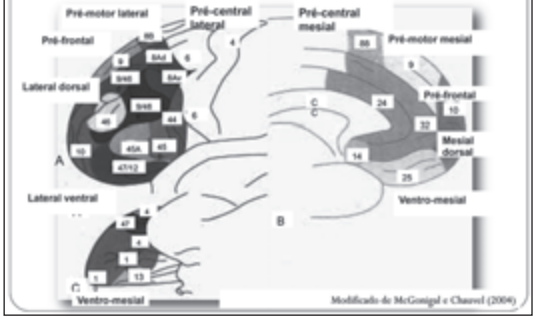
Alice in the Wonderland Syndrome: metamorphopsia (Zwijnenburg et al, 2001)

Ilustração de John Tenniel, 1865

Aspecto históricos



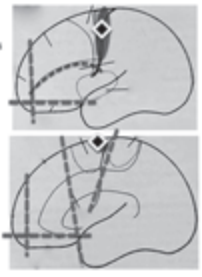
Lobo frontal: anatomia e funções



Modificado de McGonigal e Chauvel (2004)

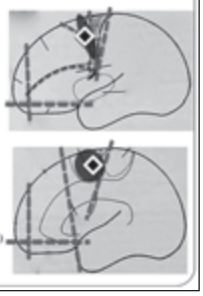
Lobo frontal: anatomia e funções

- **Área motora primária**
  - Giro pré-central e porções posteriores dos giros frontais médio, superior e inferior
  - Aferências sensitivas gerais, visuais, auditivas e talâmicas
  - Eferências córtico-espinhais, córtico-corticais e subcorticais
  - Estimulação: contrações tônicas/clônicas contralaterais



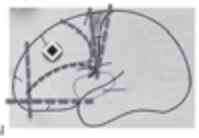
Lobo frontal: anatomia e funções

- **Área motora suplementar (SMA)**
  - Área pré-SMA
  - SMA propriamente dita
  - Estimulação
    - SMA: movimentos tônicos ipsi, contra ou bilaterais, respostas sensoriais ipsi ou contralaterais
    - Pré-SMA: inibe respostas motoras voluntárias (Luis et al, 1994; Rizzolatti et al, 1996)



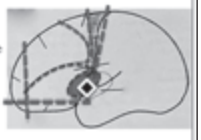
Lobo frontal: anatomia e funções

- **Área de campo visual do lobo frontal**
  - Movimento ocular conjugado, sacádico, contralateral
  - Aferências:
    - Córtex occipital e tálamo dorsal
  - Eferências:
    - Colículo superior e córtex pré-occipital



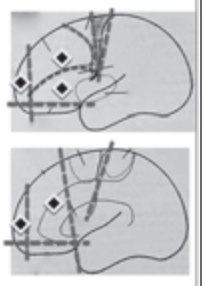
Lobo frontal: anatomia e funções

- **Área da expressão da linguagem**
  - Área de Broca, *pars opercularis* e *triangularis* do giro frontal inferior do hemisfério dominante para a linguagem
  - Conexões:
    - Área motora primária (língua e laringe)
    - Área de compreensão da linguagem
  - Estimulação: interrompe a expressão com compreensão perfeita da linguagem (Lesser et al, 1984; Schaffler et al, 2004)



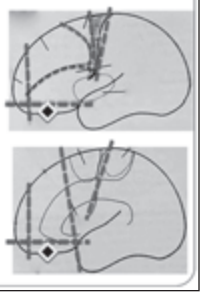
Lobo frontal: anatomia e funções

- **Córtex pré-frontal**
  - Áreas de associação heteromodal: regiões dorsolateral, ventrolateral e frontopolar
  - *Working memory*
    (Fletcher & Henson, 2001; Goethals et al, 2004)
  - Conexões: áreas límbicas e para-límbicas
  - Processamento de informações sensoriais
    (Damasio et al, 1995)
  - Planejamento, espontaneidade, iniciativa, comportamento social



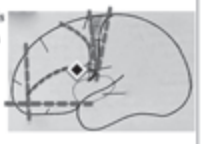
Lobo frontal: anatomia e funções

- **Córtex orbitofrontal**
  - Integração sensorial
  - Integração visceromotora (hipotálamo)
    (Damasio et al, 1990; Ongur & Price, 2000)
  - Comportamento
  - Expressão de emoções

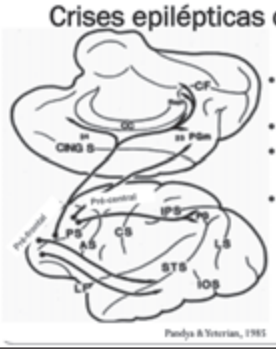


Lobo frontal: anatomia e funções

- **Áreas motoras negativas**
  - Aferências: áreas motoras pré-frontais
    - Oposição à execução dos movimentos
  - Estimulação inibe:
    - Movimentos voluntários distais
    - Movimentos da faringe e da língua



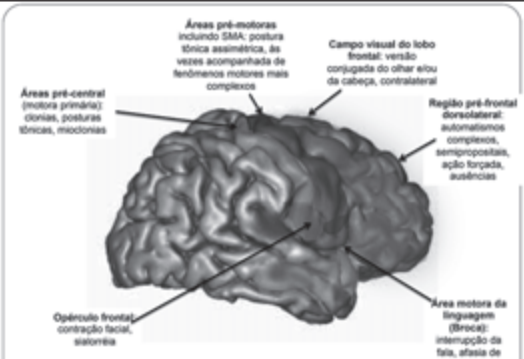
Crises epilépticas do lobo frontal



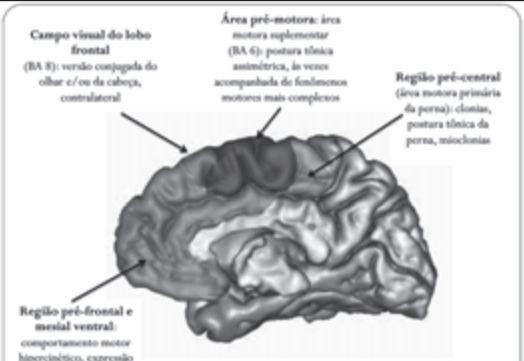
- Sinais e sintomas: rápida sucessão ou simultaneamente
- Complexos e súbitos
- Ativação de diferentes estruturas dentro de sistema dinâmico
- Padrões de propagação: comportamentos bizarros, atípicos, com EEG normal
  (Bautista et al, 1998)

Crises epilépticas do lobo frontal

- Crise epiléptica?
- Genuinamente oriunda lobo frontal?
- Identificação da zona de início ictal no lobo frontal
- Diagnóstico diferencial
  - 1981:"distonia paroxística noturna" (Lugaresi & Cirignotta, 1981)
  - 1992: eventos reconhecidos como crises epilépticas (Meierkord et al, 1992)
  - Transtornos psiquiátricos
  - Distúrbios do sono

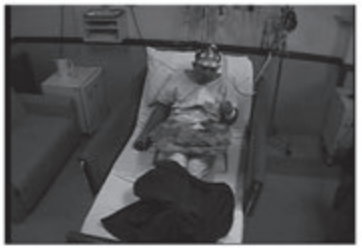


Modificado de McGonigal e Chauvel (2004)



Modificado de McGonigal e Chauvel (2004)

Região pré-central
(área motora primária da perna)



Área pré-motora (SMA)

Postura tônica assimétrica

SMA → Pré-frontal/ventro-mesial
crise tônica → hipercinética

SMA → Pré-frontal/ventro-mesial
crise tônica → hipercinética

Funções Cognitivas & Lobo Frontal

Teste de Fluência Verbal	Capacidade de produção de palavras sob condições delimitadas
Teste de Stroop	Atenção seletiva e controle de respostas irrelevantes (capacidade de controle inibitório)
Teste de Trilhas	Velocidade de varredura visual, flexibilidade mental, atenção sustentada, atenção alternada e função motora
Wisconsin Card Sorting	Habilidades de raciocinio abstrato e de mudar estratégias cognitivas em resposta às mudança do ambiente

Funções Cognitivas & Epilepsias do Lobo Frontal

Síndrome do Lobo Frontal

- Alterações globais da personalidade e funções cognitivas associadas com injúrias no lobo frontal
- Casos lesionais
- Phineas Gage, injúria frontal esquerda em 1848

Funções Cognitivas & Epilepsias do Lobo Frontal

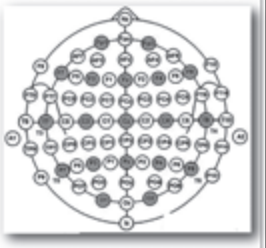
- Hospital de Bicêtre, *Monsieur Leborgne*
  - Crises epilépticas e distúrbio de linguagem durante 21 anos
  - Só conseguia pronunciar a sílaba "tan"
- Paul Broca (1861)
  - Lesão "na terceira circunvolução do hemisfério esquerdo"
  - Outros casos com distúrbio de linguagem foram estudados por Broca e seus colaboradores

Funções Cognitivas & Epilepsias do Lobo Frontal

- Paciente K.M. (Penfield, final dos anos 1930)
  - Lesão frontal bilateral, alteração comportamental e epilepsia
  - Lobectomia frontopolar bilateral: controle de crises e "melhora" do comportamento
- Brenda Milner (anos 1950):
  - Sem significativa alteração das funções cognitivas (Milner, 1998)
- Egas Moniz e colaboradores (1940):
  - Leucotomia pré-frontal como tratamento para distúrbios psiquiátricos
  - Até 50% dos desenvolviam sintomas catatônicos prolongados e mutismo

Diagnóstico

- Anamnese
- EEG
- Semiologia
- Vídeo-EEG
- Neuroimagem



Diagnóstico - Eletrencefalografia

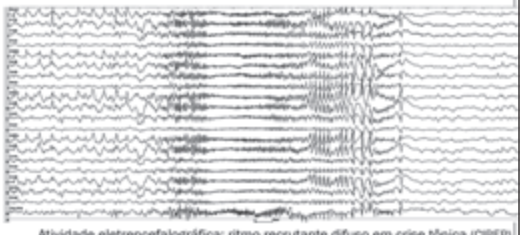
- Interictal
  - Limitação do EEG (Bautista et al, 1998)
  - Até 40% dos casos sem anormalidade no EEG de escalpo (Kellinghaus & Lüders, 2004)
  - Paroxismos multifocais, campo amplo
- Ictal
  - Artefatos obscurecem o traçado: 20% dos casos (Quesney, 1992; Lankowitz et al, 1995)
  - 30-40%: atividade localizada (Swarts et al, 1991; Blume & Oliver, 1996)
  - Convexidade versus face mesial e região frontobasal

* Eletrodos subdurais: paroxismos epileptiformes de alta voltagem, atividade rapidamente disseminada e registrada por vários eletrodos simultaneamente

Diagnóstico - Eletrencefalografia

- Eletrocorticografia
  - Localização da zona de início ictal:
    - Satisfatória em 50 a 80% dos pacientes submetidos à avaliação invasiva (Salanova et al, 1993; Tocsik et al, 1997; Blume et al, 2001)
  - 80% das crises:
    - Propagação contígua
    - Mais rápida nas crises iniciadas na superfície mesial do que nas regiões orbitais e dorsolaterais do lobo frontal (Blume et al, 2001)

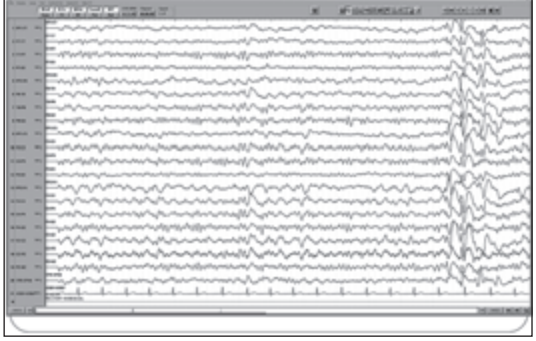
Diagnóstico - Eletrencefalografia



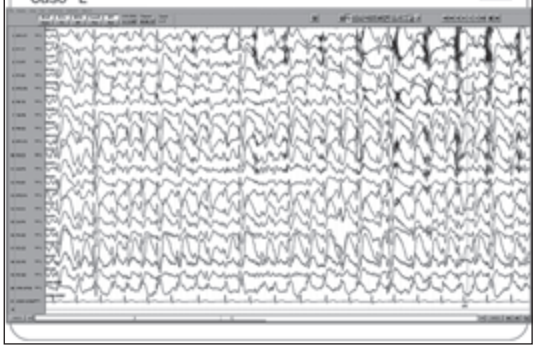
Atividade eletrencefalográfica: ritmo recrutante difuso em crise tônica (CIREP)

Gastaut e Fischer-Williams (1959)

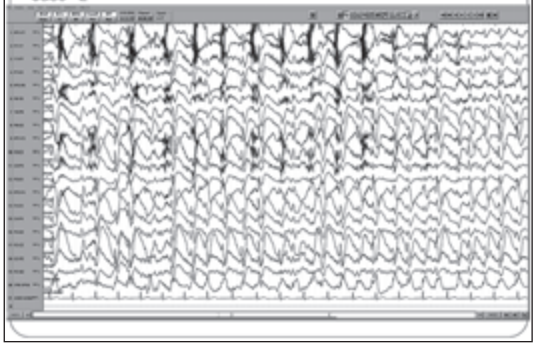
Diagnóstico – Eletrencefalografia
Caso "L"



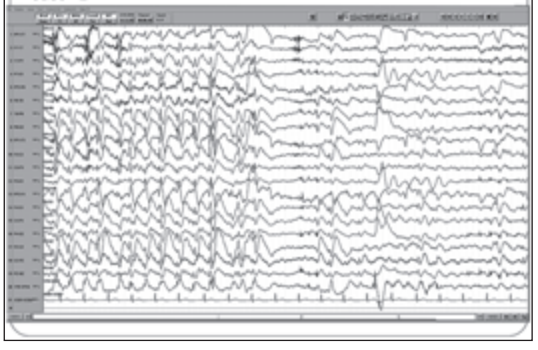
Diagnóstico – Eletrencefalografia
Caso "L"



Diagnóstico – Eletrencefalografia
Caso "L"

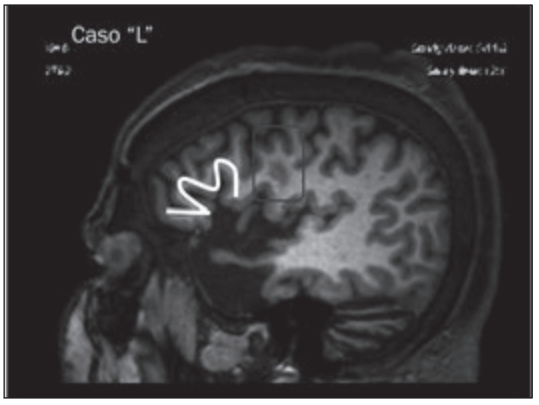


Diagnóstico – Eletrencefalografia
Caso "L"



Diagnóstico - Neuroimagem

- Estrutural
  - Ressonância magnética do encéfalo (MRI)
  - 50% dos pacientes com FLE: lesões observadas na MRI
  - Inspeção de anormalidades pré e após tratamento cirúrgico
- Funcional
  - *fonctional*-MRI: córtex eloquente
  - PET e SPECT: alterações do metabolismo de glicose e perfusão sanguínea
    - Zona de déficit funcional: SPECT interictal e PET
    - Zona de início ictal: SPECT ictal
  - Marcadores: Tc99m no SPECT e FDG no PET
  - Valor diagnóstico do SPECT é maior na FLE do que na TLE (Spencer et al, 1995)



Tratamento

- Epilepsia focal farmacorresistente: 0,15-0,2% dos pacientes (Forsgren et al, 2005)
- Epilepsias controláveis com AEDs: 63,9% (Picot et al, 2008)
  - Farmacorresistência nas epilepsias focais
    - (1) Uma crise/mês em 18 meses (Berg et al, 2001): 26%
    - (2) Uma crise por ano (Loiseau & Jallon, 1995): 17%

Tratamento

- Farmacorresistência (Picot et al, 2008)
  - 57.1% farmacorresistência, duas AED (1ª linha)
  - 23.8% três AED
  - 16.7% quatro ou mais AED

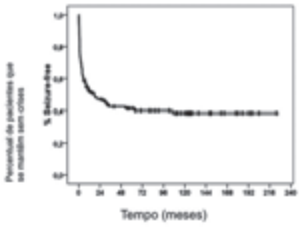
Série de 110 pacientes com FLE cirurgicamente tratados (CIREP)			
	min	max	med
AED no último retorno	0	4	1.7
AED previamente utilizados com ou sem farmacorresistência	1	7	3.5
AED quando da cirurgia	1	5	2.4

(Pinheiro-Martins, 2014)

Tratamento cirúrgico

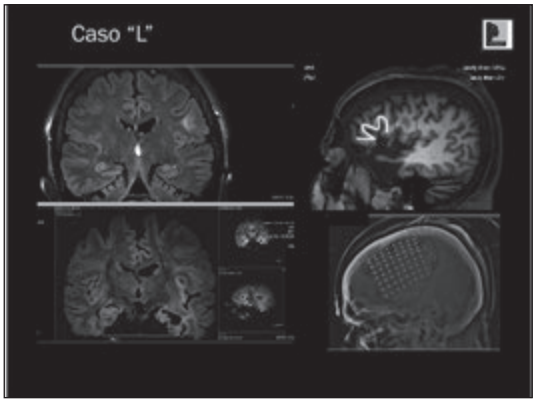
- Desconexão ou ressecção da zona epileptogênica (Rosenow & Lüders, 2001)
- Controle de crises após cirurgia:
  - 55–70%: lobectomia temporal
  - 30–50%: ressecções extra-temporais
- Pacientes com FLE livres de crises epilépticas após o tratamento cirúrgico: 13%-80% (Talairach et al, 1992; Wieser & Hajek, 1995; Mosewich et al, 2000; Jobst et al,2000; Jansky et al, 2000; Ferrier et al, 2001; Schramm et al, 2002; Zaatreh et al, 2002; Chung et al, 2005; Lee et al, 2008; Jeha et al, 2007; Simasathien et al, 2013)

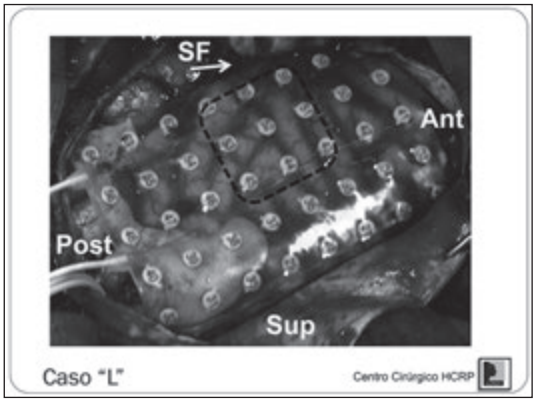
Tratamento cirúrgico

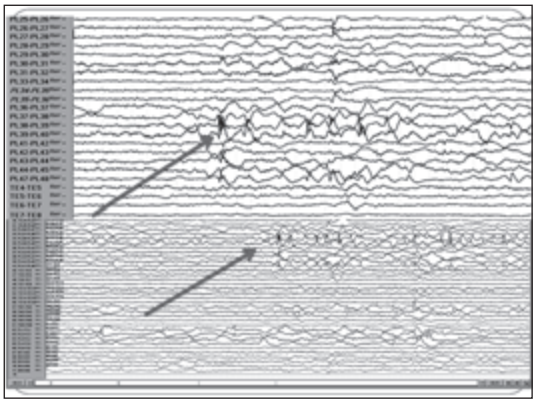


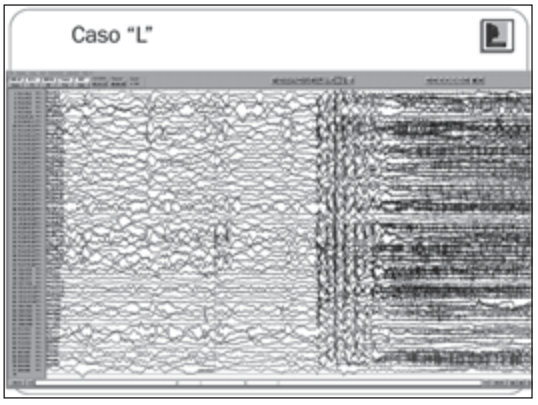
- 110 pacientes com FLE farmacorresistente, Brasil
- 41% de pacientes livres de crises
- 7,9 (0,5-18,6) anos de seguimento

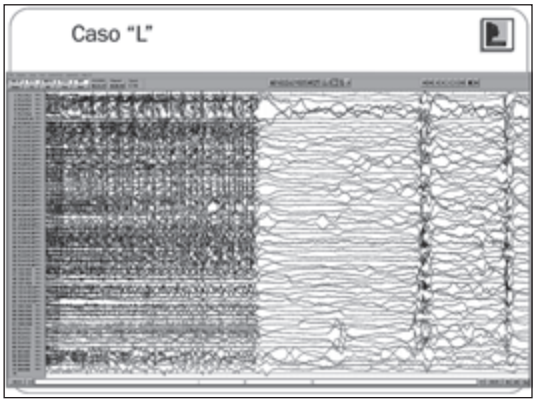
Palmeiro-Martins et al, em preparação

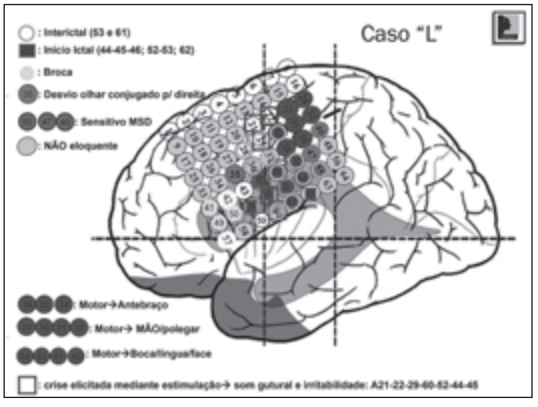


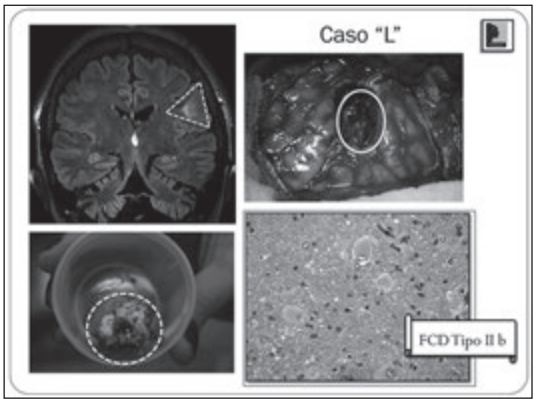




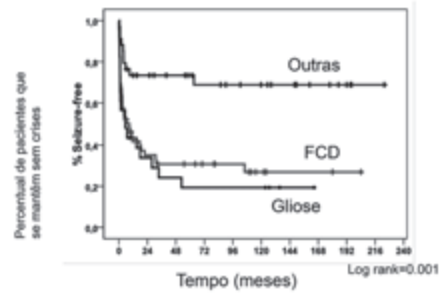

Caso "L"


Caso "L"


Caso "L"
: Interictal (53 e 61)
: Início Ictal (44-45-46; 52-53; 62)
: Broca
: Desvio olhar conjugado p/ direita
: Sensitivo MSD
: NÃO eloquente
: Motor→Antebraço
: Motor→ MÃO/polegar
: Motor→Boca/língua/face
crise elicitada mediante estimulação→ som gutural e irritabilidade: A21-22-29-60-52-44-45

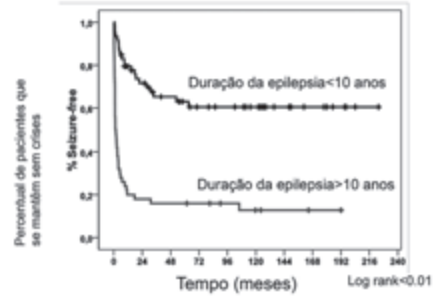

Caso "L"
FCD Tipo II b

Tratamento cirúrgico



Palheiro-Martins et al, em preparação

Tratamento cirúrgico



Palheiro-Martins et al, em preparação

Preditores de tratamento cirúrgico satisfatório

Regressão de Cox

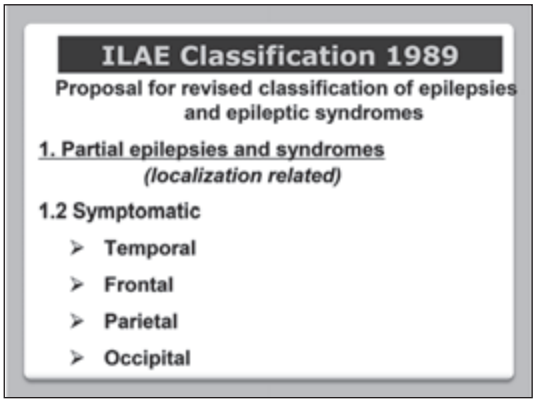
Variável	H.R.	(IC: 95%)	*p*
Tempo de duração da epilepsia	1.08	1.12-1.39	0.002*
Idade (quando da cirurgia)	1.05	1.02-1.08	0.003*
Intercorrências obstétricas/perinatais	1.68	0.89-3.20	0.110
Atividade de base anormal no EEG interictal	1.93	1.07- 3.51	0.030*
Atividade ictal difusa no EEG	1.82	1.02-3.24	0.041
MRI sem anormalidades	1.92	0.85-4.36	0.116
Córtex eloquente (linguagem) coincidente com lesão epileptogenica na MRI	2.20	1.17-4.14	0.014*
Tipo de ressecção cirúrgica: lesionectomia ou corticectomia versus lobectomias/hemisferotomias	1.12	0.62-2.03	0.701
Crises durante o primeiro mês após a cirurgia	6.61	3.55-12.30	<0.0001*
Neoplasia do SNC	1.25	0.29-5.40	0.764
Displasia cortical focal	3.91	1.14-13.40	0.030*
Anatomopatológico: gliose/lesões sequelares	5.75	1.49-22.23	0.011*

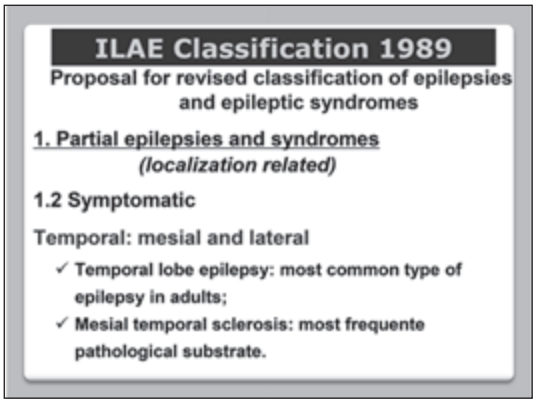
Mensagens

- O que é passível de intervenção?
  - "Tempo de Duração da Epilepsia"
  - Diagnóstico precoce
  - Tratamento é consequência
- Diagnóstico é o desafio:
  - Anamnese
  - Semiologia
  - Ouvir, observar, estudar

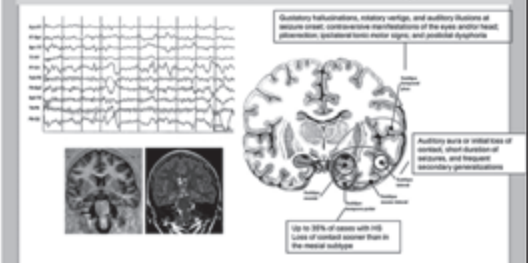
Elza Márcia Yacubian (Brazil)

TEMPORAL LOBE EPILEPSIES





SUBTYPES OF TEMPORAL LOBE EPILEPSY- depth EEG recordings



Kahane & Bartolomei. Epilepsia 2010;51(Suppl.1):S59-62

Temporal lobe epilepsies

MESIAL SUBTYPE

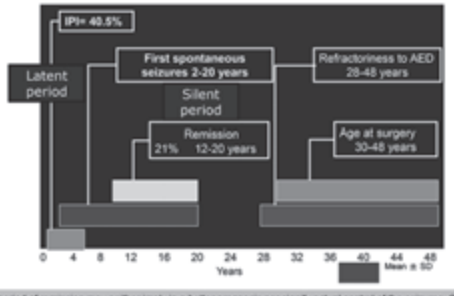
- Hippocampal epilepsy (mesiobasal limbic or rhynencephalic or psychomotor seizures)

  Most common type of epilepsy in adults
- Seizures may originate in the hippocampus, amygdala, parahippocampal gyrus or entorhinal córtex;
- Initial precipitant insult. In 50% of the cases: febrile seizures;
- 70-80% of temporal lobe epilepsies;
- Better surgical results; 80% of the patients are operated without invasive monitoring.

Commission on Classification ILAE, 1981; French et al., 1993

Course of epilepsy related to mesial temporal sclerosis in 180 patients

Miyashira et al., 2004



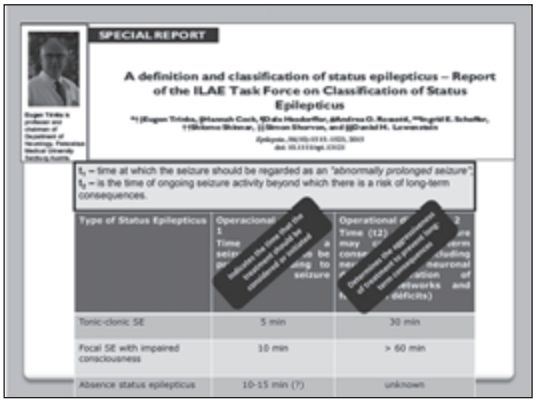
A period of remission may neither imply in a better prognosis nor signify actual control of the seizures. Course of epilepsy may be fluturant

What are febrile seizures?

- Seizures that occur in febrile children between 6-60 months who do not have intracranial infection, metabolic disturbance, or history of afebrile seizures- AAP 2008;
- Prevalence is 3-8% in children up to 7 years old;
- 12-30 months (mean:18 months);
- In general, generalized tonic-clonic seizures, but can manifest as limpness, apnea, altered mental state (*suggestive of focal onset*).

Classification

- **SIMPLE FEBRILE SEIZURES**:
  - Generalized
  - Less than 15 minutes in duration
  - Once per 24 hour period
- **COMPLEX FEBRILE SEIZURES** (any 1 of the following):
  - Focality (ictal or post-ictal paralysis- Todd paralysis)
  - Greater than 15 minutes in duration
  - More than one in 24 hour
- **FEBRILE STATUS EPILEPTICUS**:
  - Less than 5% of all febrile seizures
  - Age between 14-23 months
  - Duration over than 30 minutes



SPECIAL REPORT

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

t_1 – time at which the seizure should be regarded as an "abnormally prolonged seizure";
t_2 – is the time of ongoing seizure activity beyond which there is a risk of long-term consequences.

Type of Status Epilepticus	Operacional 1 Time (t1)	Operational 2 Time (t2)
Tonic-clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	> 60 min
Absence status epilepticus	10-15 min (?)	unknown

Do Prolonged Febrile Seizures Cause Hippocampal Sclerosis?

- Retrospective studies report that many patients with refractory epilepsy who undergo temporal lobectomy and have MTS give a history of febrile seizures in childhood;
- Prospective studies of febrile seizures have not found this effect.

Shinnar S. Ann Neurol 1998;43:411-2

Consequences of Prolonged Febrile Seizures: FEBSTAT

- Prospective, multicenter study;
- Recruit 200 children (aged 1 month through 5 years), presenting with a febrile seizure lasting 30 minutes or longer;
  - Children with known severe neurological disability before study entry are excluded;
- Procedures:
  - MRI and EEG within 72 hours of the episode of status epilepticus;
  - Virology studies withing 72 hours and at 1 month;
  - Baseline neuropsychological testing at 1 month;
  - Repeated MRI, EEG, and neuropsychological testing at 1, 5 and 10 years and at development of epilepsy.

Shinnar et al. Neurology 2008;71(3):170-6
Hersdorffer et al. Epilepsia 2012;53:1471-80

Consequences of Prolonged Febrile Seizures: FEBSTAT

- Outcomes to be studied include:
  - Development of hippocampal sclerosis;
  - Development of epilepsy and in particular temporal lobe epilepsy;
  - Occurrence of specific neuropsychological deficits in children with and without hippocampal sclerosis.

Hersdorffer et al. Epilepsia 2012;53:1471-80

Consequences of Prolonged Febrile Seizures: FEBSTAT- controls

- For comparison with Febrile Status:
  - 144 children with first FS or first complex FS (not SE);
  - MRI imaging using a similar protocol within 72 hours of the FS;
  - This cohort recruited at Columbia University, serves as controls for:
    - Imaging abnormalities in MRIs done withing 72 hours and one year later;
    - Behavioral outcomes at baseline and one year.

Hersdorffer et al. Epilepsia 2008;49:765-771
Hersdorffer et al. Annals of Neurology 2011;70:93-100
Hersdorffer et al. Epilepsia 2012;53:1471-80

Consequences of Prolonged Febrile Seizures: FEBSTAT- Clinical Characteristics of the cohort N=199

• Median seizure duration	70 min (IQR 47-110)
• Mean seizure duration	90 min (range 30-702)]
• 30-59 min	81 (41%)
• > 60 min	118 (59%)
• Continuous vs Intermittent	
• Continuous	114 (57%)
• Intermittent	85 (43%)
• Focal vs Generalized	
• Generalized	46 (23%)
• Focal	153 (77%)

- > 85% did not stop spontaneously but required administration of benzodiazepines to stop it

Shinnar et al. Neurology 2008;71(3):170-6
Hersdorffer et al. Epilepsia 2012;53:1471-80

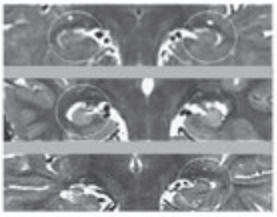
FEBSTAT MRI READINGS: Acute Post Ictal

- Total acute FSE MRIs reviewed: 191;
  - Normal 67%;
  - Abnormal 33%;
- Breakdown of abnormalities:
  - Increased hippocampal T2- 11.5%;
  - Hippocampal malrotation: 8%;
    - 1 of 15 HIMAL also had hippocampal T2 signal increase;
  - Extrahippocampal abnormalities- 16%.

Shinnar et al. Neurology 2012;79:871-7

T2 Intensity in Hippocampi after Febrile Status Epilepticus

11.2%



Both hippocampi have normal T2 intensity

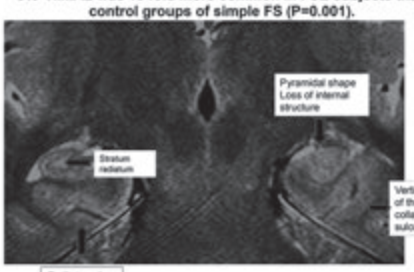
Left hipppocampus slightly increased T2 and reduced anatomical landmarks

Right hippocampus marked increase T2 in lateral inferior aspect, near CA1

S. Shinnar

Hippocampal malrotation- HIMAL

8%- HIMAL was 15 fold more common in FSE subjects than control groups of simple FS (P=0.001).



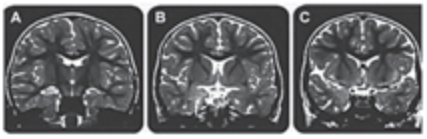
Hippocampal malrotation- HIMAL

- More common in FSE than in children with simple FS:
  - 20 (8.8%) vs 2 (2.1%)- Odds ratio 4.56;
- Almost exclusively left sided:
  - Left sided in 18 and bilateral in 4;
- Predominantly in males:
  - 18.1% of males vs 3.7% of females;
  - Adjusted Odds Ratio 5.36 (95%CI 1.5-19.4);
- Even within FEBSTAT group associated with more prolonged SE:
  - 17.3% of those with duration > 60 min vs 2.8% of those with duration ≤ 60 min;
  - Adjusted Odds Ratio 6.73 (95% CI 1.5-30.5);
- Left hippocampal volumes smaller than in simple FS controls (p<0.004).

Chan et al. A J Roentgen 2015 (in press)

Extrahippocampal temporal lobe abnormalities following febrile status epilepticus

16%



MRI of a 11-month-old child with focal FSE. Seizure was continuous and lasted 120 minutes. MRI 3 days after FSE shows increased T2 signal and enlargement of right hippocampus, accompanied by increased T2 signal in right amygdala and right mesial temporal cortex.

Shinnar et al. Neurology 2012;79:871-7

FEBSTAT Acute EEG Findings

199 EEG Readings

- Normal 109 (55%)
- Abnormal 90 (45%)
  - Focal slowing 47 (24%)
    - Temporal 45 (23%)
  - Focal attenuation (12 with slowing) 25 (13%)
    - Temporal 15 (8%)
  - Focal spikes (8 with slowing) 13 (7%)
    - Temporal 6 (3%)
  - Diffuse slowing 22 (11%)

Nordli et al. Neurology 2012;79:2180-6

Human Herpesvirus (HH-6 and -7), Febrile seizures and Future Epilepsy: Background and Rationale

- Both HHV-6 and -7 have been associated with FS:
  - HHV-6 one third of FS in children below age 2 yrs.;
  - HHV-6 and -7 combined account for 53% of 1st FS and 5% of those with recurrent FS in children < 3 yrs;
- HHV-6 and -7 are neuroinvasive and have been implicated in hippocampal injury:
  - HHV-6B has been isolated from hippocampal specimens at surgery for refratory TLE but not from extratemporal resections;
  - HHV-6 may selectively localize in the mesial temporal lobe, resulting in limbic seizures and hippocampal damage in bone marrow transplant recipientes.

Roseola- common in children ages 3 months to 4 years, and most common in those aged 6 months to 1 year.

Theodore et al. Epilepsia 2006;49:1828-37

FEBSTAT Virology Results

Data available on 169/199 (84.9%) of children with FSE	
HHV-6B viremia	54 (32%)
HHV-7 viremia	12 (7.1%)
No HHV-6B or HHV-7 viremia	111 (65.7%)

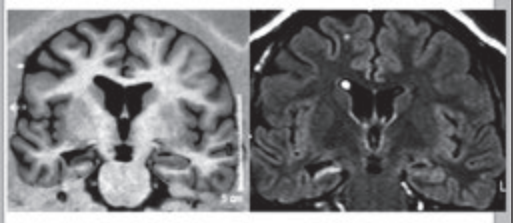
Roseola

- HHV-6B/HHV-7 are most common cause of febrile illness associated with FSE;
- No diferences in clinical semiology or acute imaging or EEG abnormalities between HHV+ and – cases.

Epstein et al. Epilepsia 2012;53:1481-8

Seizure semiology

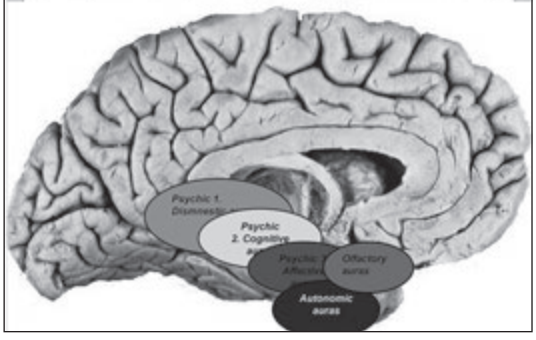
Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis



Seizures originate in hippocampus, amygdala, parahippocampal gyrus or entorhinal cortex

SEMIOLOGY OF COMPLEX PARTIAL SEIZURES – AURAS

Experiential or Psychic Auras, Olfactory Auras, Autonomic Auras



ANNALS of Neurology

Characteristics of Medial Temporal Lobe Epilepsy: I. Results of History and Physical Examination

French et al. Ann Neurol 1993; 34: 774-80.

Table 2. Auras

	No. (%)
Patients with auras	64 (86)
Patients without auras	5 (4)
Type of aura	
Abdominal visceral sensation	39
Only aura	13
Combined with other symptoms	26
Fear	6
Light-headed	6
Feeling of warmth	3
Gustatory	2
Olfactory	2
Urge to micturate	2
Micropsia	2
Indescribable	2
Vertigo	1
Euphoria	1
Compulsive thoughts	1
Generalized numbness	1
Depersonalization	1
Feeling of having to vomit	1
Auras not including visceral sensations	25
Fear	5
Olfactory	5
Light-headed	3
Déjà vu	3
Generalized somaesthesia	3
Indescribable	3
Feeling of warmth	2
Gustatory	2
Urge to micturate	2
Intellectual (spiritual darkness)	1
Breathless	1
Disorientation	1
Vertigo	1
Elementary auditory	1
Elementary visual	1

Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

ABDOMINAL VISCERAL SENSATION- up to 80% of the cases

- Unpleasant feeling, often indescribable, located in the abdominal area;
- Typically manifests as a rising epigastric sensation.

The role of temporal lobe neocortex and mesial structures is discussed

- Evoked by insula stimulation (Penfield and Faulk, 1955);
- Viscero-sensory phenomena, epigastric and pharyngeal sensations were evoked by rhinal, amygdala and hippocampal stimulation (Bartolomei et al., 2004).

ICTAL FEAR

Clearly distinguished from the fear of a seizure, spontaneous, out of context, associated with a rising epigastric sensation, palpitation, mydriasis and pallor

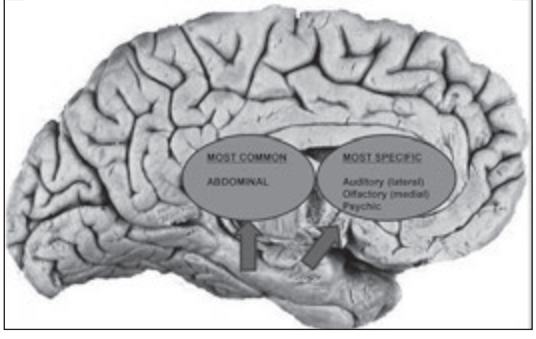
Video- Ictal Fear

Relative incidence of auras in focal epilepsies

	Temporal [a] Binder 2008	Temporal [a] Ferrari-Marinho 2012	Frontal [a] Jobst 2000	Parietal [a] Salenova 1998	Parietal [a] Kim 2004	Occipital [a] Salenova 1992	Occipital [a] Lee 2006
Incidence of auras	114/150 (76%)	188/205 (91%)	18/28 (69%)	77/82 (94%)	27/40 (67.5%)	57/42 (68%)	22/28 (85%)
Somatosensory	12%	8%	12%	63%	32.5%	-	-
Auditory	5%	6%	-	3%	2.5%	-	-
Visual	8%	14%	-	17%	15%	73%	77%
Olfactory		2%	-	-	-	-	-
Gustatory	11%	4%	-	-	7.5%	2%	-
Vertiginous	2%	2%	-	11%	10%	-	15%
Autonomic	1%	30%	12%	-	7.5%	-	-
Abdominal	28%	52%	-	1%	-	14%	7.7%
Cephalic	-	15%	35%	3%	-	12%	-
Psychic, experiential	12%	16%		8%	-	8% (complex visual hallucinations)	-
Fear	14%	19%	19%	-	15%	2%	-
Affective (not fear)	-	6%	-	-	-	-	-
Other	-	-	8%	3%	2.5%	-	-
Unclassified	10%	6%	15%	8%	-	2%	-

a. Percentage is determined by the frequency of a particular aura of total auras reported
b. Percentage is determined by percentage of patients reporting a particular aura

Auras in temporal lobe epilepsies



Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Complex partial seizures:

- Various degrees of conscious impairment
- *Staring*
- Automatisms
  - oroalimentary
  - manual
  - complex
- Head deviation
- Dystonic posture of the contralateral arm

Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Complex partial seizures:

- **Various degrees of conscious impairment**
- *Staring*
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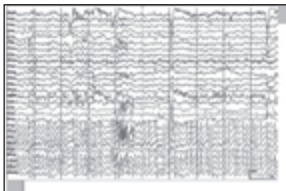
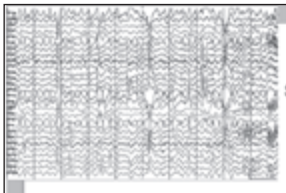


Seizure:

Video- right temporal lobe- spontaneous speech



Seizure: comprehension

Video- right temporal lobe- comprehension

Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Complex partial seizures:

- Various degrees of conscious impairment
- ***Staring***
- Automatisms
  - oroalimentary
  - manual
  - complex
- Head deviation
- Dystonic posture of the contralateral arm

Staring

Charles Antoine Coypel, Medea
Paris 1694–1752

Video "STARING"

VIDEO
Oroalimentary automatisms

VIDEO
Sign of the Cross automatism

VIDEO
Whistling automatism

Temporal lobe epilepsies
Epileptic automatisms

Epileptic Disord. 2010;12(2):133-5.
Ictal whistling: a rare automatism during temporal lobe seizures.
Raghavendra S, Mirsattari S, McLachlan RS.

Epilepsia. 2003;44(8):1064-9.
Ictal spitting: clinical and electroencephalographic features.
Kellinghaus C[1], Loddenkemper T, Kotagal P.

Epilepsy Behav. 2011 Nov;22(3):602-5.
Ictal yawning in a patient with drug-resistant focal epilepsy: video/EEG documentation and review of literature reports.
Specchio N[a], Carotenuto A, Trivisano M, Cappelletti S, Vigevano F, Fusco L.

Epilepsy Behav Case Rep. 2013;1:85-8.
Ictal singing due to right mesial temporal lobe epilepsy involving a bihemispheric network.
Lee EM[a], Kang JK[a], Park GY[a], Oh JS[a], Kim JS[a].

Epilepsy Behav. 2013;29(2):326-8.
Ictal kissing behavior: neurological and psychodynamic overview.
Tapiuran E[1], Cirmen M, Kılıc O, Sentürk A, Ozkara C.

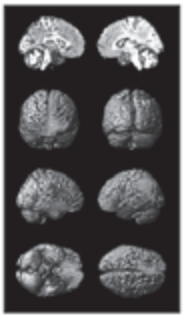
Seizure. 2006;15(6):462-7.
Ictal spitting in left temporal lobe epilepsy: report of three cases.
Caboclo LO[a], Mugahina FS, Hamad AP, Lin K, Carrete H Jr, Sakamoto AC, Yacubian EM.

Epilepsy Behav. 2009;14(2):400-3. **Sign of the Cross (Signum Crucis): observation of an uncommon ictal manifestation of mesial temporal lobe epilepsy.**
Lin K[1], Marx C, Caboclo LO, Centeno RS, Sakamoto AC, Yacubian EM.

Mesial Temporal Lobe Epilepsy
Related to Mesial Temporal Sclerosis

Complex partial seizures:

- Various degrees of conscious impairment
- *Staring*
- Automatisms
  - oroalimentary
  - manual
  - complex
- **Head deviation**
- Dystonic posture of the contralateral arm



- SPECT 1-1.5 minute after a temporal lobe CPS onset;
- Marked increase in blood flow in the temporal lobe;
- Reduced blood flow involving wide frontoparietal association cortices of the default mode network.

Blumenfeld et al. Cerebral Cortex 2004;14(8):892-902.

Eyes and head deviation *versus* version of the head and eyes

Video
Deviation x Version of the head +
Figure four sign

VIDEO
Left TLE + cephalic deviation

Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Complex partial seizures:

- Various degrees of conscious impairment
- *Staring*
- Automatisms
  - oroalimentary
  - manual
  - complex
- Head deviation
- **Dystonic posture of the contralateral arm**

VIDEO
Right TLE and dystonic posture

Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Secondarily generalized tonic-clonic seizures:

- rare (mainly after treatment onset);
- preceded by eyes and head version.

VIDEO
Secondary generalization

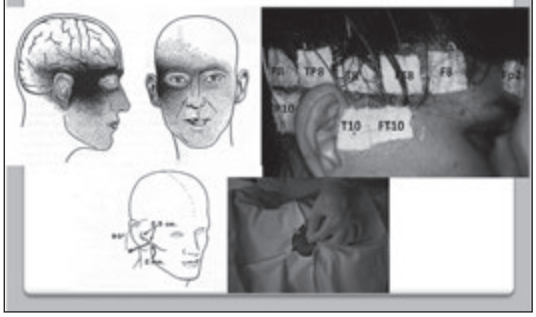
Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Post ictally:

- mental confusion
- aphasia (dominant temporal lobe)

VIDEO
Post Ictal Aphasia

Mesial Temporal Lobe Epilepsy Video-Electroencephalogram



Semiological biomarkes

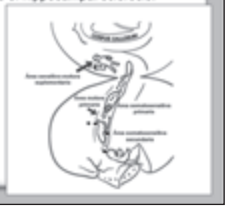
The meaning of auras

THE MEANING OF AURAS IN TLE-HS

- 205 patients, 157 submitted to surgery

- Multiple auras did not predict seizure focus laterality;
- Multiple auras were not associated with post surgical outcome;
- Extratemporal auras were predictive of worse surgical outcome;
- Different types of auras did not predict the side of hippocampal sclerosis.

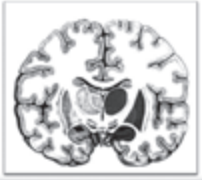
- Somatosensory auras (18) and visual auras (27): Engel II, III and IV



Ferrari-Marinho T, Cabocio LO, Marinho MM, Centeno RS, Neves RS, Santana MT, Brito FS, Junior HC, Yacubian EM. Epilepsy Behav. 2012 May;24(1):120-5.

THE MEANING OF DYSTONIC POSTURE IN TLE-HS

Involvement in a network of both temporal and mesial and lateral temporal lobes areas beyond the insula and basal ganglia



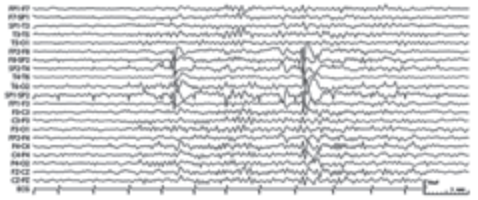
- Inhibitory role in seizure propagation
  CPC – CTCG
- Indicative of poor surgical prognosis?
  Not in our series (161 cases) 2 and 5 years after surgery

Dal-Cól *et al.*, 2008; Bossi *et al.*, 1980; Janszky *et al.*, 2005; Uchida *et al.*, 2013

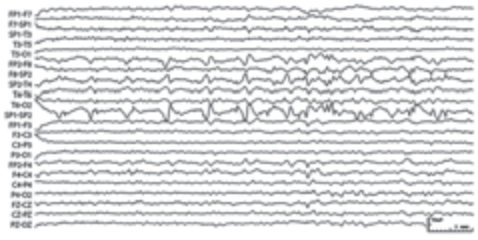
Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

- Interictal EEG:
  - anterior temporal sharp waves
  - temporal slow waves
- Ictal EEG: rhythmic theta waves
- MRI: hippocampal sclerosis

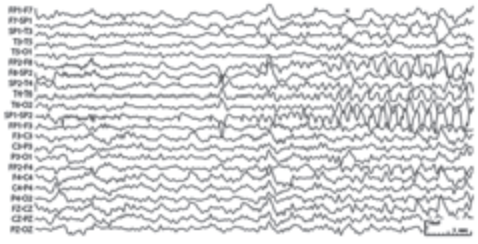
Mesial Temporal Lobe Epilepsy Interictal EEG

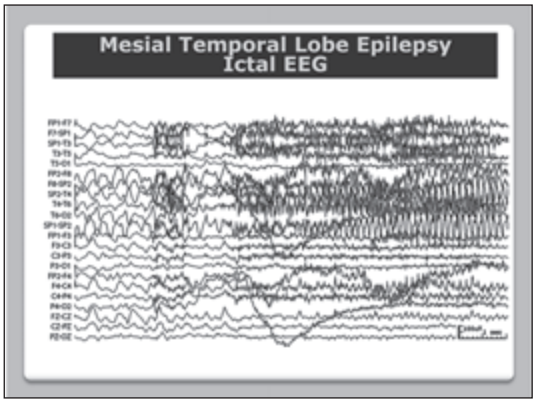


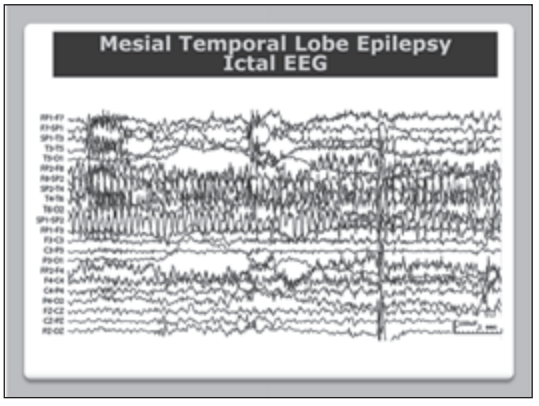
Mesial Temporal Lobe Epilepsy Interictal EEG

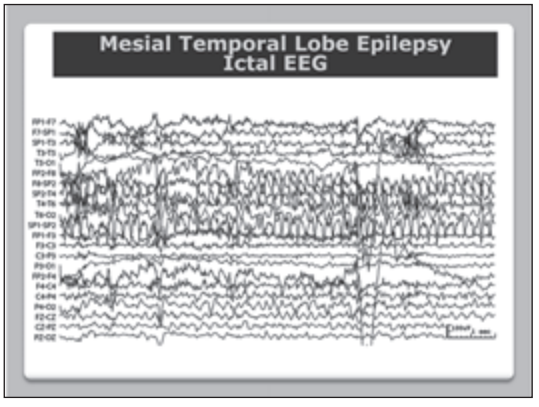


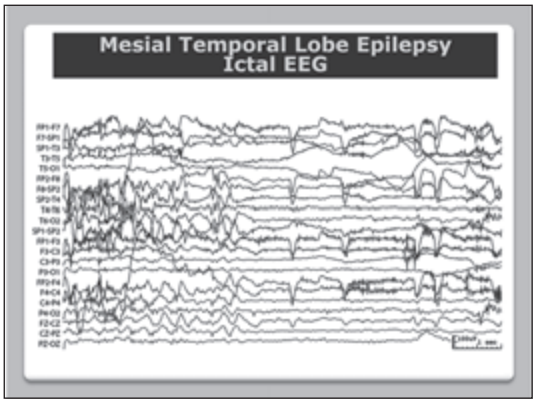
Mesial Temporal Lobe Epilepsy Ictal EEG




Mesial Temporal Lobe Epilepsy
Ictal EEG

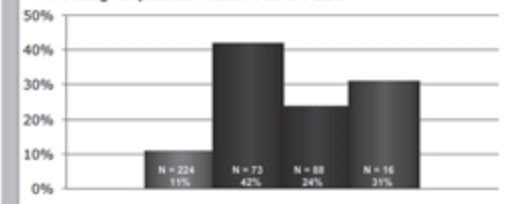

Mesial Temporal Lobe Epilepsy
Ictal EEG


Mesial Temporal Lobe Epilepsy
Ictal EEG


Mesial Temporal Lobe Epilepsy
Ictal EEG

Mesial Temporal Lobe Epilepsy Related to Mesial Temporal Sclerosis

Percentage of patients seizure free on AEDs

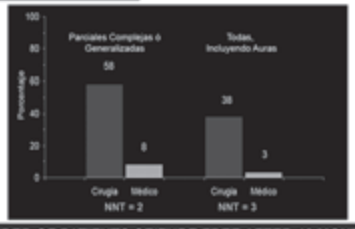


Semah et al. Neurology, 1998 (8% recém diagnosticada) Kim et al. Epilepsia, 1999 (previamente tratada)

Stephen et al. Epilepsia, 2001 (70% recém diagnosticada) Kim et al. Epilepsia, 1999 (recém diagnosticada)

Surgical treatment


The New England Journal of Medicine



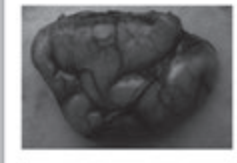
NUMBER OF PATIENTS SEIZURE FREE AFTER 12 MONTHS

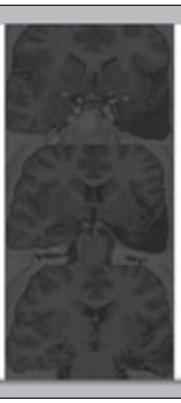
Should I have Temporal Lobe Surgery? What are my odds?

- **GOOD if:**
  - Short duration of epilepsy
  - No history of GTCS
  - Unilateral MRI findings
  - Concordant pre-operative data
- **BAD if:**
  - Bilateral MRI abnormalities
  - No clear path diagnosis
  - Spikes persist after resection

Surgery

CORTICO- AMYGDALOHIPPOCAMPECTOMIA

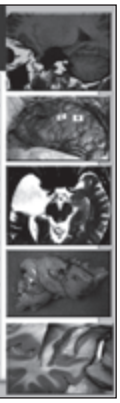




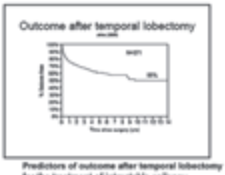
Surgical treatment- HS

PROCEDIMENTO	AUTOR
1. Neocorticectomia temporal	1947
2. Neocorticectomia e Uncus-Hipocampectomia	
3. Lobectomia temporal em bloco	
4. Lobectomia temporal e Amígdala e	956
5. Abordagem transventricular e A	yer, 1958
6. Abordagem transilviana e A	sargil, 1982
7. Lobectomia subpial e A	Olivier, 1983
8. Abordaje transulca	Olivier, 1988
9. Reoperações	Awad,1991
10. Endoscop	Silbergeld, 1995
11. Abor Hipoca	Amígdalo- Park, 1996
12. Ab Hipoca	Amígdalo- Vajkoczy, 1998
13. Amíg neuronave	va guiada por Wurm, 2000
14. Amígdalo- temporal inferior	seletiva através do sulco ctaxia Miyagi, 2003
15. Abordagem subtemporal transventricular /transcoroidea	Miyamoto, 2004

SAME RESULTS



Outcome after temporal lobectomy



Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy.
Jeha LE et al. Neurology 2006;66(12):1938-40.

TEMPORAL LOBE HISTORY AND THE TECHNIC OF HEMITOTAL TEMPORAL LOBECTOMY*

Ann Surg 1952;136(4):625-34.

- The 55% challenge:
  - 3801 publications later, 60 years later, we should do better;
  - Why aren't we?

Predictors of recurrence after temporal lobe surgery

- Long duration of epilepsy;
- Seizure frequency (>20/month);
- History of GTCS;
- Bilateral MRI lesions;
- Posterior ictal/interictal findings on scalp EEG;
- Spikes on postoperatory EEG;
- Non-congruent PET findings;
- Indeterminate ictal SPECT;
- Need for invasive EEG;
- Gliosis.

Jeha LE. Neurology 2006;66(12):1938-40.

CONCLUSIONS

- Historically considered a single syndrome, MTLE with hippocampal sclerosis should be seen as a group of syndromes related to extension and pathological variables findings;
- The improvement in surgical prognosis will only be possible when syndromic subgroups are firmly established.

QUESTIONS- 2016

1. Why 45% of the patients continue presenting complex partial seizures?
2. Why up to 62% continue presenting auras?
3. Why up to 75% of the patients will present seizure recurrence after withdrawal of AEDs?

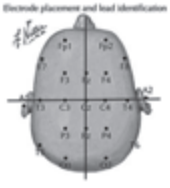
Wiebe et al., 2001; Schmidt et al., 2004

Thank you very much!

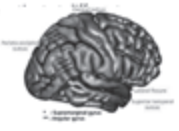
Loreto Rios (Chile)

POSTERIOR QUADRANT EPILEPSIES

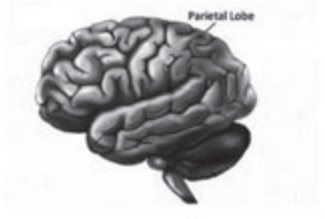
Posterior quadrant epilepsies
Occipital and parietal lobe epilepsies



- Epileptic seizures of parietal and occipital origin are heterogeneous and mainly characterised by :
  - Focal seizures without impairment of awareness.
  - They manifest as subjective auras.
  - The most dramatic clinical manifestations may reflect spread, and overshadow the focal origin.
    - Sensitive Aura →Focal seizures with impairment of awareness usually indicate spread of the seizure into the temporal lobe.
- Various seizure types may occur in a single times.
- They are generally considered rare.
  - Occipital seizures 8% .
  - Parietal seizures 1.4% of



Parietal Lobe Epilepsy



Positive signs:

- Somatosensory seizures: paraesthetic, dysaesthetic and painful sensations.
- Seizures with sexual phenomenology.
- Disturbances of body image and somatic illusions/A desire to move.
- Complex symptomatology

Negative Signs:

- Somatoagnosia: (soma = body; agnosia = ignorance, inability to recognise) Inability to recognise the affected body part as one's own.

Positive signs:

- Somatosensory seizures: paraesthetic, dysaesthetic and painful sensations.
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Negative Signs:

- Somatoagnosia: (soma = body; agnosia = ignorance, inability to recognise) Inability to recognise the affected body part as one's own.

Possitive signs

- All sensory modalities may be represented:
  - **Paraesthesia: tingling and numbness,** alone or together.
  - **Pain** often described as stabbing, intense, torturing, agonising or dull. **(area 5a)**
  - **Thermal perceptions** are less common and rarely occur without other sensory phenomena. A burning sensation is more common than the feeling of cold.
- **Post-central gyrus** is most commonly site of arising seizures.
- The arms and the face are the most common sites.
- Seizures present with contralateral, or rarely ipsilateral, or bilateral sensations (secondary sensory area).
- Spreading in a Jacksonian manner can happen. When this occurs motor activity in the affected body member follows the sensations in about 50% of cases.

Other somatosensory features:

- **Body image disturbances:** The peripheral parts of the extremities and tongue are most commonly affected.
  - **Illusion of distorted or changed body shape:** a body part may be felt to be swollen or shrunken **(macro- and microsomatognosia)**, or elongated or shortened **(hyper- and hyposchematica)**.
  - Sensation of a supernumerary or phantom limb.
  - **Feeling of movement or altered posture in a stationary limb:** feeling of floating, twisting or even disintegration of a body part.

There is also sensory representation in the posterior insula and in the supplementary motor area, so seizures involving these parts may have prominent sensory symptoms.

- **Seizures with sexual phenomenology**:
  - Seems to originate in the paracentral lobule where the primary somatosensory area for the genitalia is thought to reside, usually involving the **non-dominant hemisphere**.
  - The seizures present with a tactile somatosensory aura affecting the genitalia, but the ensuing seizure may exhibit other features of sexual behaviour.

Complex symptomatology
Emanates from posterior parietal lobe regions

- **Vertigo and other vertiginous sensations** (10%).
  - They are elicited predominantly from the temporo parietal border. Inferior parietal Lobe
- **Visual illusions and complex formed visual hallucinations** (12%)
  - non-dominant parietal regions.
- **Linguistic disturbances:**
  - Dominant temporoparietal lobe seizures are associated with a variety of linguistic disturbances, alexia with agraphia and significant calculation defects.

Positive signs:

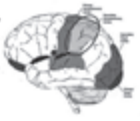
- Somatosensory seizures: paraesthetic, dysaesthetic and painful sensations.
- Seizures with sexual phenomenology.
- Disturbances of body image and somatic illusions/A desire to move.
- Complex symptomatology

Negative Signs:

- Somatoagnosia: (soma = body; agnosia = ignorance, inability to recognise) Inability to recognise the affected body part as one's own.
- Inability to move feeling

Negative Signs (secondary Sensory Area)

- **Somatoagnosia (soma = body; agnosia = ignorance, inability to recognise)**
  - Inability to recognise the affected body part as one's own.
  - **Ictal limb agnosia and phantom limb sensations .Non-dominant cerebral hemisphere.**
- A feeling of inability to move. **(Suprasylvian border).**
  - Such seizures may be preceded by a psychic aura ('psychoparetic).

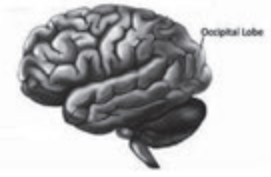


Differential diagnosis:

- Simple somatosensory seizures alone:
  - Psychogenic NEPEs.
  - Transient ischaemic attacks.
  - Migraine with aura: Sensory jacksonian seizures may imitate migraine with sensory aura.
  - Transient ischaemic attacks:older patients.

Seizures with visual symptomatology

Sz from occipital lobes and the parieto-occipital junction

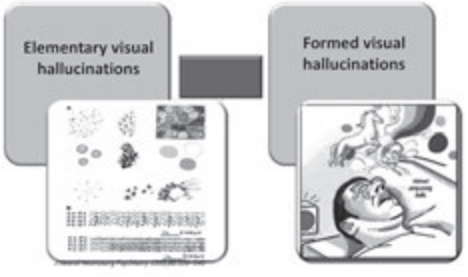


Positive signs:

- Visual auras may occur in epilepsy affecting any part of the visual pathways.
- **It is always a seizure phenomenom.**
- Elementary visual hallucinations / formed visual hallucinations.

Negative Signs:

- Visual loss (Amaurosis) , either total or partial are especially common in children.
  - It can be an Ictal phenomenon or **post ictal.**
  - Usually is bilateral / blackout or whiteout.



- **Elementary visual hallucinations:**
  - Are most common.
  - Crude sensations of light or colours, which may take various shapes, be continuous, steady or moving, or be interrupted flashes of light.
- **Formed visual hallucinations:**
  - They are experienced fairly often in epilepsy.
  - Usually, patients are aware of the unreality of the experience.
  - are usually brief, and may be associated with slow head and eye turning, with the gaze towards the direction of the moving images perceived.
  - Pictures of people, animals or scenes may be perceived, either static or moving.
    - One subtype is epileptic autoscopia, where the subjects see mirror images of themselves, sometimes in long-lived situations.

Differential diagnosis

- Illusion of movement in vertigo.
- Visual Aura in migraine:
  - Usually associated with sharp lines and fortification spectra
  - Usually evolves much more slowly, over several minutes.

- Parasomnias.

- **Visual illusions and visuo-spatial perceptions :**
  - Also occur as a seizure phenomenon.
  - Usually localized the ictal onset in the **non-dominant parietal lobe**.
    - Micro- or macropsia objects seen as moving, or motion appears too slow or too fast.
    - Teleopsia, where objects appear both small and at a distance.
    - Palinopsia, or visual perseveration

Other seizure phenomena from occipital and parietal regions.

- Ictal anosognosia, apraxia, acalculia, alexia and aphemia may occur in epilepsy from the posterior brain regions, often presenting as confusional states.
- Gustatory seizures sometimes have their origin on the suprasylvian border close to the sensory region for the mouth and tongue.
- Vertiginous sensations are also thought to originate in the suprasylvian and possibly the occipito-parietal region.

Oculotonic and oculoclonic seizures

- It is the only primary motor seizures from the posterior brain region.
- Its origin is in the occipito-parietal cortex.
- Consciousness is usually retained.
  - **Epileptic nystagmus:**
    - It is usually contraversive: fast beating component goes to the opposite site of the EEG focus.
    - The nystagmus may occur as an isolated manifestation, or be associated with head or trunk version, but rarely other motor activity accompanies.
  - **Eyelid flutter and rapid blinking:**
    - It is other features of occipital epilepsy.
    - Often at the very beginning of seizures.

Provoking and Post – Ictal Phenomena.

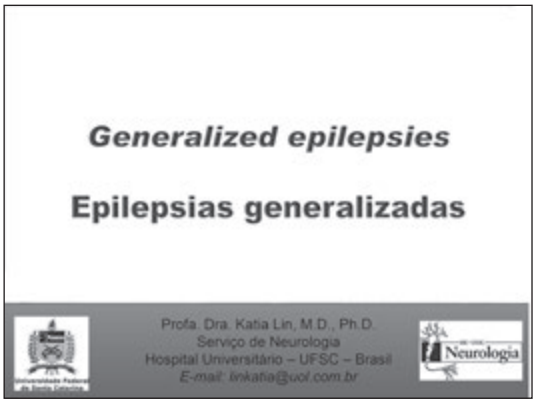
- May be provoked by various stimuli involving the receptive, interpretive and connective function of the parietal and occipital lobes.
- The most common precipitating factor is photic stimulation., but other well-known inducers are tactile stimulation, reading, drawing, calculation and other mental activity.
- **Post-ictal phenomena** are transient numbness, inability to move despite no loss of power in affected limbs and post-ictal blindness.
  - There is no correlation between duration and severity of seizures and the duration of the post-ictal neurological deficits.
  - Post-ictal numbness and paralysis are usually short lasting, but postictal blindness may be prolonged .
  - Fixed hemianopia may help confirm occipital lobe onset.

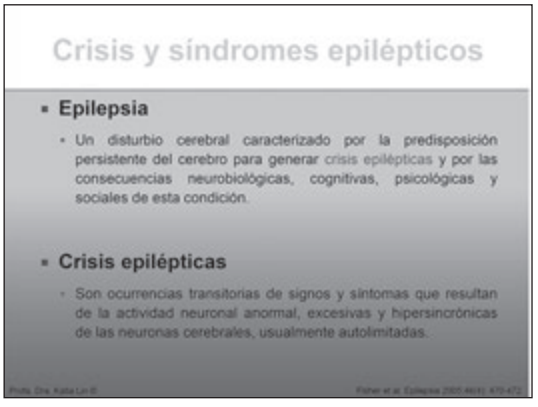
Electroencephalographic features

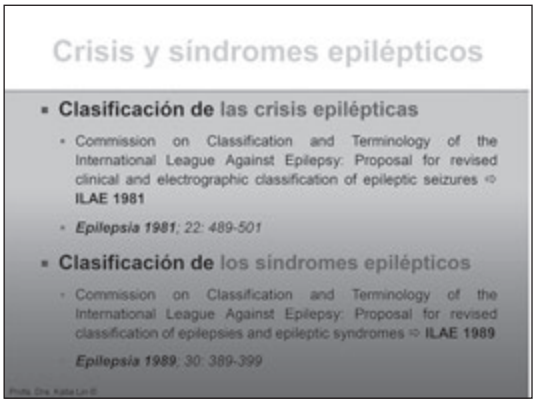
- Scalp EEG oft en cannot be correlated with a clinical ictal pattern and the seizures areoften electrically silent.
- EEG changes may be lateralising rather than localising.
- Changes in the posterior background activity may be helpful in occipital lobe epilepsy.
- Occipital foci are often widespread and may move between the occipital pole and the anterior temporal lobes.
  - If the focus arise from the **supracalcarine region**: Spread seems to be to the parietal and frontal regions.
  - If the focus arise from the **infracalcarine region**: Spread seems to be to the ipsilateral temporal lobe.
  - Spread to the contralateral occipital lobe via the corpus callosum seems to occur late in adult cases.

KATIA LIN (BRAZIL)

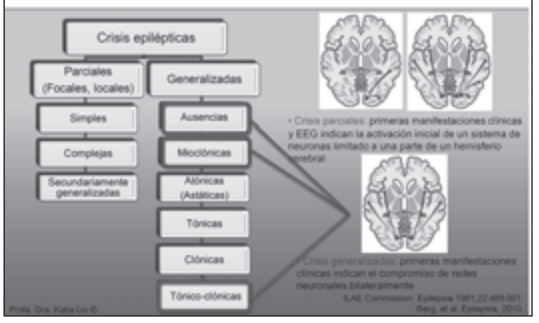
GENERALIZED EPILEPSIES







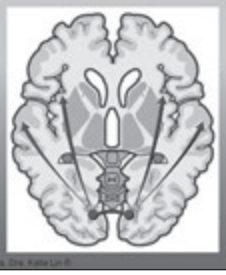
Clasificación de las crisis epilépticas, 1981 ILAE



ILAE Commission. Epilepsia 1981;22:489-501
Berg, et al. Epilepsia, 2010

Profa. Dra. Katia Lin ©

"Epilepsias Generalizadas Idiopáticas/Genéticas"
"Epilepsias de sistemas"



- Crisis generalizadas son aquellas que se originan en algún punto de una red neuronal y rápidamente son distribuidos en redes neuronales bilateralmente.
- Estas redes pueden incluir estructuras corticales y subcorticales, pero no necesariamente toda la corteza cerebral.
- Mientras que algunos de estos pueden parecer crisis localizadas cuando se analizan individualmente, lateralización no es constante de una crisis a otra.
- Las crisis generalizadas pueden ser asimétricas.

Berg, et al. Epilepsia, 2010
Avanzini, et al. Epilepsia, 2013

Profa. Dra. Katia Lin ©

Epilepsias Generalizadas Idiopáticas/Genéticas (EGI)

- Las EGI constituyen 1/3 del total de las epilepsias
- Las EGI son un continuo neurobiológico que se extiende desde los primeros meses de la vida hasta la edad adulta y presenta la mayor expresividad clínica y los síndromes epilépticos más característicos en la edad escolar y la adolescencia.

Epilepsia, 30(4):389–399, 1989
Raven Press, Ltd., New York
© International League Against Epilepsy

Proposal for Revised Classification of Epilepsies and Epileptic Syndromes

Commission on Classification and Terminology of the International League Against Epilepsy

Tabla I. Epilepsias generalizadas idiopáticas admitidas en la Clasificación internacional de epilepsias y síndromes epilépticos de 1989.

Edad	Epilepsias/Síndromes epilépticos
Recién nacido a 3 meses	Convulsiones neonatales familiares benignas Convulsiones neonatales benignas
3 meses a 3 años	Epilepsia mioclónica benigna del niño
3 años a pubertad	Epilepsia ausencia infantil
Pubertad a adulto	Epilepsia ausencias juvenil Epilepsia mioclónica juvenil Epilepsia con crisis de gran mal del despertar
Cualquier edad	Otras epilepsias generalizadas idiopáticas no definidas Epilepsia con crisis caracterizadas por modos específicos de precipitación (epilepsia fotogénica)

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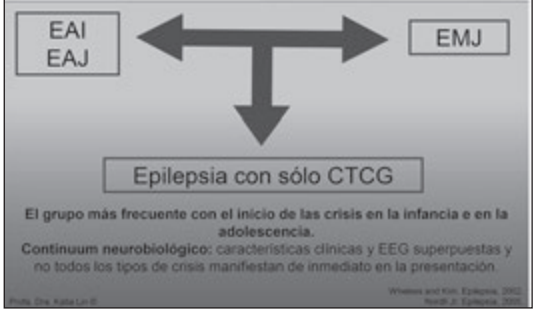
ILAE Commission. Epilepsia 1989;30:389–399

Epilepsias Generalizadas Idiopáticas/Genéticas



El grupo más frecuente con el inicio de las crisis en la infancia e en la adolescencia.

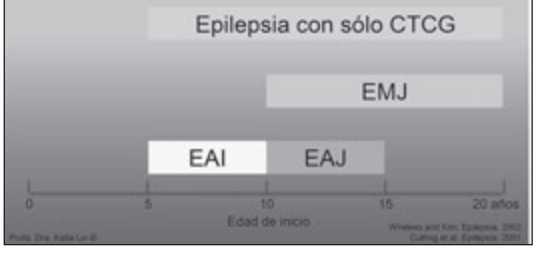
Continuum neurobiológico: características clínicas y EEG superpuestas y no todos los tipos de crisis manifiestan de inmediato en la presentación.

Wheless and Kim. Epilepsia. 2002
Berdt Jr. Epilepsia. 2005

Profa. Dra. Katia Lin ©

Epilepsias Generalizadas Idiopáticas/Genéticas

"El inicio de EGIs es inusual arriba la edad de 25 años."



Wheless and Kim. Epilepsia. 2002
Cutting et al. Epilepsia. 2001

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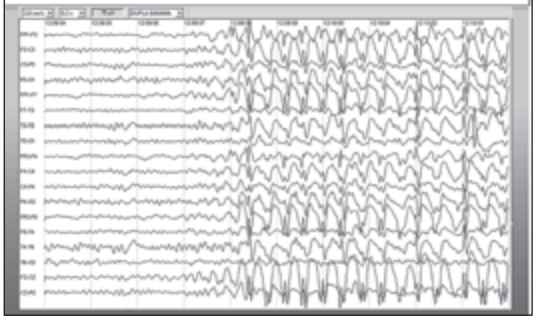
Crisis de ausencia típicas Picnolépticas

VÍDEO

Breves episodios de alteración de la consciencia, de inicio y final abruptos, pudiendo estar acompañados de síntomas motores, automatismos orales y manuales y signos autonómicos. Desencadenadas por la hiperventilación (> 90%).

Profa. Dra. Katia Lin ©

EEG background: normal. Interictal y ictal: Complejos punta-onda a 3/segundo, regulares.



Crisis de ausencia típicas Espaniolépticas

VÍDEO

La alteración de la consciencia puede ser total o parcial, con el mantenimiento de la actividad en curso de forma automática. Al inicio y al final son graduales, pudiendo haber dificultad en la identificación de ellas.

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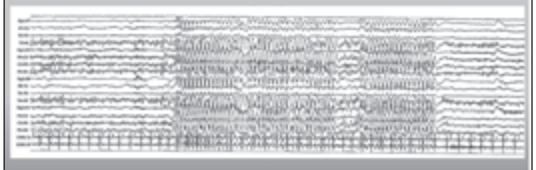
Crisis de ausencia

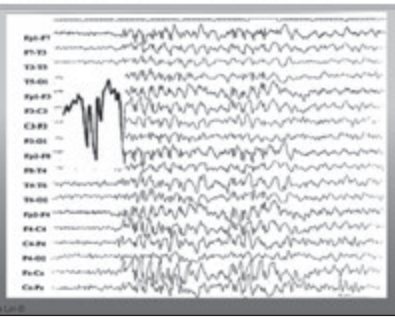


	Tiempo de duración
Epilepsia ausencia infantil	12,4 ± 2,1 seg.
Epilepsia ausencia juvenil	16,3 ± 7,1 seg.
Epilepsia mioclónica juvenil	6,6 ± 4,2 seg.

Asadi-Pooya et al., 2012
Obeid, 1994

Profa. Dra. Katia Lin ©

EEG background: normal. Interictal y ictal: Complejos punta-onda a 3,5-4/segundo y más irregulares. A menudo, la onda lenta es precedida por 2-3 espigas.



Profa. Dra. Katia Lin ©

Crisis mioclónicas

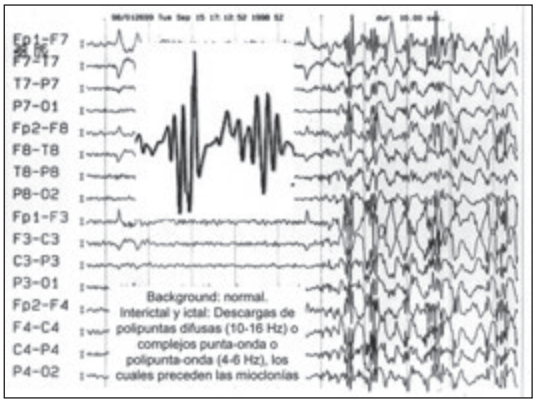
Myoclonus (gr.) = músculo + perturbación

VÍDEO

Contracciones musculares breves y súbitas semejantes a sacudidas.
Generalizadas o focales.
Aisladas o en salvas, rítmicas o no.
Miembros, cabeza o tronco – bi- o unilateral, sim- o asimétrica.
Sin alteración de la conciencia.

Profa. Dra. Katia Lin ©

Blume, et al., Epilepsia, 2001



Crisis tónico-clónicas generalizadas (CTCG)

VÍDEO

Estas se caracterizam por la pérdida abrupta de la conciencia, contracción tónica y clónica de los cuatro miembros, apnea, pérdida de control esfinteriano, sialorrea y mordedura de lengua, con una duración aproximada de un minuto.

Profa. Dra. Katia Lin ®

Crisis tónico-clónicas generalizadas (CTCG)

- Cinco fases
  1. Signos y síntomas premonitorios
     - Horas o días antes de la CTCG: dolor de cabeza, cambios de humor, inestabilidad emocional, letargo, alteraciones del sueño, cambios de apetito, mareos,...
  2. Preictal inmediata
     Sacudidas mioclónicas en EMJ
  3. Fase ictal
  4. Fase postictal mediata
  5. Período de recuperación postictal

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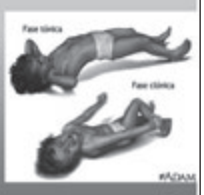
Gastaut & Broughton, 1974
Scarmeli et al., 2005

Crisis tónico-clónicas generalizadas (CTCG)

3. Fase ictal
   - Tónica: 10-20 seg.
     - Contracción tónica de la musculatura axial (espasmo flexor breve seguido por extensión tónica), desviación ocular hacia arriba y dilatación de la pupila, boca rígida y entreabierta seguido por cerradura forzada quando se produce traumatismos orales. La contracción de los músculos del tórax fuerza el aire a través de la glotis cerrada, produciendo el "grito epiléptico".
   - Clónica: 40 seg.
     - Espasmos flexores, seguidos de atonía, estes que se vuelven progresivamente más prolongados e irregulares hasta el último espasmo flexor.



Profa. Dra. Katia Lin ®

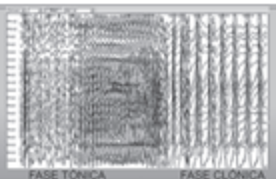
Gastaut & Broughton, 1974

Crisis tónico-clónicas generalizadas (CTCG)

4. Fase postictal inmediata
   - Liberación de estructuras del tronco cerebral, semejante a la rigidez que se observa en sujetos descerebrados con temblor y trismus y puede observarse el signo de Babinski y la enuresis.
5. Período de recuperación postictal
   - Sueño postictal o un despertar con confusión, acompañado de fatiga, dolor muscular y cefalea.

Gastaut & Broughton, 1974

Crisis tónico-clónicas generalizadas (CTCG) – EEG



FASE TÓNICA: actividad sincronizada, difusa y monorrítmica, que aumenta gradualmente de amplitud y disminuye en frecuencia (*ritmo reclutante*).

FASE CLÓNICA: interposición de ondas lentas con fragmentos de ritmo reclutante y espigas de gran amplitud, que constituyen complejos de poliespigas-onda que se enlentece hasta 1 Hz.

Gastaut & Fischer-Williams, 1956

Epilepsia ausencia infantil

- Inicio: 3-10 años (pico 6-7)
- Niñas > niños (6:4)
- 100% crisis de ausencia
  - Picnolépticas – 10-100x/dia
  - Supresión brusca de la conciencia, sin respuesta verbal, automatismos (2/3)
  - Más cortas (10 seg.)
- Durante la adolescencia evoluciona a menudo hacia una epilepsia con CTCG (40%)
  - O las ausencias pueden remitir
- Fuerte componente genético
- Pronóstico favorable (70-80%)
  - Evitar los factores desencadenantes
  - VPA, ESM, LTG

Epilepsia ausencia juvenil

- Inicio: 9-13 años (pico 10-12)
- 100% crisis de ausencia
  - Espaniolépticas - 9-10x/dia
  - Deterioro parcial de la conciencia, automatismos
  - Más prolongadas (4-30seg.)
- CTCG (por la mañana) y mioclónias (1/5 personas)
- Síndrome intermedio entre EAI y EMJ
- Fuerte componente genético
- Pronóstico favorable (70-80%)
  - Evitar los factores desencadenantes
  - VPA, ESM, LTG

Ausencias precipitadas por la hiperventilación

VÍDEO

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Epilepsia mioclónica juvenil

- Comumentemente infradiagnosticada
- Inicio: 12-18 años (media = 14,2)
- 100% Mioclonias
  - 95% CTCG y 30% Ausencias
  - Precipitado por la falta de sueño, la fatiga, el alcohol
- 30% fotosensible
- Heterogeneidad genética
- Pronóstico favorable (90%)
  - Evitar los factores desencadenantes
  - VPA, CZP, TPM

Síndrome de Janz
Prof. Dieter Janz
Impulsiv-Petit mal (1957)

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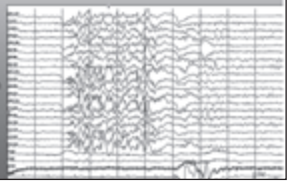
VÍDEO

Descargas epileptiformes y convulsiones precipitadas por fotoestimulación

Fotosensibilidad

- Genéticamente determinado
- Las manifestaciones clínicas dependen del síndrome subyacente y la gravedad de fotosensibilidad



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Epilepsia com sólo CTCG

- Inicio: 6-47 años (pico 16-17)
- 100% CTCG
  - Poco frecuentes durante el día
- Hombres > Mujeres
- Precipitado por privación de sueño y alcohol
- Fotosensibilidad (13%)
- Genética: poligénica
- Pronóstico favorable
  - Evitar los factores desencadenantes
  - VPA, PB, LTG, TPM

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Investigación

Diagnóstico

SUGESTIVO DE EGI

- Inicio en la infancia o en la adolescencia
- Precipitada por la privación del sueño y alcohol
- CTCG o mioclonias en las mañanas
- Ausencias
- Fotosensibilidad
- EEG: punta-onda o polipunta-onda a 3/seg. generalizadas

SUGESTIVO DE EPILEPSIAS FOCALES

- Hx de una causa potencial
- Aura
- Actividad motora focal durante las crisis
- Automatismos

CTCG sin ningún patrón o manifestación focal de un EGI no puede ser clasificado!

Investigación

- Diagnóstico preciso
  - Implicaciones físicas, psicosociales y económicos para el paciente
  - Hx de crisis depende de un testigo
- "El arte de escuchar"
- EEG (métodos de activación)***
- Neuroimagen no es necesario cuando hay un diagnóstico clínico de EGI y pronta respuesta al tratamiento farmacológico

Tratamento farmacológico

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

2013

SPECIAL REPORT

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

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE Subcommission on AED Guidelines

Con base en la mejor evidencia disponible, cuál es la monoterapia inicial ideal para los pacientes con epilepsia recién-diagnosticada o no tratada?

Revisión de la literatura: 1940-2012

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	24	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized-onset tonic–clonic seizures	0	0	17	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: TPM, VPA

Glauser et al. Epilepsia, 2014.

Tipo de crise ou síndrome epiléptica	Nível de evidência (eficácia e efetividade)
Crianças com crises parciais	**Nível A:** OXC **Nível B:** Nenhum **Nível C:** CBZ, PB, PHT, TPM, VPA, VGB **Nível D:** CLB, CZP, LTG, ZNS
Crianças com CTCG	**Nível A:** Nenhum **Nível B:** Nenhum **Nível C:** CBZ, PB, PHT, TPM, VPA **Nível D:** OXC
Crianças com crises de ausência	**Nível A:** ESM, VPA **Nível B:** Nenhum **Nível C:** LTG **Nível D:** Nenhum
Epilepsia benigna com espículas centrotemporais	**Nível A:** Nenhum **Nível B:** Nenhum **Nível C:** CBZ, VPA **Nível D:** GBP, LEV, OXC, STM

Glauser et al. Epilepsia, 2013. UFSC

Tipo de crise ou síndrome epiléptica	Nível de evidência (eficácia e efetividade)
Adultos com crises parciais	**Nível A:** CBZ, LEV, PHT, ZNS **Nível B:** VPA **Nível C:** GBP, LTG, OXC, PB, TPM, VGB **Nível D:** CZP, PRM
Idosos com crises parciais	**Nível A:** GBP, LTG **Nível B:** Nenhum **Nível C:** CBZ **Nível D:** TPM, VPA
Adultos com CTCG	**Nível A:** Nenhum **Nível B:** Nenhum **Nível C:** CBZ, LTG, OXC, PB, PHT, TPM, VPA **Nível D:** GBP, LEV, VGB
Epilepsia mioclônica juvenil	**Nível A:** Nenhum **Nível B:** Nenhum **Nível C:** Nenhum **Nível D:** TPM, VPA

Glauser et al. Epilepsia, 2013. UFSC

Guidelines

- Falta de RCT bien diseñados
  - Niños y epilepsias generalizadas

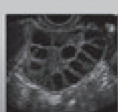
The ultimate judgment for therapy must be made in the light of all the clinical data presented by the patient and by the treatment options that are locally available for the patient and his/her clinician.

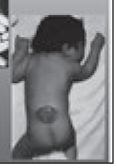
Glauser et al. Epilepsia, 2013.

UFSC UNIVERSIDADE FEDERAL DE SANTA CATARINA

Dilemas en el tratamiento

Valproato – MAE de elección

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Practical Management Issues for Idiopathic Generalized Epilepsies

Selim R. Benbadis

TABLE 1. [illegible]

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Practical Management Issues for Idiopathic Generalized Epilepsies

Selim R. Benbadis

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

AED	Seizure or epilepsy type studied	Reference
CBZ	IGE	*N Engl J Med* 1985;313:916–21
CBZ	JME	*Neurology* 2000;55:1106–9
CBZ	Unclear	*Epilepsia* 1994;35:1154–9
GBP	Childhood absence	*J Chil Neurol* 1996;11:470–5
TGB	IGE	*Seizure* 1999;8:314–7
CBZ	Unclear	*Neurology* 1983;33:1487–9
CBZ	Mixed	*Pediatr Neurol* 1986;2:340–5
CBZ	Unclear	*Epilepsia* 1994;35:1026–8
CBZ	Unclear	*Epilepsia* 1994;35:1154–9
PHT	IGE	*Neurology* 1965;15:716–22
PHT, CBZ	JME	*Epilepsia* 1994;35:285–96
PHT, CBZ	JME	*Neurology* 2000;55:1106–9
OXC	IGE	*Epilepsia* 2002;43(suppl 7):208 [abstract]
OXC	IGE	*Epilepsia* 2004;45:1282–6

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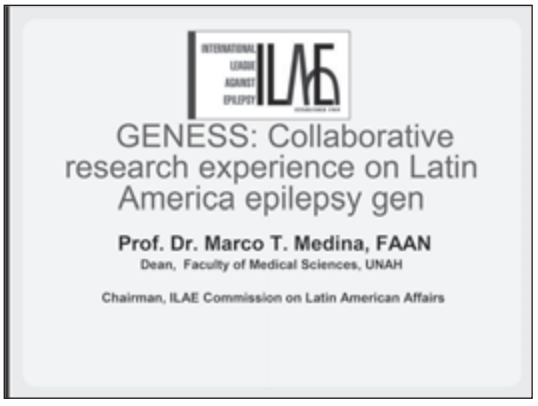
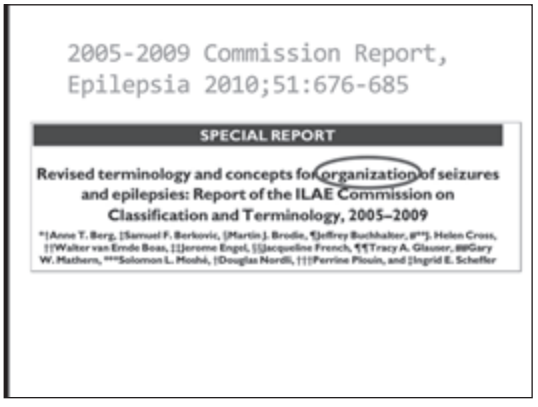
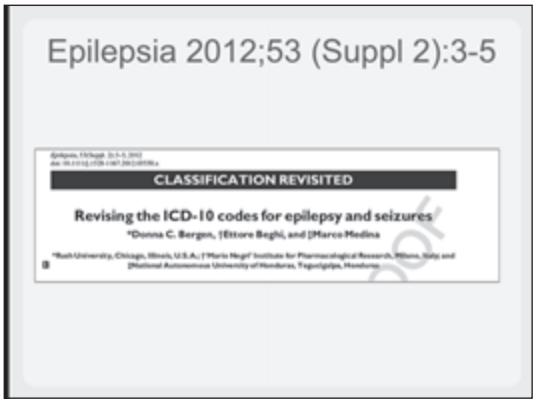
Neurologia

Marco Tulio Medina (Honduras)

GENESS – COLLABORATIVE RESEARCH EXPERIENCE ON LATIN-AMERICA EPILEPSY GENE







Recommended terminology for etiology

Use terms which mean what they say:

- Genetic
- Structural-Metabolic
- Unknown

Previously used terms denoting old concepts: Idiopathic, cryptogenic, symptomatic

Genetic

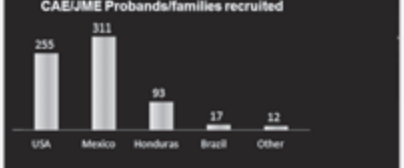
- Concept: *the epilepsy is the direct result of a known or inferred genetic defect(s).* Seizures *are the core symptom of the disorder.*
- Evidence: *Specific molecular genetic studies (well replicated) or evidence from appropriately designed family studies.*
- Genetic does *not* exclude the possibility of environmental factors contributing

GENESS

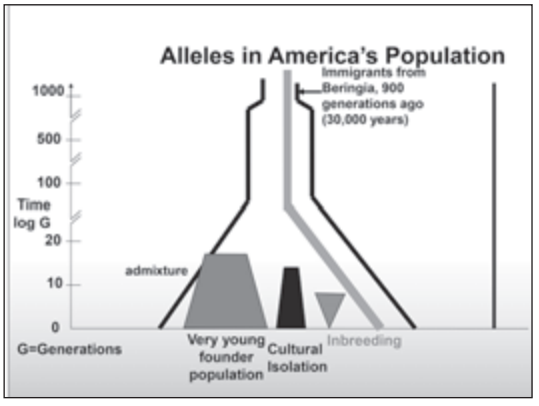
- Since 1992, the participating study sites follow the same protocol for consent and enrollment, and an intake form is used to collect demographic, clinical, EEG and imaging data. Validation of families is done by site visits from the principal investigators and by a remote system with a study coordinator.
- Delgado Escueta, Medina, Alonso, Yacubian, et al 2013

GENESS

This collaboration has resulted in the participation of **688** families: 39% from USA, 47% from Mexico, 14% from Honduras, 3% from Brazil and 2% from collaborators in other countries.



To date, 57 additional families from Brazil and Honduras are being validated and will be entered in the series.



Epilepsy Genes

Disease	Lafora Disease	JME	CAE
Phenotype	Progressive and fatal AR myoclonus epilepsy with ataxia and dementia	Myoclonic, grand mal epilepsy, 1/3 with absences	Pyknoleptic (2-200/day) absences of childhood
Pathology	*PAS+ inclusion bodies*	*Microdysgenesis-Displaced and dystopic cells*	*Normal*
Gene	*Laforin(60%) Malin(35%)*	*Myoclonin/ EFHC1*	*GABRB3*
Transgenic mice	KO and Kin mice replicate pathology	KO mice replicate pathology and susceptibility	KO mice replicate epilepsy

Gene	*Laforin/Malin*	*Myoclonin/ EFHC1*	*GABA B3*
Function	**Purge glycogen and polyglucosan bodies from neurons**	"Prunes" branches of dendritic tree	Inhibition especially in nucleus reticularus of thalamus
Epileptogenicity	Cell death Epilepsy secondary	A susceptibility gene; seizures triggered by sleep deprivation, alcohol, menses	Epileptogenic gene – spontaneous absences
Phenotype	Progressive and fatal autosomal recessive myoclonus epilepsy with ataxia and dementia	Myoclonic, grand mal epilepsy, 1/3 with absences	Pyknoleptic (2-200/day) absences of childhood
Remission	No	No	Yes

Childhood absence epilepsy

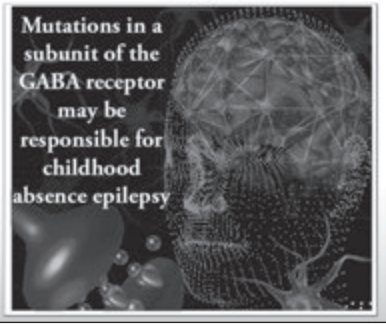
- Childhood absence epilepsy a common idiopathic generalized epilepsy accounts for 10% to 12% of epilepsy in children under 16 years of age according to prospective community-based epidemiologic studies.
- Tanaka M, Olsen RW, Medina MT, et al Am J Hum Genet. 2008 Jun;82(6):1249-61.

Fong et al. Am J Hum Gen 1998;63:1117-1129

Childhood Absence Epilepsy with Tonic-Clonic Seizures and Electroencephalogram 3–4-Hz Spike and Multispike–Slow Wave Complexes: Linkage to Chromosome 8q24

G. C. Y. Fong,[1,*] Pravina U. Shah,[4] Manyee N. Gee,[1,2] Jose M. Serratosa,[1,3] Ignacio Pascual Castroviejo,[4] Sonia Khan,[1] Sangeeta H. Ravat,[4] Jayanthi Mani,[4] Y. Huang,[1] H. Z. Zhao,[1] Marco T. Medina,[1,8] Lucy J. Treiman,[1,2] Gregorio Pineda,[1] and Antonio V. Delgado-Escueta[1,2,5,7]

Future Neurology 2008: 371



Tanaka M, Olsen RW, Medina MT, et al Am J Hum Genet. 2008 Jun;82(6):1249-61.

ARTICLE

Hyperglycosylation and Reduced GABA Currents of Mutated *GABRB3* Polypeptide in Remitting Childhood Absence Epilepsy

Miyabi Tanaka,[1,2,14] Richard W. Olsen,[1,14] Marco T. Medina,[4] Emily Schwartz,[1] Maria Elisa Alonso,[4] Reyna M. Duron,[3,4] Ramon Castro-Ortega,[3] Iris E. Martinez-Juarez,[3,4] Ignacio Pascual-Castroviejo,[6] Jesus Machado-Salas,[2] Rene Silva,[9] Julia N. Bailey,[2,10] Dongsheng Bai,[2] Adriana Ochoa,[4] Aurelio Jara-Prado,[4] Gregorio Pineda,[3] Robert L. Macdonald,[11,12,13] and Antonio V. Delgado-Escueta[2,3,*]

CAE

- We screened for mutations in the GABAA receptor (GABAR) b3 subunit gene (GABRB3) in 48 probands and families with remitting CAE
- We found that four out of 48 families (8%) had mutations in GABRB3

- Tanaka M, Olsen RW, Medina MT, et al Am J Hum Genet. 2008 Jun;82(6):1249-61.

Table 2. Clinical Characteristics of Pyknoleptic[a] Absences and Associated Seizure in Probands of Families with *GABRB3* Mutations

Family	Present Age (Yrs) and Years of Remission	Onset (Yrs)	Clinical Semiology
M120	30 (18 yrs w/o treatment, w/o seizures)	5	Staring with eyelid myoclonia[a] as eyeballs roll up. No grand mal seizure (GM).
MMD10	14 (2 yrs w/o treatment, w/o absence or atonic seizures)	2	Staring with 3 Hz eye blinks as eyeballs roll up. Rarely absences Absences appears at 2 yrs of age. Increased frequency (more than 20 attacks per day) between 4 and 5 yrs. Rare episodes of atonic seizures with flaccid limbs and vomiting. No GM.
M12	18 (no seizures and GM seizures for 2 yrs but still on treatment)	11	Staring with eyelid myoclonia[a] triggered by sunlight. GM at 12 yrs.
M08	15 (5 yrs w/o treatment, w/o absence seizures)	7	Staring as eyeballs roll up triggeredby light, No GM.

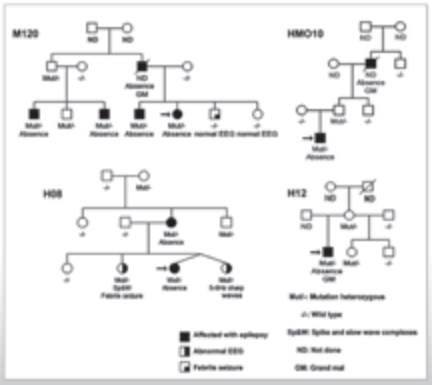
CAE GABRB3

- One heterozygous missense mutation (P11S) in exon 1a segregated with four CAE-affected persons in one multiplex, two-generation Mexican family. P11S was also found in a singleton from Mexico

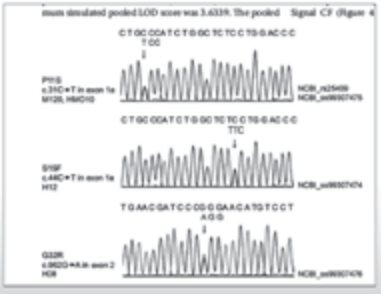
- Tanaka M, Olsen RW, Medina MT, et al Am J Hum Genet. 2008 Jun;82(6):1249-61.

CAE GABRB3

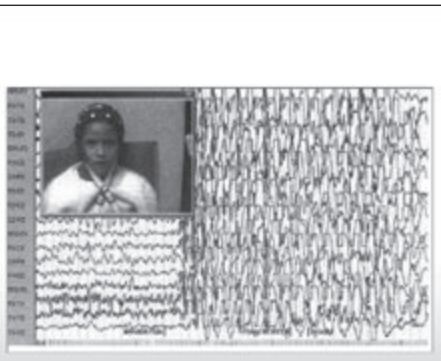
- Another heterozygous missense mutation (S15F) was present in a singleton from Honduras. An exon 2 heterozygous missense mutation (G32R) was present in two CAE affected persons and two persons affected with EEG-recorded spike and/or sharp wave in a two-generation Honduran family
- Tanaka M, Olsen RW, Medina MT, et al Am J Hum Genet. 2008 Jun;82(6):1249-61.


M120
HMO10
H08
H12
Mut+ Mutation heterozygous
-/- Wild type
ND: Not done
GM: Grand mal

MUTATIONS

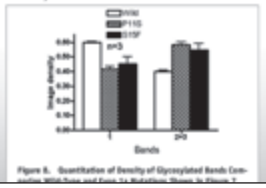



LAS EPILEPSIAS EN CENTROAMERICA



CAE GABRB3

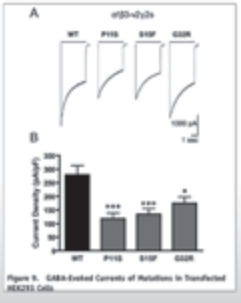
- Expression levels did not differ from those of controls, but all mutations showed hyperglycosylation in the in vitro translation and translocation system with canine microsomes



CAE GABRB3

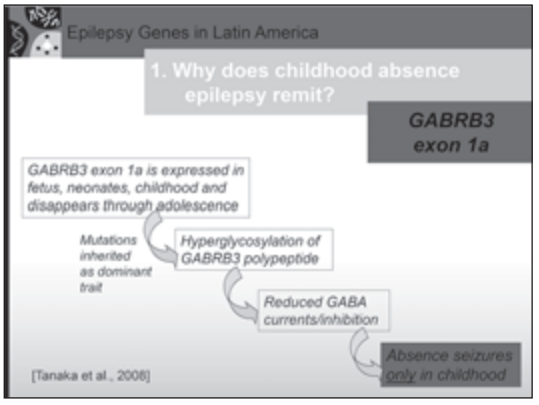
- Functional analysis of human GABAA receptors (a1b3-v2g2S, a1b3-v2[P11S]g2S, a1b3-v2[S15F]g2S, and a1b3-v2[G32R]g2S) transiently expressed in HEK293T cells with the use of rapid agonist application showed that each amino acid transversion in the b3-v2 subunit (P11S, S15F, and G32R) reduced GABA-evoked current density from whole cells.

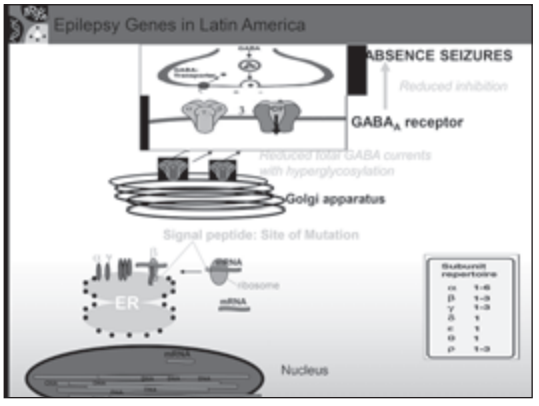
GABA-Evoked currents

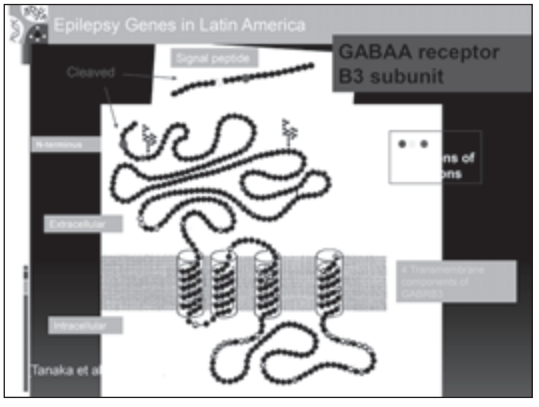


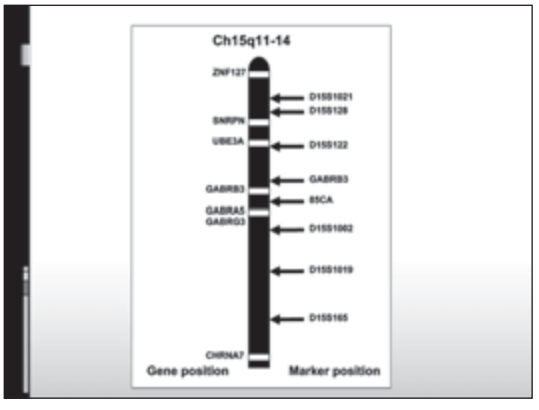
GABRB3

- Mutated b3 subunit protein could thus cause absence seizures through a gain in glycosylation of mutated exon 1a and exon 2, affecting maturation and trafficking of GABAR from endoplasmic reticulum to cell surface and resulting in reduced GABA-evoked currents.


Epilepsy Genes in Latin America
1. Why does childhood absence epilepsy remit?
GABRB3 exon 1a
GABRB3 exon 1a is expressed in fetus, neonates, childhood and disappears through adolescence
Mutations inherited as dominant trait
Hyperglycosylation of GABRB3 polypeptide
Reduced GABA currents/inhibition
Absence seizures only in childhood
[Tanaka et al., 2008]


Epilepsy Genes in Latin America
ABSENCE SEIZURES
Reduced inhibition
GABA$_A$ receptor
Reduced total GABA currents with hyperglycosylation
Golgi apparatus
Signal peptide: Site of Mutation
ER
ribosome
Nucleus
Subunit repertoire


Epilepsy Genes in Latin America
GABAA receptor B3 subunit
Cleaved
Signal peptide
Extracellular
Intracellular


Ch15q11-14
ZNF127
SNRPN
UBE3A
GABRB3
GABRA5
GABRG3
CHRNA7
D15S1021
D15S128
D15S122
GABRB3
85CA
D15S1002
D15S1019
D15S165
Gene position
Marker position

IDIOPATHIC GENERALIZED EPILEPSIES:

JUVENILE MYOCLONIC EPILEPSY

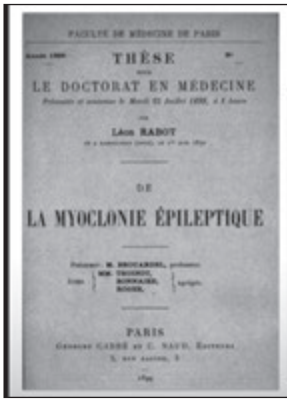
TH. Herpin 1867


DES ACCÈS INCOMPLETS

D'ÉPILEPSIE

TH. HERPIN

PARIS


FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MÉDECINE

Par

Léon RABOT

DE

LA MYOCLONIE ÉPILEPTIQUE

PARIS

Herpin, 1867
"secousses"
"impulsions"

Rabot, 1899
"sacudidas breves"
"mioclonias"

Sole-Sagarra, 1952
"benigno"

Janz, 1955
"impulsiv petit mal"

IMPULSIV-PETIT MAL (1957 Berlin)

-


Impulsiv-Petit mal

Von

D. Janz und W. Christian

Janz D, Christian W. Impulsive-petit mal. J Neurol 1957;176:344–386.

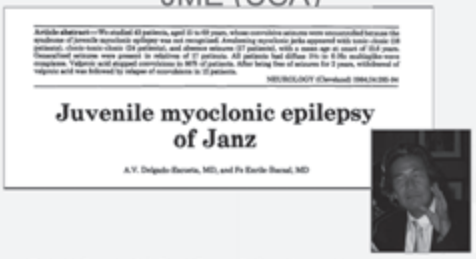
Contributions:"The bilateral and aware myoclonic epilepsy" (1954-1958 Montevideo, Uruguay)

La epilepsia mioclónica bilateral y consciente

Constancio Castells

- Carlos Mendilaharsu

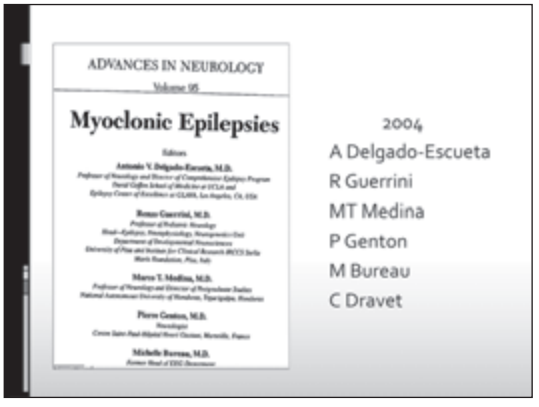
Delgado Escueta and E. Bacsal JME (USA)



Juvenile myoclonic epilepsy of Janz

A.V. Delgado-Escueta, MD, and Fe Enrile-Bacsal, MD

- Delgado-Escueta AV, Enrile-Bacsal F. Juvenile myoclonic epilepsy of Janz. Neurology 1984;34:285–294.



ADVANCES IN NEUROLOGY

Volume 95

Myoclonic Epilepsies

Editors

Antonio V. Delgado-Escueta, M.D.

Renzo Guerrini, M.D.

Marco T. Medina, M.D.

Pierre Genton, M.D.

Michelle Bureau, M.D.

2004

A Delgado-Escueta

R Guerrini

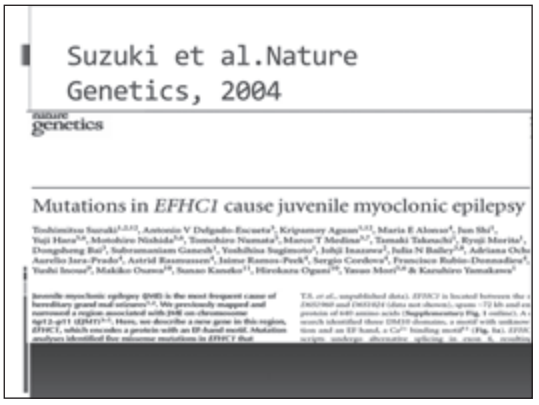
MT Medina

P Genton

M Bureau

C Dravet

Suzuki et al.Nature Genetics, 2004



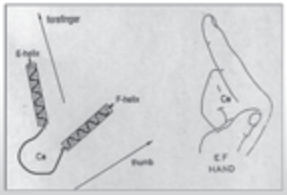
nature genetics

Mutations in *EFHC1* cause juvenile myoclonic epilepsy

Epilepsy Genes

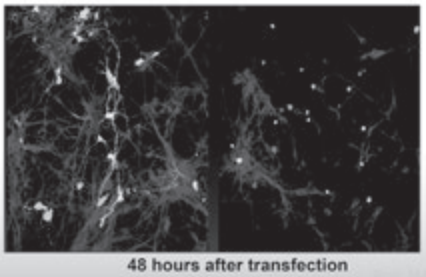
JME - Myoclonin/EFHC1

- Domain search through Interpro and Pfam databases revealed an EF hand motif connected by a calcium binding loop (Kretsinger et al., 1973) (pfam00036; E-value 0.00066) between amino acid residues 578 and 660 and three DM10 domains
- We named the gene myoclonin because function was initially unknown and EFHC1 for EFH containing one EF hand.



Epilepsy Genes

EFHC1 caused cell death in mouse hippocampal neuron culture



48 hours after transfection

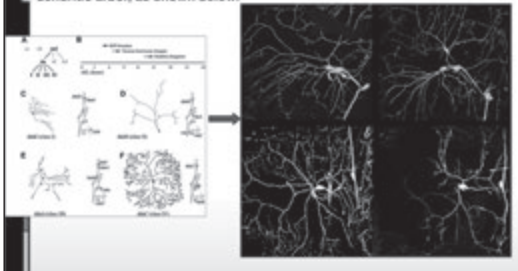
Epilepsy Genes

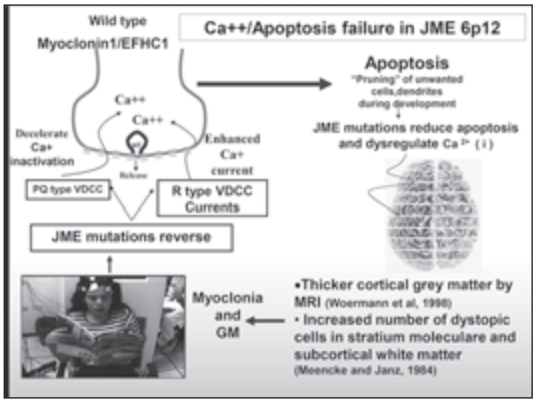
Myoclonin/EFHC1 enhances R type VDCC currents (voltage-dependent Ca2+ channels)

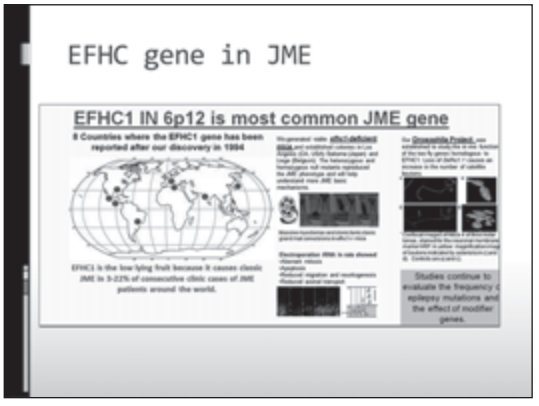
JME mutations reverse myoclonin effects.

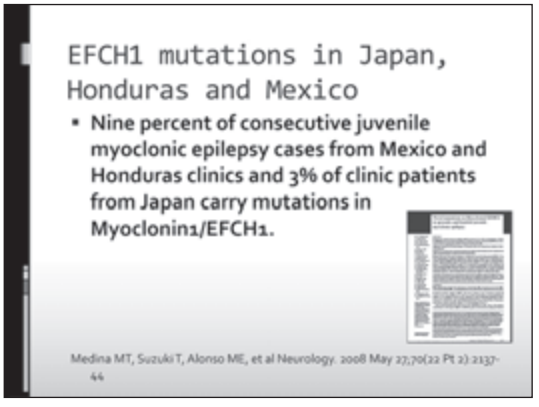
[Suzuki et al., 2004]

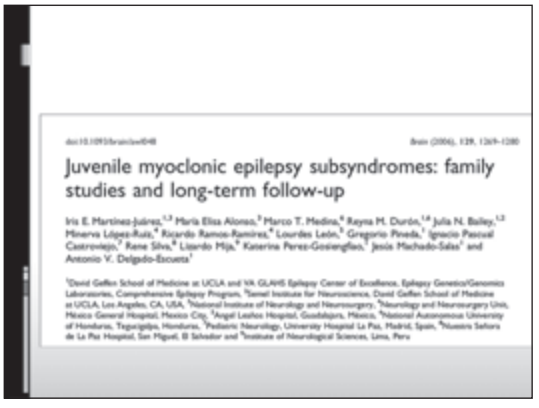
Loss of 8959 in sensory neurons results in a subtle dendrite phenotypes. In contrast, overexpression causes a clear under development of the dendritic arbor, as shown below.



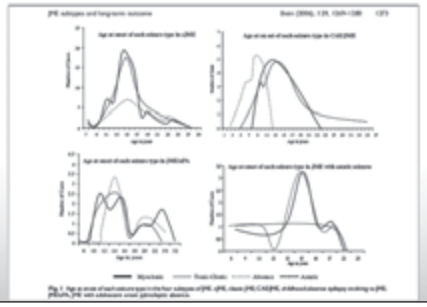

Wild type
Myoclonin1/EFHC1
Ca++/Apoptosis failure in JME 6p12
Apoptosis
"Pruning" of unwanted cells,dendrites during development
JME mutations reduce apoptosis and dysregulate Ca 2+ (i)
Ca++
Ca++
Decelerate Ca+ inactivation
Enhanced Ca+ current
Release
PQ type VDCC
R type VDCC Currents
JME mutations reverse
Myoclonia and GM
•Thicker cortical grey matter by MRI (Woermann et al, 1998)
• Increased number of dystopic cells in stratium moleculare and subcortical white matter
(Meencke and Janz, 1984)


EFHC gene in JME
EFHC1 IN 6p12 is most common JME gene
8 Countries where the EFHC1 gene has been reported after our discovery in 1994
EFHC1 is the low-lying fruit because it causes classic JME in 3-23% of consecutive clinic cases of JME patients around the world.
Studies continue to evaluate the frequency of epilepsy mutations and the effect of modifier genes.

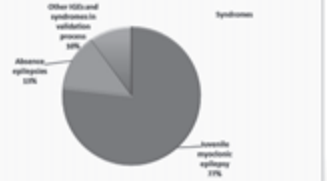

EFCH1 mutations in Japan, Honduras and Mexico
• Nine percent of consecutive juvenile myoclonic epilepsy cases from Mexico and Honduras clinics and 3% of clinic patients from Japan carry mutations in Myoclonin1/EFCH1.
Medina MT, Suzuki T, Alonso ME, et al Neurology. 2008 May 27;70(22 Pt 2):2137-44


Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up

SUBSYNDROMES



- The data has helped us understand the existence of subsyndromes not reported in the literature before, such as CAE evolving to JME.



Childhood Absence Epilepsy Evolving to Juvenile Myoclonic Epilepsy: Electroclinical and Genetic Features

Medina et al 2005

Subsyndromes

- In a large cohort of JME patients mainly from USA and Latin America four JME subsyndromes where reported: classic JME (72%), CAE (childhood absence epilepsy) evolving to JME (18%), JME with adolescent absence (7%), and JME with astatic seizures (3%).

ONG TERM FOLLOW-UP OF 222 JME PATIENTS MEAN PERIOD 11.6 YEARS)

	Myoclonias only	Myoclonias + TCS	Myoclonias + TCS + absence
Seizure free	80%	63%	46%

- Conclusion: the more seizure phenotypes, more progression to epileptogenicity, the lower success rate.
- Treatment during susceptibility stage has higher success rate.

Phenotypes

Phenotypes of JME Genes studied by GENESS Consortium

MUTATED EPILEPSY GENE(S) AND CHROMOSOME LOCI	SEIZURE PHENOTYPES		EPILEPSY SYNDROME	NORMAL FUNCTION OF JME GENES
	CHILDHOOD	ADOLESCENCE		
[illegible]	–	[illegible]	Classic JME	[illegible]
[illegible]	–	[illegible]	Classic JME	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	Absence seizures	[illegible]	[illegible]	[illegible]
[illegible] 2p	–	[illegible]	Classic JME	Unknown
[illegible]	[illegible]	[illegible]	[illegible]	Unknown
[illegible]	–	[illegible]	Classic JME	Unknown

Absence seizures in Juvenile Myoclonic Epilepsy: whole exome sequencing results and subsyndromes

- Reyna M. Durón, Marco T. Medina, Iris E. Martínez-Juarez, et al.

- To refine the classification of Juvenile Myoclonic Epilepsy (JME) subsyndromes in 298 cases according to presence and age at onset of absence seizures (ABS) and results of whole exome sequencing (WES).

2015

METHODS

- JME cases were regrouped according to age onset of ABS: early childhood (1-5 yr) [eCA/JME], childhood (6-11y) [CA/JME], adolescence [adolABS/JME] (12-21y), and JME with ABS in adulthood (22y+). Whole exome sequencing (WES) of 12 large JME families followed linkage and haplotype analysis. Discovered epilepsy genes were then screened in the 298 cases.

Results

- In total, 52% of probands had JME with ABS and 48% had JME without ABS.
- Of 298 probands with JME, 134 probands (45%) had classic JME (cJME), 60 (20%) had CA/JME, 70 (23%) had adolABS/JME, 20 (7%) had eCA/JME, 9 (3%) had astatic seizures with JME, and only 5 (2%) had adulthood ABS/JME. EFHC1 variants were implicated in cJME (16 cases) and CA/JME (1 case).

Results

- ICK variants were implicated in cJME (7 probands) and adolABS/JME (1 proband). IPO8 variants were implicated in photosensitive CA with/without EM evolving to JME (6 probands)

Results

- JME with adolABS (2 probands), JME with astatic seizures (1 proband), and JME with adult onset ABS (1 proband), and 7 cases of childhood ABS only from another cohort. PROSER1 variants were implicated with adolABS/JME (6 probands) and one case with cJME. MYOFERLIN variant was implicated in one case of photosensitive self-induced eCA evolving to JME.

2016

Molecular Genetics & Genomic Medicine

Open Access

ORIGINAL ARTICLE

Chromosome loci vary by juvenile myoclonic epilepsy subsyndromes: linkage and haplotype analysis applied to epilepsy and EEG 3.5–6.0 Hz polyspike waves

Jenny E. Wight[1,2], Viet-Huong Nguyen[1,2], Marco T. Medina[2,3], Christopher Patterson[1,2], Reyna M. Durón[1,3,4,5], Yolly Molina[3,5], Yu-Chen Lin[1,2], Iris E. Martínez-Juárez[3,4], Adriana Ochoa[3,4], Aurelio Jara-Prado[3,4], Miyabi Tanaka[1,4,5], Dongsheng Bai[1,3,5], Sumaya Aftab[1,3,5], Julia N. Bailey[1,2,5,*] & Antonio V. Delgado-Escueta[1,2,3,5]

[1]Epilepsy Genetics/Genomics Laboratories, VA GLAHS – West Los Angeles, Los Angeles, California
[2]GENES International Consortium, Los Angeles, California
[3]National Autonomous University of Honduras, Tegucigalpa, Honduras
[4]Universidad Tecnológica Centroamericana (UNITEC), Tegucigalpa, Honduras
[5]Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California
[6]National Institute of Neurology and Neurosurgery, Mexico City, Mexico
[7]Department of Epidemiology, Fielding School of Public Health at UCLA, Los Angeles, California

Conclusions

- EFHC1 and ICK variants are most common in cJME, while IPO8 and MYOFERLIN variants predominate in eCA/JME, adolABS/JME, CA/JME and JME with adult onset ABS. PROSER1 variants associated with JME with pyknoleptic adolABS

Conclusions

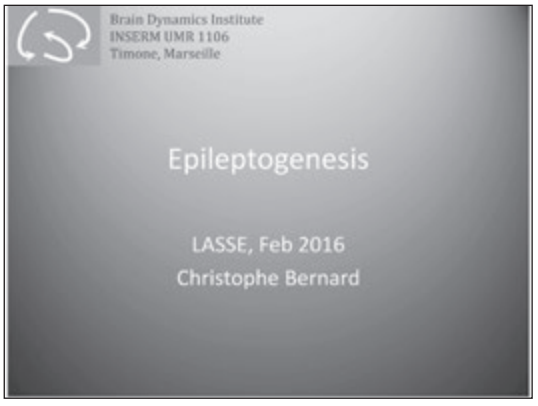
- Finding variants of epilepsy genes in the subsyndromes of JME described mean they are true entities and separate diseases. As we reach 1000 JME families, we expect more refinement in the classification of these JME subsyndromes and new CAE genes.

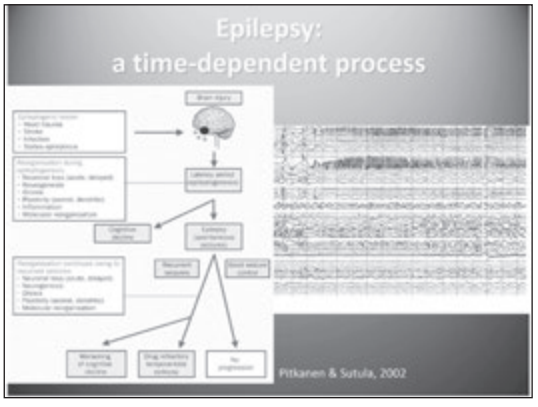
Conclusions

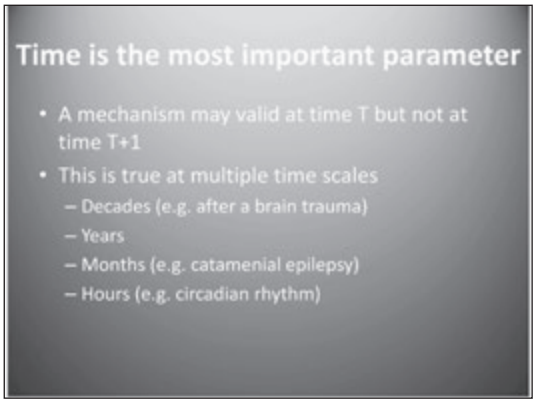
- Genetic of Epilepsies studies in Latin America have improved our knowledge of the most common epilepsy syndromes.

Christophe Bernard (France)

EPILEPTOGENESIS





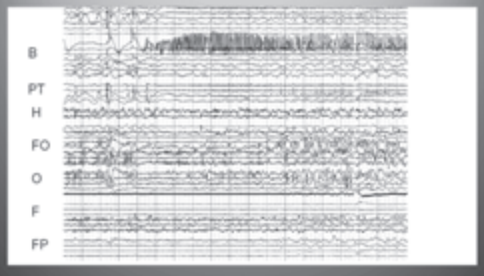


How do we study a brain disease?

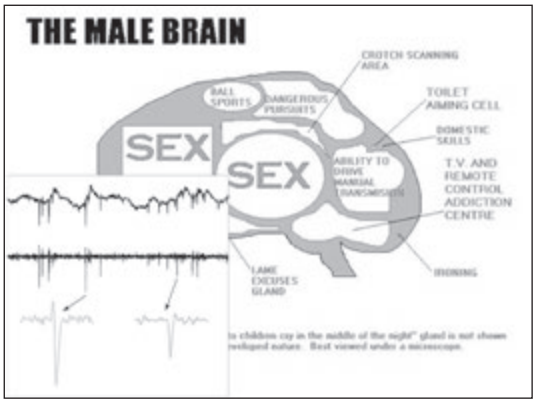
Common strategy

- Describe the reorganization within circuits
- Try to infer a potential functional impact
- But this inference relies on the way we think how the brain works
- We don't know how the brain works

Where do these signals come from?

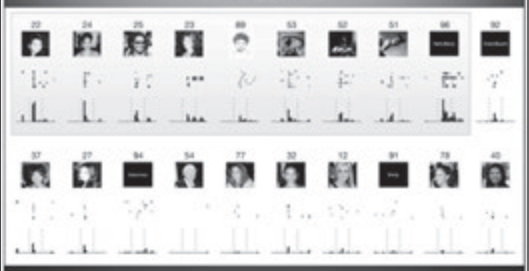


THE MALE BRAIN

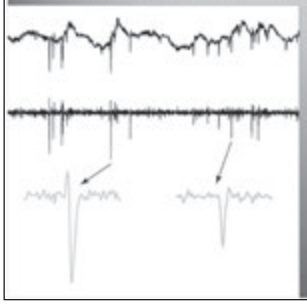


A neuron specific for an identity

Halle Berry Neuron



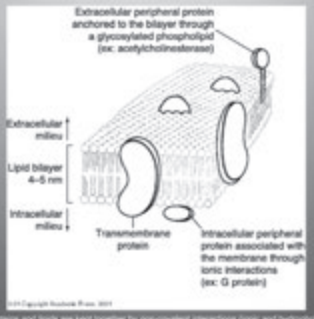
Action potentials as a basic unit to process/transmit information



The question: What makes a neuron fire an action potential?

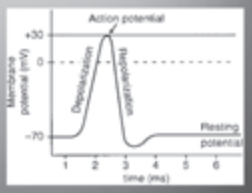
What is so specific about neurons?

The plasma membrane



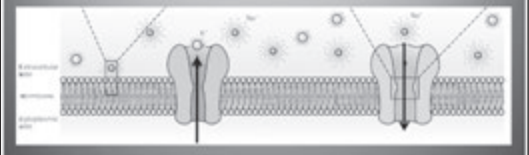
Transmembrane proteins and lipids are kept together by non-covalent interactions (ionic and hydrophobic)

Neuron vs. extracellular space: a constant ionic unbalance



Ion channels are proteins that span the membrane and allow ion passage

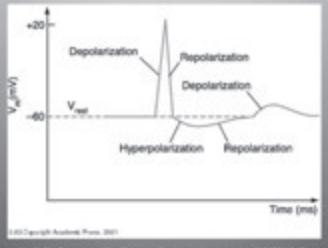
$[K^+]$=3 mM $[Na^+]$=140 mM



$[K^+]$=140 mM $[Na^+]$=7 mM

Some channels are permeable to specific ions and let them pass according their gradient at rest

The membrane potential can vary

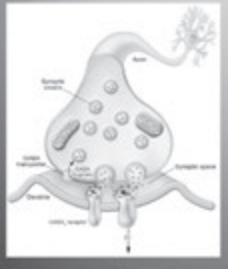


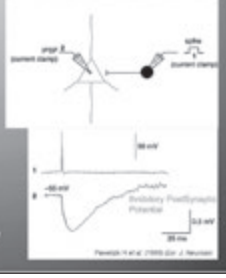
When the membrane potential is less negative than resting membrane potential (V_{rest}), the membrane is said to be depolarized. In contrast, when the membrane potential is more negative than V_{rest}, the membrane is said to be hyperpolarized. When the membrane varies from a depolarized or hyperpolarized value back to rest, the membrane repolarizes.

14

The GABAergic Inhibitory synapse

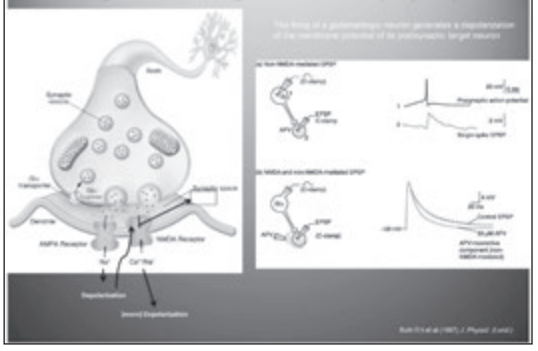
The firing of a GABAergic neuron generates a hyperpolarization of the membrane potential of its postsynaptic target neuron



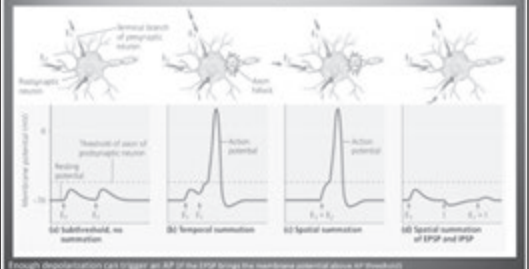


$GABA_A$ receptor-mediated IPSPs recorded in pyramidal cells of the hippocampus

The glutamatergic excitatory synapse



The postsynaptic potentials affect the membrane potential

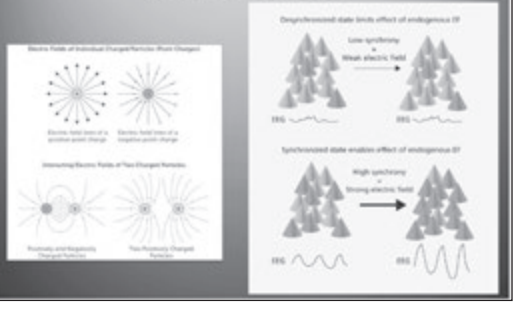


Enough depolarization can trigger an AP (if the EPSP brings the membrane potential above AP threshold)

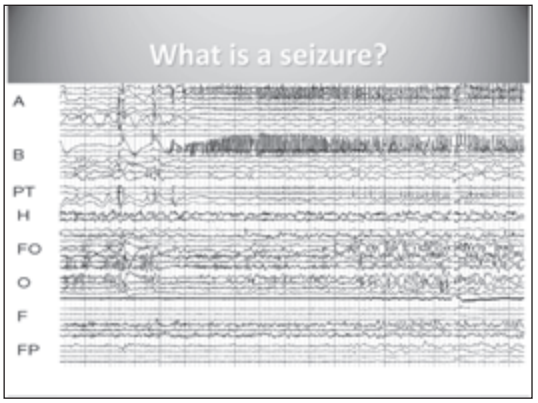
And enough hyperpolarization can prevent the neuronal firing (if the IPSPs keep the membrane potential below AP threshold)

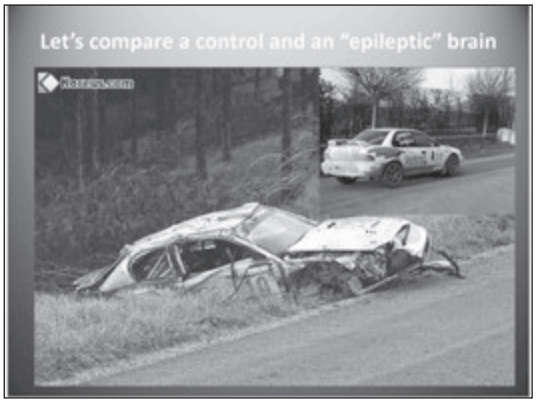
Both spatial and temporal summation occur

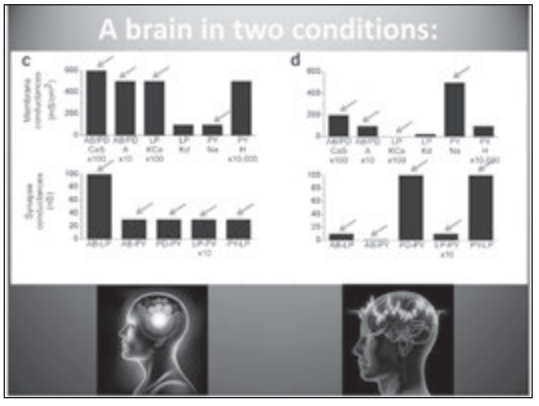
EEG is just the result of fluctuations of an electrical field

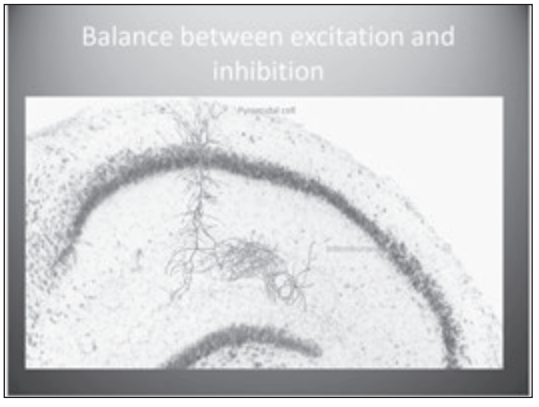


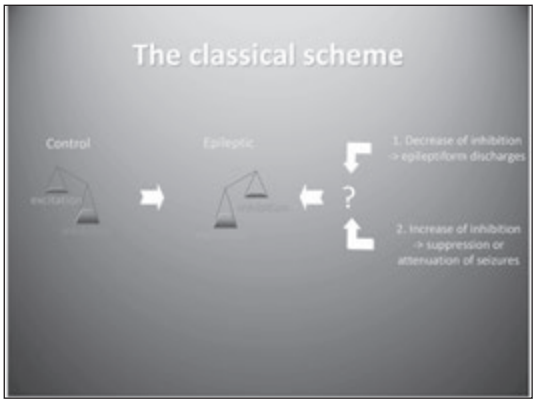
What is a seizure?

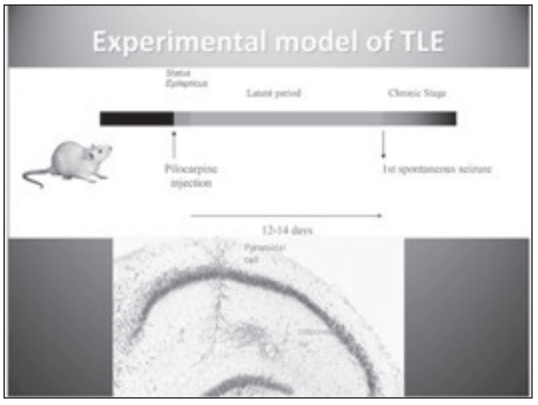


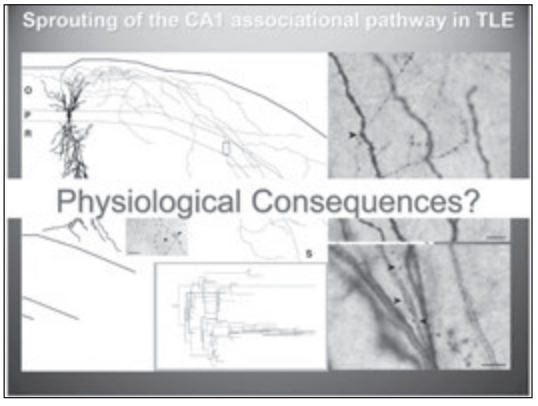

Let's compare a control and an "epileptic" brain

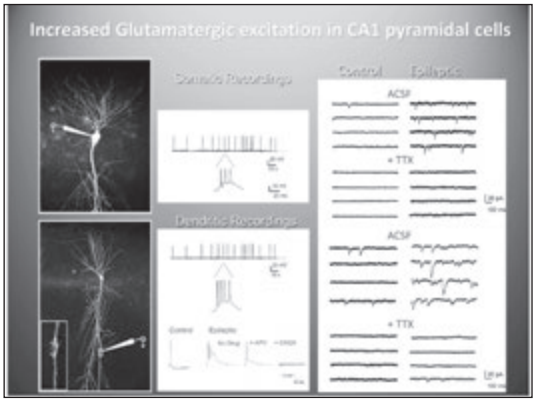

A brain in two conditions:

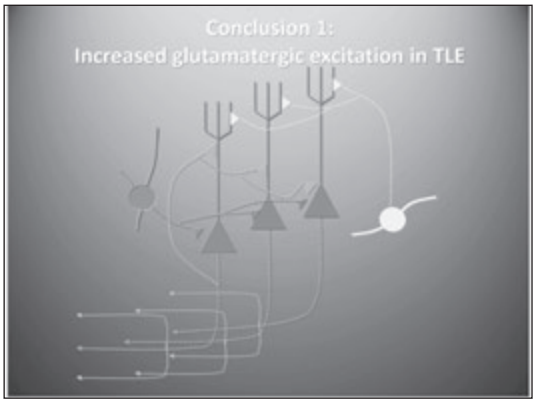

Balance between excitation and inhibition

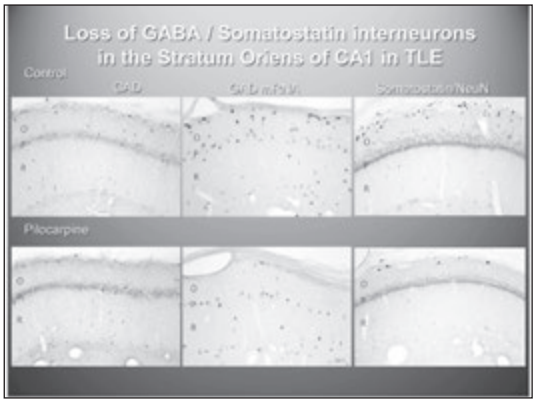

The classical scheme
Control
Epileptic
1. Decrease of inhibition
-> epileptiform discharges
?
2. Increase of inhibition
-> suppression or
attenuation of seizures

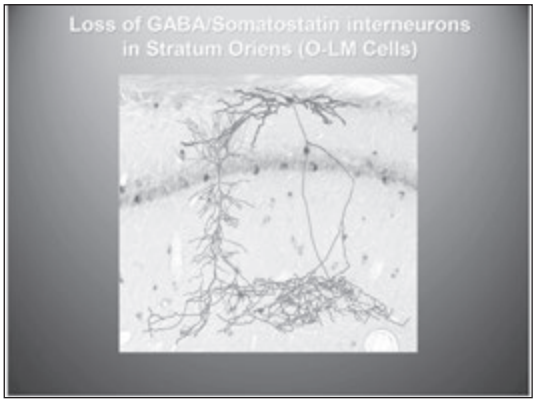

Experimental model of TLE
Status Epilepticus
Latent period
Chronic Stage
Pilocarpine injection
1st spontaneous seizure
12-14 days

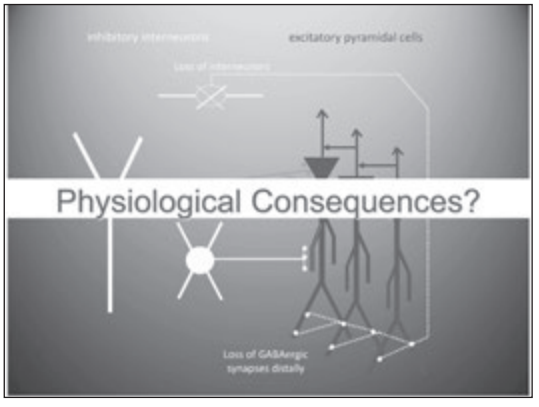

Sprouting of the CA1 associational pathway in TLE
Physiological Consequences?

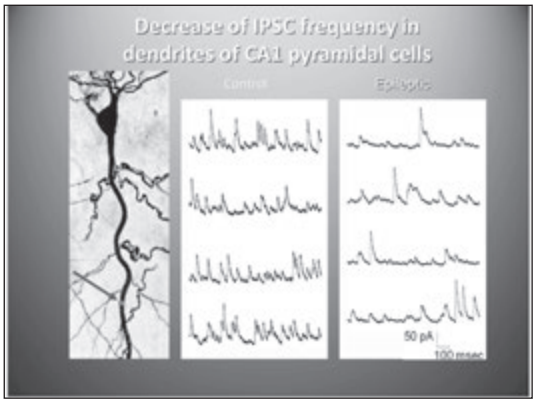

Increased Glutamatergic excitation in CA1 pyramidal cells
Control
Epilepsy
ACSF
+ TTX
ACSF
+ TTX


Conclusion 1:
Increased glutamatergic excitation in TLE

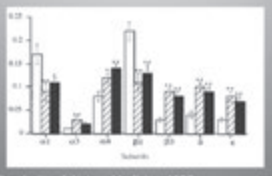

Loss of GABA / Somatostatin interneurons
in the Stratum Oriens of CA1 in TLE
Control
Pilocarpine


Loss of GABA/Somatostatin interneurons
in Stratum Oriens (O-LM Cells)


inhibitory interneurons
excitatory pyramidal cells
Physiological Consequences?
Loss of GABAergic
synapses distally

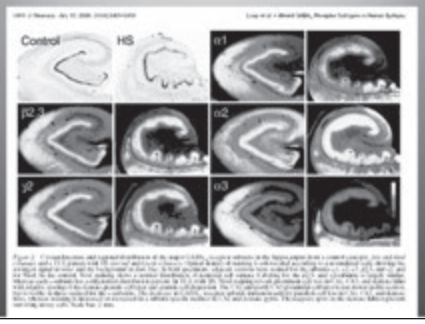

Decrease of IPSC frequency in
dendrites of CA1 pyramidal cells
Control
Epileptic
50 pA
100 msec

Change in subunit expression in epilepsy

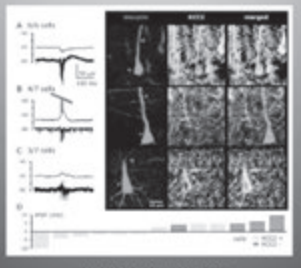


Brooks-Kayal, Nature Medicine, 1998

Changes in human TLE

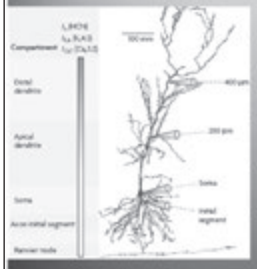


Change in Cl reversal potential in epilepsy



Huberfeld, J Neurosc, 2007

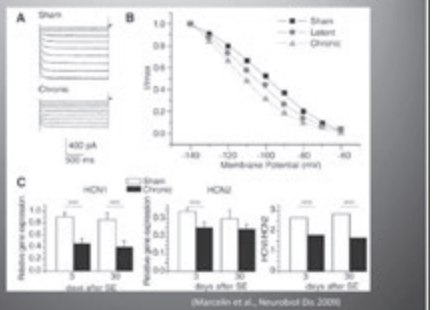
HCN channels



- Make I_h current
- Non specific cationic channel
- Activated by hyperpolarization
- Density increases with the distance from the soma
- Controls resting membrane potential and input resistance
- Controls integration of synaptic inputs

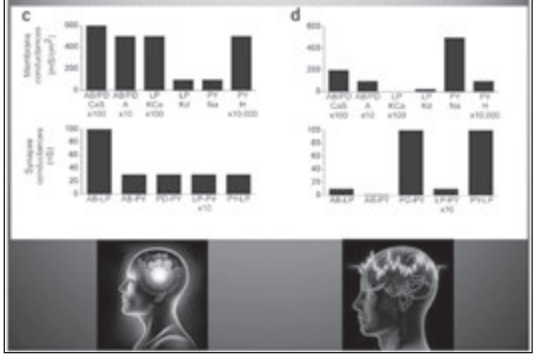
Beck & Yaari Nature Rev Neurosc 2008

Decrease of HCN1 & I_h in epilepsy

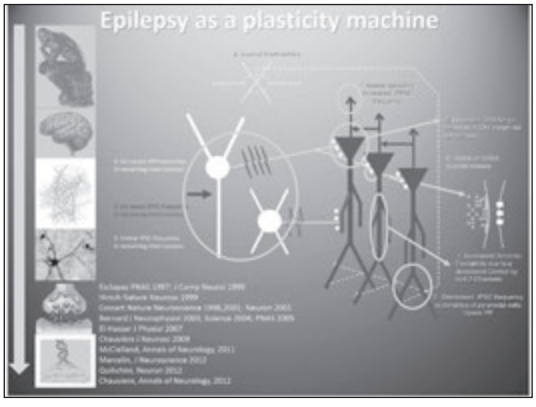


(Marcelin et al., Neurobiol Dis 2009)

A brain in two conditions:

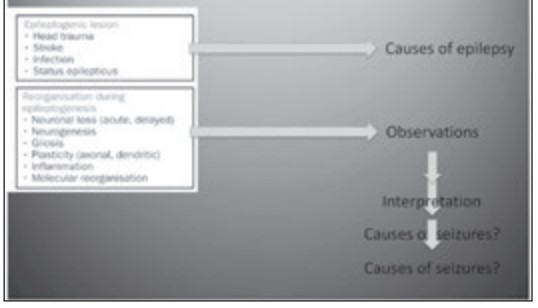


Epilepsy as a plasticity machine



Cell function and dysfunction

How do we perform causal inferences?

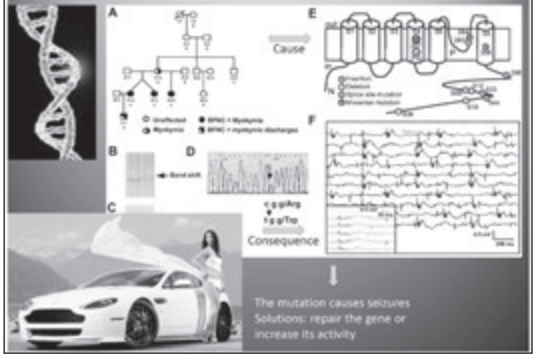


The problem of data interpretation

- In general, when scientists interpret data, they attempt to explain what they observe through analysis, bringing all of their background knowledge and relate their data to existing scientific ideas.
- Given the personal nature of the knowledge they draw upon, this step can be subjective.

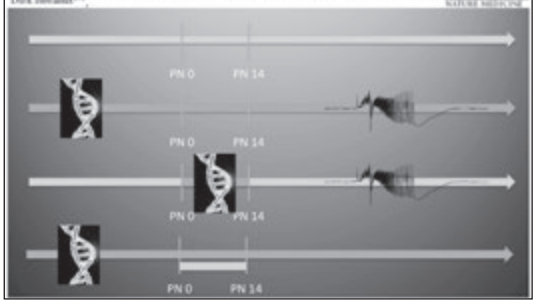
Brain disorders and the broken car

Genetic forms of epilepsy: ex KCNQ2

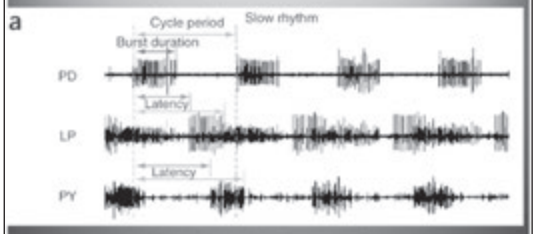


Treatment during a vulnerable developmental period rescues a genetic epilepsy

Stephan Lawrence Margues[1–3,7], Vu Thao Quyen Le-Schulte[1,7], Andrea Mereseburg[1–3], Axel Neu[3], Ronny Eichler[1], Igor Jakovcevski[1,2], Anton Ivanov[4], Ileana Livia Hanganu-Opatz[5], Christophe Bernard[4], Fabio Morellini[3,6] & Dirk Isbrandt[1–3]*



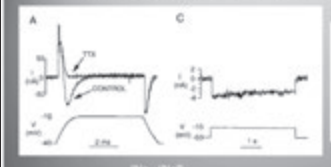
Lessons from lobsters



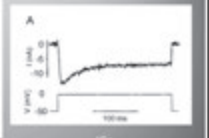
Marder, 2010

Question: how is the rhythm generated?
Depends upon neuronal intrinsic properties
Depends upon connections

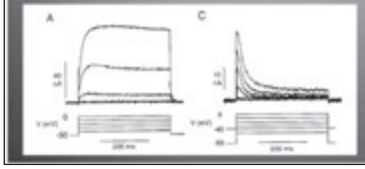
Let's characterize everything



INa - INaP



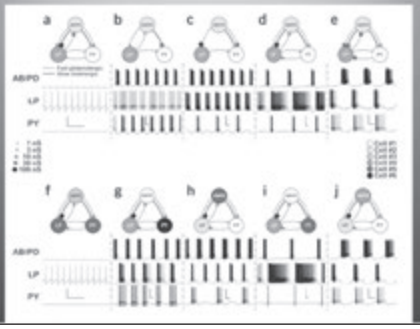
ICa



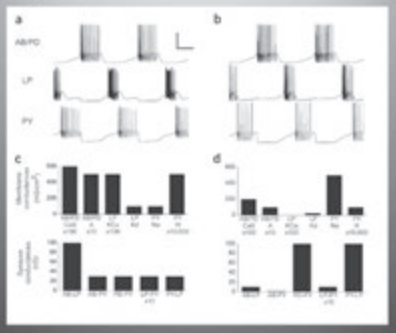
Ikd - IA

Too many parameters
Let's try a model
But which values?

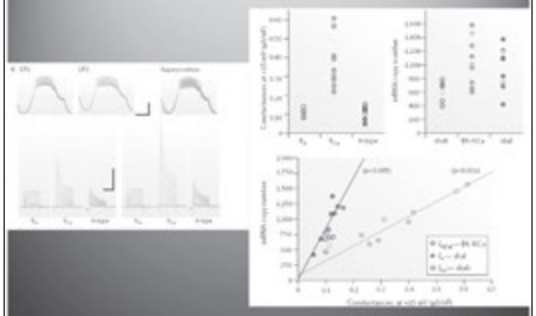
Trying all possible combinations ...



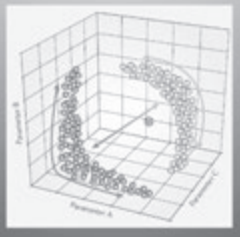
… generates millions of solutions



Variability in silico = in vivo



Rules of co-variance



What kind ok knowledge did we gain?

- Where is my magic bullet for epilepsy?
- A change in parameter could be homeostatic or an epiphenomenon
- There are too many free parameters
- We don't have the blueprint

Lessons from Human genetics

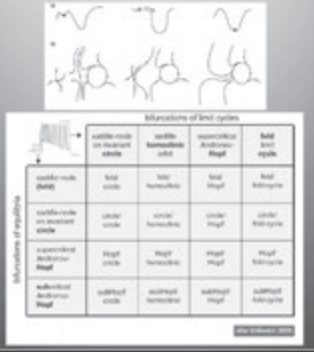
Klassen, Cell, 2011

What is epilepsy?

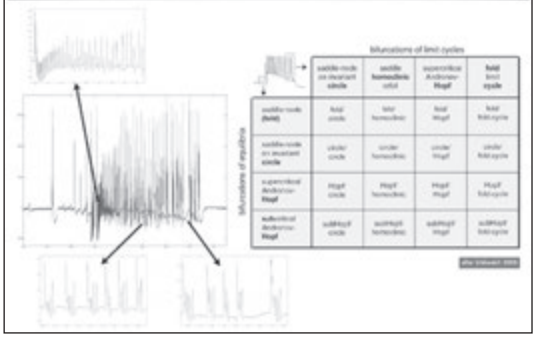
- Any "healthy" brain can have a seizure
- Seizures are latent activities (idem for status epilepticus and spreading depression)
- What are the mechanisms underlying seizure genesis and propagation?
- Two concepts: a threshold and a force that pushes the system over the threshold

All roads lead to seizures

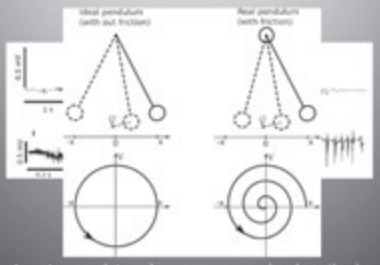
Different ways to cross a threshold



Taxonomy of seizures: 16 types



Seizure description



Any time evolving phenomenon can be described by differential equations and state variables

How many state variables?

Ensemble 1 — **At least 3 state variables**

2 fast, 1 one very slow variable

Onset bifurcation off the equilibrium point (slow manifold) with non-zero frequency and non-zero amplitude:

1. Saddle-node bifurcation
2. Subcritical Andronov-Hopf bifurcation

Offset bifurcation off the limit cycle with non-zero amplitude and slowing down (logarithmic scaling of frequency)

1. Saddle-Node-Invariant-Circle (SNIC) bifurcation
2. Homoclinic bifurcation

Ensemble 2 — **At least 2 state variables**

Spike-wave complex on slow time scales shows excitable features

SNIC bifurcation

Oscillations in spike-wave complex only during the wave part

The Epileptor equations

Ensemble 1

$$\dot{x}_1 = y_1 - f_1(x_1, x_2) - z + I_{ext}$$
$$\dot{y}_1 = c_1 - d_1 x_1^2 - y_1$$

Ensemble 2

$$\dot{x}_2 = -y_2 + x_2 - x_2^3 + I_{ext2} + 2g(x_1) - c_2 z$$
$$\dot{y}_2 = \frac{1}{\tau}(-y_2 + f_2(x_1, x_2))$$

Energy $\dot{z} = r(s(x_1 + x_2 - x_0) - z)$

$$g(x_1) = \int_{t_0}^{t} e^{-\gamma(t-\tau)} x_1(\tau) d\tau$$

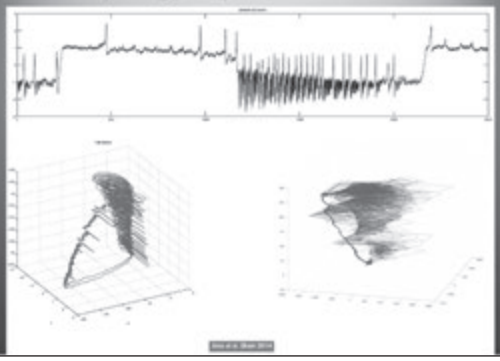
$$f_1(x_1, x_2) = \begin{cases} a_1 x_1^3 - b_1 x_1^2 \text{ for } x_1 < 0 \\ -(m - x_2 + c_1(z-4)^2) x_1 \text{ for } x_1 \geq 0 \end{cases}$$

Inhibitory coupling from 2 to 1

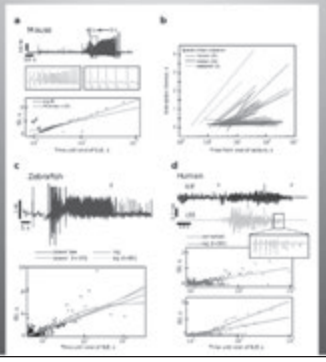
$$f_2(x_1, x_2) = \begin{cases} 0 \text{ for } x_2 < -0.25 \\ a_2(x_2 + 0.25) x_1 \text{ for } x_2 \geq -0.25 \end{cases}$$

Excitatory coupling from 1 to 2

The topology of partial onset seizures



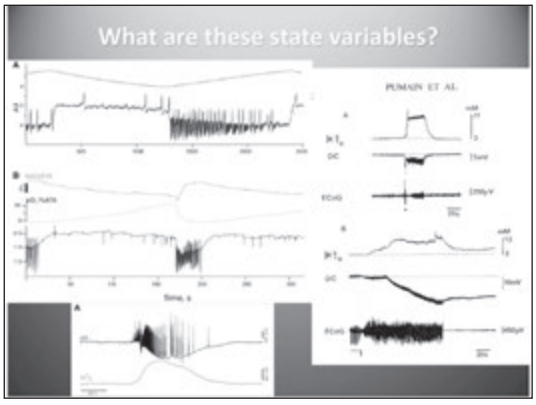
Prediction: Seizure offset: logarithmic scaling



Dynamics are invariant across species and brain regions

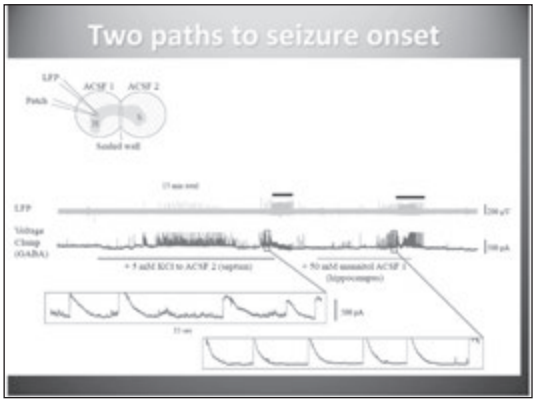
Jirsa et al., Brain, 2014

What are these state variables?

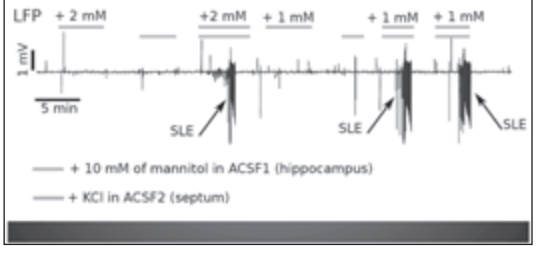


Two roads seizures

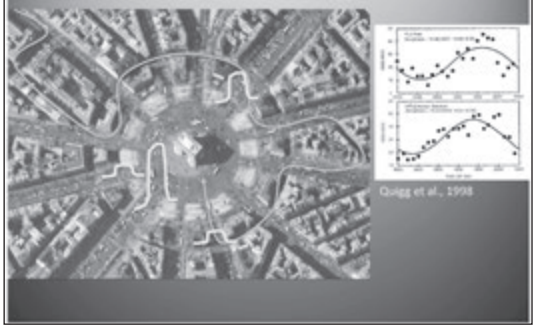
Two paths to seizure onset



There can be an infinite number of ways to cross the threshold



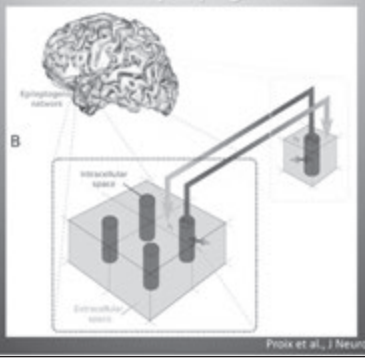
Why do patients have seizures?



Conclusions 1.

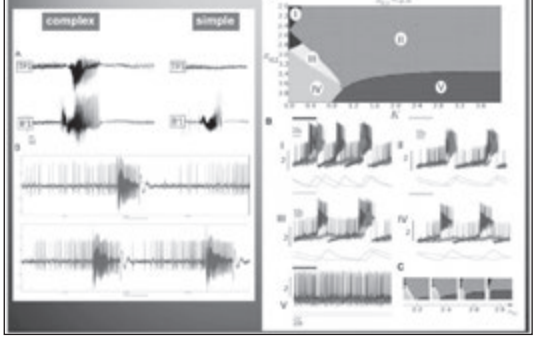
- Complementary classification of seizures based on their dynamics properties
- Seizures with partial onset follow simple dynamic rules
- There is an infinite number of possibilities to reach seizure threshold
- But the biophysics is constrained by these rules (Naze et al., PLoS Comp Biol, 2015)
- What is now important:
  - Exploring thresholds
  - What pushes the system to the threshold
- Beyond the Epileptor

Seizure propagation



Proix et al., J Neuroscience 2014

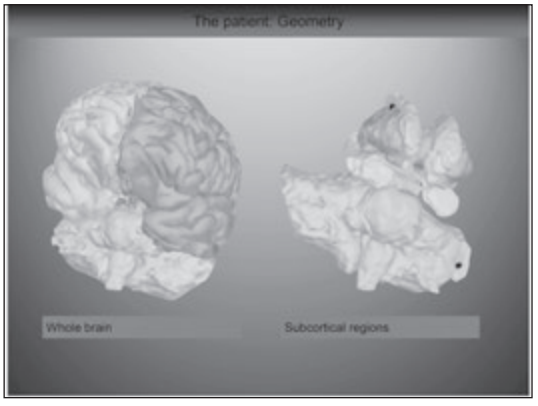
Rules of propagation

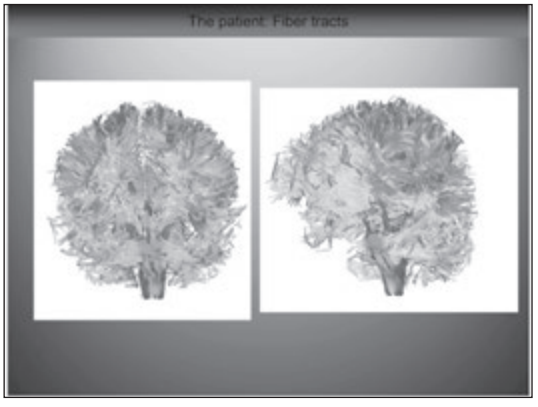


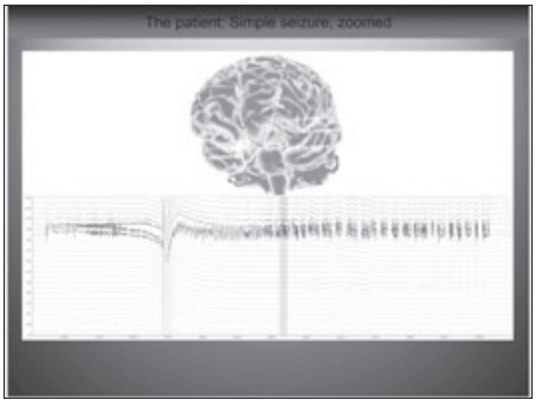
Conclusions 2.

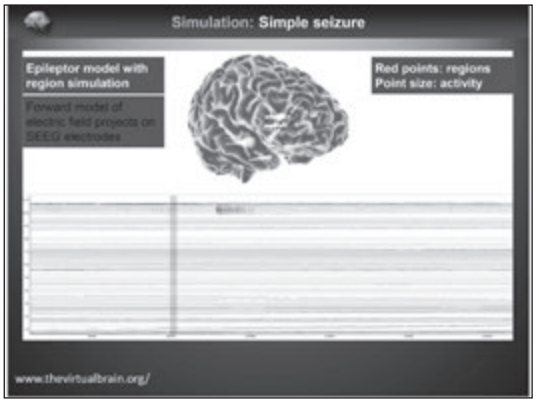
- Status epilepticus and spreading depression are also « built-in »
- They have their own dynamics rules
- Seizure propagation depends upon the effect on the slow variable of downstream regions

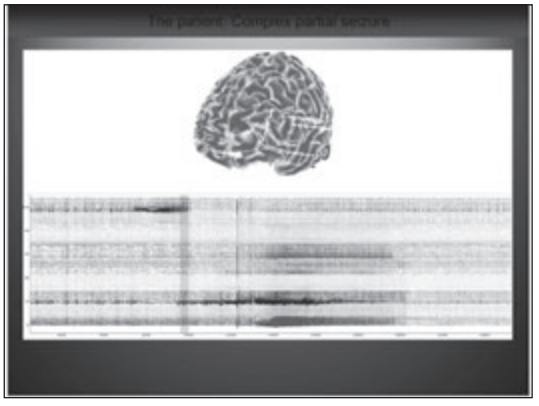

The epileptic patient
Female, 30 years old
Marseille/France
The virtual epileptic patient (Neuroimage, in revision)

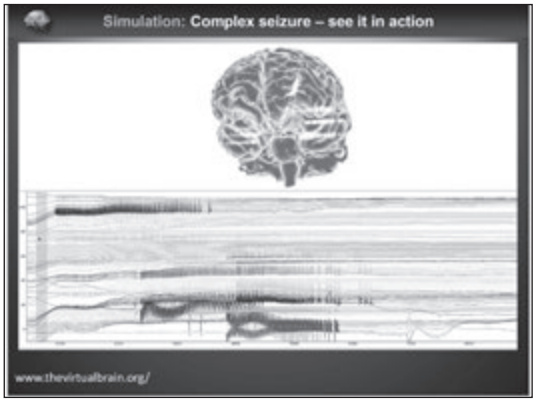

The patient: Geometry
Whole brain
Subcortical regions

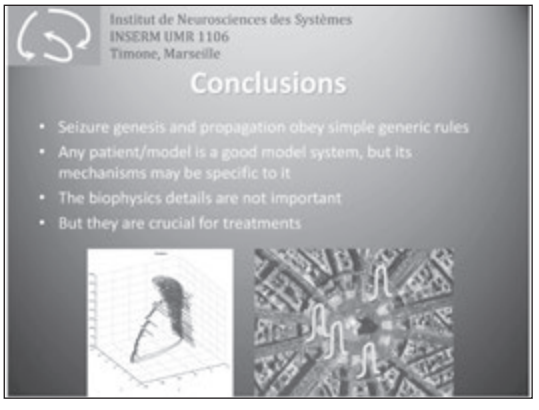

The patient: Fiber tracts


The patient: Simple seizure, zoomed

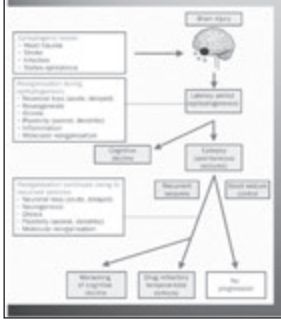

Simulation: Simple seizure
Epileptor model with region simulation
Forward model of electric field projects on SEEG electrodes
Red points: regions
Point size: activity
www.thevirtualbrain.org/


The patient: Complex partial seizure


Simulation: Complex seizure – see it in action
www.thevirtualbrain.org/


Institut de Neurosciences des Systèmes
INSERM UMR 1106
Timone, Marseille
Conclusions
• Seizure genesis and propagation obey simple generic rules
• Any patient/model is a good model system, but its mechanisms may be specific to it
• The biophysics details are not important
• But they are crucial for treatments

Is it possible to study epileptogenesis?

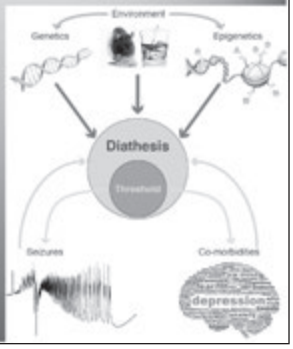


Perhaps in a controlled environment?

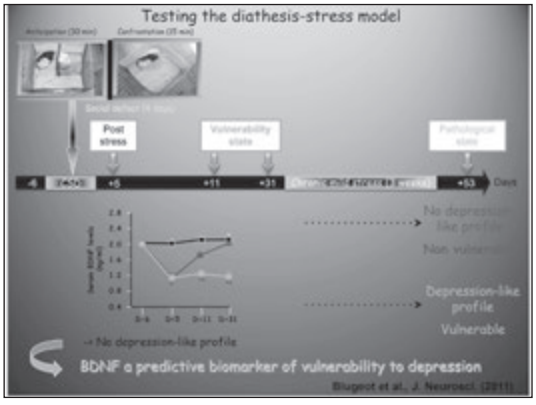
The diathesis-epilepsy model

The diathesis-stress model

- Diathesis: intrinsic vulnerability of an individual
- Unresolved stress increases the allostatic load
- When diathesis and stress cross a given threshold → depression
- Only a few individuals develop epilepsy after a given insult
- Not all patients develop co-morbidities
- Can the past explain the present?



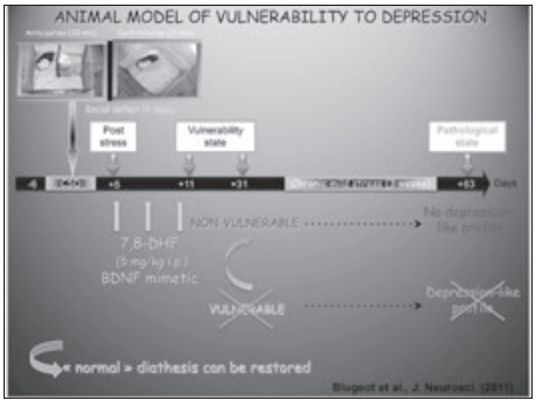
Testing the diathesis-stress model



BDNF a predictive biomarker of vulnerability to depression

Blugeot et al., J. Neurosci. (2011)

ANIMAL MODEL OF VULNERABILITY TO DEPRESSION



« normal » diathesis can be restored

Blugeot et al., J. Neurosci. (2011)


Annals of NEUROLOGY
Brief Communication
Predicting and treating stress-induced vulnerability to epilepsy and depression
Christel Becker[1,2,3,4], Elodie Bouvier[1,2,3], Antoine Ghestem[5,6], Safia Siyoucef[5,6], Damien Claverie[1,2,3,7], Françoise Camus[1,2,3], Fabrice Bartolomei[5,6], Jean-Jacques Benoliel[1,2,3,8] and Christophe Bernard[5,6,*]
Elodie Bouvier
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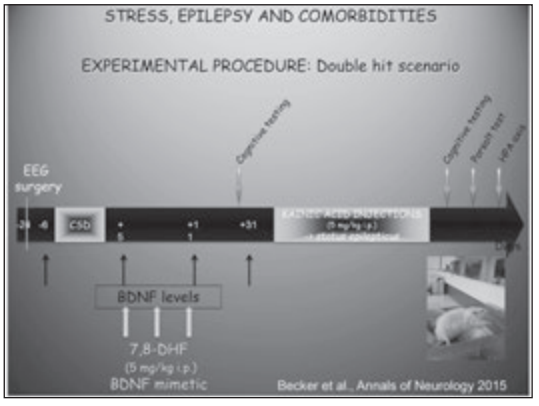
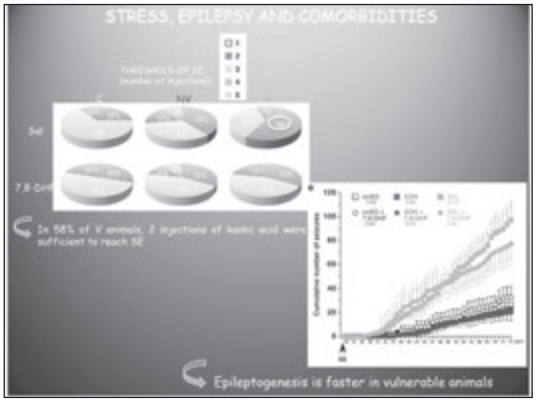
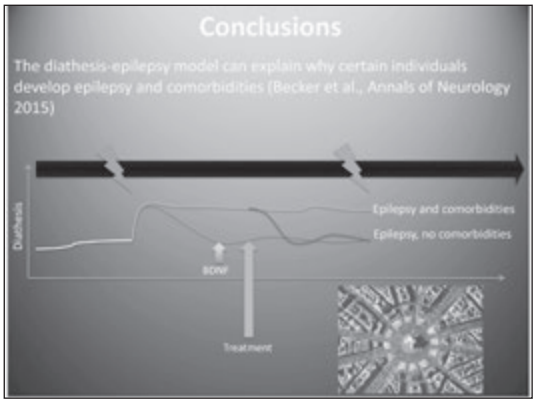
Safia Siyoucef
Damien Claverie
Fabrice Bartolomei
Françoise Camus
Christel Becker
JJ Bénoliel

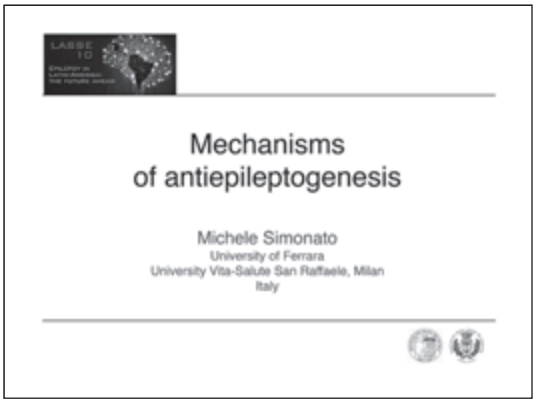

STRESS, EPILEPSY AND COMORBIDITIES
EXPERIMENTAL PROCEDURE: Double hit scenario
EEG surgery
Cognitive testing
Cognitive testing
Forced test
CSD
BDNF levels
7,8-DHF
(5 mg/kg i.p.)
BDNF mimetic
Becker et al., Annals of Neurology 2015

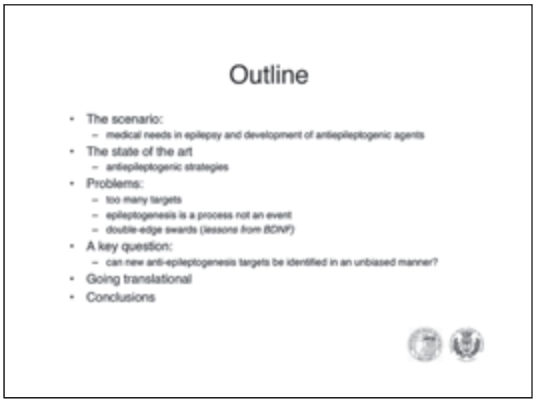

STRESS, EPILEPSY AND COMORBIDITIES
Epileptogenesis is faster in vulnerable animals


Conclusions
The diathesis-epilepsy model can explain why certain individuals develop epilepsy and comorbidities (Becker et al., Annals of Neurology 2015)
Diathesis
Epilepsy and comorbidities
Epilepsy, no comorbidities
BDNF
Treatment

MICHELE SIMONATO (ITALY)

ANTIEPILEPTOGENESIS

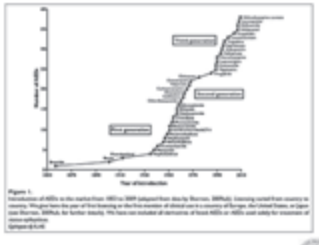




The scenario

Medical needs in epilepsy and development of antiepileptogenic agents

Introduction to the market of antiepileptic drugs



Where are we now

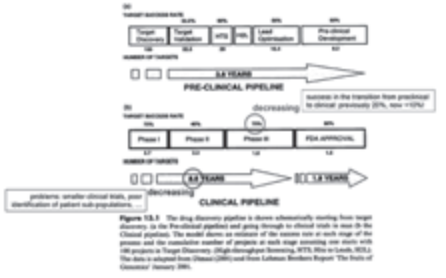
- We have many drugs!
- However
  - Antiepileptic drugs in use are anti-seizure, symptomatic agents. Must be taken daily, even for rare seizures.
  - About a third of the patients do not respond to pharmacological therapy.
  - Third generation antiepileptic drugs that entered the market in the last two decades offered more treatment options and improved ease of use (less toxicity, interactions, ...) but did not significantly modify this situation.

Unmet medical needs in epilepsy

- New anti-seizure agents
  - effective in resistant patients;
  - with less side effects (do not impact quality of life);
  - effective in difficult syndromes (Dravet, Lennox-Gastaut, infantile spasms, ...);
  - age/gender-specific.
- Ways to assess the seizure threshold in real time
  - so AED therapy does not have to be constant.
- Anti-epileptogenic treatments:
  - disease-modifying treatments that modify the natural history of the disease (for example, arrest progression);
  - that treat co-morbidities (cognitive impairment, depression, ...);
  - that prevent associated risks (SUDEP, ...).

Drug discovery

- Approaches
  - Phenotypic screening:
    - intentional;
    - serendipity.
  - Natural products.
  - Target-based.
- Costs
  - Approximately 2 billion $.
- Phases
  - Discovery phase (1-1.5 years).
  - Preclinical development (4-5 years).
  - Clinical development (4-6 years).



How did we discover anti-epileptic drugs thus far?

- Serendipity.
- Screening [NB: false positive and false negatives]:
  - maximal electroshock (MES) (plus kindling) for anti-partial seizure agents;
  - pentylentetrazole (PTZ) (plus genetic models: GAERS, WAG/Rij) for anti-absence seizure agents.
- Structural modifications.
- Rationale approaches:
  - increase GABA;
  - decrease glutamate.

How can we find new anti-epileptic drugs?

- Improve screening:
  - use "new" seizure models (*in vitro* models, 6 Hz, kindling, …);
  - use epileptogenesis models (post-status, insult-specific, genetic, …);
  - develop models for co-morbidity.
- Rational approach:
  - identify new targets;
  - identify biomarkers (for epileptogenicity and for epileptogenesis).
- Improve preclinical protocols:
  - better methods (inclusion/exclusion criteria, sample size, blindness, …);
  - evaluation of pharmacokinetics;
  - evaluation of key parameters (therapeutic gain, therapeutic window, therapeutic index).

How can we find new anti-epileptic drugs?

- Identify the patient population that could benefit from the treatment.
- Get preclinical and clinical people together: ILAE and AES initiatives.

The start point: a new target

- Are there new targets?
- Are new targets amenable to classical pharmacology (small molecules)?
- Are there alternatives to classical pharmacology? For example, are gene or cell therapy approaches a concrete alternative?

The state of the art
Antiepileptogenic strategies

Antiepileptogenesis after status epilepticus

Treatment	Mechanism	Reference
Atipamezole	α2-adrenergic receptor	*Pitkänen et al., 2004*
Celecoblx	COX-2 inhibition	*Jung et al., 2006*
α4-integrin-specific Ab	integrin α4	*Fabene et al., 2008*
Erythropoietin	erythropoietin receptor	*Chu et al., 2008*
BDNF + FGF-2 gene therapy	TrkB and FGFR	*Paradiso et al., 2009*
Rapamycin	mTOR inhibition	*Zeng et al., 2009; Huang et al., 2010; Van Vliet et al., 2012*
Parecoblx	COX-2 inhibition	*Polascheck et al., 2010*
NRSE-sequence decoy oligodeoxynucleotides	Neuron restricted silencing factor	*McClelland et al., 2011*
Aspirin	COX-2 inhibition	*Ma et al., 2012*
Fingolimod	anti-inflammatory	*Gao et al., 2012*
Pentylenetetrazol	GABA-A antagonist	*Ratika et al., 2012*
Adenosine	reduced DNA methylation	*Williams-Karnesky et al., 2013*
Melatonin	antioxidant	*Tchekalarova et al., 2013*
1NMPP1	TrkB kinase inhibition	*Liu et al., 2013*
WP1066	JAK/STAT inhibition	*Grabenstatter et al., 2013*
Ketogenic diet	Multiple	*Kobow et al., 2013*
miR-134 antagomir	Multiple	*Jimenez-Mateos et al., 2011*

Antiepileptogenesis after traumatic brain injury

Treatment	Mechanism	1° Outcome	Ref
Rimonabant (SR141716A)	CB1-R antagonist	Sz suscept ↓	*Echegoyen et al. (2009)*
Minocac	Inflammation	Sz suscept ↓	*Chrousos et al. (2010)*
Rapamycin	mTOR inhibition	% of mice w/ epilepsy ↓	*Guo et al. (2013)*
Atipamezole	α2-adrenergic antagonist	Sz suscept ↓	*Pitkänen et al. (in prep)*
Ceftriaxone	Glu transport	Sz frequency ↓	*Goodrich et al. (2013)*
Hypothermia	Multiple	Sz suscept ↓	*Atkins et al. (2010)*
		Sz frequency ↓	*D'Ambrosio et al. (2013)*
Exercise	Oxidative stress	Sz suscept ↓	*Almeida Silva et al. (2013)*
Enriched environment	Multiple	Sz suscept ↓	*Pitkänen et al. (in prep)*

(Pitkänen and Immonen, Neurotherapeutics 2014)

Antiepileptogenesis in genetic epilepsy

Treatment	Model	Adult Phenotype	Reference
Levetiracetam	SER rat	Tonic convulsions ↓ Absences ↓	*Yan et al. (2005)*
	WAG/Rij rat	Absences ↓	*Russo et al. (2010)*
	WAG/Rij rat	Absences ↓	*Russo et al. (2011a)*
	GAERS rat	Absences (↓)	*Deleuwaerdere et al. (2005)*
Ethosuximide	WAG/Rij rat	Absences ↓	*Blumenfeld et al. (2008)*
	WAG/Rij rat	Absences ↓	*Sarkisova et al. (2010)*
	WAG/Rij rat	Absences ↓	*Russo et al. (2010)*
	WAG/Rij rat	Absences ↓	*Russo et al. (2011a)*
	GAERS rat	Absences ↓	*Dezsi et al. (2013)*
Zonisamide	WAG/Rij rat	Absences ↓	*Russo et al. (2011a)*
Vigabatrin	WAG/Rij rat	Absences ↓	*Russo et al. (2011b)*
Carbamazepine	WAG/Rij rat	**No effect**	*Russo et al. (2011a)*
Rapamycin	WAG/Rij rat	Absences ↓	*Russo et al. (2013)*

Antiepileptogenesis in cortical malformations

Rapamycin

Animal Data	Species	Effect	Reference
Tuberous sclerosis - *Tcs1*^{GFAP} KO	Mouse	+	*Zeng et al. (2008)*
Cortical dysplasia - *Pten* KO	Mouse	+	*Zhou et al. (2009)*
	Mouse	+	*Ljungberg et al. (2009)*

(Pitkänen & Engel, Neurotherapeutics 2014)

Status epilepticus	Traumatic brain injury	Genetic
Atipamezole	Rimonabant (SR141716A)	Levetiracetam
Celecobix	Minocac	Ethosuximide
α4-integrin-specific Ab	Rapamycin	Zonisamide
Erythropoietin	Atipamezole	Vigabatrin
BDNF + FGF-2 gene therapy	Ceftriaxone	Rapamycin
Rapamycin	Hypothermia	Furosemide
Parecobix	Exercise	
NRSE-sequence decoy oligodeoxynucleotides	Enriched environment	
Aspirin		
Fingolimod		
Pentylenetetrazol		
Adenosine		
Melatonin		
1NMPP1		
WP1066		
Ketogenic diet		
miR-134 antagomir		

Favorable proof-of-concept antiepileptogenesis studies

Outcome
- no complete prevention of epilepsy
- delayed onset
- milder epilepsy

(Pitkänen & Engel, Neurotherapeutics 2014)

ClinicalTrials.gov

Study	Identifier	Status	PTE
Seizure prophylaxis with **Lacosamide**	NCT01110187	terminated	2° outcome
Levetiracetam to Prevent Post-Traumatic Epilepsy	NCT01463033	completed reported	2° outcome
Preventing Epilepsy After Traumatic Brain Injury With **Topiramate**	NCT00598923	unknown	2° outcome
Use of **Biperiden** for the Prevention of Post-traumatic Epilepsy	NCT01048138	not yet recruiting	1° outcome
Allopregnanolone for the Treatment of Traumatic Brain Injury	NCT01673828	recruiting	2° outcome
Prevention of Post-traumatic Seizures With **Levetiracetam**	NCT00566046	terminated	2° outcome
Effects of **Huperzine A** in treatment of moderate to severe TBI	NCT01676311	not yet recruiting	2° outcome

Summary

- Many experimental treatments have shown favorable effects
- Clinical trials ongoing

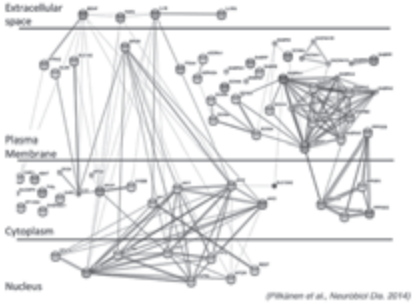
…However...

- Preclinical evidence → no clinical trial
- Weak/no preclinical evidence → clinical trials

Antiepileptogenic strategies

Problems:
too many targets

Location of targets and interactions

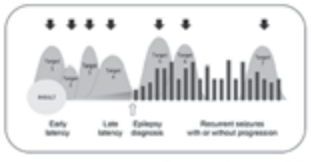


(Pitkänen et al., Neurobiol Dis. 2014)

Antiepileptogenic strategies

Problems:
epileptogenesis
is a process not an event

Different targets at different stages of epileptogenesis



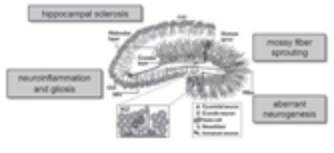
(Pitkanen et al., Lancet Neurol 2013)

Antiepileptogenic strategies

Problems:
double-edge swards

Lessons from BDNF

Epileptogenesis-associated alterations in the hippocampus



Neurotrophic factors (NTFs) may be involvement in many (all?) of these alterations.

Neurotrophic factors for the treatment of epileptogenesis-associated damage: candidates

- FGF-2 (fibroblast growth factor-2) and BDNF (brain-derived neurotrophic factor)
  - both FGF-2 and BDNF (brain-derived neurotrophic factor) increase survival of neurons *(Sairanen et al., 2005)*
  - FGF-2 potently induces proliferation of hippocampal progenitors *(Crespel et al., 2005; Bull & Bartlett, 2005)*
  - BDNF is required for neuronogenesis in the hippocampus *(Lee et al., 2002; Sairanen et al., 2005; Scharfman et al., 2005)*
  - synergy:
    - generation of spontaneously active neural networks in cultures of rat hippocampal neural progenitors *(Mistry et al., 2002)*
    - increased survival and integration of fetal hippocampal CA3 cell grafts in the injured hippocampus *(Rao et al., 2006)*

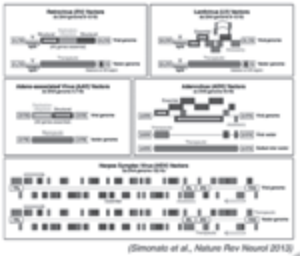
Local delivery of NTFs: viral vectors

herpes simplex based vectors

(Simonato et al., TINS 2000)

Why herpes?

- Efficient infection of non-replicating cells (neurons)
  - remarkable neurotropism
  - capacity of entering a latent state in neurons without compromising neuronal function
- Accommodation of large inserts
  - large, completely sequenced, easy to manipulate, genome
  - approximately half of the genome composed of non-essential genes that can be replaced with heterologous genes
- Retrograde transport in neurons
  - transgene expression can be obtained in remote areas through the nerve terminals afferent to the injection area
- Transient transgene expression

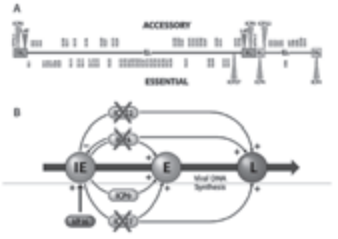


(Simonato et al., Nature Rev Neurol 2013)

Replication-defective herpes vectors

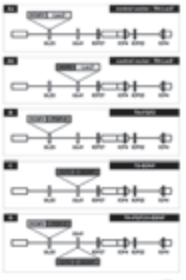
(Simonato et al., TINS 2000)

Replication-defective herpes vectors

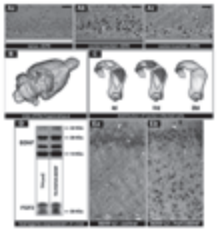


(Simonato et al., TINS 2000)

Herpes-based vectors



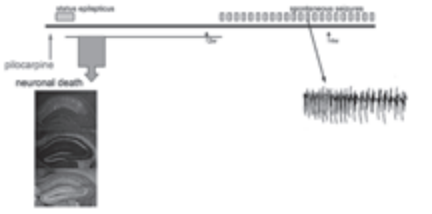
In vivo transgene expression after vector injection in the hippocampus



- bilateral expression
- time-course of FGF-2 expression: transient (<2 weeks)
- time-course of BDNF expression: more persistent (>2 weeks)

(Paradiso et al., PNAS 2009)

The pilocarpine model



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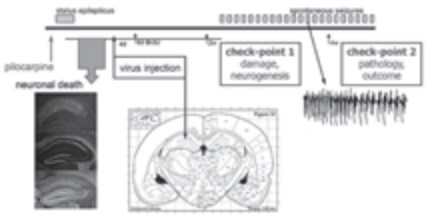

Local supplementation of FGF-2 and BDNF…

- attenuates seizure-induced cell **damage**

(Paradiso et al., PNAS 2009; Bovolenta et al., J. Neuroinflamm. 2010; Paradiso et al., Epilepsia 2011)

Local supplementation of FGF-2 and BDNF…

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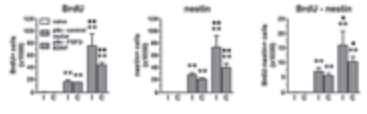
- **increases hippocampal neural stem cell proliferation**



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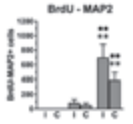
Local supplementation of FGF-2 and BDNF…

- attenuates seizure-induced cell **damage**
- increases hippocampal neural stem cell **proliferation**
- **favors neuronal differentiation**



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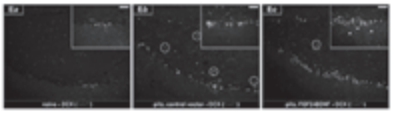
- favors neuronal **differentiation**
- **reduces the aberrant aspects of epileptogenesis-associated neurogenesis**



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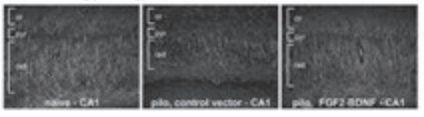
- **ameliorating pathology**



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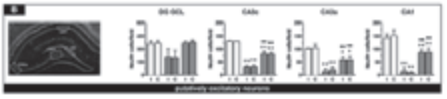

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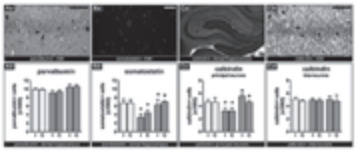
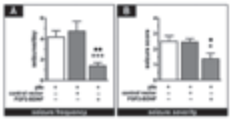
- **ameliorating pathology**



Local supplementation of FGF-2 and BDNF…

- attenuates seizure-induced cell **damage**
- increases hippocampal neural stem cell **proliferation**
- favors neuronal **differentiation**
- reduces the aberrant aspects of epileptogenesis-associated **neurogenesis**

- ameliorating the pathology
- **and reducing the frequency and severity of spontaneous seizures**

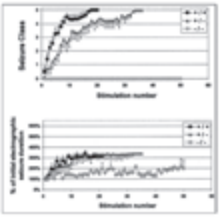


(Paradiso et al., PNAS 2009; Bovolenta et al., J. Neuroinflamm. 2010; Paradiso et al., Epilepsia 2011)

In summary

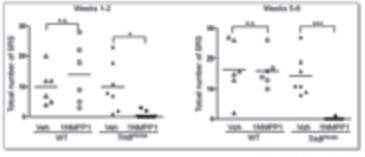
- Gene therapy with FGF-2 and BDNF
  - reduces (heals) SE-induced damage;
  - produces more "physiological" neurogenesis;
  - exerts a disease-modifying effect.

All that simple?
The dark side of NTF:
BDNF can be pro-epileptogenic



TrkB KO mice do not kindle
(Hu et al., 2004)

Transient (2 weeks) inhibition of TrkB
starting after kainate-induced status epilepticus
prevents development of spontaneous seizures



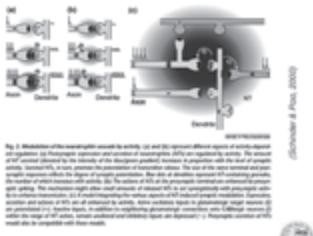
(Liu et al., Neuron 2013)

Angels and Demons

(M.C. Escher)

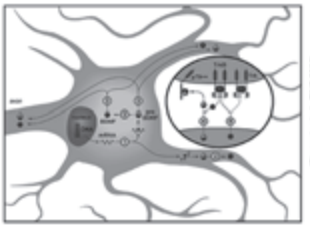
(Simonato et al., TINS 2006)

A possible pro-epileptic mechanism for BDNF: synaptic potentiation

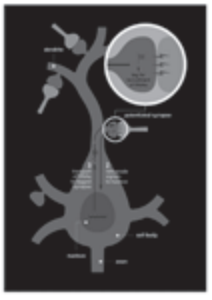


(Schuman & Poo, 2000)

How can a single NTF be both "angel" and "demon"?



(Simonato et al., Trkß 2006)



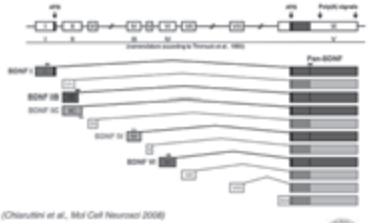
Locally synthesized proteins can be made from mRNAs that are synthesized *ad hoc*.
Synaptic activity tags the synapse and regulates transcriptional activation.

HYPOTHESIS: To exert pro-epileptic effects, BDNF mRNA is targeted to dendrites and locally translated by epileptogenic stimuli.

(Tongiorgi et al., J. Neurosci. 2004)

How can a neuron sort "bad" BDNF to the dendrites?

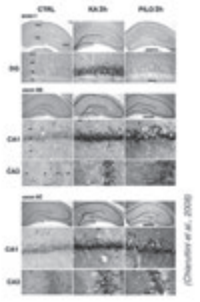
Rat BDNF gene structure



(Chiaruttini et al., Mol Cell Neurosci 2008)

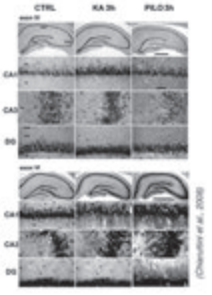
Dendritic targeting of BDNF splice variants

Exon I **is regulated by kainate seizures, but** is not targeted **to dendrites.** Exons II are targeted **to dendrites.**



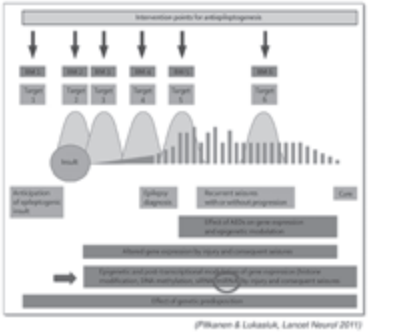
Dendritic targeting of BDNF splice variants

Exon IV **is regulated by kainate seizures, but** is not targeted **to dendrites.** Exon VI is targeted **to dendrites.**



A key question

Can new anti-epileptogenesis targets be identified in an unbiased manner?



(Pitkanen & Lukasiuk, Lancet Neurol 2011)

Focus on the dentate gyrus

- A "gate" to inhibit hippocampal over-excitation *(Krook-Magnuson et al., J Physiol 2015)*:
  - optogenetic granule cell hyperpolarization stops spontaneous seizures;
  - optogenetic granule cells activation exacerbates spontaneous seizures;
  - activating granule cells in non-epileptic animals evokes acute seizures.
- Undergoes important functional changes during epileptogenesis (neurogenesis, mossy fiber sprouting, increased excitation, …).
- Very often involved in seizure generation in TLE patients, and very often removed at surgery.
- A compact layer of (almost) identical cells.
- Well characterized from developmental, neurochemical, morphological, physiological point of view.

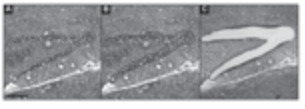
Background: microRNAs

- Small size endogenous non-coding RNAs. Regulate the expression of target mRNAs at post-transcriptional level.
- More than 1000 human miRNAs. More than 50% expressed in the brain.
- **Therapeutic targets**:
  - involved in several brain functions, many of which implicated in epilepsy and epileptogenesis (cell death, neurogenesis, synaptic plasticity).
- **Biomarkers**:
  - found in the plasma and serum, associated with proteins or with extracellular vesicles; very stable; levels affected by disease states.

Recently, alterations in miRNA expression levels have been described both in the brain of epilepsy patients *(Zucchini et al,PLoS One 2015)* and in animal models of epilepsy *(Jimenez-Mateos et al, Nature Med 2011; Bot et al, PLoS One 2013; Gorter et al, Neurobiol Dis 2014)*.

Aims

- Fill the gaps left by the previous studies of this kind.
- Specifically, a systematic evaluation of the miRNAome
  - in a **specific cell population of the hippocampus** (laser microdissected granule cell layer) and in **plasma samples**;



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  - at **multiple time-points** in the course of pilocarpine-induced epilepsy in rats (early and late latency, at the time of the first spontaneous seizure and in the chronic period);

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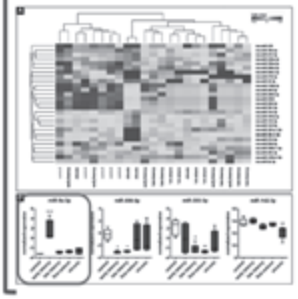
- Fill the gaps left by the previous ones of this kind.
- Specifically, a systematic evaluation of the miRNAome
  - in a specific cell population of the hippocampus (laser microdissected granule cell layer) and in plasma samples;
  - at multiple time-points in the course of pilocarpine-induced epilepsy in rats (early and late latency, at the time of the first spontaneous seizure and in the chronic period);
  - in **comparison with post-mortem human** epileptic and control granule cell samples.

Blood samples. Collected and analyzed only by Gorter et al. (2013) and Wang et al. (2015).

Circulating miRNAs: microarray study



Microarray analysis detected significant changes in the plasma levels of **27 miRNAs**.

Hierarchical clustering revealed **two main clusters** that separated the control to other groups.
Within the cluster including all pilocarpine animals, rats belonging to the single experimental groups displayed a clear tendency to form distinct sub-clusters.

Four *miRNAs* levels **patterns** were identified.

Granule cell layer (GCL) microarray study

Microarray analysis detected significant changes in the expression levels of **63 miRNAs**.

Hierarchical clustering revealed **three main clusters** that separated the control and chronic phase groups from rats killed during latency and from those sacrificed after the first spontaneous seizure.

(Roncon et al., Sci. Rep. 2015)

Expression patterns

Six different expression patterns.

(Roncon et al., Sci. Rep. 2015)

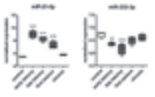
Expression patterns

Six different expression patterns.

1) Eighteen miRNAs **increased during latency**, then gradually return to control levels (**miR-21-5p**).

(Roncon et al., Sci. Rep. 2015)

Expression patterns

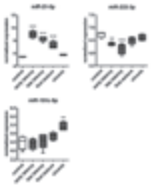


Six different expression patterns.

1) Eighteen miRNAs **increased during latency**, then gradually return to control levels (**miR-21-5p**).
2) Nine miRNAs **decreased during latency**, then gradually return to control levels (**miR-223-3p**).

(Roncon et al., Sci. Rep. 2015)

Expression patterns

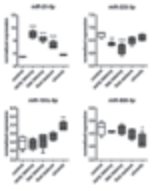


Six different expression patterns.

1) Eighteen miRNAs **increased during latency**, then gradually return to control levels (**miR-21-5p**).
2) Nine miRNAs **decreased during latency**, then gradually return to control levels (**miR-223-3p**).
3) Eight miRNAs **up-regulated in the chronic phase (miR181a-5p)**.

(Roncon et al., Sci. Rep. 2015)

Expression patterns



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4) Three miRNAs **down-regulated only in the chronic phase (miR-500-3p)**.

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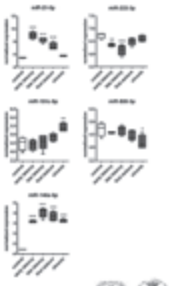
4) Three miRNAs **down-regulated only in the chronic phase** (**miR-500-3p**).
5) Twelve miRNAs **up-regulated during all phases** of the disease (**miR-146a-5p**).

(Roncon et al., Sci. Rep. 2018)



Expression patterns

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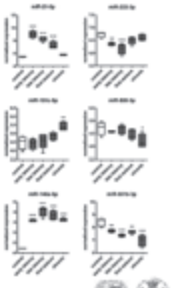
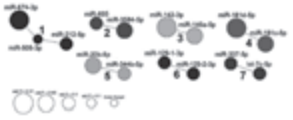
4) Three miRNAs **down-regulated only in the chronic phase** (**miR-500-3p**).
5) Twelve miRNAs **up-regulated during all phases** of the disease (**miR-146a-5p**).
6) Eight miRNAs **down-regulated during all phases** of the disease (**miR-551b-3p**).

(Roncon et al., Sci. Rep. 2018)



GCL- network analysis



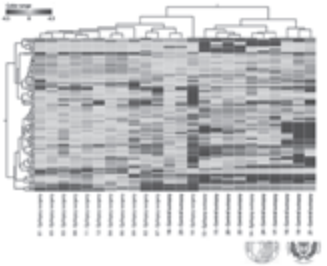
Targets for each miRNA obtained using the mirDB and TargetScan algorithms and filtered to include only those expressed in the rat dentate gyrus.

Clusters 3 (with 146a-5p) and **4** (with miR-181) may influence neuro-inflammation (cytokine signaling).
Clusters 1, 4 and **5** may influence neuronal activity (axon guidance; neurotrophin signaling; GABA-B and galanin receptors).

Human tissue

Cluster analysis of miRNAs differentially expressed in the GCL of TLE patients (including 2 autoptic epileptic cases) and in the control autoptic cases.

Samples obtained from autopsies of epilepsy patients segregate with the other autoptic samples
→ restrict comparison to autopsy cases.



TLE-patients vs. chronic epileptic rats

miRNAs up-regulated in epileptic chronic rats and in patients.

	Chronic rats		Patients	
	Fold change	Regulation	Fold change	Regulation
miR-23a-5p	1.83	Up	3.35	Up
miR-146a-5p	21.24	Up	3.63	Up
miR-181c-5p	1.91	Up	1.99	Up

(Roncon et al., Sci. Rep. 2015)

Conclusions (1)

- **Plasma**
  - The analysis of plasma samples revealed that 27 miRNAs were able to discriminate the controls from all other groups. Those miRNAs that are altered before the first spontaneous seizure, like **miR-9a-3p**, may be worth further investigation into their use as biomarker of epileptogenesis.
- **Granule cells layer**
  - We identified clusters of miRNAs that separated control and chronic phase rats from those sacrificed during latency or after the first spontaneous seizure.
  - An overlap can be observed between miRNAs differently expressed during epileptogenesis in the dentate gyrus in this study with in other studies that employed different models *(Gorter et al., 2013; Bot et al., 2013)*.
  - Comparison with data from epileptic patients identified at least 3 miRNAs (**miR-23a-5p**, **miR-146a-5p** and **miR-181c-5p**) that were up-regulated in both the human and rat epileptic hippocampus.

Question

Are the miRNAs identified in this study model-specific or disease-specific?

PURSUE OF AN ANSWER
Meta-analyses of available datasets.

miRNA datasets

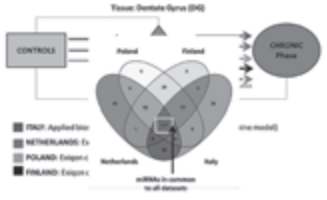
Inclusion criteria: miRNAs array studies in the dentate gyrus of epileptic vs. controls.
Exclusion criteria: miRNAs array studies in large brain areas (whole hippocampus).

	Roncon et al, Sci Rep 2015	Bot et al, PLoS One 2013	Gorter et al, Neurobiol Dis 2014	Pitkanen et al, unpublished
GEO ID	-	GSE45649	-	-
Rat model	Pilocarpine	Amygdala stimulation	Electrical tetanic stimulation of the angular bundle	Traumatic brain injury
Sample count for latency cases:controls	5:5	5:5	8:10	-
Sample count for chronic stage cases:controls	4:5	5:5	6:10	5:5
Latency duration (days after SE)	11±1		7.2±1.5	-
Platform	Rat miRNA Microarray Kit, Agilent Technologies	miRCURY LNA™ microRNA Array 7th, Exiqon services	miRCURY LNA™ microRNA Array 6th, Exiqon Services	miRCURY LNA™ microRNA Array 7th, Exiqon Services
Tissue collection	Laser-microdissected DG	Mechanically dissected DG	Mechanically dissected DG	Mechanically dissected DG

Meta-analysis: general overview

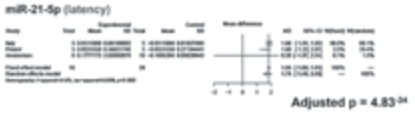
- Meta-analysis is a statistical technique, or set of statistical techniques, for summarizing the results of several studies into a single estimate.
- Since selected datasets were obtained in different ways, we must assume the presence of variability and run the analysis using a method that considers the variance among and within all studies.
- A meta-analysis consists of three main parts:
  1. a test for **heterogeneity** of the effect on outcome between the included studies;
  2. a **pooled estimate** and confidence interval for the "treatment effect" after combining all studies;
  3. a test for whether the "treatment effect" is **statistically significant or not**.

Meta-analysis: experimental plan



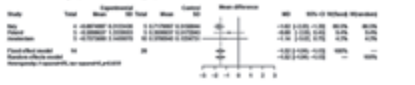
Meta-analysis: ramdom effect model

miR-21-5p (latency)



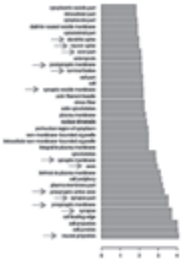
Adjusted p = 4.83^{-04}

miR-551b-3p (chronic stage)



Adjusted p = 9.0^{-15}

GO enrichment



- Gene Ontology enrichment analysis on the validated targets of those miRNAs that are differentially expressed in latency revealed many "neuronal" GO terms.

Conclusions (2)

- The meta-analysis identified **44 miRNAs in the latency period** and **8 in the chronic stage** that were differentially expressed between cases and controls in a highly significant manner.
- The high number of miRNAs that shown significant changes during latency suggests a role of these molecules in regulating the molecular and cellular processes that guide the transformation of an healthy brain into epileptic (epileptogenesis).
- Among the differentially expressed miRNAs, 23 from latency and 4 from the chronic stage were not identified previously as significantly dys-regulated in either of the studies.
- We identified a down-regulation in the chronic stage of the brain-enriched **miR-130a-3p**. High levels of this miRNA have been detected in the serum of TLE patients *(Wang et al, Sci Rep 2015)*. This inverse correlation leads to the idea that serum miR-130a-3p may originate from the brain, and may become a biomarker for the identification of TLE patients.

Ongoing analyses

- GO and KEGG enrichment analyses to investigate the involvement of the miRNAs identified by the meta-analysis in the regulation of neuronal pathways.
- Identification *in silico* of the **predicted** mRNA targets of miRNAs de-regulated during the different phases of the disease, and **filtering** based on transcriptomic data of the DG of epileptic rats *(Bot et al., Plos One 2013)* and the hippocampus of TLE patients *(Johnson et al., Nature Comm 2015)*.
- Validation.

Goal

- We expect to ultimately obtain a set of new potential therapeutic targets.
- These new targets will add to existing strategies that were identified based on the modulation of the cellular alterations occurring during epileptogenesis *(Pitkanen & Lukasiuk, Lancet Neurol 2011)* or of the excitation/inhibition balance in chronic epilepsy *(Simonato, Epil & Behav 2014)*.

Going translational

Focus

The therapy development process using animal models, from target identification to initial clinical trials.

- Not discussed: early proof-of-concept studies leading to target or compound identification.

Contents:

1. Animal models of epilepsy
2. Discovery of new antiseizure treatments
3. Discovery of disease-modifying treatments
4. Identification of biomarkers
5. Technical and methodological issues
6. Preclinical trials

1

Animal models

- Acute seizure models: models of induced seizures without evidence of persisting changes in seizure threshold or spontaneous seizures.
  - Advantages:
    - high-throughput;
    - validated for use in screening.
  - Disadvantages:
    - do not select disease-modifying therapies;
    - cannot discriminate efficacy in specific epilepsy syndromes or drug resistant epilepsy;
    - may miss potentially efficacious therapies;

(French et al., Epilepsia 2013)

    - may fail to predict certain adverse effects observed in humans.

(Galanopoulou et al., Epilepsia 2013)

1

Animal models

- Chronic models of high propensity for induced seizures or epileptogenesis: models with persisting decrease in seizure threshold in provocation tests but no evidence yet of spontaneous seizures (e.g., kindling).
  - Advantages:
    - testing propensity for provoked seizures yields faster results;
    - offer an alternative to develop treatments ameliorating the propensity to develop seizures;
    - may be useful to test anti-comorbidity therapies.
  - Disadvantages:
    - cannot test the effects on spontaneous seizures;
    - higher propensity to induced seizures may not necessarily be an accurate marker of the epileptic state.

1

Animal models

- Chronic models: models of epileptogenesis with documented spontaneous seizures in long-term video-EEG studies.
  - Advantages:
    - may better represent the human condition, modeling the development of epileptogenesis including drug-sensitive and drug resistant spontaneous seizures;
    - allow better testing of potential for adverse events.

(Wilcox et al., Epilepsia 2013)

  - Disadvantages:
    - a specific insult (e.g. stroke, status epilepticus) may not produce results that are generalizable to epilepsy resulting from other types of injury (e.g., traumatic brain injury);
    - the majority of human epilepsies do not result from a known insult;
    - unproved validity: no therapy to date has been brought to clinic solely based on efficacy in a chronic model (exception may be the use of mTOR inhibitors in epilepsy due to tuberous sclerosis: *Zeng et al., Ann Neurol 2008; Krueger et al., Ann Neurol 2013*).

1

Animal models: challenges

- Brain development:
  - target validation should be explored for infancy and childhood epilepsies.
- Time course:
  - different targets in different stages of epileptogenesis.

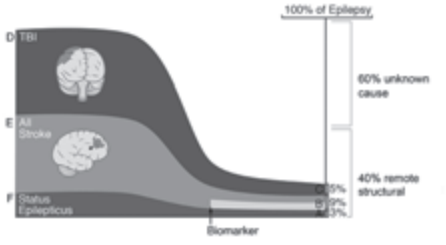
2

Disease-modifying therapies

- Primary endpoint: reduction in seizure frequency and/or percentage of seizure-free animals (or 50% reduction in seizure frequency).
  - This is a lot of work!
- Many promising candidates:
  - anti-inflammatory, mTOR inhibitors.
- Ongoing clinical trials with LEV and TPM following TBI.
  - Decision based on mechanisms and not on preclinical testing in animal models.
- To date, no successful trial demonstrating antiepileptogenesis.

3

Anti-epileptogenesis

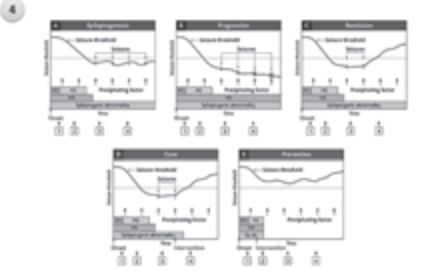


4

The need of biomarkers

- An objectively measurable characteristic of a biological process that reliably identifies the development, presence, severity, progression, or localization of an epileptogenic abnormality.
- Biomarkers will be essential both in preclinical and clinical research
  - to reduce the Number of cases;
  - to improve the risk/benefit ratio if a treatment has potential harms;
  - to reduce the time to outcome.

4



(Engel et al., Epilepsia 2013)
(Simonato et al., Lancet Neurol 2014)

4

The need of biomarkers

- Potential biomarkers are currently under investigation
  - EEG (e.g. high frequency oscillation);
  - Imaging (MRI- or PET-identified alterations);
  - Blood (e.g. miRNA).
- A single biomarker of a panel of biomarkers?

5

Technical and methodological issues

- Rationale
  - Clinically relevant.
- Experimental design
  - Adherence to ethical and animal care guidelines.
  - Blinded, randomized, placebo-controlled, dose-response design.
  - Adequate pre-specified sample size.
  - Appropriate statistical analysis.
- Treatment delivery
  - Certify purity and stability of the selected chemicals or biologicals.
  - Specify criteria for dose selection and perform dose-response studies.
  - Provide evidence for target relevance and engagement.

5

Technical and methodological issues

- Outcome assessment
  - Clinically relevant and reliably quantifiable.
  - Evaluate tolerability.
- Data collection, analysis, and reporting
  - Pre-set inclusion and exclusion criteria
  - Report positive, negative or missing data.
- Interpretation
  - Discuss clinical relevance and impact of findings.
  - Discuss evidence for reproducibility and robustness.

5

The issue of statistical power

- Most preclinical studies are underpowered.

Power failure: why small sample size undermines the reliability of neuroscience

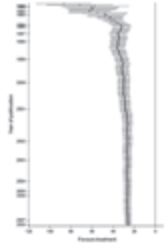
Katherine S. Button[1], John P. A. Ioannidis[2], Claire Mokrysz[1], Brian A. Nosek[3], Jonathan Flint[4], Emma S. J. Robinson[5] and Marcus R. Munafò[1]

Abstract | A study with low statistical power has a reduced chance of detecting a true effect, but it is less well appreciated that low power also reduces the likelihood that a statistically significant result reflects a true effect. Here, we show that the average statistical power of studies in the neurosciences is very low. The consequences of this include overestimates of effect size and low reproducibility of results. There are also ethical dimensions to this problem, as unreliable research is inefficient and wasteful. Improving reproducibility in neuroscience is a key priority and requires attention to well-established but often ignored methodological principles.

(Button et al., Nature Rev Neurosci 2013)

6

Data: more are better



Cumulative meta-analysis of the efficacy of lytic treatments (tissue Plaminogen Activator, tPA) in thrombotic animal models of stroke

(Sena et al., JCBFM 2010)

6

Clinical trials and *in vivo* studies: stroke people came first

	Animal / preclinical studies	Clinical trials
Centres	Many single-centre studies	1 or 2 large multicentre trials
Stuff	Academic / laboratory	Academic / clinical
Dose-response studies	Variable	Common
Time-response studies	Variable - most assess early administration	Uncommon
Size	Small (10s)	Large (100s, 1000s)
Outcomes: functional outcome	Uncommon	Common
Outcomes: death	Animals sacrificed and death not reported	Common
Publication bias	Common	Uncommon
Publication quality	May be limited	Moderate
Data sharing	Limited	Moderately common
Systematic reviews based on summary (group) data	Uncommon (except by the applicants)	Common
Regulatory involvement	Minimal, often towards end of preclinical development	Considerable, throughout clinical development
Ethical review	Common, may be institutional	Common, usually external

(Bath et al., Int J Stroke 2009)

6

A proposal: Phase II preclinical trial

- Multi-center studies designed along the lines of Phase II/III clinical studies:
  - Primary endpoints relate to efficacy, but may include some toxicity and PK assessments.
  - Standardized methods and endpoints, rigorous statistical and sample size calculations, rigorous blinding, independent data monitoring and analysis.
  - In total, a large number of animals (divided between many centers).
  - A central coordinating site independent from the data collections sites.

(O'Brien et al., Epilepsia 2013)
(Simonato et al., Lancet Neurol 2014)

The place of multicenter studies in the pipeline

- It is neither appropriate nor desirable that every *in vivo* study be conducted as part of a multicenter program.
- Hypothesis-generating/testing experiments can and should remain as single-center studies.

- Goal of Phase II preclinical trials is
  - generating more rigorous pre-clinical efficacy data (with transparent analysis and reporting) to address current gaps in epilepsy treatment;
  - de-risk clinical development, enhancing the attractiveness of funders (industry and government) to invest in epilepsy therapy.

Phase II preclinical trials

Evidence based translational medicine

Multi-PART

Funding

- The Phase II multicenter pre-clinical studies will be expensive, and resource and time intensive.
  - However, significantly less that of failed Phase II/III clinical studies.
- The funding model will likely require a combination of government funding infrastructure and private investment complimented by grant funding.
  - The government funding: establish the basic structures, protocols, laboratory credentialing, databases etc.
  - Industry or venture capital would fund the primary costs of undertaking the study, potentially supplemented by grants (govern, philanthropy).

(O'Brien et al., Epilepsia 2013)

Funding epilepsy research

Table	Prevalence, number of patients, and NIH funding for 6 neurologic diseases					
Disease	Epilepsy	Stroke	AD	PD	MS	ALS
Prevalence (total/1,000)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
No. US patients (in millions)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
No. relative to epilepsy	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2007						
NIH funding ($ in millions)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
# Relative to epilepsy	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
# Relative to epilepsy adjusted for relative prevalence	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2010						
NIH funding ($ in millions)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
# Relative to epilepsy	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
# Relative to epilepsy adjusted for relative prevalence	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2011 (estimated)						
NIH funding ($ in millions)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
# Relative to epilepsy	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
# Relative to epilepsy adjusted for relative prevalence	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

(Meador et al., Neurology 2011)

Publication issues

- Provide equal opportunity for the publication of both positive or negative studies or studies that aim to reproduce the findings in the same or a different model of seizures or epilepsy.
- Provide a forum to report the results the preclinical studies that could not be completed, so as to allow their inclusion in meta-analyses.

Conclusions

- Vision:
  - to develop transformational new treatments for people with epilepsy that address the current major clinical gaps in care, in particular:
    - antiepileptogenic and disease modifying treatments;
    - drug-resistant seizures;
    - therapies for comorbidities.

(Galanopoulou et al., Epilepsia 2013)

Practically

- Primary steps:
  - Harmonize video-EEG interpretation and analysis methods across studies using in vivo and in vitro models of seizures.
  - Undertake systematic reviews of animal model data for particular clinical syndromes, including treatments, biomarkers, and comorbidities through a Cochrane-like collaboration.
  - Development of Preclinical Common Data Elements (CDEs) and standardized procedures and protocols based on minimal requirements defined in experimental CDEs. Create standardized data acquisition forms for preclinical research, that will allow consistent data collection across different experiments and different laboratories.
  - Formulate a system for publishing results of negative preclinical studies.
  - Develop the infrastructure to organize multi-center preclinical studies for epilepsy research, through a partnership among government-related funding organizations (NIH, European Commission), industry, philanthropic foundations and academia.

(Galanopoulou et al., Epilepsia 2013)

Conclusions

Giuseppe Bertini (Italy)

HOW TO DESIGN A RESEARCH PROJECT

Andres Kanner (USA)

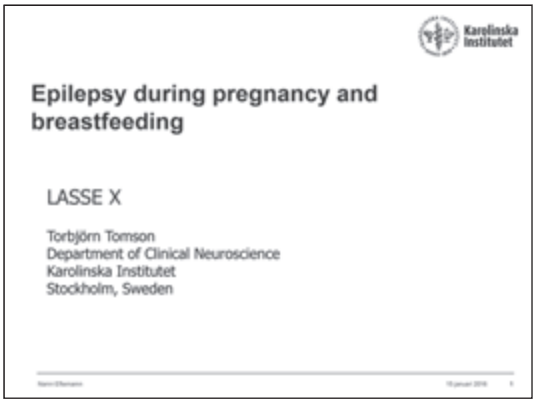
COMMON PSYCHIATRIC COMORBIDITIES OF EPILEPSY: WHAT EVERY NEUROLOGIST NEEDS TO KNOW

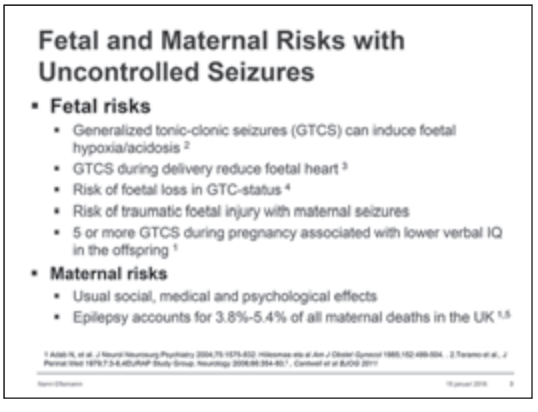
Andres Kanner (USA)

DO NEUROBIOLOGICAL ASPECTS OF MOOD DISORDERS EXPLAIN THEIR HIGH COMORBIDITY IN EPILEPSY?

Torbjörn Tomson (Sweden)

EPILEPSY DURING PREGNANCY AND BREASTFEEDING





Maternal Risks with Uncontrolled Seizures

BRIEF COMMUNICATION

SUDEP and epilepsy-related mortality in pregnancy

Period	Maternal deaths, n	Deaths due to epilepsy, n (%)	Epilepsy related deaths/100,000
1991-1993	228	9 (4%)	0.39
1994-1996	268	19 (7%)	0.86
1997-1999	242	9 (4%)	0.42
2000-2002	261	13 (5%)	0.65
2003-2005	295	11 (4%)	0.52
2006-2008	261	14 (5%)*	0.61

*11/14 (79%) deaths in SUDEP, other 3 seizure –related 2006-2008
SUDEP accounted for 15/24 (63%) 2000-2005

Research

Original Investigation

Mortality and Morbidity During Delivery Hospitalization Among Pregnant Women With Epilepsy in the United States

JAMA Neurol. doi:10.1001/jamaneurol.2015.3017
Published online July 6, 2015.

Retrospective cohort study of pregnant women identified through delivery hospitalization records 2007-2011 in the US
69.385 women with epilepsy diagnosis
20.449.532 women without epilepsy

Mortality 80/100,000 pregnancies of women with epilepsy
6/100,000 pregnancies of women without epilepsy

Limitations:
Epilepsy diagnosis not validated
Causes of death not known
Correction/adjustment for psychiatric comorbidities not made
Correction for longer hospitalisation of epilepsy patients not made

Treatment of Epilepsy in Pregnancy
The Goal

→Prevent major convulsive seizures during pregnancy
→Minimize exposure of foetus to potentially teratogenic drugs

Seizure control during pregnancy
Prospective data from EURAP

1,736 pregnancies any AED treatment

EURAP Study Group 2006
Neurology 2006; 66:354–360

3,806 pregnancies with monotherapy CBZ, LTG, VPA, PB

Information on seizure control was available in 3784 of the 3806 pregnancies

Battino D et al. 2013.
Epilepsia 2013; 54(9):1621–1627.

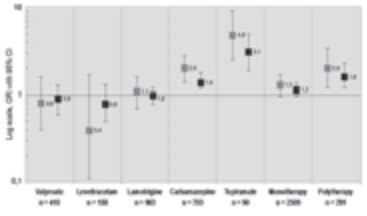
The critical question

- Which is the best treatment for my epilepsy during pregnancy?
  - →With minimized teratogenic risks
    - Major congential malformations
    - Cognitive development
    - Behavioural development
    - Growth
  - →With maintained efficacy

Growth restrictions

Fetal growth restriction and birth defects with newer and older antiepileptic Drugs during pregnancy Veiby G et al. J. Neurol. 2014; 261; 579-588

Figure: Risk of in utero growth restriction in children exposed to AEDs compared to the reference group.



Risk of SGA head circumference < 2.3 percentile ■, and SGA birth weight < 10th percentile ■. AED = Antiepileptic drug.
Odds ratio with 95% confidence interval, ajusted for maternal age, parity, smoking and chronic disease other than epilepsy.

SGA: Small for gestational age

First signals of teratogenic risks with AEDs more than 50 years ago

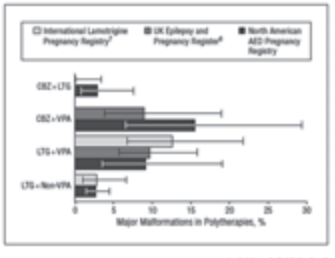
>50 years since first clinical report on malformations in a child exposed to AEDs
Mullers-Kupper M Acta Paedopsychiatr 1963; **30**: 401-5

47 years since first retrospective case series of malformations after AED exposure
Meadow SR Lancet 1968;292;1296


Letters to the Editor

Fetal Effects of Anticonvulsant Polytherapies

Major congenital malformations All polytherapies are not equal!



Arch Neurol. Published online June 13, 2011
doi:10.1001/archneurol.2011.133

Adding one other AED to valproate has no major impact on MCM frequency

Dose-dependent teratogenicity of valproate in mono- and polytherapy
An observational study

Tomson et al., Neurology 2015;85:866-

	VPA mono N=1224	VPA+LTG N=159	VPA+Other N=205	P-value
MCM Rate (95% CI)	10.0 % (8.4-11.8)	11.3% (7.3-17.2)	11.7% (8.0-16.8)	P=0.6900*
Median VPA dose, mg/day (IQ range)	800 (500)	800 (500)	1000 (900)	P<0.0001**

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Dose-dependent teratogenicity of valproate in mono- and polytherapy
An observational study

2015 ahead of print

Table 3 Frequency of MCMs at different dose categories of VPA, in association with VPA in monothe different types of AEDs polytherapy

	VPA dose		
Type of treatment	<700 mg/d	≥700 to <1,500 mg/d	≥1,500 mg/d
VPA monotherapy	5.9; 4.2–8.3 (31/522)	11.0; 8.8–13.8 (86/598)	24.0; 16.8–33.1 (25/104)
VPA + LTG	7.0; 3.0–15.4 (5/71)	6.8; 2.7–16.2 (4/59)	31.0; 17.3–49.2 (9/29)
VPA + other AEDs	5.4; 1.9–14.9 (3/55)	11.2; 6.4–19.0 (11/98)	19.2; 10.8–31.9 (10/52)
Total	6.0; 4.4–8.1 (39/648)	10.7; 8.7–13.1 (81/755)	23.6; 18.2–30.4 (44/186)

Malformation (MCM) risks higher with valproate: Data from pregnancy registries

Tomson et al., Lancet Neurol 2011, Tomson et al., Neurology 2015, Hernandez-Diaz et al., Neurology 2012, Campbell et al., JNNP 2014

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MCM risks in monotherapy
More data needed on other newer AEDs

Tomson et al., Lancet Neurol 2011, Hernandez-Diaz et al., Neurology 2012, Hunt et al., Neurology 2008, Mawhinney et al., Neurology 2013,

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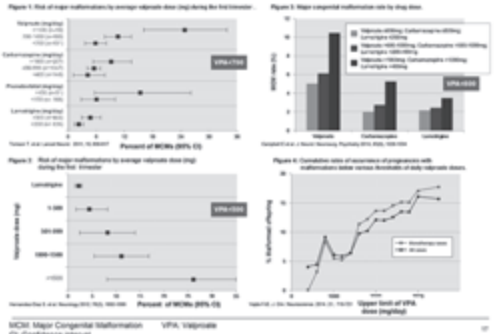
MCM risk in population based studies

Table 3 Risk of major congenital malformation in children exposed to antiepileptic drugs

Exposed groups[b,c,d]	Antiepileptic drug monotherapy $n = 2,309$		
	% (no./total)	OR (95 % CI)[a]	*p* value
References ($n = 771,412$)	2.9		
All antiepileptic drugs	3.4 (79/2,309)	1.27 (1.02–1.59)	0.036
Valproate sodium	6.3 (21/333)	2.47 (1.58–3.84)	<0.001
Carbamazepine	2.9 (20/685)	1.06 (0.68–1.66)	0.79
Phenobarbital	7.4 (2/27)	2.75 (0.65–11.6)	0.17
Clonazepam	1.8 (2/113)	0.65 (0.16–2.62)	0.54
Lamotrigine	3.4 (28/833)	1.26 (0.87–1.84)	0.22
Levetiracetam	1.7 (2/118)	0.63 (0.16–2.55)	0.52
Oxcarbazepine	1.8 (1/57)	0.64 (0.10–4.61)	0.66
Topiramate	4.2 (2/48)	1.66 (0.40–6.85)	0.48

Vejby et al., J Neurol 2014

The MCM risk depends on the dose



MCM: Major Congenital Malformation VPA: Valproate
CI: Confidence interval

Factors other than AEDs can play a role!

MCMs Multivariable Logistic Analysis EURAP Data

	Odd Ratio (95% CI)	p value
Non-drug covariates		
Americas vs Europe	2.1 (0.82-5.33)	0.1227
South-East Asia vs Europe	1.3 (0.59-2.94)	0.5064
Western Pacific vs Europe	1.0 (0.67-1.63)	0.8570
Parental history of major congenital malformations	4.4 (2.06-9.22)	0.0001
Maternal age	1.0 (0.97-1.04)	0.8209
Educational level father (low vs medium/high)	1.0 (0.64-1.55)	0.9941
Educational level mother (low vs medium/high)	1.1 (0.70-1.73)	0.6829
Generalized tonic-clonic seizures during first trimester	0.6 (0.31-1.11)	0.103
Folic acid use (appropriate vs inappropriate)	1.4 (1.02-1.82)	0.035
Sex (male vs female)	1.0 (0.75-1.29)	0.8982
Idiopathic generalized epilepsy vs localisation-related epilepsy	0.9 (0.62-1.23)	0.4421
Undetermined/unclassifiable vs localisation-related epilepsy	0.8 (0.47-1.22)	0.2531
Parity	0.8 (0.67-1.04)	0.1074

Odd ratios for maternal age and parity show the risk associated with an increase of 1 year in age an d an increase of 1 point in parity, respectively

Tomson et al., Lancet Neurol 2011

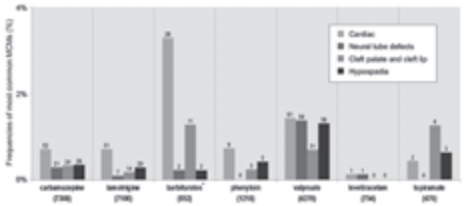
Consider outcome of previous pregnancy!

- WWE on AEDs with MCM in previous pregnancy had 35.7% risk of MCM in next pregnancy if on same AED (vs 3%)
- Higher rates with VPA: 57.2% vs. 7.0%, respectively

- WWE on AEDs with CM in 1 previous pregnancy had 16.8% risk of CM in next pregnancy if on same AED (vs. 9.8%)
- Higher recurrence rates with VPA (21.9%) and TPM (50%)

Different patterns of Major Congenital Malformations (MCMs) with AED monotherapies

Pooled data from 32 studies



The number of exposed fetuses or infants are shown in parenthesis for each antiepileptic drug, and the number of those with specific malformations are shown on top of the bars

*Barbiturates include phenobarbital, methylphenobarbital and primidone

Adapted from Tomson T, et al. Lancet Neurol; e-pub 12-5-2015

Valproate can affect cognitive development

The NEW ENGLAND JOURNAL of MEDICINE

Meador et al., NEJM 2009

Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Outcome at 3 year

Neurodevelopmental **E**ffects of **A**ntiepileptic **D**rugs, **NEAD** Study

309 mother/child pairs from 25 centers in US & UK

Table 2. IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs.*

Variable	Carbamazepine (N=75)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–101)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.4)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

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AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

NEAD: Outcome at 6 years and dose-

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

Meador et al., Lancet Neurol 20

	CBZ	LTG	PHT	VPA
Completers, n	61	74	40	49
Mean IQ (95% CI)	106 (103-109)	108 (105-111)	109 (105-113)	98 (95-102)

Dose	CBZ	LTG	PHT	VPA
Low	107	106	108	104
High	106	109	106	**94**

Median Dose

CBZ 800 mg
LTG 500 mg
PHT 400 mg
VPA 1000 mg

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AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

IQ at 6 years after in utero exposure to antiepileptic drugs

A controlled cohort study

Baker et al., Neurology 2015

- 173 children of women with epilepsy with AEDs (17% drop-out)
  - 143 monotherapy; 30 polytherapy
- Significant overlap with the NEAD study, 46%
- 25 children of untreated women with epilepsy
- 210 control children of healthy mothers

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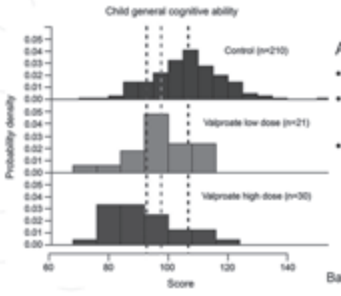
AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING

IQ at 6 years in VPA exposed and controls



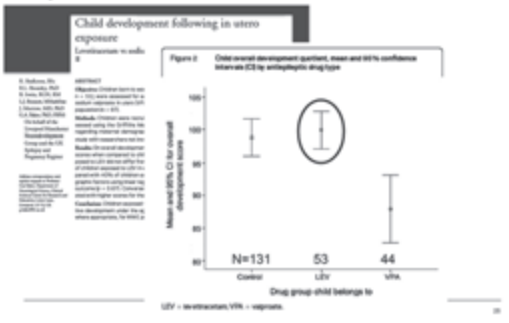
At VPA <800 mg/d

- IQ not different
- Verbal abilities impaired
- Educational interventions increased

Baker et al., Neurology 2015

Cognitive outcomes after levetiracetam exposure

Shallcross et al, Neurology 2014



Cognition at 42 months (36-54)

	Controls	LEV	VPA
N	131	53	44
Griffiths			
Gross Motor	111	110	97 C,L
Social	120	116	108 C,L
Visuospatial	110	110	111
Reasoning	114	113	109 C
Reynell Language			
Comprehension	52	50	46 C,L
Expressive	47	52	43 L

C=sig less than Controls
L=sig less than LEV

Shallcross et al, Neurology 2014

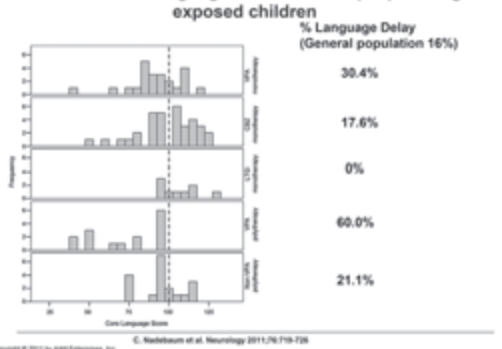
Language skills of school-aged children prenatally exposed to antiepileptic drugs

Nadebaum et al, Neurology 2011;76:719–726

102 AED-exposed children tested 6-8 years old
Clinical Evaluation of Language Fundamentals, 4th edition (CELF-4)

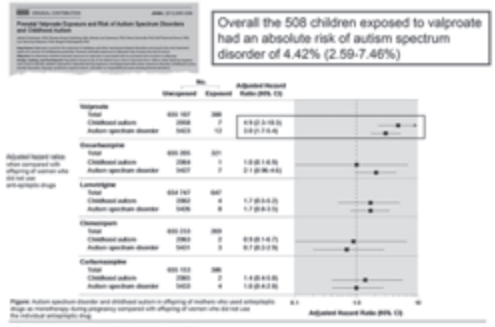
Antiepileptic Drugs	
Monotherapy	
Valproate	n=23
Carbamazepine	n=34
Lamotrigine	n=9
Polytherapy + VPA	n=15
Polytherapy – VPA	n=19

Distributions of language scores of antiepileptic drug–exposed children



C. Nadebaum et al. Neurology 2011;76:719-726

Behavioural outcomes after exposure to AEDs



Overall the 508 children exposed to valproate had an absolute risk of autism spectrum disorder of 4.42% (2.59-7.46%)

Christensen J et al. JAMA 2013; 309(16):1696-703

Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child (Review)

Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG

THE COCHRANE COLLABORATION®

- Participants
  - → Pregnant WWE taking a single AED
- Controls
  - → Pregnant WWE taking an AED
  - → Pregnant WWE not taking AED
  - → Pregnant women without epilepsy

Bromely et al., The Cochrane Library 2014, volume 10

This is a regular of Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 10
http://www.thecochranelibrary.com

Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child (Review)

Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, Tudur Smith C, Marson AG

THE COCHRANE COLLABORATION®

Authors' conclusions

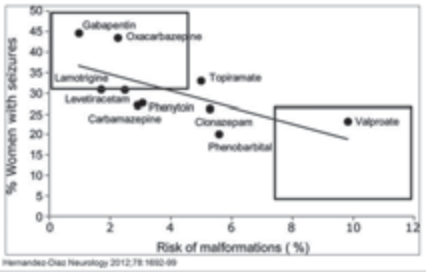
"The most important finding is the reductions in IQ in the VPA exposed group, which are sufficient to affect education and occupational outcomes in later life. ..." "We have insufficient data about newer AEDs, some of which are commonly prescribed, and further research is required. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk."

The Cochrane Library 2014, volume 10

This is a regular of Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 10
http://www.thecochranelibrary.com

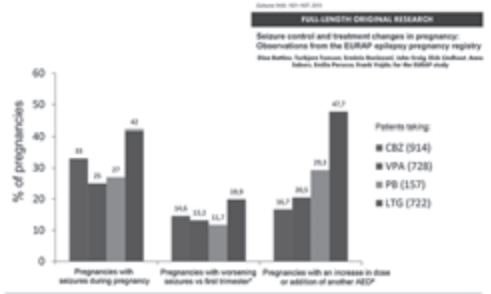
Teratogenic potential has to be weighed against efficacy

Seizure Control and Risk of Malformations NAAPR



Hernandez-Diaz Neurology 2012;78:1692-99

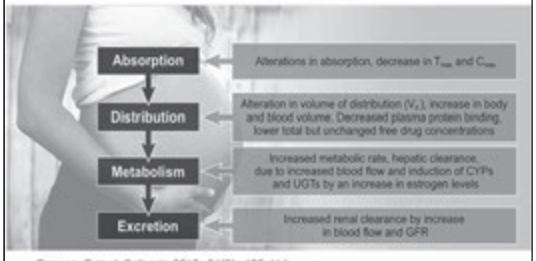
Teratogenic potential has to be weighed against seizure control



*worsening seizures during the second and third trimester vs the 1st trimester
†increase in dose and/or addition of another AED addition between 1st and 3rd trimester

Effects of pregnancy on pharmacokinetics of AEDs

Tomson T et al., Epilepsia 2013



Tomson T et al. Epilepsia 2013; 54(3): 405-414

Diffrential Effects of Pregnancy on serum concentrations of different AEDs

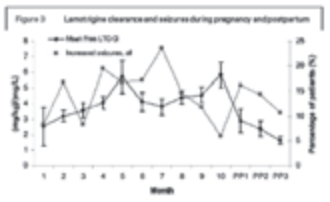
AED	Total conc.	Unbound conc.
Phenobarbital	-10-20%	-10-20%
Phenytoin	-60%	-20%
Carbamazepine	-10%	minor
Valproate	-30%	minor
Lamotrigine	-30-75%	-30-75%
Levetiracetam	-40-50%	Probably -40-50%
Oxcarbazepine	-30-50%	Probably -30-50%
Topiramate	-30-35%	Probably -30-35%

Tomson et al ., Epilepsia 2013

Do changes in drug levels matter?
The case of lamotrigine

Increased seizure frequency in 39% of 36 pregnancies associated with a lower ratio to target concentration (RTC)

RTC < 0.65 is a predictor of seizure worsening



Pennell *et al.* Neurology 2008;70:2130–6

Epilepsy and Pregnancy
Implications for management

Re-assess AED treatment before pregnancy

- → Consider withdrawal in women in remission
  - If the recurrence risk is low and the woman is willing to take the risk
  - If sufficient time available for assessment before pregnancy
- → Consider conversion from poly- to monotherapy
  - If risk of deterioration is low
- → Select the most appropriate AED with respect to teratogenicity as well as seizure control based on data available currently
  - If possible avoid valproate in particular at doses >500 mg/day
  - If possible avoid phenobarbital at doses >150 mg/day
  - If possible avoid topiramate
- → Establish lowest effective dose
- → Offer prenatal diagnosis where appropriate and possible
- → Monitor AED levels where available
  - In particular lamotrigine, but also oxcarbazepine and levetiracetam

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2014
EMA/709243/2014

CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls

Women to be better informed of risks of valproate use in pregnancy and need for contraception

The CMDh,* a regulatory body representing EU Member States, has agreed to strengthen warnings on the use of valproate medicines in women and girls due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. The warnings aim to ensure that patients are aware of the risks and that they take valproate only when clearly necessary.

Doctors in the EU are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproate is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

Concerns from the epilepsy community

- Treatment alternatives are few for generalized idiopathic/genetic epilepsies
  - → Efficacy of alternatives may not be comparable to VPA, and/or teratogenic risks significant, or not yet fully assessed
- Unlike men, women and girls with epilepsy risk to be denied the most effective treatment
- The risks with uncontrolled seizures may be neglected
- Women may be encourged to rapid discontinuation or switch from VPA, even during pregnancy
  - → With potentially serious consequences for them and for fetus
  - → With lack of evidence for reduction in teratogenic risks

SPECIAL REPORT

Task Force appointed by ILAE-CEA and European Academy of Neurology

Valproate in the treatment of epilepsy in girls and women of childbearing potential

[illegible]

Epilepsia 2015;56:1006-19

Wherever possible, valproate should be avoided in the treatment of girls and women of childbearing potential

…but which are the situations when valproate cannot be avoided? And when can valproate still be used within the remit of the new EMA restrictions?

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General recommendations

1. Female patients on VPA should be informed about the teratogenic risks, and of possibilities and limitations of prenatal screening, which cannot identify children whose neurodevelopment will be affected.
2. VPA should preferably not be used for focal epilepsy. Withdrawal or switch to alternatives should be considered for women of childbearing potential established on VPA for focal seizures and who consider pregnancy.
3. If used in women of childbearing potential, VPA should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500-600 mg/day.
4. Women of childbearing potential who are not planning pregnancy and continue treatment with VPA should utilize effective birth control.

Epilepsia 2015;56:1006-19 21

Newly diagnosed epilepsy

- VPA and alternatives should be considered for generalized epilepsies (e.g. JME, JAE) where VPA is more effective than other drugs. VPA may be prescribed provided that
  - → The fully informed woman chooses VPA, and
  - → Is not planning pregnancy
- When most appropriate for seizure/epilepsy type, VPA may be considered for girls with epilepsies with high likelihood of remission and AED withdrawal before puberty
- When most appropriate for seizure/epilepsy type VPA may be considered when the epilepsy is so severe, or concurrent disabilites so severe, that pregnancy is extremely unlikely

Epilepsia 2015;56:1006-19 22

Patient established on valproate, not considering pregnancy

- For those in remission on VPA, withdrawal should be considered if likelihood of relapse is acceptable to patient
- For those with suboptimal seizure control or adverse effects on VPA, a switch should be considered
- VPA can be continued in GGE, when, after careful information, patient and clinician agree that benefits of remaining outweigh risks of withdrawal or switch
- Those whose seizures were only controlled after failing other appropriate alternatives, and for whom risks of withdrawal are not acceptable, can continue on VPA
- Women who wish to continue on VPA, but are willing to accept risks with dose reduction, aim for doses not exceeding 500-600 mg/day

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Epilepsia 2015;56:1006-19

Patient established on valproate considering future pregnancy

- Treatment should be reassessed and changes carefully considered for every women considering pregnancy
- Switch or withdrawal should always be considered in focal epilepsy
- Treatment changes shuld be completed and evaluated before conception. Lowest effective dose established before conception
- For those in remission on VPA, withdrawal should be considered if likelihood of relapse is acceptable to patient
- Switch from VPA to alternative should be considered for those not suitable for, or who have failed, treatment withdrawal
- Continued VPA can be considered for those well controlled on low dose VPA (up to 500-600 mg/day), AND who consider risk of withdrawal or switch unacceptable

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Epilepsia 2015;56:1006-19

Women already on valproate while pregnant

- The general rule is to continue treatment with VPA in patients discovering that they are pregnant
- Withdrawal of VPA in a pregnant woman should only be initiated if the risk of doing so is acceptable to the patient.
  - Usually the case only when there is agreement that treatment is not needed for acceptabe seizure control
- Reduction in VPA dose can be considered when the risk of doing so is acceptable to the patient.
  - Usually only the case when prior history suggests that dose is higher than needed for acceptable seizure control
- Switch to other treatment generally not recommended during pregnancy in patient with good seizure control

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Epilepsia 2015;56:1006-19

Breast-feeding and AED Exposure

AED	Milk/maternal serum	Infant/Maternal level
Phenytoin	0.1-0.6	<10%
Phenobarbital	0.3-0.8	50-100%
Ethosuxumide	0.8-1.0	40-60%
Carbamazepine	0.3-0.6	10-20%
Valproate	0.01-0.1	<5%
Lamotrigine	0.4-0.8	5-50%
Oxcarbazepine*	0.5-0.8	5-10%
Topiramate*	0.7-1.1	9-17%
Zonisamide*	0.7-0.9	n.a.
Levetiracetam	0.8-1.3	<20%
Gabapentin*	0.7-1.3	4-12%
Other newer AEDs	n.a.	n.a.

*few observations; n.a. no data avaiable

Ohman et al, 2000, 2002, 2005, 2007, 2009, Reimers 2014

NEAD Follow-up at 6 years of age

Table 3. Adjusted IQs at Age 6 Years Across Antiepileptic Drugs (AEDs) Comparing Breastfed vs Nonbreastfed Children*

AED Group	IQ, Mean (95% CI)			
	Breastfed	Nonbreastfed	Difference	P Value
All AEDs	108 (105 to 111) (n = 78)	104 (101 to 106) (n = 183)	4 (0 to 8)	.04
Carbamazepine	107 (101 to 113) (n = 23)	105 (99 to 110) (n = 24)	2 (−6 to 11)	.61
Lamotrigine	113 (110 to 117) (n = 27)	110 (107 to 113) (n = 34)	3 (−1 to 8)	.23
Phenytoin	104 (99 to 110) (n = 17)	108 (103 to 113) (n = 20)	−4 (−12 to 4)	.23
Valproate	108 (97 to 115) (n = 11)	96 (88 to 103) (n = 25)	12 (1 to 24)	.04

* Adjusted for other significant factors in the model (ie, maternal IQ, AED group, AED dosage, periconception folate use, and breastfeeding) plus the propensity score. The following were not significant: socioeconomic status, educational level, race/ethnicity, seizure or epilepsy type, maternal age, number of convulsions (none vs >1), United Kingdom site, any use of alcohol during pregnancy, any use of tobacco during pregnancy, employment (at the time of enrollment), pregnancy complications, prior pregnancy complications, prior pregnancy birth defects, and whether the pregnancy was unwanted.

JAMA Pediatr. 2014;168(8):729-736.
doi:10.1001/jamapediatrics.2014.118

Breast-feeding and AEDs

- Sufficient data for safe breast-feeding
  - phenytoin, carbamazepine, valproate, levetiracetam
- Reasonable data, significant levels, uncertain if AE
  - lamotrigine
- Reasonable data AE could occur
  - Phenobarbital, ethosuximide
- Limited data, no signals of AE
  - Gabapentin, topiramate
- Insufficient data
  - Oxcarbazepine, zonisamide, pregabalin, lacosamide, eslicarbazepinacetate

No difference in IQ at 3 years between breast-fed and not breast-fed infants of mothers taking valproate, lamotrigine, carbamazepine, or phenytoin

Meador et al Neurology 2010

Take home messages

- Managing epilepsy in pregnancy is to balance the risk associated with uncontrolled seizures against teratogenic risks with antiepileptic drugs
- Antiepileptic drugs differ in their teratogenic potential and valproate is best avoided when possible
- Major treatment changes should be completed and assessed before conception, and avoided during pregnancy
- The lowest effective dose should be established before conception,
- Pregnancy can affect serum concentrations of antiepileptic drugs, and dose adjustments may be needed to maintain seizure control
- Breast-feeding can generally be recommended despite maternal use of antiepileptic drugs

Alejandro Scaramelli (Uruguay)

INTERRELATION BETWEEN EPILEPSY AND PREGNANCY: THE ROLE OF PRE-CONCEPCIONAL EDUCATION AND NONPHARMACOLOGICAL MEASURES

ORGANIZACIÓN DE LA PRESENTACIÓN

- Etapa pre-concepcional
- Impacto de la Educación en esta etapa
- Balance entre buen control de crisis y prevención de teratogenicidad
- Rol de las medidas no farmacológicas
  - Higiene de sueño
  - Dieta Cetogénica
  - Atención a síntomas prodrómicos
  - Omega 3

ETAPA PRE-CONCEPCIONAL

- En virtud de que en la etapa intrauterina:
  - Pueden originarse malformaciones
  - Se generan las primeras bases neurobiológicas del desarrollo intelectual
  - Existe potencial exposición a efectos negativos de posibles crisis epilépticas
- LA FASE PRE-CONCEPCIONAL ES CRUCIAL DESDE EL PUNTO DE VISTA *PREVENTIVO*

EL PERÍODO GESTACIONAL Y EL PRE-CONCEPCIONAL TIENEN RELACIÓN CON "*LOS ORÍGENES DE LA SALUD Y LA ENFERMEDAD*"


ITALIAN JOURNAL OF PEDIATRICS

REVIEW Open Access

The origins of health and disease: the influence of maternal diseases and lifestyle during gestation

Capra et al, 2013

- "Melieu" en el que se desarrolla el feto es determinante de enfermedades
  - A) Por patología(s) de la madre gestante
  - B) Por medio ambiente y estilo de vida materno

A) Por patología(s) de la madre gestante

- La depresión materna durante el embarazo ↑ el riesgo de RN de bajo peso pero con distrib. central del tejido adiposo (TA) y la depresión post-parto se asocia con ↑ global del TA del niño (Erfei et al, 2010). Razón: mayor exposición de eje hipot-hipof a Corticotrophin RH ⟹ distribución central de TA en niño (Gillman et al, 2006)
- Trastornos del sueño (AOS, etc.) y privación de sueño durante embarazo facilitan RN pequeño (RR= 3.45), diabetes gestacional y resistencia a insulina
- Asma, anemia, etc.

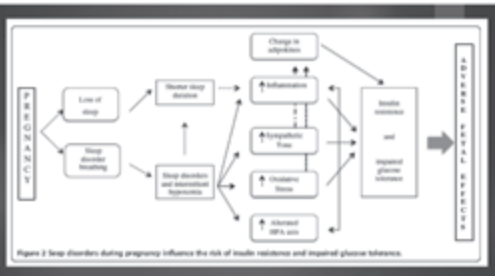


Figure 2 Sleep disorders during pregnancy influence the risk of insulin resistance and impaired glucose tolerance.

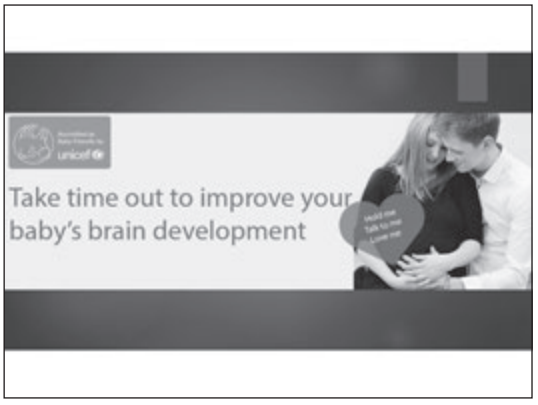
Tomado de Facco et al, 2010

B) Por medio ambiente y estilo de vida materno

- La exposición a stress psico-social materno durante la vida intrauterina ⟹ menor *longitud telomérica leucocitaria* en el adulto joven, predictor etario de inicio de enfermedad y de mortalidad (Entringer et al, 2011)
- Los hijos de madres que fuman cigarrillos tienen mayor riesgo de ser pequeños para la EG, de asma, sobrepeso, obesidad y peor neuro-desarrollo (Hermann et al, 2008)

B) Por medio ambiente y estilo de vida materno (II)

- Polución ambiental: La exposición intrauterina a Hidrocarburos Aromáticos Policíclicos x el tránsito ↑ más del doble el riesgo de retardo cognitivo a los 3 y 5 años de edad (Choi et al, 2008), y ↑ chances de mutaciones y carcinogésis
- La presencia de antioxidantes en la dieta parece disminuir efectos de sustancias carcinogenéticas. El consumo de algunos pescados puede en parte proteger el desarrollo de los sistemas neurológico, inmunológico, y CV



ETAPA PRE-CONCEPCIONAL
(Período de "Educación y Prevención")

- Consejos en mujeres con Epilepsia en edad fértil:
  - Tener en cuenta que algunos FAE (como FNT, CBZ, PB) pueden disminuir niveles de ACO
  - Si desean tener hijos, aconsejar que planifiquen su embarazo y que AVISE AL NEURÓLOGO CON ANTELACIÓN!!

ETAPA PRE-CONCEPCIONAL (II)
(Período de "Educación y Prevención")

- En lo posible, evitar uso de Valproato (VPA)
- Se podrá cambiar FAE con potencial teratogénico
- Recomendar Ácido Fólico peri-concepcional
- Aconsejar a la paciente que se "prepare" para la gestación:
  - Higiene de sueño
  - Ejercicios físicos
  - Alimentación

BALANCE ENTRE BUEN CONTROL DE CRISIS Y PREVENCIÓN DE TERATOGENICIDAD

- Por un lado, es fundamental minimizar las chances de teratogenicidad vinculada a los fármacos antiepilépticos (FAE)
- A la vez, es necesario lograr un razonable control de las crisis a través de medidas farmacológicas u otras

TERATOGENICIDAD Y MALFORMACIONES CONGÉNITAS (MC)

- El factor que más incide en la génesis de MC es la presencia de FAE durante la gestación (s/t en el 1. trimestre)
- MC mayores y menores
- Teratogenicidad diferente según FAE

FAE Y TERATOGENICIDAD

- El VPA es el FAE con mayor potencial teratogénico (s/t defectos del tubo neural; t/b déficit cognitivo y autismo)
- Existen datos nuevos para Fenobarbital (PB): se confirma mayor riesgo para MC mayores, s/t cardiacas (Hernández-Díaz et al 2012)
- TPM: conlleva > riesgo de hendiduras labio-palatinas (10 veces > población general)

EL RIESGO DE TERATOGENICIDAD AUMENTA SI:

- Politerapia
- Dosis relativamente altas de FAE individual
- Dosis poco repartidas en el día

EFECTOS COGNITIVOS en los hijos

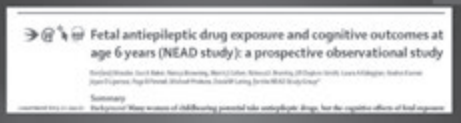
- El IQ (s/t el verbal) es menor que el esperado en niños ≥ 6 años, cuyas madres recibieron VPA en embarazo

SPECIAL REPORT

Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes

EFECTOS COGNITIVOS

- Estos efectos son menos evidentes, pero ocurren también con PB
- El autismo es 7 veces más frecuente en los niños expuestos a VPA in útero
  (Cohen et al 2011)


Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

Summary

El uso de ÁCIDO FÓLICO peri-concepcional se relaciona con mejores scores de IQ en niños expuestos

¿POR QUÉ IMPORTA *LIMITAR LAS CRISIS* DURANTE EL EMBARAZO?

- Obviamente, primero por el bienestar de la paciente (QOL)
- Reduce riesgo de SUDEP durante la gestación
- Se disminuyen chances de traumatismos
- Las crisis GTC que ocurren en el 1. trimestre, pueden aumentar el % de Malformaciones Congénitas (Lindhout, 1992)

¿POR QUÉ IMPORTA *LIMITAR LAS CRISIS* DURANTE EL EMBARAZO? (II)

- La ocurrencia de ≥ 5 crisis GTC en el embarazo se ha relacionado con ↓ del IQ en ~7 puntos en hijos a los 6 años (Adab et al, 2004)
- Durante las propias crisis, pueden ocurrir arritmias fetales, generalmente sin consecuencias. Raramente, hemorragia intracraneana fetal
- Si crisis en el embarazo, mayor probabilidad de que el RN sea pequeño para la edad gestacional

PARA EL MEJOR CONTROL DE LAS CRISIS

- Además del uso apropiado de los Fármacos Antiepilépticos (FAE)
  - Selección de FAE adecuado a forma clínica
  - Evitar los de mayor teratogenicidad
  - Monoterapia y dosis bajas en lo posible
  - Etc.
- Existe un lugar para las medidas no farmacológicas

MEDIDAS NO FARMACOLÓGICAS

- En algunos casos puede optarse por no tratar con FAE
- Dieta Cetogénica
- Calidad del sueño
- Factores precipitantes
- Síntomas prodrómicos
- Omega 3 / Otros

OPCIÓN NINGÚN FAE

- Si el control de las crisis es bueno, en algunas mujeres puede optarse por abstenerse de tratar con FAE
- Razón: no teratogenicidad
- Por ej. en pacientes con EGI con crisis poco frecuentes
- Se puede plantear a la paciente, pero ella debe estar de acuerdo
- A/v es la misma paciente que lo propone

DIETA CETOGÉNICA

- Modalidad terapéutica aceptadamente eficaz en el tratamiento de ERF
- Inicialmente indicada en niños, actualmente en niños y adultos
- Cada vez existe mayor difusión e indicación en el mundo
- Creciente N° de publicaciones

Características de la DC

- Alto contenido en *lípidos*, adecuado en *proteínas* y bajo en *carbohidratos*
  - Lípidos: crema de leche, manteca y mayonesa
- Dieta hipocalórica: 75%
- Nº de comidas diarias: 3 o 4

Variantes de la DC

- Dieta Clásica 4:1
  - 90% calorías por grasa
- DC de Triglicéridos de cadena media
- Dieta de Atkins modificada
- Dieta de bajo índice glicémico

EN EL CASO DE MUJERES CON EPI CURSANDO EMBARAZO O QUE PLANEAN GESTACIÓN

- Puede indicarse en aquellas mujeres con una epi no severa y que prefieren no recibir FAE
- También en aquellas con cualquier forma de epi que optan decididamente por no tomar ninguna medicación durante su embarazo

MEJORAR CALIDAD DEL SUEÑO

- Es una de las medidas generales que tiene mayor impacto en el control de las crisis
- El evitar privación de sueño tiene *mayor eficacia en las EG idiopáticas*, pero útil en todas las formas clínicas
- Los EEG con privación (parcial) de sueño → *mayor % de descargas* (Degen 1987, Larsson 2010)

MEJORAR CALIDAD DEL SUEÑO (II)

- Dormir demasiado tiempo (> 10 h): parece ↑ probabilidad de crisis
- Según etapa de sueño:
  - Sueño no-REM (↓↑ Etapa 2):
    - > frecuencia de crisis
    - > N° de descargas en EEG
  - REM:
    - < tasa de crisis
    - < N° de descargas interictales

(Durante el REM, el incremento de actividad dejaría menor N° de neuronas disponibles para reclutar en una descarga epiléptica)

RELACIÓN CON *APNEAS DEL SUEÑO* (AOS)

- Las apneas del sueño → mayor N° de crisis (mecanismo discutido)
  - desaturación de O_2 ?
  - fragmentación del sueño?
- El tratamiento de las apneas del sueño → mejor control de crisis (Vaughn 1996)
- La CPAP es eficaz para las AOS y segura en el embarazo (Guilleminault et al. 2004)

Empleo de MELATONINA en algunos pacientes

a) Puede ordenar el ritmo circadiano (mejorando transposición de fase)

b) Puede ↓ Frecuencia de crisis (Goldberg-Stern 2012)

- "Per se" ?
- A través de la mejoría del sueño?

RECOMENDACIONES - SUEÑO

- Dedicar tiempo en la consulta al tema sueño
- "Cuidar" N° de horas de sueño, máxime en las EGI
- Indagar y tratar posibles AOS
- En algunos casos, considerar Melatonina

FACTORES PRECIPITANTES (FFPP)

- Las crisis epilépticas pueden precipitarse o desencadenarse más fácilmente frente a diferentes factores
- Algunos pacientes los identifican y para ellos resultan facilitadores de las crisis en repetidas ocasiones
- En estudios retro y prospectivos en pacientes adultos en diferentes tipos de epi, los factores emocionales fueron el 1º y la privación de sueño fue el 2º en frecuencia de los FFPP (Martínez et al 1999, Scaramelli et al 1999)

SÍNTOMAS PRODRÓMICOS

- Son aquellos cambios clínicos que preceden en minutos u horas a las crisis
- Cada paciente suele reconocer siempre el (o los) mismo(s) pródromos (PP)
- Pueden ser útiles en la predicción o anticipación de crisis
- Algunos autores han recurrido a distintos análisis bio-matemáticos del EEG en la fase pre-ictal


Seizure

Prodromal symptoms in epileptic patients: Clinical characterization of the pre-ictal phase

- En muestra aleatorizada de 100 pacientes adultos con epilepsia
- Entrevistas personales, incluyendo familiares, y Protocolo semi-estructurado
- Se encontraron PP en 28% de los pacientes
- Los más frecuentes fueron cambios conductuales, cognitivos y del humor
- Mayor presencia en epilepsias parciales
- Si el paciente los identifica, pueden ser valiosos para medidas preventivas o terapéuticas

RECOMENDACIONES

- Preguntar por posibles PP
- Si la paciente los identifica, aconsejar:
  - Tomar precauciones, como acostarse, no exponerse a lugar inseguro, etc.
  - y/o utilizar dosis adicional de FAE o Benzodiacepina
  - Eventualmente otra modalidad terapéutica

OMEGA 3

- Los ácidos grasos poli-insaturados de tipo Omega 3 están presentes en buena proporción en ciertos pescados y en ciertas semillas (chia, etc.)
- Se han relacionado con varios efectos "protectores", aunque existen algunos puntos de discusión
- Se les atribuye capacidad para prevenir arritmias fatales, ↓ los triglicéridos y los niveles de PCR (Breslow et al, 2006)
- La AHA incluye a los Omega 3 de origen marino en su "dieta cardioca saludable" (Lichtenstein et al, 2006)

OMEGA 3 (II)

- El consumo materno de cantidades "adecuadas" (± 340 g a la semana) de pescado oleoso, se ha asociado a mejores scores de IQ, psicomotricidad y habilidades sociales en el niño + menor incidencia de depresión post-parto (Hibbeln, 2007)
- Ingesta de pescado en embarazada es recomendación de FDA (2014)
- Contrapartida: contaminación con Metil-Mercurio en ciertos pescados (mayor en pez espada, lenguado, atún)
- En el balance, predomina beneficio de Omega 3, máxime seleccionando fuente (sardina, salmón, abadejo, camarones)
- Suplementos de Omega 3 vs presencia natural (que incluye antioxidantes y otras sust.)

OMEGA 3 (III)

- La administración de DHA x 14 d (vs placebo) prolongó x 3 la latencia de las crisis inducidas por PTZ (Trépanier et al 2014)
- El pre-tratamiento con Omega 3 fue neuroprotector contra el daño neuronal x SE inducido x Pilocarpina (Ferrari et al, 2008 y Cysneiros et al, 2010)

OMEGA 3 (IV)

- El supiemento con Omega 3 puede reducir frecuencia de crisis y disminuir riesgo de SUDEP en niños y adolescentes con epilepsia resistente a los fármacos (ERF) (Scorza, 2015)
- En niños con ERF, los que recibieron suplemento con aceite de pescado redujeron significat. frecuencia de crisis vs placebo (Reda et al, 2015)
- Estudio aleatorizado, controlado con placebo, cross-over en pacientes con ERF: aquellos con dosis bajas de Omega 3 redujeron frecuencia de crisis en 33.6% y descendieron levemente la PA vs no efecto con dosis altas y placebo (DeGiorgio et al, 2015)

CONCLUSIONES

- El embarazo y el periodo pre-concepcional **son etapas cruciales para la salud estructural, cognitiva y emocional del nuevo ser**
- **Éstos son momentos propicios para realizar** educación **y** prevención
- **Se destacan: información suficiente y apropiada a la paciente en edad fértil / advertir de que avisen con antelación si planean concebir / adecuar tipo de FAE y dosis según la situación clínica / Ácido Fólico**

CONCLUSIONES (II)

- **Procurar BALANCE entre** prevención de teratogenicidad **y** limitar las crisis **epilépticas**
- **Para el mejor control de las crisis:**
  - **Buen manejo de los** FAE
  - **En ciertos casos** Dieta Cetogénica
  - **En todos los casos tener en cuenta y dedicar un espacio a** Higiene del sueño
  - **Actuar sobre posibles** Factores Precipitantes
  - **Cuando el paciente identifica** Pródromos, **aconsejar medidas protectoras**
  - **Considerar dieta rica en ciertos pescados o suplemento de** Omega 3

Torbjörn Tomson (Sweden)

SUDDEN-UNEXPECTED DEATH IN EPILEPSY (SUDEP)

Karolinska Institutet

Sudden Unexpected Death in Epilepsy SUDEP

LASSE X, 2016

Torbjörn Tomson
Department of Clinical Neuroscience
Karolinska Institutet
Stockholm, Sweden

Karolinska Institutet

On Modes of Death in Epilepsy

- Those arising from the long continued effects of the disease on the body;
- Deaths after a rapid succession of fits;
- Sudden deaths in a fit;
- Accidents due to fits.

The Lancet, May 2, 1868

Cause of death in people with epilepsy

- Causes of death:
  - →unrelated to epilepsy
  - →related to the underlying cause of epilepsy
  - →related to the treatment of epilepsy
  - →related to epilepsy and seizures
    - Status epilepticus
    - Accidents
    - SUDEP
    - Suicide

3

SUDEP Definitions & Awareness

On 19 March 2011, Knut collapsed and died in his enclosure. Witnesses reported that after the bear's rear **left leg began shaking**, he became agitated before **convulsing** several times and **falling backwards into the pool**. Approximately 600 to 700 zoo visitors witnessed Knut's death. On 1 April, pathology experts announced that the bear's apparent seizure was due to his suffering from **encephalitis**. This suspected infection must already have been there for a long time ... at least several weeks, possibly months". It was also announced that **had Knut not drowned after collapsing, he would not have survived.** Knut's sudden death caused an international outpouring of grief. The Zoo plans to erect a monument in Knut's honor, financed by donations from fans.

Wikipedia 2012-04-20

Defining SUDEP

- Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death

Nashef Epilepsia1997;38

SCIENTIFIC REPORTS

OPEN

Anti-NMDA Receptor Encephalitis in the Polar Bear (*Ursus maritimus*) Knut

H. Prüss[1,2,*], J. Leubner[1,*], N. K. Wenke[1], G. Á. Czirják[1], C. A. Sieberls[3] & A. D. Greenwood[3]

Received: 20 December 2014
Accepted: 08 July 2015
Published: 27 August 2015

Knut the polar bear of the Berlin Zoological Garden drowned in 2011 following seizures and was diagnosed as having suffered encephalitis of unknown etiology after exhaustive pathogen screening. Using the diagnostic criteria applied to human patients, we demonstrate that Knut's encephalitis is almost identical to anti-NMDA-receptor encephalitis which is a severe autoimmune

Epilepsia, 53(3):371–373, 2012
doi: 10.1111/j.1528-1167.2011.03386.x

CRITICAL REVIEW AND INVITED COMMENTARY

Unifying the definitions of sudden unexpected death in epilepsy

*Lina Nashef, †Oliver L. So, ‡Philippe Ryvlin, and §Torbjörn Tomson

- Unified definition and classification proposed

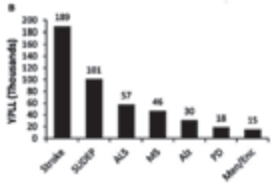
Nashef , So, Ryvlin, Tomson Epilepsia 2012;53:227

- Distinction between cases with competing cause (Possible SUDEP) and cases with insufficient information (Unclassified)
- Distinction between combined causes (SUDEP plus) and competing non-SUDEP related cause of death (Possible SUDEP)
- Separate category for cases surviving resuscitation (Near-SUDEP)
- Criteria for "Sudden" specified (<1hour)

SUDEP a major cause of death at least in in high income countries

- The risk of Sudden Unexpected Death among young people with epilepsy 24- to 28-fold higher than in the general population
  Holst A Epilepsia 2013, Ficker DM. Neurology 1998

- In years of potential life lost SUDEP ranks second only to stroke among other neurological conditions in the US.
  Thurman et al., Epilepsia 2014



SUDEP most common epilepsy related death accounting for 30% of all deaths among people with epilepsy

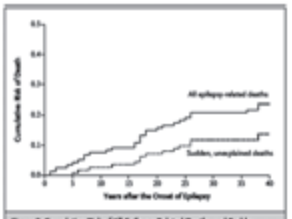
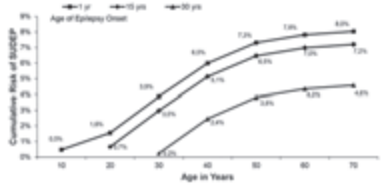


Figure 2. Cumulative Risk of All Epilepsy-Related Deaths and Sudden, Unexplained Deaths in Subjects with Epilepsy.
Data shown are for patients at risk (i.e., receiving medication, with or without 5-year terminal remission).

Cumulative risk of SUDEP 7-9% after 40 years follow-up of childhood onset epilepsy

Sillanpää and Shinnar NEJM 2010

Cumulative risk of SUDEP in epilepsy populations



Thurman et al., Epilepsia 2014

Sillanpää and Shinnar NEJM 2010

Age distribution

Sudden unexpected death in epilepsy: Assessing the public health burden

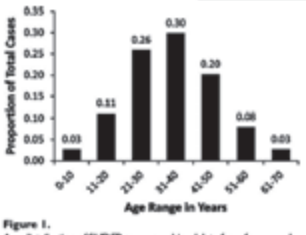


Figure 1.
Age distribution of SUDEP cases: combined data from four population-based studies.[4,33–34]
Epilepsia © ILAE

Estimated SUDEP incidence by age

Population	SUDEP/1000 pt-years (CI)	Confidence
Overall	0.58 (0.31 to 1.08)	Low
Childhood	0.22 (0.16 to 0.31)	Moderate
"Adulthood"	1.2 (0.64 to 2.32)	Low

Incidence of SUDEP varies with the epilepsy population

Karolinska Institutet

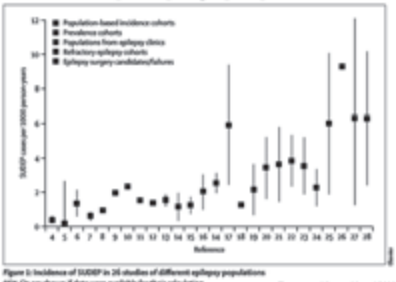


Figure 1: Incidence of SUDEP in 26 studies of different epilepsy populations
95% CIs are shown if data were available for their calculation.

Tomson et al Lancet Neurol 2008

Epilepsia, 52(6):1150–1159, 2011
doi: 10.1111/j.1528-1167.2010.03052.x

FULL-LENGTH ORIGINAL RESEARCH

Combined analysis of risk factors for SUDEP

*Dale C. Hesdorffer, †Torbjorn Tomson, *Emma Benn, ‡§Josemir W. Sander, ¶Lena Nilsson, ‡Yvonne Langan, **Thaddeus S. Walczak, ††Ettore Beghi, ‡‡Martin J. Brodie, and *Allen Hauser, for the ILAE Commission on Epidemiology; Subcommission on Mortality

*Columbia University, New York, New York, U.S.A.; †Karolinska Institutet, Stockholm, Sweden; ‡SUDEP, Institute of Neurology, Queen Square, London, United Kingdom; §SUDEP—Epilepsy Institute in the Netherlands Foundation, Heemstede, The Netherlands; ¶Department of Neurological Rehabilitation, Stora Skärhult Hospital, Stockholm, Sweden; **University of Minnesota, Minneapolis, Minnesota, U.S.A.; ††Mario Negri Institute, Milan, Italy; and ‡‡University of Glasgow, Glasgow, United Kingdom

Study	Number cases and controls	Matching factors	Inclusion criteria
US (Walczak et al, 2001)	20 cases 60 controls	Month and study center	
Sweden (Nilsson et al, 1999)	56 cases 157 controls	Birth year, sex, and assessment period	15-70 years ≥1 year of VPA, PHT, or CBZ
Scotland (Hitiris et al, 2007)	64 cases 119 controls	Birth year, gender and syndrome classification	Active seizure disorders
England (Langan et al, 2005)	149 cases 602 controls	Age and geographic location	16 to 50 years

Generalized tonic-clonic seizures most important risk factor

GTC frequency per year	Crude OR (95% CI)	Fully adjusted OR (95% CI)
0	1.0 (Referent)	1.0 (Referent)
1-2	5.1 (3.0-8.6)	5.1 (2.9-8.8)
>=3	15.6 (10.1-24.0)	15.5 (9.9-24.1)
Unknown	6.1 (3.8-9.9)	5.4 (3.2-8.9)
No GTCS	1.0 (Referent)	1.0 (Referent)
>=1 GTCS/year or Unknown # GTCS/year	8.0 (5.2-12.3)	7.1 (4.5-11.0)

Adjusted for data source, gender, age at death and duration of epilepsy

Hesdorffer et al Epilepsia 2011

Adjusted Odds Ratios

For data source, gender, age at death and duration of epilepsy

Variable	Adjusted OR (95% CI)
Gender	
Female	1.0 (Referent)
Male	1.42 (1.07-1.88)
Onset age	
<16 years	1.72 (1.23-2.40)
16-60 years	1.0 (Referent)
>60 years	0.41 (0.08-2.14)
Duration of epilepsy	
<15 years	1.0 (Referent)
>15 years	1.95 (1.45-2.63)
Idiopathic Etiology	
No	1.0 (Referent)
Yes	0.71 (0.50-1.01)

Hesdorffer et al Epilepsia 2011

AEDs or Seizures?

Extended analysis

Adjusting for data source, gender, age at death and GTCS frequency

Variable	Adjusted OR (95% CI)
No AED therapy	1.0 (Referent)
1 AED	0.5 (0.3-0.995)
2 AEDs	0.9 (0.4-1.8)
3 AEDs	2.0 (0.9-4.1)
>3 AEDs	1.6 (0.6-4.1)

No increased risk associated with any AED as monotherapy
GTCS frequency remained strongly associated with SUDEP

Hesdorffer et al in manuscript

Can specific AEDs increase SUDEP risk?

FULL-LENGTH ORIGINAL RESEARCH

Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: A nested, case-control study

16 definite, 3 probable SUDEPs
Controls: living epilepsy patients

Population	Cases Exposed/All	Controls Exposed/All	Odds Ratio (95% CI)
Patients on LTG	8/19	15/63	2.6 (0.8-8.4)
Women on LTG	7/12	10/41	5.6 (1.1-28.2)

- Possible association between LTG and SUDEP could hypothetically be due to
  - → Direct pharmacological effects of LTG
  - → Poorer control of GTCS in women on LTG
- Control of GTCS not known and not adjusted for

FULL-LENGTH ORIGINAL RESEARCH

Do antiepileptic drugs or generalized tonic–clonic seizure frequency increase SUDEP risk? A combined analysis

Analysis of lamotrigine, data from England and USA

Treatment	Crude analysis Odds ratio (95% CI)	Adjusted analysis* Odds ratio (95% CI)
No AED	1.00 (reference)	1.00 (reference)
Other AED	1.1 (0.6-1.9)	0.7 (0.4-1.4)
LTG monotherapy	1.5 (0.4-6.2)	0.7 (0.1-3.6)
LTG polytherapy	2.9 (1.4-6.0)	0.95 (0.4-2.2)

*Adjustment for GTCS frequency

FULL-LENGTH ORIGINAL RESEARCH

Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials

*Torbjörn Tomson, †Lawrence J. Hirsch, ‡Daniel Friedman, §Nicolette Bester, ¶Anne Hammer, #Michael Irizarry, ‡Lianna Ishihara, ¶Alok Krishen, ¶Theodore Spaulding, ¶Art Wanni, and ¶Robert Leadbetter

7,774 subjects in 42 RCTs, 8 definite or probable SUDEPs (4 in LTG arm)

Table 3. Crude, pooled rates for definite or probable SUDEP in patients exposed to lamotrigine, combined for all study types but not adjusted for study type or other factors

Body population subgroups	Number of patients	SUDEP rate per 1,000 person-years (95% CI)
All patients exposed to LTG	4 SUDEPs/4,631 patients	1.32 (0.79–1.5)
Sex*		
Male	3 SUDEPS/2,170 patients	1.1 (0.43–4.1)
Female	1 SUDEPS/2,431 patients	1.0 (0.24–4.6)
Epilepsy population*		
Newly diagnosed	1 SUDEPS/1,695 patients	1.1 (0.43–4.1)
Refractory	1 SUDEPS/1,484 patients	1.1 (0.38–7.4)
Seizure type*		
Generalized*	0 SUDEPS/47 patients	N/A
Partial*	2 SUDEPS/1,022 patients	17 (0.45–68)
Both generalized and partial	1 SUDEPS/1,861 patients	1.4 (0.45–8.0)

Definite/probable SUDEP on LTG treatment vs. Comparator

- OR 0.22 (95% CI 0.00-3.14) in placebo-controlled parallel-group trials
- OR 2.18 (95% CI 0.17-117) in active-comparator parallel-group trials
- OR 1.08 (95% CI 0.00-42.2) in placebo-controlled cross-over trials

Lack of supervision as risk factor for SUDEP

	Cases (n)	Controls (n)	OR 95%CI
No supervision	109	169	1
Same room	34	156	0.4 (0.2-0.8)
Special precautions*	11	42	0.1 (0.0-0.3)

*regular checks throughout night or listening device

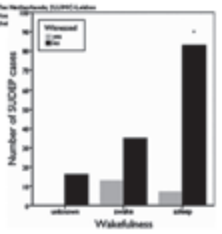
Langan Neurology 2005;64:1131 (n=154)

FULL-LENGTH ORIGINAL RESEARCH

Sudden unexpected death in epilepsy: People with nocturnal seizures may be at highest risk

*Robert J. Lamberts, *†Roland D. Thijs, ‡Aoife Laffan, §Yvonne Langan, and *‖Josemir W. Sander

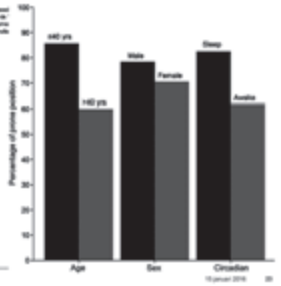
- 154 SUDEP
- 616 living epilepsy controls
- Nocturnal seizures
  → OR 2.6 (1.3-5.0)

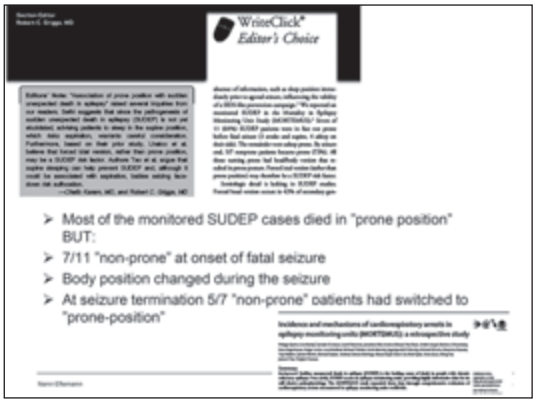


Association of prone position with sudden unexpected death in epilepsy

Lieberthal et al Neurology 2015

Prone position
4-fold more prevalent than non-prone position in SUDEP cases where information on body position was available





Risk factors in case-control studies

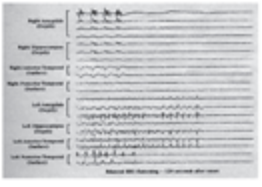
Combined analysis
Hedoffer et al Epilepsia 2011

- GTCS frequency
- Young age at onset
- Long duration
- Male gender
- Symptomatic etiology

Other sources

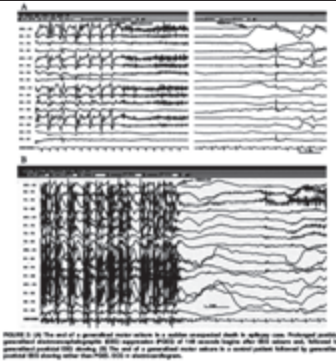
- Lack of supervision at night
  → 10-fold increased risk vs. special precautions
  Langan et al Neurology 2005
- Nocturnal seizures
  → OR 2.6 (1.3-5.0)
  Lamberts et al Epilepsia 2012

Electroencephalographic biomarker of SUDEP
Prolonged Postictal EEG Suppression PGES as Predictor of SUDEP? 1st monitored SUDEP case



Bird et al Epilepsia 1997

Duration of preceding tonic phase and severity of perictal hypoxemia linked to PGES. *Semmelroch et al., epilepsia 2012; Seyal et al., Epilepsia 2012*



Prolonged Postictal EEG Suppression as Predictor of SUDEP

PGES= postictal generalised absence of EEG-activity>10µV

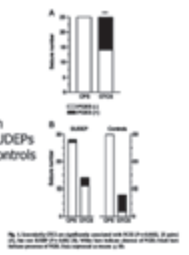
10 SUDEPs and 30 controls

PGES >50 sec associated with increased risk, OR 5.2

Lhatoo et al Annals Neurol 2010

Epilepsy & Behavior

Postictal generalized electroencephalographic suppression is associated with generalized seizures



PGES in
4/17 SUDEPs
3/17 Controls

17 SUDEPs with both CPS and sGTCS

17 Controls

- No association between PGES and SUDEP
- PGES inconsistent finding between seizures in same patient

Electrophysiological biomarkers of SUDEP risk
Cardiac measures

Seizure related ECG feature	Occurence with seizures	Association with SUDEP
Bradycardia	Up to 6% of seizures Up to 40% of patients	Not reported
AV-conduction blocks	Rare	Not reported
Asystole	0.3-1% of patients	Not established
Transient prolongation of corr. QT intervals	6-13% of seizures 12-23% of patients	No evidence (negative case-control study)
Transient shorteting of corr. QT intervals	4-45% of focal seizures 90% of sec GTCS	No evidence (negative case-control study)
T-wave alternans	Amplitudes incresed in sGTCS vs. focal	Not investigated
Heart rate variability	Decreased in chronic epilepsy	No evidence (negative case-control study)

Modified from Tomson et al., Epilepsia 2016

ORIGINAL ARTICLE

Genetic investigation of sudden unexpected death in epilepsy cohort by panel target resequencing

- Panel target (9 SUDEP related and 88 other genes) resequencing in 14 cases with personal or family history of probable SUDEP

24 rare genetic variants were identified in 13 SUDEP cases.
4 cases showed rare variants in *SCN1A, FBN1, HCN1, SCN4A, EFHC1* with complete segregation
1 case with a rare variant in *KCNQ1* with incomplete inheretance
4 cases with rare variants in *CACNA1A, SCN11A,SCN10A, KCNQ1* but familial segregation was not possible due to lack of DNA from relatives
4 remaining cases, the rare variants did not segregate in the family.

New potential candidate genes for SUDEP: *FBN1, HCN1, SCN4A, EFHC1, CACNA1A, SCN11A,* and *SCN10A.*

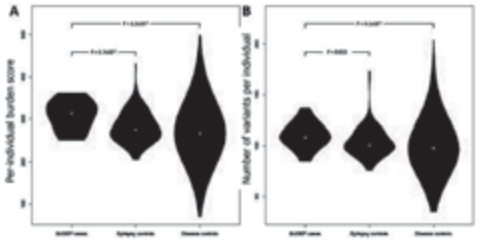
EBioMedicine

Research Paper

Genome-wide Polygenic Burden of Rare Deleterious Variants in Sudden Unexpected Death in Epilepsy

- 18 people who died of SUDEP (8 definite)
- 87 living people with epilepsy
- 1,479 non-epilepsy controls
- Whole-exome sequencing for rare protein-changing variants

Number of variants per group



Significantly increased polygenic burden in SUDEP cases, with more than a thousand genes contributing
No singel gene common to SUDEP cases

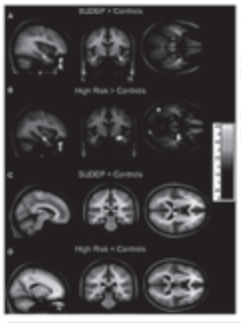
Structural SUDEP biomarkers?

BRAIN

Structural imaging biomarkers of sudden unexpected death in epilepsy

Britta Wandschneider,[1,2] Matthias Koepp,[1,2] Catherine Scott,[1,2] Caroline Micallef,[1,2] Simona Balestrini,[1,2,3] Sanjay M. Sisodiya,[1,2,4] Maria Thom,[1,2,4] Ronald M. Harper,[4,5] Josemir W. Sander,[1,2,4,6] Sjoerd B. Vos,[1,2,7] John S. Duncan,[1,2] Samden Lhatoo[4,8] and Beate Diehl[1,2,4]

- 12 cases of SUDEP (of which 2 definite)
- 34 high risk epilepsy patients
- 19 low risk epilepsy patients
- 15 healthy controls
- Voxel-based analysis of T1 volume scans obtained 2 years before death

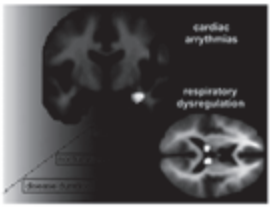


- SUDEP and High Risk Epilepsy patients

Increased grey matter volume right hippocampus/parahippocampus

Decreased grey matter bilaterally in the pulvinar

Interpretation



- Right-sided predominance reflects asymmetric central influnce on autonomic outflow, contributing to cardiac arrhythmia
- Pulvinar damage may impair hypoxia regulation

Hypothesized model for SUDEP mechanisms

Massey, C. A. *et al. Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.64

Predisposing (Risk) factors and triggers

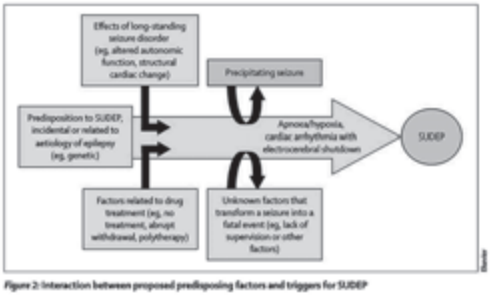
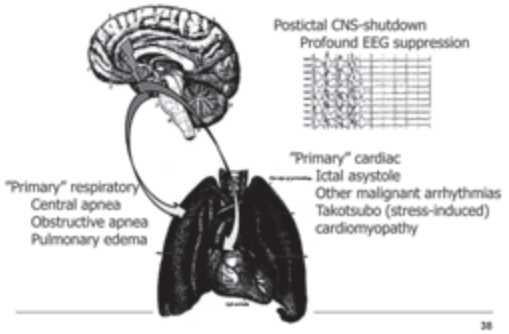


Figure 2: **Interaction between proposed predisposing factors and triggers for SUDEP**

Tomson et al Lancet Neurol 2008

SUDEP Mechanisms- Final events



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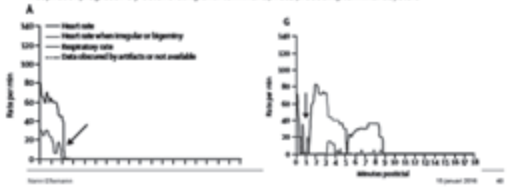
Clues from monitored SUDEP

- 147 EMUs surveyed
- 16 SUDEP and 9 near-SUDEP identified (2 dealyed fatalities)
- 11/18 SUDEP occurred during active monitoring (5 previously published)
  - → All fatalities adults
  - → All SUDEP and fatal near-SUDEP during evening or night
  - → Preceded by a GTCS in all fatalities
  - → Cardiorespiratory resuscitation with a delay of >10 minutes after apnoea in all fatalities
  - → Postictal cardiorespiratory dysfunction in all

Generalized tonic-clonic seizure

- Short period of normal or increased heart and respiratory rates
- Combination of central apnea, severe bradycardia
- Transient asystole together with generalised EEG suppression

- In a proportion of cases transient restoration of cardiac function together with abnormal ineffective respirationprogressively deteriorating until terminal apnea, preceding terminal asystole



How can SUDEP be prevented?

Figure 2: Interaction between proposed predisposing factors and triggers for SUDEP

Tomson et al Lancet Neurol 2008

Improving seizure control

- By use of anitepileptic drugs
  - →Treatment rather than no treatment
  - →Add-on in refractory patents
  - →Enhance compliance
- By use of epilepsy surgery
- With information

AEDs protective against SUDEP?

Extended analysis of pooled data

Adjusting for data source, gender, age at death and GTCS frequency

Variable	Adjusted OR (95% CI)
No AED therapy	1.0 (Referent)
1 AED	0.5 (0.3-0.995)
2 AEDs	0.9 (0.4-1.8)
3 AEDs	2.0 (0.9-4.1)
>3 AEDs	1.6 (0.6-4.1)

Hesdorffer et al Epilepsia 2012

Adding placebo vs. effective AED SUDEP risk factor in patients with refractory seizures

18 Definite or Probable SUDEPs

SUDEP rate per 1000 patient years
6.9 (3.8-11.6) in Placebo arm
3.7 (0.1-20.6) Non-efficacious dose
0.9 (0.2-2.7) in Efficacious arm

Lancet Neurol 2011;10:962.

Cause of Death	Efficacious AED vs. Placebo Odds Ratio (95% CI)	P-value
Definite & Probable SUDEP	0.17 (0.05-0.57	0.0046
Other causes of death	0.89 (0.28-2.79)	0.8407

44

Compliance with AED therapy and mortality

Nonadherence to antiepileptic drugs and increased mortality

Findings from the RANSOM Study

Neurology. 2008 Nov 11;71(20):1572-6.

Nonadherence vs Adherence to prescribed AEDs
Hazard Ratio (95%CI) 3.32 (3.11-3.54)

45

Compliance with AED therapy and mortality

Research Br J General Practice May 2011

Epilepsy mortality and risk factors for death in epilepsy:

a population-based study

Time since last AED prescription	Controls	Cases	Odds ratio Death (95% CI)
<90 days	10 847	8250	Reference
91-182 days	768	1117	1.83 (1.66-2.03)

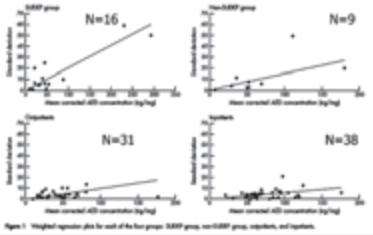
46

Compliance with AEDs and SUDEP

PAPER

Variability of antiepileptic medication taking behaviour in sudden unexplained death in epilepsy: hair analysis at autopsy

J Williams, C Lawthom, F D Dunstan, T P Dawson, M P Kerr, J F Wilson, P E M Smith



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Can successful epilepsy surgery reduce mortality?

Source	Cases n	Deaths	Association with seizure control
Vickrey 1997	202 surgery 46 non-surgery	14 (7%) 9 (20%)	
Salanova 2002	215 TLE	11 (%)	seizure free: 3 (2%) recurrent : 8 (12%)
Nilsson 2003	586 surgery 212 non-surgery	14 SMR 4.9 5 SMR 7.9	None of 5 SUDEP seizure free
Sperling 2005	583 surgery	19 SMR 3.6	seizure free: 1 SMR 0.5 recurrent : 18 SMR 5.8
Bell 2009	561 surgery 641 non-surgery	19 (7 epilepsy-rel) 40 (24 epilepsy-rel)	None of 5 SUDEP seizure free
Seymour 2012	360 TLE	19 SMR 2.0	2 of 6 SUDEPs seizure free

Adequate supervision of high risk patient may reduce risk

	Cases (n)	Controls (n)	OR 95%CI
No supervision	**109**	**169**	**1**
Same room	**34**	**156**	**0.4 (0.2-0.8)**
Special precautions*	**11**	**42**	**0.1 (0.0-0.3)**

*regular checks throughout night or listening device

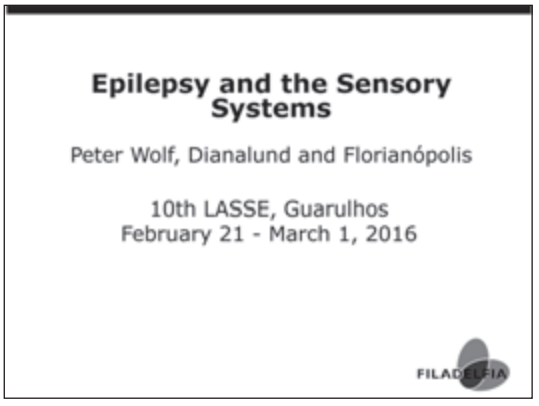
Langan Neurology 2005;64:1131 (n=154)

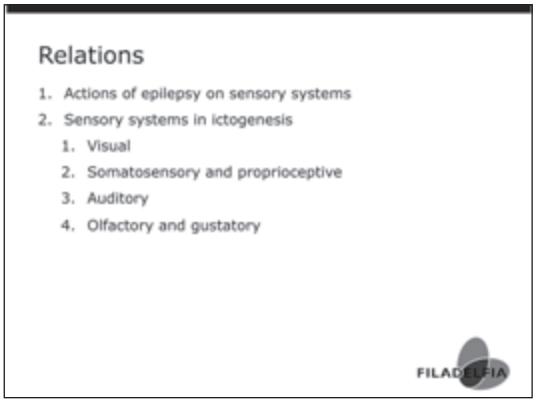
Conclusions

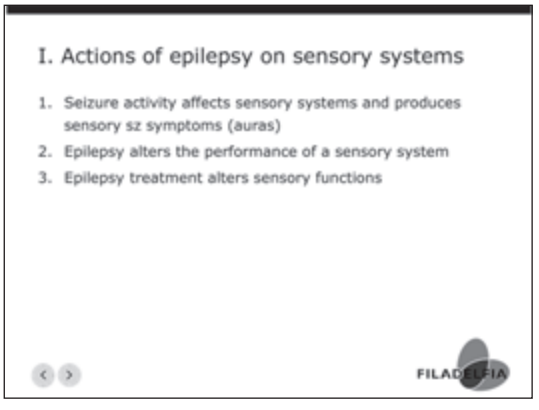
- SUDEP is the most common epilepsy related cause of death and a major cause in chronic epilepsy
- Poor control of GTCS most important risk factor
- SUDEP in general in conjunction with a GTCS
  - → But most patients with GTCS will not die in SUDEP
  - → And most SUDEP victims have hade many non-fatal GTCS
- Final mechanisms unclear, probably multiple
- Possible preventive measures include
  - → Improved drug treatment to reduce GTCS
  - → Epilepsy surgery in suitable patients
  - → Night time supervision in high risk patients
  - → Adequate information

Peter Wolf (Denmark)

EPILEPSY AND THE SENSORY SYSTEMS







Ictal affection of sensory systems

Seizure activity affects sensory systems and produces sensory sz symptoms (auras)

- Visual
- Auditory
- Somatosensory
- Olfactory / gustatory

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Visual auras: calcarine cortex

Phosphenes, photomes

- related to contralateral visual hemifield
- mobile (centrifugal or centripetal) or stationary
- spectral colours, white and black
- usually simple geometrical shapes
  - distinguish from migraine auras: duration, fortification figures
- Cave: visual simple focal status and visual epilepsia partialis continua

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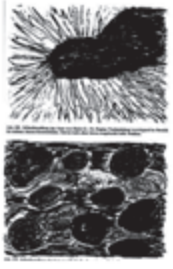
Visual auras



Epilepsy

Migraine

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Visual EPC

- Man age 52, at 43 sudden defect left visual field, right occ av malformation, radiosurgery ⇒ sz
- Semiology: Photome left VF of four white dots in lower left quadrant (like the "4" on a dice), rotating with increasing speed. With further increase he becomes blind; feels his head dissolves, lasts up to 3 min, rarely evolves into GTCS
- In addition: continuous visual disturbance: light, nebulous filaments at the border of left VF, in constant "hopping" movement
- episodically they cover larger area, disturbing his vision, e.g. if he walks along a wall to his left, he cannot steer clear of it, extremely irritated
- Onset 1 ½ years before acute event

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Visual auras: other

- Simple visual hallucinations: secondary visual cortex
  - ✓non-spectral colours, variable shapes
  - ✓Concentric changes of visual field ("tunnel vision")
- Visual illusions (metamorphopsias, dyschromatopsias, macropsias and micropsias etc): occipito-parieto-temporal junction, rarely temporo-anterior
- Complex visual hallucinations: temporo-posterior

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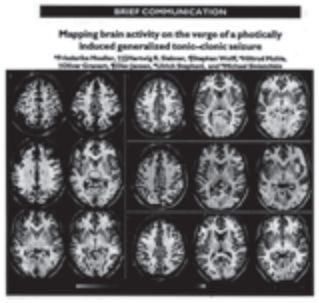
Thalamus, FS + visual aura: fMRI


BRIEF COMMUNICATION

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

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Auditory auras

- Simple noises
- Rarely clear tones
- Rhythms
- Often directed ("with which ear you hear it?"): contralateral gyrus Heschl
- Rarely musical hallucination: temporal lobe
- Extremely rare: musical status epilepticus

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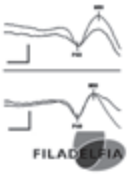
Somatosensory auras

- Local onset paresthesias, usually centripetal Jacksonian march
- Often accompanied by focal motor signs
- Contralateral postcentral gyrus
- Rare variant: focal tonic seizure accompanied by intense pain (often misdiagnosed as psychogenic because of painful expression, voluntary reactive movements)
- Cave: somatosensory EPC!



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Proprioceptive auras

- Kinesthetic (movement-related)
- Rare: illusion of movement
- Distortion of body image
- Hemineglect

Olfactory auras

- Herpin (1867), Jackson (1888: relation to temporal lobe).
- Gowers (1881) reported by 7/119 patients (5.9%)
- Chen C, Shih YH, Yen DJ et al Epilepsia 2003; 44: 257-260
  - 217 medically intractable surgical cases
  - 12 (5.5%) reported olfactory auras
  - All but one unpleasant
  - Usually combined with others (epigastric, nausea, fear)
  - Once combined with gustatory aura
- Olfactory aura continua (variant of EPC) very rare

Altered performance of sensory systems

- By epilepsy:
  - epilepsia partialis continua: visual, auditory, somatosensory, proprioceptive, olfactory
  - Reduced olfactory performance in TLE
- By treatment: AED side effects
  - Polyneuropathy (several AED, infrequent)
  - Visual field defects (vigabatrin, frequent)
  - Anosmia, ageusia (anecdotic)
  - Hearing reduction (rare)

II. Sensory systems in ictogenesis

The emerging concept of system epilepsies (Avanzini et al 2012) raises the question if and which sensory systems can be involved in the generation of seizures, and how?

- Seizure precipitation by sensory stimuli (reflex epilepsy)
- Seizure inhibition or arrest by sensory stimuli

Sensory reflex epileptic seizures

- Visual
  - Photosensitivity
  - Eye closure sensitivity
  - Pattern sensitivity
  - Fixation-off sensitivity
- Somatosensory
- Proprioceptive
- Auditory
- Olfactory

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Photosensitivity

- Most often seen in Idiopathic Generalised Epilepsies, especially Juvenile Myoclonic Ep.
- Homogeneous?
- Myoclonic sz > absences > GTC > focal occipital
- Stimulation of occipital cortex
- Response quantitative and variable, rapid with right frequency (~ 14 - 30 hz) but rarely immediate

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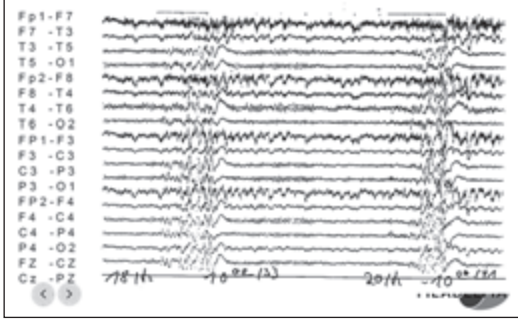
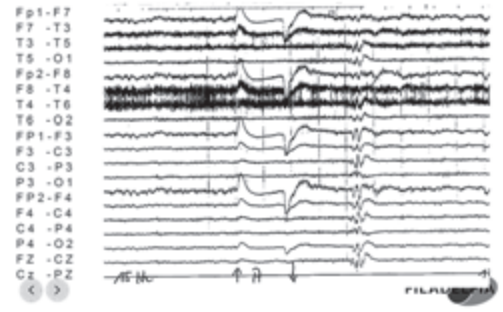
TV-induced seizures: photoparoxysmal EEG response (PPR)



Photosensitivity: attenuation by dark glasses (- 30%)



DOI: 10.1093/brain/awg109 *Brain* (2003), 126, 1164–1172

Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception?

J. Parra,[1] S. N. Kalitzin,[1] J. Iriarte,[2] W. Blanes,[1] D. N. Velis[1] and F. H. Lopes da Silva[1]

MEG: "Enhancement of phase synchrony in the γ band (30-120 hz), harmonically related to the frequency of stimulation, preceded those stimulation trials that evolved into PPRs, and differed significantly from that encountered in trials not followed by PPR or in control subjects": "a pathological deviation of normally occurring synchronization of γ oscillations underlying perceptional processes mediates the epileptic transition in PSE".

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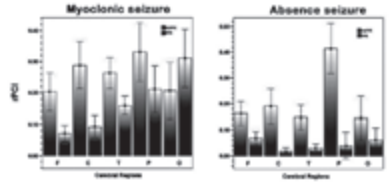
rPCI = relative phase clustering index



Red: stimulation with photoparoxysmal response (PPR)

Blue: stimulation without PPR

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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 (MEG)

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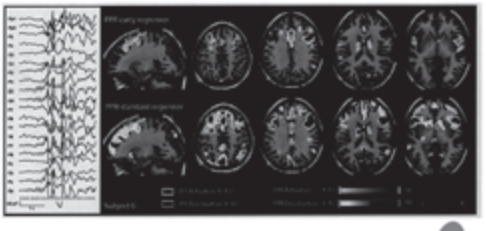
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2 years. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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Authors' conclusion

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

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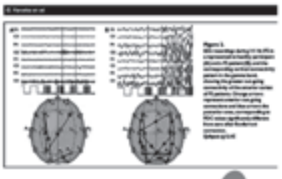
FULL-LENGTH ORIGINAL RESEARCH

Enhanced frontocentral EEG connectivity in photosensitive generalized epilepsies: A partial directed coherence study

Partial directed coherence: (a method of EEG analysis) Focus on β and γ band. 10 photosensitive pts, sz free, 7 with AED, and 10 healthy controls. Enhanced connectivity in resting state (β) and under ILS (γ).



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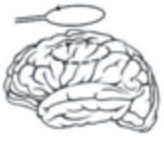
Transcranial magnetic stimulation (TMS): visual cortex and motor cortex

A noninvasive method to cause depolarization or hyperpolarization in the neurons of the brain. TMS uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field; this can cause activity in specific or general parts of the brain, allowing for study of the brain's functioning and interconnections.



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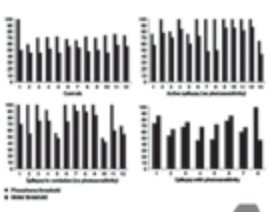
Visual cortex TMS

Comparison of resting motor threshold (cortical excitability) with phosphene threshold:

- rMT in epileptic pts increased (AED effect)
- Only in photosensitive patients phosphene threshold < motor threshold = visual cortex hyperexcitability in ph.sensitivity

Epilepsy & Behavior

Visual cortex hyperexcitability in idiopathic generalized epilepsies with photosensitivity: A TMS pilot study



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Animal models?

- Genetic photosensitivity exists in 2 animal strains:
  - Papio papio Senegalensis
  - Fayumi chicken
- They are similar to human photosensitivity but not identical

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Eye closure sensitivity

- SW within 2 (-3) sec after eye closure (= immediate, qualitative)
- mostly occipital dominant
- often overlapping, but not identical with photosensitivity
- found in about 3 - 4% of IGE
- related to absences with eyelid myocloni (seizure type) or eyelid myclonus with absence (syndrome): short reflex loop
- Visual factor? Dark and lit environment!

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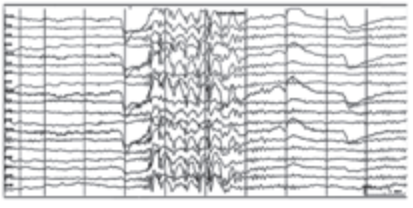
Eye closure sensitivity



video 6.mpg

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The Visual System in Eyelid Myoclonia with Absences

Anna Elisabetta Vaudano, MD, PhD,[1] Andrea Ruggieri, MD,[1] Manuela Tondelli, MD, PhD,[1] Pietro Avanzini, PhD,[1,2] Francesca Benuzzi, PhD,[1] Giuliana Gessaroli, REGT,[1] Gaetano Cantalupo, MD,[3] Massimo Mastrangelo, MD,[4] Aglaia Vignoli, MD,[5] Carlo Di Bonaventura, MD, PhD,[6] Maria Paola Canevini, MD, PhD,[5] Bernardo Dalla Bernardina, MD,[3] Paolo Frigio Nichelli, MD, PhD,[1] and Stefano Meletti, MD, PhD[1]

Ann. Neurol. 2014;76: 412-427

EEG-fMRI study of patients with Jeavons syndrome.
Conclusion: altered functional anatomic properties of visual system responsible for myoclonic response.
Problem: all patients were photosensitive, so the findings could relate to PPR rather than ECS

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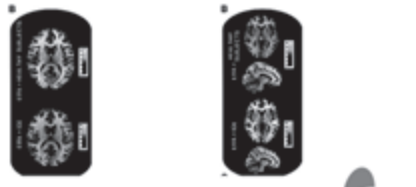
Epilepsy & Behavior

At eye closure

Following 3 sec



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Seizure

Blinking and eyelid myoclonia: Characteristics and correlations of eyelid movements

Priscila Oliveira da Conceição a,*, Mirian Salvadori Bittar Guaranha a, Carina Gonçalves Pedroso Uchida a, Kelly Carvalho a, Laura M.F.F. Guilhoto a, Gerardo M. De Araújo-Filho a, Henrique Carrete Júnior a, Peter Wolf b, Elza Márcia Targas Yacubian a

Seizure 2015; 24: 12-16

ECS only in response to slow eye closure (supplementary motor area) not automatic or nociceptive blinks (brainstem)
Conclusion: key role of SMA in reflex myocloni but role for visual cortex.

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Pattern sensitivity

Definition: precipitation of seizures (mostly absences) or spike-wave activity by vertical stripes of strong contrast.

Response immediate and qualitative

Environmental: heater grids, striped clothing, wall-papers, escalators etc etc
Self-induction of seizures: trance-like states with continuous SW patterns

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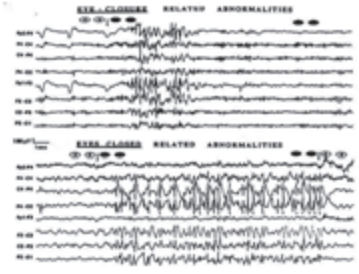
Fixation-off sensitivity: "eye-closure" vs "eyes closed"



Panayiotopoulos C in: Wolf P (Ed) Epileptic seizures and syndromes, 1994, 55-66

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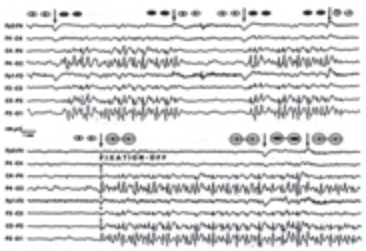
Fixation-off sensitivity in 11 yr old boy with benign occipital childhood epilepsy



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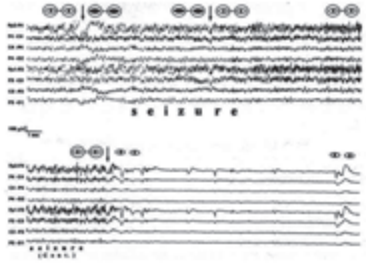
FOS: a rare condition in children, ictogenesis?



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Somatosensory and proprioceptive

Seizure precipitation by

- Local touch (trigger zones)
- Movement (specific, individual)
  - Both relating to anatomical focus
- Hot water: no focus relation
  - role of systemic hyperthermia?
  - infants: bottom
  - adults: head

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Animal models?

- Absences in rodents are typically triggered by stimulation of the vibrissae
- This has not yet been considered under the aspect of reflex epilepsy
- No good model of human touch-induced seizures which are focal
- More analogous to photosensitivity
- Should be investigated

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Auditory

- Noise: well-known reflex epileptic mechanism in rodents
  - Extremely rare in humans
- Musicogenic seizures (temporal lobe, emotional involvement)
- Defined musical tones (anecdotal)
- Talking in phone (genetic)

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Smells and inhibition

Gowers WR. *Epilepsy and other chronic convulsive diseases*. London 1881: "Sensations of smell preceded the fit in seven cases" (of 119 = 5,9%)

Arrest of attacks: strong olfactory impression (application of ammonia to the nostrils); inhalation of nitrite of amyl: most frequently successful with a deliberate olfactory aura. "It is scarcely conceivable that the effect … is produced through the olfactory nerve." (vasodilatation?)

Surprising: missed connection olfactory aura - olfactory stimulus

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Efron's case: *Brain 1956;79:267–81 & 1957;80:251–62*

THE EFFECT OF OLFACTORY STIMULI IN ARRESTING UNCINATE FITS

BY

ROBERT EFRON

Lieut. Medical Corps, USNR
Department of Neuropsychiatry
U.S. Naval Hospital
St. Albans, N.Y.[1]

THE CONDITIONED INHIBITION OF UNCINATE FITS

BY

ROBERT EFRON

Department of Neuropsychiatry,[1] *U.S. Naval Hospital, St. Albans, N.Y.*

Only after his own observation Efron discovers that Gowers had been there before him

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Efron's case

- 41 yr old female singer with 2nd GTCS since age 15, not responding to PB, DPH
- Long-lasting complex aura starting with a kind of depersonalisation and derealisation, loses the sense of time, smells are altered. Knows that a seizure will invariably happen. Restless behaviour. After several minutes "halfway point": loses interest, more remote, feeling that she will experience a smell. Then intense sweetish olfactory hallucination like a cheap parfume, hears a voice calling her name and feels compelled to look after the voice: versive movement evolving into GTCS.

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Efron's case

- Patient's idea to arrest seizure during aura stage by applying an olfactory counter-stimulus.
- Successful but dependent on right timing of stimulus and to some extent on quality of stimulus.
- Patient eventually became seizure free without drugs

Fascinating well-studied case but never replicated

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Anti-seizure effects of olfactory stimuli

Betts T. Use of aromatherapy in the treatment of intractable epilepsy. Seizure 2003;12:534-538

Jaseja H. Scientific basis behind traditional practice of application of "shoe-smell" in controlling epileptic seizures in the eastern countries. Clinical Neurology & Neurosurgery 2008;110:535-538

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Shoe-smell

"The practice consisted of bringing the sole of shoe near the nostrils of the patient during the epileptic attack by near-by attendants or passers-by in the event of the attack occurring in a public place".

The author believes that the practice is founded in olden times when shoes stank more and abortion of seizures by such a strong smell may occasionally have been observed.

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Olfactory seizure precipitation by paint thinner

Reflex Epilepsy Triggered by Smell

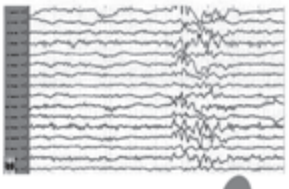
Faik Ilik, MD[1], and Ahmet Cemal Pazarli, MD[1]

SAGE

EEG 1 min after thinner inhalation: irregular generalized pattern

"Pat. started to have mini myoclonic seizures in her upper limbs"

The EEG sample is pre-ictal



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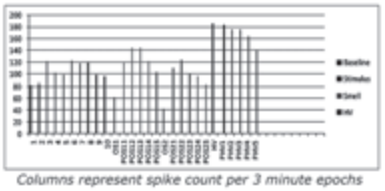
Patient with IGE, high spontaneous spike density. Increase with hyperventilation, over some minutes returning to baseline (typical reaction to HV)
During both periods of olfactory stimulation (OS) reduction of spikes, immediate return to baseline



Columns represent spike count per 3 minute epochs

Presumably non-specific effect of increased attention during OS

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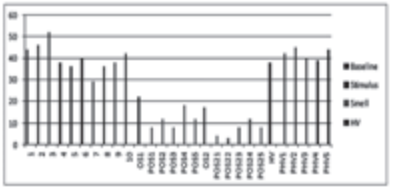
IGE patient with rather high spontaneous spike density and no hyperventilation reaction.
An inhibitory response develops during both OSs and increases after their termination .



Not explainable by any non-specific effect

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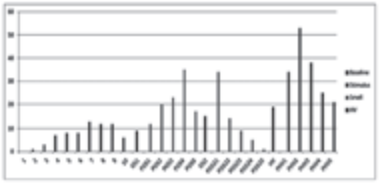
Patient with TLE, low spontaneous spike density
Delayed spike increase following OSs
Typical hyperventilation response



The effects of OS and HV look similar but need different explanations. HV produces alcalosis which does not immediately return to baseline
HV during OS was carefully avoided!

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Results

Epilepsy type	all
Post OS 1 inhibition	28 (25.9%)
unchanged	54 (50.0%)
excitation	26 (24.1%)
Post OS 2 inhibition	18 (16.8%)
unchanged	68 (63.6%)
excitation	21 (19.6%)

p < .05 **p < .01**

One TLE seizure in OS2

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Olfaction and epilepsy summary

- Olfactory auras occur in about 5 – 6% of patients with epilepsy
  - Related to temporal lobe epilepsy
- Reduced olfactory performance in TLE
- Seizure arrest by olfactory stimuli described in rare cases
  - Relation to TLE?
- Seizure provocation by olfactory stimuli likewise rare, without indication of relation to epilepsy type
  - Few case reports and not always convincing
- Systematic study: both inhibition and excitation frequent but syndrome-dependent. Delayed responses need explanation

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Conclusions

Manifold relations between epilepsy and sensory systems:

- Seizures often expressed via sensory channels
- AED treatment may affect sensory systems
- Sensory input into ictogenesis frequent
  - Both excitatory (reflex seizures) and inhibitory

Exogenous modification of ictogenesis as part of the natural history of epilepsies provides excellent opportunities to study pathophysiology of epilepsy. This research is only beginning.

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Marina Bentivoglio (Italy)

THE NEGLECTED BRAIN AND EPILEPSY IN NEGLECTED TROPICAL BRAIN DISEASES

Jaime Carrizosa (Colombia)

EPILEPSY AND DEVELOPMENTAL DISORDERS

EPILEPSIA Y TRASTORNOS PERVASIVOS DEL DESARROLLO

Jaime Carrizosa Moog

Neurólogo Infantil
Universidad de Antioquia
Medellín – Colombia

LASSE 2016

DEFINICIONES DSM V: TRASTORNO DEL ESPECTRO AUTISTA - TEA

A. Déficits persistentes en comunicación social e interacción social
B. Patrones repetitivos y restringidos de conductas, actividades e intereses
C. Los síntomas deben estar presentes en el período de desarrollo temprano
D. Los síntomas causan alteraciones clínicamente significativas
E. Estas alteraciones no se explican mejor por la presencia de una discapacidad intelectual (trastorno del desarrollo intelectual) o un retraso global del desarrollo.

A. Déficits persistentes en comunicación social e interacción social

a. Déficits en reciprocidad socio-emocional

b. Déficits en conductas comunicativas no verbales usadas en la interacción social

c. Déficits para desarrollar, mantener y comprender relaciones

B. Patrones repetitivos y restringidos de conductas, actividades e intereses

a. Movimientos motores, uso de objetos o habla estereotipados o repetitivos
b. Insistencia en la igualdad, adherencia inflexible a rutinas o patrones de comportamiento verbal y no verbal ritualizado
c. Intereses altamente restringidos, obsesivos, que son anormales por su intensidad o su foco
d. Hiper- o hipo-reactividad sensorial o interés inusual en aspectos sensoriales del entorno

ESPECIFICAR SI:

- Se acompaña o no de discapacidad intelectual.
- Se acompaña o no de un trastorno del lenguaje.
- Se asocia con una condición médica o genética o con un factor ambiental conocido
- Se asocia con otro trastorno del neurodesarrollo, mental o del comportamiento
- Con catatonia

SEVERIDAD

SEVERO: APOYO PERMANENTE

MODERADO: APOYO INTERMITENTE

LEVE: APOYO OCASIONAL

DATOS EPIDEMIOLÓGICOS

Prevalencia
2-6 / 1000 habitantes

Rasgo Autista
14 / 1000 hombres
3 / 1000 mujeres

Mol Psychiatry 2002;7:54–6
JAMA 2003;289:49–55
Arch Gen Psychiatry 2003;60:524–30

Epilepsia, 53(6):1095–1103, 2012
doi: 10.1111/j.1528-1167.2012.03500.x

FULL-LENGTH ORIGINAL RESEARCH

Epilepsy and psychiatric comorbidity: A nationally representative population-based study

*Dheeraj Rai, †Michael P. Kerr, ‡Sally McManus, §Vesna Jordanova, *Glyn Lewis, and ¶Traolach S. Brugha

Table 2. Prevalence of psychiatric conditions in people with epilepsy, and results of logistic regression analysis comparing psychopathology in people with epilepsy with the general population of England without epilepsy

Mental disorder	Prevalence in people with epilepsy % (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Any depressive or anxiety disorder	30.6 (21.5–41.4)	2.3 (1.4–3.8)**	1.9 (1.2–3.2)*
Depression and an anxiety disorder	4.3 (2.3–7.8)	4.1 (2.1–8.0)**	3.1 (1.5–6.3)**
Depression	9.6 (5.3–16.9)	3.7 (1.9–7.1)***	2.7 (1.4–5.4)**
Generalized anxiety disorder	12.5 (7.6–20.1)	3.3 (1.8–5.9)***	2.6 (1.5–4.7)**
Social phobia	14.8 (9.7–22.0)	3.1 (2.0–5.1)***	2.5 (1.5–4.1)***
Specific phobias	1.8 (0.6–5.7)	2.0 (0.6–6.7)	1.2 (0.3–4.5)
Panic disorder	No observation	–	–
Agoraphobia	4.9 (2.7–11.4)	4.7 (1.8–12.3)*	3.2 (1.2–8.7)*
Obsessive compulsive disorder	3.1 (1.5–6.3)	2.9 (1.3–6.4)*	1.8 (0.8–4.4)
Nonspecific psychiatric morbidity	12.2 (6.4–21.9)	1.3 (0.8–2.1)	1.3 (0.6–2.6)
Suicide and self-harm			
Suicidal thoughts/lifetime	26.5 (18.8–37.1)	2.3 (1.4–3.8)**	2.0 (1.2–3.2)**
Suicidal thoughts in last year	12.3 (6.9–20.8)	3.2 (1.7–6.2)***	2.5 (1.3–4.8)**
Suicide attempts lifetime	12.5 (6.7–21.2)	3.0 (1.5–5.9)**	2.3 (1.1–4.6)*
Suicide attempts last year	4.1 (1.5–10.5)	7.3 (2.4–21.9)***	4.6 (1.6–13.6)*
Deliberate self-harm	12.7 (7.3–21.1)	2.9 (1.3–6.5)*	2.3 (1.2–4.5)*
Near-ordevelopmental other conditions			
Autism spectrum disorder	8.1 (2.3–25.9)	9.3 (2.9–42.4)**	7.4 (1.8–30.6)*
Psychotic disorder	1.7 (0.7–4.2)	3.7 (0.4–28.8)	1.7 (0.2–11.8)
Eating disorder (SCREEN)	5.0 (1.9–12.6)	3.4 (1.2–9.7)*	2.9 (1.1–7.7)*
Posttraumatic stress disorder (SCREEN)	4.9 (2.0–11.4)	1.8 (0.7–4.4)	1.2 (0.5–3.9)
Attention deficit disorder (SCREEN)	13.4 (9.3–24.7)	2.0 (1.1–3.7)*	1.6 (0.9–3.0)

Adjusted OR, model adjusted for age, gender, marital status, highest educational qualification, employed or economically inactive, and number of comorbid physical illnesses. Verbal IQ score further included in the final model for association between autism spectrum disorder and attention deficit disorder screen (it had no confounding effect on other conditions under study).
OR, odds ratio; 95% CI, 95% confidence interval.
*p < 0.05; **p < 0.01; ***p < 0.001.

Epilepsia, 44(11):1494–1497, 2003
Blackwell Publishing, Inc.

The Prevalence of Autistic Spectrum Disorder in Children Surveyed in a Tertiary Care Epilepsy Clinic

*Dave F. Clarke, †Wendy Roberts, ‡Mina Daraksan, †Annie Dupuis, ‡Jane McCabe, ‡Halsey Wood, †O. Carter Snead III, and ‡Shelly K. Weiss

*Department of Pediatrics, Division of Neurology, Le Bonheur, University of Tennessee Health Science Center Comprehensive Epilepsy Program, Memphis, Tennessee, U.S.A; †Department of Neurology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

TABLE 1. *Demographic and epilepsy characteristics in children in the ASD versus non-ASD group*

	All children (97)	ASD group = 31 (32%)	Non-ASD group = 66 (68%)
Mean age (yr) (s.d.)	12.7 (4.09)	10.53 (4.17)	13.07 (4.17)
Body mass index (s.d.) (n = 69)	20.08 (5.4)	19.84 (5.8) (n = 17)	20.16 (5.3) (n = 52)
Sex—male	51.6 (53%)	19 (61%)	32 (49%)
Mean age 1st Sz/mo (s.d.)	44.57 (44.63)	21.30 (29.17)*	55.47 (46.59)
Mean number of AEDs (s.d.)	1.56 (0.92)	1.77 (0.80)*	1.45 (0.91)
0 meds or monotherapy	55 (57%)	13 (42%)	42 (64%)
Ave. Sz. frequency (months)*	7.17 (n = 88)	10.5 (n = 25)	5.38 (n = 63)
Seizure type gen—c/n (%)	41/90 (46)	12/29 (41)	29/61 (47)

¿RELACIÓN DE EPILEPSIA AUTISMO?

30% con epilepsia
80% con EEG anormal

Dev Med Child Neurol 1970:12; 422-429

64% con EEG anormal

Biol Psychiatry 1975:10;385-397

¿RELACIÓN DE EPILEPSIA AUTISMO?

Prevalencia en autismo

5-38%

Brain Develop 1995: 17; 169-174
Lancet Neurol 2002: 1; 352-358
Epilepsia 2005: 46:918-923

¿RELACIÓN DE EPILEPSIA AUTISMO?

PICOS DE INCIDENCIA DE EPILEPSIA:
< 5 años y adolescencia

J Am Acad Child Adolesc Psychiatry 1990: 29; 127-129

¿RELACIÓN DE EPILEPSIA AUTISMO?

PROBABILIDAD ACUMULADA DE EPILEPSIA EN AUTISMO

CONDICIÓN	1 AÑO	5 AÑOS	10 AÑOS
SIN RETARDO O PCI	ND	2%	8%
RM SEVERO	7%	16%	27%
RM SEVERO Y PCI	20%	35%	67%

REMISIÓN SOLO EN UN 16%

Lancet Neurol 2002: 1; 352-358
Epilepsia 2005: 46:918-923

Epilepsia, 48(5):1724–1730, 2007
Blackwell Publishing, Inc.

Autism Spectrum Disorders in Children with Seizures in the First Year of Life—A Population-based Study

*Evald Saemundsen, †Petur Ludvigsson, ‡Ingibjorg Hilmarsdottir, and §Vilhjalmur Rafnsson

*State Diagnostic and Counseling Center, Division of Autism and Communication Disorders, Kopavogur, Iceland; †Landspitali University Hospital, Department of Pediatrics, Reykjavik, Iceland; ‡Health Care Center Efstaleiti, Reykjavik, Iceland; and §Department of Preventive Medicine, University of Iceland, Reykjavik, Iceland

spasms. In a more recent study of 246 children with autism spectrum disorder (ASD), the majority of those who also had epilepsy (13 of 16) had their seizure onset in the first year of life, and four had infantile spasms (Wong, 1993).

¿Previene el tratamiento precoz de los espasmos infantiles la aparición del TEA?

- TEA se presentó solo en EI sintomáticos
- Descargas frontotemporales posteriores a hypsarritmia
- Raza no blanca

- El tratamiento precoz NO previno la aparición de TEA

EPILEPSIA, 56(6): 856-863, 2015

POSIBLES FACTORES DE RIESGO

- ETIOLOGÍA
- COMORBILIDAD
- GÉNERO
- EDAD DE PRIMERA CRISIS

HIPÓTESIS NEUROBIOLÓGICA

HIPÓTESIS NEUROBIOLÓGICA

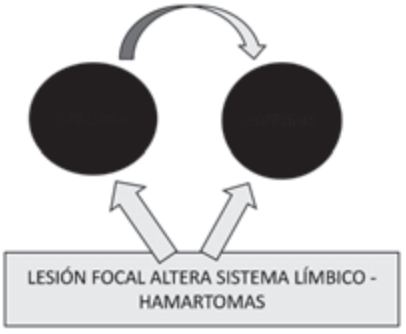
HIPÓTESIS NEUROBIOLÓGICA

HIPÓTESIS NEUROBIOLÓGICA

HIPÓTESIS NEUROBIOLÓGICA 2

HIPÓTESIS NEUROBIOLÓGICA 3

HIPÓTESIS NEUROBIOLÓGICA 4



AMERICAN ACADEMY OF PEDIATRICS

Committee on Children With Disabilities

The Pediatrician's Role in the Diagnosis and Management of Autistic Spectrum Disorder in Children

RECOMENDACIONES

1. Escucha cuidadosa de preocupaciones de los padres
2. Evaluación juiciosa del desarrollo psicomotor
3. Considerar uso de pruebas de tamización para autismo
4. En retardo del desarrollo de lenguaje, evaluar con pruebas audiológicas y examen de lenguaje

RECOMENDACIONES

5. Mantener los esquemas de inmunización

6. Estudios:

   Nivel de plomo en pica en niño mayor. Estudios genético como análisis del DNA, cariotipo de alta resolución, FISH etc. en caso de dismorfias, antecedente de X-frágil o retardo mental de causa no determinada.

RECOMENDACIONES

6. Estudios

   EEG en sospecha de crisis epilépticas o regresión autista. Los demás estudios como neuroimágenes o tamizaje metabólico se realizan acorde a la historia clínica y al examen físico.

RECOMENDACIONES

7. Información clara y actualizada sobre el diagnóstico a los padres
8. Consejería genética

9. Programas de intervención precoz!!!

10. Conocer las terapias alternativas y saber orientar a los padres

RECOMENDACIONES

11. Cuidado integral
12. Posibilidad de estudios de investigación

TRATAMIENTO

PSICOLÓGICO ESPECÍFICO E INTEGRAL

FARMACOLÓGICO

INTEGRACIÓN

SIGNOS PRECOCES A LOS 6 MESES

- No trata de agarrar cosas que están a su alcance
- No demuestra afecto por quienes le cuidan
- No reacciona ante los sonidos de alrededor
- Tiene dificultad para llevarse cosas a la boca
- No emite sonidos de vocales (“a”, “e”, “o”)
- No rueda en ninguna dirección para darse vuelta
- No se ríe ni hace sonidos de placer
- Se ve rígido y con los músculos tensos
- Se ve sin fuerza como un muñeco de trapo

SIGNOS PRECOCES A LOS 12 MESES

- No gatea
- No puede permanecer de pie con ayuda
- No busca las cosas que la ve esconder
- No dice palabras sencillas como “mamá” o “papá”
- No aprende a usar gestos como saludar con la mano o mover la cabeza
- No señala cosas
- Pierde habilidades que había adquirido

SIGNOS PRECOCES A LOS 18 MESES

- No señala cosas para mostrárselas a otras personas
- No puede caminar
- No sabe para qué sirven las cosas familiares
- No copia lo que hacen las demás persona
- No aprende nuevas palabras
- No sabe por lo menos 6 palabras
- No se da cuenta ni parece importarle si la persona que le cuida se va a o regresa
- Pierde habilidades que había adquirido

SIGNOS PRECOCES A LOS 24 MESES

- No usa frases de dos palabras (por ejemplo, "tomo leche")
- No sabe qué hacer con cosas comunes como por ejemplo un cepillo, el teléfono, el tenedor, o la cuchara
- No imita acciones o palabras
- No sigue instrucciones simples
- Pierde el equilibrio con frecuencia
- Pierde habilidades que había adquirido

SIGNOS PRECOCES A LOS 36 MESES

- Se cae mucho o tiene problemas para subir y bajar escaleras
- Se babea o no se le entiende cuando habla
- No puede operar juguetes sencillos (tableros de piezas para encajar, rompecabezas sencillos, girar una manija)
- No usa oraciones para hablar
- No entiende instrucciones sencillas
- No imita ni usa la imaginación en sus juegos
- No quiere jugar con otros niños ni con juguetes
- No mira a las personas a los ojo

MUCHOS INTERROGANTES SIN RESOLVER…

Epilepsia, 52(2):341–357, 2011
doi: 10.1111/j.1528-1167.2010.02899.x

FULL-LENGTH ORIGINAL RESEARCH

The EL mouse: A natural model of autism and epilepsy

Joshua J. Meidenbauer, John G. Mantis, and Thomas N. Seyfried

Biology Department, Boston College, Chestnut Hill, Massachusetts, U.S.A.

MODELO ANIMAL

Purpose: Autism is a multifactorial disorder that involves impairments in social interactions and communication, as well as restricted and repetitive behaviors. About 30% of individuals with autism develop epilepsy by adulthood. The EL mouse has long been studied as a natural model of multifactorial idiopathic generalized epilepsy with complex partial seizures. Because epilepsy is a comorbid trait of autism, we evaluated the EL mouse for behaviors associated with autism.

MODELO ANIMAL

Methods: We compared the behavior of EL mice to age-matched control DDY mice, a genetically related nonepileptic strain. The mice were compared in the open field and in the light–dark compartment tests to measure activity, exploratory behavior, and restricted and repetitive behaviors. The social transmission of food preference test was employed to evaluate social communication. Home-cage behavior was also evaluated in EL and DDY mice as a measure of repetitive activity.

MODELO ANIMAL

Key Findings: We found that EL mice displayed several behavioral abnormalities characteristic of autism. Impairments in social interaction and restricted patterns of interest were evident in EL mice. Activity, exploratory behavior, and restricted behavior were significantly greater in EL mice than in DDY mice. EL mice exhibited impairment in the social transmission of food preference assay. In addition, a stereotypic myoclonic jumping behavior was observed in EL mice, but was not seen in DDY mice. It is of interest to note that seizure activity within 24 h of testing exacerbated the autistic behavioral abnormalities found in EL mice.

MODELO ANIMAL

Significance: These findings suggest that the EL mouse expresses behavioral abnormalities similar to those seen in persons with autism. We propose that the EL mouse can be utilized as a natural model of autism and epilepsy.

MUCHO POR HACER...

GIUSEPPE BERTINI (ITALY)

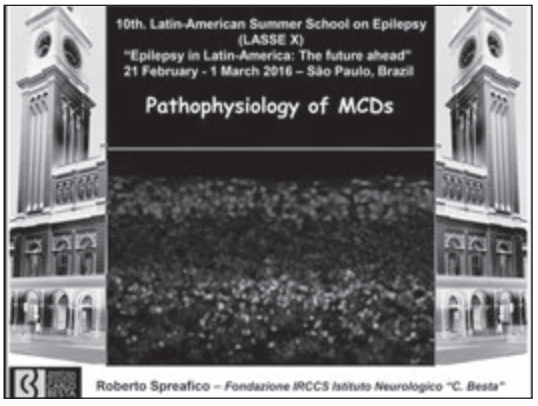
A MOUSE MODEL OF SLEEP RELATED SPIKE-WAVE DISCHARGES

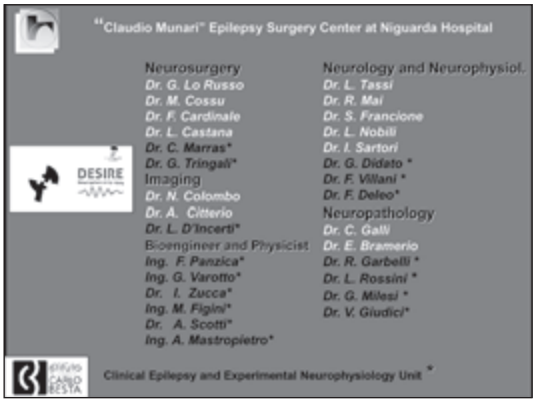
Marina Bentivoglio (Italy)

HOW TO WRITE A SCIENTIFIC PAPER

Roberto Spreafico (Italy)

PATHOPHYSIOLOGY OF MCDS





Genetic of MCD

Review — Guerrini et al. - 2008 - Trends in Neurosciences Vol.31 No.3

Table 1. Genetic malformations of cortical development

Malformation	Gene	Locus	Refs
Malformations from abnormal proliferation			
Focal cortical dysplasia			
Tuberous sclerosis	TSC1	9q34.13	[76]
Tuberous sclerosis	TSC2	16p13.3	[76]
Malformations from abnormal migration			
Lissencephaly (XL, AD)			
X-linked heterotopia with abnormal genitalia	ARX	Xp22.1	[18]
Isolated lissencephaly sequence (ILS) or subcortical band heterotopia (SBH)	DCX	Xq22.3–q23	[19]
ILS or SBH	TUBA1A	12q13.12	[20]
ILS or SBH	LIS1	17p13.3	[21]
Miller–Dieker syndrome	LIS1 + YWHAE	17p13.3	[76]
Lissencephaly (AR)			
Lissencephaly with cerebellar hypoplasia (LCH) group b	RELN	7q22.1	[76]
LCH group b	VLDLR	9p24.2	[77]
Heterotopia (XL, AD)			
Periventricular nodular heterotopia (PVNH)	FLNA	Xq28	[22]
PVNH	–	5p15.1	[23]
PVNH	–	9p19.3/20	[24]
PVNH	–	7q11.23	[25]
Heterotopia (AR)			
Microcephaly and PVNH	ARFGEF2	20q13	[26]
Cobblestone cortical malformations (AR)			
Fukuyama congenital muscular dystrophy or Walker-Warburg syndrome (WWS)	FCMD	9q31.2	[27]
Muscle-eye-brain disease (MEB) or WWS	POMGnT1	1p34.1	[28]
MEB	LARGE	22q12.3	[29]
MEB	POMGnT1	1p34.1	[30]
MEB or WWS	POMT1	9q34.13	[31]
MEB or WWS	POMT2	14q24.3	[32]
Bilateral frontoparietal cobblestone malformation (pronounced polymicrogyria)	GPR56	16q13	[33]
CEDNIK syndrome	SNAP29	22q11.2	[34]
Malformations from abnormal cortical organization			
Polymicrogyria (XL, AD)			
Rolandic seizures, oromotor dyspraxia	ARX(?)	Xp22	[35]
Agenesis of the corpus callosum (ACC), microcephaly and polymicrogyria (PMG)	TBR2	3p21	[36]
Aicardi plus	PIGB	17q12	[37]
PMG	–	1p36.3-plter	[38]
Microcephaly, PMG	–	1p34-qter	[39]
ACC, PTAH and PMG	–	2p16-qter	[40]
PMG	–	2?q2	[41]
Ohtahara syndrome	–	2?q?1.2	[42]
Polymicrogyria (AR)			
Dubowitz–Shortman syndrome	ASAH1/2?	10q25.3	[43]
Micro syndrome	RAB18/GAPI	2q21.3	[44]
Schizencephaly	None known but EMX2?		[45]

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

European Epilepsy Brain Bank

DESIRE

brain lesions (major histopathology groups) resected in epilepsy patients

All Lesions (major groups)	All Cases		Gender Female	Male	Side Left	Right	Other	Age at Onset	OP	DoE
HS	2903	37,0%	53,4%	46,6%	50,8%	49,1%	0,1%	11,3	33,9	22,6
Tumor	1757	22,4%	46,7%	53,3%	50,9%	48,9%	0,2%	15,4	26,0	10,7
MCD	1504	19,1%	47,7%	52,3%	46,3%	52,5%	1,1%	5,8	17,2	11,3
No Lesion	543	6,9%	42,9%	57,1%	49,0%	49,7%	1,3%	13,3	28,9	15,6
Vascular	453	5,8%	45,7%	54,3%	45,5%	53,9%	0,7%	23,1	34,7	11,6
Scar	366	4,7%	36,9%	63,1%	46,2%	52,7%	1,1%	10,9	25,6	14,7
Dual Pathology	211	2,7%	42,2%	57,8%	45,5%	54,5%	"	9,6	27,0	17,4
Encephalitis	107	1,4%	42,1%	57,9%	44,9%	55,1%	"	10,6	17,9	7,2
Double Pathology	12	0,2%	33,3%	66,7%	58,3%	41,7%	"	6,8	11,9	5,3
TOTAL	7856		48,4%	51,6%	49,1%	50,4%	0,5%	11,9	27,8	15,9

Courtesy from Prof. I. Blumcke

European Epilepsy Brain Bank

DESIRE

brain lesions (major histopathology groups) in children

All Lesions (major groups) - Children	All Cases		Gender Female	Male	Side Left	Right	Other	Age at Onset	OP	DoE
MCD	895	38,9%	46,9%	53,1%	48,2%	50,2%	1,7%	2,0	7,0	4,9
Tumor	605	26,3%	47,1%	52,9%	53,6%	46,3%	0,2%	6,1	10,2	4,2
HS	347	15,1%	51,3%	48,7%	53,9%	46,1%	"	4,1	11,5	7,4
Scar	124	5,4%	37,1%	62,9%	41,9%	56,5%	1,6%	2,9	8,7	5,8
No Lesion	122	5,3%	36,1%	63,9%	45,9%	52,5%	1,6%	4,1	10,5	6,4
Dual Pathology	69	3,0%	46,4%	53,6%	52,2%	47,8%	"	3,3	9,1	5,9
Encephalitis	66	2,9%	47,0%	53,0%	43,9%	56,1%	"	4,3	8,5	4,2
Vascular	64	2,8%	50,0%	50,0%	45,3%	53,1%	1,6%	4,3	8,1	3,7
Double Pathology	9	0,4%	44,4%	55,6%	77,8%	22,2%	"	1,7	4,0	2,6
TOTAL	2301		46,6%	53,4%	50,0%	49,1%	0,9%	3,7	8,9	5,2

Courtesy from Prof. I. Blumcke

DESIRE

European Epilepsy Brain Bank

Clinico-pathological findings in epilepsy patients with MCD

Malformations of Cortical Development													
		Side		Age at			Location						
	All Cases	Left	Right	Onset	Surgery	DoE	FRON	TEMP	MULTI	PARI	OCCI	OTHER
FCD II	638	42,4%	45,6%	54,4%	5,0	17,8	12,7	51,9%	21,9%	15,2%	6,3%	4,2%	0,5%
FCD I	244	16,2%	47,5%	52,0%	6,8	15,9	9,0	23,4%	34,8%	29,1%	5,7%	7,0%	"
mMCD	229	15,2%	52,0%	47,6%	10,2	23,9	13,7	30,1%	52,4%	13,1%	1,7%	1,7%	0,9%
FCD NOS	164	10,9%	50,6%	48,2%	6,8	19,8	13,1	27,4%	42,7%	12,2%	9,8%	7,3%	"
Tuber (TSC)	100	6,6%	44,0%	54,0%	1,7	8,5	6,7	49,0%	24,0%	15,0%	7,0%	5,0%	"
Polymicrogyria	54	3,6%	31,5%	68,5%	3,2	9,7	6,5	22,2%	20,4%	51,9%	3,7%	1,9%	"
Hemimegalencephaly	47	3,1%	40,4%	59,6%	"	1,2	1,2	"	8,5%	91,5%	"	"	"
Nodular Heterotopia	15	1,0%	40,0%	53,3%	8,2	20,7	12,5	6,7%	26,7%	53,3%	13,3%	"	"
Hypothalamic hamartoma	13	0,9%	15,4%	7,7%	0,8	13,2	12,3	"	7,7%	"	"	"	92,3%
TOTAL	1504		46,3%	52,5%	5,8	17,2	11,3	37,5%	30,5%	20,7%	5,7%	4,4%	1,2%

Courtesy from Prof. I. Blumcke

- **Malformations of cortical development (MCD)**
  - *Classifications*
  - Neuropathology
  - Imaging
  - electroclinical
- **Future research**

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

A developmental and genetic classification for malformations of cortical development: update 2012

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Group I: malformations secondary to abnormal neuronal and glial proliferation or apoptosis

Group II: malformations due to abnormal neuronal migration

Group III: malformations secondary to abnormal postmigrational development

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Group I: malformations secondary to abnormal neuronal and glial proliferation or apoptosis

(A) SEVERE CONGENITAL MICROCEPHALY (MIC),
(B) MEGALENCEPHALY (MEG) including both congenital and early postnatal
(C) CORTICAL DYSGENESIS WITH ABNORMAL CELL PROLIFERATION BUT WITHOUT NEOPLASIA
- (2) Focal and multifocal cortical and subcortical dysgenesis
  - Clinically defined with putative postzygotic mosaicism
    - (a) HMEG isolated (Flores-Sarnat, 2002)
    - (b) HMEG with neurocutaneous syndromes (Flores-Sarnat, 2002)
    - (c) FCD Type II with large, dysmorphic neurons (FCDIIa) (Blumcke et al., 2011)
    - (d) FCD Type II with large, dysmorphic neurons and balloon cells (FCDIIb) including transmantle dysplasia and bottom of sulcus dysplasia (Blumcke et al., 2011)
  - Genetically defined with AD inheritance
    - (e) Tuberous sclerosis with cortical hamartomas and mutations of TSC1 at 9q34.13
    - (f) Tuberous sclerosis with cortical hamartomas and mutations of TSC2at 16p13.3
    - (g) Tuberous sclerosis with HMEG

(D) CORTICAL DYSPLASIAS WITH ABNORMAL CELL PROLIFERATION AND NEOPLASIA
- (1) Neoplastic dysgenesis with primitive cells
  - (a) DNET
- (2) Neoplastic dysgenesis with mature cells
  - (a) Gangliogliomas
  - (b) Gangliocytoma

Group II: malformations due to abnormal neuronal migration

(A) MALFORMATIONS WITH NEUROEPENDYMAL ABNORMALITIES:
PERIVENTRICULAR HETEROTOPIA (PNH)
(B) MALFORMATIONS DUE TO GENERALIZED ABNORMAL TRANSMANTLE MIGRATION (radial and non-radial)
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Group III: malformations secondary to abnormal postmigrational development

(A) MALFORMATIONS WITH PMG OR CORTICAL MALFORMATIONS RESEMBLING PMG
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(C) FOCAL CORTICAL DYSPLASIAS (WITHOUT DYSMORPHIC NEURONS) DUE TO LATE DEVELOPMENTAL DISTURBANCES
- (1) Minor malformations of Cortical Development (mMCD)
- (2) Type I FCD(Blumcke et al., 2011)
  - (a) Abnormal radial cortical lamination
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  - (c) Abnormal radial and tangential lamination
- (3) Type III FCD
  - (a) Associated with hippocampal sclerosis
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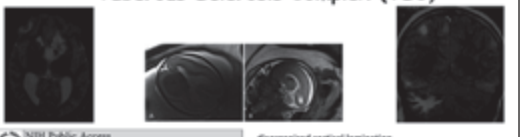
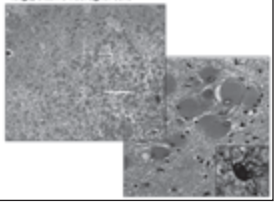
Tuberous Sclerosis Complex (TSC)



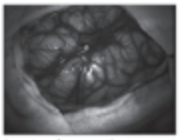
disorganized cortical lamination with abnormal cell types, including large, bizarre neuroglial cells

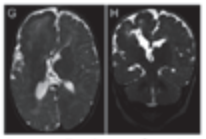


the absence of dysmorphic neurons in our study, as well as in previously described TSC fetal cases may suggest that **in the temporal evolution of these lesions the giant cells (balloon cells) appear before dysmorphic neurons**

Hemimegalencephaly (HME)

Is an hamartomatous malformation in which the individual cells are altered in their growth and/or differentiation, in addition to the disorganization of tissue architecture with disorientation and heterotopic placement of cells or groups of otherwise normal cells.





There is diversity of gross and microscopic lesions, as well as degrees of severity.
Even syndromic cases associated with :

- **epidermal nevus syndrome,**
- **hypomelanosis of Ito**
- **Proteus syndrome**

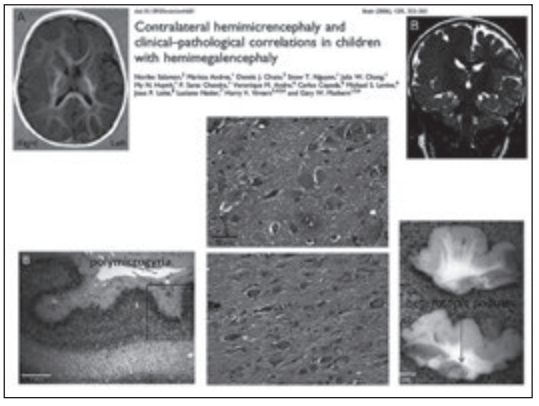
show no distinctive features to separate them on neuropathologic grounds from isolated hemimegalencephaly,

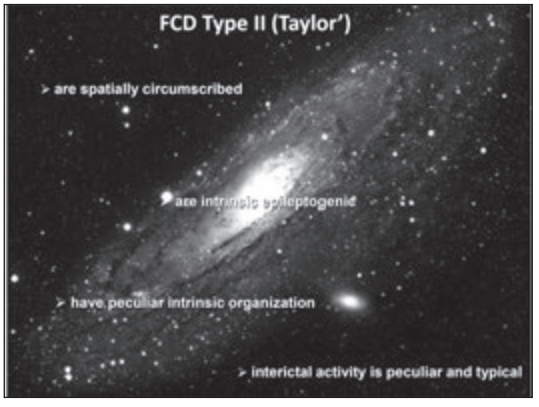
Macroscopic (Gross) Findings in Published Cases

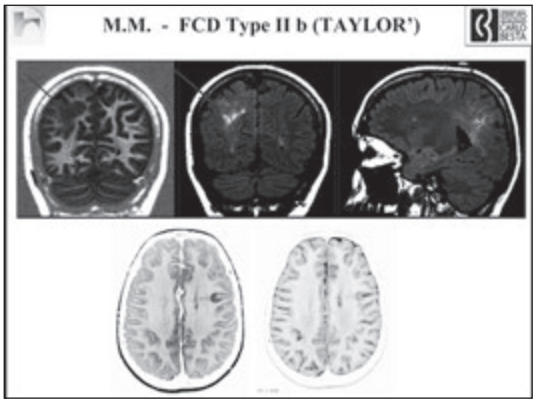
- **Pachygyria**
- Mixed with zones of **polymicrogyria**.
- **Thickened** cortical gray matter,
- The subcortical white matter is also larger than normal volume
- Gray–white matter **blurring**.
- Small **nodules of heterotopic** gray matter (occasionally) in the centrum semiovale

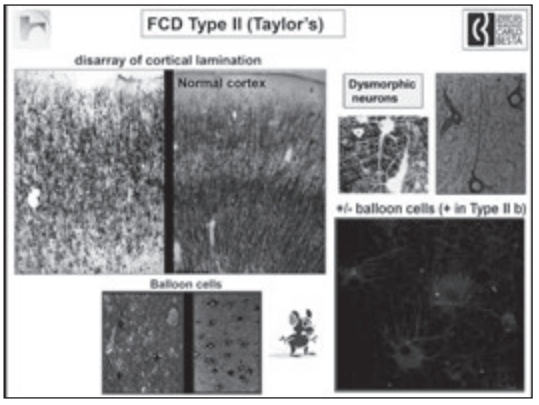
Microscopic Findings

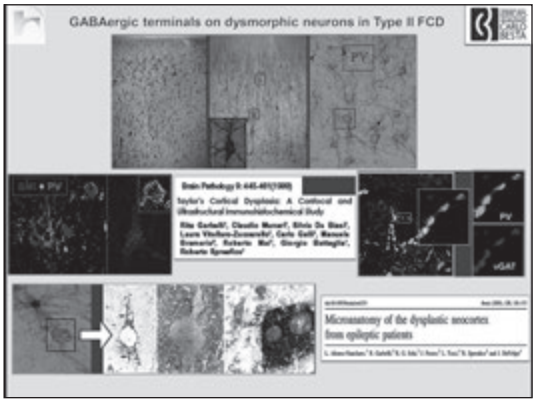
- Disorganization of cortical lamination
- The architecture of the cortex often is more columnar than layered
- Many neurons are greatly enlarged (**dysmorphic**), with extensive cytoplasmic Nissl bodies
- **Presence of "balloon neurons" similar to those seen in FCD Type IIb and TSC** .

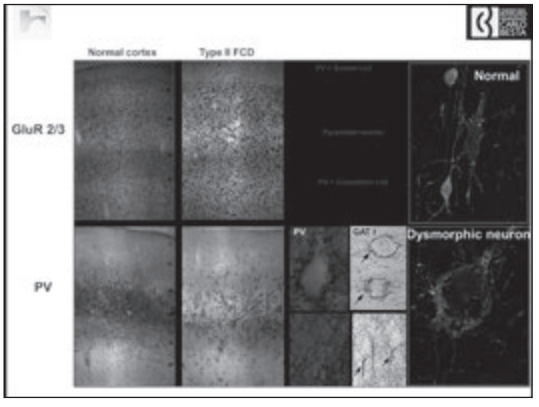


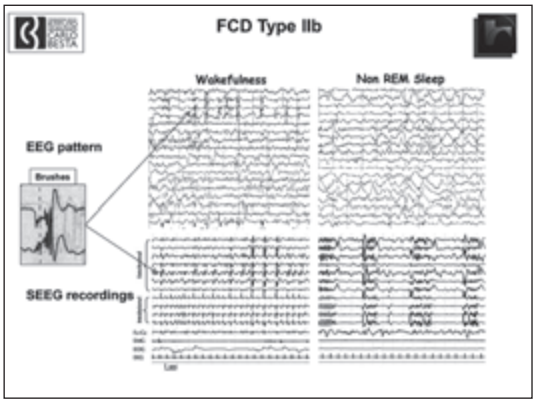




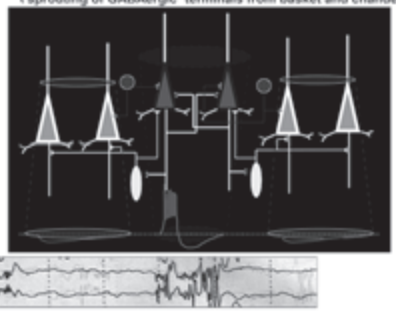

FCD Type II (Taylor's)
disarray of cortical lamination
Normal cortex
Dysmorphic neurons
+/- balloon cells (+ in Type II b)
Balloon cells


GABAergic terminals on dysmorphic neurons in Type II FCD
PV
Micronatomy of the dysplastic neocortex from epileptic patients


Normal cortex
Type II FCD
GluR 2/3
PV
Normal
Dysmorphic neuron


FCD Type IIb
Wakefulness
Non REM Sleep
EEG pattern
Brushes
SEEG recordings

Type II FCD
- abnormal intrinsic membrane properties of dysmorphic cells
- sprouting of GABAergic terminals from basket and chandelier cells



Main clinical characteristics of 100 consecutive patients with Type II FCD operated on from 1996 to 2007

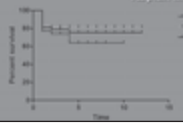
Histopathology (N°)	Ant.	FS	Normal MRI	Sleep Related Epilepsy*
Type IIb (66) with BC	20 (30%)	2 (3%)	5 (8%)	44 (67%)
Type IIa (34) without BC	9 (27%)	2 (6%)	11 (32%)	9 (34%)
Fisher exact test	p=0.69	p=0.48	p<0.01	p<0.01
Total (100)	29 (%)	4 (%)	16 (%)	53 (%)

* Sleep Related Epilepsy (SRE) = patients with > than 75% seizures during sleep

Surgical outcome of FCD Type II

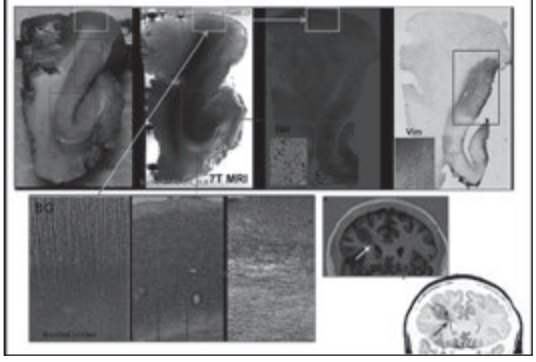
Engel's Class	I				II (%)	III (%)	IV (%)	Tot. (%)
	Ia + Ic (%)	Ib (%)	Id (%)	Tot. class I (%)				
Type IIb with BC	54 (81.8)	3 (4.5)	1 (1.5)	58 (87.8)	0	2 (3)	6 (9.1)	66
Type IIa without BC	23 (67.6)	2 (5.9)	0	25 (73.5)	3 (8.8)	0	6 (17.6)	34
Total	77	5	1	83	3	2	12	100

Kaplan Meier for Class I patients

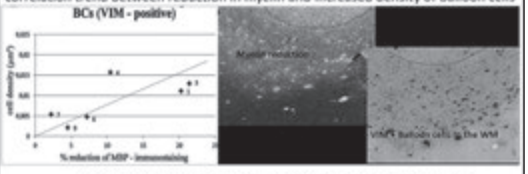


No significant difference between the two groups (Log-Rank test = 0.77)

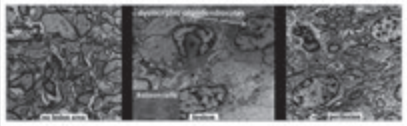
FCD Type II b



correlation trend between reduction in myelin and increased density of Balloon cells

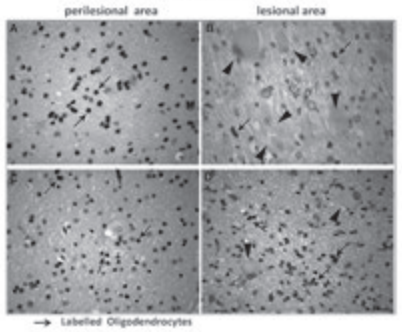


EM analysis revealed a process of dysmyelination in FCD type IIb



Suggesting that the white matter abnormalities present in type IIb FCD are due to defect of the myelination processes and maturation, impaired by the presence of BCs

Olig2 – ICC in FCD Type IIb



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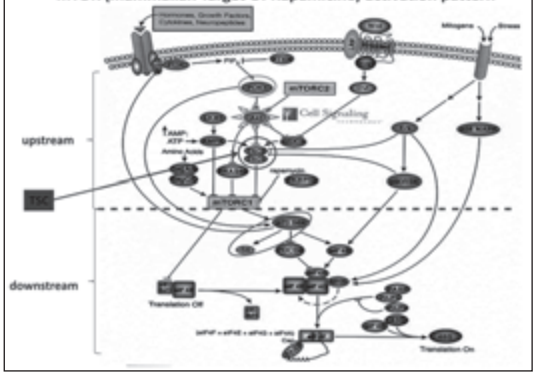
Rapamycin

mTOR was first named as the **mammalian Target Of Rapamycin,** discovered in a soil sample from **Easter Island** (known in Polynesian as **Rapa** Nui) in the 1970s.The bacterium *Streptomyces hygroscopicus*, isolated from that sample, produces an antifungal that researchers named **rapamycin** after the island.

mTOR is a protein-kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy and transcription.

The mTOR pathway is regulating different stimuli from a large variety of cellular signals and it is critically involved in cellular proliferation and surviving

mTOR (mammalian Target Of Rapamicine) activation pattern

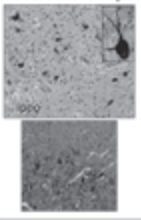


RESEARCH Open Access

Evidence for mTOR pathway activation in a spectrum of epilepsy-associated pathologies

pS6 regarded as a biomarker of these 'mTORopathies'

Pathology	DNs	BC	pS6 Expression
HME	+++	++	+
FCD IIa	+++	--	+
FCD IIb	+++	+++	+
TSC	++	++	+
RE	+/-	--	+
Electrode track	--	+	+
HS	+/-	--	+



Conclusions: pS6 is not a specific marker for the cytopathology of FCD IIb. Although mTOR activation has been more studied in the FCD IIb and TSC, our observations suggest this pathway is activated in a variety of epilepsy-associated pathologies, and in varied cell types

Original article

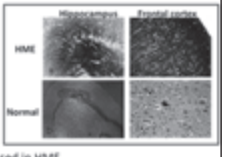
Infantile tuberous sclerosis complex; focal cortical dysplasia 2; gangliogioma

Hemimegalencephaly: foetal tauopathy with mTOR hyperactivation and neuronal lipidosis

Tau is a protein belonging to the large family of MAPs

Microtubules are cytoskeletal structures involved in

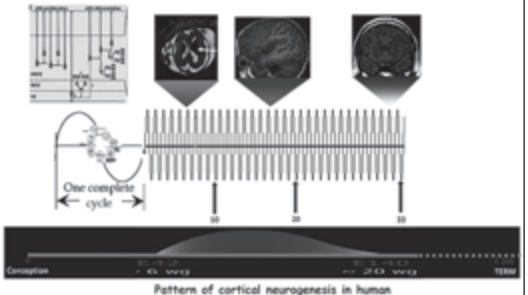
- Cellular polarity
- Growth
- Lineage
- Differentiation
- Migration
- axonal transport of molecules



Abnormal phosphorilated tau protein is strongly expressed in HME

Because HME tissue exhibited enhanced levels of phosphorylated tau protein and evidence of mTOR hyperactivation, we propose that the pathogenesis of HME may involve an early defect in microtubules, likely related to the AKT3 gene.

H.B. Sarnat Hypothesis on somatic mutation and cell cycle



Pattern of cortical neurogenesis in human

Limited to one hemisphere since the mutation only occurs in the neuroepithelium of one side

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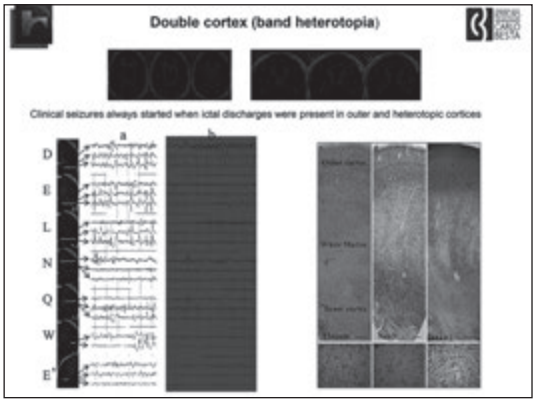
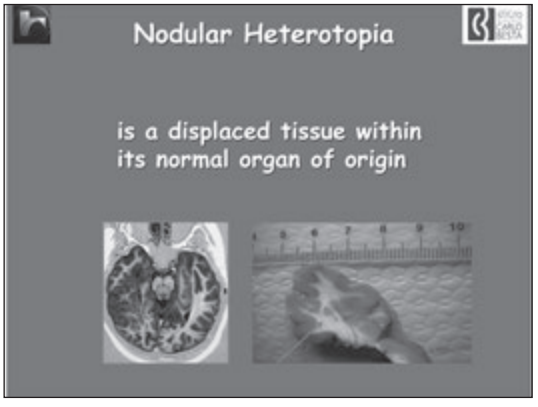
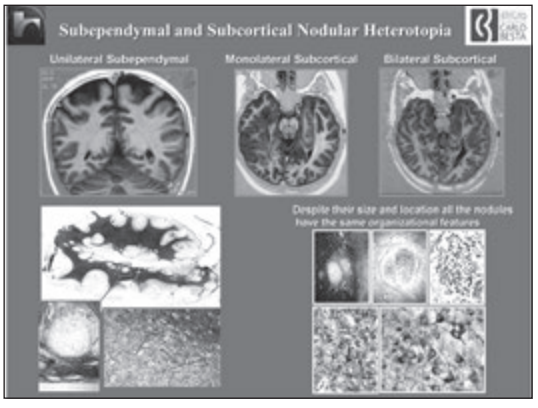
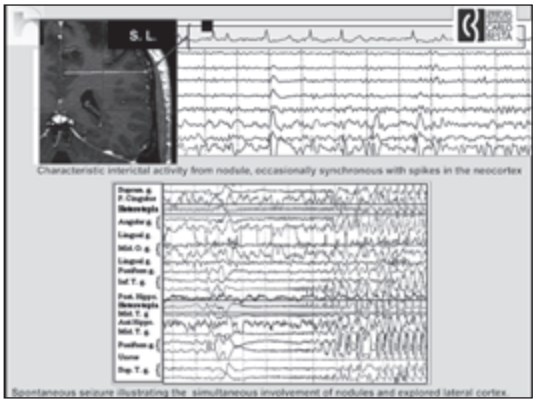
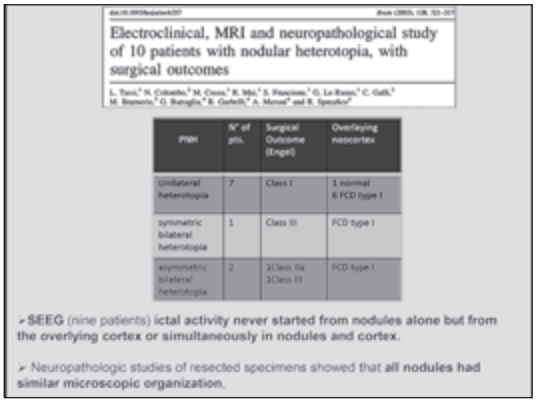
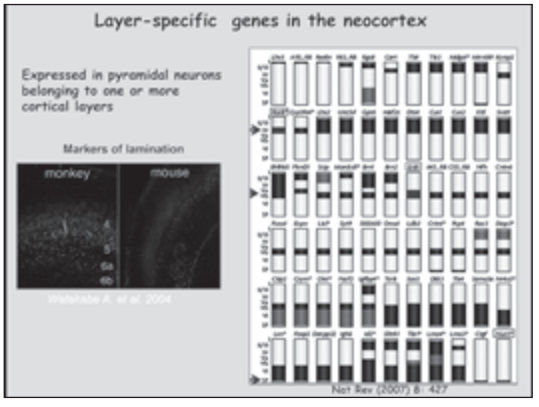


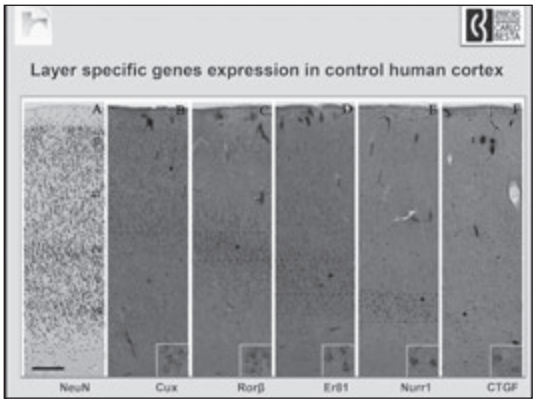


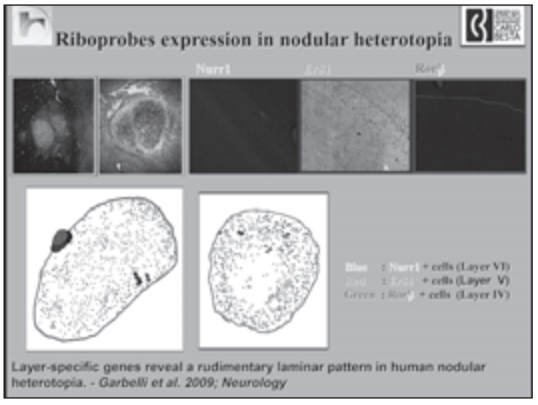


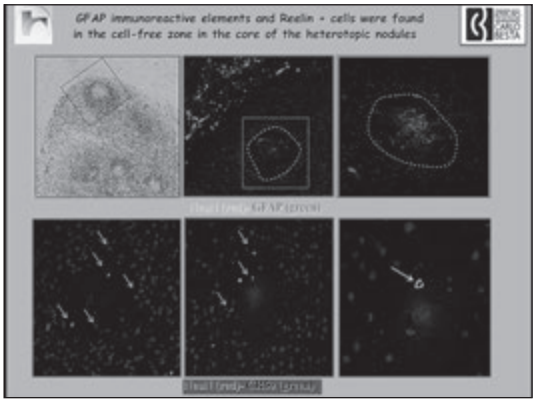

S. L.
Characteristic interictal activity from nodule, occasionally synchronous with spikes in the neocortex
Spontaneous seizure illustrating the simultaneous involvement of nodules and explored lateral cortex.

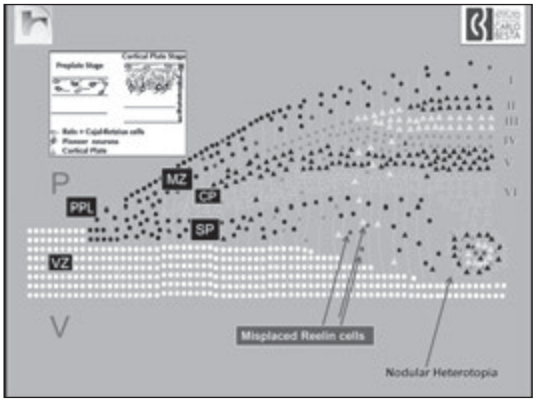

Electroclinical, MRI and neuropathological study of 10 patients with nodular heterotopia, with surgical outcomes
PNH | N° of pts. | Surgical Outcome (Engel) | Overlying neocortex
Unilateral heterotopia | 7 | Class I | 1 normal 6 FCD type I
symmetric bilateral heterotopia | 1 | Class III | FCD type I
asymmetric bilateral heterotopia | 2 | 1Class IIa 1Class III | FCD type I
SEEG (nine patients) ictal activity never started from nodules alone but from the overlying cortex or simultaneously in nodules and cortex.
Neuropathologic studies of resected specimens showed that all nodules had similar microscopic organization.

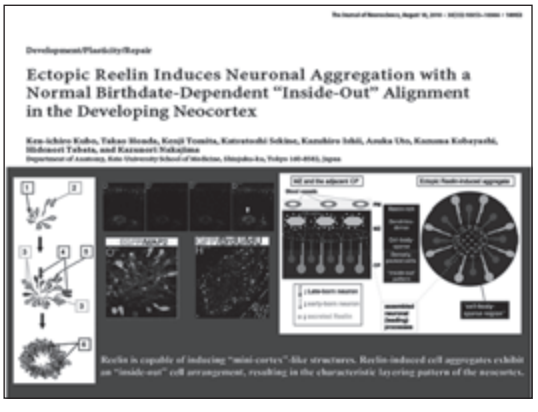

Layer-specific genes in the neocortex
Expressed in pyramidal neurons belonging to one or more cortical layers
Markers of lamination
monkey
mouse
Nat Rev (2007) 8: 427


Layer specific genes expression in control human cortex
NeuN
Cux
Rorβ
Er81
Nurr1
CTGF


Riboprobes expression in nodular heterotopia
Nurr1
Reelin
Ror-β
Blue : Nurr1 + cells (Layer VI)
Red : Reelin + cells (Layer V)
Green : Ror-β + cells (Layer IV)
Layer-specific genes reveal a rudimentary laminar pattern in human nodular heterotopia. - Garbelli et al. 2009; Neurology


GFAP immunoreactive elements and Reelin + cells were found in the cell-free zone in the core of the heterotopic nodules


Preplate Stage
Cortical Plate Stage
Cajal-Retzius cells
Pioneer neurons
Cortical Plate
P
MZ
CP
PPL
SP
VZ
V
I
II
III
IV
V
VI
Misplaced Reelin cells
Nodular Heterotopia


Development/Plasticity/Repair
Ectopic Reelin Induces Neuronal Aggregation with a Normal Birthdate-Dependent "Inside-Out" Alignment in the Developing Neocortex
Ken-ichiro Kubo, Takao Honda, Kenji Tomita, Katsutoshi Sekine, Kazuhiro Ishii, Asuka Uto, Kazuma Kobayashi, Hidenori Tabata, and Kazunori Nakajima
Department of Anatomy, Kobe University School of Medicine, Hyogo-ku, Tokyo 105-8461, Japan
Reelin is capable of inducing "mini-cortex"-like structures. Reelin-induced cell aggregates exhibit an "inside-out" cell arrangement, resulting in the characteristic layering pattern of the neocortex.

Group II: malformations due to abnormal neuronal migration

(A) MALFORMATIONS WITH NEUROEPENDYMAL ABNORMALITIES: PERIVENTRICULAR HETEROTOPIA (PNH)
(B) MALFORMATIONS DUE TO GENERALIZED ABNORMAL TRANSMANTLE MIGRATION (radial and non-radial)
  (1) *Anterior predominant or diffuse classic (four-layered)* LIS *and* SBH
(C) MALFORMATIONS PRESUMABLY DUE TO LOCALIZED ABNORMAL LATE RADIAL OR TANGENTIAL TRANSMANTLE MIGRATION
(D) MALFORMATIONS DUE TO ABNORMAL TERMINAL MIGRATION AND DEFECTS IN PIAL LIMITING MEMBRANE

Group III: malformations secondary to abnormal postmigrational development

(A) MALFORMATIONS WITH PMG OR CORTICAL MALFORMATIONS RESEMBLING PMG
(B) CORTICAL DYSGENESIS SECONDARY TO INBORN ERRORS OF METABOLISM
(C) FOCAL CORTICAL DYSPLASIAS (WITHOUT DYSMORPHIC NEURONS) DUE TO LATE DEVELOPMENTAL DISTURBANCES
  (1) *Minor malformations of Cortical Development (mMCD)*
  (2) Type I FCD(Blumcke et al., 2011)
    (a) *Abnormal radial cortical lamination*
    (b) *Abnormal tangential cortical lamination*
    (c) *Abnormal radial and tangential lamination*
  (3) Type III FCD
    (a) *Associated with hippocampal sclerosis*
    (b) *Associated with tumors*
    (c) *Associated with vascular malformations*
    (d) *Associated with other principal lesions during early life*

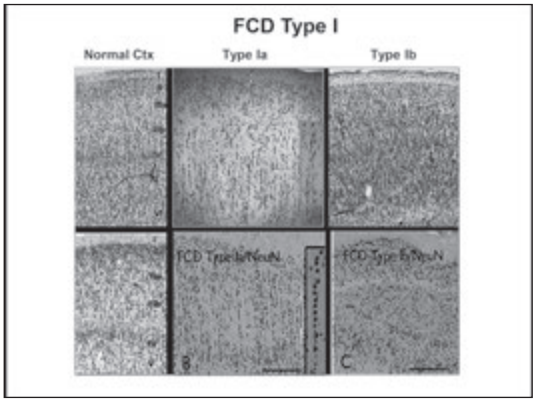
SPECIAL REPORT

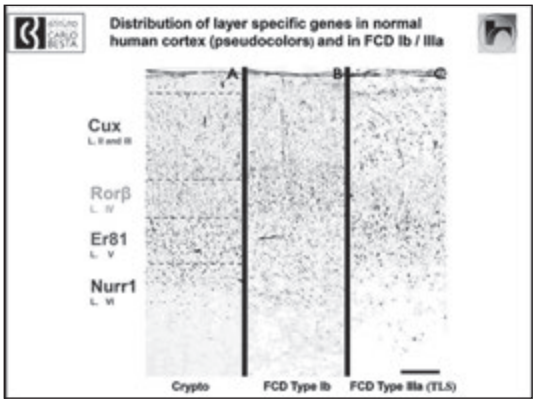
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

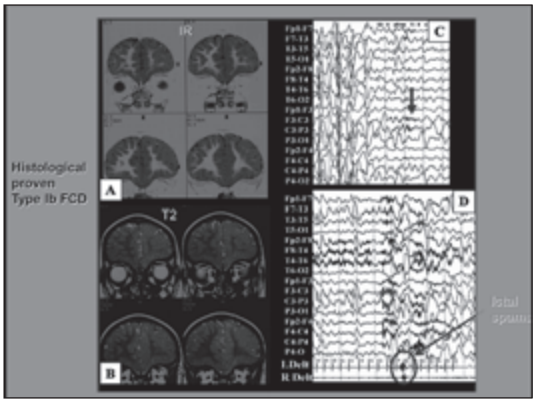
Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

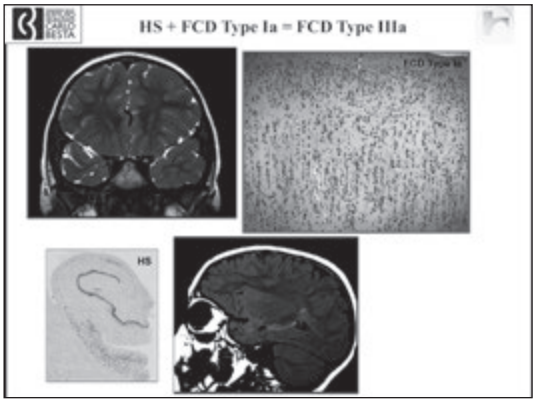
FCD Type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)	
FCD Type II (isolated)	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.









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

Laura Tassi[1], Rita Garbelli[2], Nadia Colombo[2], Manuela Bramerio[2], 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 IIIa = FCD I + HS	76 pts (35%)	(69%)
FCD IIIb = FCD I + tumors	49 pts (23%)	
FCD IIIc = FCD I + other MCD	16 pts (7%)	
FCD IIId = 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)

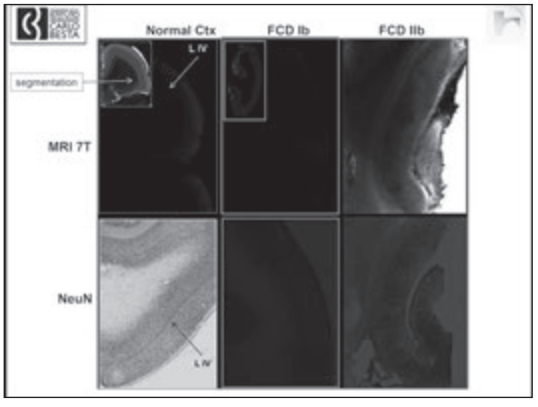
Surgical outcome in FCD I

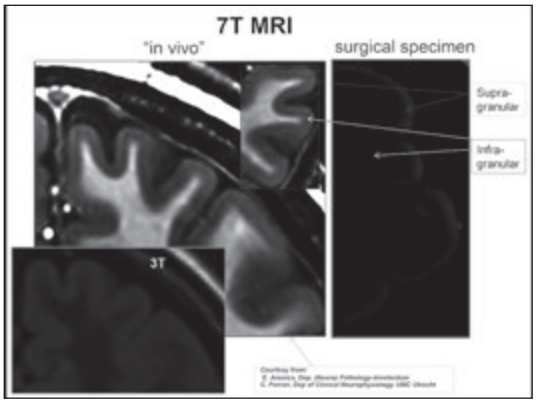
Histopathology	Class Ia + Ic (%)	Class I (%)	Class II (%)	Class III (%)	Class IV (%)
FCD isolated	23 (35)	30 (46)	7 (11)	10 (15)	19 (29)
FCD + HS	50 (66)	62 (82)	7 (9)	3 (4)	4 (5)
FCD +Tumors	38 (78)	40 (82)	3 (6)	5 (10)	1 (2)
FCD + MCD	10 (63)	14 (88)	0	1 (6)	1 (6)
FCD + Other	2 (25)	2 (25)	2 (25)	2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

➢ Malformations of cortical development (MCD)

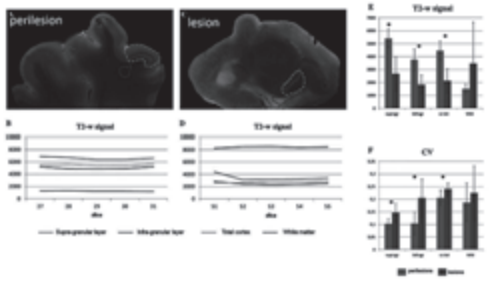
- ❖ Classifications
- ❖ Neuropathology
- ❖ Imaging
- ❖ electroclinical

➢ Future research





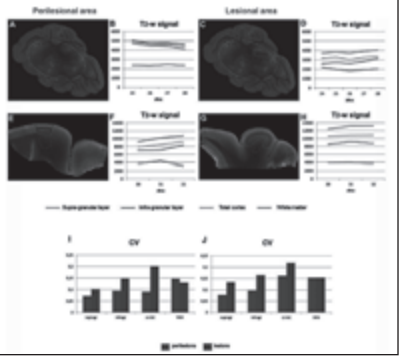
Representative T2-weighted MR images and derived quantitative measures in FCD type IIb specimens



The Coefficient of variation (CV), is an index of signal variability defined as the ratio between the standard deviation and mean value in the considered region.

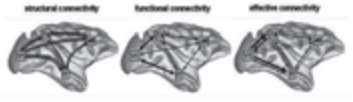
Representative T2-weighted MR images and derived quantitative measures in type IIa specimens

MRI negative case



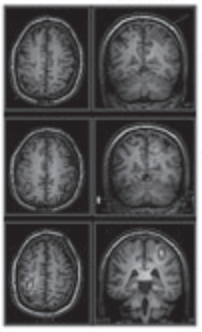
BRAIN CONNECTIVITY

- **Anatomical connectivity (fiber pathways)**
- **Functional connectivity (correlations)**
- **Effective connectivity (information flow)**



- **Anatomical connectivity**: set of all structural and physical connectivity
- **Functional connectivity**: estimate how different area are working together (statistical interdependence, model free, time dependent)
- **Effective connectivity**: estimation of directional connectivity → causal relationship. **It defines the influence that one neuronal system exerts on another (who drives whom).(model dependent, time dependent)**

Combined MEG and HD-EEG analysis



T1 MRI signal used for the localization of the generator

HD-EEG (Multiple Signal Classification Analysis – MUSIC)

MEG (LORETA)

To improve the diagnosis of MCD (particularly FCD and mMCDs)

- **Neurophysiology**: improve methodologies for invasive/non-invasive recordings, HD(HR)-EEG, MEG, Mathematical algorithms
- **Imaging**: *PET/MRI coregistration, increase magnetic field, to develop new sequences, and new post processing procedures, to develop new i.v. "functional" contrast (pH sensitive).*
- **Neuropathology**: *new specific histochemical and ICC stainings, new biomolecular biomarkers for neurons and glial cells.*

The need for non traditional teams of MD, biological scientists, engineers, mathematicians, physical scientists, computer scientists and others

FERNANDO CENDES (BRAZIL)

NEUROIMAGING FINDINGS IN THE EPILEPSIES ASSOCIATED WITH BRAIN MALFORMATIONS

NEUROIMAGING FINDINGS IN THE EPILEPSIES ASSOCIATED WITH BRAIN MALFORMATIONS

Fernando Cendes, MD, PhD
University of Campinas - UNICAMP
Campinas – São Paulo, Brazil

Brain development

Congenital anomalies of brain are commonly encountered in day to day practice.

Although there is a very wide spectrum of anomalies with over 2000 different congenital cerebral malformations described, the number of anomalies routinely encountered is limited.

Brain development

- **Embryology CNS is complex and orderly**
- **The somatic and psychic development depends on the SNC**
- **A better understanding of the processes and stages of normal development and abnormal CNS may clarify the mechanisms involved in several diseases**

A number of classification systems have been proposed, but none is universally accepted

In terms of imaging, the congenital malformations of brain can be broadly categorized into disorders of:

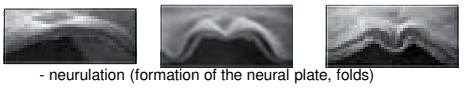
- Hindbrain herniations and miscellaneous malformations
- Hindbrain malformations (Posterior fossa malformations and cysts)
- Disorders of diverticulation and cleavage
- Malformations of cortical development

Brain development

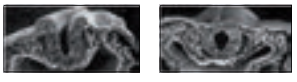
1. Early Events

- neurulation (formation of the neural plate, folds)
- neural tube
- formation of primitive vesicles
- cephalic flexure
- separation of the surface ectoderm and neuroectoderm
- diverticulation and cleavage forming the forebrain, midbrain and rhombencephalon

1. Early Events

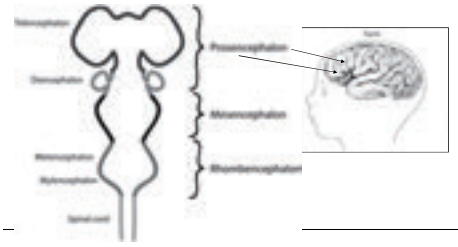


- neurulation (formation of the neural plate, folds)



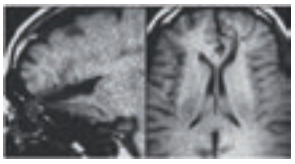
- **Neural tube**
- ~~**primitive vesicles, cephalic flexure** ~ 24th day of gestation~~

Early Events



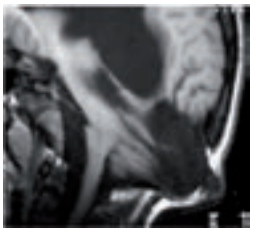
Disorders of neural tube closing
3rd and 4th weeks of gestation

- **Cephaloceles**
  - **Cephaloceles involve a skull defect associated with herniation of intracranial contents ("brain hernias")**



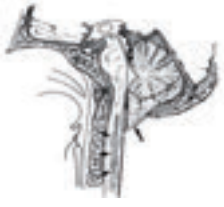
Disorders of neural tube closing
3rd and 4th weeks of gestation

- **Cephaloceles**



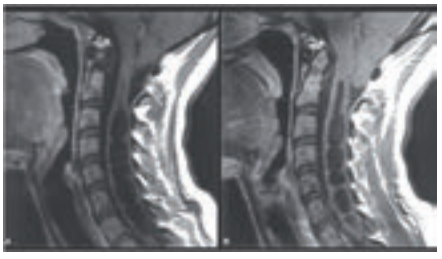
Chiari malformations

Chiari type I

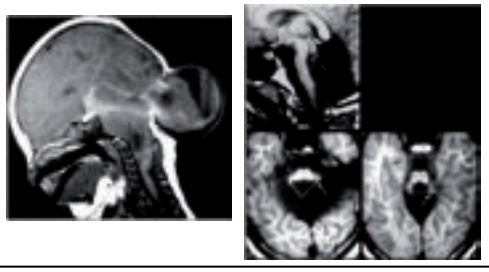


Chiari type II
(Arnold-Chiari and Cleland-Chiari)

Chiari I associated with Syringomyelia



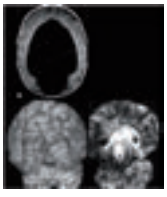
Chiari III and IV



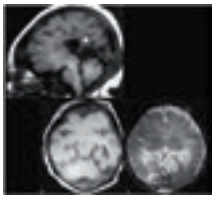
Holoprosencephaly

- **It is a spectrum of congenital structural forebrain anomalies and is the commonest malformation involving face and brain together.**
- **Its hallmark is monoventricle with non-cleaved frontal lobes.**
- **Also there is non-cleavage of diencephalon, and at times basal ganglia and thalami.**

Holoprosencephaly

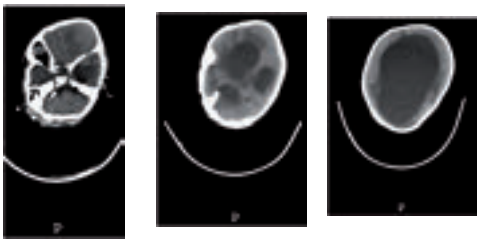


Holoprosencefalia alobar

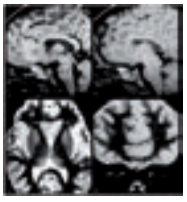
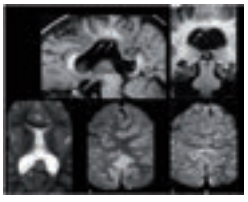


Holoprosencefalia semilobar

Holoprosencephaly

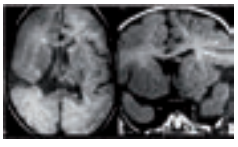
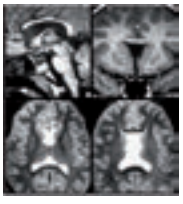


Holoprosencephaly

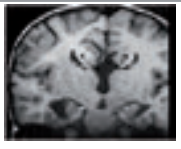
Lobar Holoprosencephaly Lobar dorsal Holoprosencephaly

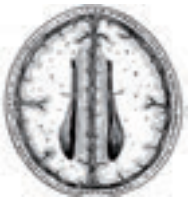
Septo-optical Dysplasia

Corpus callosum agenesis

between 8 and 20 weeks of gestation



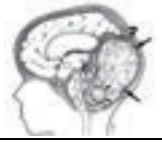
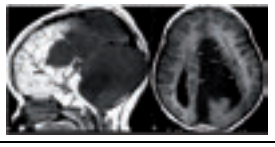


- Probst bands

Posterior fossa
Dandy-Walker Complex

Spectrum of malformations
3 classic features

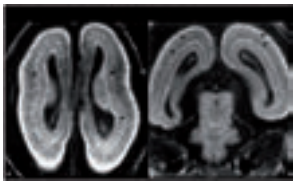
- Vermis agenesis complete or partial
- Dilation of IV ventricle
- Enlargement of posterior fossa

Brain development

- **2. Between 2 and 5 months**
  - **formation of germinal matrix**
  - **migration of neurons from the subependymal region to the cortex**
  - **Sulci and gyri**
  - **formation of commissural fibers (corpus callosum, etc)**
- **Third trimester => adult**
  - **myelination and function**
    - caudal to cephalic, dorsal to ventral, central to peripheral, sensory before motor

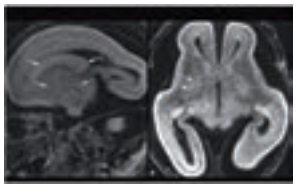
Fetal brain, 14 weeks of gestation



axial and coronal - 3D GRE images

Germinative matrix (A) and neuronal migration (B)

Fetal brain, 14 weeks of gestation



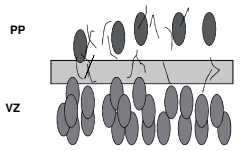
primitive caudate and lenticular striatum

Malformations of cortical development

- **Proliferation**
- **Migration**
- **Organization**

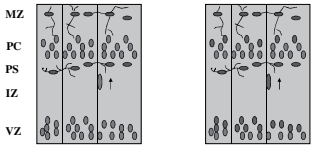
Proliferation and neuroglial diferentiation

✓ precursors proliferate in the Ventricular Zone (VZ)



4/5th until 17/18th weeks

Migration

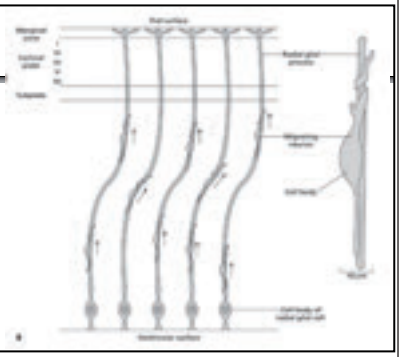


6/7th until 20/24th weeks

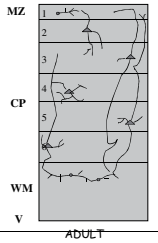
✓ radial migration ⟶ glia cels

✓ *inside/out*

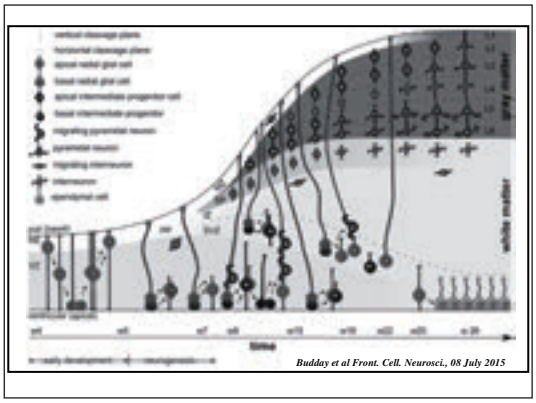
Formation of the cortical plate



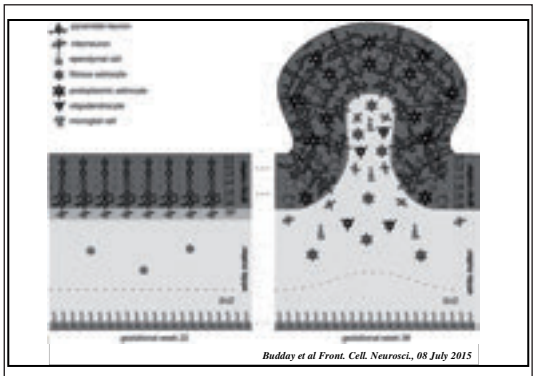
Organization



ADULT



Budday et al Front. Cell. Neurosci., 08 July 2015

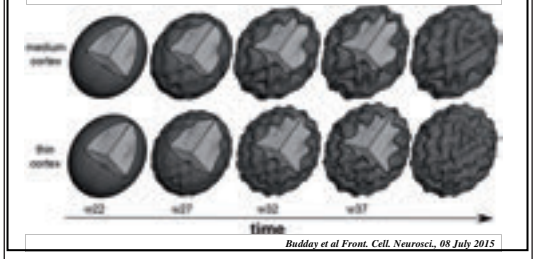

Budday et al Front. Cell. Neurosci., 08 July 2015

Physics-based modeling of differential growth

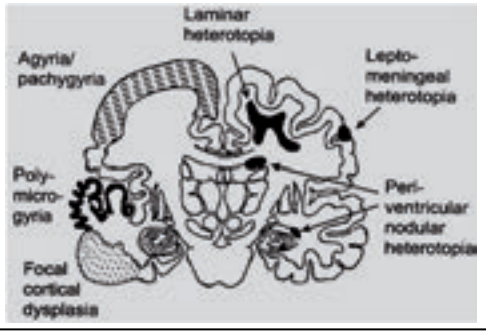
The surface morphology varies significantly with cortical thickness and gestational time.

Decreasing the cortical thickness, from top to bottom, increases the number of folds and decreases the gyral wavelength.

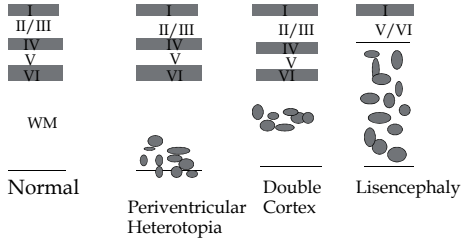
After the onset of folding around mid-gestation, the formation of new connections causes an excessive tangential expansion of the cortex, which increases the folding amplitude and surface complexity, from left to right.



Budday et al Front. Cell. Neurosci., 08 July 2015



Cortical patterns



Malformations of cortical development

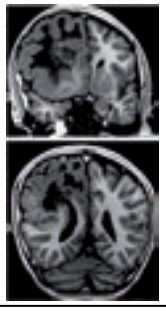
- **MCD due to abnormal neuronal proliferation**
  - **focal cortical dysplasia**
  - **hemimegalencephaly**
- **MCD due to abnormal neuronal migration**
  - **periventricular nodular heterotopia**
  - **subcortical laminar heterotopia**
  - **agyria/pachigyria**
- **MCD due to abnormal cortical organization**
  - **polymicrogyria**
  - **schizencephaly**

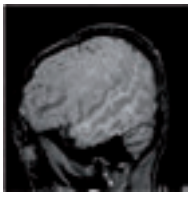
Barkovich et al, 1996

abnormal neuronal proliferation

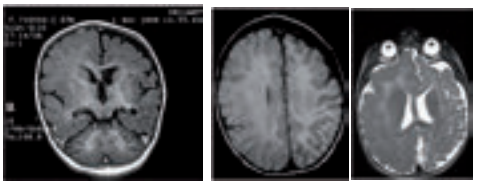
- **non neoplasic**
  - Hemimegalencephaly **(isolated or in neurocutaneal sind.)**
  - FCD with ballon cells
  - **Tuberous sclerosis**
- **neoplasic (associated with cortical dysorganization)**
  - **DNTs**
  - **ganglioglioma, gangliocitoma**

Hemimegalencephaly

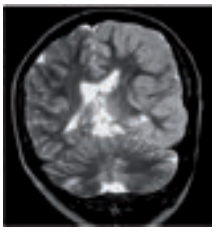




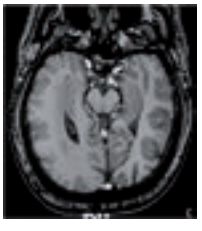
Hemimegalencephaly

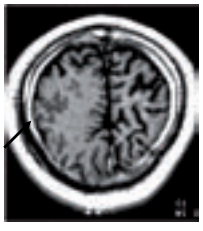


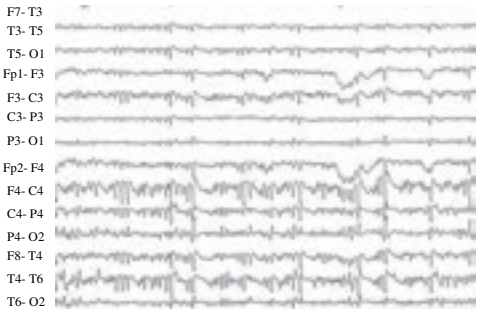
Hemimegalencephaly



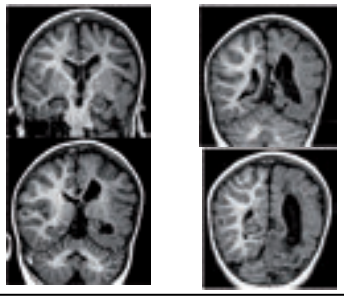
Hemimegalencephaly







Hemimegalencephaly – 2 y.o.; Seizures since birth



SPECIAL REPORT

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

Ingmar Blümcke, Maria Thom, Eleonora Aronica, Dawna D. Armstrong, Harry V. Vinters, Andre Palmini, Thomas S. Jacques, Giuliano Avanzini, A. James Barkovich, Giorgio Battaglia, Albert Becker, Carlos Cepeda, Fernando Cendes, Nadia Colombo, Peter Crino, J. Helen Cross, Olivier Delalande, François Dubeau, John Duncan, Renzo Guerrini, Philippe Kahane, Gary Mathern, Emad Najm, Gideon Oguni, Charles Raybaud, Alfonso Represa, Steven M. Rogers, Noriko Salamon, Andreas Schulze-Bonhage, Laura Tassi, Annamaria Vezzani, and Roberto Spreafico

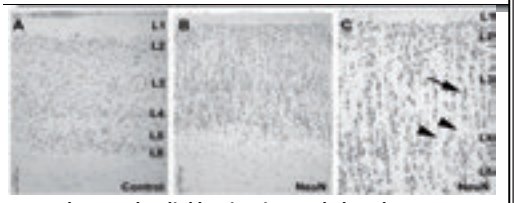
Revised three-tiered classification system for FCDs

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)
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 IA-IIB may always be visible in adjacent cortex		
FCD Type III (associated with principal lesion)	FCD: Type IIIA Focal Cortical Dysplasia in the temporal lobe associated with mesial temporal sclerosis (MTS)	FCD: Type IIIB Focal Cortical Dysplasia associated with a glial or glio-neuronal tumor	FCD: Type IIIC Focal Cortical Dysplasia associated with vascular malformation or scar/gyrus	FCD: Type IIID Focal Cortical Dysplasia associated with any other principal lesion

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

Epilepsia
Volume: 52, Issue: 1, pages 158-174, 10 NOV 2010 DOI: 10.1111/j.1528-1167.2010.02777.x

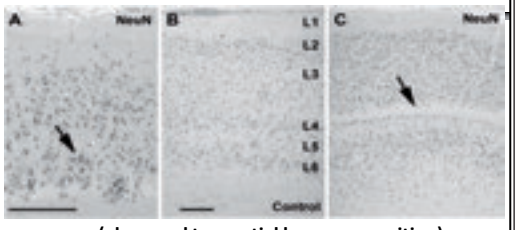
Histopathology in FCD Type IA



abnormal radial lamination and abundant microcolumns

Epilepsia
Volume 52, Issue 1, pages 158-174, 10 NOV 2010 DOI: 10.1111/j.1528-1167.2010.02777.x

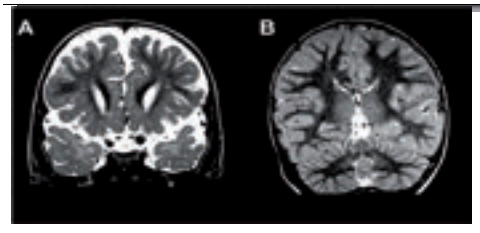
Histopathological findings in FCD Type IB



(abnormal tangential layer composition)

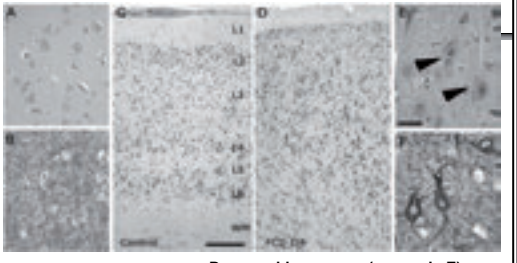
Epilepsia
Volume 52, Issue 1, pages 158-174, 10 NOV 2010 DOI: 10.1111/j.1528-1167.2010.02777.x

MRI findings in isolated FCD Type I



H. Holthausen and T. Piper

Histopathology in FCD Type IIA



Dysmorphic neurons (arrows in E)

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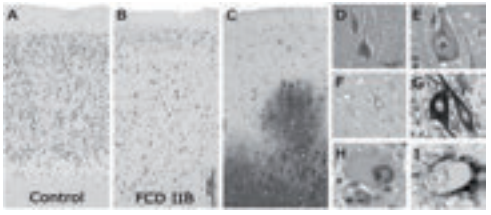
Volume 52, Issue 1, pages 158-174, 10 NOV 2010 DOI: 10.1111/j.1528-1167.2010.02777.x

Histopathologiy in FCD Type IIB



H: Balloon cells are a hallmark of this FCD variant

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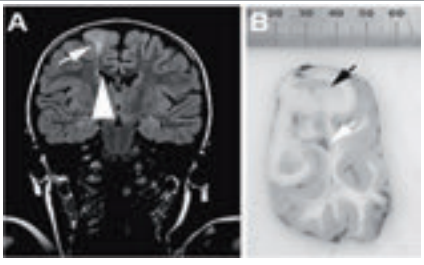
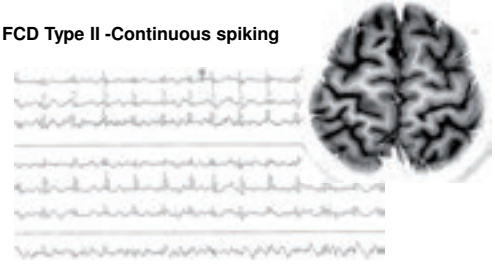
Neuroradiological-neuropathological correlation in FCD Type IIB

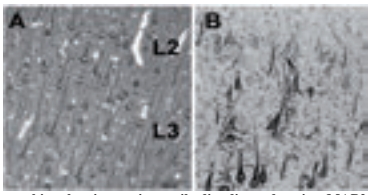


FCD Type II -Continuous spiking



Cortesy Drs. Eliseu Paglioli Neto and André Palmini

FCD associated with MTS (Type IIIA)



- **Immunohistochemistry using antibodies directed against MAP2. Cortical Layers 2 and 3 (L2, L3) cannot be separated as many neurons in L2 and L3 are hypertrophic. B: Immunohistochemistry using antibody SMI311. Intracytoplasmic accumulation of neurofilaments in hypertrophic neurons of Layer 2 and Layer 3. These abnormal neurons retain their pyramidal cell shape and apical dendrite. Scale bar in A = 100 µm.**

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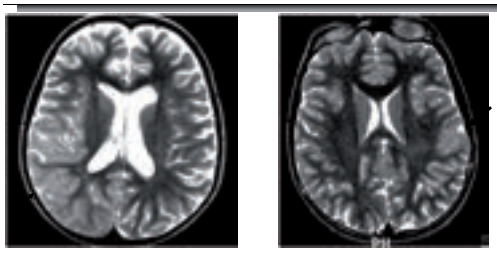
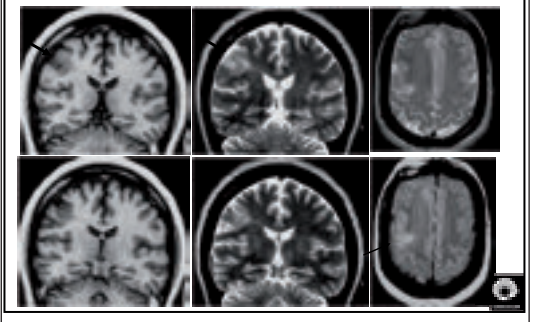
Volume 52, Issue 1, pages 158-174, 10 NOV 2010 DOI: 10.1111/j.1528-1167.2010.02777.x

Focal cortical dysplasia



diffuse localized

focal cortical dysplasia

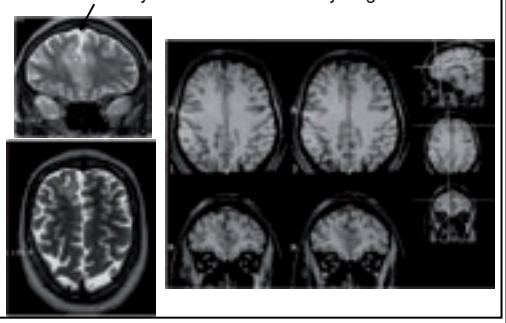


FCD and Epilepsy

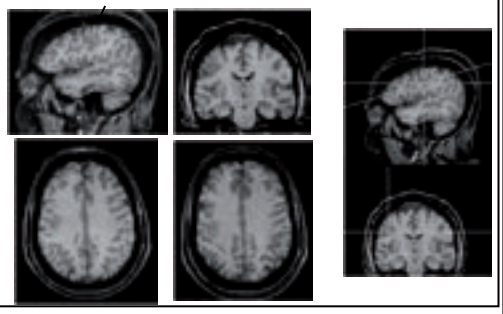
Gradient of morphologic changes

- **from dysplastic lesions that can be easily identified by conventional MRI techniques**
- **to minor structural abnormalities**
  - small areas of discrete cortical thickening and/or blurring of the gray-white matter interface
  - often go unrecognized

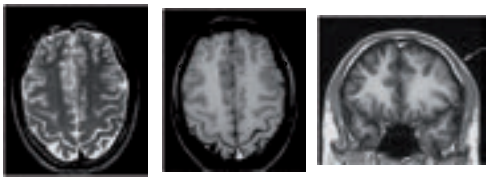
32 years old woman with dyscognitive seizures



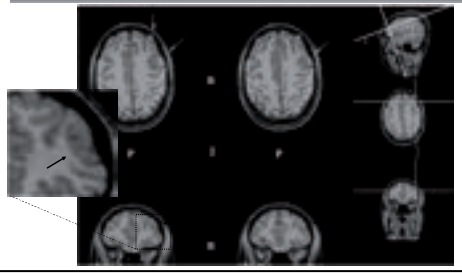
42 years old woman with partial seizures starting in the left side of the face



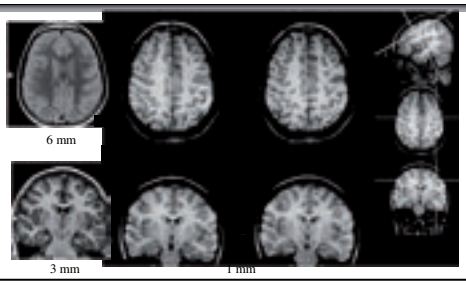
17 years old; FLE

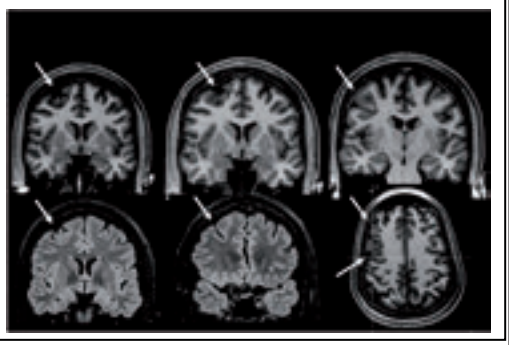


MPR shows FCD



MPR:
7 years old girl focal motor seizures in the right hand

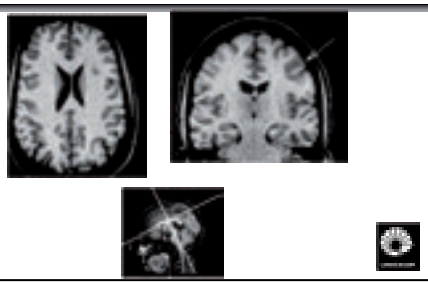




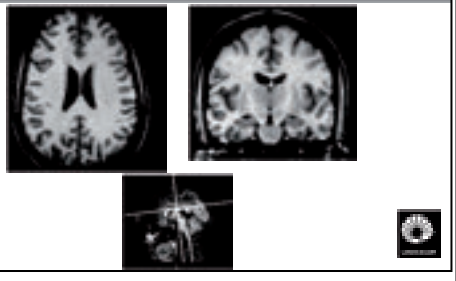
FCD and MPR

- The identification of these small FCD lesions by conventional MRI is often limited by the elaborate, contorted and irregular three-dimensional gyral structure
- The elaborate anatomy predisposes to the impression of cortical thickening due to obliquity of the plane of section in relation to the gyrus
- and volume averaging when using thick slices

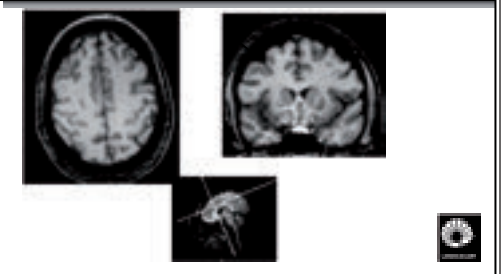
A) MPR: partial volume effect leading to false cortical thickening in a normal person



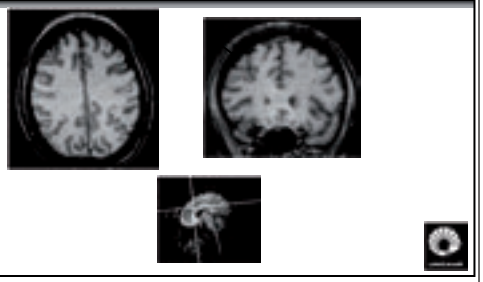
B) MPR: correction of partial volume effect by changing angulation

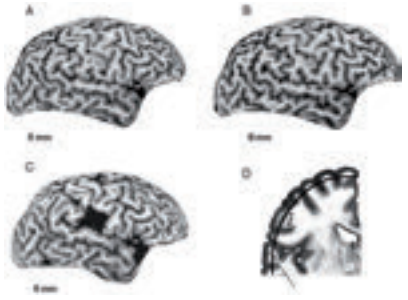


MPR: FCD in a patient with frontal lobe epilepsy



MPR: FCD in a patient with frontal lobe epilepsy
- no effect by changing angulation -

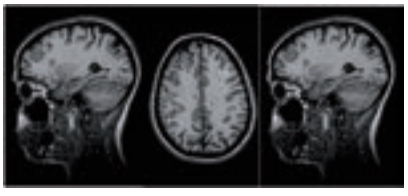




Bastos *et al*

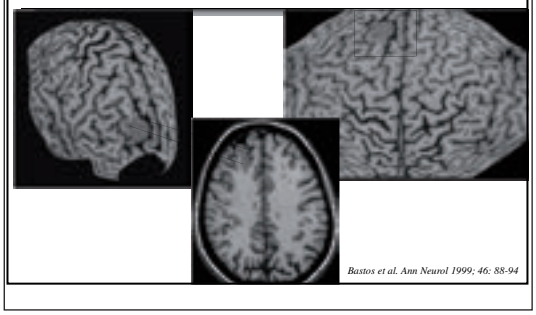
Curvilinear Reconstruction

Patient 1, FCD



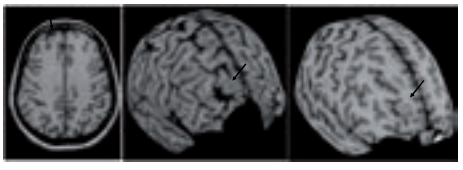
Bastos *et al*

Curvilinear reconstruction in cortical dysgenesis



Bastos et al. Ann Neurol 1999; 46: 88-94

focal cortical dysplasia



Bastos *et al*

Neuronal migration disorders

Period: 6th to 7the weeks until 20/24th weeks

- May persist until post-natal

Neuronal migration disorders

During normal brain development, in early gestation, the neurons start their migration outward, forming the functional hexalaminar cortex.

If this process is disrupted, the neurons assume an abnormal position.

These ectopic neurons may stop in any area between the subependimal region and the cerebral cortex.

Neuronal migration disorders

These malformations can be divided into four subcategories:

1. Abnormalities of the neuroependima that occurs in the begining of migration, mainly comprising periventricular nodular heterotopia (PNH);

2. Generalized abnormalities of transmantle migration such as the lissencephalies;

3. Localized abnormalities of transmantle migration including subcortical band heterotopia (SBH);

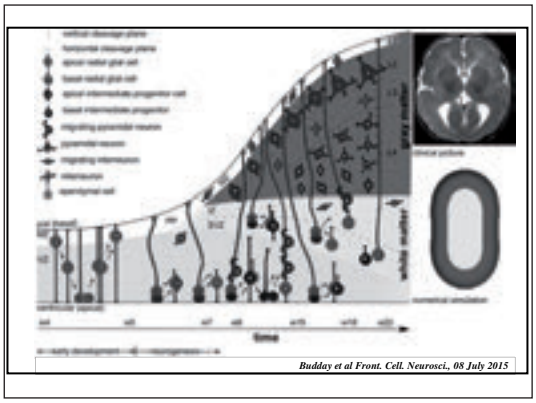
4. Abnormalities due to abnormal terminal migration comprising cobblestone malformations

Neuronal migration disorders

- **Agyria-pachigyria / lisencephaly**
  - **focal, multifocal, generalized**
- **Heterotopias**
  - **Subcortical nodular**
  - **subcortical "band" heterotopias ("double cortex ")**
  - **Subependimal nodular or Periventricular**

Normal cortex

Classic lissencephalic cortex

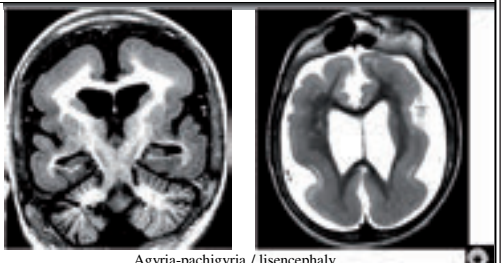


Budday et al Front. Cell. Neurosci., 08 July 2015

Neuronal migration disorders

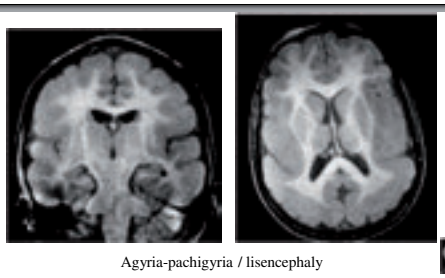
Although the etiology of GMH is not yet fully elucidated, genetics may play an important role. Patients often present with pharmaco-resistant epilepsy, in addition to focal neurologic deficits

N. 10 years old - Lennox-Gastaut syndrome



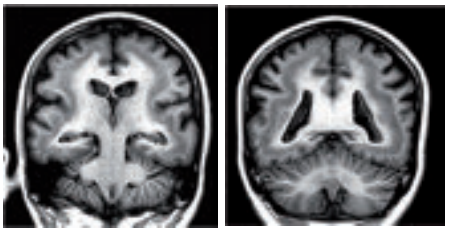
Agyria-pachigyria / lisencephaly

J., 3 years old – refractory seizures and mental retardation

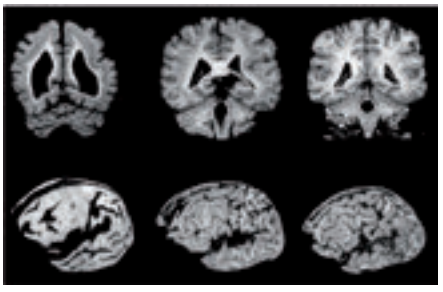


Agyria-pachigyria / lisencephaly

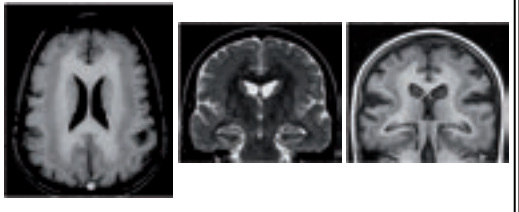
Subcortical subcortical ("double cortex")



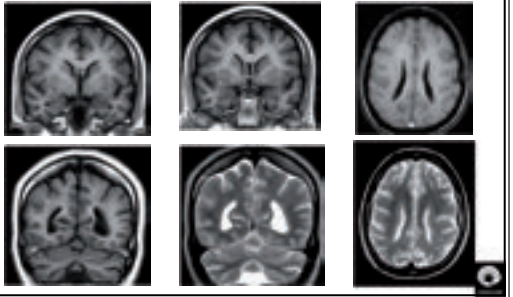
Subcortical subcortical ("double cortex") - spectrum



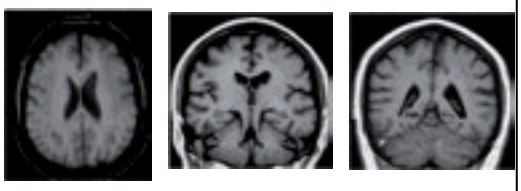
Subcortical subcortical ("double cortex")



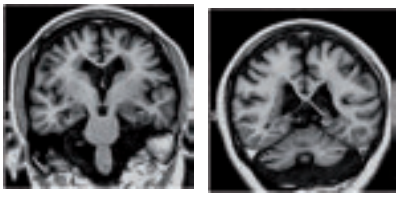
Subcortical subcortical ("double cortex")



Subcortical laminar heterotopia, in a male patient
40 years old, secondary generalized epilepsy with focal features



Nodular Periventricular Heterotopia



Nodular Periventricular Heterotopia

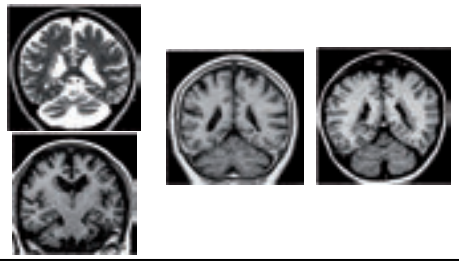
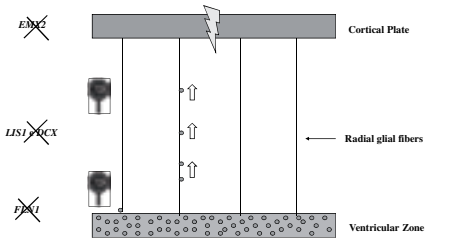


Table 1 | **Defects of neocortical-layer formation in humans**

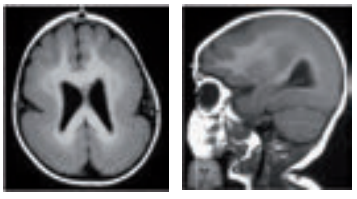
Gene affected	Disease	Gene locus	Mode of inheritance
LIS1	MDS and ILS	Chromosome 17p13.3	Sporadic
DCX	ILS and SBH	Chromosome X	X linked
RELN	LCH	Chromosome 7q22	Recessive
FLNA	PH	Chromosome Xq28	Dominant

DCX, doublecortin; FLNA, filamin A; a, ILS, isolated lissencephalic sequence; LCH, lissencephaly with cerebellar hypoplasia; LIS1, lissencephaly 1; MDS, Miller–Dieker syndrome; PH, periventricular heterotopia; RELN, reelin; SBH, subcortical band het

neuronal migration and organization disorders

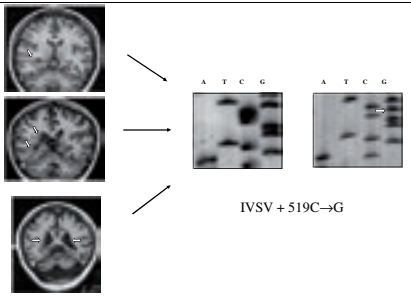


LIS1



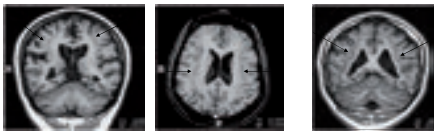
✓ grade 3a (posterior agyria – anterior pachigyria)

FLN1



IVSV + 519C→G

DCX



Cortical organization

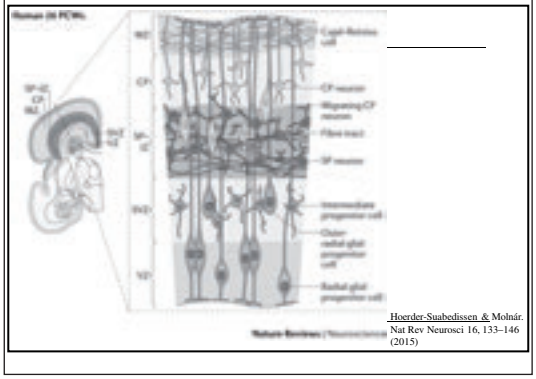
Cortical organization

The first cells to arrive at the cortex (cells of Cajal-Retzius) are placed in the outermost layer of the cortical plate, determining its outer limit

Then come the neurons that will be positioned immediately below the cortical plate (Sub-laminar neurons)

The neurons that reach the cortex after that will be positioned between these two limits, forming 6 layers

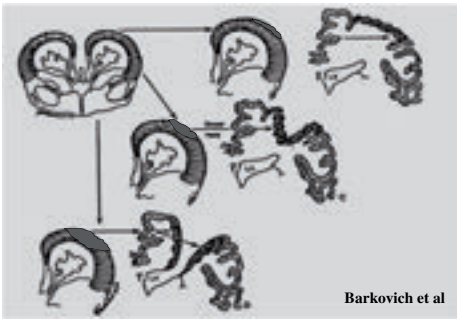
inside-out

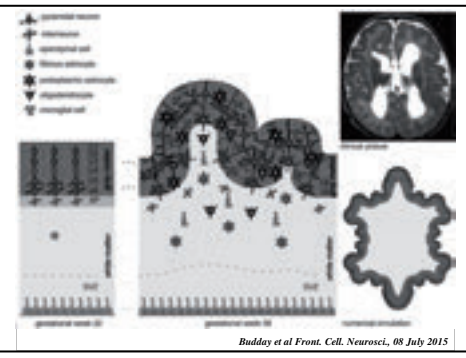


Hoerder-Suabedissen & Molnár. Nat Rev Neurosci 16, 133–146 (2015)

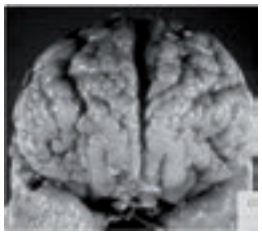
Cortical organization disorders

- **Polymicrogyria**
- **Schizencephaly**

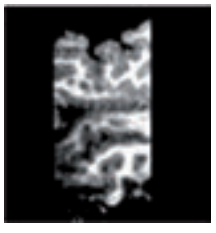


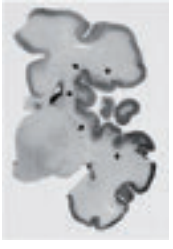


Polymicrogyria

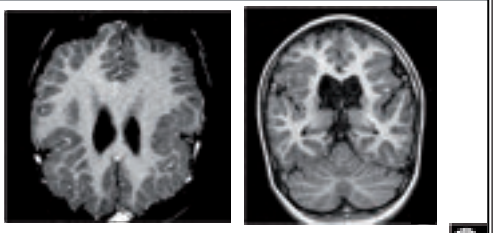


Perisylvian polymicrogyria

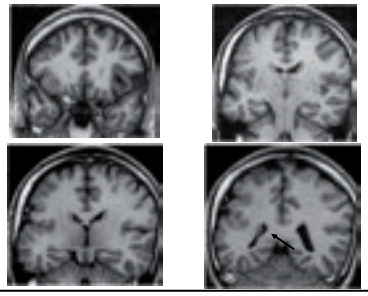




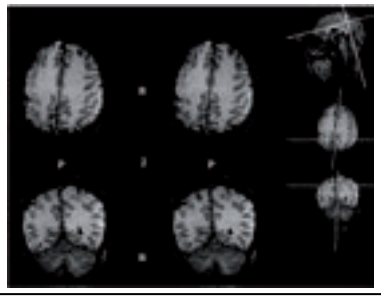
W., 11 years - Lennox-Gastaut syndrome



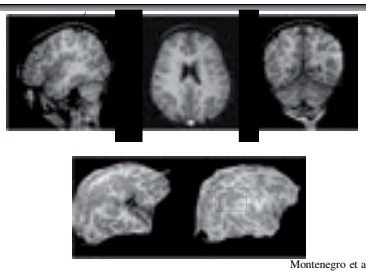
Unilateral Perisylvian Polymicrogyria
Associated with Periventricular Nodular Heterotopia



Unilateral Perisylvian Polymicrogyria

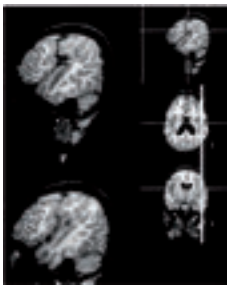


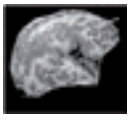
Bilateral Posterior Parietal Polymicrogyria: A Mild Form of Congenital Bilateral Perisylvian Syndrome?



Montenegro et al; Epilepsia 2001

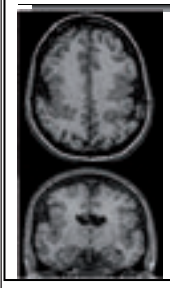
Bilateral Perisylvian Polymicrogyria



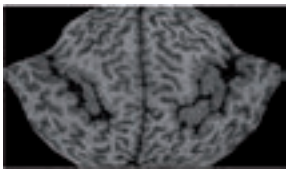


12 mm

Polymicrogyria



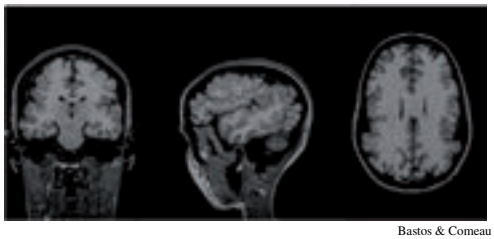
Patient 8, bilateral PMG



Bastos & Comeau

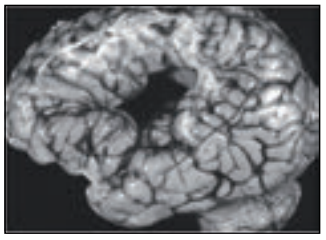
Polymicrogyria

Patient 9, bilateral PMG



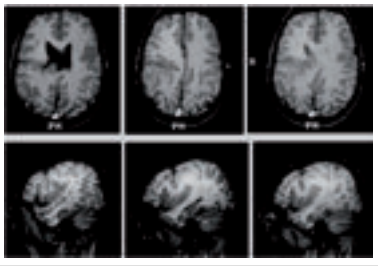
Bastos & Comeau

schizencephaly

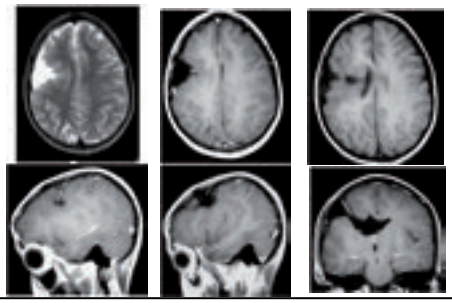


Scott Atlas, 1996

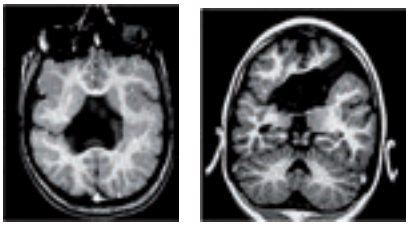
schizencephaly



schizencephaly

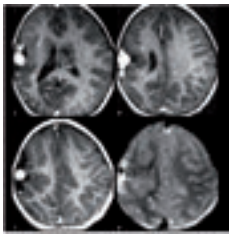


8 old girl, mental retardation, microcephaly, bilateral hemiparesis and seizures since birth. Now with seizures well controlled with AEDs

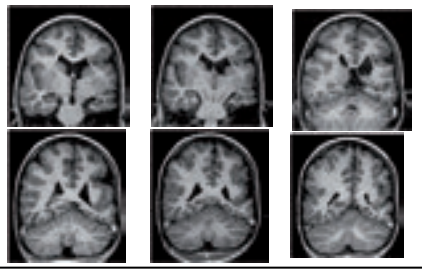


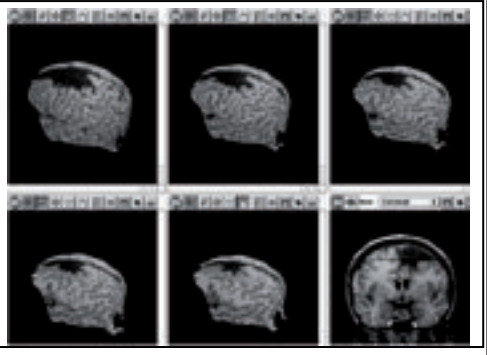
Bilateral schizencephaly

Polymicrogyria *vs* schizencephaly



9 year old girl with seizures and cognitive and motor impairment



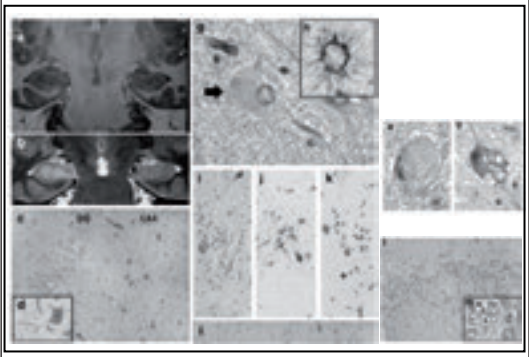


J Neurol
DOI 10.1007/s00415-014-7486-5

LETTER TO THE EDITORS

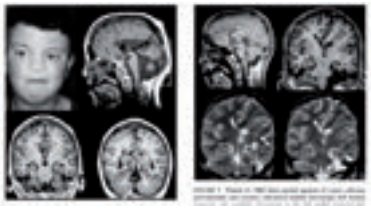
Hippocampal dysplasia with balloon cells: case report and discussion on classification

Fabio Rogerio · Marcia Elisabete Morita · Ana Carolina Coan · Carlos Alberto Mantovani Guerreiro · Helder Tedeschi · Roland Coras · Luciano de Souza Queiroz · Ingmar Blümcke · Fernando Cendes



Malformations of Cortical Development in Patients With Midline Facial Defects and Ocular Hypertelorism

Silvya David Araújo Gifoni, M.D., Fernando Cendes, M.D., Ph.D., Marcelo Valente, M.D., Ph.D., Vera Lucia Gil-da-Silva-Lopes, M.D., Ph.D.

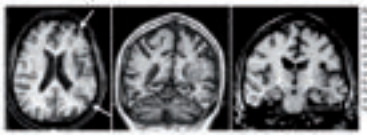


Cleft Palate Craniofac J. 2010 Jul;47(4):343-51

PAPER

Patterns of hippocampal abnormalities in malformations of cortical development

M A Montenegro, D Kinay, F Cendes, A Bernasconi, N Bernasconi, A C Coan, L M Li, M M Guerreiro, C A M Guerreiro, I Lopes-Cendes, E Andermann, F Dubeau, F Andermann



Conclusion - I

Abnormal Proliferation

- **More frequent and severe epilepsy**
  - **Functional and morphologically abnormal neurons**
  - **Intrinsic epileptogenicity**

Conclusion - II

Abnormal Migration

- **Frequency of epilepsy is lower than in FCD and higher than in polymicrogyria**
  - **Abnormal layering of neurons**
  - **Abnormal neuronal network ?**
    - Variable degrees of epileptogenicity

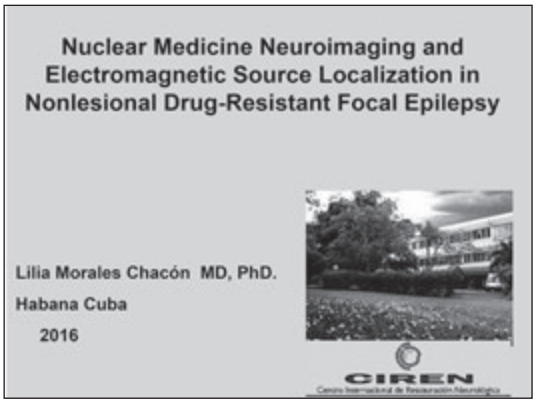
Conclusion - III

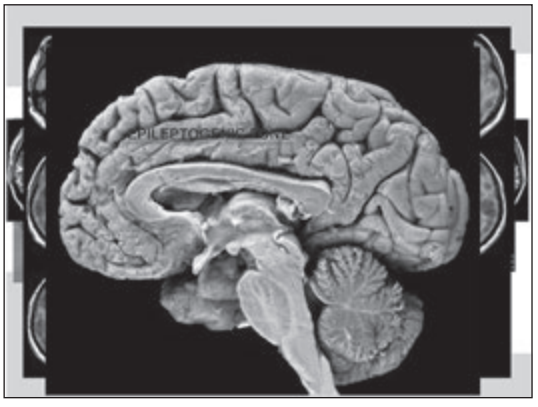
Abnormal Organization

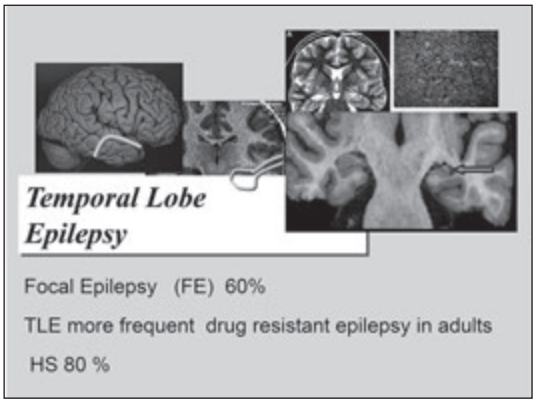
- **Epilepsy is less frequent and more easily controlled**
  - **Abnormal layering of neurons**
  - **"Less" abnormal neuronal network ?**
    - Absent or mild intrinsic epileptogenicity

Lilia Morales (Cuba)

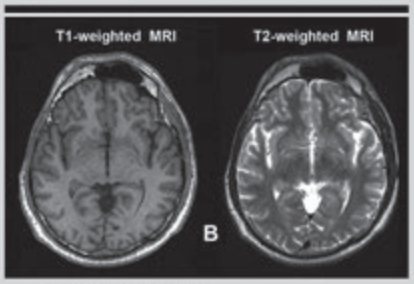
NUCLEAR MEDICINE NEUROIMAGING AND ELECTROMAGNETIC SOURCE LOCALIZATION IN NONLESIONAL DRUG-RESISTANT EPILEPSY





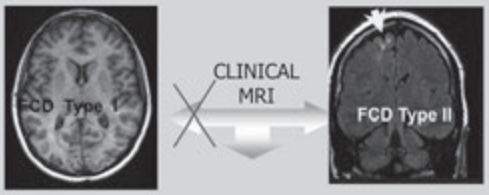


MRI remains without pathologic findings in up 30%
MRI negative TLE, nonlesional TLE or cryptogenic TLE



Yatsuda et al 2010

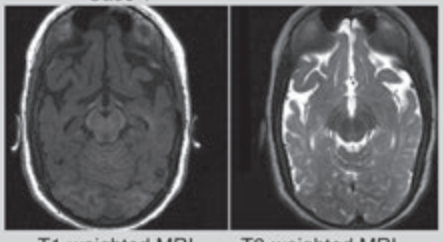
MRI / FCD



In type I FCD , MRI imaging is often normal, and also in both types the lesion MRI seen may be smaller than the seizure –generating region seen in the EEG

Palmini A, Luders HO. Neurosurg Clin. N Am 2002, Palmini A, y cols Neurology 2004, Najm 2007, Krsek 2008, Guerrini 2010., Kabat J 2012..

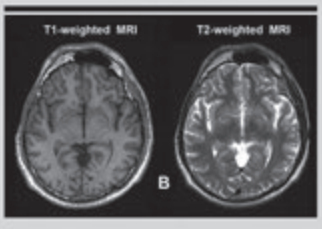
Case 1



T1-weighted MRI T2-weighted MRI

Magnetic resonance imaging. (a) A 5-year-old female patient with right frontal lobe . T1- and T2-weighted sequences showed widespread bilateral cortical atrophy that did not fully explain EEG and clinical data of the patient.

CASE 2



Images from one of our patients (a 36-year-old man) with nonlesional left temporal lobe epilepsy and postoperative seizure-free outcome.

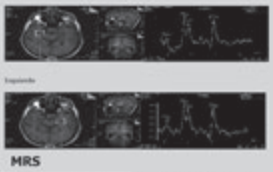
PURPOSE

To review the value of nuclear medicine neuroimaging combined with source analysis based on electrophysiological information (EEG/MEG) to improve EZ localization in drug-resistant nonlesional focal epilepsy, with a significant positive impact on surgery outcome.

CLINICAL DATA.

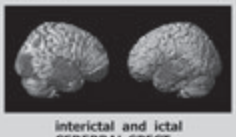
Age at surgery	34.1±7.9 A m:35
Sex	F: 12 M: 10
Risk factors	Febril convulsion : 25% Encephalitis: 20%
Sz onset age	12.28±9.3 (8m-29 y) m: 14
No. AED	2 (1-3)
Seizure duration	20.21±10.59 (2- 36 A) m: 21
Seizures Frecuency	4-16/m
Histopathological Diagnostic	16 FCD III , 6 EH

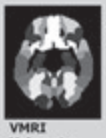
Pre- surgical evaluation in Temporal lobe epilepsy patients CIREN Epilepsy Program



V-EEG

MRS





- Clinical evaluation
- NPS
- Evoked Potentials

interictal and ictal CEREBRAL SPECT

VMRI Volumetry

Tissue characterization and histopathological examination for mild Palmini FCD diagnosis

Haematoxylin–eosin, and Kluver–Barrera myelin special stain. In selected cases, immunohistochemical reaction with glial fibrillary acid protein (GFAP) and Synaptophysin were performed. In order to distinguish between specimens with and without FCD we used Palmini's classification. **Neurology 2004;62:S2-S8**

Electroclinical outcome

The postoperative follow-up ranged from 12 to 48 months. For seizure prognosis assessment, patients were classified according to Engel's classification.

QUANTITATIVE METHODS FOR CHARACTERIZING MRI.

TEMPORAL LOBE EPILEPSY

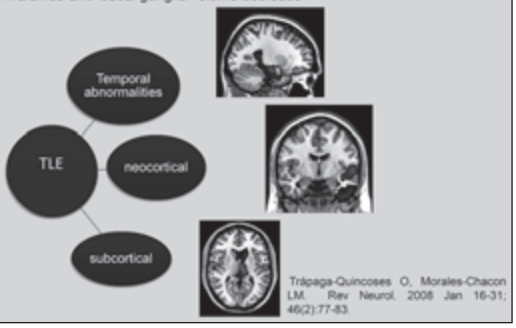
- VOLUMETRY
- VOXEL BASED MORPHOMETRY → IBASPM
- NEURORADIOLOGICAL REPORT → SPM 5
- NEUROPATHOLOGICAL REPORT

MRI examinations were performed on a MRI scanner Siemens Symphony 1.5 T (Erlangen, Germany).
160 contiguous slices of 1-mm thickness in sagittal orientation.

12

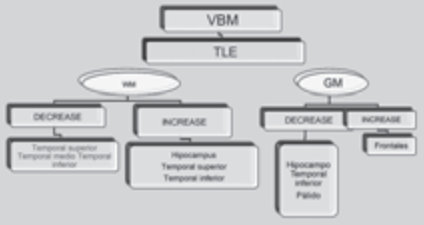
VOLUMETRIC MRI in mTLE-mild FCD

Mesial and neocortical temporal volume decrease
Thalamus and basal ganglia volume decrease

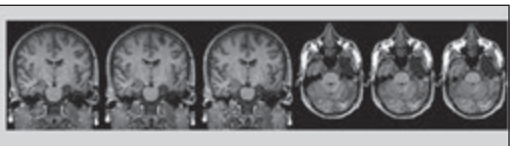


Trápaga-Quincoses O, Morales-Chacon LM. Rev Neurol. 2008 Jan 16-31; 46(2):77-83.

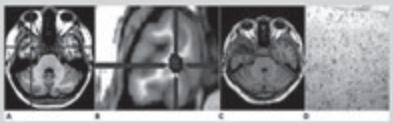
VOXEL BASED MORPHOMETRY IN TLE-mild FCD

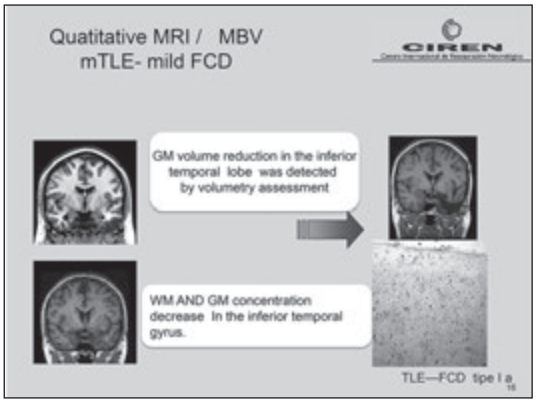


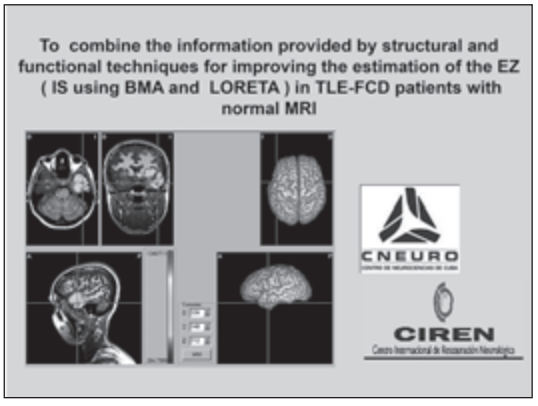
62,5%

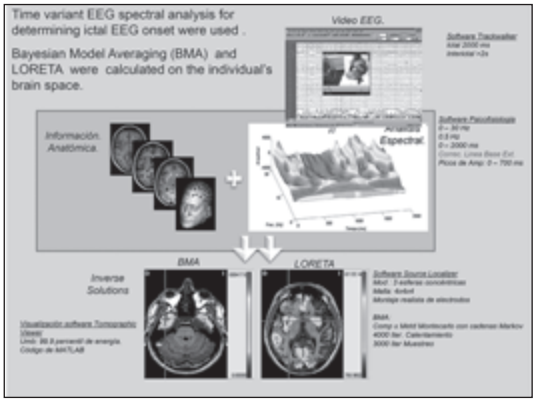


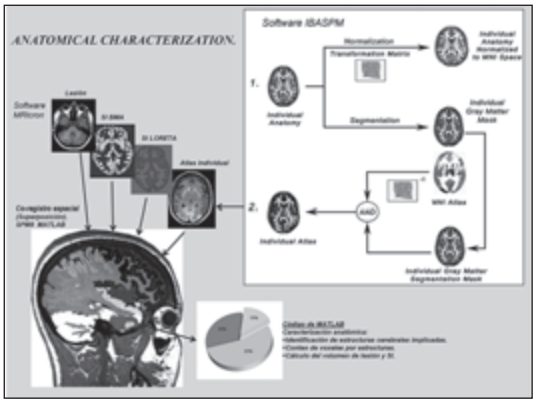
Contrast of patient versus respective control group resulted in the t-statistic map, which was thresholded at a p-value of <0.001 . FDR= (1.323)

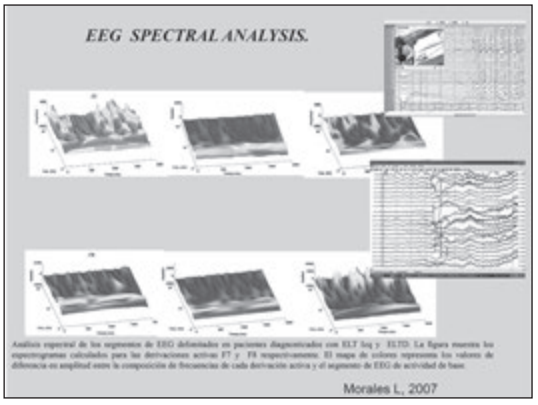


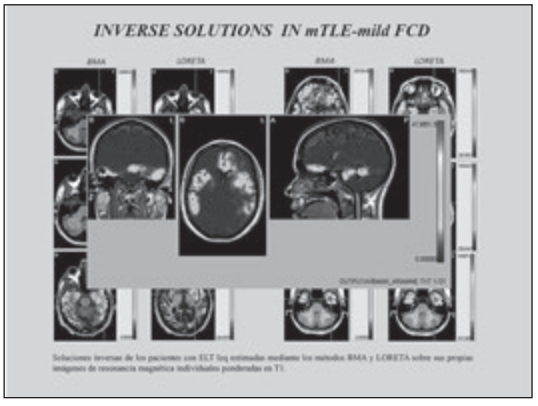

Quatitative MRI / MBV
mTLE- mild FCD
CIREN
GM volume reduction in the inferior temporal lobe was detected by volumetry assessment
WM AND GM concentration decrease In the inferior temporal gyrus.
TLE—FCD tipe I a
16

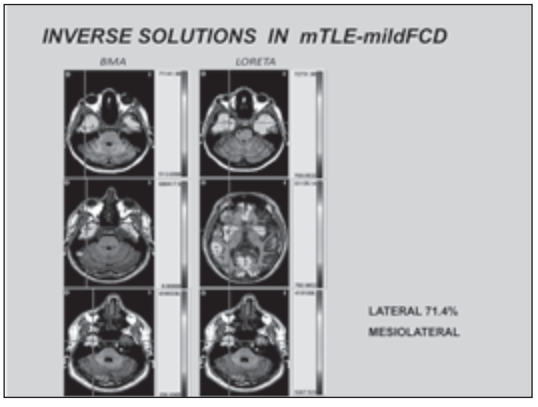

To combine the information provided by structural and functional techniques for improving the estimation of the EZ (IS using BMA and LORETA) in TLE-FCD patients with normal MRI
CNEURO
CIREN

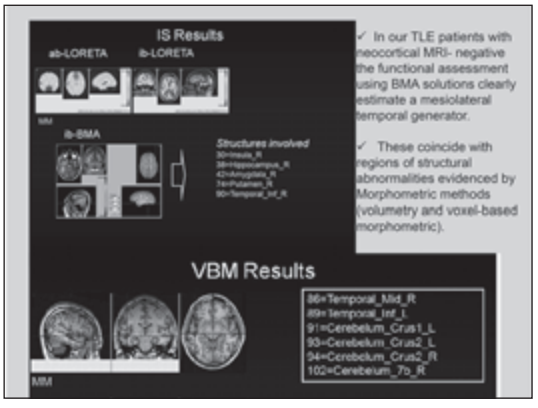

Time variant EEG spectral analysis for determining ictal EEG onset were used .
Bayesian Model Averaging (BMA) and LORETA were calculated on the individual's brain space.
Video EEG.
Información Anatómica.
Espectral
BMA
LORETA
Inverse Solutions

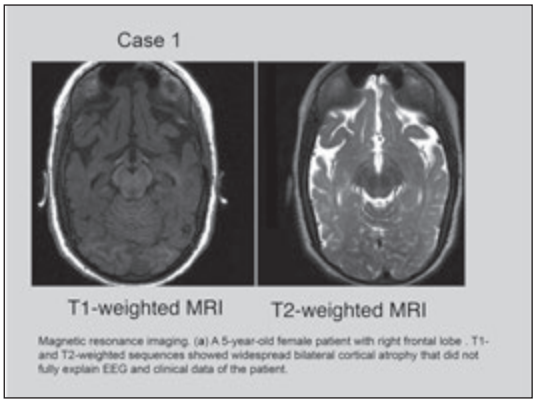

ANATOMICAL CHARACTERIZATION.
Software iBASPM
Normalization
Transformation Matrix
Individual Anatomy
Segmentation
Individual Gray Matter Mask
MNI Atlas
Individual Atlas
Individual Gray Matter Segmentation Mask


EEG SPECTRAL ANALYSIS.
Morales L, 2007

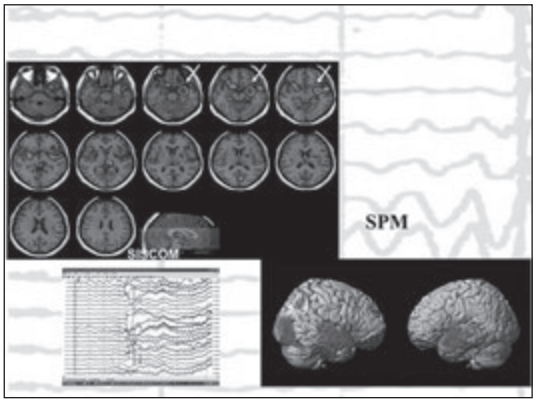

INVERSE SOLUTIONS IN mTLE-mild FCD
BMA
sLORETA
BMA
sLORETA

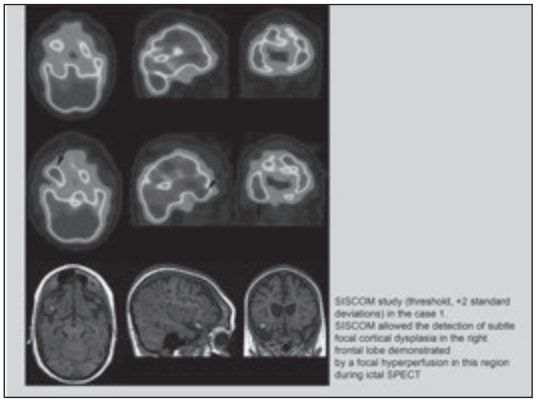

INVERSE SOLUTIONS IN mTLE-mildFCD
BMA
LORETA
LATERAL 71.4%
MESIOLATERAL


IS Results
ab-LORETA
ib-LORETA
MM
ib-BMA
Structures involved
✓ In our TLE patients with neocortical MRI- negative the functional assessment using BMA solutions clearly estimate a mesiolateral temporal generator.
✓ These coincide with regions of structural abnormalities evidenced by Morphometric methods (volumetry and voxel-based morphometric).
VBM Results
86=Temporal_Mid_R
89=Temporal_Inf_L
91=Cerebelum_Crus1_L
93=Cerebelum_Crus2_L
94=Cerebelum_Crus2_R
102=Cerebelum_7b_R
MM

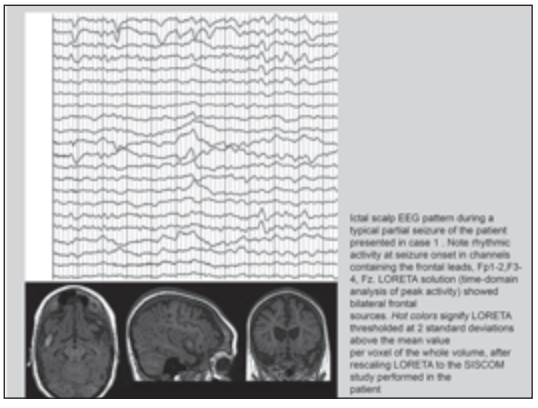


Magnetic resonance imaging. (a) A 5-year-old female patient with right frontal lobe . T1- and T2-weighted sequences showed widespread bilateral cortical atrophy that did not fully explain EEG and clinical data of the patient.



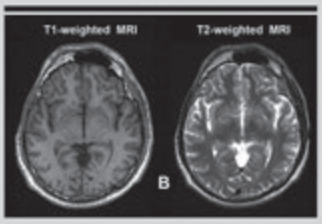


SISCOM study (threshold, +2 standard deviations) in the case 1. SISCOM allowed the detection of subtle focal cortical dysplasia in the right frontal lobe demonstrated by a focal hyperperfusion in this region during ictal SPECT

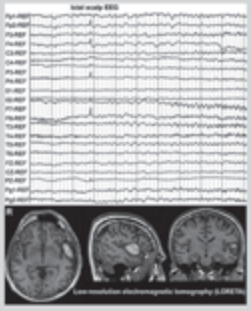


Ictal scalp EEG pattern during a typical partial seizure of the patient presented in case 1 . Note rhythmic activity at seizure onset in channels containing the frontal leads, Fp1-2,F3-4, Fz. LORETA solution (time-domain analysis of peak activity) showed bilateral frontal sources. *Hot colors* signify LORETA thresholded at 2 standard deviations above the mean value per voxel of the whole volume, after rescaling LORETA to the SISCOM study performed in the patient

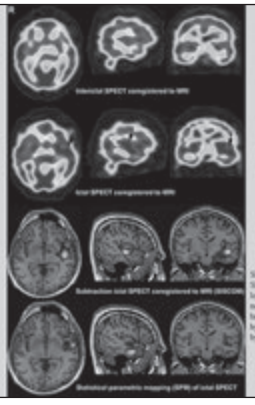
CASE 2



Images from one of our patients (a 36-year-old man) with nonlesional left temporal lobe epilepsy and postoperative seizure-free outcome.



Ictal scalp EEG pattern during a typical complex partial seizure of the case 2. Note rhythmic theta activity at seizure onset in F7, T3 and Pg1. LORETA demonstrated a left temporal source



SISCOM study (threshold, + 2 standard deviations) in the case 2 SISCOM showed a focal cerebral hyperperfusion in the left temporal lobe, concordant with EEG and clinical data, in a region apparently normal by MRI. Ictal SPECT compared with a control brain SPECT database by using SPM also showed a focal cerebral hyperperfusion partially overlapping the left temporal regions detected by SISCOM

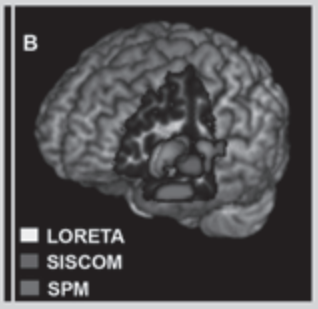
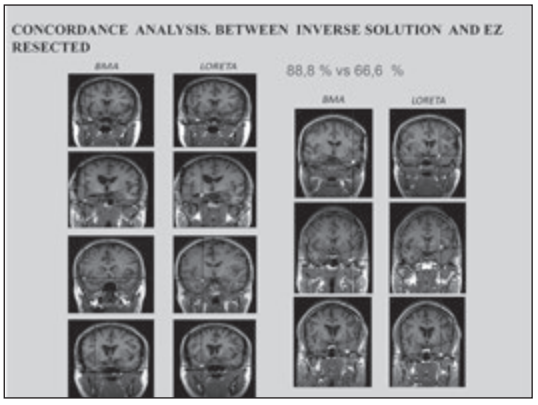
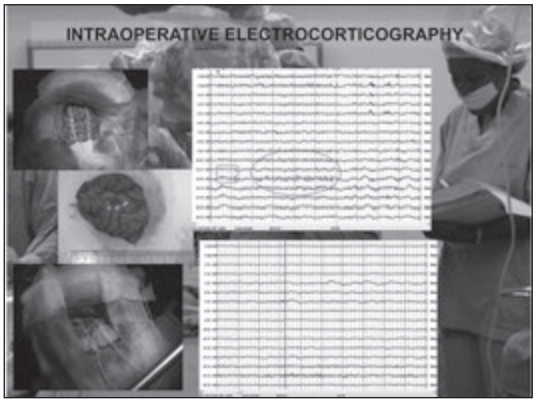
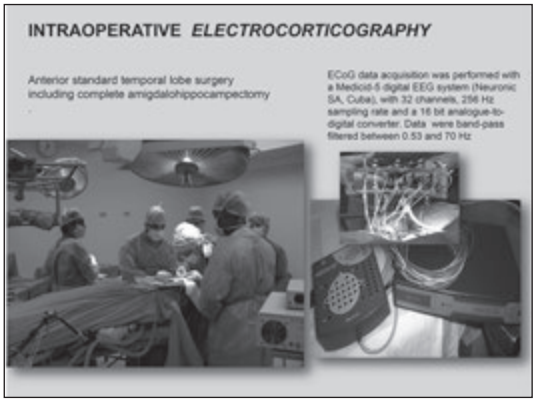
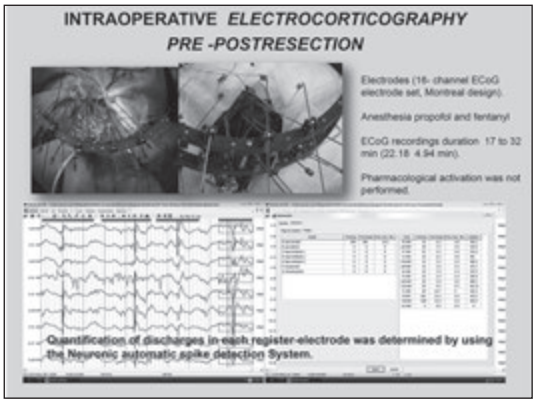


Figure 6.
Multimodal registration. (A) rendering of MRI (T1-weighted in the native space) with a right anterior brain view of the case 2 . The image includes SISCOM and LORETA that helped to improve the detection of epileptogenic zone in this patient in which MRI findings did not fully explain EEG and clinical data. (B) rendering of MRI with a left anterior view of the brain belonging to the patient presented in figures 1.B, 3 and 5. The image was cutout to show medial aspect of left temporal lobe and includes multiples approaches t o localize epileptogenic zone, which helped to improve surgical outcome in this patient with nonlesional left temporal lobe epilepsy.


CONCORDANCE ANALYSIS. BETWEEN INVERSE SOLUTION AND EZ RESECTED
BMA
LORETA
88,8 % vs 66,6 %
BMA
LORETA

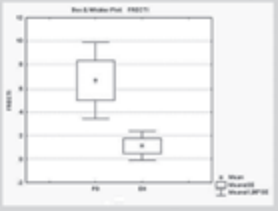

INTRAOPERATIVE ELECTROCORTICOGRAPHY


INTRAOPERATIVE ELECTROCORTICOGRAPHY
Anterior standard temporal lobe surgery including complete amigdalohippocampectomy
ECoG data acquisition was performed with a Medicid-5 digital EEG system (Neuronic SA, Cuba), with 32 channels, 256 Hz sampling rate and a 16 bit analogue-to-digital converter. Data were band-pass filtered between 0.53 and 70 Hz

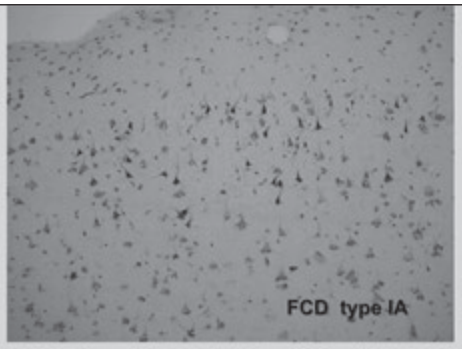

INTRAOPERATIVE ELECTROCORTICOGRAPHY
PRE -POSTRESECTION
Electrodes (16- channel ECoG electrode set, Montreal design).
Anesthesia propofol and fentanyl
ECoG recordings duration 17 to 32 min (22.18 4.94 min).
Pharmacological activation was not performed.
Quantification of discharges in each register-electrode was determined by using the Neuronic automatic spike detection System.

Electrocorticographic patterns and mild Palmini Type-I FCD patients with temporal lobe epilepsy

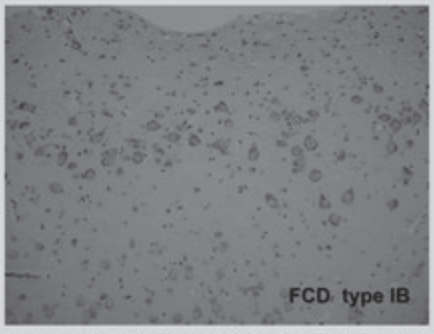
The mean spike frequency was 6.67 min and 1.14min1 in patients with DP (dual pathology) and thosewith HS, respectively.Mann–Whitney U-test p = 0.03.



Interictal absolute spike frequency during intraoperative electrocorticography recording (inferior temporal gyrus) in patients with dual pathology (hippocampal sclerosis (HS) associated with neocortical temporal mild Palmini Type-I FCD), and those with HS.

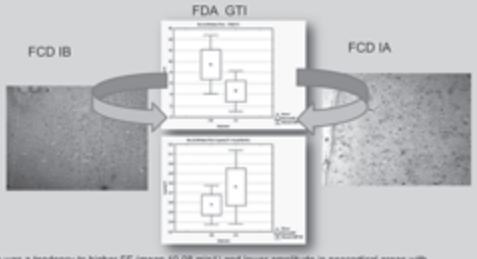


Histopathological features of focal cortical dysplasia (FCD Type-IA), isolated architectural abnormalities (dyslamination). There is focal loss of neurons involving cortical layers two, three and four.

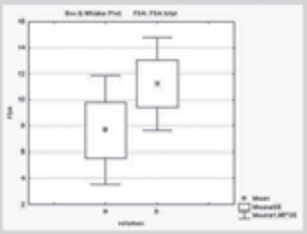


Histopathological features of focal cortical dysplasia Type-1B (dyslamination associated with giant and immature neurons).

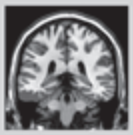
Intraoperative electrocorticographic interictal discharge frequency recorded in the neocortical inferior temporal gyrus may help to characterize the histopathologic subtypes of mild Palmini Type-I FCD in patients with temporal lobe epilepsy.



There was a tendency to higher SF (mean 10.08 min1) and lower amplitude in neocortical areas with histopathologic subtype-IB FCD in relation with that one with IA (mean 5.10 min1), during intraoperative ECoG.

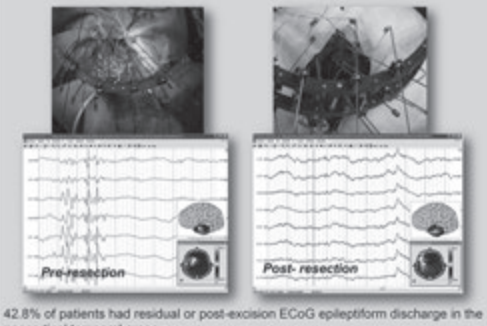


Volumetric MRI



SF was significantly higher in patients with temporal neocortical atrophy evaluated by volumetric MRI, although this did not reach statistical significance (7.7 min1 in normal vs. 11.2 min1 in patients with atrophy).

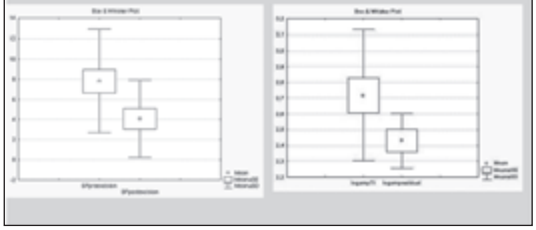
Mesial and neocortical post-excision ECoG epileptiform discharge vs. electroclinical outcome



42.8% of patients had residual or post-excision ECoG epileptiform discharge in the neocortical temporal areas.

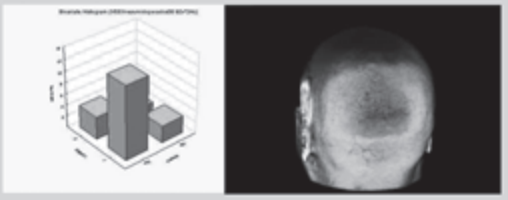
Mesial and neocortical post-excision ECoG epileptiform discharge vs. electroclinical outcome

The SF and amplitude were significantly lower during neocortical post-excision intraoperative ECoG(mean 3.37min1) than during neocortical preexcision recording (mean 7.79min1, p = 0.04 Wilcoxon matched pairs test)

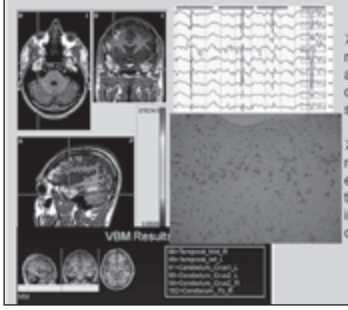


Mesial and neocortical post-excision ECoG epileptiform discharge vs. electroclinical outcome

There was no difference in the clinical outcome between patients with and without FCD. 66.6% of patients with HS were also seizure free, p = 0.54, Fischer exact test. In general, 72.7% of our patients were in Engel 1a Scale two year after surgery



CONCLUSIONS



- Pre and intraoperative multimodal imaging assessment help in distinguishing TLE subtypes.
- ECoG patterns are relevant to determine the extent of the resection in these patients which can influence the electroclinical outcome

CONCLUSIONS

Multimodal imaging using nuclear medicine and electromagnetic source localization helps to improve the selection of surgical candidates, as well as surgical outcome in nonlesional drug-resistant focal epilepsy patients, particularly in children with neocortical epilepsy. In our view, the multimodal approach provides additional relevant information not only to determine the EZ in patients initially rejected for surgery but also to guide intracranial electrode implantation.

Future evidence-based imaging studies are required to clarify to what extent is the multimodal approach useful, rather than a single modality, and under what circumstances.

Cost-effectiveness studies are also necessary to identify the most cost-effective method.

Mario Fales (Italy)

THE NEVER-ENDING HISTORY OF EPILEPSY: FROM ANTIQUITY TO THE PRESENT

VICENTE VILLANUEVA (SPAIN)

WHAT TO EXPECT FROM THE NEW ANTI-EPILEPTIC DRUGS

What to expect from the new anti-epileptic drugs (adults)

Vicente Villanueva
Multidisciplinary Epilepsy Unit
Neurology Service
Hospital Universitario y Politécnico La Fe
Valencia (Spain)

Saturday 27th February 2016

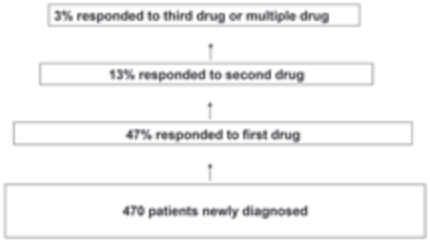
Summary

- Is there a need of new AEDs?
- Pros / cons new AEDs
- Last decade new AEDs
- Upcoming new AEDs

Summary

- **Is there a need of new AEDs?**
- Pros / cons new AEDs
- Last decade new AEDs
- Upcoming new AEDs

Early identification of refractory epilepsy



Kwan P et al. NEJM 2000

Patients seizure-free across the years

Drug regimens	N° of patients	SZ-free on monotherapy	Sz-free on combination	Total n sz-free	% sz-free
First	1098	543	0	543	49.5
Second	398	101	45	146	13.3
Third	168	26	15	41	3.7
Fourth	68	6	4	11	1.0
Fifth	32	1	3	4	0.4
Sixth	16	1	1	2	0.2
Seventh	9	1	1	2	0.2
Eighth	3	0	0	0	0.0
Ninth	2	0	0	0	0.0

Years sz free	2	5	10
%	69	61	52

Series	2000 (NEJM)	2012 (Neurology)
Seizure free	63	68

Brodie et al, NEJM 2000
Brodie et al, Neurology 2012

Effect of treatment changes in apparently drug-resistant epilepsy

- All adults with refractory epilepsy in a single epilepsy clinic who had started on a new AED
  - Active epilepsy (defined as ≥1 seizure per month in the previous 3 months)
  - History of epilepsy for ≥5 years and a history of treatment with ≥2 appropriate AEDs

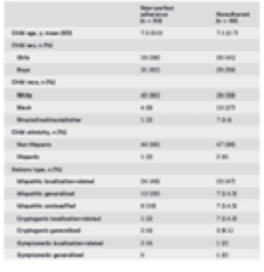
Seizure outcome following 265 / 448 medication changes in 155 / 139 people in follow-up (2004 / 2009)

Seizure outcome of AED change, n (%)	2004	2009
<50% reduction in seizure frequency	166 (63)	336 (75)
50%–99% reduction in seizure frequency	56 (21)	74 (17)
Seizure freedom (minimum 12 months without a seizure)	43 (16)	37 (8)
Total number of AED changes	265 (100)	448 (100)

Better outcome:
2004: ↓ previous AEDs, ↓ epilepsy duration, idiopathic epilepsy
2009: no seizures in 2004, ↓ previous AEDs, ↓ concomitant AEDs

Luciano AL, et al. Ann Neurol 2007;62:375–81
Neligan A, et al. Neurol Neurosurg Psychiatry 2012;83:610–13

Early pediatric antiepileptic drug nonadherence is related to lower long-term seizure freedom



Children who exhibited AED nonadherence during the first 6 months of therapy were 3.24 times more likely not to have achieved ≥1 year of seizure freedom at the 4 years postdiagnosis milestone compared to children in the near-perfect adherence group (p 0.02)

Modi AC et al, Neurology. 2014 Feb 25;82(8):671-3

Historical perspective

"The combinations of bromide with other drugs are of much value in the treatment of epilepsy. In many cases a greater effect is produced by the combination than by other drugs given alone"

(William Gowers, 1881)

The Marison Lectures
on
EPILEPSY.
Delivered before the Royal College of Physicians of Edinburgh.
by
WILLIAM ALDREN TURNER, M.D.,
LECTURE III.—Treatment of Epilepsy.

Bromide, Picrotoxin, and the Arseniate of Antimony.

Of the combinations of the bromides with other remedies I have found Gélineau's formula the most useful and satisfactory. It is prescribed in the form of *draguie* containing 1 gram of the potassium bromide, ½ mg. of picrotoxin, and ½ mg. of antimony arseniate. It has been used extensively in France, but does not seem to have been adopted to any extent in Britain. I have been in the habit of prescribing it during the past two years in those cases of epilepsy in which the pure salts of bromides are either not well borne or have been proved to be ineffective. In large doses picrotoxin is a professor of convulsions, leading to spasms of a tetanic character, with death in coma. In small doses it is theoretically supposed to lessen the tendency to cerebral vaso-constrictics, which is believed by some writers to be a fundamental factor in the causation of epileptic fits. I have used the *draguie* in all forms of epilepsy with considerable success.

Gowers W. Epilepsy and other chronic convulsive disorders, Churchill:London (1881)
Turner WA. Br Med J 1910;1:669–71

Historical perspective

40 patients, grand mal and / or partial epilepsy, **long-term treatment (≥2 AEDs)**
12 months' follow-up on polypharmacy → treatment reduction → 12 months' monotherapy

	Number of patients	
	Polytherapy	Monotherapy
Phenytoin	32	10
Primidone	19	3
Phenobarbitone	18	3
Carbamezapine	11	11
Sulthiame	4	0
Valproate	3	1
Clonazepam	2	0
Mesantoin	1	1
Pheneturide	1	0
Troxidone	1	0

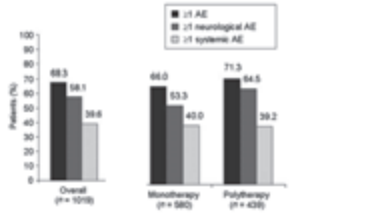
AED, antiepileptic drug

Effect on efficacy: reducing polytherapy to monotherapy	N
Total	29
Improved (≥50% reduction in seizure frequency)	16
Unchanged	8
Worse (≥50% increase in seizure frequency)	5

Combination therapy should be improved

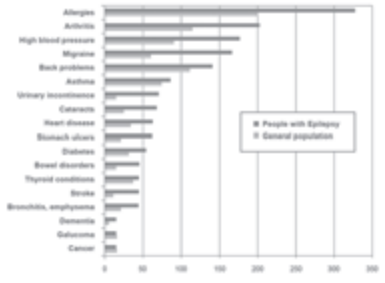
Shorvon SD, et al. Br Med J 1979;2:1023–5

Non-interventional surveillance study of adverse events in patients with epilepsy



Cramer J et al, Acta Neurol Scand 2011; 124: 13–21

Somatic Comorbidity of Epilepsy in the General Population in Canada



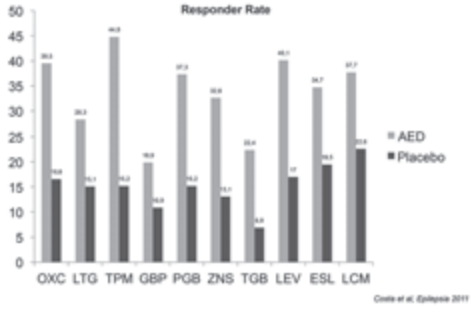
11

Adapted from Téllez-Zenteno JF, et al. Epilepsia. 46(12):1955-1962, 2005

Summary

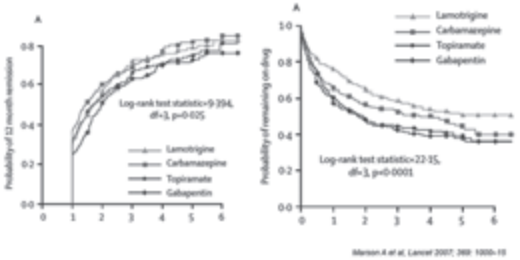
- Is there a need of new AEDs?
- **Pros / cons new AEDs**
- Last decade new AEDs
- Upcoming new AEDs

Randomized controlled trials: comparability of the new AEDs in refractory partial epilepsy



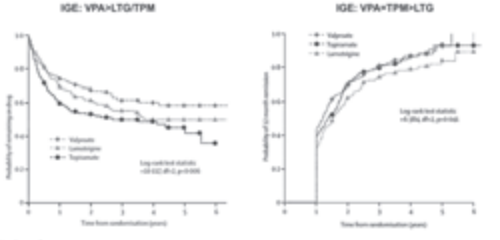
Cross et al, Epilepsia 2011

SANAD partial epilepsy: CBZ, GBP, LTG, OXC, TPM



Marson A et al, Lancet 2007; 369: 1000–15

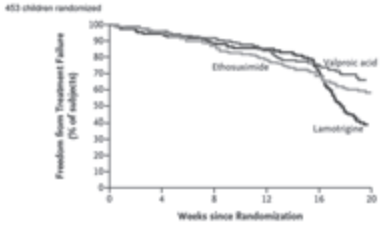
The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial



716 patients

Anthony G Marson et al, Lancet 2007; 369: 1016–26

Etosuximide, Valproic acid, and Lamotrigine in Childhood absences

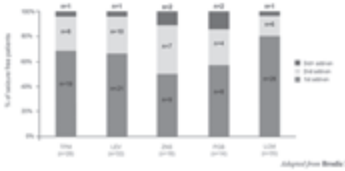


No. at Risk						
Ethosuximide	154	147	136	117	108	88
Lamotrigine	146	139	131	126	115	49
Valproic acid	146	139	132	124	111	86

Glauser T et al, N Engl J Med 2010;362:790-9.

Prospective audits with newer antiepileptic drugs in focal epilepsy: Insights into population responses?

AED	N	Seizure-free (%)	Withdrawal (%)	Side effects (%)
TPM	135	20.7	31.1	31.1
LEV	136	23.5	32.4	32.4
ZNS	141	12.8	41.8	41.8
PGB	136	10.4	50.4	50.4
LCM	160	21.9	22.5	22.5



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Adapted from **Brodie M** *et al, Epilepsy & Behavior 11 (2007) 73–79*

Main mechanisms of AED action

	Na	GABA	Ca	Glutamate	SV2A	CA	K
Carbamazepine	Fast	-	-	-	-	-	-
Lamotrigine	Fast	-	N,P/Q	-	-	-	-
Oxcarbazepine	Fast	-	-	-	-	-	-
Phenytoin	Fast	-	-	-	-	-	-
Eslicarbazepine	Slow	-	-	-	-	-	-
Lacosamide	Slow	-	-	-	-	-	-
Ethosuximide	-	+	T	-	-	-	-
Gabapentin	-	-	α2δ1	-	-	-	-
Pregabalin	-	-	α2δ1	-	-	-	-
Benzodiazepines	-	Chloride	-	-	-	-	-
Phenobarbital	-	Chloride	-	-	-	-	-
Tiagabine	-	Re	-	-	-	-	-
Vigabatrin	-	TA	-	-	-	-	-
Levetiracetam	-	-	-	-	+	-	-
Retigabine	-	-	-	-	-	-	Kv7
Perampanel	-	-	-	AMPA	-	-	-
Felbamate	Fast	-	L	NMDA	-	-	-
Topiramate	Fast	+	L	Kainate	-	+	-
Valproic acid	Fast	+	T	-	-	-	+
Zonisamide	Fast	+	T	-	-	+	-

Please refer to the full prescribing information in your country before prescribing

AMPA, 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid
GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartic acid
Re, reuptake; SV2A, synaptic vesicle glycoprotein 2A
TA, transaminase;

Lason W, et al. Pharmacol Rep 2011;63:271–82
White HS, et al. Infect Disord Drug Targets 2007;7:217–226
Levy RH, et al. In Antiepileptic Drugs (5th ed). Lippincott Williams & Wilkins (2002)
Cheah C, et al. Neurochem Int 2012 Mar 10
Rothlingshuis C. Ther Clin Risk Manag 2008;4:1707–26
Stockflows Mc. abstract p433. ECE London 2012

Does Mechanism of Drug Action Matter to Inform Rational Polytherapy in Epilepsy?

1. Studies in animals: AED combinations are more effective when using **drugs with different mechanisms of action**
2. The most effective combination **Drug with a single mechanism of action and another with multiple mechanisms of action**
3. Studies in humans: AED combinations between a **blocker of voltage-gated sodium channels and a drug with multiple mechanisms of action**

Ouassini G, **Bagh C**. CNS Neurol Disord Drug Targets. 2010 May 1;10(3):408-30

Unknown physiopathology of drug-responsive seizures…so how to combine drugs?

"Unless and until we have direct evidence in what way, if any, drug-resistant seizures are different from drug responsive seizures, it may be worthwhile to consider that the failure in treating drug-resistant seizures is related, at least in part, to the failure of current drugs in targeting the mechanisms underlying epilepsy"

Adapted from Loscher W et al, Epilepsia 2011; Schmidt D et al, Epilepsy Currents 2009; Schmidt et al, Epilepsy & Behaviour 2011; Loscher W et al, Nature Reviews 2012

Cholesterol synthetic pathway

Mintzer et al, Epilepsia 2009

AED induction: Real-world clinical practice

160 adult patients on AED monotherapy, enzyme inducers (CBZ, PHT), enzyme-inhibitor (VPA), noninducer (LTG) > 2 years, and 60 controls

	LTG	CBZ	PHT	VPA	Controls	p-Value
Total Cholesterol (mM)	4.85	5.67	5.88	4.94	4.84	<0.0001
HDL-Cholesterol	1.55	1.64	1.61	1.46	1.55	0.355
LDL-Cholesterol	2.83	3.29	3.51	2.84	2.83	<0.0001
Trygliceride (mM)	1.14	1.17	1.48	1.47	1.06	0.022
Right CCA IMT	0.521	0.586	0.643	0.571	0.490	<0.0001
Left CCA IMT	0.514	0.574	0.635	0.567	0.519	<0.0001
Mean CCA IMT	0.518	0.580	0.639	0.571	0.505	<0.0001

CCA, common carotid artery; IMT, intima media thickness

Chuang et al, Epilepsia 2012; 53: 120-8

AED Interactions in Clinical Practice: old AEDs

AED	CYP (+)	CYP (-)	(+) by CYP	(-) by CYP	Protein binding	Other
Carbamazepine	+++	++	+ (+ auto)	++	++	-
Ethosuximide	-	-	++	++	-	-
Phenobarbital	++	-	+	+	-	+ (antiacids ↓ absortion)
Phenytoin	+++	-	+	++	+++	+ (antiacids ↓ absorption)
Primidone	++	+	+	+	-	-
Valproate	-	++	-	-	+++	+ (glucuronidation; Food ↓ absorption)

St. Louis. Current Neuropharmacology 2009

Drug Interactions with the Newer AEDs-between AEDs-

AED	Propensity to interact with other AEDs		Number of interactions	
	Affects other	Affected by other	PK	PD
Eslicarbazepine	Minimal	Minimal	9	1
Felbamate	Minimal	Minimal	15	0
Gabapentin	Non-Interacting	Non-interacting	2	0
Lacosamide	Non-interacting	Minimal	4	5
Lamotrigine	Minimal	Moderate	17	5
Levetiracetam	Non-interacting	Minimal	8	3
Oxcarbazepine	Minimal	Minimal	14	0
Perampanel	Minimal	Moderate	10	0
Pregabalin	Non-interacting	Non-interacting	6	0
Retigabine	Minimal	Minimal	6	0
Rufinamide	Minimal	Minimal	13	0
Stiripentol	Substantial	Substantial	10	0
Tiagabine	Minimal	Minimal	5	1
Topiramate	Minimal	Minimal	10	4
Vigabatrin	Non-interacting	Non-interacting	3	3
Zonisamide	Minimal	Minimal	4	0

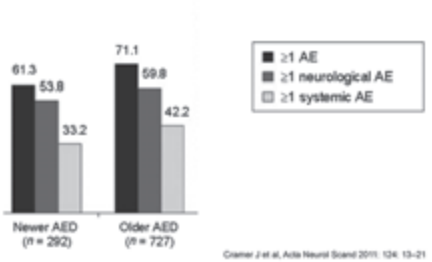
Patsalos Ph, Clin Pharmacokinet (2013) 52:927–966

Pharmacokinetic Interactions: AEDs vs Drugs Used to Treat Non-Epilepsy Disorders

AED	N	Non-AEDs involved
Eslicarbazepine	5	Digoxin, metformin, oral contraceptives, simvastatin, warfarin
Felbamate	2	Oral contraceptives, warfarin
Gabapentin	5	Aluminum hydroxide and magnesium hydroxide,cimetidine, hydrocodone, morphine, naproxen
Lacosamide	0	-
Lamotrigine	22	Acetaminophen, antituberculous agents (rifampicin, isoniazid, ethambutol), aripiprazole, atanazavir/ritonavir, atorvastatin, fluoxetine, hormone replacement therapy, lithium, lopinavir/ritonavir, olanzapine, oral contraceptives, orlistat, sertraline, quetiapine
Levetiracetam	1	Probenecid
Oxcarbazepine	7	Cyclosporine, glufosfamide, imatinib, oral contraceptives, verapamil, viloxazine
Perampanel	2	Ketoconazole, oral contraceptives
Pregabalin	0	-
Retigabine	1	Ethanol
Rufinamide	2	Oral contraceptives, triazolam
Stiripentol	0	-
Tiagabine	2	Cimetidine gemfibrozil
Topiramate	18	Amitriptyline, diltiazem, glibenclamide (glyburide), haloperidol, hydrochlorothiazide, imatinib, lithium, metformin, oral contraceptives, pioglitazone, posaconazole,propranolol, risperidone, sumatriptan
Vigabatrin	0	-
Zonisamide	1	Risperidone

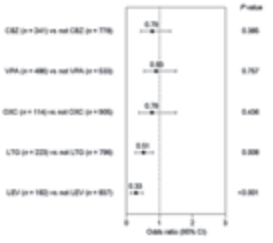
Patsalos Ph, Clin Pharmacokinet (2013) 52:1045–1061

Non-interventional surveillance study of adverse events in patients with epilepsy



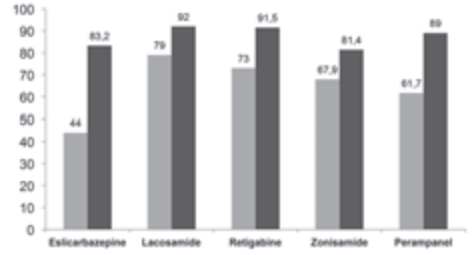
Cramer J et al, Acta Neurol Scand 2011: 124: 13–21

Non-interventional surveillance study of adverse events in patients with epilepsy



Cramer J et al, Acta Neurol Scand 2011: 124: 13–21

RCT: Side effects withdrawal



Ben-Menachem and Falter 2000; Elger et al 2009; Gil-Nagel et al 2009; Ben-Menachem et al 2007; Ben-Menachem and Falter 2000; Cereghino et al 2000; Shorvon et al 2000; Brodie et al 2012; French et al 2011; Brodie et al 2005; Semrádová, Villanueva et al; Acta Neurol Scand 2013

Side effects: Avoid overlapping toxicity

Adverse effect	More favourable	Less favourable	Comments
Hepatic disease	Gabapentin Levetiracetam Pregabalin	Phenytoin Phenobarbital Carbamazepine Valproate	Valproate can be hepatotoxic and cause platelet dysfunction
Skin rash	Valproate Gabapentin Topiramate Levetiracetam Pregabalin	Phenytoin Phenobarbital Carbamazepine Lamotrigine Oxcabazepine	Risk of rash is lower with oxcarbazepine than with carbamazepine
Cognition	Lamotrigine Lacosamide	Phenytoin Phenobarbital Topiramate Zonisamide	Cognitive effects are far less with topiramate 100 mg/d monotherapy. Most AEDs at high doses can adversely effect cognition
Sedation	Lamotrigine	Phenytoin Phenobarbital Levetiracetam Gabapentin Oxcabazepine Tiagabine Topiramate Zonisamide Pregabalin	Agents are described as sedating if somnolence is one of the five most common adverse effects
Weight	(Weight loss) Topiramate Zonisamide	(Weight gain) Gabapentin Pregabalin Valproate	Weight loss may not always be considered a favourable outcome

Privitera M. Am J Manag Care 2011; 17: S193-202

RCT VS Real-life: Optimizing Dose

- Doses used in **regulatory trials** are frequently different from those subsequently found to be effective in **routine clinical practice**
  - Eg. Gabapentin doses originally studied was 900–1800 mg daily and subsequently licensed was up to 2400 mg daily but is prescribed in higher doses up to 4800 mg daily.
- Sometime trials can use **higher dose and aggressive titration** to demonstrated efficacy.
  - Eg. Topiramate schedules (50 mg weekly) and maintenance doses (200–800 mg daily) in regulatory studies were more robust than now recommended producing high responder rates but at the expense of numerous adverse events

Seizure 2003; 12: 413–443

Side effects Lamotrigine: Clinical trials

Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures

G J Schapel, R G Beran, P J E Yiels, S F Berkovic, M L Maddibd, P M Donegan, W C Yiels, G Davies

Journal of Neurology, Neurosurgery, and Psychiatry 1993;56:648–653

Table 3 Rates of occurrence of adverse experiences on placebo and lamotrigine

Adverse experience	Incidence on placebo (%)	Incidence on lamotrigine (%)	95% CI for placebo–lamotrigine
Ataxia	7	27	(−39, 2)
Dizziness	9	23	(−39, 0)*
Nausea	7	17	(−34, 5)
Headache	4	15	(−33, 3)
Tiredness	4	13	(−31, 4)
Rash	0	13	(−26, 0)†
Diplopia	22	13	(−4, 35)
Dyskinesia	4	13	(−29, 4)
Pain	3	10	(−26, 5)
Vision abnormality	0	10	(−26, 0)
Rhinitis	0	7	(−26, 0)
Somnolence	13	7	(−4, 31)

Lamotrigine High-Dose Tolerability and Safety in Patients with Epilepsy: A Double-Blind, Placebo-Controlled, Eleven-Week Study

Matsuo, Fumisuke; Gay, Patricia; Madsen, Jack; Tolman, Keith G.; Rollins, Douglas E.; Risner, Marcus E.; Lai, Allen A.†

Epilepsia 1996; 37 (5): 457–62

AE	Treatment group: Add-on LTG (N = 5), incidence (%)	Add-on placebo (N = 4), incidence (%)
Headache	5 (63)	3 (75)
Drowsiness	5 (63)	2 (50)
Faintness	4 (50)	2 (50)
Diplopia	4 (50)	0
Dyspepsia	1 (13)	2 (50)
Nasal congestion	1 (13)	2 (50)
Fatigue	0	2 (50)
Flushing	0	2 (50)

AE, adverse event; LTG, lamotrigine.

Adverse events…can be not that bad
Long-term experience (48 months) with LTG in clinical practice

Adverse event	Frequency	%
Dizziness	41	15.7
Headache	22	8.4
More active	**20**	**7.7**
Skin reaction	19	7.3
Sleeping complaints/ insomnia	19	7.3
Sleeping complaints / sleepiness	17	6.5
Vision disorders	16	6.1
Exhaustion	16	6.1
More clear/more responsive	12	4.6
Gastrointestinal complaints	10	3.8
Mood disorders—agitation	9	3.4
Other non-CNS	8	3.1

Beviens HPP et al, Epilepsy & Behavior 12 (2008) 260–268

Rare adverse events

- The detection of rare **idiosyncratic effects** of *new* drugs is a critical function of large real world studies.
- Even for AED arena, many examples exist of serious AEs that were uncovered only in the **postapproval period.**
- Examples:
  - **Hepatic failure and pancreatitis** caused by **valproic acid**
  - **Aplastic anemia and hepatic failure** caused by **felbamate**
  - **Visual field** defects caused by **vigabatrin**
- Other less **serious concerns** detected or better quantified later included:
  - catastrophic **safety hypohydrosis** caused by **topiramate and zonisamide (ZNS)**
  - **weight changes** caused by **VPA, GBP, TPM, and ZNS**

Epilepsia, 43 (8):851–855, 2002

Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry

	Sample size	Congenital malformation up to birth to 2 months	Congenital malformation up to 1 year
CBZ			
<400	148	2 (1.3% 0.16–4.80)	5 (3.4% 1.11–7.71)
≥400 to < 1000	1047	34 (3.2% 2.26–4.51)	56 (5.3% 4.07–6.89)
≥1000	207	16 (7.7% 4.48–1.25)	18 (8.7% 5.24–13.39)
LTG			
<300	836	14 (1.7% 0.92–2.79)	17 (2.0% 1.19–3.24)
≥300	444	16 (3.6% 2.07–5.79)	20 (4.5% 2.77–6.87)
PB			
<150	166	7 (4.2% 1.71–8.50)	9 (5.4% 2.51–10.04)
≥150	51	7 (13.7% 5.70–26.26)	7 (13.7% 5.70–26.26)
VPA			
<700	431	18 (4.2% 2.49–6.52)	24 (5.6% 3.60–8.17)
≥700 to <1500	480	43 (9.0% 6.56–11.88)	50 (10.4% 7.83–13.50)
≥1500	99	23 (23.2% 15.33–32.79)	24 (24.2% 16.19–33.89)

Tomson et al, Lancet Neurol 2010

Teratogenicityof new AEDs

Risk of foetal malformations in pregnancies in **exposed women** (n = 1572) and **not exposed** (n = 153)

	Number	% Malformed	RR	95% CI
CBZ	346	5.5	1.68	0.64, 4.42
VPA	253	**13.8**	**4.23**	**1.68, 10.57**
PHT	41	2.4	1.49	0.30, 7.42
CZP	24	0	0	
PB/PRM	4	0	0	
ESM	4	0	0	
VGB	1	0	0	
BZPs	3	0	0	
LTG	307	4.6	1.40	0.51, 3.80
TPM	42	2.4	0.73	0.09, 6.07
LEV	82	2.4	0.75	0.15, 3.76
GBP	14	0	0	
TGB	1	0	0	
OXC	17	5.9	1.8	0.22, 14.52

Vajda FE et al, Acta Neurol Scandinavica, 2014

Number of intakes

MoA	1 intake	2 intakes	3 intakes
SCB	ESL, PHT	OXC, LCM, LTG	CBZ
Ca channel		PGB	ESX, GBP
GABA	PB	VGB	BZD, TGB
SV2A		LEV	
Glutamate	PMP	FBM	
Others	ZNS	TPM	VPA, RTG

Claxton et al, Clin Ther 2001
Faught E et al, Epilepsy and Behaviour 2012

Add-on treatment choices considering co-morbidities and special situations

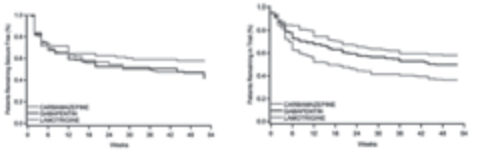
		Epilepsies with focal seizures		
		1st choice	2nd choice	Avoid
Co-morbidities	Migraine	TPM, ZNS	LTG, VPA	
	Anxiety	GBP, PGB	LTG, ZNS, LCS	
	Depression	LTG	OXC, VPA	LEV, TPM, ZNS, GABAergics,
	Cognitive disturbances	LTG, OXC	ZNS, LEV, VPA (slow titration)	GABAergics, TPM
	Psychosis	CBZ, VPA	LTG, OXC, PGB	LEV
Special situations	Photosensitivity			
	Women of childbearing potential	LTG, CBZ	LEV, TPM, BZD	VPA, PB, PHT
	If possible avoid polytherapy			
	Elderly people	LTG, GBP, LEV	VPA, TPM, ZNS	PB, PHT
	Patients under immunosuppressants	LTG, LEV, VPA	ZNS, GBP, PGB	Enzyme-inducers (Especially CBZ, PHT, immunosuppressant screening)
	Renal insufficiency	LTG, OXC, CBZ, VPA	LEV	TPM, ZNS (renal calculi)
	Hepatic insufficiency	LTG, LEV, GBP	PGB, TPM, ZNS	VPA, Enzyme-inducers, GABAergics
	Insomnia	PGB, GBP	LEV	LTG (sedative)
	Over weight	ZNS, TPM	LTG, LEV (both are neutral), ACZ	CBZ, VPA, PGB, GBP

57

Adapted from Crede B et al, Expert Opin. Pharmacother. (2010);11(7):1057-1067

Elderly onset epilepsy

593 patients, >65 years, GBP 1,500 mg/day, LTG 150 mg/day, CBZ 600 mg/day



Rowan AJ, Neurology 2005;64:1868–1873

Add-on LEV in elderly patients with focal epilepsy who failed monotherapy

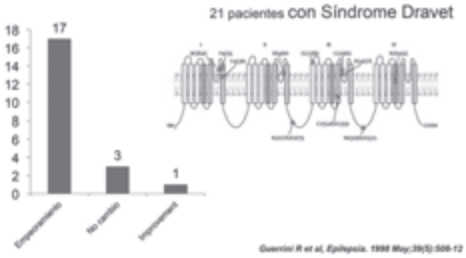
Open-label study: 491 patients ≥ 65 years
LEV dose range was 1000–3000 mg per day
Follow-up visits after 3, 6 and 12 months

Werham et al, Seizure 2011

Side effects	n
Fatigue	6
Restlessness	6
Depressive disorder	5
Gait instability	5
Vertigo	5
Aggressiveness/irritability	4
Sleep disturbance	3
Tremor	3
Allergic rash	2
Drowsiness	2
Mental slowing	2
Pruritus	2
Urinary tract infection	2
Worsening of hypertension	2
Adaptative disorder	1
Cerebrovascular insufficiency	1
Confusion	1
Disturbance of memory	1
Headache	1
Incontinence	1
Joint pain	1
Nausea	1
Paranoid disorder	1
Polyneuropathy	1
Tachycardia	1
Weight gain	1

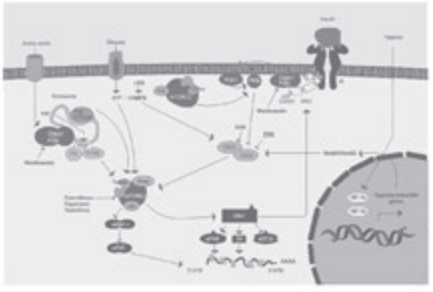
Lamotrigina y empeoramiento de crisis en Síndrome de Dravet

21 pacientes con Síndrome Dravet



Guerrini R et al, Epilepsia. 1998 May;39(5):508-12

Role of mTOR inhibitors in tuberous sclerosis complex



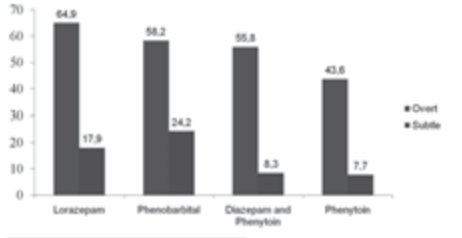
Adapted from Curatolo P, et al. Current Neuropharmacology, 2012, 10, 404-415

Established status epilepticus

	Starting dose	Maintenance dose	Blood levels in SE
PHT	15-20 mg/Kg (50 mg/min)	4-6 mg/kg/dia (After 12 h)	20-40 µg/ml
VPA	25-45 mg/kg 4-6 mg/kg/min)	0.5-1 mg/kg/h (After ¼ h)	50-150 µg/ml
PB	10-20 mg/kg (100 mg/min)	2-4 mg/kg/dia (After 12-24 h)	15-40 µg/ml
LEV	20 mg/Kg 25/3000 mg/bolus	20-30 mg/kg/24 h (after 12 h)	25-60 mg/l
LCM	200-400 mg/bolus	200 mg/12 h (after 12 h)	

Spanish Neurological Society Guidelines, SEN 2012

A comparison of four treatments for generalized status epilepticus



No of patients				
Overt	97	91	95	101
Subtle	39	33	36	26

Treiman et al, NEJM 1998; 339:792-8

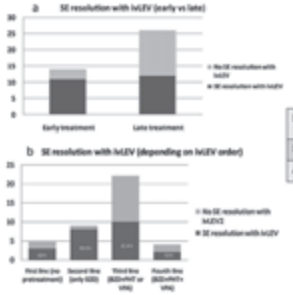
Adverse events

Type of GCSE and AE	Lorazepam	Phenobarbital	Diazepam and phenytoin	Phenytoin
Overt				
No. of patients	97	91	95	101
Hypoventilation (%)	10.3	13.2	16.8	9.9
Hypotension (%)	25.8	34.1	31.6	27.0
Cardiac-rhytm disturbances (%)	7.2	3.3	2.1	6.9
Subtle				
No. of patients	39	33	36	26
Hypoventilation (%)	12.8	15.2	2.9	7.7
Hypotension (%)	59.0	48.5	58.3	57.7
Cardiac-rhytm disturbances (%)	7.7	9.1	5.6	0.0

GCSE: Generalized convulsive status epilepticus
AE: adverse events

Treiman et al, NEJM 1998; 339:792-8

Efficacy of intravenous levetiracetam as add-on treatment in status epilepticus: a multicenter observational study



40 patients Status epilepticus

Side effects	6/40	15%
Somnolence	5/6	83%
Agitation	1/6	17%

Aiguabella M et al, Seizure 2011; 20: 60-64

LCM IV: Adverse events

Adverse events	N (%)
Somnolence	8 (8.2%)
Nauseas	4 (4.1%)
Dizziness	3 (3.1%)
Diplopia	1 (1%)
Blurred vision	1 (1%)
Vomiting	1 (1%)
PR prolongation	1 (1%)
AV Block	1(1%)

*** Bisoprolol + amlodipine**

Garcés M et al, Epilepsy Behaviour 2014

The Established Status Epilepticus Trial 2013

- Patients **older than 2 years of age** with witnessed, clinically apparent seizures in the ED for at least 5 min after receiving an adequate dose of benzodiazepines for generalized, tonic–clonic convulsion(s)
- Adequate **doses of benzodiazepines** for this study are: diazepam 10 mg intravenous (IV), lorazepam 4 mg IV, or midazolam 10 mg IV or intramuscular (IM) for subjects >40 kg; and diazepam 0.3 mg/kg IV, lorazepam 0.0.1 mg/kg IV, or midazolam 0.3 mg/kg IV or IM for subjects between 10 and 40 kg
- The study drugs will be formulated in the **following strengths**: **fPHT** 16.66 mg/ml, **VPA** 33.33 mg/ml, and **LVT** 50 mg/ml so as to allow identical infusion times in order to maintain blinding

Bleck T et al, Epilepsia, 54(Suppl. 6):89–92, 2013

Summary

- Is there a need of new AEDs?
- Pros / cons new AEDs
- **Last decade new AEDs**
- Upcoming new AEDs

AED approval by regulatory agencies: last decade

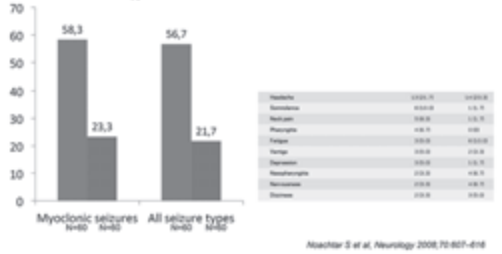
Antiepileptic drug	EMA	FDA
Zonisamide	2005	2000
Rufinamide	2005	2008
Lacosamide	2008	2008
Eslicarbazepine acetate	2009	2013
Retigabine	2011	2011
Perampanel	2012	2012

EMA: European Medicines Agency
FDA: Food and Drug Administration

Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures

Randomized, double-blind, placebo-controlled multicenter trial

Adjunctive treatment with LEV 3.000 mg/day in idiopathic generalized epilepsy (myoclonic seizures) Add-on to monotherapy



Noachtar S et al, Neurology 2008;70:607–616

KOMET: an unblinded, randomised, two parallelgroup, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy

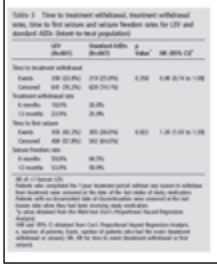
Table 2 Time to treatment withdrawal and time to first seizure by VPA and CBZ strata for subgroups of patients with focal or generalised seizures only (intent-to-treat population excluding unclassified/unknown seizure types)

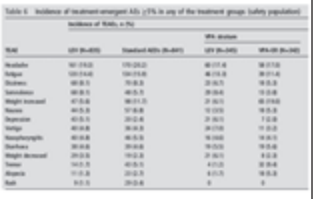
	LEV		Standard AEDs		
	N	Event	N	Event	HR (95% CI)*
Time to treatment withdrawal					
VPA stratum					
Focal seizures only	99	75	91	70	0.75 (0.57 to 1.44)
Generalised seizures only	224	54	232	49	1.16 (0.79 to 1.71)
CBZ stratum					
Focal seizures only	418	109	440	133	0.84 (0.65 to 1.08)
Generalised seizures only	46	5	40	8	0.49 (0.16 to 1.49)
Time to first seizure					
VPA stratum					
Focal seizures only	99	44	91	37	1.03 (0.67 to 1.60)
Generalised seizures only	224	76	232	67	1.28 (0.93 to 1.78)
CBZ stratum					
Focal seizures only	418	198	440	172	1.24 (1.01 to 1.52)
Generalised seizures only	46	15	40	10	1.17 (0.53 to 2.60)

*HR of <1 favours LEV.
AED, antiepileptic drug; CBZ, carbamazepine; LEV, levetiracetam; VPA, sodium valproate; N, number of patients; Event, number of patients who had the event (treatment withdrawal or seizure); HR, HR for time to event (treatment withdrawal or first seizure).

Trinka E, et al. J Neurol Neurosurg Psychiatry 2013;84:1138–1147

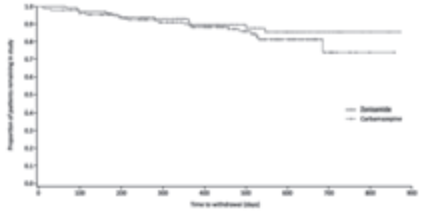
KOMET: an unblinded, randomised, two parallelgroup, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy





Trinka E, et al. J Neurol Neurosurg Psychiatry 2013;84:1138–1147

Long-term safety and efficacy of zonisamide versus carbamazepine monotherapy for treatment of partial seizures in adults with newly diagnosed epilepsy: Results of a phase III, randomized, double-blind study



Baulac et al, Epilepsia 2014

Original article

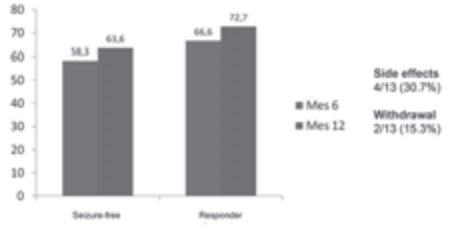
Efficacy and tolerability of zonisamide in idiopathic generalized epilepsy

Trece pacientes con EGI tratados con ZNS entre 2006-2008

6 months: 12/13 (92.3%)

12 months: 11/13 (84.6%)

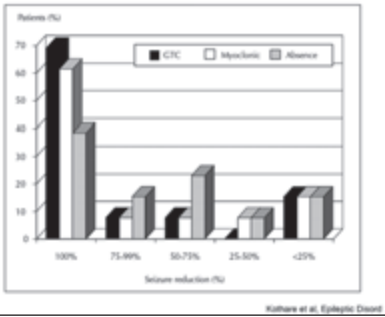
Better outcome absences and GTCS



Side effects
4/13 (30.7%)

Withdrawal
2/13 (15.3%)

Zonisamide: Juvenile myoclonic epilepsy

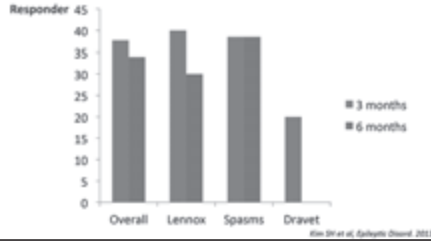


Kothare et al, Epileptic Disord 2004; 6: 267-70

Short-term efficacy and tolerability of rufinamide adjunctive therapy in children with refractory generalised epilepsy

We evaluated the efficacy and tolerability of rufinamide adjunctive therapy in children with **refractory generalised epilepsy**

20 patients with Lennox-Gastaut, 5 with Dravet, and 28 with unclassified refractory GE.

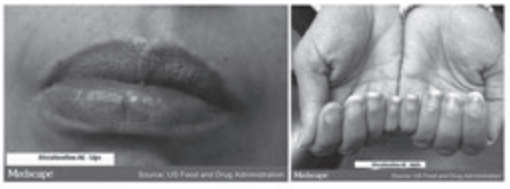


Kim SH et al, Epileptic Disord. 2013 Mar;15(1):49-54

Therapeutic Advances in Drug Safety — Review

New antiepileptic medication linked to blue discoloration of the skin and eyes

Sarah Clark, Alexandra Antell and Kimberly Kaufman



Pediatric Neurology

Clinical Observations

Ring Chromosome 20: A Pediatric Potassium Channelopathy Responsive to Treatment with Ezogabine

Diana J. Walleigh MD, Agustin Legido MD, Ignacio Valencia MD*

ABSTRACT

BACKGROUND: Ring chromosome 20 is a genetic disorder characterized by intractable epilepsy, behavioral problems, and cognitive deficit. The potassium channel–coding gene KCNQ2 is localized at the locus q13.3 on the chromosome 20, the most common site where the ring occurs. Ezogabine is the first potassium channel opener marketed in the United States. METHODS: We describe an 8-year-old girl with mosaic ring chromosome 20 and refractory epilepsy who had a remarkable improvement in seizure control with ezogabine. CONCLUSIONS: This is the first report using the new antiepileptic drug ezogabine to treat pediatric epilepsy. We hypothesize that ring chromosome 20 patients have epilepsy related to abnormalities in the potassium channels, making it susceptible for treatment with potassium channel openers.

Keywords: ring chromosome 20, epilepsy, ezogabine, potassium channel openers

Pediatr Neurol 2013; 49: 368-369

LACO-EXP: Inclusion /exclusion criteria

- **Inclusion criteria**
  - Written informed consent by the patients or legal representative
  - Patients older than **18 years** and reliable to follow the protocol
  - Diagnosis of **partial seizures**.
  - Treated with partial seizures according to **clinical practice (on-label)**
  - All the patients had **at least 1 partial seizure** in the year prior to inclusion.
- **Exclusion criteria**
  - Patients enrolled in other protocols with AED or medical devices.
  - Antecedents of alcoholism or drug abuse in the year before

Villanueva V et al. Epilepsy Behavior 2013; 29: 349-56

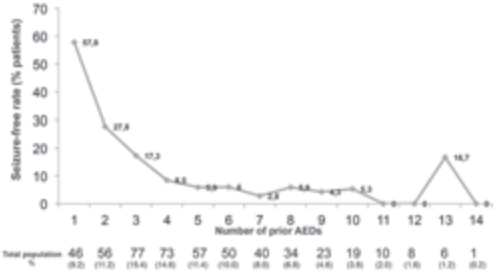
Patients

Characteristics	Patients (N=500)
Female , n (%)	232 (46.4)
Age, mean (DS)	42.4 [18-88]
Time since epilepsy onset, mean (SD) years	21.5 [14.3]
Monthly seizure frequency	
Mean (SD)	10.5 (24.2)
Median	3.3
Prior AED	
Mean	5.0 (2.9)
Median	4

Characteristics	Patients (N=500)
Epilepsy type, n (%)	
Frontal	126 (25.2)
Temporal	266 (53.2)
Parietal	15 (3.0)
Occipital	10 (2.0)
Unknown lobe	83 (16.6)
Etiology	
Cryptogenic	174 (34.8)
Vascular	34 (6.8)
MTS	76 (15.2)
CDM	43 (8.6)
Perinatal hypoxia	42 (8.4)
Tumor	41 (8.2)
Trauma	33 (6.6)
Brain infection	22 (4.4)
Other	35 (7)

Villanueva V et al. Epilepsy Behavior 2013; 29: 349-56

Seizure-free: Prior AEDs



Villanueva V et al. Epilepsy Behavior 2013; 29: 349-56

Results: Adverse events

Adverse events	6-12 months n (%)
Dizziness	97 (20%)
Drowsiness / Weakness	57 (11.8%)
Blurred vision / diplopia	32 (6.6%)
Gait disturbance (ataxia)	31 (6.4%)
Headache	17 (3.5%)
Irritability	12 (2.5%)
Gastrointestinal disturbances	11 (2.2%)
Mental slowness/memory disturbances	10 (2.1)
Skin reaction	6 (1.2%)
Other	18 (4.8%)

Other	6-12 months n (%)
Tremor	4 (0.8%)
Paresthesias	2 (0.4%)
Weight loss	1 (0.2%)
Sexual dysfunction	3 (0.6%)
Depression	2 (0.4%)
Leg stiffness	1 (0.2%)
Hallucinations	1 (0.2%)
Not specified	4 (0.8%)

No deaths no serious adverse events

Villanueva V et al. Epilepsy Behavior 2013; 29: 349-56

Seizure-free at 12 months: AED combination

AED combination*	Seizure-free n/N(%)
LEV	**22/67 (32.8%)**
CBZ + LEV	3/32 (9.4%)
CBZ	6/24 (25%)
VPA	**8/17 (47.1%)**
CLB + LEV	2/17 (11.8%)
CBZ + CLB	3/15 (20%)
OXC	2/14 (14.3%)
LTG	**3/11 (27.3%)**
CBZ + ZNS	1/8 /(12.5%)
LEV + VPA	1/8 (12.5%)
LEV + OXC	2/7 (28.6%)
GBP	4/5 (80%)
CLB + ESL	1/5 (20%)
LEV + PB	1/5 (20%)

AED combination	Seizure-free n/N (%)
None	3/3 (100%)
TPM + VPA	2/3 (66.7%)
CBZ + PB	1/3 (33.3%)
CLZ + LEV	1/3 (33.3%)
OXC + VPA	1/3 (33.3%)
PB	1/3 (33.3%)
LEV + LTG + OXC	1/2 (50%)
VPA + ZNS	1/2 (50%)
CLZ + LEV + ZNS	1/1 (100%)
PRM + TPM + VPA	1/1 (100%)

Not statistically significant

*AEDs added to LCM

Villanueva V et al. Epilepsy Behavior 2013; 29: 349-56

Monotherapy Historical Control

FULL-LENGTH ORIGINAL RESEARCH

Historical control monotherapy design in the treatment of epilepsy

*Jacqueline A. French, †Steven Wang, ‡Bob Warnock, and §Nancy Tramble

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Summary

Purpose: Monotherapy approvals have been difficult to obtain from the U.S. Food and Drug Administration (FDA), and have almost all been achieved using a trial design entitled "withdrawal to monotherapy" in treatment-resistant patients, which employs a so-called "pseudo-placebo" as a comparator arm. The authors submitted a white paper to the FDA advocating use of a virtual placebo historical control as an alternative to pseudo-placebo. Such an approach reduces patient risk that would result from exposure to pseudo-placebo. In this article, we present the data submitted to the FDA to justify a historical control.

Methods: We analyzed individual patient data from eight previously completed withdrawal to monotherapy studies, which we determined had similar design. All studies employed percent meeting predetermined exit criteria (denoting worsening of seizure control) as the outcome measure. Kaplan–Meier estimates of the percent exiting were calculated at 112 days.

Results: The percent meeting exit criteria were uniformly high, ranging from 74.9–89.9%. The eight studies appear to meet the criteria set forth for use of historical control. The estimate of the combined percent exit based on the nonlinear mixed-effects model is 85.1%, with a lower bound of the 95% prediction interval of 80.3%, and 75.3% for an 80% prediction interval.

Conclusions: There is justification for proposing that these data can serve as a historical control for future monotherapy studies, obviating the need for a placebo/pseudo-placebo arm in trials intended to demonstrate the efficacy of approved drugs as monotherapy in treatment-resistant patients.

KEY WORDS: Clinical trial design, Epilepsy, Antiepileptic drugs, Monotherapy.

Epilepsia, 51(10):1934–1943, 2010

ESLIBASE: Design

- **Retrospective, multicenter**, non-interventional study designed to assess the **efficacy and tolerability** of ESL in patients with focal seizures over **1 year**

Villanueva V et al, Epilepsy Research 2014; 108(7): 1243-52

Demographic characteristics

Characteristic	All patients (n= 327)
Female / Male	157 (48%) / 170 (52%)
Age at baseline, mean, range	41,9 (14-87)
Age at epilepsy onset, median, IQR	17 (7-29)
Duration of epilepsy, median, IQR	19 (9-33)
Monthly seizure frequency Median, IQR Median, SD	 4 (2-10) 9,7 (18.2)
Number of previous AEDs Mean, SD Median	 5,28 (3,24) 5

Villanueva V et al, Epilepsy Research 2014; 108(7): 1243-52

Adverse events (II)

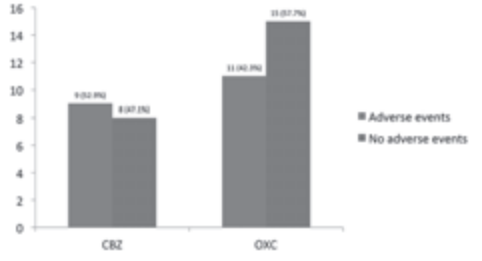
Adverse events	N (327)
Dizziness/Nausea	37 (11.3%)
Somnolence	20 (6.1%)
Ataxia	17 (5.1%)
Rash / pruritus	12 (3.6%)
Bradipsychia/ Memory disturbance	11 (3.3%)
Hyponatremia	9 (2.7%)
Tremor	7 (2.1%)
Diplopia/Blurred vision	7 (2.1%)
Weight increase	4 (1.2%)

Adverse events	N (327)
Other	
Headache	3 (0.9%)
Insomnia	3 (0.9%)
Edema	2 (0.6%)
Paresthesia	2 (0.6%)
Gastric disturbances	2 (0.6%)
Aggressiveness	2 (0.6%)
Peri-ictal psychosis	2 (0.6%)
Anxiety	1 (0.3%)
Depression	1 (0.3%)
Emotional Lability	1 (0.3%)
Sexual dysfunction	1 (0.3%)
Restlessness	1 (0.3%)
Asthenia	1 (0.3%)
Visual hallucinations	1 (0.3%)
Polyuria	1 (0.3%)
AST/ALT increase	1 (0.3%)
Status	1 (0.3%)

No deaths, no unexpected side-effects

Villanueva V et al, Epilepsy Research 2014; 108(7): 1243-52

Adverse events:
Patients that switched OXC/CBZ to ESL because of AE



CBZ N=17 OXC N=26

Villanueva V et al, Epilepsy Research 2014; 108(7): 1243-52

FULL-LENGTH ORIGINAL RESEARCH

Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: Results of a phase III, double-blind, randomized, placebo-controlled trial

Dr. Michael R. Sperling, a Boston Kevin Professor of Neurology at Thomas Jefferson University

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Fydata study

- **Multicenter, retrospective, 1-year,** observational study which examined the efficacy and safety of adjunctive perampanel in patients with partial-onset seizures across hospital centers in Spain

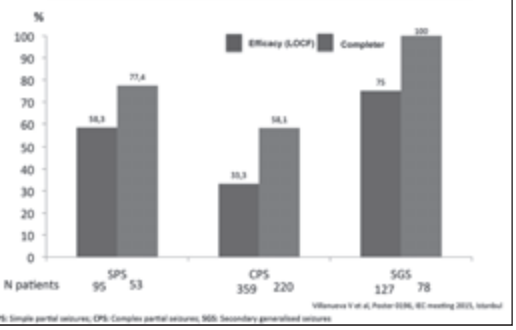
Villanueva V et al, Poster 0196, IEC meeting 2015, Istanbul

Demographics characteristics

	1-year follow-up (n= 464)
Male / Female, n(%)	229 (49.4%) / 235 (50.6%)
Age, mean, SD	40.5 (13,9) (12-82)
Age at onset, median, IQR Adolescent (12-18) ≥ 65 yo	12 (4-21) 21 (4.5%) 25 (5.4%)
Time since diagnosis , median, IQR	24 (14,5-36)
Number of seizures Median, IQR Mean, SD SPS CPS SGS	 6 (3-20) 19.3 (36.9) 98 (21.2%) 363 (78.2%) 127 (27.4%)
Prior AEDs Mean, SD Median	 7.8 (3.6) (1-18) 7

Villanueva V et al, Poster 0196, IEC meeting 2015, Istanbul

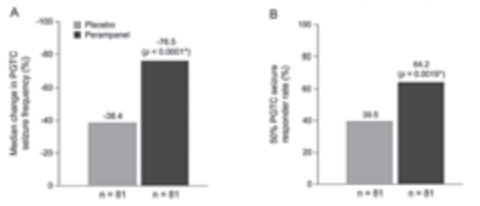
Median seizure reduction by seizure type (12 months)



SPS: Simple partial seizures; CPS: Complex partial seizures; SGS: Secondary generalised seizures

Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy A randomized trial

162 patients (placebo, 81; perampanel, 81)



French J et al, Neurology 2015; 85: 1-8

Summary

- Is there a need of new AEDs?
- Pros / cons new AEDs
- Last decade new AEDs
- **Upcoming new AEDs**

AEDs in pipeline

- Adenosina
- Alprazolam
- AntagoNAT Platform
- Asian Herbs for Epilepsy
- AV-101
- BGG492
- Antagonista canbes BK
- C-10068
- CNV1061436
- CPP-115
- CPT-354
- 2DG
- Diazepam Intranasal
- Midazolam intranasal
- MPP-021
- Transferencia génica NPI
- NTP-A
- P529 (Paloma6)
- Hemisuccinato Propofol
- T2000
- T-20007
- Dinamina
- Galanina
- Tonabersat
- UCB 0942
- VX765
- Gimeng
- ICA-105665
- Alopregnenolona (SAGE-547)
- AMP-X-0079
- Brivaracetam
- Bumetanida
- Cannabidiol
- Cannabidivarina
- 2-(Deoxy)-D-Glucosa
- Everolimus
- Ganaxolona
- Huperzina A
- Imepitoina
- Minociclina
- NAX-810-2
- Pitolisant (Tripoliisant)
- PRX 0023 (Nalutozan)
- SAGE-217
- Valnoctamide sec-Butylpropylacetamide (SPD)
- VLB-01 (Beprodone)
- YKP3089

http://www.epilepsy.com/accelerating-new-therapies

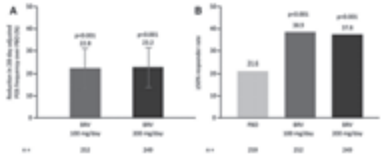
Bialer M et al. Epilepsy Res. 2015 Mar;111:85-141

Upcoming AEDS: New formulations

- Carbamazepina IV
- Autoinyector Diazepan
- GDNF liberación local en cerebro
- Valproato Magnesio
- Topiramato XR
- Topiramato IV
- Lamotrigina IV

http://www.epilepsy.com/accelerating-new-therapies

A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures



Klein P et al. *Epilepsia*, 56(12):1890–1898, 2015

A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures

Table 3. Summary of treatment-emergent adverse events (safety population)

Parameter, n (%)	PBO (n = 341)	BRV 100 mg/day (n = 353)	BRV 200 mg/day (n = 354)	Combined BRV (n = 707)
Any TEAE	133 (39.4)	175 (49.6)	167 (46.8)	342 (47.6)
TEAE leading to discontinuation of study drug	19 (5.6)	31 (8.5)	17 (4.8)	38 (7.4)
Drug-related TEAEs[b]	58 (17.2)	97 (26.5)	115 (34.3)	207 (41.2)
Nervous system disorders[a]	68 (20.1)	94 (27.1)	105 (30.3)	199 (29.6)
Psychiatric disorders[a]	39 (7.7)	36 (10.5)	106 (11.3)	54 (10.7)
Severe TEAE[c]	11 (5.2)	16 (5.2)	13 (3.7)	31 (5.2)
Serious TEAE[c]	9 (2.4)	8 (2.3)	8 (2.3)	16 (2.3)
Death	0	0	1 (0.3)	1 (0.1)
TEAEs reported by ≥5% of patients in any treatment group				
Somnolence	20 (7.7)	49 (14.4)	42 (14.8)	91 (18.1)
Dizziness	13 (5.8)	26 (10.5)	36 (14.4)	62 (13.3)
Fatigue	10 (3.8)	19 (7.5)	19 (11.6)	48 (9.5)
Headache	23 (8.4)	17 (6.7)	20 (8.5)	37 (7.4)
Urinary tract infection	8 (3.1)	15 (5.1)	3 (0.8)	15 (3.0)

BRV, brivaracetam; PBO, placebo; TEAE, treatment-emergent adverse event.
[a]As judged by the investigator.
[b]Classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 15 System organ class.
[c]Serious TEAEs were defined as those that resulted in death, were life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability or incapacity, or were important medical events, congenital anomalies, or birth defects.

Klein P et al. *Epilepsia*, 56(12):1890–1898, 2015

Clinical Evaluation of Ganaxolone in Pediatric and Adolescent Patients with Refractory Epilepsy

Week	Intent to treat			Subjects evaluated at time point		
	Substantial	Moderate	Nonresponder	Substantial	Moderate	Nonresponder
6[a]	27% (4/15)	20% (3/15)	53% (8/15)	31% (4/13)	23% (3/13)	46% (6/13)
18[a]	27% (4/15)	13% (2/15)	60% (9/15)	50% (4/8)	25% (2/8)	25% (2/8)

15 patients

Single dose (mg/kg) and frequency	Total daily dose (mg/kg)	Adverse events
1.0 b.i.d	2	None
2.7 b.i.d	5	None
3.0 t.i.d	9	Agitation, hostility, hallucinations
5.0 b.i.d	10	None
7.5 b.i.d	15	None
6.0 t. i. d	18	Somnolence
10.0 b.i.d	20	Somnolence (3), constipation, agitation
7.0 t.i.d	21	Somnolence
9.0 t.i.d	27	Somnolence, convulsion (2)
12.0 t.i.d	36	Somnolence (3), convulsion

Pieribone V, *Epilepsia*, 48(10):1870–1874, 2007

044

YKP3089 IN PARTIAL-ONSET SEIZURES: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Gasior M[1], Kowalski J[2], Maciejewski W[3], Ramkumaran P[4], Kamin M[4]

[1]*New York University School of Medicine, New York, NY, USA,* [2]*NZOZ NZOZ-MED Sp. Zoł, Gliwice, Poland,* [3]*NZOZ Diagnomed, Katowice, Poland,* [4]*BK Life Science Inc., Fair Lawn, NJ, USA*

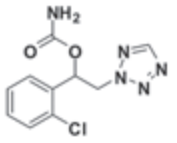
Purpose: YKP3089, a tetrazole alkyl carbamate derivative, is a new investigational antiepileptic drug (AED) with a potentially unique mechanism of action and a pharmacokinetic profile suited to once-daily dosing. This randomized, double-blind, placebo-controlled study assessed efficacy and tolerability in patients with refractory epilepsy.

Methods: Adults with partial-onset seizures (≥3/28 days in 8-week baseline despite 1–3 AEDs) were randomized to placebo or to adjunctive 100 mg YKP3089 which was titrated over 6 weeks (50 mg increments at 1-week intervals) and maintained for 6 weeks. Primary endpoint was median% seizure reduction from baseline. Secondary endpoints included % patients with ≥50% seizure reduction (responder rate); % of study completers with no seizures in maintenance; median% seizure reduction by seizure type.

Results: Patient characteristics were similar at baseline (YKP3089, N = 113; placebo, N = 108). Median seizure reduction (YKP3089 vs. placebo, 34% vs. 22%, p < .0001; % patients' rate, 30% vs. 16%, p = .0008). Seizure free patients numbered three times more in YKP3089 than placebo groups. YKP3089 was effective against partial-onset seizure types. Seizure reduction was observed during titration when patients were receiving 50–100 mg YKP3089. Most common adverse events were somnolence (22% vs. 12%), dizziness (21% vs. 12%), fatigue (11% vs. 6%), headache (10% vs. 8%), nausea (9% vs. 6%), vertigo (8% vs. 1%), vomiting (8% vs. 3%), and ataxia (7% vs. 1%). Most adverse events were mild or moderate in severity. Fewer YKP3089 than placebo patients withdrew due to adverse events (7% vs. 11%), nausea (6% vs. 3%), constipation (5% vs. 0), diarrhea (5% vs. 0), vomiting (5% vs. 3%).

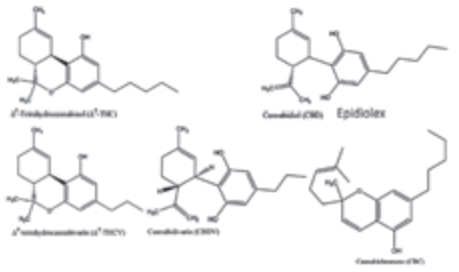
Conclusions: YKP3089 was highly effective vs. placebo in reducing partial-onset seizures in patients with refractory epilepsy. No unexpected safety or tolerability issues were identified.

Study sponsored by BK Life Science Inc.



Epilepsia, 55(Suppl. 2):4–246, 2014

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders



Devinsky O et al, Epilepsia, 55(6):791–802, 2014

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders

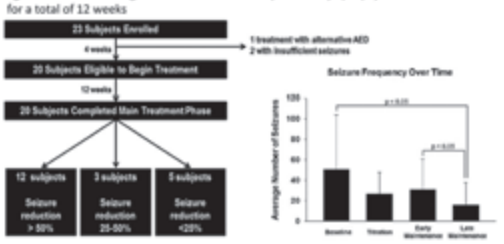
Study	Treatments (subjects per group)	Duration	Outcome	Toxicity	Limitations
Pfeiffer and Carlini, (1978)[36]	THC CBD 200 mg/day (4) THC Placebo (5)	2 months	CBD: 3 seizure free, 1 partial improvement, 1 no change	None	No baseline seizure frequency, no definition of improvement, unclear if AEDs were changed, small fulltested power, not truly randomized-blinded, unknown if groups were matched
Carlini et al. (1980)[37]	THC-TLE CBD (7) * THC-TLE/Placebo (8)**	200–300 mg/day for 3–18 weeks	Last visit: 4 CBD, 1 placebo	Somnolence	Non-clearly blinded, since one patient transferred groups and doses were adjusted in CBD, but no mention of this in placebo group and CBD group received had longer average treatment
Ames and Cridland (1986)[38]	IDD-TRE/CBD (76)* IDD-TRE/Placebo (76)* < 4 weeks	CBD 300/day < 1 week 200/day < 3 weeks	No difference between CBD/< Placebo	Somnolence	This was a letter to the editor and details are lacking
Trembly and Sherman (1986)[39]	TRE (10 or 12)*	3 months baseline; 6 months placebo; Randomized to either 6 months placebo < CBD <300 m.d.; then crossover for 6 months on alternative treatment	No change in seizure frequency or cognitive/ behavioral tests	None	Only only double blind study. Unclear why sample size differed in two reports. Data reported is incomplete

TRE, treatment-resistant epilepsy; TLE, temporal lobe epilepsy; IDD, intellectual developmental disability.
*Frequent convulsions for (1 year— 1 GTCS) per week.
**Once patient transferred from placebo to treatment after 1 month.
*12 subjects were divided into two groups, but distribution is uncertain.
*Alternate and subsequent bouts chagrar here different N's (3 and 12).

Devinsky O et al, Epilepsia, 55(6):791–802, 2014

Everolimus Treatment of Refractory Epilepsy in Tuberous Sclerosis Complex

Prospective, multicenter, open-label, phase I/II clinical trial with patients 2 years of age with confirmed diagnosis of TSC and medically refractory epilepsy were treated for a total of 12 weeks



Krueger DA et al, Ann Neurol 2013;74:679–687

Everolimus: Adverse events

Category	Grade 1	Grade 2	Drug-Related	Terms (No.)*
Allergy	0	1	0	—
Hematologic	0	1	1	—
Constitutional	8	6	13	Fever (7); fatigue (4)
Dermatologic	11	3	4	Rash (4)
Gastrointestinal	34	2	29	Stomatitis/mucositis (18); diarrhea (6); nausea/vomiting (5); anorexia (4)
Infectious	2	29	29	Upper respiratory infection (19); otitis media (5); gastroenteritis (4)
Neurologic	3	4	1	—
Pain	1	1	0	—
Pulmonary	13	0	6	Congestion/rhinorrhea (7); cough (6)
Genitourinary	1	0	0	—
Total	73	47	83	

*Includes only event types with occurrence ≥3% of all reported adverse events.

Krueger DA et al, Ann Neurol 2013;74:679–687

Bumetanide reduces seizure frequency in patients with temporal lobe epilepsy

- Alterations in the balance of K-Na-2Cl cotransporter (NKCC1) and Na-Cl cotransporter (KCC2) activity may cause depolarizing effect of c-aminobutyric Acid (GABA), and contribute to epileptogenesis
- Bumetanide act as a specific NKCC1 antagonist

Number of days with seizure/aura before and after treatment initiation

	4 Months before treatment initiation		4 Months after treatment initiation	
Patient	No. days with seizures	No. seizure days ± aura	No. days with seizures	No. seizure days ± aura
1	9	47	0	15
2	6	10	7	7*
3	9	4	0	1*

*Attacks exclusively happened after stressful situations and fatigue.

Long-term video-EEG monitoring results before and after treatment initiation

	LTM before treatment initiation		LTM after treatment initiation	
Patient	No. interictal discharges	Nonepileptiform discharges	No. interictal discharges	Nonepileptiform discharges
1	15	Rare	38	Rare
2	3	Rare	0	Rare
3	74	Frequent	34	Moderate

Eftekhari S et al, Epilepsia, 54(1):e9–e12, 2013

The NEW ENGLAND JOURNAL of MEDICINE

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Efficacy of **intramuscular midazolam with that of intravenous lorazepam** for children and adults in status epilepticus treated by paramedics

Outcome	Intention-to-Treat Analysis† (N=893)		Per-Protocol Analysis‡ (N=732)	
	IM Midazolam (N=448)	IV Lorazepam (N=445)	IM Midazolam (N=362)	IV Lorazepam (N=370)
Primary outcome				
Seizures terminated, no rescue therapy given				
No. of subjects	329	282	271	238
% of subjects (95% CI)§	73.4 (69.3–77.5)	63.4 (58.9–67.9)	74.9 (70.4–79.3)	64.3 (59.4–69.2)
Treatment failed — no. of subjects (%)	119 (26.6)	163 (36.6)	91 (25.1)	132 (35.7)
Seizures not terminated, no rescue therapy given	30 (11.2)	64 (14.4)	42 (11.6)	51 (13.8)
Seizures not terminated, rescue therapy given	22 (4.9)	42 (9.4)	14 (3.9)	36 (10.3)
Seizures terminated, rescue therapy given	47 (10.5)	57 (12.8)	35 (9.7)	43 (11.6)

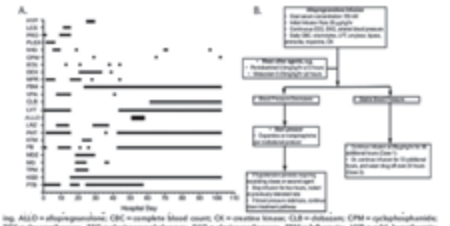
Pediatric Super-Refractory Status Epilepticus Treated with Allopregnanolone

- The **neurosteroid** allopregnanolone is a metabolite of progesterone, and has been proposed as a novel treatment for status epilepticus (SE)
- 4,5 Allopregnanolone acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors, and terminates benzodiazepine-refractory SE in animal models
- The potentiating effect of allopregnanolone on extrasynaptic $GABA_A$ receptors enhances tonic inhibition

Broomall E et al, Ann Neurol 2014;76:911–915

Pediatric Super-Refractory Status Epilepticus Treated with Allopregnanolone

- 2 children

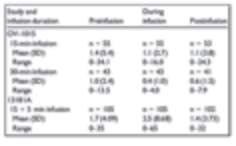


Broomall E et al, Ann Neurol 2014;76:911–915

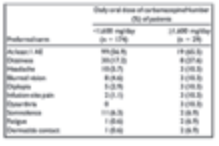
Intravenous carbamazepine as short-term replacement therapy for oral carbamazepine in adults with epilepsy: Pooled tolerability results from two open-label trials

203 patients receiving a stable oral dosage of CBZ were switched to an IV CBZ formulation solubilized in a cyclodextrin matrix for either a 15- or a 30-min infusion every 6 h for up to 7 days and then switched back

Weekly seizure rates by treatment period



Adverse events reported ≥5% of patients during the infusion period by dose groups



Lee D et al, Epilepsia, 1–9, 2015

Conclusion

- New AEDs are needed because there are still patients drug resistant and side effects
- PK and side effects profile are the main advantages of new AEDs
- New and upcoming AEDs can improve the care of epilepsy in the patients

Silvia Kochen (Argentina)

TRANSLATIONAL RESEARCH ON EPILEPSY

AngelinaKakooza (Uganda)

EPILEPSY IN THE TROPICS

Epilepsy is a common chronic neurological disorder of major public health concern, estimated to affect approximately 70 million people of all ages worldwide. The majority (over 85%) of people with epilepsy are found in the tropical countries, found in Asia, Latin America and sub-Saharan Africa. The higher frequency of seizures and epilepsy in tropical countries than in temperate countries is often attributed to the geographic, social and biological characteristics typically found in the large numbers of human populations living there.

These characteristics range from a higher predisposition of vector-borne diseases such as malaria or trypanosomiasis; lack of diagnostic support facilities; poor maternal and child care; social stigma and cultural beliefs affecting health seeking behaviour and attitudes; and the interplay of poverty, illiteracy and poor sanitation predisposing to undernutrition and various communicable diseases.

A major challenge facing studies of epilepsy in the tropics is the scarcity of large population based studies, lack of reliable medical records and hospital registers. Secondly there have been varying definitions of epilepsy employed in the various studies making comparability across studies problematic.

A large population epidemiological study conducted in five demographic surveillance sites in Africa showed that adults who had been exposed to parasitic diseases were 1.5 to 3 times more likely to have epilepsy than those who had not. On the contrary in children, the greatest risk factors for developing epilepsy were complications associated with delivery and head injury.

This implies that many cases of epilepsy in the tropics could be entirely preventable with elimination of parasites some of which - for example, onchocerciasis, - have been controlled in some areas. Furthermore interventions to improve antenatal and perinatal care could substantially reduce the prevalence of epilepsy in the tropics.

The issues of epilepsy in the tropics, its epidemiology, clinical and diagnostic evaluation, risk factors and aetiology, the inherent management challenges will be further discussed in the lectures of this course.

Manuel Campos (Chile)

HISTORY AND DEVELOPMENT OF EPILEPSY SURGERY IN LATIN AMERICA

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Introducción:

Las epilepsias y sus tratamientos son tan antiguos como la humanidad misma, pero en los pueblos sudamericanos prehispánicos es difícil conocer su historia, por que los incas y sus predecesores no conocían la escritura. Sin embargo, ellos tenían importantes representaciones gráficas en cerámicas, como son los llamados "*huacos*", estas figuras representan diferentes enfermedades y procedimientos médicos.

Los conocimientos llegan hasta nuestros días a través de la ciencia llamada paleopatología, la cual estudia las enfermedades que se pueden demostrar en restos humanos o animales de los tiempos antiguos. Por lo tanto, previo a la invención de la escritura es poco o nada lo que se puede saber sobre las epilepsias, ya que los materiales que utiliza la paleopatología son fundamentalmente restos óseos de cuevas, yacimientos o necrópolis. Las principales patologías que se pueden diagnosticar son: lesiones traumáticas (fracturas), infecciones (osteomielitis, sífilis, tuberculosis, etc.), metabólicas (raquitismo, escorbuto), degenerativas (artrosis, espondilosis, etc.), tumores óseos o meningeomas (Fig. 1) y patologías dentarias[1,2].

Figura 1: Cráneo con meningeoma exofítico. Museo Nacional de Antropología y Arqueología en Lima, Perú.

Trepanaciones en América precolombina:

La palabra "trepanación" significa retirada de secciones del hueso del cráneo, el instrumento utilizado se denomina trepano, cuyo nombre viene del griego *tripanon* (perforador)[3].

En la América pre-colombina se realizaron trepanaciones muy ocasionalmente en Norteamérica, Centro América (Mayas) y en el actual México, donde en la ciudad monumental de Monte Alban, Oaxaca, se desarrollo la cultura Zapoteca y luego la Mixtéca. Ellos realizaron trepanaciones probablemente como rituales, ya que los cráneos encontrados son de personas jóvenes de ambos sexos[4, 5].

Pero fue en la costa del océano Pacifico de Sudamérica donde las trepanaciones tuvieron su máximo desarrollo, en el clima árido de lo que hoy es Perú y norte de Chile (culturas paracas, nazca y mochica) y en el altiplano andino de Bolivia y Perú (culturas huari o wari, tiahuanaco o tiwanaku, chimú e inca)[6]. El clima seco de la costa peruana ha permitido la conservación excelente de más de 15.000 momias de la época precolombina, gran parte de las cuales están almacenadas en el Museo Nacional de Antropología y Arqueología en Lima, Perú[7]. La antigüedad de las momias es de hasta 2.500 años y un 5% de ellas muestran evidencias de trepanación "in vivo". El 70% de los cráneos del Perú precolombino pertenecen a hombres.

Las crónicas españolas de la conquista no mencionan las trepanaciones, por lo cual se sospecha que estos actos ya no se practicaban en esa época o bien se hacían en secreto. Además se ignoraron por largos años los "instrumentos quirúrgicos" que adornaban los museos. Como atenuante se debe considerar que la mayoría de los conquistadores no eran hombres ilustrados y pocos miembros de las expediciones realizaban crónicas. Un caso excepcional lo constituyó Felipe Guaman Poma de Ayala[8], quien ilustró sus observaciones en cientos de dibujos. Es así como llegó a nosotros el probable primer relato de epilepsia precolombina del Perú. Se trata de la señora Chimbo Mama Cava, esposa de Capac Yupanqui, uno de los últimos emperadores Incas, quien gobernó hasta su muerte en 1525[9]. Otras referencias a epilepsias en los incas vienen de los escritos de Gracilazo de la Vega en "*Comentarios Reales de los Incas*", allí se describen probables epilepsias focales.

La "epilepsia" no tenía una palabra específica en "*Quechua*" (lenguaje usado por los incas), para definirla como una condición neurológica especial. Sin embargo, varias expresiones en quechua pueden haber sido utilizada para denominar a las Epilepsias (Tabla 1), como por ejemplo "*Sonko-Nanay*". Esto se basa en que "*Sonko*" tiene diferentes significados: corazón, mente y en algunos casos cerebro; es decir lo esencial del ser humano. Mientras que la palabra "*Nanay*" puede significar dolor o enfermedad[9]. Por lo tanto "*Sonko*

Nanay" puede haber usado para denominar casos de epilepsia, sincopes, enfermedades de la mente, etc.

TABLA N°1: Nombres pre-incas e Incas para Epilepsia (basado en referencia N° 10)

Nombre	Descripción
Sonko nanay	Enfermedad del corazón, alma o cerebro
Aya huayra	Viento (aire) de la muerte
Chayapuk oncuy	
Hueanuy oncuy	Enfermedad de la muerte
Huani keshia	Enfermedad de la muerte
Llaqui oncuy	Enfermedad de la tristeza
Tlucu	Pájaro de la noche
Urmachiscan	"Él está deprimido"

También se ha planteado que la palabra quechua "*ayahuayra*" se puede haber usado para denominar a las epilepsias, esta deriva de la expresión *aya*, que significa muerte y *huayra*, que significa viento o aire. Por lo tanto, las culturas quechuas habrían asociado a las epilepsias con la muerte[10].

La palabra "*Perlesía*", fue usada por los conquistadores españoles para denominar una serie de "síndromes neurológicos", tales como accidente vascular cerebral, hemiplejía y posiblemente epilepsia o "enfermedades no--neurológicas", por ejemplo: enfermedades del corazón o sincopes.

El primer cráneo trepanado "incaico" fue descrito por Samuel G. Morton en su tratado "*Crania Americana*" en 1839, pero se interpretó como una herida de guerra. En el año 1865 Efraín G. Squier, explorador y encargado de negocios de EE.UU. en Perú, publicó su libro "Incidentes de un viaje al Perú, país de los Incas" y presentó parte de un cráneo trepanado en la Academia de Medicina de Nueva York (Fig. 2)[11]. Squier llevó este cráneo trepanado a Paul Broca (1824-1880), quien había descrito la localización del lenguaje y la dominancia hemisférica, además de fundar la Sociedad de Antropología de Paris. Broca planteó que el cráneo incaico era de una persona que había sobrevivido 1 o 2 semanas[12]. Este descubrimiento fue incluso previo a muchos cráneos trepanados encontrados posteriormente en Europa (Francia, Alemania, Inglaterra, Republica Checa, etc.), los cuales también fueron estudiados por Paul Broca, quien fue el primer médico de la era moderna en plantear a la trepanación como una posible cirugía de la epilepsia (antes ya lo había mencionado Hipócrates), esto también fue planteado posteriormente por Víctor Horsley (1857-1916) al examinar la colección de cráneos trepanados de Broca[13].

Figura 2: Trepanación linel, en que se aprecian marcas del elemento cortante en los hordes.

Antecedentes históricos:

Se tiende a hablar de trepanaciones incas, lo cual en gran parte es erróneo, ya que el imperio incaico era relativamente nuevo, se estima que fue fundado por *Manco Capac* hacia el 1200 d.C., luego de unir a todos los pueblos de la región bajo un solo emperador. Es decir la llegada de los españoles, el imperio Inca solo tenía 300 años de antigüedad. Realmente la gran mayoría de las trepanaciones fueron echas por pueblos preincaicos (culturas Paracas, Nazca, Mochica, Ica, Huari, Tiahuanaco, Chimú), quienes las practicaron mucho antes y en mayor cantidad que los incas[6]. Los cráneos más antiguos proceden de la cultura paraca (1000 al 200 a.C.), ubicados en la costa centro sur del Perú y de la cultura Tiahuanaco, alrededor del lago Titicaca, actual Bolivia, donde se han encontrado cráneos trepanados y deformados datados en 1500 a.C.

Los incas auto denominaban su imperio como *Tahuantinsuyu* o tierra de las cuatro esquinas. En 1492, cuando Cristóbal Colon descubrió América, el imperio Inca ya era el más grande del mundo. Este incluía a los actuales países de: Perú, Ecuador, Bolivia y partes de Chile, Colombia y Argentina. Lamentablemente el imperio incaico cayó en menos de cien años, luego del arribo del español Francisco Pizarro, en Tumbes junto con 179 conquistadores en 1532[7].

Causas de las trepanaciones:

Las craneotomías parecen ser un elemento cultural de muchas sociedades, independiente de la época (desde el neolítico hace 10.000 años a la actualidad) o del lugar geográfico (Europa, Latinoamérica, Oceanía, África del norte, etc.) (13-19). Sin embargo, en ningún otro lugar del mundo como en Sudamérica del pacifico, se logró un número tan importante procedimientos y con una sobrevida estimada entre un 50% a 70% de los "pacientes"[7].

Las probables motivaciones de los pueblos preincaicos para trepanar pueden ser:

1. **Tratamientos de traumatismos de cráneo**: Lo anterior se basa en que eran pueblos guerreros, quienes usaban mazos de piedra. Por lo tanto estaban expuestos a traumas con fracturas de cráneo, incluidos hundimientos óseos. Además las fracturas pueden asociarse a hematomas intracraneanos. Existen múltiples cráneos trepanados asociados a fracturas que apoyan esta hipótesis (Fig. 3), varios de ellos tienen las lesiones en la zona temporal o fronto-parietal izquierda, lo que indica que su atacante fue un contrincante diestro. Además se han encontrado cráneos trepanados en recintos militares incas del altiplano, en el valle del Urubamba, cerca de Cuzco (capital de imperio Inca). Se ha planteado que entre el 30% a 50% de las trepanaciones en el altiplano eran por heridas de combate[11,20].

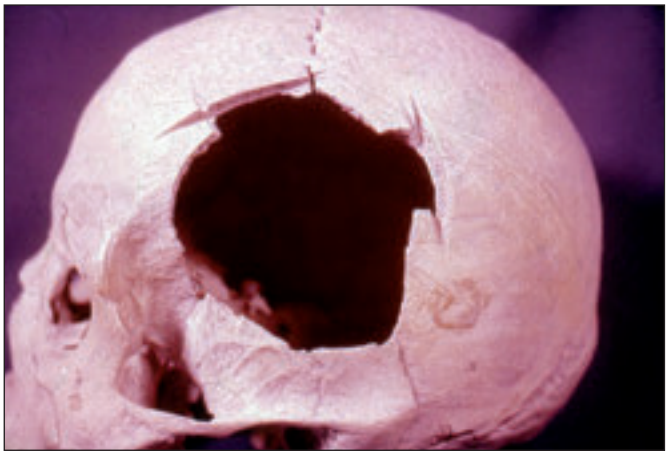

Figura 3: Cráneo procedente del cementerio inca del valle del Yucay, con trepanación cuadrilátera frontal izquierda y signos leves de cicatrización. Obtenido por EG Squier en la casa de una dama en Cuzco. Cráneo datado entre 1400 a 1530. Actualmente se encuentra en el Museo de Historia Natural de Nueva York.

2. **Procedimientos religiosos**: Muchos cráneos trepanados presentan deformaciones, las cuales fueron hechas en las personas desde su infancia, con almohadillas y madera amarradas a su cabeza (Fig. 4). Algunos de estos cráneos deformados presentan trepanaciones. Incluso en la actualidad existen algunas tribus costeras, las cuales realizan trepanaciones rituales en el occipital, lo cual también se ve en cráneos precolombinos de adultos de la cultura huara[2,21].

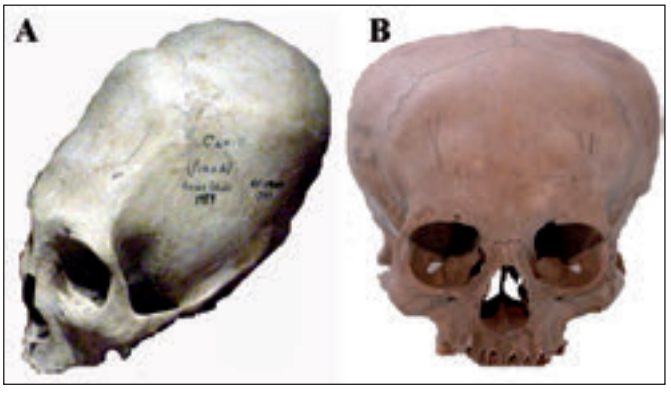

Figura 4: Fractura fronto temporal operada, sin supervivencia del paciente (sin signos de cicatrización), puede corresponder a un soldado herido en batalla.

3. **Cirugía de la epilepsia**: La extracción de la causa de la enfermedad ha sido planteada como probable causa de las trepanaciones. Esto se basa en que la mayoría de los cráneos trepanados no tienen fracturas, ni deformaciones, pero sin embargo muchos cráneos presentan más de una trepanación y en diferentes tiempos (Fig. 5). Esto se sabe, ya que existen diferentes grados de cicatrización en las trepanaciones (Fig. 6). Por lo tanto se trataría de individuos con patologías crónicas (epilepsias, cefaleas, etc.) o bien personas predestinadas a trepanaciones múltiples, por motivos desconocidos (19,20). Lo que atenta contra esta hipótesis es que en muy pocos cráneos de niños se han encontrado trepanaciones. Es bueno señalar que los Incas, a diferencia de lo Mayas, no invocaban a las "posesiones demoníacas" como causa de epilepsia[22].

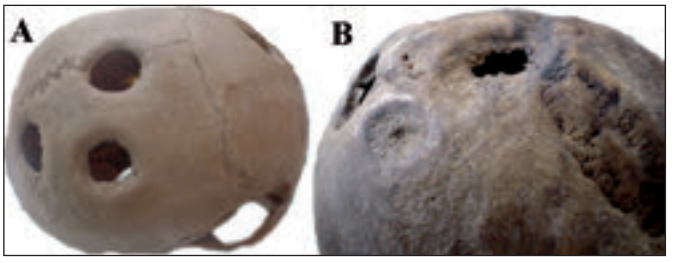

Figura 5: A- Deformación craneana. B- Deformación en niño (vista frontal).

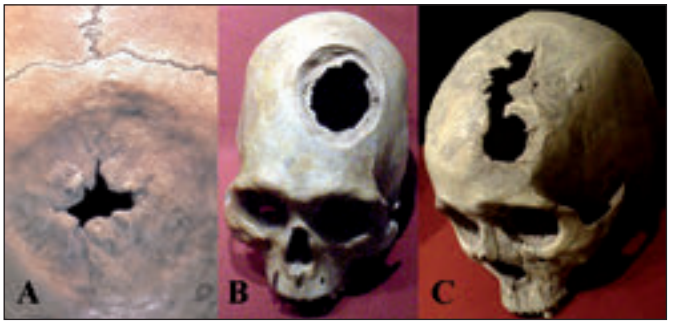

Figura 6: A-Regeneración ósea en craneotomía circular. B- Regeneración parcial de los bordes. C- Extensa osteomielitis con porosidad extensa del hueso.

Los pueblos preincaicos como neurocirujanos:

A) **Pabellones quirúrgicos**: En todo el imperio incaico, con la excepción de la amazonia se practicaban craneotomías, esto corresponde a gran parte del Perú actual, parte de Bolivia y norte de Chile, pero hay necrópolis que fueron verdaderos centros de trepanación. Incluso se ha sugerido la existencia de centros o escuelas de entrenamiento neuroquirúrgico en Paracas y Cuzco, donde se han encontrado ruinas de posibles hospitales[23].

B) **El "neurocirujano":** Es probable que existieran 2 tipos de "cirujanos", unos entrenados llamados "*Hampicamayac*" y los Chamanes "*Soncoyoc*", estos últimos sin conocimiento, ni habilidad técnica[6,11]. También se conoce la expresión "*Sirkak*", para denominar al cirujano o sangrador. La mayoría de los cráneos trepanados muestran una "cirugía" realizada con conocimientos anatómicos, por ejemplo fuera de trayecto de los senos venosos. Además más de la mitad de los cráneos encontrados muestran signos de supervivencia, ya sea por cicatrización u osteomielitis. Los riesgos de infección existían y en múltiples cráneos se encontraron signos de osteomielitis en diferentes grados (Fig. 6-C).

C) **Sedación:** Esta se puede haber realizado en pacientes concientes con mandioca fermentada o bebidas alcohólicas. También se cree que se uso polvo de coca y su hoja para masticar, la coca (*Erytroxylon coca*) tiene propiedades anestésicas y es originaria de los Andes[24]. Lo anterior alivia el dolor de la incisión del cuero cabelludo, única parte dolorosa de la cirugía.

D) **Instrumentos quirúrgicos:** Se usaron tanto instrumentos cortantes de piedra, como el pedernal y la roca volcánica llamada Obsidiana (Fig.7-A), así como metal en forma de cuchillos de bronce o cobre, cuya forma clásica es el llamado "Tumi", el cual corresponde a un cuchillo en forma de mitad de circulo (Fig. 7-B), a veces tenía un mango esculpido con una figura humana o animal. También existían pinzas, las cuales se pueden haber utilizado para depilar o retirar fragmento de huesos[4, 11, 25, 26].

Figura 7: A- Cuchillo de obsidiana, tipo punta de flecha para craneotomías. B-Cuchillos en forma de media luna, llamados Tumi, su origen es un hacha, la cual se usaba en múltiples actividades como elemento cortante. Por lo tanto no era un instrumento quirúrgico específico y posiblemente se usaba para abrir la piel del paciente y no el hueso, a menos que fuera un Tumi tipo cincel.

E) Hemostasia: El control del sangrado se puede haber realizado con la aplicación de extractos de la raíz *ratania* y de la liana *pumacbuca*, ambas ricas en ácido tánico y muy conocidas por los pueblos precolombinos[7, 24].

F) La técnica quirúrgica: Los cráneos sin grandes signos de regeneración y los fallecidos en forma inmediata, nos permiten conocer mejor las diferentes técnicas empleadas, las cuales básicamente eran tres: **1°** La primera corresponde a craneotomías con cortes rectos que limitan bordes cuadriláteros, poligonales o circulares (Fig. 8), posiblemente se utilizaban cuchillos duros de Obsidiana, con bordes muy pulidos. **2°** Este segundo tipo son trepanaciones por raspados el instrumento utilizado fue probablemente una piedra abrasiva frotada sobre la superficie del hueso, hasta lograr atravesar la tabla interna del cráneo y llegar a ver las meninges. Luego se realizaba un ensanche de la apertura fracturando progresivamente los bordes adelgazados del hueso. Esta técnica fue utilizada por la cultura paraca, pero estos cráneos suelen no mostrar signos de supervivencia (Fig.8). **3°** La última técnica corresponde a múltiples agujeros de barreno que delimitaban la zona ósea a extirpar. Se utilizaban punzones de perfil poligonal que se rotaban hasta perforar el cráneo[6, 7, 11, 27].

G) Sutura: Se han encontrado agujas de metal y hebras de algodón en enterramientos, esto nos puede señalar el como suturaban la piel, otras hipótesis es que ataban el cabello de los bordes de la herida y así unían los márgenes [24].

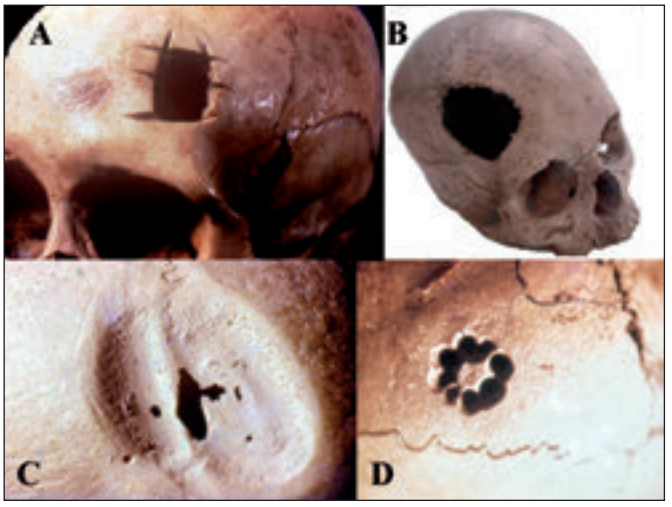

Figura 8: A) Trepanación lineal, donde se ven en los bordes marcas del elemento cortante tipo Tumi. B) Craniectomía con elemento cortante tipo punzón, el que deja marcas en los bordes. No hay signos de regeneración o infección, por lo tanto la persona falleció. C- Acercamiento de cráneo, donde puede verse regeneración ósea indicando que hubo sobrevida. D- Craneotomía con múltiples pequeños trépanos.

H) Tiempo quirúrgico: Se estima que un neurocirujano experto, demoraba entre 30 a 60 minutos en realizar una trepanación. Lo anterior ha sido demostrado en 2 ocasiones en el Perú. El primer caso fue en Cuzco en 1944, donde 2 neurocirujanos operaron con instrumentos preincaicos originales, obtenidos del museo Arqueológico de la ciudad, a un joven de 22 años con un trauma de cráneo por caerle un árbol en la cabeza. Ellos usaron un Tumi para la incisión de la piel y la separación del periostio, luego con un cincel de obsidiana esterilizado lograron abrir el hueso y realizaron una trepanación de 6 x 3 cm. Los bordes de la herida la suturaron con una aguja de *champi*. La cirugía duró una hora, pero el paciente falleció a los siete días de

una neumonía, debemos recordar que aún no se disponían de antibióticos[28].

El segundo caso fue en 1953, donde 2 neurocirujanos peruanos (Graña y Rocca)[29] realizaron primero una cirugía experimental en un cadáver. Ellos obtuvieron un Tumi y cuchillos de obsidiana del Museo Nacional de Antropología y Arqueología de Lima, luego ellos realizaron una cirugía "*in vivo*" en un paciente con trauma de cráneo, con hemiplejia y afasia. El paciente fue intubado y sedado, para luego proceder con instrumentos preincaicos estériles a realizar una craniectomía oval, con exposición de las meninges y drenaje de un hematoma.

I) **Complicaciones**: La primera era la muerte, lo cual ocurría en menos del 50% de los "pacientes". Sin embargo las infecciones óseas (osteomielitis) eran muy frecuentes, ya sea como pequeñas porosidades alrededor de la trepanación, o bien grandes infecciones con signos de regeneración, estas no permiten conocer la forma de la trepanación original e indican supervivencia por años. Incluso existen momias que muestran el reemplazo de la piel normal por tejido fibroso, e cual hace cuerpo con las meninges. Algunos individuos que fallecieron durante la cirugía y luego fueron momificados, nos permiten saber como el "neurocirujano" abría la piel del cráneo, con incisiones en forma de cruz[11].

J) **Craneoplastías:** Se planteo que la corrección del defecto óseo pudiera haber sido hecho con elementos orgánicos, tales como hojas de coca, mate o cáscaras de calabazas, lo cual es biológicamente imposible. Sin embargo se han encontrado reparaciones de los defectos con pequeñas láminas de oro, lo cual se cree que era para pacientes de la nobleza, pero varios de estos cráneos no presentan elementos de sobrevida, lo cual sugiere que era un intento fallido de cerrar el defecto óseo[30].

Variante de la trepanación:

Una variante de la trepanación clásica corresponde a una pseudotrepanación (raspado o pequeñas trepanaciones) realizadas sobre el inion de la región occipital, en la unión masto-occipital, sobre los llamados "huesos wormianos", estos son pequeños huesos intercalados. El 52% de estos cráneos con huesos wormianos, además presentan deformaciones intencionales [21], en contraste a un 33% de los cráneos sin deformaciones. Algunos autores plantean que no fueron verdaderas trepanaciones, sino, necrosis ósea por presión.

Historia del siglo XIX:

La primera cirugía formal de la epilepsia de la era moderna fue realizada en Londres por el Dr. Victor Horsley el día 25 de Mayo de 1886, en un caso del Dr. John H. Jackson. Se trató de un paciente de 22 años, quien tenía una epilepsia focal secundaria a una fractura deprimida producto de un trauma a los 15 años.

En Latino América el Dr. Razetti en Venezuela y el Dr. Maldonado en Colombia operaron los primeros pacientes con crisis "Jacksonianas" en

1893 y 1897 respectivamente[31]. Ambas cirugías fueron en epilepsias post-traumáticas.

Historia del siglo XX:

La cirugía de la epilepsia comenzó formalmente en Montreal, Canadá con J. Penfield y en Inglaterra por M. Falconer, en la década de los cuarenta. Luego del advenimiento de la electroencefalografía por el alemán Hans Berger, en el año 1931.

En nuestra Latinoamérica se comenzó con lesionectomías también en la década de los 40, siendo probablemente el primer reporte, el realizado por el Dr. Schroeder de Uruguay durante el tercer Congreso Sudamericano de Neurocirugía[32], quién reportó 10 pacientes con estudio pre-operatorio con EEG de 8 canales y angiografía cerebral, además de electrocorticografía intra-operatoria, lo cual fue el criterio principal para realizar la resección, por lo tanto estas fueron las primeras cirugías de la epilepsia con orientación funcional en Latinoamérica.

Alfonso Asenjo, el padre de la neurocirugía chilena, publicó en 1951 una serie de 221 pacientes con cirugía de la epilepsia[33], la cual fue por casi 50 años la serie más grande publicada en Latinoamérica. En ellos se incluían 96 epilepsias "per se", la mayoría frontales y temporales post-traumáticas. La serie tenía un 69% de buen resultado en el control de las crisis.

La cirugía de la epilepsia del lóbulo temporal es actualmente la cirugía de la epilepsia más frecuente, esta fue iniciada en Latinoamérica por el Dr. Martínez en Venezuela en 1955, quien hasta 1972 había intervenido 13 pacientes, de ellos 9 libres de crisis[34]. También hay series Argentinas (Ghersi) y Uruguayas (Bogacz)[35].

Mención especial se debe hacer al Dr. Niemeyer de Río de Janeiro, Brasil, quien describió en 1957 la amigadlo hipocampectomía selectiva, a través de abordaje transventricular[36]. Una variación de esta técnica por abordaje trans-silviano fue popularizada a comienzos de la década de los 80´ por los Drs. M.G. Yasargil y H.G. Wieser en Suiza[37].

Enfoques estereotáxicos fueron en usados en forma pionera por los Drs. A. Basso y O. Betti en Argentina[38], siguiendo la escuela de Bancaud y Talairach del Hospital Santa Ana, en Paris, Francia, así como el Dr. R. Marino en Brasil, con la callosotomía por estereotaxia[39] y el Dr. R. Zamboni en Chile[40], lamentablemente estas técnicas no trajeron los resultados esperados y han caído prácticamente en desuso.

Cirugías resectivas en epilepsia como casos aislados han sido comunicados en Perú (Rocca)[41] y Argentina (Ferrarese)[42].

Dada la gran complejidad diagnóstica y terapéutica, la cirugía de la epilepsia solo se realizó formalmente en pocos centro en el mundo, hasta fines de la década de los 80´, donde gracias al advenimiento de la Resonancia Magnética de Cerebro y la introducción masiva del video-EEG digital, la cirugía de la epilepsia tuvo un renacer, siendo hoy una probada herramienta terapéutica, para los casos de epilepsia refractaria a medicamentos[43]. La epilepsia del lóbulo temporal es

la cirugía mas frecuente y además la con mejor resultado, esto avalado por estudios prospectivos y aleatorios.

Es interesante señalar que en los centros más importantes de cirugía de la epilepsia del mundo trabajan destacados epileptólogos latinos, como es el caso del Dr. Hans Lüders, quien nació en Chile, estudio en la P. Universidad Católica de Chile y quien fue jefe de Neurología de la Fundación Cleveland de Ohio, de igual país y universidad fue el Dr. Luis Felipe Quesney, quien trabajó por largos años en el Instituto Neurológico de Montreal y falleció el año 2004. El Dr. Rubén Kuzniecky, quien nació en Panamá y estudió medicina en Argentina, es el co-director de epilepsia en Nueva York y autor de importantes textos de Resonancia y epilepsia.

Historia del siglo XXI:

Pese a que la cirugía de la epilepsia tiene más candidatos que los aneurismas cerebrales y sus resultados son mucho mejores, ya que optimizan la calidad de vida de los pacientes y permiten su reinserción laboral o estudiantil, actualmente sólo pocos países en Latinoamérica cuentan con programas formales de cirugía de la epilepsia y con publicaciones: Argentina, Brasil, Chile, Colombia, Guatemala, México y Uruguay.

De los países antes mencionados, solo Brasil en Latinoamérica cuenta con un programa gubernamental, que apoya centros Universitarios, estos centros cuentan con todos los recursos humanos y materiales, para realizar todos los tipos de cirugía de la epilepsia y el gobierno paga una suma fija por cada paciente. En Brasil destacan neurofisiólogos de gran prestigio que trasciende las fronteras de Latinoamérica, como son los Drs. E. Yacubian, A. Palmini, F. Cendes, A. Sakamoto, C. Guerreiro, M. Guerreiro, I. Lopes-Cendes, J. Da Costa, C. Silvado, etc y neurocirujanos como: R. Centeno, A. Cukiert, E. Paglioli, H. Machado, etc.

En Colombia hace largos años el Dr. J. Fandiño fundó el Hospital de la Liga Colombiana Contra la Epilepsia, en la ciudad de Cartagena de Indias. En este centro se realiza el diagnóstico y tratamiento quirúrgico de la epilepsia, con un alto estándar y a bajo costo, gracias a un gran esfuerzo de todo un equipo de trabajo sin fines de lucro[44]. También actualmente Bogotá, Medellín y Pereira cuentan también programas de cirugía de la epilepsia.

En Argentina existen varios grupos importantes, uno liderado por el neurocirujano infantil Hugo Pomata pionero en la cirugía de la epilepsia en Argentina, otro centro de gran nivel en el Hospital Italiano (Drs. W. Silva y P. Ciraolo), así como FLENI y otros en Buenos Aires. Además en Córdoba se comenzó el primer centro Argentino en provincia (Dr. A. Muñoz).

En Chile se re-inicio por el suscrito el tratamiento quirúrgico de la epilepsia es el Hospital Clínico de la Pontifica Universidad Católica de Chile, en el año 1996[45]. Este centro tuvo dentro de sus pioneros al Dr. C. Vera, formado en Montreal con el Dr. Penfield en la década de los sesenta, luego a comienzos de los noventa el gru-

po de neurofisiólogos se entrenó en Cleveland y el neurocirujano en Bonn, Alemania. La cirugía de la epilepsia nació en Chile en el Instituto de Neurocirugía, que hoy lleva el nombre de su fundador (A. Asenjo), este centro hoy cuenta con un programa de cirugía de la epilepsia en niños y adultos. El problema en Chile, esta dado como en mayoría de los países latinoamericanos, en que los gobiernos no apoyan con la infraestructura necesaria a los centros públicos.

Actualmente el mayor centro de Cirugía de la Epilepsia en Chile es Clínica Las Condes, la cual cuenta con un Centro Avanzado de Epilepsias, que realiza aproximadamente 40 cirugías al año, además de formar especialistas y apoyar a centros en Bolivia, Perú[46] y Ecuador, para desarrollar cirugía de la Epilepsia.

En México los Drs. Velasco fueron pioneros en su país en la cirugía de la epilepsia, además lideres en estimulación cerebral profunda. Actualmente el mayor programa de cirugía de la epilepsia es el Instituto Neurológico liderado por el Dr. Mario Alonso-Vanegas, quien además ha formado a múltiples especialistas en cirugía de la epilepsia con el apoyo de la ILAE. Por otro lado existen centros nacientes en diferentes estados mexicanos.

Actualmente la Comisión Latinoamericana de la Liga Internacional Contra la Epilepsia, tiene una comisión de Cirugía de la epilepsia, cuya meta es crear pautas de requerimientos mínimos[47], para poder desarrollar la cirugía de la epilepsia en todos los países que carecen de esta gran y probada herramienta terapéutica[48]. Además de promover la formación de especialistas.

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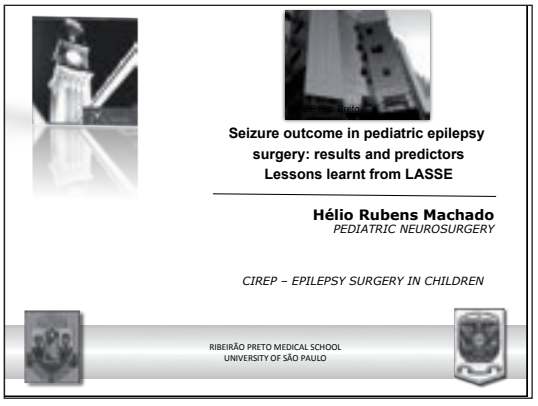
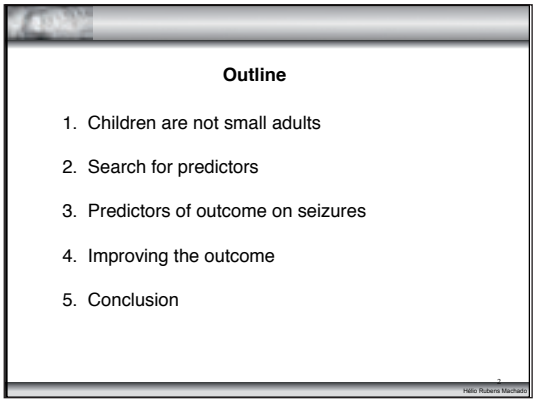
Mario Alonso (Mexico)

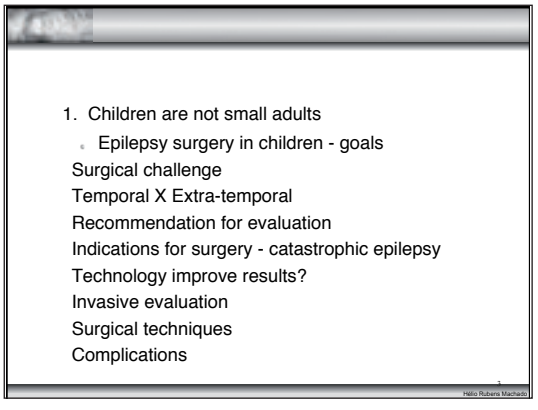
INDICATIONS FOR EPILEPSY SURGERY ALONG THE AGE CONTINUUM

Helio R. Machado (Brazil)

SEIZURE OUTCOME IN PEDIATRIC EPILEPSY SURGERY: RESULTS AND PREDICTORS. LESSONS LEARNT FROM LASSE







TREATMENT GOAL

Eliminate seizures quickly

Optimize cognitive development

Improve behavior and quality of life

1. Children are not small adults
   - Epilepsy surgery in children - goals
   - Surgical challenge

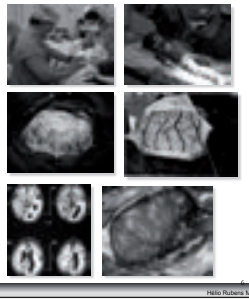
Temporal X Extra-temporal
Recommendation for evaluation
Indications for surgery - catastrophic epilepsy
Technology improve results?
Invasive evaluation
Surgical techniques
Complications

Complexity of pediatric surgery

- Early surgery = major risk

Focal resection	200 – 500 ml
Hemispherectomy	1500 ml
Hemispherotomy	500 ml

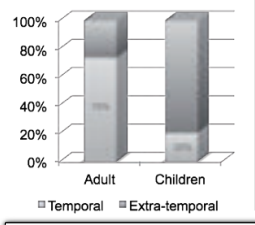
Age	Weight (kgs)	Blood volume (ml)
6 me	6 - 8	450 – 750
1 a	8 – 12	600 – 900
2 a	12 – 15	750 – 1100
3 a	15 – 18	850 – 1300
10 a	23 – 51	1700 - 3800



1. Children are not small adults
   - Epilepsy surgery in children - goals
   - Surgical challenge
   - Temporal X Extra-temporal

Recommendation for evaluation
Indications for surgery - catastrophic epilepsy
Technology improve results?
Invasive evaluation
Surgical techniques
Complications

Epidemiology – ADULTS X CHILDREN



Temporal lobe

CIREP 1996 -2013 : 1610 patients

Hélio Rubens Machado

1. Children are not small adults
   - Epilepsy surgery in children - goals
   - Surgical challenge
   - Temporal X Extra-temporal
   - Recommendation for evaluation (ILAE)

Indications for surgery - catastrophic epilepsy
Technology improve results?
Invasive evaluation
Surgical techniques
Complications

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Original Research

Proposed Criteria for Referral and Evaluation of Children for Epilepsy Surgery: Recommendations of the Subcommission for Pediatric Epilepsy Surgery

- Rationale for pediatric epilepsy surgical services
- Typical surgical syndromes
- Pediatric epilepsy unit
- Outcome assessment for pediatric surgical patients

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Diagnostic test utilization in evaluation for resective epilepsy surgery in children.

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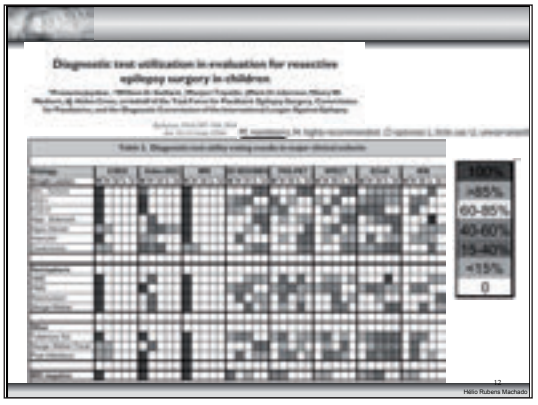

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   - Recommendation for evaluation (ILAE)
   - Indications for surgery - catastrophic epilepsy

Technology improve results?
Invasive evaluation
Surgical techniques
Complications

13
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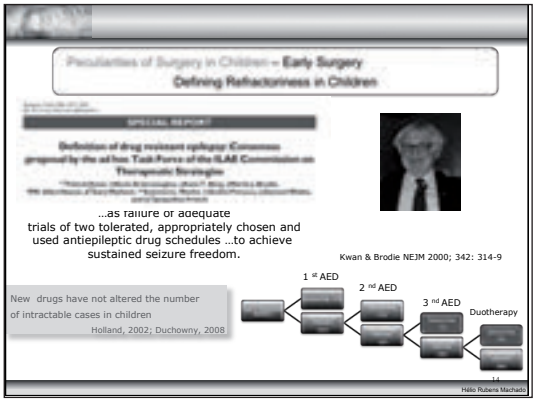

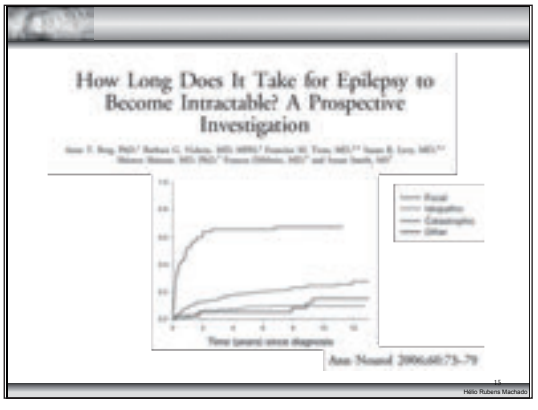

Catastrophic epilepsy

Seizures 666,9 / mês
Status epilepticus 40,7%

Refractory epilepsy

Progressive neurologic deficit

spastic hemiplegia

Developmental delay

Behavior deterioration

16
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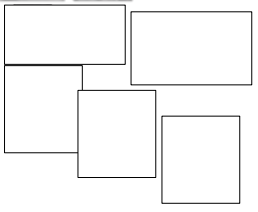
Catastrophic epilepsy

- Sturge Weber syndrome
- Hemimegalencephaly
- Rasmussen encephalitis
- Tuberous Sclerosis complex
- Cortical dysplasia
- Porencephaly



17
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1. Children are not small adults
   - Epilepsy surgery in children - goals
   - Surgical challenge
   - Temporal X Extra-temporal
   - Recommendation for evaluation (ILAE)
   - Indications for surgery - catastrophic epilepsy
   - Technology improve results?

Invasive evaluation

Surgical techniques

Complications

18
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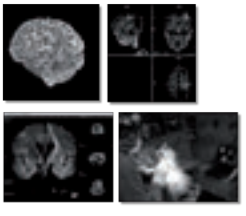
- Which technologies?
  - Neuroimaging
    - 3T, DTI, spectroscopy, fMRI, spect, MEG
  - Surgical tools
    - Neuronavigation
    - Endoscopic techniques, ultrasonic aspirator, brain sonography
    - Robotic surgery
    - Minimally invasive techniques, disconnective surgery



19
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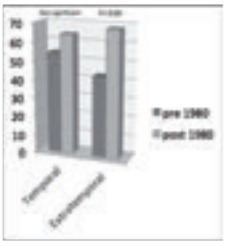
Do outcomes improve as technology improves?

Long term outcome
Temporal - Extratemporal



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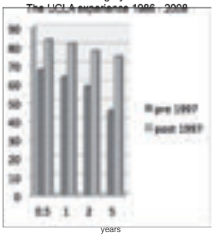
Do outcomes improve as technology improves?

Improved outcomes in pediatric epilepsy surgery



Neurology 2010, 74

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1. Children are not small adults
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   - Surgical challenge
   - Temporal X Extra-temporal
   - Recommendation for evaluation (ILAE)
   - Indications for surgery - catastrophic epilepsy
   - Technology improve results?
   - Invasive evaluation

Surgical techniques

Complications

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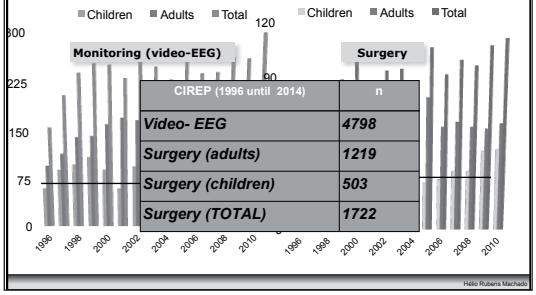
- Presurgical evaluation



CIREP (1996 until 2014)	n
Video- EEG	*4798*
Surgery (adults)	*1219*
Surgery (children)	*503*
Surgery (TOTAL)	*1722*

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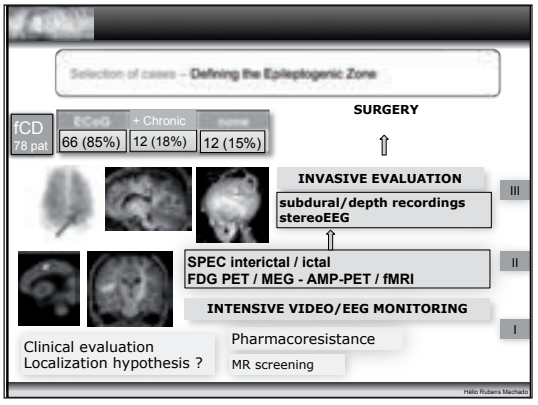
Selection of cases – Defining the Epileptogenic Zone
SURGERY
fCD
78 pat
+ Chronic
66 (85%)
12 (18%)
12 (15%)
INVASIVE EVALUATION
subdural/depth recordings
stereoEEG
III
SPEC interictal / ictal
FDG PET / MEG - AMP-PET / fMRI
II
INTENSIVE VIDEO/EEG MONITORING
I
Clinical evaluation
Localization hypothesis ?
Pharmacoresistance
MR screening
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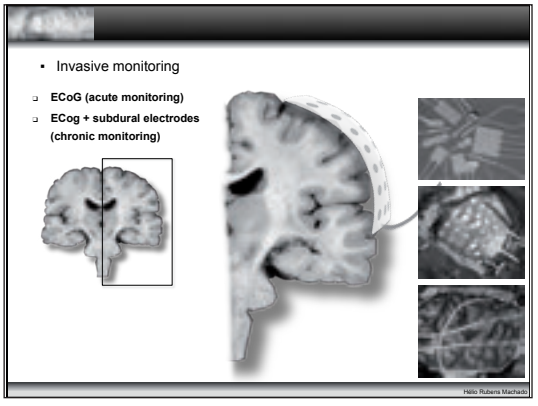
Invasive monitoring
ECoG (acute monitoring)
ECog + subdural electrodes (chronic monitoring)
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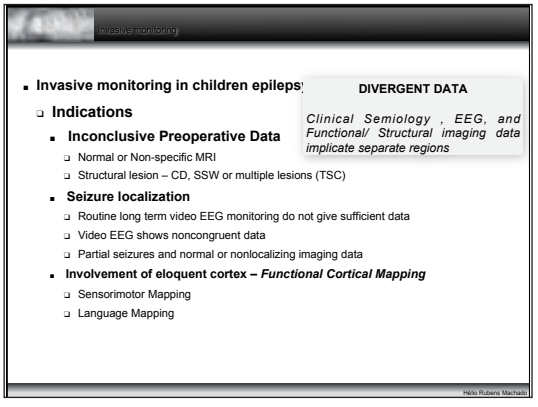
Invasive monitoring
Invasive monitoring in children epilepsy
Indications
Inconclusive Preoperative Data
Normal or Non-specific MRI
Structural lesion – CD, SSW or multiple lesions (TSC)
Seizure localization
Routine long term video EEG monitoring do not give sufficient data
Video EEG shows noncongruent data
Partial seizures and normal or nonlocalizing imaging data
Involvement of eloquent cortex – Functional Cortical Mapping
Sensorimotor Mapping
Language Mapping
DIVERGENT DATA
Clinical Semiology , EEG, and Functional/ Structural imaging data implicate separate regions
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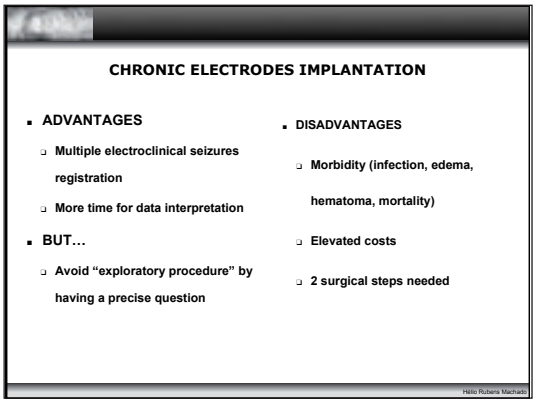
CHRONIC ELECTRODES IMPLANTATION
ADVANTAGES
Multiple electroclinical seizures registration
More time for data interpretation
BUT…
Avoid "exploratory procedure" by having a precise question
DISADVANTAGES
Morbidity (infection, edema, hematoma, mortality)
Elevated costs
2 surgical steps needed
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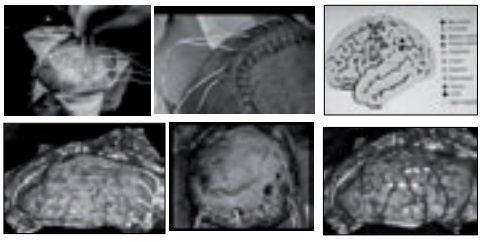
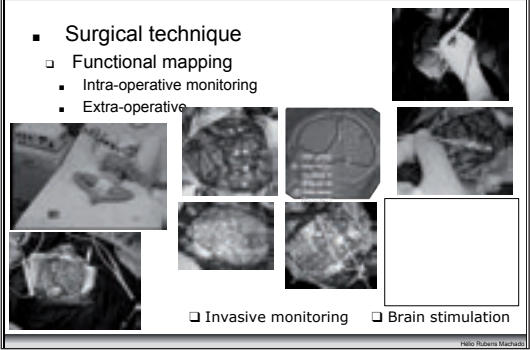
▪ Chronic electrodes implantation



▪ Surgical technique

- ❑ Functional mapping
  - ▪ Intra-operative monitoring
  - ▪ Extra-operative



❑ Invasive monitoring ❑ Brain stimulation

1. Children are not small adults
   - Epilepsy surgery in children - goals
   - Surgical challenge
   - Temporal X Extra-temporal
   - Recommendation for evaluation (ILAE)
   - Indications for surgery - catastrophic epilepsy
   - Technology improve results?
   - Invasive evaluation
   - Surgical techniques

Complications

SURGERY

1996 to 2015

Patients 538

CIREP Children – Ribeirão Preto
Ribeirão Preto Medical School
UNIVERSITY OF SÃO PAULO
BRAZIL

Surgical technique	
Hemispherotomy (24%)	128
Temporal Lobectomy	117
Lesionectomy	102
VNS	49
Frontal Lobectomy	35
Posterior(par-occipital) cortex	34
Callosotomy	26
Occipital Lobectomy	15
Multilobar Resection	3
Focal Corticectomy	17
other	12
Total	538

❑ Hemispherotomy – surgical technique

Delalande, 92
vertical parasagittal hemispherotomy

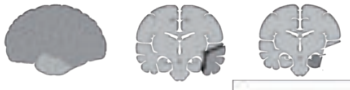
Schramm, 94
hemispherical deafferentation

Villemure, 93

Mathern, 04
modified lateral hemispherotomy

Surgical technique

Temporal lobe surgery



Hemispherotomy

1. Children are not small adults
   - Epilepsy surgery in children - goals
   - Surgical challenge
   - Temporal X Extra-temporal
   - Recommendation for evaluation (ILAE)
   - Indications for surgery - catastrophic epilepsy
   - Technology improve results?
   - Invasive evaluation
   - Surgical techniques
   - Complications

Neurological complications after epilepsy surgery in children
CIREP - 503 cases

Transient Hemiparesis	
Frontal lobectomy	*2*
Multi-lobar resection	*10*
Posterior quadrantectomy	*2*
Temporal lobectomy	*1*
Callosotomy	*1*
Lesionectomy (motor area)	*6*

Hemianopia	
Temporal lobectomy	*1*
Lesionectomy	*6*

Miscellaneous	
Meningitis	*3*
Sagital sinus laceration	*1*
Epidural hematoma	*1*
Intracerebral hematoma	*1*

General complications after epilepsy surgery in children

General complications (more than 1/patient)	
Pneumonia	7
Scalp laceration	1
CSF leak	5
Infection VNS site (explantation)	1
Osteomyelitis	3

Long term complications	
Hemiparesis	3
Hydrocephalus	3

Mortality brain edema/ infarction	
Frontal resection	2
Hemispherotomy	1

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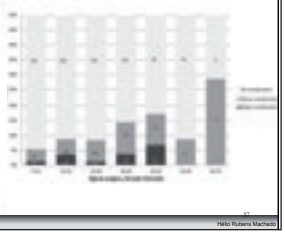
Complications of epilepsy surgery in Sweden 1996–2010: a prospective, population-based study

Johan Ejeltvi, MD,[1] Roland Flink, MD, PhD,[1] Bertil Rydenhag, MD, PhD,[1] and Kristina Malmgren, MD, PhD[2]

J Neurosurg October 31, 2014



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1. Children are not small adults
2. Search for predictors
   - Specific pathology

Incomplete resection
Anatomical lesion
Epileptogenic zone
Multifocal MR abnormalities
Prep generalized EEG abnormalities
Prior surgery
Multifocal resection
Epileptic abnormalities on post EEG

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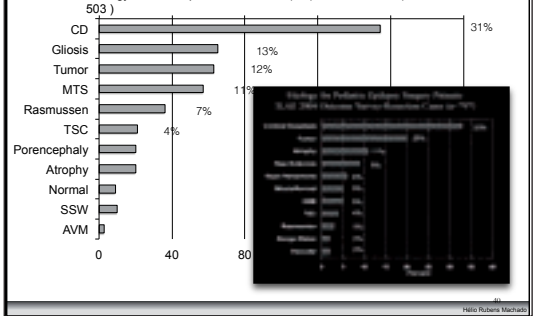
Etiology of cases operated at CIREP (RP) - 1996 to 2014 (n= 503)



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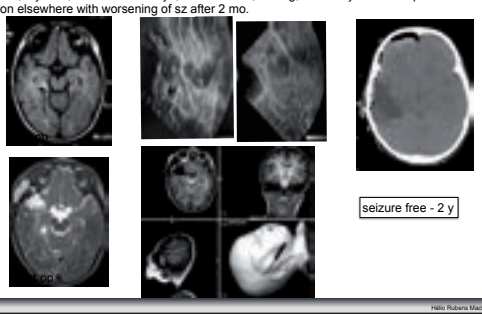
1. Children are not small adults

2. Search for predictors
   - Specific pathology
   - Incomplete resection
     - Anatomical lesion
     - Epileptogenic zone

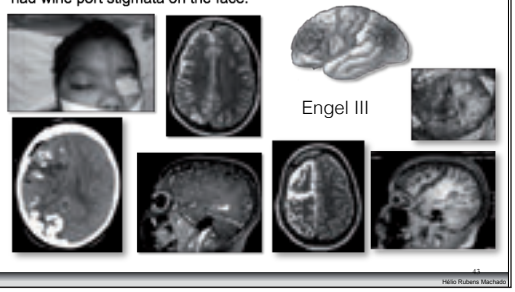
Multifocal MR abnormalities
Prep generalized EEG abnormalities
Prior surgery
Multifocal resection
Epileptic abnormalities on post EEG

- CV, 2 ya old, seizures since 1yo, automatisms, staring, refractory to AED. Operated on elsewhere with worsening of sz after 2 mo.



seizure free - 2 y

- SOP, 8 yo, seizures since 8 mo old. Sz fall to the ground followed by tonic posture on the left, short duration, loss of conciousness. She had wine port stigmata on the face.

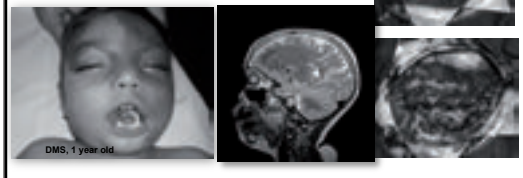


Engel III

Incomplete disconnection

Hemispherotomy

Engel III

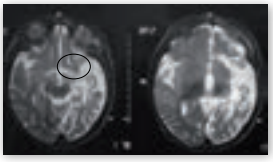


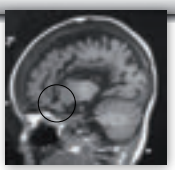
DMS, 1 year old

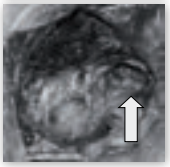
Hemispherotomy and pediatric epilepsy

Reoperation

Hemispherotomy
Engel I







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1. Children are not small adults

2. Search for predictors
   - Specific pathology
   - Incomplete resection
     - Anatomical lesion
     - Epileptogenic zone
   - Multifocal MR abnormalities

Prep generalized EEG abnormalities
Prior surgery
Multifocal resection
Epileptic abnormalities on post EEG

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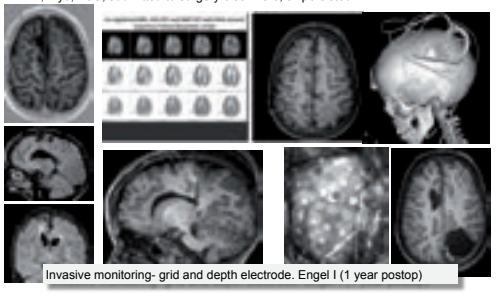
- PLT, 4 yo, TSC, submitted to surgery elsewhere, sz persisted.



Invasive monitoring- grid and depth electrode. Engel I (1 year postop)

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1. Children are not small adults

2. Search for predictors
   - Specific pathology
   - Incomplete resection
     - Anatomical lesion
     - Epileptogenic zone
   - Multifocal MR abnormalities
   - Pre op generalized EEG abnormalities
   - Prior surgery
   - Multifocal resection
   - Epileptic abnormalities on post EEG

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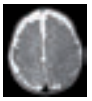
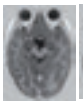
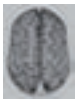
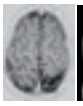
CMG, 3y 7mo age, sz since 25 d age. EEG- hemi-hypsarritmia left hemisphere. Progressively worsening. Video-EEG Dec 2014 - L Post quadrant. Ictal SPECT - Increased perfusion L rolandic + TPO . PET - Hypometabolism L TP + L frontal. EPI conference - Disconnect L TPO. Sz since 2 day po



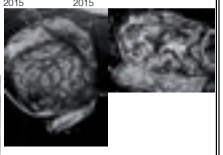

2012 2012



CD type IIA

2015 2015



MR post op




Invasive recording
Hemispherotomy
Sz free since surgery (nov)

49
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1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
   - Pre surgical variables
   - Surgical variables
   - Post surgical variables

50
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1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
   - Pre surgical variables
     - MRI - unifocal lesion
     - Older age at Sz onset
     - Partial sz

51
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1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
   - Pre surgical variables
   - Surgical variables
     - Temporal unilobar resection
     - Complete resection

52
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1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
   - Pre surgical variables
   - Surgical variables
   - Post surgical variables
     - CD type II
     - Glial - neuronal tumor

PREDICTORS OF SEIZURE FREEDOM

EARLY SURGERY	shorter interval from epilepsy onset to surgery < 5 years of epilepsy onset (Simasathien, Jehi et al, 2013)
MRI +	concordance EEG MRI negative - negative predictor
AED withdrawal	early AED withdrawal does not affect long-term Sz outcome (TimeToStop group - 15 centres in Europe-766 included)- Boshuisen, Arzimanoglou, 2012.
AGE AT Sz ONSET	older age better prognosis
COMPLETE LESIONECTOMY / EZ	

Bast, 2013; Boshuisen et al 2012; Cossu et al 2008; Chapman et al 2005; Dalmagro et al 2005; Jayakar et al 2008; Jonas et al 2007; Liava et al 2012 & 2014; Kim et al 2009; Krsec et al 2013; Lerner et al 2009; Loddenkemper et al 2007; Paolichi et al 2004; Roulet-Perez et 2010; Simasathien et al 2013; Tellez-Zenteno et al 2010; Tonini et al 2004.

PREDICTORS OF SEIZURE FREEDOM
Type of Surgery

TEMPORAL LOBE	Poor outcome: MRI outside temp lobe; generalized Sz; mental retardation; previous status; neg histology; postop Sz.
POSTERIOR CORTEX	Good prognosis: Older age at epilepsy onset; restricted EZ; complete resection of EZ
EXTRATEMPORAL EPILEPSY	Good prognosis: early surgery; MRI +, complete resection; EEG/MRI concordance, no APOS,; type II CD
HEMISPHERECTOMY	Poor outcome: Bilateral PET abnormalities, APOS; CD (hemimegalencephaly)
MULTILOBAR SURGERY	Poor outcome: Fronto-temporal / Parieto-temporal localization; incomplete resection; preop aura; postop interictal discharges

Cossu et al 2008; Dalmagro et al 2005; D'Argenzio et al 2012; Kossoff et al 2003; Liava et al 2012 & 2014; Lippé et al 2010; Miserocchi et al 2013; Moosa et al 2013; Sarkis et al 2012; Terra-Bustamante et al 2007; Thomas et al 2010; Tonini et al 2004.

PREDICTORS OF SEIZURE FREEDOM
Etiology

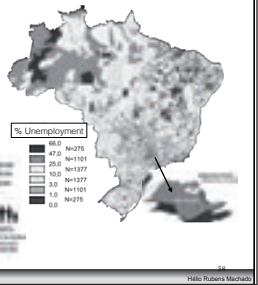
CORTICAL DYSPLASIA	Good outcome: Complete resection, MRI +, CD type II
TSC	Good outcome: Complete removal of epileptogenic tissue detected MRI & ECoG; regional scalp interictal EEG patterns; agreement interictal x ictal EEG
GLIONEURONAL TUMORS	Good outcome: complete lesionectomy; "strong" prognostic indicator of Sz remission
RASMUSSEN	Surgery X Immunotherapy dilemma
MTS	"Strong"predictor of success; outcome similar to adults

Cossu et al 2008; Bien et al 2013; Gataullina & Dulac 2010; Kim et al 2009; Lerner et al 2009; Kim et al 2009; Krsec et al 2013; Rowland et al 2012; Terra-Bustamante et al 2007 & 2009; Tonini et al 2004; Tubbs et al 2005; Varadkan et al 2014

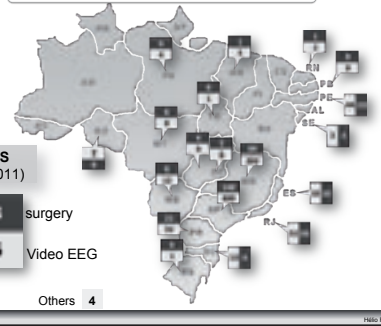
1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
4. Improving the outcome
   - Centralization of epilepsy program

Peculiarities of Surgery in Children – National referral

- ***the big challenge***
  - country with large disparities
    - demographic density
    - economic diversity and drive
    - social stratification



Peculiarities of Surgery in Children – National referral



RESULTS
(2005 to 2011)

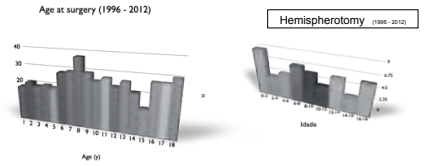
373 surgery

886 Video EEG

Others 4

1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
4. Improving the outcome
   - Centralization of epilepsy program
   - Time to surgery

- Surgery should be indicated early
  - Effect on brain development
  - Early surgical intervention (avoid epileptic encephalopathy)



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1. Children are not small adults
2. Search for predictors
3. Predictors of outcome on seizures
4. Improving the outcome
   - Centralization of epilepsy program
   - Time to surgery
   - Rehabilitation program

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Intensive mobility training and rehabilitation after hemispherotomy

Methods	
Acute Intensive mobility training	first postop week 2h/ day 7 d/w
	reevaluation 30, 90, 180 & 360 days postop

Results: 14 children
-13 children walking 30 d after surgery
-1 child walking with assistance - 90 days -

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Intensive mobility training and rehabilitation after hemispherotomy

12 d postop 11 d postop 12 mo postop

Hemispherotomy Rasmussen Encephalitis

Hélio Rubens Machado


Thank you
CIREP – CENTER FOR EPILEPSY SURGERY
2 w post op
RIBEIRÃO PRETO MEDICAL SCHOOL
UNIVERSITY OF SÃO PAULO

Jorge Gonzalez (USA)

SURGICAL TREATMENT OF TEMPORAL LOBE EPILEPSIES

Samuel Wiebe (Canada)

COGNITION, EMOTIONS, AND QUALITY-ADJUSTED SURVIVAL.

Patricia Braga (Uruguay)

EPILEPSY SURGERY AND RESEARCH: HISTORY OF A RELATIONSHIP AND FUTURE PERSPECTIVES

La epilepsia ha sido considerada como una ventana a la comprensión del funcionamiento cerebral. Podríamos decir que la epileptología clínica moderna nace de la investigación neurofisiológica y ha alimentado tradicionalmente, a su vez, múltiples líneas de investigación clínica y básica.

La cirugía de epilepsia, por otra parte, nace como una alternativa terapéutica para pacientes con crisis recurrentes, sea en la época en que no se contaba con fármacos, o actualmente, cuando el arsenal medicamentoso resulta insuficiente para lograr el control de las crisis. Este lugar pragmático puede ser artificial, y el divorcio entre la terapia quirúrgica y las neurociencias básicas, resultar engañoso. La cirugía de epilepsia ha contribuido a gestar múltiples líneas de investigación, y sus avances se intrincan mutuamente, contribuyendo a la génesis de nuevos paradigmas, hipótesis y escuelas filosóficas en el área de la neurociencia.

Así, recordamos que la cirugía de epilepsia, eminentemente resectiva, proporciona un material biológico fundamental para la investigación fisiológica sobre tejido nervioso humano in vitro, para la histo-patología, e incluso con las técnicas más recientes, para la investigación genética y molecular del cerebro epiléptico. Por otra parte, los requerimientos del algoritmo de investigación prequirúrgica han propulsado la investigación aplicada y el desarrollo de tecnología médica en el área de la neurofisiología, la imagen estructural y funcional. El desarrollo en cada una de estas áreas ha llevado a nuevos descubrimientos y preguntas adicionales, desafiando constantemente los límites del conocimiento en el área. Son un ejemplo los aportes de la neurofisiología invasiva no sólo para comprender la dinámica de la zona epileptógena y redes epileptogénicas, sino aportando estudios funcionales, in vivo, de conectividad y funcionamiento de redes sensoriales y cognitivas.

En otra perspectiva, la evolución de los pacientes luego de la cirugía ha sido y es fuente de investigación. En primer lugar, en lo filosófico o conceptual, aportando a las definiciones y criterios de remisión y cura de una enfermedad clásicamente considerada como crónica en forma ineludible. En segundo lugar, agregando constantes desafíos en la comprensión de la zona de inicio ictal, los paradigmas de inicio focal, zona epileptógena, red epileptógena, ictogénesis y epileptogénesis. Finalmente, le ha brindado nuevos horizontes a la dimensión psico-social de la epilepsia, ofreciendo un modelo real de ajuste de expectativas, adaptación y re-adaptación en el contexto de una enfermedad estigmatizante como pocas, y con clara repercusión en la calidad de vida de quien la padece y su entorno.

La historia de la relación entre la cirugía de epilepsia y la investigación epileptológica, oculta para muchos, es patente y rica. A medida que profundizamos en sus interacciones resulta

aún inabarcable. ¿Cuál es la proyección futura? ¿En qué áreas esperamos que haya un mayor desarrollo? ¿Es aún posible que surjan áreas completamente nuevas de investigación? ¿Qué puede aportar la comunidad epileptológica latinoamericana en este futuro?

Samuel Wiebe (Canada)

THE AGE OF "OMICS" AND BIG DATA IN EPILEPSY SURGERY: HYPE OR REALITY

Manuel Campos, Helio Machado, Mario Alonso, Jorge Gonzalez

EPILEPSY SURGERY: FUTURE DEVELOPMENT